NCT #NCT02606305

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Mirvetuximab Soravtansine (IMGN853) in Combination with Bevacizumab, Carboplatin, Pegylated Liposomal Doxorubicin, Pembrolizumab, or Bevacizumab + Carboplatin, in Adults with Folate Receptor Alpha Positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer
Study Number	IMGN853-0402
Study Phase:	1b/2
Product Name:	Mirvetuximab soravtansine (IMGN853)
Indication:	Folate Receptor Alpha Positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer
Investigators:	Multicenter
Sponsor:	ImmunoGen, Inc. 830 Winter Street Waltham, MA 02451 USA
Sponsor Contact:	[redacted] Phone: [redacted] E-mail: [redacted]
Original Protocol Date:	11 Aug 2015
Amendment No. and Date:	Amendment 1: 23 Sep 2015 Amendment 1A: 11 Feb 2016 Amendment 1B: 13 May 2016 Amendment 2: 21 Jun 2016 Amendment 3: 26 Jun 2017 Amendment 4: 14 Nov 2017 Amendment 5: 21 Sep 2018

SPONSOR SIGNATURE PAGE

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for mirvetuximab soravtansine (IMGN853). I have read the ImmunoGen Protocol IMGN853-0402 and agree to conduct the study as outlined and in conformance with 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, Institution, and Address of Investigator

Signature of Investigator

Date

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
AIBW	Adjusted ideal body weight
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response/remission
CRC	Cohort Review Committee
CRF	Case report form
CRO	Clinical Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DM4	N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
DM4-Me	Methylated-N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
DOR	Duration of response
ECG	Electrocardiogram

Abbreviation or Specialist Term	Explanation
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOC	Epithelial ovarian cancer
FDA	Food and Drug Administration
FIH	First in human
FRα	Folate receptor α
GCIG	Gynecologic Cancer Intergroup
GCP	Good clinical practice
GI	Gastrointestinal
HFS	Hand-foot syndrome
HGSOC	High-grade serous ovarian carcinoma
IBW	Ideal body weight
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMGN	ImmunoGen
IMGN853	Mirvetuximab soravtansine
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional review board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IV	Intravenous
LDH	Lactic acid dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
MUGA	Multigated acquisition

Abbreviation or Specialist Term	Explanation
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PFT	Pulmonary function tests
PgP	P-glycoprotein
PK	Pharmacokinetics
PO	Per orem (by mouth)
PR	Partial response/remission
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PT	Prothrombin time
PTT	partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red blood cell (count)
RP2D	Recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of the longest diameters
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
t_{max}	Time that maximum plasma concentration occurs

Abbreviation or Specialist Term	Explanation
TSH	Thyroid-stimulating hormone
ULN	Upper limit of the normal range
UPC	Urine protein creatinine ratio
US	United States
V_{ss}	Volume of distribution at steady state
WBC	White blood cell (count)
WCBP	Woman of childbearing potential
WHO-DD	World Health Organization – Drug Dictionary
WNL	Within normal limits

PROTOCOL SYNOPSIS

Title of Study: A Phase 1b/2 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Mirvetuximab soravtansine (IMGN853) in Combination with Bevacizumab, Carboplatin, Pegylated Liposomal Doxorubicin, Pembrolizumab, or Bevacizumab + Carboplatin in Adults with Folate Receptor Alpha Positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer	
Study center(s): approximately 16 in the United States (US), Spain, Belgium, and Canada	
Study period (months): approximately 48 months (including treatment and 30-Day Follow-up visit) First patient enrolled: December 2015	**Phase of development:** 1b/2
Purpose/rationale: Mirvetuximab soravtansine, also known as IMGN853, is a targeted antibody-drug conjugate (ADC) that binds with high affinity to folate receptor alpha (FRα), a glycophosphatidylinositol-linked protein that shows limited normal tissue expression and high expression in several solid tumors (Kelemen 2006), most notably serous epithelial ovarian cancer (EOC) (Miotti 1987, O'Shannessy 2013). Mirvetuximab soravtansine consists of a humanized anti-FRα monoclonal antibody (mAb) attached via a cleavable disulfide containing linker to the cytotoxic maytansinoid DM4. Once released within the target cell, DM4 acts as an anti-mitotic agent that inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. In vitro studies have demonstrated that mirvetuximab soravtansine binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (50% inhibitory concentration ≤ 1 nM) and selective cytotoxicity against tumor cells expressing FRα. Mirvetuximab soravtansine demonstrates significant activity against FRα-positive xenografts, with partial and complete remissions observed in ovarian models (Ab 2015). The in vitro and in vivo pharmacologic properties of mirvetuximab soravtansine, along with the high expression of FRα in EOC, provided the rationale for exploring mirvetuximab soravtansine in a clinical setting. In the first-in-human (FIH) Phase 1 study (Study IMGN853-0401) of single-agent mirvetuximab soravtansine, objective responses were observed in patients with heavily pretreated FRα-positive EOC (≥ 25% of cells with ≥ 2+ staining intensity by immunohistochemistry [IHC]) and endometrial cancer. As of February 2018, mirvetuximab soravtansine had a 27% objective response rate (ORR) (95% CI, 18.5%, 37.1%) and median progression-free survival (PFS) of 4.2 months (95% CI, 3.7, 5.4 months) in the 96 patients with platinum-resistant EOC in the patient expansion cohort in Study 0401. The ORR was 47% (95% CI, 30.4%, 64.5%) and the median PFS was 6.7 months (95% CI, 4.1, 8.3 months) in the subset of 36 patients with FRα-positive (medium/high expression [≥ 50% of cells with ≥ 2+ intensity]) platinum-resistant EOC with one to three prior regimens treated as part of a 96-patient expansion cohort in Study 0401 (clinical study report Table 16). Similarly, results of a pooled analysis of 113 patients showed an ORR of 30% (95% CI, 21.8%, 39.4%), a median PFS of 4.3 months (95% CI, 3.9, 5.4), and a duration of response of 19.3 weeks (95% CI, 18, 34 weeks). Treatment-related adverse events (AEs) occurring in > 20% of patients in this cohort included diarrhea, blurred vision, fatigue, nausea, and increased aspartate aminotransferase (AST), and were mostly low grade. Blurred vision was likely related to the development of corneal keratopathy, transient microcysts that form in the corneal epithelium, causing temporary symptoms. Bevacizumab, carboplatin, and pegylated liposomal doxorubicin are currently in use for the treatment of EOC. Doublet combinations of mirvetuximab soravtansine with bevacizumab, carboplatin, and pegylated liposomal doxorubicin have all demonstrated additive activity in nonclinical models. Pembrolizumab, an anti-programmed death receptor-1 (PD-1) mAb, is approved for the treatment of melanoma, non–small-cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability high solid tumors, and gastric/gastroesophageal junction adenocarcinoma and has shown preliminary anti-tumor activity as a single agent in EOC (Varga 2015). The mirvetuximab soravtansine + bevacizumab and mirvetuximab soravtansine + carboplatin dose escalation cohorts in this study have been completed, with dose levels explored to the highest allowable per this protocol. The safety and tolerability data show that each of the doublets was generally well tolerated; no new safety signals were observed at the highest dose levels explored. The	

safety profile is consistent with the reference safety profile information for each drug and in line with expectations for a population of previously treated ovarian cancer patients.
Furthermore, initial signs of anti-tumor activity were seen both doublet combinations explored in this study. The ORR and the median PFS observed in the mirvetuximab soravtansine + bevacizumab combination across all dose levels and FRα expression levels (n = 14) were 29% (95% CI, 8, 58) and 9.5 months (95% CI, 3.5, 15.2), respectively (O'Malley 2017). The observed anti-tumor activity in a heavily pre-treated (median of 6 prior lines of therapy [range, 2-8]), platinum-resistant population compares favorably with what has been demonstrated in less heavily pre-treated, platinum-resistant ovarian cancer patients following treatment with bevacizumab + standard chemotherapy (Pujade-Lauraine 2014). The ORR and median PFS observed in the mirvetuximab soravtansine + carboplatin combination across all dose levels and FRα expression levels (n = 17) were 65% (95% CI, 38, 86) and 12.1 months (95% CI, 9.0, 15.0) (O'Malley 2017). The observed anti-tumor activity in a pre-treated (median 3 prior regimens [range 1-5]), platinum-sensitive (72% with a PFS 6-12 months) population compared favorably with what has been demonstrated in standard platinum-based doublets in a recurrent platinum-sensitive setting (Aghajanian 2012, Coleman 2017, and Gladieff 2012).
Bevacizumab, in combination with carboplatin-based doublets, has been approved for frontline treatment of patients with EOC in the European Union since 2011; more recently (December 2016) the use of bevacizumab + carboplatin–based doublet regimens have been approved in the US for the treatment of patients with recurrent, platinum-sensitive EOC. These approvals have supported an increased and broader use of triplet therapy for platinum-sensitive EOC. Therefore, given the preliminary safety and initial anti-tumor activity of mirvetuximab soravtansine both with bevacizumab and with carboplatin, and the increased use of bevacizumab and carboplatin in triplet therapy, this study will explore the safety and anti-tumor activity of the triplet therapy mirvetuximab soravtansine + bevacizumab + carboplatin in patients with recurrent platinum-sensitive EOC. Because of the successful full dose experiences with each of the combination partners as doublets with mirvetuximab soravtansine, the triplet therapy will initially explore a combination using full doses of all 3 agents. The dose will be explored in a stepwise manner, with a pause to review safety data after the first six and then 12 patients have completed their first cycle of treatment.
The study is designed to establish the maximum tolerated dose (MTD) and determine the recommended Phase 2 dose (RP2D) of mirvetuximab soravtansine when administered in combination with either bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab. The study will also investigate activity signals and safety and tolerability of a triplet dose regimen of mirvetuximab soravtansine + bevacizumab + carboplatin. All study treatments will be administered intravenously (IV) to adult patients with FRα-positive ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
The safety, tolerability, immunogenicity of mirvetuximab soravtansine, and preliminary anti-tumor activity of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin, pembrolizumab, or bevacizumab + carboplatin will be characterized. The pharmacokinetics (PK) and immunogenicity of mirvetuximab soravtansine will be characterized along with bevacizumab, carboplatin, and pegylated liposomal doxorubicin concentrations. Pembrolizumab concentrations may be evaluated, if warranted, because of a safety signal.

Primary Objectives

Dose Escalation (Regimens A Through D)

- Evaluate the safety and tolerability of mirvetuximab soravtansine when given in combination with bevacizumab, carboplatin, or pegylated liposomal doxorubicin, or pembrolizumab (Regimens A, B, C and D, respectively) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

Dose Expansion (Regimens A and D) and Regimen E (Triplet)

- Assess preliminary response-based anti-tumor activity of mirvetuximab soravtansine when administered in combination with bevacizumab (Regimen A) or pembrolizumab (Regimen D) and in combination with bevacizumab and carboplatin (Regimen E) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

Primary Endpoints

Dose Escalation (Regimens A Through D)

- Treatment-emergent AEs, laboratory test results, physical examination, electrocardiograms (ECGs), and vital signs

Dose Expansion (Regimens A and D) and Regimen E (Triplet)

- Objective response rate, defined as percentage of patients with confirmed response (complete response/remission [CR] + partial response/remission [PR]) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Secondary Objectives

- Evaluate the safety and tolerability of mirvetuximab soravtansine when administered in combination with bevacizumab or pembrolizumab (Dose Expansion, Regimens A and D, respectively) and in combination with bevacizumab and carboplatin (Regimen E [Triplet]) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer
- Assess preliminary response-based anti-tumor activity of the combination Regimens (Dose Escalation, Regimens A through D)
- Assess PFS
- Measure duration of response (DOR): the time from first objective response (CR/PR) to the time of progressive disease (PD) among those who have achieved a PR or CR
- Assess Gynecologic Cancer Intergroup (GCIG) CA125 response rate of the combination Regimens
- Characterize PK of mirvetuximab soravtansine when used in combination Regimens
- Evaluate bevacizumab, carboplatin, and pegylated liposomal doxorubicin concentrations when administered in combination with mirvetuximab soravtansine
- Characterize immunogenicity of mirvetuximab soravtansine

Secondary Endpoints

- Treatment-emergent AEs, changes in laboratory test results, physical examination, ECGs, and vital signs (Dose Expansion [Regimens A and D] and Regimen E [Triplet]).
- Objective response rate, defined as percentage of patients with confirmed response (CR + PR) as assessed by RECIST Version 1.1 (Dose Escalation, Regimens A through D)
- Progression-free survival, defined as time from first dose to PD or death, whichever occurs first
- Duration of response, defined as the time from first objective response (CR/PR) to the time of PD among those who have achieved a PR or CR
- Number of patients with GCIG CA125 criteria clinical responses
- Mirvetuximab soravtansine PK parameters for intact ADC, total antibody, DM4, and *S*-methyl DM4 include, but are not limited to, Cycle 1 and Cycle 3 maximum plasma concentration (C_{max}), area under the time-concentration curve (AUC), terminal half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), and time that C_{max} occurs (t_{max})
- Concentration data of bevacizumab, carboplatin, and pegylated liposomal doxorubicin will be measured before and after bevacizumab, carboplatin, and pegylated liposomal doxorubicin infusions (Cycle 1 through Cycle 6)
- Immunogenicity: presence of anti-drug antibodies to mirvetuximab soravtansine

Exploratory Objectives

- Assess any association between FRα expression levels and clinical response
- Identify or evaluate potential biomarkers in blood and tumor tissue that might predict response to each of the four combinations
- Evaluate pembrolizumab concentrations if warranted by a safety signal (Regimen D only)

- Assess anti-tumor activity of the combination with pembrolizumab per immune-related RECIST (irRECIST) (Regimen D only)

Exploratory Endpoints

- Correlation of FRα expression, by IHC (protein), quantitative reverse transcriptase-polymerase chain reaction (mRNA), or other quantitative methods, to clinical endpoints
- Measure biomarkers in blood and tumor tissue including, but not limited to, mutational and genomic alterations of tumor samples; expression and activation of oncogenic genes and pathways in tumor samples; expression and polymorphism of drug transporters such as multidrug-resistance protein-1 (p-glycoprotein); the genotype of FcγR; expression and of immune-related genes and gene signatures (Regimen D only), and infiltration of tumor-related immune cells (Regimen D only)
- Concentration data for pembrolizumab if warranted by a safety signal (Regimen D only)
- Evaluate efficacy endpoints per irRECIST (Regimen D only)
  - Progression-free survival, ORR, and DOR per irRECIST are defined as specified for the respective endpoints using RECIST Version 1.1 above, except that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment after documented PD per RECIST Version 1.1. Subjects who discontinue treatment after documented PD assessment per RECIST Version 1.1 will be counted as having PD on the date of the documented PD assessment.

Note: Unless specifically warranted by relevance to safety or efficacy endpoints, the exploratory endpoints will not be reported in the clinical study report.

Number of patients (planned): It is estimated that approximately 311 to 355 patients will be enrolled into the study.

Dose Escalation Phase:

- ***Regimen A (mirvetuximab soravtansine + bevacizumab):*** approximately 16 patients; additional patients will be recruited to ensure that 10 patients are treated at the MTD
- ***Regimen B (mirvetuximab soravtansine + carboplatin):*** approximately 22 patients; additional patients will be recruited to ensure that 10 patients are treated at the MTD
- ***Regimen C (mirvetuximab soravtansine + pegylated liposomal doxorubicin):*** approximately 22 patients; additional patients, up to 10 patients, will be recruited and treated at the MTD
- ***Regimen D (mirvetuximab soravtansine + pembrolizumab):*** approximately 16 patients; additional patients will be recruited to ensure that 10 patients are treated at the MTD

Dose Expansion Phase:

Regimen A: mirvetuximab soravtansine + bevacizumab

Patients enrolled in this phase may be assigned to one of three Dose Expansion Cohorts according to previous exposure to bevacizumab as follows:

1. Dose Expansion Cohort 1: bevacizumab naïve; will enroll approximately 20 patients
2. Dose Expansion Cohort 2: bevacizumab pretreated; may enroll approximately 35 patients
3. Dose Expansion Cohort 3: patients with at least one but no more than three prior systemic treatment regimens, where prior regimens may have included bevacizumab; may enroll approximately 60 patients

Regimen D: mirvetuximab soravtansine +pembrolizumab

The Dose Expansion phase will enroll sufficient patients to ensure that 35 patients are FRα ≥ 50% of tumor staining at ≥ 2 + intensity

Regimen E (Triplet): mirvetuximab soravtansine + bevacizumab + carboplatin

This cohort will enroll approximately 50 patients to ensure that 40 patients will be treated at the MTD. The estimated study duration is approximately 48 months for patient accrual, dosing, treatment and follow-up.

Study Design Overview and Schema: This is an open label, Phase 1/2b, non-randomized combination study of mirvetuximab soravtansine with bevacizumab, carboplatin, pegylated liposomal

doxorubicin, pembrolizumab, or bevacizumab + carboplatin in adult patients with FRα-positive advanced EOC, primary peritoneal cancer, or fallopian tube cancer.

The treatment regimens and planned dose levels for the dose escalation phase of the study are outlined below and in Table 1, Table 2, Table 3, and Table 4.

Intermediate or lower dose levels of pegylated liposomal doxorubicin, bevacizumab, or carboplatin may be explored if dose-limiting toxicities (DLTs) can be attributed to their mechanism of action. Higher doses of pegylated liposomal doxorubicin (up to 50 mg/m^2) and carboplatin (AUC6) also may be considered. The maximum allowable doses of each study drug are as follows: mirvetuximab soravtansine 6.0 mg/kg adjusted ideal body weight (AIBW) every 3 weeks (Q3W), mirvetuximab soravtansine 6.0 mg/kg every 4 weeks (Q4W), bevacizumab 15 mg/kg Q3W, carboplatin AUC6 Q3W, pegylated liposomal doxorubicin 50 mg/m^2 Q4W, and pembrolizumab 200 mg Q3W.

If a patient is eligible for more than one Regimen, the investigator will assign the patient to a Regimen on the basis of the patient's medical history, prior treatment, and/or patient preference.

Regimen A: mirvetuximab soravtansine + bevacizumab administered on Day 1 of each 21-day cycle
Regimen B: mirvetuximab soravtansine + carboplatin administered on Day 1 of each 21-day cycle
Regimen C: mirvetuximab soravtansine + pegylated liposomal doxorubicin administered on Day 1 of each 28-day cycle
Regimen D: mirvetuximab soravtansine + pembrolizumab administered on Day 1 of each 21-day cycle

A triplet cohort will be opened because enrollment and safety from Regimens A and B have been established, and Regimen A (Dose Expansion Cohorts) enrollment is currently ongoing. The planned doses for patients receiving the triplet dose (Regimen E) are derived from all available data in Regimens A and B and shown in Table 5 below.

Regimen E: mirvetuximab soravtansine + bevacizumab + carboplatin administered on Day 1 of each 21-day cycle

Table 1: Planned Dose Levels (Dose Escalation) for Regimen A

Dose Level	Regimen A	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	**Bevacizumab[c] (mg/kg, D1q3W)**
-1	4	15
1	**5**	**15**
2	**6**	**15**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of bevacizumab is 15 mg/kg.

Table 2: Planned Dose Levels (Dose Escalation) for Regimen B

Dose Level	Regimen B	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	**Carboplatin[c] (AUC, D1q3W)**
-1	4	AUC4
1	**5**	**AUC4**
2	**5**	**AUC5**
3	**6**	**AUC5**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of carboplatin is AUC6, subject to Cohort Review Committee review.

Table 3: Planned Dose Levels (Dose Escalation) for Regimen C

Dose Level	Regimen C	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q4W)[b]	Pegylated Liposomal Doxorubicin[c] (mg/m^2, D1q4W)
-1	4	30
1	**5**	**30**
2	**5**	**40**
3	**6**	**40**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 4 weeks.
[c] The approved dose of pegylated liposomal doxorubicin for ovarian cancer is 50 mg/m^2; however, a decrease in the incidence of hand-foot syndrome was observed at a dose of 40 mg/m^2 without significant loss in efficacy. Maximum allowable dose is 50 mg/m^2, subject to Cohort Review Committee review.

Table 4: Planned Dose Levels (Dose Escalation) for Regimen D

Dose Level	Regimen D	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	Pembrolizumab[c] (mg, D1q3W)
-1	4	200
1	**5**	**200**
2	**6**	**200**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of pembrolizumab is 200 mg.

Table 5: Planned Dose Levels (Triplet Cohort) for Regimen E

Dose Level	Regimen E		
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	Bevacizumab (mg/kg, D1q3W)	Carboplatin[c] (AUC, D1q3W)
-2	5	15	AUC 4
-1[d]	6	15	AUC 4
-1[e]	5	15	AUC 5
1	6	15	AUC 5

[a] Mirvetuximab soravtansine dose calculated using AIBW.
[b] Day 1, every 3 weeks.
[c] Carboplatin dose may be reduced to AUC4 if safety data from the first six or 12 patients suggest that the triplet dose is not being tolerated.
[d] Dose reduction of carboplatin due to carboplatin-associated toxicity.
[e] Dose reduction of mirvetuximab soravtansine due to mirvetuximab soravtansine–associated toxicity.

The starting dose of mirvetuximab soravtansine will be 5 mg/kg, with the dose calculated using AIBW, which is one dose level lower than the RP2D (6 mg/kg using AIBW) defined in the FIH Study IMGN853-0401. All mirvetuximab soravtansine doses will be calculated according to AIBW. Regimens A through D, inclusive, will be evaluated in parallel and independently.

This Phase 1b study comprises a Dose Escalation phase followed by an MTD Expansion phase to further characterize the safety profile and confirm the MTD as the RP2D. A triplet Regimen (Regimen E: mirvetuximab soravtansine + bevacizumab + carboplatin) will be opened to evaluate the safety and tolerability and to assess any early signs of activity in patients dosed with the combination Regimen.

The Dose Escalation phase will follow a standard 3 + 3 cohort design. No intra-patient dose-escalation will be allowed. The MTD will be determined from the assessment of DLTs during the first treatment cycle (Table 6). The primary aim of the Dose Escalation phase is to evaluate the safety and tolerability of the four dosing Regimens, and to identify the MTD and characterize the PK of mirvetuximab soravtansine, bevacizumab, carboplatin, and pegylated liposomal doxorubicin. The PK profile of pembrolizumab may be characterized if warranted because of a safety signal.

Table 6: DLT Definitions

Toxicity	DLT Definition Criteria[a]
Dose delays	Failure to meet re-treatment criteria within the specified time frame
Hematology	• CTCAE Grade 4 neutropenia ≥ 7 days • CTCAE ≥ Grade 3 febrile neutropenia, defined as ANC < 1,000/mm^3 with a single temperature reading of > 38.3°C or sustained temperature of ≥ 38°C for > 1 hour • CTCAE Grade 3 thrombocytopenia, associated with clinically significant bleeding that requires transfusion therapy • CTCAE Grade 4 thrombocytopenia
Non-hematologic and other DLTs	• CTCAE ≥ Grade 3 nausea or vomiting despite the use of optimal anti-emetic treatments • CTCAE ≥ Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments • CTCAE Grade 2 diarrhea lasting > 14 days (Regimen D only) • CTCAE ≥ Grade 3 ocular AEs • CTCAE ≥ Grade 3 pneumonitis • Other non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following: – AEs related to underlying disease. – CTCAE Grade 3 fatigue. – Isolated, asymptomatic Grade 3 abnormalities in biochemistry laboratory values that last for ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention.

[a] An AE meeting criteria is considered a DLT if the event occurred during the first cycle.
For any dose-limiting hepatic toxicity, evaluations should be performed to determine the underlying etiology and rule out drug-induced liver injury (Hy's Law).
ANC = absolute neutrophil count, CTCAE = Common Terminology Criteria for Adverse Events.

To better characterize safety, 10 patients may receive mirvetuximab soravtansine and the assigned combination agent at the MTD established for Regimens A, B, C, and D.
The Dose Expansion phase of the trial, which is planned for mirvetuximab soravtansine in combination with bevacizumab (Regimen A) and for mirvetuximab soravtansine in combination with pembrolizumab (Regimen D), will open after the Cohort Review Committee (CRC) reviews safety data from Dose Escalation and agrees the dose is safe to proceed to Expansion. Dose Expansion will commence enrollment pending Sponsor decision. In addition, the CRC will assess safety of the triplet after six and then 12 patients have completed Cycle 1 at each dose levels evaluated.

Regimen A (mirvetuximab soravtansine + bevacizumab)
Patients in the dose expansion phase may be assigned according to prior exposure to bevacizumab and disease diagnosis into three dose expansion cohorts as follows:

1. Dose Expansion Cohort 1: bevacizumab naïve; will enroll approximately 20 patients
2. Dose Expansion Cohort 2: bevacizumab pretreated; may enroll 35 patients
3. Dose Expansion Cohort 3: with one to three prior systemic therapies, and one prior therapy could have been bevacizumab; may enroll 60 patients

Regimen D (mirvetuximab soravtansine + pembrolizumab):
The Dose Expansion phase will enroll sufficient patients such that 35 patients are FRα ≥ 50% of tumor staining at ≥ 2+ intensity in the Dose Expansion phase.

The aims of the Dose Expansion phase are to further evaluate the safety, tolerability, and anti-tumor activity of mirvetuximab soravtansine in combination with bevacizumab or pembrolizumab.
The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used to grade AEs.

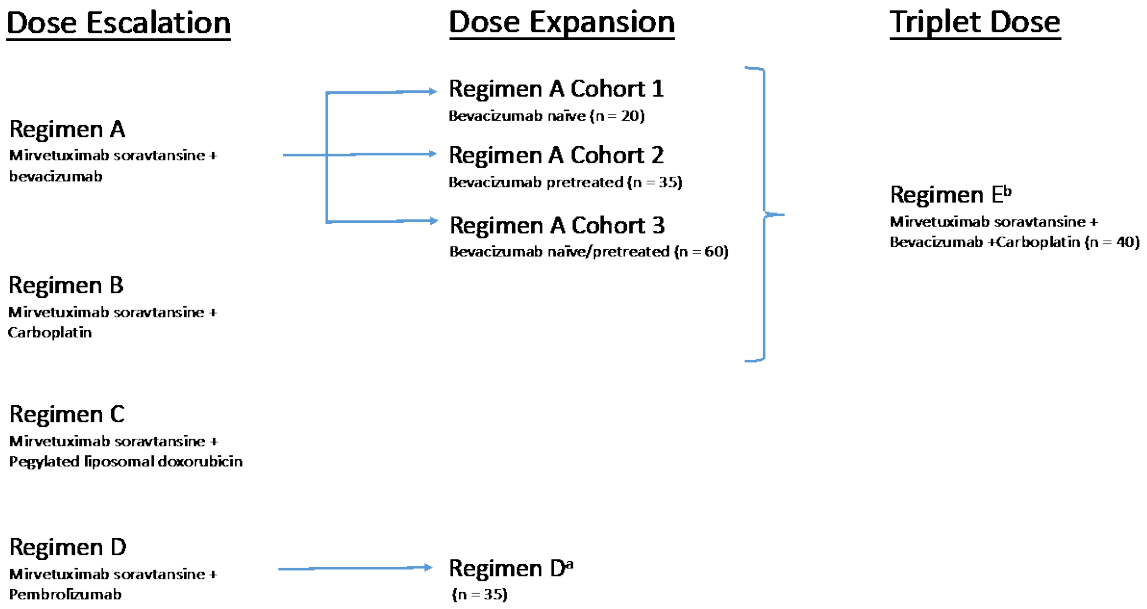
Regimen E (triplet dose: mirvetuximab soravtansine + bevacizumab + carboplatin)

This cohort may enroll up to approximately 50 patients, as exploration of alterative doses is required to enroll approximately 40 planned patients to be dosed at the maximum dose level determined to be safe.
The aims of this cohort are to evaluate safety and tolerability of the combination and to assess for early signs of activity. The starting doses used in this cohort will be derived from all evaluable data from Regimens A and B. The MTD will be determined from the assessment of DLTs during the first treatment cycle (Table 6).
Initially, six patients will be dosed at the target triplet dose (Table 5). If there are < 2 Cycle 1 DLTs (total), another six patients will be dosed. If there are < 4 Cycle 1 DLTs (total) in all 12 patients, the remaining 28 patients will be enrolled for a total of approximately 40 planned patients.
If either ≥ 2 DLTs or ≥ 4 DLTs are observed in the first six or 12 patients, respectively, either the mirvetuximab soravtansine dose or the carboplatin dose will be reduced. The reduced triplet doses will always be explored in the same step-wise manner as detailed above. A total of 12 patients (6 + 6 patients) will be assessed at a dose before the remaining 28 patients being enrolled. The decision of whether to reduce the mirvetuximab soravtansine dose or the carboplatin dose will be made according to the DLTs observed, and the new dose levels will be explored as follows:

a. For DLTs that cannot solely be attributable to mirvetuximab soravtansine, the carboplatin dose will be reduced.
b. For DLTs that are solely attributable to mirvetuximab soravtansine, the mirvetuximab soravtansine dose will be reduced.

If after the doses of carboplatin (a) or mirvetuximab soravtansine (b) are reduced, ≥ 2 DLTs or ≥ 4 DLTs are observed in the first six or 12 patients, respectively, the dose of the other agent (mirvetuximab soravtansine [for a] or carboplatin [for b]) will also be reduced. The triplet dose with the reduced mirvetuximab soravtansine and carboplatin doses will then be evaluated.

Study Design Schema



[a] Enrolled 46 patients to ensure 35 patients with tumors expressing FRα at ≥ 50% of tumor staining at intensity ≥ 2+ and 11 patients with a FRα 25%-49% of tumor staining at intensity ≥ 2+.
[b] Enroll approximately 50 patients to evaluate 40 patients at the MTD.

Study Eligibility Criteria:

Inclusion Criteria

Inclusion Criteria for All Patients (Dose Escalation and Dose Expansion, Regimen-Specific)

1. Pathologically documented advanced EOC (including primary peritoneal cancer and fallopian tube cancer).
2. Female and ≥ 18 years of age at the time of the first screening visit.
3. Eastern Cooperative Oncology Group performance status 0 or 1.
4. Measurable disease:
   a. Dose Escalation: Patients may have measurable or non-measurable disease.
   b. Dose Expansion (Regimens A and D) and Regimen E (Triplet): Patients must have at least one lesion that meets the definition of measurable disease according to RECIST Version 1.1.
5. Willing to provide an archival tumor tissue block or slides, or a new biopsy if archival tumor tissue is unavailable.
   a. Regimen D only: Patients must be willing to undergo two tumor biopsy collections using a non-significant risk procedure (see Section 2.1.1). The first biopsy will be taken before the first dose of study treatment and the second, taken on Cycle 2 Day 8 (± 3 days).
6. Confirmation of FRα positivity by IHC. If the archival tumor tissue does not meet FRα criteria, a new tumor biopsy may be submitted and used to meet this criterion. FRα expression levels must meet the following criteria:
   a. Dose Escalation (Regimens A through D): ≥ 25% of tumor staining at ≥ 2+ intensity
   b. Dose Expansion (Regimens A and D) and Regimen E (Triplet): ≥ 50% of tumor staining at ≥ 2+ intensity
7. Time from prior therapy:
   a. Systemic anti-neoplastic therapy: five half-lives or 4 weeks, whichever is shorter. Hormonal therapy is not considered anti-neoplastic therapy.
   b. Radiotherapy: wide-field radiotherapy (eg, > 30% of marrow-bearing bones) completed at least 4 weeks, or focal radiation completed at least 2 weeks, before starting study treatment.
8. Recovered or stabilized to NCI CTCAE ≤ Grade 2 from all therapy-related toxicities (Regimens A through C and Regimen E).

9. Resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention (Regimen D only).
10. Platinum sensitivity:
    a. Dose Escalation and Dose Expansion: Regimens A (Cohorts 1 and 2) and D and Dose Escalation Regimen C: Patients must have disease that is resistant to platinum therapy. Platinum-resistant disease is defined as disease that responded to primary platinum therapy and then progressed within 6 months (182 days) after the date of the last dose of platinum therapy, or disease that progressed during or within 6 months (182 days) after the date of the last dose of the subsequent platinum therapy.
    b. Dose Escalation, Regimen B: Patients must have platinum-sensitive disease. Platinum-sensitive disease is disease that responded to the last platinum therapy received before study entry and did not progress within 6 months (182 days) after the date of the last dose of platinum therapy.
    c. Regimen E (Triplet): Patients must have platinum-sensitive disease. Platinum-sensitive disease is disease that responded to the last platinum therapy received before study entry and did not progress within 6 months (182 days) after the date of the last dose of platinum therapy. The requirements to demonstrate platinum sensitivity (responsiveness and time to progression) apply to each of the patient's prior platinum-containing regimens.
    d. Dose Expansion: Regimen A, Cohort 3: Patients may have either platinum-resistant disease or platinum-sensitive disease, where a non-platinum doublet is an appropriate next line of therapy.
11. Number of prior therapies (where adjuvant ± neoadjuvant will be considered one regimen and maintenance therapy will be considered to be part of the preceding regimen; hormonal therapy counts as a separate line of therapy unless given as maintenance):
    a. Dose Escalation (Regimens A through D): There is no upper limit to the number of prior treatment regimens received.
    b. Dose Expansion Regimen A, Cohort 1: Patients must have received ≤ two prior systemic treatment regimens.
    c. Dose Expansion Regimen A, Cohort 2: Patients must have received at least one but not more than five prior systemic treatment regimens. At least one of the prior systemic treatment regimens must have included bevacizumab.
    d. Dose Expansion Regimen A, Cohort 3: Patients must have received at least one but no more than three prior systemic treatment regimens, where prior regimens may have included bevacizumab.
    e. Dose Expansion Regimen D: Patients must have received at least two but not more than four prior systemic treatment regimens.
    f. Regimen E (Triplet): Patients must have received at least one but not more than two prior systemic treatment regimens; prior systemic treatment regimens may have included vascular endothelial growth factor inhibitors (including bevacizumab) and must have included at least one platinum-based chemotherapy.
12. Prior folate receptor–targeting investigational agents treatment:
    a. Dose Escalation (Regimens A through C): Prior treatment with folate receptor–targeting investigational agents, including mirvetuximab soravtansine (provided it was not discontinued because of AEs), is allowed.
    b. Dose Escalation (Regimen D), Dose Expansion (Regimens A and D), and Regimen E (Triplet): Patients who have received prior mirvetuximab soravtansine are excluded.
13. Major surgery (not including placement of vascular access device or tumor punch/scrape biopsies) must be completed 4 weeks before Day 1. Patients must have recovered or stabilized from the side effects before study treatment.
14. Adequate hematologic, kidney, and liver function as defined by the following parameters:
    a. Absolute neutrophil count ≥ 1.5×10^9/L (1,500/µL).
    b. Platelet count ≥ 100×10^9/L (100,000/µL); must not be transfused within previous 10 days.
    c. Hemoglobin ≥ 9.0 g/dL.
    d. Serum creatinine ≤ 1.5 times the upper limit of the normal range (ULN) or 24-hour creatinine clearance of ≥ 60 mL/minute.

e. AST ≤ 2.5 times the ULN; alanine aminotransferase ≤ 2.5 times the ULN.
f. Serum bilirubin ≤ 1.5 times the ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin is < 3.0 times the ULN).
g. International normalized ratio or prothrombin time (PT) ≤ 1.5 times the ULN unless patient is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants.
h. Activated partial thromboplastin time ≤ 1.5 times the ULN unless patient is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
i. Dose Escalation and Dose Expansion (Regimen D): thyroid-stimulating hormone within normal limits (WNL). If TSH is not WNL, the patient is eligible if total triiodothyronine (T3) or free T3 and free thyroxine (T4) are WNL.

15. Willing and able to sign the informed consent form and to adhere to the study visit schedule and other protocol requirements.
16. Woman of childbearing 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 effective contraceptive methods. Acceptable single methods include intrauterine device, vasectomy of a female patient's male partner, and contraceptive rod implanted into the skin. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and independent ethics committees/institutional review boards. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable combination methods (requiring use of two of the following) are acceptable: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide); cervical cap with spermicide (nulliparous women only); contraceptive sponge (nulliparous women only); male condom or female condom (cannot be used together); hormonal contraceptive such as oral contraceptive pill, estrogen/progestin pill, or progestin-only pill; contraceptive skin patch; vaginal contraceptive ring; or subcutaneous contraceptive injection. Acceptable methods of contraception must be used while on study treatment and for at least 12 weeks after the last dose of mirvetuximab soravtansine, for at least 6 months after the last dose of bevacizumab, carboplatin, or pegylated liposomal doxorubicin, and for at least 4 months after the last dose of pembrolizumab.
17. WCBP must have a negative pregnancy test within 3 days before the first dose of study treatment.

Exclusion Criteria

1. Male patients.
2. Primary platinum-refractory disease. Platinum refractory is defined as disease that has not responded to a primary platinum-based regimen or progressed within 30 days after primary platinum-based therapy.
3. Clear-cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low-grade ovarian cancer.
4. Active or chronic corneal disorders, including but not limited to the following: Sjogren syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, monocular vision, and/or other active ocular conditions requiring ongoing treatment/monitoring, such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, and/or presence of papilledema.
5. > Grade 1 peripheral neuropathy.
6. Serious concurrent illness or clinically relevant active infection (testing not required), including but not limited to the following:
   a. Known active hepatitis B or C
   b. Known HIV infection
   c. Varicella-zoster virus (shingles)
   d. Cytomegalovirus infection

e. Any other known concurrent infectious disease requiring IV antibiotics within 2 weeks before study enrollment

7. Clinically significant cardiac disease including any one of the following:
   a. Recent myocardial infarction (≤ 6 months before Day 1)
   b. Unstable angina pectoris
   c. Uncontrolled congestive heart failure (New York Heart Association > Class II)
   d. Uncontrolled hypertension (≥ CTCAE Version 4.03 Grade 3)
   e. History of hypertensive crisis or hypertensive encephalopathy
   f. Uncontrolled cardiac arrhythmias
   g. Clinically significant vascular disease (eg, aortic aneurysm or dissecting aneurysm)
   h. Severe aortic stenosis
   i. Clinically significant peripheral vascular disease
   j. ≥ Grade 3 cardiac toxicity following prior chemotherapy
   k. Heart rate–corrected QT interval > 470 msec on the screening ECG
8. History of multiple sclerosis or other demyelinating disease and/or Eaton-Lambert syndrome (para-neoplastic syndrome).
9. History of hemorrhagic or ischemic stroke within the last 6 months.
10. History of cirrhotic liver disease.
11. History of non-infectious interstitial lung disease, including non-infectious pneumonitis that required steroids or current pneumonitis.
12. Prior hypersensitivity to monoclonal antibodies and/or severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
13. Women who are pregnant or lactating or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of study treatment (Regimens A, B, and C only).
14. Carcinomatous meningitis, untreated central nervous system (CNS) disease, or symptomatic CNS metastasis. Patients with previously treated CNS metastasis (excluding carcinomatous meningitis) may participate if their disease is stable (without evidence of progression by imaging, using identical imaging modality at each assessment, for at least 4 weeks before the first dose of study treatment), have no evidence of new or emerging CNS metastasis, and are not using steroids for at least 7 days before the first dose of study treatment.
15. History or evidence of thrombotic or hemorrhagic disorders within 6 months before the first dose of study treatment.
16. Required used of folate-containing supplements (eg, folate deficiency).
17. Known additional malignancy that is progressing or required active treatment within 3 years before the first dose of study treatment, excluding adjuvant hormonal therapy for breast cancer that was completed. Other exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and other in situ cancers.

Additional Exclusion Criteria for Regimen A and Regimen E

18. History of bowel obstruction (including sub-occlusive disease) related to underlying disease within 6 months before the start of study treatment.
19. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography scan, or clinical symptoms of bowel obstruction.
20. Prior radiotherapy to the pelvis or abdomen (Dose Escalation phase only).
21. Surgery (including open biopsy) within 4 weeks before starting study therapy (within 24 hours for minor surgical procedures) or anticipated need for major surgery during study treatment.
22. Non-healing wound, ulcer, or bone fracture.
23. Hemoptysis ≥ 0.5 teaspoon of red blood within 4 weeks before first study treatment.
24. History of posterior reversible encephalopathy syndrome.
25. Clinically significant proteinuria: urine-protein (UPC) ratio ≥ 1.0 or urine dipstick result ≥ 2+; patients with UPC ratio ≥ 1.0 or ≥ 2+ proteinuria should undergo 24-hour urine collection and must show result ≤ 1 gram of protein in 24-hour period.
26. History of pulmonary embolization.
27. History of Grade 4 thromboembolic events.

Additional Exclusion Criteria for Regimen C

28. Prior treatment with pegylated liposomal doxorubicin and/or doxorubicin.
29. Left ventricular ejection fraction defined by multigated acquisition scan/echocardiogram that is below the institutional lower limit of normal.

Additional Exclusion Criteria for Regimen D

30. Received a live vaccine within 30 days before study enrollment. Seasonal flu vaccines that do not contain live virus are permitted.
31. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
32. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
33. Prior anti-cancer mAb within 4 weeks before study Day 1 or has not recovered (ie, ≤ Grade 1 at baseline) from AEs due to agents administered more than 4 weeks earlier.
34. Received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks before study Day 1.
35. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
36. Pregnant or breastfeeding or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study treatment.
37. Severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.

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

Investigational product, dosage, and mode of administration: Mirvetuximab soravtansine–containing combination regimens will be investigated:

Regimen A (mirvetuximab soravtansine + bevacizumab): Mirvetuximab soravtansine will be given IV on Day 1 of a 21-day cycle (Q3W); bevacizumab will be administered IV after completion of the mirvetuximab soravtansine infusion.

Regimen B (mirvetuximab soravtansine + carboplatin): Mirvetuximab soravtansine will be given IV on Day 1; carboplatin will be administered IV after completion of the mirvetuximab soravtansine infusion; cycles will repeat every 21 days (Q3W).

Regimen C (mirvetuximab soravtansine + pegylated liposomal doxorubicin): Mirvetuximab soravtansine will be given IV on Day 1; pegylated liposomal doxorubicin will be administered IV after completion of the mirvetuximab soravtansine infusion; cycles will repeat every 28 days (Q4W).

Regimen D (mirvetuximab soravtansine + pembrolizumab): Mirvetuximab soravtansine will be given IV on Day 1; pembrolizumab will be administered IV after completion of the mirvetuximab soravtansine infusion; cycles will repeat every 21 days (Q3W).

Regimen E (mirvetuximab soravtansine + bevacizumab + carboplatin): Mirvetuximab soravtansine will be given IV on Day 1 of a 21-day cycle (Q3W). Bevacizumab will be administered IV after completion of the mirvetuximab soravtansine infusion on Day 1 of a 21-day cycle (Q3W). Carboplatin will be administered IV after completion of the bevacizumab infusion; cycles will repeat every 21 days (Q3W).

For all dosing regimens, the dose of mirvetuximab soravtansine will be calculated using AIBW.

Duration of treatment: The period of observation extends from the time the patient receives the first dose of study treatment until the final follow-up study visit. Patients will continue to receive study treatment until they develop PD per RECIST Version 1.1, unacceptable toxicity, or withdraw consent, whichever comes first, or until the Sponsor terminates the study. Pembrolizumab (Regimen D) will be

continued for up to 2 years. Patients who discontinue study drug for reasons other than PD will be followed until PD, start of new anti-cancer therapy, or death, whichever occurs first.

Statistical methods: All statistical analyses will be performed using the most recently released SAS statistical software, unless otherwise noted. Patient disposition, patient demographics, and baseline characteristics will be tabulated. Pharmacokinetic parameters and plasma concentrations will also be presented (if available).

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the CRC upon completion of each Dose Escalation Cohort. A statistical analysis plan will fully describe the planned analyses for this study.

Sample size: Ascending doses of mirvetuximab soravtansine and combination therapy will be evaluated to identify the MTD for each of the four doublet combination regimens. The actual number of patients accrued during the Dose Escalation phase will be determined largely by the findings observed during the course of their treatment. Regimen A (mirvetuximab soravtansine + bevacizumab) and Regimen D (mirvetuximab soravtansine + pembrolizumab) are expected to enroll 16 patients, whereas Regimen B (mirvetuximab soravtansine + carboplatin) and Regimen C (mirvetuximab soravtansine + pegylated liposomal doxorubicin) are expected to enroll 22 patients. Additional patients will be recruited into each regimen to ensure that 10 patients are treated at the MTD. Overall, the Dose Escalation phase of the study is expected to enroll approximately 76 to 120 patients.

Following MTD determination, there will be a Dose Expansion phase for Regimens A and D.

Regimen A (mirvetuximab soravtansine + bevacizumab):

Patients enrolled in the Dose Expansion phase will be assigned to three Dose Expansion Cohorts according to prior exposure to bevacizumab as follows: 1) Dose Expansion Cohort 1: bevacizumab naïve; 2) Dose Expansion Cohort 2: bevacizumab pretreated; and 3) Dose Expansion Cohort 3: with one to three prior therapies including one prior therapy with bevacizumab (per Protocol Amendment 5).

For the bevacizumab-naïve Cohort (Cohort 1), assuming a response rate of 55%, there is a 94.2% probability of detecting at least 8 responders if 20 patients are recruited. The response rate assumption is based on an ORR of 53% observed with the standard of care therapy of paclitaxel in combination with bevacizumab in patients with platinum-resistant EOC.

For the bevacizumab-pretreated Cohort (Cohort 2), assuming a response rate of 50%, there is a 91.2% probability of detecting at least 14 responders if 35 patients are recruited.

For the bevacizumab expansion Cohort (Cohort 3), assuming a response rate of 50%, there is a 95.4% probability of detecting at least 24 responders if 60 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 20 to 40 of 60 patients.

Responses Observed, 60 Patients	90% Exact Confidence Interval for True ORR
20/60 (33%)	(23%, 45%)
21/60 (35%)	(25%, 46%)
22/60 (37%)	(26%, 48%)
23/60 (38%)	(28%, 50%)
24/60 (40%)	(29%, 51%)
25/60 (42%)	(31%, 53%)
26/60 (43%)	(32%, 55%)
27/60 (45%)	(34%, 56%)
28/60 (47%)	(36%, 58%)
29/60 (48%)	(37%, 60%)
30/60 (50%)	(39%, 61%)
31/60 (52%)	(40%, 63%)
32/60 (53%)	(42%, 64%)
33/60 (55%)	(44%, 66%)
34/60 (57%)	(45%, 68%)
35/60 (58%)	(47%, 69%)
36/60 (60%)	(49%, 71%)
37/60 (62%)	(50%, 72%)

38/60 (63%)	(52%, 74%)
39/60 (65%)	(54%, 75%)
40/60 (67%)	(55%, 77%)

Regimen D (mirvetuximab soravtansine + pembrolizumab):
In the Dose Expansion phase for Regimen D, a total of 35 patients will be enrolled at FRα ≥ 50% of tumor staining at intensity ≥ 2+ and 11 patients with a FRα 25% to 49% of tumor staining at intensity ≥ 2+. Assuming a response rate of 50%, there is a 91.2% probability of detecting at least 14 responders if 35 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 12 to 18 of 35 patients.

Responses Observed, 35 Patients	90% Exact Confidence Interval for True ORR
12/35 (34%)	(21%, 50%)
13/35 (37%)	(24%, 52%)
14/35 (40%)	(26%, 55%)
15/35 (43%)	(29%, 58%)
16/35 (46%)	(31%, 61%)
17/35 (49%)	(34%, 64%)
18/35 (51%)	(36%, 66%)

Regimen E (mirvetuximab soravtansine + bevacizumab + carboplatin):
In Regimen E (Triplet), approximately 50 patients will be enrolled to ensure that 40 patients will be treated at the MTD. Assuming a response rate of 60%, there is a 92.6% probability of detecting at least 20 responders if 40 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 20 to 26 of 40 patients.

Responses Observed, 40 Patients	90% Exact Confidence Interval for True ORR
20/40 (50%)	(36%, 64%)
21/40 (52.5%)	(38%, 66%)
22/40 (55%)	(41%, 69%)
23/40 (57.5%)	(43%, 71%)
24/40 (60%)	(46%, 73%)
25/40 (62.5%)	(48%, 75%)
26/40 (65%)	(51%, 77%)

Overall, the Dose Expansion phase is expected to enroll up to 211 patients. Assuming that approximately 90% of enrolled patients in the Dose Expansion phase will be evaluable, the study is expected to accrue approximately 311 to 355 patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Target Background

Folate receptor alpha (FRα) (gene symbol *FOLR1*) is a glycophosphatidylinositol-linked protein that shows limited normal tissue expression and high expression in several solid tumors (Kelemen 2006), most notably serous epithelial ovarian cancer (EOC) (Miotti 1987, O'Shannessy 2013). FRα binds and internalizes folate, which is an essential co-factor for one-carbon transfer reactions that are required for DNA and RNA synthesis, cell growth, and proliferation. Marked upregulation of FRα occurs during neonatal development and in cancer, suggesting that the receptor functions primarily under conditions of high folate demand. In contrast, normal adult tissues generally lack FRα expression and employ alternative transporters such as folate receptor β, reduced folate carrier, and proton-coupled folate transporter for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004).

Several additional studies have further validated FRα as a target in serous ovarian cancer. First, quantitative polymerase chain reaction studies show ubiquitous FRα messenger RNA (mRNA) expression in serous ovarian cancer (Hoskins 2001, 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 immunohistochemistry (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 ovarian cancer 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 (IMGN853)

Because of its tumor-specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a promising target for antibody-drug conjugate (ADC) therapy. ADCs combine the specificity of monoclonal antibodies (mAbs) to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target proliferating cells. Mirvetuximab soravtansine, also known as IMGN853, is a targeted ADC that binds with high affinity to FRα, a glycophosphatidylinositol-linked protein that shows limited normal tissue expression and high expression in several solid tumors (Kelemen 2006), most notably serous EOC (Miotti 1987, O'Shannessy 2013). This ADC consists of a humanized anti-FRα mAb attached via a cleavable disulfide containing linker to the cytotoxic maytansinoid DM4. Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. The antibody component of mirvetuximab soravtansine is composed of two immunoglobulin (Ig) G1 heavy chains of 447 amino acids and two kappa light chains of 218 amino acids and has a molecular weight of 145,676 Da (non-glycosylated form). Each antibody molecule is conjugated to an average of three to four molecules of DM4.

In vitro studies have demonstrated that mirvetuximab soravtansine binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (50% inhibitory concentration [IC_{50}] ≤ 1 nM)

and selective cytotoxicity against tumor cells expressing FRα. Cytotoxic effects of mirvetuximab soravtansine in vitro correlate with the level of cell-surface expression of FRα. Mirvetuximab soravtansine demonstrates significant activity against FRα-positive tumor xenografts, with partial and complete remissions observed in ovarian models (Ab 2015). The in vitro and in vivo pharmacologic properties of mirvetuximab soravtansine, along with the high expression of FRα in EOC, provided the rationale for exploring mirvetuximab soravtansine in a clinical setting.

1.3. Epithelial Ovarian Cancer

This study will enroll patients with FRα-positive EOC.

Epithelial ovarian cancer is the most lethal of gynecologic cancers worldwide. There are an estimated 22,240 new cases of ovarian cancer and 14,070 deaths expected in 2018 in the United States (US) (National Cancer Institute - SEER 2018), and in the European Union and North America, 89,113 new cases of ovarian cancer with 59,754 deaths are estimated (GLOBOCAN 2012). Because of the lack of effective screening tools and the non-specific nature of the presenting symptoms, more than 70% of patients with EOC are diagnosed with recurrent disease (Stage 3C and Stage 4) (Timmermans 2017). Late-stage EOC is rarely curable despite intensive adjuvant or neo-adjuvant chemotherapy and optimal surgical resection. Heintz et al reported the 5-year survival for patients with Stage 3C and Stage 4 disease as 32.5% and 18.6% respectively. Similarly, Timmermans et al reported that patients with recurrent disease have an expected 5-year survival rate of 24%. In patients who have developed platinum-resistant disease, the median overall survival is < 12 months (Naumann 2011).

Key signs and symptoms of EOC at presentation include persistent bloating, pelvic or abdominal pain, urinary symptoms (urgency or frequency), decreased appetite, and feeling full quickly. Other symptoms can include fatigue, indigestion, constipation, back pain, pain with intercourse, and menstrual irregularities. Many of these symptoms are frequently seen in women who do not have EOC, making symptom-based diagnosis difficult.

Risk factors associated with development of EOC include age (approximately 50% of women with EOC are > 63 years of age), weight (body mass index ≥ 30), germline *BRCA1* and *BRCA2* mutations (in about 15% of ovarian cancer [Risch 2001]), and reproductive history (eg, increased risk with fertility treatment and decreased risk with birth control pills [American Cancer Society 2016]).

Ovarian tumors are derived from one of three common cell types: epithelial cells (accounting for 90% of all cases [Rosen 2009]), germ cells, or stromal cells. 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.

Epithelial ovarian cancer is staged according to the International Federation of Gynecology and Obstetrics staging system. At Stage I, the tumor is confined to either one or both ovaries or fallopian tubes, the ovary capsule may be ruptured, and there could be tumor on the ovarian surface; malignant cells may be found in the ascites or peritoneal washings. At Stage II, the tumor involves one or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer. At Stage III, the tumor may involve one or both ovaries, or

fallopian tubes, or primary peritoneal cancer with either cytologically or histologically confirmed metastasis to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes. Stage IV consists of distant metastasis, excluding peritoneal metastases (Prat 2015).

Epithelial ovarian cancer is also classified by histology and grade. Serous ovarian carcinomas, which account for 75% of EOC tumors, are graded as either low-grade serous ovarian carcinoma (approximately 3% of all serous EOC) or high-grade serous ovarian carcinoma (HGSOC) (approximately 97% of all serous EOC [Bergstrom 2017]). Other histologic subtypes (eg, endometrioid) are graded 1 through 3, high differentiation through low differentiation, respectively (ASCO 2017). HGSOCs are associated with the poorest outcomes. Despite a typical rapid response to frontline platinum-based therapy, HGSOC is associated with rapid relapse and development of platinum resistance (Alkema 2016).

1.4. Current Therapies

Current management of advanced-stage EOC typically involves surgical de-bulking either before or after platinum-based chemotherapy (commonly carboplatin and paclitaxel). However, most patients will experience recurrence of disease (Garcia 2013). Patients who relapse > 6 months after platinum-based treatments are considered platinum sensitive and typically will be re-treated with a platinum-based combination regimen, with or without maintenance therapy. Patients who relapse ≤ 6 months after treatment are considered platinum-resistant. Almost all platinum-sensitive patients will eventually develop resistance, at which point they are considered to have acquired secondary platinum-resistant disease. Patients with platinum-resistant disease may be treated with a variety of agents, including topotecan, bevacizumab, and pegylated liposomal doxorubicin alone or in combination with weekly paclitaxel.

1.4.1. Bevacizumab

Bevacizumab is a humanized mAb that binds to vascular endothelial growth factor A and has antiangiogenic activity. Bevacizumab is approved for use in combination with chemotherapy both in the EOC frontline setting (Burger 2011, Perren 2012) and in the platinum-resistant setting with up to 2 prior treatments (Pujade-Lauraine 2014). In two frontline trials (GOG218 and ICON7) in EOC, the addition of bevacizumab to carboplatin and paclitaxel, followed by maintenance therapy with bevacizumab, was shown to significantly prolong progression-free survival (PFS) compared with carboplatin and paclitaxel (GOG218: 14.1 vs 10.3 months; ICON7: 19.0 vs 17.3 months) (Burger 2011, Perren 2012). In patients with platinum-sensitive disease at first relapse, the addition of bevacizumab to carboplatin and gemcitabine demonstrated a PFS advantage of 4 months. The AURELIA trial demonstrated a 3.3-month improvement in PFS for patients who received bevacizumab in combination with chemotherapy, followed by maintenance with bevacizumab, compared with those who received chemotherapy alone (Pujade-Lauraine 2014).

1.4.2. Carboplatin

Carboplatin is often used in relapsed ovarian cancer that remains potentially platinum sensitive, based on a platinum-free interval of > 6 months, and may be used as a single agent or in combination (Aghajanian 2012, Raja 2012). Conventional frontline chemotherapy for EOC consists of paclitaxel and carboplatin administered every 3 weeks (Q3W) for six cycles. Although the outcomes are comparable, carboplatin in combination with docetaxel or pegylated

liposomal doxorubicin has a better tolerability profile than that of carboplatin in combination with paclitaxel. For instance, carboplatin and pegylated liposomal doxorubicin have been associated with a lower frequency of alopecia, neuropathies, hypersensitivity reactions, and arthralgia compared with the carboplatin and paclitaxel combination. Carboplatin in combination with pegylated liposomal doxorubicin has been evaluated in platinum-sensitive or partially sensitive patients with gynecological malignancies. Patients with platinum-sensitive EOC treated with this regimen had a lower frequency of alopecia, neuropathies, hypersensitivity reactions, and arthralgia compared with those treated with carboplatin in combination with paclitaxel. Carboplatin given at either AUC6 or AUC5 and pegylated liposomal doxorubicin administered at either 40 mg/m^2 or 50 mg/m^2 every 28 days resulted in objective response rates (ORRs) of 60% to 70%, PFS of 9.2 to 11.2 months, and median overall survival of 23 months in platinum-sensitive or partially sensitive patients (Ferrero 2004, Vorobiof 2004).

1.4.3. Topotecan

Topotecan inhibits topoisomerase 1, leading to both single- and double-stranded DNA breaks that eventually promote apoptosis. Topotecan (administered once daily for 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 paclitaxel, with a response rate of 21% versus 13%, and median PFS of 23 weeks versus 14 weeks, respectively (ten Bokkel Huinink 1997). Unfortunately, topotecan 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 topotecan treatment (Armstrong 2004, Hoskins 1998). For example, one Phase 2 trial tested the effect of the standard dosing of topotecan (1.5 mg/m^2 daily for the first 5 days of 21-day cycles) compared with an alternative dosing regimen (1.75 mg/m^2 once weekly for 4 weeks, repeated every 6 weeks) in patients with recurrent EOC. The alternative dosing regimen led to a lower response rate (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 for the first 3 days of 21-day cycles) (Markman 2000). Compared with historical controls, this alternative dosing regimen seemed to decrease the toxicity of topotecan. In a meta-analysis of various clinical trials, it was concluded that modification of the topotecan dose, and potentially the dosing schedule, can indeed reduce hematologic toxicity without decreasing the efficacy of the drug (Armstrong 2004).

1.4.4. Pegylated Liposomal Doxorubicin

Pegylated liposomal doxorubicin is approved as monotherapy for relapsed ovarian cancer (Pisano 2013) and has also been combined with carboplatin in the frontline setting with similar activity (Gladieff 2012). Studies with single-agent pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer have yielded ORRs of approximately 10% to 20%. Palmar-plantar erythrodysesthesia (hand-foot syndrome [HFS]) and mucositis were the most commonly reported toxicities and the most common cause of dose reduction and treatment discontinuation (Pisano 2013). Decreased rates of HFS and stomatitis/mucositis and comparable

response rates and outcomes have been observed when pegylated liposomal doxorubicin is administered at a dose of 40 mg/m^2 every 28 days compared with the approved dose of 50 mg/m^2 given on a similar schedule (Pisano 2013). Pegylated liposomal doxorubicin administered in combination with various agents has demonstrated increased activity compared with pegylated liposomal doxorubicin alone. Pegylated liposomal doxorubicin in combination with oxaliplatin has been associated with an ORR of 60% to 70%, whereas ORRs of 30% to 40% have been observed in patients treated with pegylated liposomal doxorubicin in combination with gemcitabine, topotecan, paclitaxel, vinorelbine, or ifosfamide (Pisano 2013). The tolerability profile of these combinations was good, except for pegylated liposomal doxorubicin/topotecan, which was associated with unacceptable levels of hematologic toxicity.

1.5. Investigational Therapies

1.5.1. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable nonclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across several indications. For more details on specific indications, refer to the Appendix E.

Refer to Appendix E and the approved labeling for detailed background information on pembrolizumab.

1.6. Nonclinical Studies of Mirvetuximab Soravtansine

1.6.1. Pharmacology

Results of nonclinical pharmacology studies demonstrate the following that support single-agent and combination studies:

- FRα has limited normal tissue expression and marked expression in epithelial tumors, particularly serous and EOCs and serous endometrial cancers, as assessed by IHC (Investigator Brochure).
- In vitro studies demonstrated that mirvetuximab soravtansine binds cell surface FRα with apparent high affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against cells expressing FRα. Mirvetuximab soravtansine–mediated cytotoxicity involves binding, internalization, and degradation of mirvetuximab soravtansine 3, which releases DM4. DM4 and a second catabolite, *S*-methyl-DM4, then inhibit tubulin polymerization and microtubule assembly, causing cell death. The lipophilic molecules *S*-methyl DM4 and DM4 can also diffuse to neighboring cells and induce bystander killing.
- In vitro cytotoxicity studies suggest that cells sensitive to mirvetuximab soravtansine express higher levels of FRα and release 10- to 100-fold more cytotoxic maytansinoid than cells resistant to mirvetuximab soravtansine.

- Mirvetuximab soravtansine retains the inherent activities of its antibody moiety, M9346A, including binding affinity (apparent affinity ≤ 0.1 nM) and selectivity for FRα, capacity for uptake, internalization and degradation by FRα-positive target cells, and ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.
- Mirvetuximab soravtansine demonstrates significant activity against FRα-positive xenografts. Partial and/or complete regressions in xenograft models of EOC were seen at doses of mirvetuximab soravtansine well below its maximum tolerated dose (MTD).
- Mirvetuximab soravtansine shows significant in vivo efficacy against ovarian (IGROV-1, OVCAR-3, and OV-90 models) and non–small-cell lung carcinoma (NSCLC) (NCI-H2110 model) tumor xenografts.
- Combination mirvetuximab soravtansine + bevacizumab is more efficacious than either agent administered as a monotherapy in ovarian (OV90 and IGROV-1) tumor xenografts and in an ovarian cancer patient–derived xenograft model (ST088). In the patient-derived xenograft model, the mirvetuximab soravtansine + bevacizumab combination is more efficacious than combination therapy consisting of paclitaxel + bevacizumab.
- Combination mirvetuximab soravtansine + carboplatin is more efficacious than either agent administered as a monotherapy in the OV90 ovarian tumor xenograft model. Combination mirvetuximab soravtansine + carboplatin is more efficacious than carboplatin + paclitaxel in the model.
- Combination mirvetuximab soravtansine + pegylated liposomal doxorubicin is more efficacious than either agent administered as a monotherapy in the ST088 ovarian cancer patient–derived xenograft model.

Pharmacology studies are further detailed in the mirvetuximab soravtansine Investigator Brochure.

1.6.2. Pharmacokinetics

Nonclinical studies with mirvetuximab soravtansine cross-reactive (monkey) and non–cross-reactive (mouse) species were conducted to define pharmacokinetic (PK) parameters and to determine the stability of the linker and impact of conjugation on antibody clearance. An additional PK study with free DM4 was conducted in monkeys. Pharmacokinetic studies demonstrated the stability of mirvetuximab soravtansine in circulation, showed clearance via a distribution phase lasting about 24 hours followed by a slower terminal elimination phase after IV administration, and suggested linear PK. These studies are further detailed in the mirvetuximab soravtansine Investigator Brochure.

1.6.3. Toxicology

Mirvetuximab soravtansine was evaluated for toxicity after a single IV injection in cross-reactive (monkey) and non–cross-reactive (mouse) species. Results of these studies supported the first-in-human (FIH) trial exploring the safety and tolerability of mirvetuximab soravtansine when administered Q3W to patients with advanced solid tumors. Potential risks suggested by these studies and by 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 mirvetuximab soravtansine Investigator Brochure.

1.7. Clinical Studies of Mirvetuximab Soravtansine

1.7.1. First-in-Human Phase 1 Study: Study IMGN853-0401

The FIH Phase 1 study evaluated the safety, PK, and pharmacodynamics of single-agent mirvetuximab soravtansine in patients with EOC and other FRα-positive tumors. Mirvetuximab soravtansine was administered using two dosing schedules: Q3W (A) and on Days 1, 8, and 15 of a 28-day cycle (B). Pharmacokinetic data and treatment-emergent adverse events (TEAEs) reported by patients enrolled in the dose escalation cohorts are listed in the Investigator Brochure.

The recommended Phase 2 dose (R2PD) for single-agent mirvetuximab soravtansine administered Q3W was determined to be 6 mg/kg adjusted ideal body weight (AIBW). As of February 2018, mirvetuximab soravtansine had a 27% ORR (95% CI, 18.5%, 37.1%) and median PFS of 4.2 months (95% CI, 3.7, 5.4 months) in the 96 patients with platinum-resistant EOC in the patient expansion cohort in Study 0401.

The ORR was 47% (95% CI, 30.4%, 64.5%) and the median PFS was 6.7 months (95% CI, 4.1, 8.3 months) in the subset of 36 patients with FRα-positive (medium/high expression [≥ 50% of cells with ≥ 2+ intensity]) platinum-resistant EOC with one to three prior regimens treated as part of a 96-patient Expansion Cohort in Study 0401 (clinical study report Table 16). Similarly, results of a pooled analysis of 113 patients showed an ORR of 30% (95% CI, 21.8%, 39.4%), a median PFS of 4.3 months (95% CI, 3.9, 5.4), and a median duration of response of 19.3 weeks (95% CI, 18, 34 weeks).

Treatment-related adverse events (AEs) occurring in > 20% of patients in this cohort included diarrhea, blurred vision, fatigue, nausea, and increased aspartate aminotransferase (AST), and were mostly low grade. Blurred vision was likely related to the development of corneal keratopathy, transient microcysts that form in the corneal epithelium, causing temporary symptoms.

1.8. Rationale for the Starting Dose

1.8.1. Mirvetuximab Soravtansine

The starting dose of mirvetuximab soravtansine in this Phase 1b/2 study will be 5 mg/kg, with the dose calculated using AIBW, which is one dose level lower than the RP2D (6 mg/kg using AIBW) defined in the FIH Study 0401. The expected exposure of patients treated at this dose level is within the range of exposure observed in patients with objective responses. Analysis of safety, tolerability, PK, and preliminary anti-tumor activity data will help guide future development of mirvetuximab soravtansine.

1.8.2. Pembrolizumab

The dose of pembrolizumab planned for this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of patients with melanoma is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 is an open-label Phase 1 study conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), and dose expansion cohorts evaluated 2 mg/kg administered Q3W and 10 mg/kg Q3W in patients with advanced solid tumors. All dose levels were well tolerated, and no dose-limiting toxicities (DLTs) were observed. This FIH study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, two randomized cohort evaluations of patients with melanoma receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response as 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. A flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, was developed. The PK profile of pembrolizumab was consistent with that of other humanized mAbs, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and, importantly, will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight dependency in clearance and volume of distribution, are consistent with no meaningful advantage of weight-based dosing versus fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce waste. The existing data suggest that 200 mg Q3W is the appropriate dose for pembrolizumab.

1.9. Safety Rationale for the Triplet Combination

Preliminary safety data from the mirvetuximab soravtansine + bevacizumab and the mirvetuximab soravtansine + carboplatin combinations exhibit TEAEs consistent with the nature and severity of the most common preferred terms listed in the respective reference safety information for each drug. The doublet combinations were generally well tolerated, and no new safety signals were observed at the highest dose levels explored per protocol.

As of July 2017, TEAEs occurring in > 20% of patients in the mirvetuximab soravtansine + bevacizumab combination (n = 41) included nausea, fatigue, blurred vision, diarrhea, peripheral neuropathy, headache, hypertension, vomiting, constipation, myalgia, abdominal pain, and decreased appetite; the TEAEs were typically ≤ Grade 2. One patient, who was dosed at the highest dose level, reported two Grade 2 DLTs (neutropenia and thrombocytopenia).

Treatment-emergent AEs occurring in > 20% of patients in the mirvetuximab soravtansine + carboplatin combination (n = 18) included nausea, thrombocytopenia, diarrhea, vision blurred, neutropenia, fatigue, hypokalemia, vomiting, hypomagnesaemia, neuropathy peripheral, decreased appetite, headache, dyspnea, anemia, constipation, myalgia, alanine aminotransferase (ALT) increased, AST increased, pneumonitis, and pyrexia. The TEAEs were typically ≤ Grade 2. One DLT (vasculitis, Grade 3) was recorded in one patient in the highest dose level cohort (6 mg/kg mirvetuximab soravtansine + AUC 5 carboplatin). Of the 10 patients dosed at the highest dose level, six patients required at least one dose delay of carboplatin for a myelosuppression event, and four patients required a dose reduction of carboplatin from AUC5 to AUC4 within the first six cycles of treatment because of a TEAE. Two of the four TEAEs that led to a dose reduction of carboplatin were myelosuppressive (Grade 2 thrombocytopenia and neutropenia).

1.10. Rationale for the Study Plan

This is an open-label, Phase 1b/2, non-randomized combination study of mirvetuximab soravtansine in adult patients with advanced EOC, primary peritoneal cancer, or fallopian tube cancer. Bevacizumab, carboplatin, and pegylated liposomal doxorubicin were selected as combination agents on the basis of nonclinical studies showing that the activity of these agents was additive with mirvetuximab soravtansine (Section 1.6.1). Pembrolizumab, an anti–PD-1 monoclonal antibody (mAb), is approved for the treatment of melanoma, NSCLC, head and neck squamous cell cancer, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability high solid tumors, and gastric/gastroesophageal junction adenocarcinoma and has shown preliminary anti-tumor activity as a single agent in EOC (Varga 2015).

This study is designed to establish the MTD and determine the RP2D of mirvetuximab soravtansine when administered in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin or pembrolizumab; and to evaluate the triplet combination of mirvetuximab soravtansine at the RP2D with bevacizumab + carboplatin. All study treatments will be administered IV. The safety, tolerability, immunogenicity to mirvetuximab soravtansine, and preliminary anti-tumor activity of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin, pembrolizumab, or bevacizumab + carboplatin will be characterized. The PK of mirvetuximab soravtansine will be characterized along with bevacizumab, carboplatin, and pegylated liposomal doxorubicin concentrations.

Concentrations of pembrolizumab may be characterized if warranted because of a safety signal. Five dosing Regimens will be evaluated in this study:

Regimen A: mirvetuximab soravtansine + bevacizumab administered on Day 1 of each 21-day cycle

Regimen B: mirvetuximab soravtansine + carboplatin administered on Day 1 of each 21-day cycle

Regimen C: mirvetuximab soravtansine + pegylated liposomal doxorubicin administered on Day 1 of each 28-day cycle

Regimen D: mirvetuximab soravtansine + pembrolizumab administered on Day 1 of each 21-day cycle

Regimen E: mirvetuximab soravtansine + bevacizumab + carboplatin administered on Day 1 of each 21-day cycle

Doublet Dosing (Escalation and Expansion)

The patient population for the Dose Escalation phase (Regimens A through D) and the triplet dose (Regimen E) will include patients with EOC, primary peritoneal cancer, or fallopian tube cancer.

In the Dose Escalation phase, patients will be enrolled in groups of three to six until the MTD is defined for each Regimen. To further evaluate the safety of each Regimen (Regimens A through D), up to 10 patients will be treated at the MTD. Dose Expansion is planned for Regimen A and Regimen D to further evaluate the mirvetuximab soravtansine and bevacizumab combination and mirvetuximab soravtansine and pembrolizumab combination, respectively, in patients with platinum-resistant, advanced EOC.

Triplet Dosing

Triplet dosing (Regimen E) will evaluate the mirvetuximab soravtansine + bevacizumab + carboplatin combination in patients with platinum-sensitive, advanced EOC. Regimen E may enroll approximately 50 patients, as exploration of alternative doses is required to enroll approximately 40 patients to be dosed at the maximum dose level determined to be safe.

The aims of triplet dosing (Regimen E) are to evaluate safety and tolerability of the combination and to assess for early signs of activity. The starting doses used in triplet dosing (Regimen E) will be derived from all evaluable data from Regimens A and B. The MTD will be determined from the assessment of DLTs during the first treatment cycle. Patients will be enrolled in a stepwise manner: Initially, six patients will be dosed at the target triplet dose. If that dose is considered tolerable, a further six patients will be dosed, followed by the remaining 28 patients.

Should the initial six or 12 patients not tolerate the starting dose, either the mirvetuximab soravtansine dose or the carboplatin dose will be reduced. The reduced triplet doses will always be explored in the same stepwise manner as detailed above. A total of 12 patients (6 + 6 patients) will be assessed at a dose before the remaining 28 patients are enrolled. The decision of whether to reduce the mirvetuximab soravtansine dose or the carboplatin dose will be made according to the DLTs.

Regimen A Cohorts

Regimen A initially included bevacizumab-naïve patients (Cohort 1) and bevacizumab pre-treated patients (Cohort 2) in the recurrent EOC, platinum-resistant population. On the basis of the preliminary results from Regimen A Cohorts 1 and 2 (O'Malley 2018), a third Cohort (Cohort 3) will be added to further evaluate the mirvetuximab soravtansine + bevacizumab combination in a defined subset of patients with ovarian cancer. Approximately 60 patients will be enrolled. The purpose of Cohort 3 is to further explore and confirm the safety and efficacy of the mirvetuximab soravtansine + bevacizumab combination in the recurrent EOC patient population, including primary peritoneal and fallopian tube cancers. Cohort 3 will include patients with one to three prior therapies who may be either platinum resistant or platinum sensitive if, in the opinion of the Investigator, a platinum-free doublet is an appropriate next line of therapy. Patients with platinum-sensitive EOC often, but not always, receive a platinum-based therapy. Platinum-free regimens are used when patients have had unmanageable toxicity with platinum-containing chemotherapy, when the maximum lifetime cisplatin dose has been reached, when an allergic reaction to carboplatin is of concern, and/or per patient preference. Patients in Regimen A Cohort 3 may or may not have received prior therapy with bevacizumab because the MITO B16/MaNGO study has demonstrated benefit of bevacizumab re-treatment in patients with ovarian cancer.

1.10.1. Rationale for FRα Expression Levels

Nonclinical data demonstrate that mirvetuximab soravtansine anti-tumor activity correlates with FRα expression: The higher the FRα expression, the greater the anti-tumor activity observed in nonclinical models (Investigator Brochure). Consistent with these nonclinical data, preliminary analysis of single-agent data across low, medium, and high FRα expression subsets, in the FIH mirvetuximab soravtansine study, confirmed that the most significant benefit (PFS and ORR) was seen in the medium and high subsets. This has led to restriction of eligibility to the medium and high subsets of FRα expression in the Forward I single-agent registration-enabling study for mirvetuximab soravtansine.

The initial hypothesis for Study IMGN853-0402 was that while low FRα expression (≥ 25% to < 50% cells with at least 2+ staining by IHC) may not be sufficient for maximal anti-tumor activity with mirvetuximab soravtansine monotherapy, it might be sufficient for anti-tumor activity when mirvetuximab soravtansine is combined with other anti-cancer agents. This hypothesis was based on additive/synergistic anti-tumor activity seen when mirvetuximab soravtansine is combined with other anti-cancer agents (Investigator Brochure). Data emerging from all four combinations (Regimens A through D) in the Dose Escalation phase of Study IMGN853-0402 reveal that, as has been observed with mirvetuximab soravtansine monotherapy, the higher the FRα expression, the greater the anti-tumor activity in terms of depth of response and duration of tumor shrinkage. While the numbers are small, the consistency of data across all combination Regimens in Dose Escalation does not support the initial hypothesis. Therefore, the Sponsor revised the eligibility criterion in the Dose Expansion phase of Study IMGN853-0402 (patients enrolled under Protocol Amendment 4 or later) to include patients with medium or high FRα expression (at least 50% of cells with at least 2+ staining by IHC), who are most likely to benefit from mirvetuximab soravtansine in combination with bevacizumab, pembrolizumab, or bevacizumab in combination with carboplatin (Section 3.1).

2. TRIAL OBJECTIVES AND ENDPOINTS

All objectives apply to all dosing Regimens and all Cohorts within a Regimen unless otherwise noted.

2.1. Primary Objectives

2.1.1. Dose Escalation (Regimens A Through D)

- Evaluate the safety and tolerability of mirvetuximab soravtansine when given in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab (Regimens A, B, C, and D, respectively) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

2.1.2. Dose Expansion (Regimens A and D) and Regimen E (Triplet)

- Assess preliminary response-based anti-tumor activity of mirvetuximab soravtansine when administered in combination with bevacizumab (Regimen A) or pembrolizumab (Regimen D) and in combination with bevacizumab and carboplatin (Regimen E) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

2.2. Primary Endpoints

2.2.1. Dose Escalation (Regimens A Through D)

- Treatment-emergent AEs, laboratory test results, physical examination, electrocardiograms (ECGs), and vital signs

2.2.2. Dose Expansion (Regimens A and D) and Regimen E (Triplet)

- Objective response rate, defined as percentage of patients with confirmed response (complete response/remission [CR] + partial response/remission [PR]) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Appendix G)

2.3. Secondary Objectives

- Evaluate the safety and tolerability of mirvetuximab soravtansine when administered in combination with bevacizumab or pembrolizumab (Dose Expansion, Regimens A and D, respectively) and in combination with bevacizumab and carboplatin (Regimen E [Triplet]) in patients with EOC, primary peritoneal cancer, or fallopian tube cancer
- Assess preliminary response-based anti-tumor activity of the combination Regimens (Dose Escalation, Regimens A through D)
- Assess PFS
- Measure duration of response (DOR): the time from first objective response (CR/PR) to the time of progressive disease (PD) among those who have achieved a PR or CR

- Assess Gynecologic Cancer Intergroup (GCIG) CA125 response rate of the combination Regimens
- Characterize PK of mirvetuximab soravtansine when used in combination Regimens
- Evaluate bevacizumab, carboplatin, and pegylated liposomal doxorubicin concentrations when administered in combination with mirvetuximab soravtansine
- Characterize immunogenicity of mirvetuximab soravtansine

2.4. Secondary Endpoints

- Treatment-emergent AEs, changes in laboratory test results, physical examination, ECGs, and vital signs (Dose Expansion [Regimens A and D] and Regimen E [Triplet])
- Objective response rate, defined as percentage of patients with confirmed response (CR + PR) as assessed by RECIST Version 1.1 (Dose Escalation, Regimens A through D) (Appendix G)
- Progression-free survival, defined as the time from first dose to PD or death, whichever occurs first
- Duration of response, defined as the time from first objective response (CR/PR) to the time of PD among those who have achieved a PR or CR
- Number of patients with GCIG CA125 criteria clinical responses (Appendix H)
- Mirvetuximab soravtansine PK parameters for intact ADC, total antibody, DM4, and *S*-methyl DM4 include, but are not limited to, Cycle 1 and Cycle 3 maximum plasma concentration (C_{max}), area under the time-concentration curve (AUC), terminal half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), and time that C_{max} occurs (t_{max})
- Concentration data of bevacizumab, carboplatin, and pegylated liposomal doxorubicin will be measured before and after bevacizumab, carboplatin, and pegylated liposomal doxorubicin infusions (Cycle 1 through Cycle 6)
- Immunogenicity: presence of anti-drug antibodies (ADA) to mirvetuximab soravtansine

2.5. Exploratory Objectives

- Assess any association between FRα expression levels and clinical response
- Identify or evaluate potential biomarkers in blood and tumor tissue that might predict response to each of the four combinations
- Evaluate pembrolizumab concentrations if warranted by a safety signal (Regimen D only)
- Assess anti-tumor activity of the combination with pembrolizumab per immune-related RECIST (irRECIST) (Regimen D only)

2.6. Exploratory Endpoints

- Correlation of FRα expression, by IHC (protein), quantitative reverse transcriptase-polymerase chain reaction (mRNA), or other quantitative methods, to clinical endpoints
- Measure biomarkers in blood and tumor tissue including, but not limited to, mutational and genomic alterations of tumor samples; expression and activation of oncogenic genes and pathways in tumor samples; expression and polymorphism of drug transporters such as multidrug resistance protein-1 (p-glycoprotein [PgP]); the genotype of FcγR; expression and of immune-related genes and gene signatures (Regimen D only), and infiltration of tumor-related immune cells (Regimen D only)
- Concentration data for pembrolizumab if warranted by a safety signal (Regimen D only)
- Evaluate efficacy endpoints per irRECIST (Appendix I) (Regimen D only)
  - Progression-free survival, ORR, and DOR per irRECIST are defined as specified for the respective endpoints using RECIST Version 1.1 above, except that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment after documented PD per RECIST Version 1.1. Subjects who discontinue treatment after documented PD assessment per RECIST Version 1.1 will be counted as having PD on the date of the documented PD assessment.

Note: Unless specifically warranted by relevance to safety or efficacy endpoints, the exploratory endpoints will not be reported in the clinical study report.

3. STUDY POPULATION

3.1. Inclusion Criteria

3.1.1. Inclusion Criteria for All Patients (Dose Escalation and Dose Expansion, Regimen-Specific)

1. Pathologically documented advanced EOC (including primary peritoneal cancer and fallopian tube cancer).
2. Female and ≥ 18 years of age at the time of the first screening visit.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
4. Measurable disease:
   a. Dose Escalation: Patients may have measurable or non-measurable disease.
   b. Dose Expansion (Regimens A and D) and Regimen E (Triplet): Patients must have at least one lesion that meets the definition of measurable disease according to RECIST Version 1.1.
5. Willing to provide an archival tumor tissue block or slides, or a new biopsy if archival tumor tissue is unavailable.

a. Regimen D only: Patients must be willing to undergo two tumor biopsy collections using a non-significant risk procedure (see Section 2.1.1). The first biopsy will be taken before the first dose of study treatment and the second, taken on Cycle 2 Day 8 (± 3 days).

6. Confirmation of FRα positivity by IHC. If the archival tumor tissue does not meet FRα criteria, a new tumor biopsy may be submitted and used to meet this criterion. FRα expression levels must meet the following criteria:
   a. Dose Escalation (Regimens A through D): ≥ 25% of tumor staining at ≥ 2+ intensity
   b. Dose Expansion (Regimens A and D) and Regimen E (Triplet): ≥ 50% of tumor staining at ≥ 2+ intensity
7. Time from prior therapy:
   a. Systemic anti-neoplastic therapy: five half-lives or 4 weeks, whichever is shorter. Hormonal therapy is not considered anti-neoplastic therapy.
   b. Radiotherapy: wide-field radiotherapy (eg, > 30% of marrow-bearing bones) completed at least 4 weeks, or focal radiation completed at least 2 weeks, before starting study treatment.
8. Recovered or stabilized to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) ≤ Grade 2 from all therapy-related toxicities (Regimens A through C and Regimen E).
9. Resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention (Regimen D only).
10. Platinum sensitivity:
    a. Dose Escalation and Dose Expansion: Regimens A (Cohorts 1 and 2) and D and Dose Escalation Regimen C: Patients must have disease that is resistant to platinum therapy. Platinum-resistant disease is defined as disease that responded to primary platinum therapy and then progressed within 6 months (182 days) after the date of the last dose of platinum therapy, or disease that progressed during or within 6 months (182 days) after the date of the last dose of the subsequent platinum therapy.
    b. Dose Escalation, Regimen B: Patients must have platinum-sensitive disease. Platinum-sensitive disease is disease that responded to the last platinum therapy received before study entry and did not progress within 6 months (182 days) after the date of the last dose of platinum therapy.
    c. Regimen E (Triplet): Patients must have platinum-sensitive disease. Platinum-sensitive disease is disease that responded to the last platinum therapy received before study entry and did not progress within 6 months (182 days) after the date of the last dose of platinum therapy. The requirements to demonstrate platinum sensitivity (responsiveness and time to progression) apply to each of the patient's prior platinum-containing regimens.
    d. Dose Expansion: Regimen A, Cohort 3: Patients may have either platinum-resistant disease or platinum-sensitive disease, where a non-platinum doublet is an appropriate next line of therapy.

11. Number of prior therapies (where adjuvant ± neoadjuvant will be considered one regimen and maintenance therapy will be considered to be part of the preceding regimen; hormonal therapy counts as a separate line of therapy unless given as maintenance):
    a. Dose Escalation (Regimens A through D): There is no upper limit to the number of prior treatment regimens received.
    b. Dose Expansion Regimen A, Cohort 1: Patients must have received ≤ two prior systemic treatment regimens.
    c. Dose Expansion Regimen A, Cohort 2: Patients must have received at least one but not more than five prior systemic treatment regimens. At least one of the prior systemic treatment regimens must have included bevacizumab.
    d. Dose Expansion Regimen A, Cohort 3: Patients must have received at least one but no more than three prior systemic treatment regimens, where prior regimens may have included bevacizumab.
    e. Dose Expansion Regimen D: Patients must have received at least two but not more than four prior systemic treatment regimens.
    f. Regimen E (Triplet): Patients must have received at least one but not more than two prior systemic treatment regimens; prior systemic treatment regimens may have included vascular endothelial growth factor inhibitors (including bevacizumab) and must have included at least one platinum-based chemotherapy.
12. Prior folate receptor–targeting investigational agents treatment:
    a. Dose Escalation (Regimens A through C): Prior treatment with folate receptor–targeting investigational agents, including mirvetuximab soravtansine (provided it was not discontinued because of AEs), is allowed.
    b. Dose Escalation (Regimen D), Dose Expansion (Regimens A and D), and Regimen E (Triplet): Patients who have received prior mirvetuximab soravtansine are excluded.
13. Major surgery (not including placement of vascular access device or tumor punch/scrape biopsies) must be completed 4 weeks before Day 1. Patients must have recovered or stabilized from the side effects before study treatment.
14. Adequate hematologic, kidney, and liver function as defined by the following parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L (1,500/μL).
    b. Platelet count ≥ 100×10^9/L (100,000/μL); must not be transfused within previous 10 days.
    c. Hemoglobin ≥ 9.0 g/dL.
    d. Serum creatinine ≤ 1.5 times the upper limit of the normal range (ULN) or 24-hour creatinine clearance of ≥ 60 mL/minute.
    e. AST ≤ 2.5 times the ULN; ALT ≤ 2.5 times the ULN.
    f. Serum bilirubin ≤ 1.5 times the ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin is < 3.0 times the ULN).
    g. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times the ULN unless patient is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants.

h. Activated partial thromboplastin time (aPTT) ≤ 1.5 times the ULN unless patient is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
i. Dose Escalation and Dose Expansion (Regimen D): thyroid-stimulating hormone (TSH) within normal limits (WNL). If TSH is not WNL, the patient is eligible if total triiodothyronine (T3) or free T3 and free thyroxine (T4) are WNL.

15. Willing and able to sign the informed consent form (ICF) and to adhere to the study visit schedule and other protocol requirements.
16. Woman of childbearing 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 effective contraceptive methods. Acceptable single methods include intrauterine device, vasectomy of a female patient's male partner, and contraceptive rod implanted into the skin. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and independent ethics committees (IECs)/institutional review boards (IRBs). Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable combination methods (requiring use of two of the following) are acceptable: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide); cervical cap with spermicide (nulliparous women only); contraceptive sponge (nulliparous women only); male condom or female condom (cannot be used together); hormonal contraceptive such as oral contraceptive pill, estrogen/progestin pill, or progestin-only pill; contraceptive skin patch; vaginal contraceptive ring; or subcutaneous contraceptive injection. Acceptable methods of contraception must be used while on study treatment and for at least 12 weeks after the last dose of mirvetuximab soravtansine; for at least 6 months after the last dose of bevacizumab, carboplatin, or pegylated liposomal doxorubicin; and for at least 4 months after the last dose of pembrolizumab.
17. WCBP must have a negative pregnancy test within 3 days before the first dose of study treatment.

3.1.2. Exclusion Criteria

1. Male patients.
2. Primary platinum-refractory disease. Platinum refractory is defined as disease that has not responded to a primary platinum-based regimen or progressed within 30 days after primary platinum-based therapy.
3. Clear-cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low-grade ovarian cancer.
4. Active or chronic corneal disorders, including but not limited to the following: Sjogren syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, monocular vision, and/or other active ocular conditions requiring ongoing treatment/monitoring, such as wet age-related macular

degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, and/or presence of papilledema.

5. > Grade 1 peripheral neuropathy.
6. Serious concurrent illness or clinically relevant active infection (testing not required), including but not limited to the following:
    a. Known active hepatitis B or C
    b. Known HIV infection
    c. Varicella-zoster virus (shingles)
    d. Cytomegalovirus infection
    e. Any other known concurrent infectious disease requiring IV antibiotics within 2 weeks before study enrollment
7. Clinically significant cardiac disease including any one of the following:
    a. Recent myocardial infarction (≤ 6 months before Day 1)
    b. Unstable angina pectoris
    c. Uncontrolled congestive heart failure (New York Heart Association > Class II)
    d. Uncontrolled hypertension (≥ CTCAE Version 4.03 Grade 3)
    e. History of hypertensive crisis or hypertensive encephalopathy
    f. Uncontrolled cardiac arrhythmias
    g. Clinically significant vascular disease (eg, aortic aneurysm or dissecting aneurysm)
    h. Severe aortic stenosis
    i. Clinically significant peripheral vascular disease
    j. ≥ Grade 3 cardiac toxicity following prior chemotherapy
    k. Heart rate–corrected QT interval > 470 msec on the screening ECG
8. History of multiple sclerosis or other demyelinating disease and/or Eaton-Lambert syndrome (para-neoplastic syndrome).
9. History of hemorrhagic or ischemic stroke within the last 6 months.
10. History of cirrhotic liver disease.
11. History of non-infectious interstitial lung disease, including non-infectious pneumonitis that required steroids or current pneumonitis.
12. Prior hypersensitivity to monoclonal antibodies and/or severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
13. Women who are pregnant or lactating or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of study treatment (Regimens A, B, and C only).
14. Carcinomatous meningitis, untreated central nervous system (CNS) disease, or symptomatic CNS metastasis. Patients with previously treated CNS metastasis (excluding carcinomatous meningitis) may participate if their disease is stable (without evidence of progression by imaging, using identical imaging modality at each assessment, for at least 4 weeks before the first dose of study treatment), have no evidence of new or emerging CNS metastasis, and are not using steroids for at least 7 days before the first dose of study treatment.

15. History or evidence of thrombotic or hemorrhagic disorders within 6 months before the first dose of study treatment.
16. Required used of folate-containing supplements (eg, folate deficiency).
17. Known additional malignancy that is progressing or required active treatment within 3 years before the first dose of study treatment, excluding adjuvant hormonal therapy for breast cancer that was completed. Other exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and other in situ cancers.

3.1.2.1. Additional Exclusion Criteria for Regimen A and Regimen E

18. History of bowel obstruction (including sub-occlusive disease) related to underlying disease within 6 months before the start of study treatment.
19. History of abdominal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography (CT) scan, or clinical symptoms of bowel obstruction.
20. Prior radiotherapy to the pelvis or abdomen (Dose Escalation phase only).
21. Surgery (including open biopsy) within 4 weeks before starting study therapy (within 24 hours for minor surgical procedures) or anticipated need for major surgery during study treatment.
22. Non-healing wound, ulcer, or bone fracture.
23. Hemoptysis ≥ 0.5 teaspoon of red blood within 4 weeks before first study treatment.
24. History of posterior reversible encephalopathy syndrome (PRES).
25. Clinically significant proteinuria: urine-protein (UPC) ratio ≥ 1.0 or urine dipstick result ≥ 2+; patients with UPC ratio ≥ 1.0 or ≥ 2+ proteinuria should undergo 24-hour urine collection and must show result ≤ 1 gram of protein in 24-hour period.
26. History of pulmonary embolization.
27. History of Grade 4 thromboembolic events.

3.1.2.2. Additional Exclusion Criteria for Regimen C

28. Prior treatment with pegylated liposomal doxorubicin and/or doxorubicin.
29. Left ventricular ejection fraction defined by multigated acquisition (MUGA) scan/echocardiogram (ECHO) that is below the institutional lower limit of normal.

3.1.2.3. Additional Exclusion Criteria for Regimen D

30. Received a live vaccine within 30 days before study enrollment. Seasonal flu vaccines that do not contain live virus are permitted.
31. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of study

treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

32. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
33. Prior anti-cancer mAb within 4 weeks before study Day 1 or has not recovered (ie, ≤ Grade 1 at baseline) from AEs due to agents administered more than 4 weeks earlier.
34. Received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks before study Day 1.
35. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
36. Pregnant or breastfeeding or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study treatment.
37. Severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.

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

4. INVESTIGATIONAL PLAN

4.1. Study Design

4.1.1. Overview and Schema

This is an open-label, Phase 1b/2, non-randomized combination study of mirvetuximab soravtansine with bevacizumab, carboplatin, pegylated liposomal doxorubicin, pembrolizumab, or bevacizumab + carboplatin in adult patients with FRα-positive advanced EOC, primary peritoneal cancer, or fallopian tube cancer.

This Phase 1b/2 study comprises a Dose Escalation phase followed by an MTD Expansion phase to further characterize the safety profile and confirm the MTD as the RP2D. A triplet Regimen (Regimen E: mirvetuximab soravtansine + bevacizumab + carboplatin) will be opened to evaluate the safety and tolerability and to assess any early signs of activity in patients dosed with the combination Regimen (Figure 1).

The Dose Escalation phase will follow a standard 3 + 3 cohort design. The MTD will be determined from the assessment of DLTs during the first treatment cycle (Table 5). A Dose Expansion phase is planned for Regimen A (mirvetuximab soravtansine + bevacizumab) and Regimen D (mirvetuximab soravtansine + pembrolizumab) and will open pending Sponsor decision; patients enrolled in the Dose Expansion phase will receive study treatment at the MTD or RP2D determined during Dose Escalation (Figure 1). For Regimen A, patients in the Dose

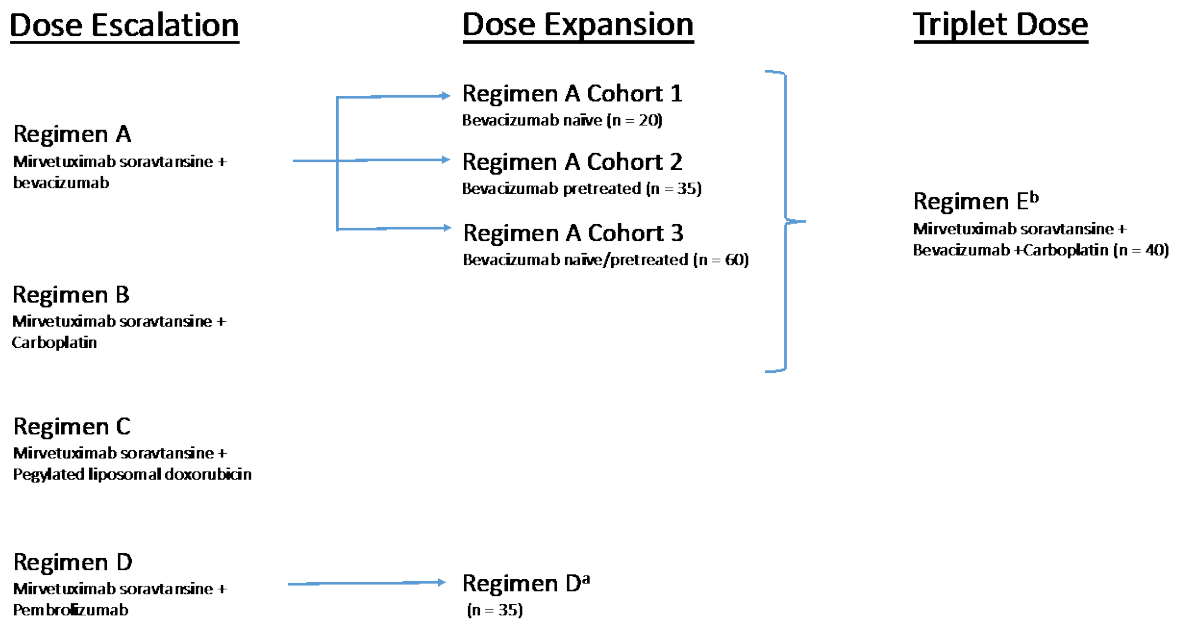
Expansion phase may be enrolled according to prior exposure to bevacizumab into three Dose Expansion Cohorts as follows: 1) Dose Expansion Cohort 1: bevacizumab naïve; 2) Dose Expansion Cohort 2: bevacizumab pretreated; and 3) Dose Expansion Cohort 3: one to three prior treatments, one of which could have been bevacizumab (Figure 1).

Regimen E (triplet dose) will be opened because enrollment and safety from Regimens A and B have been established, and Regimen A (Dose Expansion Cohorts) enrollment is currently ongoing. The planned doses for patients receiving the triplet dose (Regimen E) were derived from all available data in Regimens A and B. Regimen E may enroll approximately 50 patients, as exploration of alternative doses is required to enroll approximately 40 patients, with a plan to be dosed at the maximum dose level determined to be safe.

Safety and tolerability will be assessed on an ongoing basis, and patients will be enrolled initially in a stepwise manner.

The period of observation extends from the time the patient receives the first dose of study treatment (mirvetuximab soravtansine and/or combination agent) until the final follow-up study visit. Patients will continue to receive mirvetuximab soravtansine and/or the combination agent until PD, unacceptable toxicity, or withdrawal of consent, whichever comes first, or until the Sponsor terminates the study. Patients who experience PD, as defined by RECIST, while on study may remain on study, provided there is evidence of clinical benefit and no unacceptable toxicity, as agreed upon by the Investigator and the Medical Monitor. Pembrolizumab (Regimen D) will be continued for up to 2 years. Patients who discontinue study treatment for reasons other than PD will be followed until PD, start of new anti-cancer therapy, or death, whichever occurs first.

Figure 1: Study Design Schema



[a] Enrolled 46 patients to ensure 35 patients with tumors expressing FRα at ≥ 50% of tumor staining at intensity ≥ 2+ and 11 patients with a FRα 25%-49% of tumor staining at intensity ≥ 2+.
[b] Enroll approximately 50 patients to evaluate 40 patients at the MTD.

4.1.2. Cohort Review Committee

The Cohort Review Committee (CRC) comprises the ImmunoGen Medical Monitor and Investigators from participating sites. Once the last patient planned for safety evaluation in a given Regimen has completed a cycle of study treatment, a CRC meeting will be convened to review all safety data and decide whether to continue or halt Dose Escalation, further expand individual dose levels to gain additional safety data, or explore lower or intermediate dose levels. In addition to meetings to review safety data at the end of each dose level, the CRC will convene to review safety data for ongoing patients and patients in follow-up, per the cohort management plan.

4.1.3. Dose Escalation Guidelines

4.1.3.1. Dose Levels and Regimens

The primary aim of the Dose Escalation phase for each Regimen is to evaluate the safety and tolerability of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab; to identify the MTD and RP2D; and to characterize the PK profile of mirvetuximab soravtansine, bevacizumab, carboplatin, and pegylated liposomal doxorubicin. The PK profile of pembrolizumab may be characterized if warranted because of a safety signal. Patients will be enrolled with 3 to 6 patients until the MTD for each of the four Regimens (A through D) is defined. If a patient is eligible for more than one combination Regimen, the Investigator will assign the patient to the most appropriate combination Regimen, taking into consideration the patient's disease history, treatment history, and/or preferences. Approximately 16 (Regimen A), 22 (Regimen B), 22 (Regimen C), and 16 (Regimen D) patients will be enrolled in each Regimen, plus an additional 10 patients in each arm to define the MTD.

The starting dose of mirvetuximab soravtansine will be 5 mg/kg, with the dose calculated using AIBW. All mirvetuximab soravtansine doses will be calculated according to AIBW. The four Regimens (A through D) will be evaluated in parallel and independently.

The treatment Regimens and planned dose levels for the Dose Escalation phase of the study are outlined below and in Table 1, Table 2, Table 3, and Table 4. Enrollment in Regimen A will open at the planned dose levels summarized in Table 1.

Intermediate or lower dose levels of pegylated liposomal doxorubicin, bevacizumab, or carboplatin may be explored if DLTs can be attributed to their mechanism of action. Higher doses of pegylated liposomal doxorubicin (up to 50 mg/m^2) and carboplatin (AUC6) also may be considered.

Table 1: Planned Dose Levels (Dose Escalation) for Regimen A (Mirvetuximab Soravtansine + Bevacizumab)

Dose Level	Regimen A	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	**Bevacizumab[c] (mg/kg, D1q3W)**
-1	4	15
1	**5**	**15**
2	**6**	**15**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of bevacizumab is 15 mg/kg.

Table 2: Planned Dose Levels (Dose Escalation) for Regimen B (Mirvetuximab Soravtansine + Carboplatin)

Dose Level	Regimen B	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	**Carboplatin[c] (AUC, D1q3W)**
-1	4	AUC4
1	**5**	**AUC4**
2	**5**	**AUC5**
3	**6**	**AUC5**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of carboplatin is AUC6, subject to CRC review.

Table 3: Planned Dose Levels (Dose Escalation) for Regimen C (Mirvetuximab Soravtansine + Pegylated Liposomal Doxorubicin)

Dose Level	Regimen C	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q4W)[b]	**Pegylated Liposomal Doxorubicin[c] (mg/m^2, D1q4W)**
-1	4	30
1	**5**	**30**
2	**5**	**40**
3	**6**	**40**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 4 weeks.
[c] The approved dose of pegylated liposomal doxorubicin for ovarian cancer is 50 mg/m^2; however, a decrease in the incidence of HFS was observed at a dose of 40 mg/m^2 without significant loss in efficacy. Maximum allowable dose is 50 mg/m^2, subject to CRC review.

Table 4: Planned Dose Levels (Dose Escalation) for Regimen D (Mirvetuximab Soravtansine + Pembrolizumab)

Dose Level	Regimen D	
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	**Pembrolizumab[c] (mg, D1q3W)**
-1	4	200
1	**5**	**200**
2	**6**	**200**

[a] Mirvetuximab soravtansine dose calculated using AIBW. Maximum allowable dose is 6 mg/kg AIBW.
[b] Day 1, every 3 weeks.
[c] Maximum allowable dose of pembrolizumab is 200 mg.

4.1.3.2. Dose Escalation Rules (3 + 3 Design)

For all patients, Dose Escalation decisions will be made in accordance with a standard 3 + 3 design. To ensure that those patients consented to a specific Regimen receive study drug in this multi-center study, Regimens may be expanded to include additional patients if such patients can be treated ≤ 14 days after the third (or sixth) patient was first dosed with mirvetuximab soravtansine. In this situation, the decision to dose escalate (or declare the MTD/RP2D) may be made after the third evaluable (or sixth evaluable) patient has completed Cycle 1. Intra-patient dose escalation will not be permitted.

- If none of the three or four patients experience a DLT, then dose escalation to the next dose level will occur (See Section 4.1.3 for dose levels).
- If one of the initial three or four patients experiences a DLT, the group will be expanded to up to six patients. If no further DLT occurs, dose escalation to the next dose level may proceed.
- If at least two of two to six patients or more than 33% of patients in any given group experience a DLT, the maximum administered dose is reached, and no further dose escalation will occur. Enrollment into a Regimen at a lower dose level will be considered.
- Each dose level will be evaluated in a similar fashion.

A patient will be deemed non-evaluable for dose escalation decisions and will not be counted toward the total number of evaluable patients in a given dose level if the patient did not receive a full course of study treatment (ie, all planned doses of mirvetuximab soravtansine and combination drug for first cycle) and did not experience a DLT; or discontinued from the study before completing necessary safety evaluations through the end of the first cycle of treatment and did not experience a DLT. Non-evaluable patients will be replaced except when accrual to the dose level has stopped because of the occurrence of at least two DLTs.

The MTD is defined as the highest dose at which one or fewer among six patients or ≤ 33% experiences a DLT.

If the maximum planned dose is reached and further dose exploration of pegylated liposomal doxorubicin or carboplatin beyond the planned maximum dose of 40 mg/m^2 and AUC5, respectively, is required to define the MTD, then the CRC will determine the dose escalation increments after review of available clinical and PK data. The maximum allowable doses of each study drug are as follows: mirvetuximab soravtansine 6.0 mg/kg AIBW every 3 weeks, mirvetuximab soravtansine 6.0 mg/kg every 4 weeks, bevacizumab 15 mg/kg every 3 weeks, carboplatin AUC6 every 3 weeks, pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks, and pembrolizumab 200 mg every 3 weeks.

If there is evidence of late-occurring or cumulative DLT(s), an ad hoc CRC may be scheduled with participating Investigators to discuss dose level or MTD reduction. If agreed, the Investigators and Sponsor may increase the number of patients treated at a given dose level, or enroll additional patients at the previously completed dose level if doing so is necessary to better define the safety of any of the combination Regimens. Additionally, upon review of the safety data from the current Cohort, the Sponsor, together with the Investigators, may decide to evaluate intermediate dose levels.

To better characterize safety, 10 patients may be enrolled and treated at the putative MTD. After the CRC reviews the safety data from the Dose Escalation phase and agrees that the dose is safe to proceed, and the Sponsor approves, the Dose Expansion phase of the trial will commence. Dose Expansion is planned for Regimen A and Regimen D; on the basis of emergent data, the CRC may decide to expand Regimens B and/or C to collect additional safety information. If expanded, Regimens B and C will each enroll a maximum of 20 patients, who will be treated at the MTD established for the corresponding Regimen.

4.1.4. Definition of Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as a TEAE or abnormal laboratory value related to mirvetuximab soravtansine and/or the combination drug (ie, assessed as unrelated to disease, intercurrent illness, or concomitant medications), including those TEAEs and abnormal laboratory values that result in a failure to meet the criteria for re-treatment (Section 5.10.1). Dose-limiting toxicities will be considered related to the study treatment unless there is clear evidence of an alternative explanation and this attribution is agreed to by the CRC.

Only DLTs that occur during the first cycle will be considered for decisions regarding dose escalation. Clinically significant toxicities or TEAEs that meet the definition of dose limiting but occur after Cycle 1 (dose-modifying events) may be considered when determining the MTD.

If a patient experiences a DLT or an AE that qualifies as a DLT at any point during study treatment as outlined in Table 5, the study treatment must be stopped, and the toxicity(ies) in question must be followed until resolution or stabilization. If treatment is to be resumed, then re-treatment criteria must be met (Section 5.10.3), and administration of mirvetuximab soravtansine and/or the combination agent must be resumed at a lower dose per dose the modification guidelines (Section 5.10.4).

Table 5: Dose-Limiting Toxicity Definitions

Toxicity	DLT Definition Criteria[a]
Dose delays	Failure to meet re-treatment criteria within the specified time frame (Section 5.10.1)
Hematology	• CTCAE Grade 4 neutropenia ≥ 7 days • CTCAE ≥ Grade 3 febrile neutropenia, defined as ANC < 1,000/mm^3 with a single temperature reading of > 38.3°C or sustained temperature of ≥ 38°C for > 1 hour • CTCAE Grade 3 thrombocytopenia, associated with clinically significant bleeding that requires transfusion therapy • CTCAE Grade 4 thrombocytopenia
Non-hematologic and other DLTs	• CTCAE ≥ Grade 3 nausea or vomiting despite the use of optimal anti-emetic treatments • CTCAE ≥ Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments • CTCAE Grade 2 diarrhea lasting > 14 days (Regimen D only) • CTCAE ≥ Grade 3 ocular AEs • CTCAE ≥ Grade 3 pneumonitis • Other non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following: – AEs related to underlying disease. – CTCAE Grade 3 fatigue. – Isolated, asymptomatic Grade 3 abnormalities in biochemistry laboratory values that last for ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention.

[a] An AE meeting criteria is considered a DLT if the event occurred during the first cycle.
For any dose-limiting hepatic toxicity, evaluations should be performed to determine the underlying etiology and rule out drug-induced liver injury (Hy's Law).

4.1.5. Dose Expansion Phase

Once the CRC determines the MTD, the CRC will determine the dose and schedule to be administered in the Dose Expansion phase. The Dose Expansion phase will begin enrollment pending Sponsor decision. The primary aims of the Dose Expansion phase are to further evaluate safety and tolerability and to assess preliminary anti-tumor activity of mirvetuximab soravtansine in combination with bevacizumab or mirvetuximab soravtansine in combination with pembrolizumab. Data obtained in the Dose Expansion phase will help define the RP2D.

Regimen A (Mirvetuximab Soravtansine + Bevacizumab)

Patients enrolled in the Dose Expansion phase may be assigned to one of three Dose Expansion Cohorts according to previous exposure to bevacizumab as follows:

1. Dose Expansion Cohort 1: bevacizumab naïve; will enroll approximately 20 patients
2. Dose Expansion Cohort 2: bevacizumab pretreated; may enroll approximately 35 patients
3. Dose Expansion Cohort 3: patients with at least one but no more than three prior systemic treatment regimens, where prior regimens may have included bevacizumab; may enroll approximately 60 patients

Regimen D (Mirvetuximab Soravtansine + Pembrolizumab)

The Dose Expansion phase will enroll sufficient patients to ensure that 35 patients are FRα ≥ 50% of tumor staining at ≥ 2+ intensity.

Dose Expansion is planned for Regimens A and D, pending Sponsor decision; however, on the basis of emerging safety and preliminary anti-tumor activity data, the CRC may make the decision to expand Regimens B and/or C to collect additional safety information. If expanded, Regimens B and C will each enroll a maximum of 20 patients, who will be treated at the MTD established for the corresponding Regimen.

Safety will be evaluated continuously, separately, and in aggregate in the Dose Expansion Cohorts. If at any time ≥ 33% of at least three patients treated in the Dose Expansion Cohort experience a Cycle 1 DLT, further enrollment to that Cohort will stop, and the CRC will be convened. The CRC will review all available safety data and PK data to determine how further dosing should proceed. If it is decided that a new dose should be investigated, enrollment to the Cohort will begin anew.

Regimen E (Triplet Dose: Mirvetuximab Soravtansine + Bevacizumab + Carboplatin)

Following evaluation of the safety, tolerability, and activity data from patients receiving Regimens A (Dose Escalation and Dose Expansion) and B (Dose Escalation) in this study, Regimen E (Triplet) will be opened. The planned doses for patients receiving the triplet dose are derived from all available data from Regimens A and B. Regimen E may enroll approximately 50 patients, as exploration of alternative doses is required to enroll approximately 40 planned patients to be dosed at the maximum dose level determined to be safe.

The MTD will be determined from the assessment of DLTs during the first treatment cycle (Table 5).

Initially six patients will be dosed at the target triplet dose (Table 5). If there are < 2 Cycle 1 DLTs (total), another six patients will be dosed. If there are < 4 Cycle 1 DLTs (total) in all 12 patients, the remaining 28 patients will be enrolled for a total of approximately 40 planned patients.

If either ≥ 2 DLTs or ≥ 4 DLTs are observed in the first six or 12 patients, respectively, either the mirvetuximab soravtansine dose or the carboplatin dose will be reduced. The reduced triplet doses will always be explored in the same stepwise manner as detailed above. A total of 12 patients (6 + 6 patients) will be assessed at a dose before the remaining 28 patients are enrolled. The decision of whether to reduce the mirvetuximab soravtansine dose or the carboplatin dose will be made according to the DLTs observed, and the new doses will be explored as follows:

a. For DLTs that cannot solely be attributable to mirvetuximab soravtansine, the carboplatin dose will be reduced.
b. For DLTs that are solely attributable to mirvetuximab soravtansine, the mirvetuximab soravtansine dose will be reduced.

If after the doses of carboplatin (a) or mirvetuximab soravtansine (b) are reduced, ≥ 2 DLTs or ≥ 4 DLTs are observed in the first six or 12 patients, respectively, the dose of the other agent (mirvetuximab soravtansine [for a] or carboplatin [for b]) will also be reduced. The triplet dose with the reduced mirvetuximab soravtansine and carboplatin doses will then be evaluated. The doses to be used in Regimen E are shown in Table 6.

Table 6: Planned Doses for Regimen E

Dose Level	Regimen E		
	Mirvetuximab Soravtansine[a] (mg/kg, D1q3W)[b]	Bevacizumab (mg/kg, D1q3W)	Carboplatin[c] (AUC, D1q3W)
-2	5	15	AUC4
-1[d]	6	15	AUC4
-1[e]	5	15	AUC5
1	6	15	AUC5

[a] Mirvetuximab soravtansine dose calculated using AIBW.
[b] Day 1, every 3 weeks.
[c] Carboplatin dose may be reduced to AUC4 if safety data from the first six or 12 patients suggest that the triplet dose is not being tolerated.
[d] Dose reduction of carboplatin due to carboplatin-associated toxicity.
[e] Dose reduction of mirvetuximab soravtansine due to mirvetuximab soravtansine–associated toxicity.

5. STUDY TREATMENT

5.1. Description of Study Treatment

The investigational study drug, mirvetuximab soravtansine, will be provided by ImmunoGen, Inc., at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution.

Bevacizumab is supplied as a commercially available formulation. Please refer to the bevacizumab prescribing information.

Carboplatin is supplied as a commercially available formulation. Please refer to the carboplatin prescribing information.

Pegylated liposomal doxorubicin is supplied as a commercially available formulation. Please refer to the pegylated liposomal doxorubicin prescribing information.

Pembrolizumab is supplied as a clinical image of the commercially available formulation by Merck, and supplied by ImmunoGen. Please refer to the Pharmacy Manual.

5.2. Mirvetuximab Soravtansine Packaging

Mirvetuximab soravtansine will be provided in a 20 mL Type I glass vial. The container closure for the Type I glass vials will consist of a 20-mm, ethylene tetrafluoroethylene–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 more information.

5.3. Storage, Handling, and Accountability

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

Please refer to the bevacizumab, carboplatin, pegylated liposomal doxorubicin, and pembrolizumab prescribing information regarding the proper storage and handling of these compounds.

Accountability and shipping documents for all drugs supplied by the Sponsor must be maintained by the Investigator or designee (eg, the study pharmacist). The Investigator or designee must maintain an accurate record of the receipt and dispensing of mirvetuximab soravtansine study drugs in a drug accountability log or equivalent. Only participants enrolled in

the study may receive study treatment, and only authorized site staff may supply or administer treatment. These records must always be available for inspection, and a copy will be supplied to ImmunoGen on request. Information recorded on these accountability and shipping documents will include quantities received, dates and amount dispensed, the recorder's initials, patient number and initials to whom administered, lot number of drug administered, and drug lost, damaged, or destroyed.

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

Drug accountability will be monitored regularly.

5.4. Study Treatment Compliance

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

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

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

5.5. Assignment of Patient Number

Patient numbers are assigned by the site after patients sign the ICF 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 before dosing.

5.5.1. Enrolled Patient Definition

Patients who have signed an IRB/IEC-approved ICF and who have received at least one dose of mirvetuximab soravtansine will be considered enrolled. Patients who are issued a patient number but who do not successfully complete the screening process and who do not receive a dose of mirvetuximab soravtansine and/or combination drug will be considered screen failures. Patient numbers for patients who fail screening will not be re-issued.

5.5.2. Patient Assignment to Dosing Regimens

Patients will be assigned to Regimen A, B, C, D, or E on the basis of eligibility criteria and slot availability as determined by the Sponsor. If a patient is eligible for more than one combination Regimen, the Investigator will assign the patient to the most appropriate combination Regimen, taking into consideration the patient's disease history, treatment history, and/or preferences.

5.6. Blinding

Not applicable; this is an open-label study.

5.7. Study Treatment Administration

5.7.1. Study Treatment Overview and Schedule

Mirvetuximab soravtansine is an experimental anti-cancer 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. Similar precautions should be taken when handling bevacizumab, carboplatin, pegylated liposomal doxorubicin, and pembrolizumab. Refer to the Pharmacy Manual, Investigator Brochures, and package inserts for more information.

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

5.8. Study Drug Preparation and Administration

5.8.1. Premedication for Study Treatment

All patients must receive 325 to 650 mg of acetaminophen/paracetamol (per orem [by mouth] [PO] or IV), 10 mg IV dexamethasone, and 25 to 50 mg diphenhydramine (PO or IV) (equivalent drugs of similar drug classes are also acceptable) approximately 30 minutes before each infusion of mirvetuximab soravtansine. If individual patients require more intensive treatment to prevent infusion-related reactions, investigators may modify the regimen accordingly. Patients being treated with bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab in the absence of mirvetuximab soravtansine may receive premedication at the discretion of the Investigator or according to institutional guidelines. Patients treated with pembrolizumab in the absence of mirvetuximab soravtansine will not receive premedication with steroids.

5.8.2. Prophylactic Use of Corticosteroid Eye Drops

Patients receiving mirvetuximab soravtansine will be required to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighs the benefit per the ophthalmologist/physician. Patients will be instructed to self-administer 1% prednisolone (Pred Forte® or generic equivalent) six times daily on Days 1 through 4 and four times daily on Days 5 through 8 of each cycle during the study (see Appendix O). 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 through 8 of each cycle at a frequency prescribed by the ophthalmologist. Patients should be advised to wait at

least 15 minutes after corticosteroid eye drop administration before instilling preservative-free, lubricating eye drops.

5.8.3. Lubricating Artificial Tears

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

5.8.4. Preparation and Administration of Mirvetuximab Soravtansine

5.8.4.1. Calculation for Adjusted Ideal Body Weight

The AIBW will be used to calculate the dose of mirvetuximab soravtansine in this study (Appendix L).

The total dose of drug will be calculated on the basis of each patient's AIBW using the following formula:

Adjusted Ideal Body Weight (AIBW)

$IBW^a + 0.4\ (\text{Actual Weight} - IBW^a)$,

where:

Ideal Body Weight (IBW)

$IBW^a\ (\text{Male}) = 0.9H^a - 88$, and

$IBW^a\ (\text{Female}) = 0.9H^a - 92$.

[a] H = height in cm; W = weight in kg.

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

5.8.4.2. Preparation of Mirvetuximab Soravtansine

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

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

5.8.4.3. Administration of Mirvetuximab Soravtansine

The starting dose level of mirvetuximab soravtansine will be 5 mg/kg using AIBW for all combinations. **Mirvetuximab soravtansine should be administered first**, followed by the

assigned combination drug (bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab) for Regimens A, B, C, and D; for Regimen E, **mirvetuximab soravtansine should be administered first**, followed by bevacizumab **and then** carboplatin. Mirvetuximab soravtansine will be administered as an IV infusion after preparation as outlined in the Pharmacy Manual. Details for required and compatible infusion materials are included in the Pharmacy Manual. For patients who have not been administered mirvetuximab soravtansine as a prior anti-cancer therapy, mirvetuximab soravtansine should be administered at a rate of 1 mg/min; after 30 minutes, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after 30 minutes at 3 mg/min, the mirvetuximab soravtansine infusion rate may be increased to 5 mg/min. Subsequent infusions may be delivered at the tolerated rate. For patients who have been administered mirvetuximab soravtansine as a prior anti-cancer therapy, mirvetuximab soravtansine should be administered at the tolerated rate of prior mirvetuximab soravtansine infusions. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. After infusion, the IV line should be flushed with 5% dextrose as needed to ensure delivery of the full dose.

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

5.8.5. Preparation and Administration of Bevacizumab

Bevacizumab will be prepared per label and administered per protocol. Total body weight at Cycle 1 Day 1 (± 14 days) is to be used to calculate the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.8.6. Preparation and Administration of Carboplatin

Carboplatin will be prepared per label and administered per protocol. Carboplatin dosing will be calculated using the Calvert formula (Appendix J). The maximum carboplatin dose should not exceed AUC (mg × min/mL) × 150 mL/min (Griggs 2012).

If the patient has a history of allergic reaction when administered carboplatin or other platinum agents or experiences an allergic reaction to carboplatin while on study, carboplatin must be administered per institutional protocol for carboplatin desensitization. Dosing information will be entered on the dosing eCRF.

5.8.7. Preparation and Administration of Pegylated Liposomal Doxorubicin

Pegylated liposomal doxorubicin will be prepared per label and administered per protocol. Body weight at Cycle 1 Day 1 (± 14 days) is to be used to calculate the body surface area (Appendix K), which will be used to determine the required pegylated liposomal doxorubicin dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.8.8. Preparation and Administration of Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes − 5 minutes or + 10 minutes).

The Pharmacy Manual contains specific instructions for preparing the pembrolizumab infusion and administering the infusion solution.

5.9. Monitoring and Management of Adverse Events

5.9.1. Potential Infusion-Related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (see CTCAE Version 4.03). The signs and symptoms may vary and include, for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (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 infusion-related reactions and for subsequent re-treatment are provided in Table 7. Delayed infusion-related reactions may occur; therefore, patients should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Patients who experience an infusion-related reaction during or immediately after mirvetuximab soravtansine administration should have blood drawn to determine drug concentration and antibodies to mirvetuximab soravtansine (ADA), if feasible. The sample should be obtained within 3 hours after the onset of the reaction and again 1 week later. These patients should undergo all scheduled anti-tumor activity and safety evaluations.

Table 7: Management Guidelines for Potential Infusion-Related Reactions

Infusion Reaction CTCAE Version 4.03 Severity Grade	Management
Grade 1: mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below. • Promethazine (or equivalent) 150 mg PO per day prn for nausea. • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn. • Methylprednisolone 125 mg (or equivalent) IV prn.
Grade 2: moderate	• Interrupt infusion and disconnect infusion tubing from subject. • Promethazine (or equivalent) 150 mg PO per day prn for nausea. • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn. • Acetaminophen (or equivalent) 650 mg PO prn. • Methylprednisolone 125 mg (or equivalent) IV prn. • After recovery from symptoms, resume the infusion at 50% of the previous rate, and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, patients should be premedicated with dexamethasone (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 minutes before dosing.
Grade 3: severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from subject. • Administer diphenhydramine (25-50 mg) IV (or equivalent). • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5 mg/kg every 6 hours) 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 be used only if all other treatment methods fail to manage the infusion-related reaction. • Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE (see Section 9.1.1.2). • Permanently discontinue study medication treatment.

BID = twice daily, IM = intramuscular, prn = as needed, SAE = serious adverse event, SQ = subcutaneous.

5.9.2. Monitoring and Management of Treatment-Emergent Ocular Disorders

5.9.2.1. Monitoring of Potential Ocular Disorders

Changes in visual acuity resulting from corneal epithelium disorders have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker (Younes 2012). Because of the observation of ocular disorders in patients treated with mirvetuximab soravtansine Q3W at dose levels > 3.3 mg/kg, ocular function will be carefully monitored. Complete ophthalmologic exams and ocular symptom assessments will be performed in all patients at baseline and post-treatment as described in Table 8.

Table 8: Schedule for Ophthalmic Assessments

Assessment	Screening	Day 1 (All Cycles)	Before Day 1 Dose (Every Other Cycle)[a]	30 Day Safety Follow-up Visit or End of Treatment Visit
Ophthalmologic history: Patients will be asked about ocular symptoms such as history of dry eye and contact lens use.	X			
Complete Exam[b]: - Visual acuity - Indirect fundoscopy - Slit lamp examination under dilatation - Intraocular pressure measurement - Corneal photography[c]	X[d]		Patients who report treatment-emergent changes in vision	X
Schirmer test[e]	X		X	
Ocular symptom assessment (blurred vision, ocular discomfort, etc)	X	X		X

[a] Within 1 week before the Day 1 dose of every other cycle; required for patients who have experienced signs or symptoms of ocular toxicity and for those with blurred vision but normal eye exams.
[b] Performed by a board-certified ophthalmologist.
[c] When feasible, to document corneal abnormalities such as the presence of microcysts or keratitis (not required at baseline).
[d] Within 14 days before Cycle 1 Day 1.
[e] For patients experiencing ocular symptoms, the Schirmer test will be repeated at the first ophthalmology exam and in subsequent ophthalmologic exams if clinically indicated.

If a patient develops > CTCAE Grade 1 ocular symptoms (Appendix M), treatment with mirvetuximab soravtansine will 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. The patient will be referred to an ophthalmologist for a complete examination including visual acuity, slit lamp examination under dilatation, intraocular pressure assessment, and indirect fundoscopy. When feasible, corneal photographs should be obtained to document corneal abnormalities such as presence of microcysts or keratitis. Therapy may resume if ocular symptoms improve to Grade 1 or baseline within one cycle. After the development of ocular AEs, a complete ocular examination will be required at every other cycle going forward (or more frequently if clinically indicated) and at either the end of treatment or at the 30-day follow-up visit.

5.9.2.2. Management Guidelines for Ocular Disorders

To prevent dry eye, which may predispose a patient to corneal irritation, patients will be required to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician) for the duration of their mirvetuximab soravtansine treatment. Patients should also be firmly advised to avoid using contact lenses while on study. Baby shampoo and a soft cloth should be used to clean the eyes, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface. The use of UVA/UVB sunglasses is recommended when outside in full daylight during the course of the study. The use

of punctal plugs to increase lubrication of the eyes is also recommended. If patients report signs or symptoms of ocular disorders including, but not limited to, blurred vision or eye irritation, the management and dose modification guidelines outlined in Table 9 should be followed.

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

Table 9: Management of Ocular Disorders

Severity Grade (CTCAE Version 4.03 Grade)[a]	Management	Guidelines for Mirvetuximab Soravtansine Dose Modifications
Grade 1	• Complete eye exam as outlined in Table 8. • Monitor for worsening symptoms.	• Continue mirvetuximab soravtansine dosing.
Grade 2 symptoms	• Complete eye exam as outlined in Table 8. Repeat complete exam as clinically indicated. • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline (Section 5.10.1) or are deemed irreversible by the Investigator. • Resume therapy when ocular symptoms improve to Grade 1 or baseline.	• Hold mirvetuximab soravtansine dosing. • Patients with ocular disorders lasting fewer than 14 days may be allowed to resume therapy at the same dose level. • Patients with ocular disorders who experience dosing delays > 14 days may resume treatment at a reduced dose level (see Table 15).
Grade 3	• Complete eye exam as outlined in Table 8. Repeat complete exam as clinically indicated. • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline (Section 5.10.1) or are deemed irreversible by the Investigator. • Resume therapy when ocular symptoms improve to Grade 1 or baseline.	• Hold mirvetuximab soravtansine dosing. • Patients may be allowed to resume therapy at a lower dose than the one they were receiving when their symptoms began (see Table 15).
Grade 4	• Complete eye exam as outlined in Table 8. Repeat complete exam as clinically indicated. • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline (Section 5.10.1) or are deemed irreversible by the investigator.	• Permanently discontinue mirvetuximab soravtansine dosing.

[a] Appendix M includes CTCAE Version 4.03 grade definitions for select ocular disorders.

5.9.3. Monitoring of Non-infectious Pneumonitis After Administration of Study Treatment

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

For patients diagnosed with pneumonitis without an infectious etiology, the management and treatment guidelines outlined in Table 10 should be followed.

Table 10: Management of Non-infectious Pneumonitis

Severity Grade (CTCAE Version 4.03 Grade)	Medical Management of Pneumonitis	Guidelines for Dose Modifications
Grade 1	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• Continue dosing after discussion with the Sponsor.
Grade 2	• 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 (Regimens A, B, C, and E only). • Treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks (Regimen D only).	• Hold dosing of mirvetuximab soravtansine until symptoms resolve to Grade 1 or better. • Hold dosing of pembrolizumab until symptoms resolve to Grade 1 or better (Regimen D only). • Mirvetuximab soravtansine may be resumed at same dose level after discussion with the Sponsor. • Pembrolizumab may be resumed at same dose level after discussion with the Sponsor. • Discontinue mirvetuximab soravtansine and pembrolizumab if recurrent Grade 2 pneumonitis occurs upon re-challenging.

Table 10: Management of Non-infectious Pneumonitis (Continued)

Severity Grade (CTCAE Version 4.03 Grade)	Medical Management of Pneumonitis	Guidelines for Dose Modifications
Grade 3	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines (Regimens A, B, C, and E only). • Immediately treat with IV steroids. Administer additional anti-inflammatory measures as needed (Regimen D only). • Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration (Regimen D only). • Bronchoscopy with lavage and/or biopsy should be performed when clinically feasible. • The pneumonitis event must be followed until resolution.	• Permanently discontinue mirvetuximab soravtansine. • Permanently discontinue pembrolizumab (Regimen D only).
Grade 4	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines (Regimens A, B, and E only). • Immediately treat with IV steroids. Administer additional anti-inflammatory measures as needed (Regimen D only). • Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration (Regimen D only). • Bronchoscopy with lavage and/or biopsy should be performed when clinically feasible. • The pneumonitis event must be followed until resolution.	• Permanently discontinue mirvetuximab soravtansine dosing. • Permanently discontinue pembrolizumab (Regimen D only).

[a] Appendix M includes CTCAE Version 4.03 grade definitions for pneumonitis.

5.9.4. Monitoring and Management of Diarrhea After Administration of Study Treatment

5.9.4.1. Mirvetuximab Soravtansine–Associated Diarrhea

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

5.9.4.2. Pembrolizumab-Associated Diarrhea and/or Colitis

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with IV steroids followed by high-dose oral steroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks.

Refer to Table 21 for dose modifications and discontinuation of pembrolizumab.

5.9.4.3. Diarrhea Associated With Mirvetuximab Soravtansine and Pembrolizumab

Management guidelines for pembrolizumab-associated diarrhea should be followed (Section 5.9.4.2).

5.9.5. Monitoring and Management of Nausea and Vomiting After Administration of Study Treatment

Nausea and vomiting have been reported in patients treated with mirvetuximab soravtansine and with carboplatin. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea. Patients should be treated according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the use of anti-emetics (Basch 2011) outlined in Table 11.

Table 11: Management of Nausea and Vomiting

Severity Grade (CTCAE Version 4.03 Grade)	Management
Grade 1	• No additional therapy is required.
Grade 2	• Administer a 5-HT_3 receptor antagonist on Day 1 (eg, palonosetron, granisetron, or ondansetron) in combination with dexamethasone on Days 1-3 or treat per institutional guidelines. Aprepitant may be added to the combination.
Grades 3 and 4	• Administer a neurokinin 1 receptor antagonist (eg, aprepitant on Days 1-3 or fosaprepitant on Day 1) in combination with a 5-HT_3 receptor antagonist on Day 1 only, and dexamethasone on Days 1-3 or 1-4, or treat per institutional guidelines.

5-HT3 = 5-hydroxytryptamine type 3.

5.9.6. Monitoring of Bevacizumab-Associated Posterior Reversible Encephalopathy Syndrome

There have been rare reports of patients treated with bevacizumab who develop signs and symptoms consistent with the neurological disorder PRES. Signs and symptoms of PRES include seizures, headache, confusion, and visual disturbance or cortical blindness, with or without associated hypertension. Magnetic resonance imaging (MRI) of the brain will confirm the diagnosis of PRES. Bevacizumab treatment should be discontinued in patients who develop signs and/or symptoms consistent with PRES, and the specific symptoms should be appropriately treated.

5.9.7. Monitoring and Management of Bevacizumab-Associated Hypertension

Patients receiving bevacizumab must be closely monitored for the development of new or worsening hypertension. Blood pressure measurements should be performed after the patient has been in a resting position for ≥ 5 minutes. If the initial blood pressure reading is ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic, the result should be verified with a repeat measurement. If bevacizumab treatment-related hypertension develops, it should be managed as described in Table 12.

Table 12: Management of Hypertension After Bevacizumab Administration

Severity Grade (CTCAE Version 4.03 Grade)	Hypertension Pattern	Bevacizumab Dose Modifications
Grade 1	Asymptomatic, transient (< 24 h) BP increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits.	Continue bevacizumab.
Grade 2	Recurrent or persistent (> 24 h) or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits.	Withhold bevacizumab. Start anti-hypertensive therapy. Once BP is < 150/100 mm Hg, patients may continue bevacizumab therapy.
Grade 3	Requires more than one anti- hypertensive drug or more intensive therapy than previously.	Hold bevacizumab for persistent or symptomatic hypertension and discontinue permanently if hypertension is not controlled according to Investigator judgment.
Grade 4	Life-threatening consequences (eg, hypertensive crisis).	Permanently discontinue bevacizumab.

BP = blood pressure.

5.9.8. Monitoring and Management of Bevacizumab-Associated Proteinuria

Proteinuria will be assessed within 48 hours before each bevacizumab treatment by urine dipstick analysis method, UPC, 24-hour urine collection, or according to local institutional guidelines. Proteinuria should be managed according to Table 13.

Table 13: Management of Bevacizumab-Associated Proteinuria

CTCAE Grade	Bevacizumab Dose Modifications
< 3	No bevacizumab dose modifications
3	Hold bevacizumab.

Nephrotic syndrome (CTCAE Grade 4)	Permanently discontinue bevacizumab.

5.9.9. Monitoring and Management of Bevacizumab-Associated Bleeding

Patients receiving bevacizumab should be monitored for signs and symptoms of CNS bleeding. Signs and symptoms include sudden and severe headache, headache associated with a recent blow to the head, mild and long-lasting headache, headache accompanied by neck stiffness, confusion, drowsiness, vomiting (more than two episodes in 24 hours), seizures, and coma. Bevacizumab should be discontinued for intracranial bleeding of any grade. If Grade 3 or Grade 4 bleeding of any kind occurs in a patient receiving bevacizumab during the study treatment period, bevacizumab should be permanently discontinued. If hemorrhagic complications occur in a patient on full-dose anticoagulation therapy, bevacizumab should be permanently discontinued, and the patient should be treated per institutional guidelines. Standard procedures such as antagonization with protamine or vitamin K, infusion of vitamin K dependent factors, or insertion of a vena cava filter should be considered, depending on the severity of the bleeding, the presence of thrombotic events, and the organ affected.

5.9.10. Monitoring and Management of Bevacizumab-Associated Gastrointestinal Fistula/Perforation

Patients receiving bevacizumab should be continually monitored for signs or symptoms of GI fistula/bowel perforation. Perforations have been shown to occur at a higher frequency in patients who have received pelvic radiation therapy. Signs and symptoms of bowel perforation include fever, nausea, vomiting, hematemesis, chills, and severe stomach pain. Signs and symptoms of GI fistula include abdominal pain, painful bowel obstruction, fever, and elevated white blood cell counts. Other symptoms include diarrhea, rectal bleeding, sepsis, dehydration, poor absorption of nutrients, and weight loss. Patients are advised to notify their treating physician immediately if they experience any of the signs or symptoms described above. If a positive diagnosis of GI fistula or perforation is made, bevacizumab should be immediately discontinued, and the patient should be treated per institutional guidelines.

5.9.11. Monitoring and Management of Peripheral Neuropathy

Peripheral sensory neuropathy is a common AE observed in patients receiving bevacizumab in combination with paclitaxel or oxaliplatin. When mirvetuximab soravtansine is administered as a single agent, peripheral neuropathy is a common AE (mirvetuximab soravtansine Investigator Brochure). Patients should be monitored for signs and symptoms of peripheral neuropathy.

If a patient is diagnosed with peripheral neuropathy, the management guidelines in Table 14 should be followed.

Table 14: Management Guidelines for Peripheral Neuropathy

Severity Grade (CTCAE Version 4.03 Grade)	Management	Guidelines for Mirvetuximab Soravtansine Dose Modifications
Grade 1	• Monitor signs and symptoms.	• Continue mirvetuximab soravtansine dosing. • Continue bevacizumab, carboplatin, or pegylated liposomal doxorubicin dosing.
Grade 2	• Monitor patient until resolution to Grade 1 or baseline. • Treat patient per institutional guidelines.	• Hold mirvetuximab soravtansine dosing until resolution to Grade 1 or baseline. • Patients with peripheral neuropathy lasting ≤ 14 days will resume mirvetuximab soravtansine therapy at the same dose level. • Patients with peripheral neuropathy who experience dosing delays > 14 days will resume mirvetuximab soravtansine treatment at a reduced dose level except if in Regimen B and second occurrence. If second occurrence and Regimen B, mirvetuximab soravtansine will resume at the same dose level. • Continue bevacizumab or pegylated liposomal doxorubicin dosing. • Continue carboplatin dosing if first occurrence. • Hold dosing of carboplatin until resolution to Grade 1 if second occurrence. Once resolved to Grade 1, carboplatin will resume at a reduced dose level.

Table 14: Management Guidelines for Peripheral Neuropathy (Continued)

Severity Grade (CTCAE Version 4.03 Grade)	Management	Guidelines for Mirvetuximab Soravtansine Dose Modifications
Grade 3	• Monitor patient until resolution to Grade 1 or baseline. • Treat patient per institutional guidelines.	• Hold mirvetuximab soravtansine dosing until resolution to Grade 1 or baseline. • Patients will resume mirvetuximab soravtansine at a lower dose level except if in Regimen B and second occurrence. If second occurrence and Regimen B, mirvetuximab soravtansine will resume at the same dose level. • Continue bevacizumab or pegylated liposomal doxorubicin dosing. • Hold dosing of carboplatin until resolution to Grade 1 if second occurrence. Once resolved to Grade 1, carboplatin will resume at a reduced dose level.

Severity Grade (CTCAE Version 4.03 Grade)	Management	Guidelines for Mirvetuximab Soravtansine Dose Modifications
Grade 4	• Monitor patient until resolution to Grade 1 or baseline. • Treat patient per institutional guidelines.	• Permanently discontinue mirvetuximab soravtansine dosing. • Permanently discontinue bevacizumab dosing. • Permanently discontinue carboplatin dosing. • Permanently discontinue pegylated liposomal doxorubicin dosing.

5.9.12. Monitoring and Management of Pembrolizumab-Associated Type 1 Diabetes Mellitus

For Type 1 diabetes mellitus (T1DM) or Grade 3 to 4 hyperglycemia:

- Insulin replacement therapy is recommended for T1DM and for Grade 3 to 4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Refer to Table 21 for dose modifications and discontinuation of pembrolizumab.

5.9.13. Monitoring and Management of Pembrolizumab-Associated Hypophysitis

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3 to 4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Refer to Table 21 for dose modifications and discontinuation of pembrolizumab.

5.9.14. Monitoring and Management of Pembrolizumab-Associated Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- Grade 3-4 hyperthyroidism:

  - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Refer to Table 21 for dose modifications and discontinuation of pembrolizumab.

5.9.15. Monitoring and Management of Pembrolizumab-Associated Hepatic Adverse Events

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids.
- For Grade 3 to 4 events, treat with IV corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no fewer than 4 weeks.

Refer Table 21 for dose modifications and discontinuation of pembrolizumab.

5.9.16. Monitoring and Management of Pembrolizumab-Associated Renal Failure or Nephritis

- For Grade 2 events, treat with corticosteroids.
- For Grade 3 to 4 events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no fewer than 4 weeks.

Refer Table 21 for dose modifications and discontinuation of pembrolizumab.

5.10. Treatment Guidelines

5.10.1. Re-treatment Criteria

In the absence of a DLT, for a patient to begin a new cycle or continue a cycle of therapy, the following criteria must be met.

- ANC must be $\geq 1.5 \times 10^9$/L (1,500/µL) (Cycle 1 Day 1 only).
- ANC must be $\geq 1.0 \times 10^9$/L (1,000/µL).
- Platelet count must be $\geq 75 \times 10^9$/L (75,000/µL).
- All non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be ≤ Grade 2 (except alopecia) or returned to baseline; the exceptions to this rule are:
  - Treatment-emergent ocular disorders, which must have recovered to ≤ Grade 1 or baseline.
  - Treatment-emergent pneumonitis, which must have recovered to ≤ Grade 1 within one cycle.

- Treatment-emergent hypertension must have recovered to blood pressure of < 150/100 mm Hg (Regimen A and Regimen E only).
- Treatment-emergent proteinuria must have recovered to ≤ Grade 1 (Regimen A and Regimen E only).
- Treatment-emergent HFS must have recovered to ≤ Grade 1 (Regimen C).
- Treatment-emergent mucositis must have recovered to ≤ Grade 1 (Regimen C).
- Treatment-emergent, pembrolizumab-associated diarrhea/colitis must have recovered to ≤ Grade 1 (Regimen D).
- Treatment-emergent, pembrolizumab-associated increased AST, ALT, and/or total bilirubin must have recovered to ≤ Grade 1 (Regimen D).
- Treatment-emergent, pembrolizumab-associated hypophysitis must have recovered to ≤ Grade 1 (Regimen D).
- Treatment-emergent, pembrolizumab-associated renal failure/nephritis must have recovered to ≤ Grade 1 (Regimen D).
- Treatment-emergent, pembrolizumab-associated infusion reaction must have recovered to ≤ Grade 1 (Regimen D).

If the patient does not meet these criteria, dosing with the two agents in the combination Regimen will be delayed, and the patient should be re-evaluated within 48 to 72 hours. Dosing with both agents may resume if these criteria have been met. If the AE can be attributed to one of the agents in the combination Regimen, that agent will be held or discontinued per the dose modification guidelines described in Section 5.10.4; however, treatment with the second agent may resume provided all the other criteria are met. However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related toxicity, this will be viewed as a DLT (Section 4.1.4). If the next cycle is delayed longer than one cycle because of treatment-related toxicity, the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

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

5.10.2. Follow-up for Dose-Limiting Toxicities and Adverse Events Leading to Discontinuation

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

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

5.10.3. Criteria for Re-initiation of Study Treatment After Occurrence of a Dose-Limiting Toxicity

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

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

If the patient does not meet these criteria, dosing will be delayed, and the patient should be re-evaluated within 48 to 72 hours. Dosing may resume if these criteria have been met. However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related toxicity, this may be viewed as a DLT (Section 4.1.4). If the next cycle is delayed longer than one cycle because of treatment-related toxicity, the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon by the Sponsor and the Investigator.

5.10.4. Dose Modification Guidelines

5.10.4.1. Mirvetuximab Soravtansine Dose Reduction After a Dose-Limiting Toxicity

Mirvetuximab soravtansine dose may be reduced at the discretion of the Investigator after discussion with the Sponsor. Patients who develop DLTs or AEs requiring an interruption of mirvetuximab soravtansine may resume treatment at a reduced dose level as shown in Table 15, provided the criteria outlined in Section 5.10.1 are met.

Table 15: Mirvetuximab Soravtansine Dose Modification Guidelines

Regimen	If the Patient Was Receiving Mirvetuximab Soravtansine at:	Dose Should Be Reduced to:
A, B, C, D, or E	6.0 mg/kg	5.0 mg/kg
	5.0 mg/kg	4.0 mg/kg

Reduction of the mirvetuximab soravtansine dose below 4.0 mg/kg will not be permitted. Dose reductions to intermediate dose levels may be allowed on the basis of emerging data with the approval of the Sponsor.

5.10.4.2. Bevacizumab Dose Modification Guidelines

5.10.4.2.1. Grade 3 or Grade 4 Adverse Events

Bevacizumab should be temporarily withheld for Grade 4 febrile neutropenia and/or Grade 4 thrombocytopenia (regardless of the causal relationship to treatment) because these conditions are predisposing factors for bleeding. If a patient experiences a Grade 3 venous thromboembolism, bevacizumab must be withheld for 3 weeks. Bevacizumab may be resumed during the period of therapeutic-dose anticoagulant therapy. In general, Grade 3 or Grade 4 bevacizumab-related events should be managed as outlined in Table 16.

Table 16: Bevacizumab Dose Modification Guidelines

First occurrence of Grade 3 or 4 AE	Hold bevacizumab until toxicity has improved to ≤ Grade 1.
Second occurrence of Grade 3 or 4 AE	Permanently discontinue bevacizumab treatment.

5.10.4.3. Pegylated Liposomal Doxorubicin Dose Modification Guidelines for Non-hematologic Adverse Events

5.10.4.3.1. General Guidelines

If patients receiving pegylated liposomal doxorubicin experience non-hematologic, treatment-related AEs, their pegylated liposomal doxorubicin dose should be reduced as indicated in Table 17. Patients who require dose reductions below 20 mg/m^2 should discontinue pegylated liposomal doxorubicin treatment.

Table 17: Dose Modification Guidelines for Pegylated Liposomal Doxorubicin for Non-hematologic Adverse Events

If the Patient Was Receiving Pegylated Liposomal Doxorubicin at:	Dose Should Be Reduced to:
40.0 mg/m^2	35.0 mg/m^2
35.0 mg/m^2	30.0 mg/m^2
30.0 mg/m^2	20.0 mg/m^2

Reduction of the pegylated liposomal doxorubicin dose below 20.0 mg/m^2 will not be permitted.

5.10.4.3.2. Pegylated Liposomal Doxorubicin Dose Reductions for Hematologic Adverse Events

Patients receiving pegylated liposomal doxorubicin are at risk of bone marrow suppression. Leukopenia is usually transient; hematologic AEs may require dose delays or reductions as indicated in Table 18.

Table 18: Pegylated Liposomal Doxorubicin Dose Reduction for Hematologic Adverse Events

Severity Grade (CTCAE Version 4.03 Grade)	Dose Modification
Grade 1	No action required.
Grade 2 and Grade 3	Hold pegylated liposomal doxorubicin until ANC and platelet levels return to normal or improve to Grade 1. Resume dosing without dose reduction.
Grade 4	Hold pegylated liposomal doxorubicin until ANC and platelet levels return to normal or improve to Grade 1. Resume dosing at a 25% dose reduction or at full dose with cytokine support.

5.10.4.3.3. Dose Reductions for Pegylated Liposomal Doxorubicin Hand-Foot Syndrome and/or Mucositis

Hand-foot syndrome 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. Hand-foot syndrome has been observed in patients receiving pegylated liposomal doxorubicin at doses of 50 mg/m^2 and, with less frequency, in those receiving pegylated liposomal doxorubicin at 30 mg/m^2. If patients present with symptoms/signs consistent with HFS, the dose of pegylated liposomal doxorubicin should be modified as indicated in Table 19.

Table 19: Pegylated Liposomal Doxorubicin Dose Modification Guidelines for Hand and Foot Syndrome and Mucositis

Severity Grade (CTCAE Version 4.03 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 pegylated liposomal doxorubicin, unless previous Grade 3 or 4 HFS. In case of previous Grade 3 or 4 HSF, 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 pegylated liposomal doxorubicin until resolved to Grade 1 or baseline. If no resolution after 2 weeks, pegylated liposomal doxorubicin should be discontinued. If no prior Grade 3-4 HFS, resume at the dose before 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 pegylated liposomal doxorubicin until resolved to Grade 1 or baseline. Decrease dose by 25%. . If no resolution after 2 weeks, pegylated liposomal doxorubicin should be discontinued.
Grade 4	Diffuse or local process causing infectious complications, a bed ridden state, or hospitalization	Requires parenteral or enteral support	

5.10.4.4. Carboplatin Dose Modification Guidelines

Severe myelosuppression, GI effects (vomiting and nausea), and peripheral neuropathy (paresthesia) have been frequently observed in patients treated with carboplatin.

Refer to Table 5 and Table 20 for specific guidelines regarding carboplatin dose reductions.

Table 20: Dose Modification Guidelines for Carboplatin

If the Patient Was Receiving Carboplatin at:	Dose Should Be Reduced to:
AUC5	AUC4
AUC4	Discontinue

5.10.4.5. Dose Modification and Toxicity Management for Immune-Related Adverse Events Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or

exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. On the basis of the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 21.

Table 21: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab

General Instructions

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first, followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE Version 4.0)	Action Taken With Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent), followed by taper.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiologic imaging, and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent), followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, or blood or mucus in stool, with or without fever) and bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Table 21: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Continued)

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE Version 4.0)	Action Taken With Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-up
AST/ALT elevation or increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent), followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent), followed by taper.	
T1DM or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.

Table 21: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Continued)

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE Version 4.0)	Action Taken With Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-up
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes in renal function.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	On the basis of on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	On the basis of type and severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue on the basis of the type of event. Events that require discontinuation include, but are not limited to, Guillain-Barre syndrome, encephalitis.		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
Note: For participants with Grade 3 or 4 immune-related endocrinopathy where withholding pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or metabolic control is achieved (in case of T1DM).

5.10.4.6. Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours after completion of infusion. Dose modification and toxicity management guidelines for pembrolizumab-associated infusion reactions are provided in Table 22.

Table 22: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant may be premedicated 1.5 h (± 30 min) before infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic)

Table 22: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines (Continued)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 and 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE Version 4.0 at http://ctep.cancer.gov.
NSAID = non-steroidal anti-inflammatory drug.

5.10.4.7. Hierarchy of Dose Reductions/Discontinuations

Patients experiencing AEs that can be clearly attributed to mirvetuximab soravtansine or to any of the combination drugs will have the corresponding agent reduced first (Table 23). In case of an AE recurrence, the other drug in the combination Regimen will then be dose reduced. If the relationship of an AE to a particular drug cannot be clearly determined, the order in which the drugs are to be reduced will require approval from the Sponsor.

Table 23: Agent to be Dose Reduced/Discontinued First on the Basis of Reported Compound-Specific Treatment-Related Adverse Events

Adverse Event	Mirvetuximab Soravtansine	Combination Agent			
		Bevacizumab	Carboplatin	Pegylated Liposomal Doxorubicin	Pembrolizumab
Ocular symptoms	●				
GI events (vomiting, nausea, diarrhea, abdominal pain, and constipation)	●				
Peripheral neuropathy events	●				
Noninfectious pneumonitis	●				●
Anemia[a]	●		●		
Metabolic disorders	●				
Infusion-related reactions	See Section 5.9.1.				
CNS hemorrhage		●			
Hemorrhage		●			
Hypertension		●			
Proteinuria		●			
PRES		●			

Table 23: Agent to be Dose Reduced/Discontinued First on the Basis of Reported Compound-Specific Treatment-Related Adverse Events (Continued)

Adverse Event	Mirvetuximab Soravtansine	Combination Agent	AE	Mirvetuximab Soravtansine	Combination Agent
GI perforation or fistula		●			
Non-GI fistula		●			
Tracheoesophageal fistula		●			
Thromboembolism		●			
HFS				●	
Stomatitis				●	
Neutropenia			●	●	
Thrombocytopenia			●	●	
Colitis					●
T1DM					●
Hypophysitis					●
Hyperthyroidism/ hypothyroidism					●
Renal failure or nephritis					●
AST, ALT, or increased bilirubin					●

[a] If patients are receiving mirvetuximab soravtansine in combination with carboplatin, then carboplatin should be reduced first.
If the relationship of the AE to a particular drug cannot be clearly determined, the order in which the drugs are to be reduced will require approval from the Sponsor.

5.10.5. Discontinuation of Study Treatment Due to Adverse Events

Each drug in the combination Regimen may be discontinued independently on the basis of tolerance and drug-specific toxicities. If a doublet combination agent is discontinued in Regimen A (mirvetuximab soravtansine + bevacizumab), Regimen B (mirvetuximab soravtansine + carboplatin), Regimen C (mirvetuximab soravtansine + pegylated liposomal doxorubicin), or Regimen D (mirvetuximab soravtansine + pembrolizumab), the patient may continue participation in the study on mirvetuximab soravtansine as monotherapy. If a patient receiving Regimen A discontinues mirvetuximab soravtansine, the patient may continue participation in the study on bevacizumab as monotherapy until a reason for discontinuation arises (toxicity or tumor progression). If a patient receiving Regimen D discontinues mirvetuximab soravtansine, the patient may continue participation in the study on pembrolizumab as monotherapy until either the patient has received 35 treatments (approximately 2 years) or a reason for discontinuation arises (toxicity or tumor progression). If one or two of the components of the triplet dose (Regimen E) is/are discontinued, the patient may continue participation in the study with a doublet/single-agent therapy. For patients receiving either Regimen B or Regimen C, if mirvetuximab soravtansine is discontinued, the patient must be discontinued from the study. If patients receiving Regimen E discontinue all drug treatment because of toxicity, they will continue to be followed until progression.

For all drugs, study treatment should not be resumed in the case of the following treatment-related events.

- ≥ Grade 3 cardiac event.
- Other non-hematologic events of Grade 4 severity.

- Failure to meet re-treatment criteria within one cycle due to insufficient recovery from a treatment-related toxicity. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon by the Sponsor and the Investigator.

5.10.6. Additional Discontinuation Guidelines

5.10.6.1. Pegylated Liposomal Doxorubicin Discontinuation

Pegylated liposomal doxorubicin should be discontinued if the patient's left ventricular ejection fraction drops below normal or by at least 15% from the baseline value.

5.10.6.2. Bevacizumab Discontinuation

Bevacizumab should be permanently discontinued in patients experiencing the AEs listed in Table 24.

Table 24: Adverse Events Requiring Permanent Discontinuation of Bevacizumab

Severity Grade (CTCAE Version 4.03 Grade)	Adverse Event
Any grade	PRES
Grade 3 or 4	Hemorrhage or bleeding
Grade 4	Venous thromboembolism
Any grade	Arterial thromboembolism
Any grade	CNS bleeding
Grade 4	Proteinuria
Grade 3 or 4	Left ventricular dysfunction
Grade 3 or 4	Congestive heart failure
Any grade	GI perforation and fistula
Any grade	Tracheo-esophageal fistula
Grade 4	Non-GI fistula
Any grade	Hypersensitivity and/or allergic reactions to bevacizumab

5.10.6.3. Carboplatin Discontinuation

Carboplatin may be discontinued after six or more cycles at the discretion of the investigator on the basis of the benefit-risk profile for the patient. If carboplatin is discontinued, mirvetuximab soravtansine may be continued as a single agent for patients receiving Regimen B and in combination with bevacizumab for patients receiving Regimen E, if the patient continues to meet treatment criteria and has at least stable disease per RECIST Version 1.1.

5.10.6.4. Pembrolizumab Discontinuation

5.10.6.4.1. Discontinuation of Study Therapy After 2 Years

Pembrolizumab will be discontinued after 35 treatments (approximately 2 years of treatment). Retreatment with pembrolizumab in combination with mirvetuximab soravtansine or as monotherapy may be considered if the patient has a CR and meets criteria in Section 5.10.6.4.2 and Section 5.10.6.4.3.

5.10.6.4.2. Discontinuation of Study Therapy After Complete Response

Discontinuation of treatment may be considered for patients who have attained a confirmed CR who have been treated for at least 24 weeks with mirvetuximab soravtansine and pembrolizumab and had at least 2 cycles of mirvetuximab soravtansine and pembrolizumab beyond the date when the initial CR was declared. Patients will follow the schedule of assessments in Appendix C. Patients who then experience radiologic PD may be eligible for up to 1 year of additional treatment with pembrolizumab in combination with mirvetuximab soravtansine or as monotherapy at the discretion of the Investigator if:

- No cancer treatment was administered since the last dose of mirvetuximab soravtansine and pembrolizumab.
- The patient meets the safety parameters listed in the inclusion/exclusion criteria (Section 3).
- The study is still open.

Patients will resume pembrolizumab in combination with mirvetuximab soravtansine or as monotherapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 5.10.6.4.3. Response or progression during this re-treatment, termed the Second Course Phase (Section 5.10.6.4.3), will not count toward ORR or PFS for the primary endpoint in this trial.

5.10.6.4.3. Second Course Phase

Patients on Regimen D (mirvetuximab soravtansine + pembrolizumab) who stop mirvetuximab soravtansine and pembrolizumab with CR per Section 5.10.6.4.1 may be eligible for up to 1 year of additional treatment with pembrolizumab in combination with mirvetuximab soravtansine or as monotherapy if they progress after stopping study treatment. This Second Course Phase of this study is available only if the study remains open and the patient meets the following conditions:

- Stopped initial treatment with mirvetuximab soravtansine and pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST Version 1.1.
  - Was treated for at least 24 weeks with mirvetuximab soravtansine and pembrolizumab before discontinuing therapy.
  - Received at least two treatments with mirvetuximab soravtansine and pembrolizumab beyond the date when the initial CR was declared.

AND

- Experienced Investigator-determined confirmed radiologic PD after stopping their initial treatment with mirvetuximab soravtansine and pembrolizumab.
- Did not receive any anti-cancer treatment since the last dose of mirvetuximab soravtansine and pembrolizumab.
- Has a performance status of 0 or 1 on the ECOG PS.
- Demonstrates adequate organ function as detailed in the inclusion criteria (Section 3.1).

- If 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): has a negative serum or urine pregnancy test within 72 hours before receiving retreatment with study medication.
- If WCBP: agrees to use effective contraceptive methods (examples include oral, parenteral, or implantable hormonal contraceptive, intra-uterine device, or vasectomy) while on study treatment and for at least 12 weeks after the last dose of mirvetuximab soravtansine and for at least 4 months after the last dose of pembrolizumab.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that a) might interfere with the patient's participation for the full duration of the study, or b) makes it not in the best interest of the patient to participate, in the opinion of the treating Investigator.

Patients who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab and mirvetuximab soravtansine. Treatment will be administered for up to 1 additional year. Patients will follow the Schedule of Clinical Assessments in Appendix C.

5.10.6.4.4. Discontinuation Due to Adverse Event

Pembrolizumab must be permanently discontinued in patients experiencing the AEs listed in Table 25.

Table 25: Adverse Events Requiring Discontinuation of Pembrolizumab

Severity Grade (CTCAE Version 4.03 Grade)	Adverse Event
Grade 4	Hyperthyroidism
Grade 3 or 4	Myocarditis
Grade 3 or 4	Pneumonitis
Grade 3 or 4	Infusion reaction
Grade 3 or 4	Renal failure/nephritis
Grade 4	Pembrolizumab-related adverse event

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

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

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

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

- The study is terminated by the Sponsor.

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

5.11.1. Replacement of Patients Who Are Withdrawn Before the End of Cycle 1

Only patients who sign the ICF and receive at least one dose of mirvetuximab soravtansine will be considered enrolled. If an enrolled patient is discontinued from study treatment for reasons other than safety (eg, withdrawal of consent, non-compliance, death due to PD) before the end of Cycle 1, the patient will be replaced (ie, an additional patient will be added to the Dose Escalation dose level or Dose Expansion Cohort or triplet dose [Regimen E]). Patients who do not complete Cycle 1 because of an AE will not be replaced. Patients who are replaced will not be considered in making dose escalation decisions or safety decisions for dose expansion but, if possible, will be followed for safety and other assessments according to the protocol.

5.12. Period of Observation

The period of safety observation for this study extends from the time of informed consent until the final evaluation during the study, including the 30-day follow-up safety visit and 120 days after the last dose of pembrolizumab (Regimen D only). Short-term follow-up for patients who discontinue study therapy without documented PD will continue every 3 months until the patient's disease worsens, until the patient begins subsequent anti-cancer treatment, or until the patient dies, whichever occurs first.

5.13. Concomitant Medications and Procedures

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

5.13.1. Antiemetic and Antidiarrheal Medications

Antiemetic (eg, 5-HT_3 [5-hydroxytryptamine type 3] serotonin receptor antagonists such as palonosetron, granisetron, or ondansetron) and antidiarrheal (eg, loperamide) medications may be used at the discretion of the treating physician.

5.13.2. Folate-Containing Vitamins

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

5.13.3. Antineoplastic Therapy

Other chemotherapy, investigational agents other than pembrolizumab (Regimen D only), immunotherapy, or biologic therapy will not be permitted during the study.

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

5.13.4. Hematopoietic Growth Factors

Patients receiving recombinant erythropoietin or darbepoetin-α before the study start may continue to receive pre-treatment doses.

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

5.13.5. Medications Metabolized Through Cytochrome P450 3A

In vitro metabolism studies demonstrated that DM4 is predominantly metabolized by thiol s-methyltransferase 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 cytochrome P450 (CYP) 3A, its exposure could potentially be increased in the presence of strong CYP3A inhibitors. Drinking more than one serving (250 mL) of grapefruit juice per day should be avoided.

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

5.13.6. Vaccinations (Regimen D Only)

Live vaccines within 30 days before the first dose of pembrolizumab and while participating in the study are not allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

5.13.7. Systemic Steroids (Regimen D Only)

Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or premedication before administration of study drugs are not allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Inhaled steroids are allowed for management of asthma. Topical steroids including corticosteroid eye drops as outlined in Section 5.8.2 are allowed.

5.13.8. 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 to moderate infusion-related reactions. Additionally, medications (not

addressed above) used to treat underlying medical conditions at study entry, including anti-emetics and anti-diarrheals, will be allowed to continue.

5.14. Overdose and Medication Error

5.14.1. Overdose

Mirvetuximab soravtansine: There is no known treatment/antidote available. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug. In the event of overdose, the patient should be observed closely for signs of toxicity.

Bevacizumab, carboplatin, or pegylated liposomal doxorubicin: Please see the package inserts for treatment of overdose. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug.

Pembrolizumab: For this trial, an overdose will be defined as ≥ 1,000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab.

Overdose involving any of the study drugs, with or without associated AE/SAE, is to be recorded on the AE page of the eCRF and on an SAE form to ensure collection of the incident details, treatment, and any associated AEs. All instances of overdose must be reported to the sponsor as described for SAEs (Section 9.2.1).

5.14.2. Medication Error

The Sponsor must be notified immediately in the event of error in prescribing, dispensing, administering, and/or use of mirvetuximab soravtansine or any study drug. The event must be reported on the eCRF. If an error resulted in an SAE, an SAE Report Form must be submitted within 24 hours after the event (see Section 9.2).

6. PHARMACOKINETIC AND IMMUNOGENEICITY ASSESSMENTS

6.1. Pharmacokinetic Assessments

Pharmacokinetic blood sample collection details are provided in Appendix D for each Regimen. Blood samples from patients will be analyzed to characterize the PK of mirvetuximab soravtansine when administered in 3- or 4-week cycles. This includes the analysis of intact conjugate, total antibody, DM4, and *S*-methyl DM4. Pharmacokinetic parameters include, but are not limited to, Cycle 1 and Cycle 3 C_{max}, AUC, $t_{½}$, CL, V_{ss}, and t_{max}.

Pre-infusion and post-infusion samples will be analyzed for pegylated liposomal doxorubicin, carboplatin, or bevacizumab concentrations. Samples may be analyzed to evaluate the concentration of pembrolizumab if warranted by a safety signal.

NOTE: Any patient who experiences a ≥ Grade 2 infusion-related reaction during administration of mirvetuximab soravtansine will have blood drawn within 3 hours after the onset of the reaction and 1 week later for determination of drug concentration, antibodies to mirvetuximab soravtansine, and factors that may be related to the development of hypersensitivity reactions (see Section 5.9.1).

Pharmacokinetic 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.

When pre-dose samples are collected, they are to be taken before the start of the first infusion.

6.1.1. Pharmacokinetic Assessments for 3-Week Cycle Schedule Regimen A (Mirvetuximab Soravtansine + Bevacizumab)

Blood Samples for Pharmacokinetic Measurements of Mirvetuximab Soravtansine

Blood samples for PK measurements of mirvetuximab soravtansine will be taken at the following time points:

Cycles 1 and 3

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes), and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2 –*** 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 3 –*** 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 8 –*** a single blood sample, which is collected when safety assessments are collected
- ***Day 15 –*** a single blood sample, which is collected when safety assessments are collected

Cycles 2, 4, 5, and 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes)
- ***End of treatment*** – a single blood sample, which is collected when safety assessments are collected
- ***30-day follow-up*** – a single blood sample, which is collected when safety assessments are collected

Blood Samples for Pharmacokinetic Measurements of Bevacizumab

Blood samples for PK measurements of bevacizumab will be taken at the following time points:

Cycles 1 through 6

- ***Day 1*** – pre-dose and immediately after the completion of infusion of bevacizumab (+ 10 minutes)

6.1.2. Pharmacokinetic Assessments for 3-Week Cycle Schedule Regimen B (Mirvetuximab Soravtansine + Carboplatin)

Blood Samples for Pharmacokinetic Measurements of Mirvetuximab Soravtansine

Blood samples for PK measurements of mirvetuximab soravtansine will be taken at the following time points:

Cycles 1 and 3

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes) and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2 –*** 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 3 –*** 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 8 –*** a single blood sample, which is collected when safety assessments are collected
- ***Day 15 –*** a single blood sample, which is collected when safety assessments are collected

Cycles 2, 4, 5, and 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes)
- ***End of treatment*** – a single blood sample, which is collected when safety assessments are collected
- ***30-day follow-up*** – a single blood sample, which is collected when safety assessments are collected

Blood Samples for Pharmacokinetic Measurements of Carboplatin

Blood samples for PK measurements of carboplatin will be taken at the following time points:

Cycles 1 and 3

- ***Day 1*** - pre-dose and immediately after the completion of infusion of carboplatin (+ 10 minutes) and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2*** – 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)

Cycles 2, 4, 5, and 6

- ***Day 1*** – pre-dose and immediately after the completion of infusion of carboplatin (+ 10 minutes)

6.1.3. Pharmacokinetic Assessments for 4-Week Cycle Regimen C (Mirvetuximab Soravtansine + Pegylated Liposomal Doxorubicin)

Blood Samples for Pharmacokinetic Measurements of Mirvetuximab Soravtansine

Blood samples for PK measurements of mirvetuximab soravtansine will be taken at the following time points:

Cycles 1 and 3

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes) and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2 –*** 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 3 –*** 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 8 –*** a single blood sample, which is collected when safety assessments are collected
- ***Day 15*** a single blood sample, which is collected when safety assessments are collected
- ***Day 22 –*** a single blood sample, which is collected when safety assessments are collected

Cycles 2, 4, 5, and 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes)
- ***End of treatment*** – a single blood sample, which is collected when safety assessments are collected
- ***30-day follow-up*** – a single blood sample, which is collected when safety assessments are collected

Blood Samples for Pharmacokinetic Measurements of Pegylated Liposomal Doxorubicin

Blood samples for PK measurements of pegylated liposomal doxorubicin will be taken at the following time points:

Cycles 1 through 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of pegylated liposomal doxorubicin (+ 10 minutes)

6.1.4. Pharmacokinetic Assessments for 3-Week Cycle Schedule Regimen D (Mirvetuximab Soravtansine + Pembrolizumab)

Blood Samples for Pharmacokinetic Measurements of Mirvetuximab Soravtansine

Blood samples for PK measurements of mirvetuximab soravtansine will be taken at the following time points:

Cycles 1 and 3

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes) and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2 –*** 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 3 –*** 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 8 –*** a single blood sample, which is collected when safety assessments are collected
- ***Day 15 –*** a single blood sample, which is collected when safety assessments are collected

Cycles 2, 4, 5, and 6

- ***Day 1*** – pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes)
- ***End of treatment*** – a single blood sample, which is collected when safety assessments are collected
- ***30-day follow-up*** – a single blood sample, which is collected when safety assessments are collected

Blood Samples for Pharmacokinetic Measurements of Pembrolizumab

Blood samples for PK measurements of pembrolizumab will be taken at the following time points:

Cycles 1 through 6

- **Day 1** – pre-dose and immediately after the completion of infusion of pembrolizumab (+ 10 minutes)

6.1.5. Pharmacokinetic Assessments for 3-Week Cycle Schedule Regimen E (Mirvetuximab Soravtansine + Bevacizumab + Carboplatin)

Blood Samples for Pharmacokinetic Measurements of Mirvetuximab Soravtansine

Blood samples for PK measurements of mirvetuximab soravtansine will be taken at the following time points:

Cycles 1 and 3

- ***Day 1*** – pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes) and 6 hours after the completion of mirvetuximab soravtansine infusion (+ 20 minutes)
- ***Day 2*** – 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 3*** – 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)
- ***Day 8*** – a single blood sample, which is collected when safety assessments are collected

- ***Day 15 –*** a single blood sample, which is collected when safety assessments are collected

Cycles 2, 4, 5, and 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of mirvetuximab soravtansine (+ 10 minutes)
- ***End of treatment*** – a single blood sample, which is collected when safety assessments are collected
- ***30-day follow-up*** – a single blood sample, which is collected when safety assessments are collected

Blood Samples for Pharmacokinetic Measurements of Bevacizumab

Blood samples for PK measurements of bevacizumab will be taken at the following time points:

Cycles 1 through 6

- ***Day 1*** – pre-dose and immediately after the completion of infusion of bevacizumab (+ 10 minutes)

Blood Samples for Pharmacokinetic Measurements of Carboplatin

Blood samples for PK measurements of carboplatin will be taken at the following time points:

Cycles 1 and 3

- ***Day 1*** - pre-dose and immediately after the completion of infusion of carboplatin (+ 10 minutes).
- ***Day 2 –*** 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours)

Cycles 2, 4, 5, and 6

- ***Day 1 –*** pre-dose and immediately after the completion of infusion of carboplatin (+ 10 minutes)

6.2. Immunogenicity Assessments of Mirvetuximab Soravtansine

Mirvetuximab soravtansine immunogenicity will be assessed in plasma samples collected for PK evaluation; no additional blood draw is necessary. The following time points will be analyzed for ADA: before dosing (pre-dose) on Day 1 of Cycles 1, 2, 4, and 5; at the end of treatment and 30-day follow-up visits.

7. TRANSLATIONAL RESEARCH STUDIES

Several biomarkers, including FRα, will be evaluated as potential biomarkers of clinical response to the different mirvetuximab soravtansine combination Regimens. These will help guide further clinical development of mirvetuximab soravtansine.

7.1. Correlation Between FRα Expression and Mirvetuximab Soravtansine Anti-tumor Activity

FRα expression varies with tumor histology, as reported in the literature and demonstrated in ImmunoGen nonclinical studies (Section 1.1 and Investigator Brochure). On the basis of the

hypothesis that tumors expressing higher levels of FRα are more likely to be susceptible to anti-tumor activity of mirvetuximab soravtansine, a threshold for FRα expression was determined for enrollment in this study. This was done on the basis of molecular epidemiology data generated in a number of patient samples representative of different tumor types, as well as clinical anti-tumor activity data from the FIH Study 0401.

7.1.1. Evaluation of FRα Expression in Tumor Tissue During Dose Escalation and Dose Expansion

FRα expression in tumors will be analyzed by IHC. All patients who are evaluated for this study must submit archived tumor tissue samples (either formalin-fixed, paraffin embedded blocks, or slides sectioned from such blocks), or new biopsy samples if archival samples are not available, for analysis of FRα expression by IHC before enrollment.

For patients in Regimen D, the pre-dose biopsy, taken either during screening or on Cycle 1 Day 1 (ie, a biopsy taken before the first dose of the study drug and before the first dose of combination drug) and the biopsy taken on Cycle 2 Day 8 (± 3) will also be submitted for FRα expression by IHC for biomarker research studies.

If the biopsy procedure is considered to be of significant risk, the biopsy will not be taken. Significant risk procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, or pancreas, and endoscopic procedures extending beyond the esophagus, stomach, or bowel.

Only patients with the required FRα expression levels by IHC (either ≥ 25% or ≥ 50% [Protocol Amendment 4] of tumor staining at ≥ 2+ intensity) will be eligible to enroll in the study. If a patient wishes to enroll and does not have archival tumor tissue available for analysis, the patient must undergo a biopsy to obtain tumor tissue for FRα expression assessment. In this case, this biopsy will also serve as the pre-dose biopsy for the biomarker research study. If a biopsy procedure to obtain tumor tissue for a patient's eligibility assessment is considered to be of significant risk, the patient cannot be enrolled in the study.

The tumor samples will be analyzed for FRα expression in the Companion Diagnostics Pharma Services College of American Pathologists (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and Pathology Services at Ventana Medical Systems, Inc. Samples from patients on Regimens A (Cohorts 1 and 2), B, and C will have their FRα levels assessed using the FOLR1-RPA assay. Samples from patients on Regimens A (Cohort 3), D, and E will have their FRα levels assessed using the FOLR1-IUO assay.

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

7.2. Exploratory Biomarker Studies

Studies in tumor tissue and blood will be performed to explore potential markers of sensitivity and resistance to the mirvetuximab soravtansine combination Regimens. The sections below describe specific activities that are planned, but additional biomarkers/biological pathways may be investigated.

7.2.1. Potential Markers of Drug Response

Cancer is a disease driven by molecular-level changes, which include mutations, DNA rearrangements, and copy number changes, and changes in the expression of proteins involved in key oncogenic pathways. Many of these changes determine or influence the aggressiveness of the disease, its response to therapy, and the development of resistance to treatment. To evaluate how these molecular changes are associated with response to the drug combinations, we will characterize the somatic mutations, gene rearrangements/fusions, and the gene expression profile of archival and biopsy tumor samples using a fit-for-purpose technology such as next-generation sequencing of tumor RNA and DNA. Mirvetuximab soravtansine, carboplatin, and pegylated liposomal doxorubicin target dividing cells; therefore, markers of cell proliferation including, but not limited to, Ki67 will be assessed in tumor samples from all patients. Potential associations between cell proliferation and clinical response will be examined.

Mirvetuximab soravtansine retains the ADCC activity of the parental M9346A antibody. FcγR is the principal leukocyte receptor that mediates ADCC, and FcγR polymorphisms modulate leukocyte ADCC activity. Potential associations between FcγR genotype and clinical response will be examined (Appendix D).

7.2.2. Potential Markers of Drug Resistance

Drug efflux transporters and PgP in particular play an important role in cancer cell resistance to cytotoxic agents, including microtubule-targeting agents. Therefore, PgP expression levels and polymorphisms will be assessed as a marker of drug resistance in tumor tissues for all patients. Potential associations between PgP levels and clinical response will be examined.

7.2.3. Potential Mechanism of Synergy Between Mirvetuximab Soravtansine and Pembrolizumab

In several different tumor types, including melanoma, NSCLC, gastric cancer, and others, biomarkers have been identified that show positive correlation with response to PD-1/PD-L1 inhibitors. These biomarkers include elevated expression of PD-L1, increased number of tumor-infiltrating lymphocytes, and expression of immune-related gene signatures. To assess the potential of these biomarkers for predicting response to the combination of mirvetuximab soravtansine and pembrolizumab, IHC will be carried out for PD-L1 and markers for infiltrating lymphocytes such as CD3, CD4 and CD8, and expression of immune-related gene signatures will be assessed using next-generation sequencing of RNA.

Recent nonclinical studies demonstrated that ADC with maytansinoid payload can enhance lymphocyte infiltration into tumor tissue, which partially contributed to the anti-tumor activity of ADC. Furthermore, a synergistic effect between ADC and multiple immune-checkpoint inhibitors was observed in vivo. Consistent with that, biopsies from patients with HER2-positive breast cancer before and after Kadcyla treatment demonstrated that treatment with Kadcyla resulted in an increased number of tumor-infiltrating T lymphocytes (Muller 2015). To evaluate the effect of mirvetuximab soravtansine and pembrolizumab treatment on immune cells, pre- and post-treatment biopsies will be stained for lymphocyte markers by IHC.

8. STUDY PROCEDURES

8.1. Informed Consent

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

8.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening. All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the patient's routine clinical management and obtained before signing an ICF may be used for screening or baseline purposes, provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Schedule of Clinical Assessments in Appendix A, Appendix B, and Appendix C. A patient is considered enrolled when administered the first dose of drug.

8.3. Confirmation of Disease Diagnosis

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

8.4. Demographic/Medical History

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

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

8.5. Physical Examination, Weight, and Height

Physical examination, height (screening only), and weight must be performed as indicated in the Schedule of Clinical Assessments (Appendix A, Appendix B, and Appendix C).

8.6. Vital Signs

Vital signs will be measured at screening, before dosing on Day 1 of every cycle, and as indicated in Table 26 and Appendix A, Appendix B, and Appendix C.

Table 26: Vital Sign Measurements

	Screen-ing	Day 1 of All Cycles (Pre-dose)[a]	Every 30 Minutes During Mirvetuximab Soravtansine Infusion[b,c]	Immediately After Completion of Mirvetuximab Soravtansine Infusion[d]	4 Hours After End of Mirvetuximab Soravtansine Infusion[c]	At Same Time as ECG Assess-ments[e]	End of Treatment and Follow-up Visits
Blood pressure	●	●	●	●	●	●	●
Pulse	●	●	●	●	●	●	●
Respiratory rate	●	●	●	●	●	●	●
Temperature	●	●	●	●	●		●

a Within 10 minutes before the start of infusion of mirvetuximab soravtansine.
b ± 10 minutes.
c **Cycle 1 only.** If the patient's infusion was well tolerated, the 4-hour post–mirvetuximab soravtansine infusion assessment will not be required in Cycles ≥ 2.
d Within 10 minutes after completion of infusion of mirvetuximab soravtansine.
e Measured pre-dose and within 10 minutes after completion of each set of triplicate ECG readings (pre-dose, end of mirvetuximab soravtansine infusion) to coincide with Cmax PK draw (+ 1 hour window), end of combination drug infusion to coincide with Cmax PK draw (+ 1 hour window), and 24 hours post-infusion (± 2 hours); see also Section 8.7. **Cycles 1 and 3 only.**

8.7. Electrocardiogram

A standard, single 12-lead ECG will be performed within 14 days before Cycle 1 Day 1 to determine study eligibility.

Triplicate ECGs will be performed at 2- to 5-minute intervals. A single ECG will also be performed at the end of treatment visit and as clinically indicated (Appendix A, Appendix B, and Appendix C).

Vital signs (blood pressure, pulse, and respiratory rate) will be measured within 10 minutes of completion of each set of triplicate ECG readings.

8.8. Pulse Oximetry

Pulse oximetry will be performed at screening, before dosing on Day 1 of every cycle, and as indicated in Appendix A, Appendix B, and Appendix C.

8.9. Pulmonary Function Tests

Pulmonary function tests will be performed at screening and in the event of pulmonary symptoms as clinically indicated (Appendix A, Appendix B, and Appendix C).

8.10. Laboratory Assessments

Patients should be in a seated or supine position during blood collection. Screening labs and any required repeat testing will be performed as outlined in the Schedule of Clinical Assessments (Appendix A, Appendix B, and Appendix C) and as clinically indicated.

Note that before each administration of mirvetuximab soravtansine, laboratory results must be reviewed to evaluate potential toxicity.

8.10.1. Clinical Laboratory Panels

A list of clinical laboratory tests is presented in Table 27.

Table 27: Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation Tests	Urinalysis[a]
• Hematocrit • Hemoglobin • WBC (with 5-part differential) • RBC • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN • Calcium • Carbon dioxide • Chloride • Creatinine • Glucose • LDH • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin • Thyroid panel (Regimen D only)[b]	• PT • aPTT • INR	• pH • Ketones • Protein • Glucose • Occult blood • Leukocyte • esterase • Nitrite (Microscopic examination of sediment will be performed only if results of urinalysis dipstick are positive.)

[a] For patients receiving bevacizumab, results from urinalysis should be available before dosing because of the increased risk of proteinuria. The test can be performed up to 48 hours before dosing. If the test result is +2, bevacizumab should be held until a 24-hour urine test is performed.
[b] Thyroid panel should include T3 or free T3, free T4, and TSH; performed every 6 weeks.
BUN, blood urea nitrogen; GFR, glomerular filtration rate; LDH, lactic acid dehydrogenase; RBC, red blood cell count; WBC, white blood cell count.

8.11. Pregnancy Screen

All female patients of childbearing potential will complete a serum beta-human chorionic gonadotropin or urine pregnancy test (not more than 3 days before the first dose of mirvetuximab soravtansine); this test must be negative for the patient to be enrolled and to receive the study drug.

If a female patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Sponsor must be informed immediately, and the patient will be withdrawn from study treatment.

8.12. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group PS (Appendix E) will be assessed during screening and at other times specified in the Schedule of Clinical Assessments (Appendix A, Appendix B, and Appendix C). An assessment is not necessary on Day 1 of Cycle 1 if the screening assessment was obtained within 3 days before Day 1.

8.13. Radiologic Imaging

Radiologic tumor evaluation by CT scan or MRI of chest, abdomen, and pelvis will be performed within 28 days before the first dose and at other time points specified in the Clinical

Schedule of Assessments (Appendix A, Appendix B, and Appendix C). The same radiologic assessment used at screening must be used at all subsequent radiologic evaluations.

8.14. Echocardiogram/Multigated Acquisition Scan

Echocardiograms or MUGA scans will be performed only in patients receiving pegylated liposomal doxorubicin (Regimen C, Appendix B). Echocardiograms or MUGA scans will be performed at screening and every four cycles of treatment or as medically indicated. The same test should be performed throughout the trial. If the patient's left ventricular ejection fraction drops below normal or by at least 15% from the baseline value, treatment with pegylated liposomal doxorubicin should be stopped.

8.15. Tumor Response Assessment

8.15.1. RECIST and CA125

Tumor response for patients with measurable lesions should be assessed using RECIST Version 1.1 (Eisenhauer 2009, Appendix G). Patients with ovarian cancer will have CA125 measured every cycle and at approximately the same time that they undergo radiologic assessment. Patients will have a baseline tumor assessment done within 28 days before Cycle 1 Day 1 and CA125 measured 14 days before Cycle 1 Day 1. Patients with measurable lesions should be assessed using CT scan or MRI approximately every second cycle, from the date of the first dose. For Regimens A, D, and E, this will continue through Week 24, and then scans will be performed every 3 months for up to 1 year from randomization, and then either every 6 months or per standard of care on the basis of symptoms until the 30-day follow-up visit. For Regimen C, the scan frequency will change 1 year after randomization to every 16 weeks or as clinically indicated. Although progression may be determined by the Investigator on the basis of clinical deterioration, every effort should be made to document progression using radiologic methods. The basis for determination of progression per clinical deterioration should be documented.

Patients experiencing CA125 response must have a confirmatory test performed as detailed in the Clinical Schedule of Assessments (Appendix A, Appendix B, and Appendix C). In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

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

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

8.15.2. Immune-Related RECIST (Regimen D Only)

RECIST Version 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial

increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST Version 1.1 will be used with the adaptions outlined in Appendix I. These assessments will be performed on the scans performed for the RECIST assessment (see Section 8.15.1).

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

8.16. Eligibility Based on FRα Expression

Instructions regarding processing and shipment of biopsy samples and archival tissues are detailed in the Laboratory Manual. Tumor samples will be analyzed for FRα expression in the Companion Diagnostics Pharma Services CAP-accredited and CLIA-certified laboratory and Pathology Services at Ventana Medical Systems, Inc. Samples from patients on Regimens A (Cohorts 1 and 2), B, and C will have their FRα levels assessed using the FOLR1-RPA assay. Samples from patients on Regimens A (Cohort 3), D, and E will have their FRα levels assessed using the FOLR1-IUO assay.

All patients must have documented expression of FRα by IHC (≥ 25% or ≥ 50% [Protocol Amendment 4] of tumor staining at ≥ 2+ intensity) before enrollment. Immunohistochemistry may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a new tumor biopsy must be obtained. De-identified pathology reports should be included with sample shipment to ImmunoGen or designee. In Study 0401, the FIH monotherapy study, most patients (98%) had available archival tissue.

8.17. Biopsy of Tumor (Regimen D Only)

A biopsy of tumor tissue will be performed on two occasions: The first biopsy will be performed before the first dose of any study treatment, and the second biopsy will be performed on Cycle 2 Day 8 (± 3) (Section 7.1.1). Instructions regarding processing and shipment of the biopsy sample are detailed in the Laboratory Manual.

9. ASSESSMENT OF SAFETY

9.1. Recording Adverse Events

Adverse events, 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.

However, those AEs that meet seriousness criteria (ie, 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 frequency of AE monitoring increases for patients who experience a DLT, and for patients who discontinue study treatment because of a study-related AE, the reporting time period may be extended. These patients must be followed at least once a week for 4 weeks, and subsequently at

4-week intervals until resolution, stabilization, or chronic state of the AE or laboratory abnormality, whichever comes first (Section 5.10.2).

To ensure the safety of the patient, the Investigator should take appropriate measures to follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the patient stabilizes, or death occurs. 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

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. Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Drug-drug interactions
- Events related to or possibly related to concomitant medications
- Clinically significant abnormalities in physical examination, vital signs, and weight

Adverse events 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 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, causes study discontinuation or constitutes in and of itself an SAE), or require therapy (eg, any hematologic abnormality that requires transfusion or growth factor treatment), 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 laboratory 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

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

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Note that hospitalization is defined as an 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).

9.1.1.3. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

All AESIs should be promptly reported per Section 9.2.1.

9.1.1.4. Mirvetuximab Soravtansine

Mirvetuximab soravtansine has one AESI, which is pneumonitis.

Radiologic findings suggestive of pneumonitis include new onset of any of the following:

- Pulmonary consolidation
- Pulmonary infiltrate
- Reticular infiltrate
- Nodular infiltrate
- Reticulo-nodular infiltrate
- Ground-glass pulmonary infiltrate
- Increased interstitial markings
- Interstitial infiltrate
- Honeycomb appearance

9.1.1.5. Pembrolizumab

Pembrolizumab has two AESIs:

- An overdose of pembrolizumab, as defined in Section 5.14.
- An elevated AST or ALT lab value that is ≥ 3 times the ULN and an elevated total bilirubin lab value that is ≥ 2 times the ULN and, at the same time, an alkaline

phosphatase lab value that is less than 2 times the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note that these criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be found in the Study Manual (or equivalent).

9.1.2. Classification of Adverse Events

All AEs will be evaluated according to the NCI CTCAE Version 4.03 (effective 14 June 2010) Appendix M. If the AE is not listed in the NCI CTCAE, it should be graded on the basis of the description given in Table 28.

Table 28: 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 drug(s) is to be determined by the Investigator on the basis of the definitions listed in Table 29. Relationship should be attributed not only to the combination Regimen, but also to each drug within the combination Regimen.

Table 29: Adverse Event Casual Relationship to Study Drug

Relationship to Study Drug(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 that 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 (de-challenge). Re-challenge information is not required to fulfill this definition. The association of the clinical event, including laboratory test abnormality, must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (de-challenge) should be clinically plausible.

9.2. Reporting of Adverse Events

9.2.1. Reporting of Serious Adverse Events and/or Adverse Events of Special Interest

Any SAE or AESI, regardless of relationship to study medications, that occurs in a patient from the time of informed consent until 30 days after the last study treatment of mirvetuximab soravtansine, bevacizumab, carboplatin, and pegylated liposomal doxorubicin and 90 days after last treatment of pembrolizumab or 30 days following cessation of pembrolizumab if the patient initiates new anticancer therapy, whichever is earlier, must be recorded by the clinical site on an SAE Report Form. The event must also be recorded on the patient's AE eCRF, including the Investigator's assessment of the relationship of the event to the study treatment (mirvetuximab soravtansine and bevacizumab, pegylated liposomal doxorubicin, carboplatin, or pembrolizumab). The Investigator will promptly supply all information requested by the Sponsor (or Contract Research Organization [CRO]) regarding the event.

The Investigator must submit the SAE Report Form to ImmunoGen Pharmacovigilance (or designee). This form must be completed and submitted within 24 hours after the Investigator learns of the event, using the contact information printed on the SAE Report Form and contained within the SAE Report Form Completion Guidelines. Follow-up information must 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 used, but rather should be recorded as an outcome of a specific SAE term. Initially, the event term of "death NOS" (not otherwise specified) can be used until the actual cause of death is known. If an autopsy was performed, the autopsy report should be provided.

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

- As described in Section 9.1.1.3, serious or non-serious events, any symptom, or sign potentially suggestive of an AESI must be promptly reported on an SAE Report Form. Please refer to the SAE Completion Guidelines and SAE Report Form for additional information.

It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any suspected unexpected serious adverse reaction (SUSAR) report (Council for International Organizations of Medical Sciences [CIOMS]/MedWatch report) regarding the study drug(s) and as submitted to the appropriate national regulatory agencies.

The Investigator (or Sponsor or designee) must promptly report all SUSARs to the IRB/IEC for review in accordance with national regulations. The IRB/IEC notification of the SUSAR may be 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 the IRB/IEC should be retained in the site's Investigator Site File.

In addition to the CIOMS/MedWatch reports, the Sponsor will notify (through annual update to the Investigator Brochure) the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study drug(s).

9.2.2. Reporting of Disease Progression

Disease progression and/or progression of the disease under study is an anticipated occurrence in oncology drug development and is part of the efficacy objectives of this study. It is not an AE per se and should not be used as an AE term.

However, any medical event or condition that is untoward in the context of PD and/or for the specific patient's disease course should be reported as an AE and assessed accordingly by the Investigator.

Progression of disease with a fatal outcome does not need to be reported as an AE term. However, the applicable protocol eCRF page(s) pertaining to death must be completed immediately to record the PD/death.

9.2.3. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria for this study. A WCBP, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months) must agree to use effective contraceptive methods while on study treatment and for the following time periods:

- At least 12 weeks after the last dose of mirvetuximab soravtansine
- At least 6 months after the last dose of bevacizumab, carboplatin, or pegylated liposomal doxorubicin
- At least 4 months after the last dose of pembrolizumab

The Sponsor must be notified immediately in the event of a pregnancy occurring during the course of the study and through the following time periods:

- 30 days after a patient's last dose of mirvetuximab soravtansine, bevacizumab, carboplatin, or pegylated liposomal doxorubicin
- 120 days after cessation of pembrolizumab or 30 days after cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier

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 Form and submitted according to the contact information on the form and the form 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, requires that a SAE Report Form also be submitted.

10. STUDY ACTIVITIES

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

10.1. Screening Visit

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

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. These include radiologic tumor assessment, physical examinations, hematology, serum chemistry results, coagulation studies, urinalysis, or other assessments that may be considered part of the normal 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.

10.2. End of Treatment Visit

Patients may voluntarily withdraw from the study treatment at any time for any reason, and without prejudice to further treatment. In addition, patients may be withdrawn by the Investigator if the Investigator does not feel that 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 5.10.5.

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

10.3. Follow-up Assessments

10.3.1. Safety Follow-up

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

All 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. Reporting of SAEs is detailed in Section 9.2.1.

10.3.2. Response Follow-up

Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST Version 1.1 (Appendix G) every 12 weeks (± 3 weeks) until documentation of PD or until the patient starts subsequent anti-cancer therapy, whichever comes first.

11. STATISTICAL METHODS

All statistical analyses will be performed using the most recent release of SAS statistical software, unless otherwise noted. For categorical variables, the number (n) and percentage of each category within a parameter will be presented. For continuous variables, the sample size (n), mean, median, standard deviation, and 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.

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the CRC after the MTD or an RP2D for each combination Regimen has been determined. Results from this data review could enable dose selection for additional studies with mirvetuximab soravtansine, before the completion of this study.

A statistical analysis plan will fully describe the planned analyses for this trial and will be finalized before database lock. All analyses will be performed for any patient who receives study drug. All analyses for anti-tumor activity will use Cycle 1 Day 1 as the start time.

11.1. Sample Size

Ascending doses of mirvetuximab soravtansine and bevacizumab, carboplatin, pegylated liposomal doxorubicin, or pembrolizumab are to be evaluated to identify the MTD for each of the four doublet combination Regimens. The actual number of patients accrued during the Dose Escalation phase will be determined largely by the findings observed during the course of their treatment. Regimen A (mirvetuximab soravtansine + bevacizumab) is expected to enroll 16 patients, whereas Regimen B (mirvetuximab soravtansine + carboplatin) and Regimen C (mirvetuximab soravtansine + pegylated liposomal doxorubicin) are expected to enroll

22 patients. Regimen D (mirvetuximab soravtansine + pembrolizumab) is expected to enroll 16 patients. For all four Regimens, up to 10 additional patients will be treated at the MTD.

Overall, the Dose Escalation phase of the study is expected to enroll approximately 76 to 120 patients.

Following MTD determination, there will be a Dose Expansion phase for Regimen A (mirvetuximab soravtansine + bevacizumab) and Regimen D (mirvetuximab soravtansine + pembrolizumab).

Regimen A (Mirvetuximab Soravtansine + Bevacizumab)

Patients enrolled in the Dose Expansion phase will be allocated to three Dose Expansion Cohorts according to prior exposure to bevacizumab as follows: 1) Dose Expansion Cohort 1: bevacizumab naïve; 2) Dose expansion Cohort 2: bevacizumab pre-treated; and 3) Dose Expansion Cohort 3: with one to three prior therapies including one prior therapy with bevacizumab (per Protocol Amendment 5).

For the bevacizumab-naïve Cohort (Cohort 1), assuming a response rate of 55%, there is a 94.2% probability of detecting at least 8 responders if 20 patients are recruited. The response rate assumption is based on an ORR of 53% observed with the standard of care therapy of paclitaxel in combination with bevacizumab in patients with platinum-resistant EOC (Bevacizumab [package insert] 2014).

For the bevacizumab-pretreated Cohort (Cohort 2), assuming a response rate of 50%, there is a 91.2% probability of detecting at least 14 responders if 35 patients are recruited.

For the bevacizumab expansion (Cohort 3), assuming a response rate of 50%, there is a 95.4% probability of detecting at least 24 responders if 60 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 20 to 40 of 60 patients.

Responses Observed, 60 Patients	90% Exact Confidence Interval for True ORR
20/60 (33%)	(23%, 45%)
21/60 (35%)	(25%, 46%)
22/60 (37%)	(26%, 48%)
23/60 (38%)	(28%, 50%)
24/60 (40%)	(29%, 51%)
25/60 (42%)	(31%, 53%)
26/60 (43%)	(32%, 55%)
27/60 (45%)	(34%, 56%)
28/60 (47%)	(36%, 58%)
29/60 (48%)	(37%, 60%)
30/60 (50%)	(39%, 61%)
31/60 (52%)	(40%, 63%)
32/60 (53%)	(42%, 64%)
33/60 (55%)	(44%, 66%)
34/60 (57%)	(45%, 68%)
35/60 (58%)	(47%, 69%)
36/60 (60%)	(49%, 71%)
37/60 (62%)	(50%, 72%)
38/60 (63%)	(52%, 74%)
39/60 (65%)	(54%, 75%)
40/60 (67%)	(55%, 77%)

Regimen D (Mirvetuximab Soravtansine + Pembrolizumab)

In the Dose Expansion phase for Regimen D, a total of 35 patients will be enrolled at FRα ≥ 50% of tumor staining at intensity ≥ 2+ and 11 patients with a FRα 25% to 49% of tumor staining at intensity ≥ 2+. Assuming a response rate of 50%, there is a 91.2% probability of detecting at least 14 responders if 35 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 12 to 18 of 35 patients.

Responses Observed, 35 Patients	90% Exact Confidence Interval for True ORR
12/35 (34%)	(21%, 50%)
13/35 (37%)	(24%, 52%)
14/35 (40%)	(26%, 55%)
15/35 (43%)	(29%, 58%)
16/35 (46%)	(31%, 61%)
17/35 (49%)	(34%, 64%)
18/35 (51%)	(36%, 66%)

Regimen E (Mirvetuximab Soravtansine + Bevacizumab + Carboplatin)

In Regimen E (Triplet), approximately 50 patients will be enrolled to ensure that 40 patients will be treated at the MTD. Assuming a response rate of 60%, there is a 92.6% probability of detecting at least 20 responders if 40 patients are recruited. In addition, the 90% confidence interval for true ORR is given in the table below if the observed number of responders is 20 to 26 of 40 patients.

Responses Observed, 40 Patients	90% Exact Confidence Interval for True ORR
20/40 (50%)	(36%, 64%)
21/40 (52.5%)	(38%, 66%)
22/40 (55%)	(41%, 69%)
23/40 (57.5%)	(43%, 71%)
24/40 (60%)	(46%, 73%)
25/40 (62.5%)	(48%, 75%)
26/40 (65%)	(51%, 77%)

Overall, the Dose Expansion phase is expected to enroll up to 211 patients. Assuming that approximately 90% of enrolled patients in the Dose Expansion phase will be evaluable, the study is expected to accrue approximately 311 to 355 patients.

Safety will be evaluated continuously, separately, and in aggregate in the expansion Regimens. If at any time ≥ 33% of patients treated in an expansion Regimen experience a Cycle 1 DLT, further enrollment to that Cohort will stop, and the CRC will be convened. The CRC will review all available safety and PK data to determine how further dosing should proceed. If the CRC determines that the dose should be revised during the expansion phase for a given expansion Cohort, that Cohort will enroll additional patients at the revised dose to fulfill the enrollment goal.

11.2. Pharmacokinetic Analyses

Pharmacokinetic parameters, if feasible, will be derived from plasma concentrations of mirvetuximab soravtansine total antibody, DM4, and *S*-methyl DM4 using the actual sampling times and non-compartmental methods. Plasma concentration data and PK parameters will be summarized by cohort, cycle, and dose level as appropriate.

Plasma or serum concentrations for pegylated liposomal doxorubicin, bevacizumab, carboplatin, and pembrolizumab will summarized by cohort, cycle, and dose level as appropriate.

Individual and mean (standard deviation) plasma concentration-time profiles will be presented graphically by cohort, cycle, and dose level as appropriate.

11.3. Immunogenicity Assessment

The percentage of patients who screen positive for ADA, the percentage of patients who are confirmed positive, and antibody titer data will be summarized by cohort and time point using descriptive statistics. The potential impact of immunogenicity against mirvetuximab soravtansine on PK, safety, and anti-tumor activity will be explored.

11.4. Safety Analyses

Adverse events, concomitant medications, and results from physical examinations will be listed.

Adverse events will also be coded with the Medical Dictionary for Regulatory Activities (MedDRA; Version 18.0 or later) and summarized by System Organ Class and Preferred Term.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD; 01 June 2012 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

All hematology, blood chemistry, vital signs, and ECG results will be listed by patient for each assessment, and descriptive statistics will be tabulated for select criteria. Changes from baseline in hematology, blood chemistry, vital signs, ECHO/MUGA scan (Regimen C), and ECG results 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 humoral responses against the M9346A antibody component or against the DM4 component (ADA).

11.5. Anti-tumor Activity

Objective Response Rate

The best objective response will be determined by the Investigator for each patient as either CR, PR, SD, or relapsed disease/PD using RECIST Version 1.1, CA125, and irRECIST Version 1.1 (Regimen D) evaluations (see Appendix G, Appendix H, and Appendix I). Confirmed objective responses for patients in the Dose Escalation phase will be summarized by dose assigned and the dose at which the response occurred. For the Dose Expansion phase, responses will be reported overall and separately for each expansion Cohort. Response rate will be calculated as the number of CRs or PRs divided by the number of response-evaluable patients. To meet the definition of response evaluable, patients must have undergone radiologic assessment at baseline, received at least one dose of combination treatment, and must have had at least one post-dose tumor assessment.

Duration of Response

Duration of response, defined as the time from initial response until PD, will be estimated for all patients who achieve a confirmed objective response (PR or CR) using the Kaplan-Meier method. Results will be summarized by dose cohort assigned and dose at which the response occurred.

Progression-Free Survival

Progression-free survival, defined as the time from initiation of study drug until PD or death, whichever occurs first, will be estimated using the Kaplan-Meier method. The median PFS and PFS rate at 6 months will be presented. Results will be summarized by dose cohort.

For DOR and PFS calculations, patients not achieving the endpoint will be censored at the time of the last endpoint assessment. Median response times and associated 95% confidence intervals will be presented.

12. QUALITY CONTROL AND ASSURANCE

Clinical sites will be monitored by ImmunoGen or its designee to ensure the accuracy of data against source documents. Data will be captured using validated electronic systems. Adverse events will be coded using MedDRA Version 18.0 or later. Concomitant medications will be coded using the WHO-DD 01 June 2012 or later version. Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals (eg, laboratory manuals and pharmacy manuals) will be provided to aid consistency in data collection and reporting across sites.

All required data will be entered into the clinical and/or safety database in accordance with Code of Federal Regulations (CFR) 21 Part 11 and International Conference on Harmonisation (ICH) E6. The database will include an audit trail to document all data processing and activity on each data field by each user. Users will be given restricted access according to their role in the study through a password-protected environment. All missing data will be explained.

Data entered in the system must be verifiable against source documents and will be reviewed manually for validity and completeness against the source documents by a clinical monitor from ImmunoGen or its designee. If necessary, the study site will be contacted for corrections or clarifications.

13. ADMINISTRATIVE CONSIDERATIONS, STUDY MONITORING, AND DATA MANAGEMENT

13.1. Investigators and Study Administrative Structure

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

The Investigator should ensure that all persons assisting with the study are qualified and trained before performing delegated study-related duties. The Investigator must maintain a list of site personnel to whom he or she has delegated significant study-related duties.

13.2. 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 study ICF, and the screening ICF (the latter ICF is applicable for sites requesting permission to pre-screen for FRα positivity 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 title page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year or per institutional guidelines. The IRB/IEC must be notified of study completion, 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. Adverse events that are subject to expedited reporting to the US FDA or other regulatory agencies (SUSARs) must be submitted promptly to the IRB/IEC.

13.3. Ethical Conduct of the Study

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor and Investigators abide by the Declaration of Helsinki; GCP as described in 21 CFR Parts 50, 56, and 312; and ICH GCP guidelines.

13.4. Patient Information and Consent

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

After the patient has been given ample time to read and ask questions regarding the informed consent document 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 at the time of consent orally and by the personally dated signature of the patient or by the patient's legally authorized representative(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the patient or the patient's legally authorized representative(s). The original signed and dated consent document will be retained by the Investigator. Patient confidentiality will be maintained as outlined in Section 13.5.

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

A model of the full study ICF will be provided to the sites separately from this protocol.

A screening ICF may be used to confirm a patient's consent to analyze archived or new tumor samples for FRα expression. If the IHC screening assay is positive for FRα, the patient will be

provided the full study consent, and only after signing the full study ICF will additional study-specific screening tests be performed. A model of the screening ICF will be provided to the sites separately from this protocol.

Participants must be re-consented to the most current version of the ICF(s) per IRB/IEC guidelines during their participation in the study.

13.5. Patient Confidentiality

Protected health information (eg, patient name) will not be collected and provided to the Sponsor and/or CRO. If protected health information appears on any documents, it must be redacted before a copy of the document is supplied to the Sponsor and/or CRO. Study findings stored on a computer will be stored in accordance with local data protection laws. Patient blood and tissue samples sent to outside laboratories and/or CROs (eg, IHC laboratory) are identified only by study patient number to ensure maintenance of confidentiality. The patient consent form will state that publications resulting from this study will not refer to patient names or include any other information that might disclose the identity of the patient. Patients will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC, monitors, auditors, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for monitoring, audit, or 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.

13.6. Study Monitoring

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

The study will be monitored by the Sponsor or its designee. On-site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (email, letter, telephone, and facsimile).

13.7. Case Report Forms and Study Reports

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

13.8. Critical Documents

Before ImmunoGen initiates the study (ie, obtains informed consent from the first patient), it is the Investigator's responsibility to ensure that the following documents are available to ImmunoGen or 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 Form/ICF, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB/IEC-approved Patient Information Form/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
- 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 available; these are the responsibility of ImmunoGen.

13.9. Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/ favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. If applicable regulatory authorities permit, the IRB/IEC 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. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

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

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

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

Prospective protocol waivers or exemptions are not permitted.

13.10. End of Study

The end of the study will occur when either all patients have discontinued, all patients have been followed to progression, or 2 years after the last patient has been enrolled into the study, whichever occurs first.

All patients who are actively enrolled in the study when the study ends will be given the opportunity to continue on study treatment until progression, either under this protocol or via a suitable rollover protocol.

13.11. Study Termination

13.11.1. Study Termination

If the Sponsor, an Investigator, or Study Clinical Monitor discovers conditions arising during the study that indicate that the clinical investigation should be halted because of 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 test material may be made at any time.

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

13.11.2. Site Termination

A specific site may be terminated separate from the general study for conditions including, but not limited to, the following:

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

13.12. Access to Source Documentation

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 CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

13.13. Data Generation and Analysis

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

13.14. Retention of Data

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

- A minimum of 2 years has elapsed following the last approval of a marketing application and there are no pending or contemplated marketing applications.

  Or

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

  Or

- The record retention policies and guidelines for countries in which the study is being conducted are followed (whichever is longer).

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

13.15. Financial Disclosure

All investigators (eg, Investigator and sub-Investigators) will 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 completed. The appropriate form will be provided to the Investigator by the Sponsor, and the form will be signed and dated by the Investigator before the start of the study.

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

13.16. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product and 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 CRFs completed as part of the study. This information may be disclosed to other physicians who are conducting similar studies and to 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. SCHEDULE OF CLINICAL ASSESSMENTS – REGIMENS A, B, AND E

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 1	Days 8 & 15	Days 15-21	Day 1	Day 2	Days 8 & 15	Day 1		
Informed consent	●[a]												
Demography	●[a]												
Medical history	●[a]												
Confirm disease diagnosis/ current stage and prognostic index evaluation	●[a]												
Record baseline signs and symptoms	●	●											
Review and document IC/EC	●												
Confirm patient continues to satisfy IC/EC		●											
Confirm patient meets re-treatment criteria					●			●			●		
Height	●[a]												
Physical examination[b]	●[c]	●		●	●	●		●			●	●	●
Weight	●[c]	●			●			●			●	●	●
Vital signs[d]	●[c]	●	●		●			●	●		●	●	●
Pulmonary function tests[e]	●[c]												
Pulse oximetry	●	●[r]	●	●	●[r]	●		●[r]	●	●	●[r]	●	●
ECOG PS	●	●[o]			●			●			●	●	●
Hematology and chemistry [f]	●[c]	●		●	●	●		●		●	●	●	●
Coagulation (PT/INR/aPTT)[f]	●[c]	●			●			●			●		●
Urinalysis[g, f]	●[c]	●			●			●			●		●
Pregnancy test (urine or serum)[h]	●	●			●			●			●		●
Ophthalmic examinations[i]	●[c]	Every other cycle (from point at which toxicity first reported)										●	●
Schirmer test[i]	●	For patients who experience treatment-emergent eye disorders, the Schirmer test will be repeated at the first on-study ophthalmic examination and subsequently if clinically indicated.											
Ocular symptom assessment[i]	●	●			●			●			●	●	●
Radiologic tumor assessments	●[a]	Every 6 weeks ± 1 week)[j]										●[k]	●[k]
CA125	●[c]	Every 3 weeks (± 1 week)[j]										●[k]	●[k]
12-Lead ECG[l]	●[c]	●	●					●	●			●	●[m]

Activity	Screen-ing	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 1	Days 8 & 15	Days 15-21	Day 1	Day 2	Days 8 & 15	Day 1		
Mirvetuximab soravtansine administration		●			●			●			●		
Bevacizumab or carboplatin or bevacizumab and carboplatin administration		●			●			●			●		
AE and SAE assessments	●[n]	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medications	●[a]	●	●	●	●	●	●	●	●	●	●	●	●
Lubricating artificial tears administration[p]		●	●	●	●	●	●	●	●	●	●		
Corticosteroid eye drop administration[q]		●	●	●	●	●		●	●	●	●		

[a] Within 28 days before the start of Cycle 1 Day 1.
[b] Directed physical examination is acceptable while on study treatment. A complete physical examination, including assessment 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 end of treatment.
[c] Screening labs (hematology, clinical chemistry, and urinalysis) and ECG may be performed within 14 days before the first dose before the start of Cycle 1 Day 1. Repeat testing on Cycle 1 Day 1 is not required if tests were obtained up to 4 days before dosing and are within acceptable ranges.
[d] Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol (Section 8.6).
[e] Pulmonary function tests should include spirometry, diffusion capacity, and lung volumes. Pulmonary function tests will be performed at screening and in the event of pulmonary symptoms as clinically indicated.
[f] Day 1 laboratory assessments may be performed up to 4 days before study agent administration. Laboratory results must be reviewed before each scheduled administration of mirvetuximab soravtansine and/or bevacizumab or carboplatin. In the event of severe toxicity, laboratory tests must be repeated as necessary until the toxicity resolves or stabilizes.
[g] For patients receiving bevacizumab, results from urinalysis should be available before dosing because of the increased risk of proteinuria. The test can be performed up to 48 hours before dosing. If the test result is +2, bevacizumab should be held until a 24-hour urine test is performed.
[h] For WCBP, a urine or serum pregnancy test will be performed at screening, before dosing on Day 1 of every cycle (it can be performed up to 3 days before Day 1), and at the 30-day follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
[i] Baseline ophthalmic exams will be performed by a board-certified ophthalmologist and will include the following: visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and corneal photography (when feasible to document corneal abnormalities). A Schirmer test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and subsequently if clinically indicated. Ophthalmic exam may be performed within 14 days before Cycle 1 Day 1. Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms, mirvetuximab soravtansine will be stopped, and the subject will be referred to an ophthalmologist for a complete examination (detailed in full protocol). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye exams. All patients will have a complete ophthalmologic exam performed at the end of treatment visit or 30-day follow-up visit.
[j] Radiologic tumor assessment by CT scan or MRI is to be performed every 6 weeks (± 1 week) through Week 24 and then every 3 months (± 1 month) for up to 1 year after randomization, and then either every 6 months (± 1 month) or per standard of care based on symptoms, until the 30-day follow-up visit for Regimens

A, B, and E. CA125 will be measured every 3 weeks and at approximately the same time as the radiologic assessment. Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

[k] If a patient discontinues before documentation of PD, a tumor assessment is to be performed at the end of treatment visit or 30-day follow-up visit, if not performed within the previous 6 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST Version 1.1 every 12 weeks (± 3 weeks) until documentation of PD, start of subsequent anti-cancer therapy, or for up to 1 year after Cycle 1 Day 1, whichever comes first.

[l] Single ECG will be performed at screening, end of treatment, and as clinically indicated. On-study ECGs will be performed in triplicate at each of the following 4 time points in Cycles 1 and 3: pre-dose (baseline), within 1 hour before first dose of mirvetuximab soravtansine; post-dose, end of mirvetuximab soravtansine infusion to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); post-dose, immediately after the end of infusion of the last drug in the Regimen to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); 24 ± 2 hours after infusion of mirvetuximab soravtansine to coincide with PK blood draw (Section 8.7).

[m] As clinically indicated.

[n] All AEs and SAEs from the time of informed consent are recorded.

[o] ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days before Day 1.

[p] Lubricating eye drops are administered every day of the cycle. Patients should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops (Section 5.8.3).

[q] Corticosteroid eye drops will be administered on Days 1 through 8 of each cycle (Section 5.8.2).

[r] Performed before dosing.

APPENDIX B. SCHEDULE OF CLINICAL ASSESSMENTS – REGIMEN C

Activity	Screening	Cycle 1				Cycle 2			Cycle 3				Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Day 2	Days 8 & 15	Day 22	Day 1		
Informed consent	●[a]														
Demography	●[a]														
Medical history	●[a]														
Confirm disease diagnosis/current stage and prognostic index evaluation	●[a]														
Record baseline signs and symptoms	●	●													
Review and document IC/EC	●														
Confirm patient continues to satisfy IC/EC		●													
Confirm patient meets re-treatment criteria						●			●				●		
Height	●[a]														
Physical examination[b]	●[c]	●		●		●	●		●				●	●	●
Weight	●[c]	●				●			●				●	●	●
Vital signs[d]	●[c]	●	●			●			●	●			●	●	●
Pulmonary function tests[e]	●[c]														
Pulse oximetry	●	●[p]	●	●		●[p]	●		●[p]	●	●		●[p]	●	●
ECOG PS	●[c]	●[o]				●			●				●	●	●
Hematology and chemistry[f]	●[c]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Coagulation (PT/INR/ aPTT)[f]	●[c]	●				●			●				●		●
Urinalysis [f]	●[c]	●				●			●				●		●
Pregnancy test (urine or serum)[g]	●	●				●			●				●		●
ECHO/MUGA[h]	●												Every four cycles or as	●	

Activity	Screening	Cycle 1				Cycle 2			Cycle 3				Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Day 2	Days 8 & 15	Day 22	Day 1		
													clinically indicated		
Ophthalmic examinations[i]	●	Every other cycle (from point at which toxicity first reported)[i]												●	●
Schirmer test[i]	●	For patients who experience treatment-emergent eye disorders, the Schirmer test will be repeated at the first on-study ophthalmic examination and subsequently if clinically indicated.													
Ocular symptom assessment[i]	●	●				●			●				●	●	●
Radiologic tumor assessments	●[a]	Every 8 weeks (± 1 week)[j]												●[k]	●[k]
CA125	●[c]	Every 4 weeks (± 1 week)[j]												●[k]	●[k]
12-Lead ECG[l]	●[c]	●	●						●	●				●	●[m]
Mirvetuximab soravtansine administration		●				●			●				●		
Pegylated liposomal doxorubicin administration		●				●			●				●		
AE and SAE assessments	●[n]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medications	●[a]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Lubricating artificial tears administration[q]		●	●	●	●	●	●	●	●	●	●	●	●		
Corticosteroid eye drop administration[r]		●	●	●		●	●		●	●	●		●		

[a] Within 28 days before the start of Cycle 1 Day 1.
[b] Directed physical examination is acceptable while on study treatment. A complete physical examination, including assessment 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 end of treatment.
[c] Screening labs (hematology, clinical chemistry, and urinalysis), CA125, and ECG may be performed within 14 days before the first dose before the start of Cycle 1 Day 1. Repeat testing on Cycle 1 Day 1 is not required if tests were obtained up to 4 days before dosing and are within acceptable ranges.
[d] Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol Section 8.6.
[e] Pulmonary function tests should include spirometry, diffusion capacity, and lung volumes. Pulmonary function tests will be performed at screening and in the event of pulmonary symptoms as clinically indicated.
[f] Day 1 laboratory assessments may be performed up to 4 days before study agent administration. Laboratory results must be reviewed before each scheduled administration of mirvetuximab soravtansine and/or pegylated liposomal doxorubicin. In the event of severe toxicity, laboratory tests must be repeated as necessary until the toxicity resolves or stabilizes.

[g] For WCBP, a urine or serum pregnancy test will be performed at screening, before dosing on Day 1 of every cycle (it can be performed up to 3 days before Day 1), and at the 30-day follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.

[h] The same assessment technique should be used throughout the study. If the patient's left ventricular ejection fraction drops below normal or by at least 15% from the baseline value, pegylated liposomal doxorubicin should be stopped. To be performed at screening, every four cycles or as clinically indicated, and at the end of treatment visit.

[i] Baseline ophthalmic exams will be performed by a board-certified ophthalmologist and will include the following: visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and corneal photography (when feasible to document corneal abnormalities). A Schirmer test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and subsequently if clinically indicated. Ophthalmic exam may be performed within 14 days before Cycle 1 Day 1. Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms, mirvetuximab soravtansine will be stopped, and the subject will be referred to an ophthalmologist for a complete examination (detailed in full protocol). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye exams. All patients will have a complete ophthalmologic exam performed at the end of treatment visit or 30-day follow-up visit.

[j] Radiologic tumor assessment by CT scan or MRI is to be performed every 8 weeks (± 1 week) for Regimen C up until 1 year after randomization, and thereafter every 16 weeks (± 4 weeks) or as clinically indicated. CA125 will be measured every 4 weeks and at approximately the same time as radiologic assessment. Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

[k] If a patient discontinues before documentation of PD, a tumor assessment is to be performed at the end of treatment visit or 30-day follow-up visit, if not performed within the previous 6 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST Version 1.1 every 12 weeks (± 3 weeks) until documentation of PD, start of subsequent anti-cancer therapy, or for up to 1 year after Cycle 1 Day 1, whichever comes first.

[l] Single ECG will be performed at screening, end of treatment, and as clinically indicated. On-study ECGs will be performed in triplicate at each of the following 4 time points in Cycles 1 and 3: pre-dose (baseline), within 1 hour before first dose of mirvetuximab soravtansine; post-dose, end of mirvetuximab soravtansine infusion to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); post-dose, immediately after the end of infusion of the last drug in the Regimen to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); 24 ± 2 hours after infusion of mirvetuximab soravtansine to coincide with PK blood draw (Section 8.7).

[m] As clinically indicated.

[n] All AEs and SAEs from the time of informed consent are recorded.

[o] ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days before Day 1.

[p] Performed before dosing.

[q] Lubricating eye drops are administered every day of the cycle. Patients should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops (Section 5.8.3).

[r] Corticosteroid eye drops will be administered on Days 1 through 8 of each cycle (Section 5.8.2).

APPENDIX C. SCHEDULE OF CLINICAL ASSESSMENTS – REGIMEN D

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 1	Days 8 & 15	Days 15-21	Day 1	Day 2	Days 8 & 15	Day 1		
Informed consent	●[a]												
Demography	●[a]												
Medical history	●[a]												
Confirm disease diagnosis/current stage and prognostic index evaluation	●[a]												
Record baseline signs and symptoms	●	●											
Review and document IC/EC	●												
Confirm patient continues to satisfy IC/EC		●											
Confirm patient meets re-treatment criteria					●			●			●		
Biopsy of tumor		●[b]				●[b]							
Height	●[a]												
Physical examination[c]	●[d]	●		●	●	●		●			●	●	●
Weight	●[d]	●			●			●			●	●	●
Vital signs[e]	●[d]	●	●		●			●	●		●	●	●
Pulmonary function tests[f]	●[d]												
Pulse oximetry	●	●[s]	●	●	●[s]	●		●[s]	●	●	●[s]	●	●
ECOG PS	●[d]	●[g]			●			●			●	●	●
Hematology and chemistry [h]	●[d]	●		●	●	●		●		●	●	●	●
Thyroid panel[i]	●[d]	●						●			●	●	●
Coagulation (PT/INR/aPTT)[h]	●[d]	●			●			●			●		●
Urinalysis[h]	●[d]	●			●			●			●		●
Pregnancy test (urine or serum)[j]	●	●			●			●			●		●
Ophthalmic examinations[k]	●[d]	Every other cycle (from point at which toxicity first reported)[k]										●	●
Schirmer test[k]	●	For patients who experience treatment-emergent eye disorders, the Schirmer test will be repeated at the first on-study ophthalmic examination and subsequently if clinically indicated.											
Ocular symptom assessment[k]	●	●			●			●			●	●	●
Radiologic tumor assessments	●[a]	Every 6 weeks (± 1 week)[l]										●[m]	●[m]

Activity	Screen-ing	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4	End of Treatment	30-Day Follow-up (+ 14 Days)
		Day 1	Day 2	Days 8 & 15	Day 1	Days 8 & 15	Days 15-21	Day 1	Day 2	Days 8 & 15	Day 1		
CA125	●[d]	Every 3 weeks (± 1 week)[l]										●[m]	●[m]
12-Lead ECG[n]	●[d]	●	●					●	●			●	●[o]
Mirvetuximab soravtansine administration		●			●			●			●		
Pembrolizumab administration		●			●			●			●		
AE and SAE assessments	●[p]	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medications	●[a]	●	●	●	●	●	●	●	●	●	●	●	●
Lubricating artificial tears administration[q]		●	●	●	●	●	●	●	●	●	●		
Corticosteroid eye drop administration[r]		●	●	●	●	●		●	●	●	●		

[a] Within 28 days before the start of Cycle 1 Day 1.

[b] A minimum of two new tumor tissue samples is required during this study (a baseline sample and Cycle 2 Day 8 sample). Before screening, all patients must submit a tumor tissue sample (pre-screening sample) for analysis of FRα. The prescreening sample may either be archived tumor tissue samples (formalin-fixed, paraffin embedded blocks, or slides sectioned from such blocks), or if archival samples are not available, new biopsy samples must be provided. If a new biopsy sample is required for a baseline sample, it will be taken before the first dose of study drug; if a new biopsy sample was provided for FRα pre-screening, it can be used as the baseline sample. A second tumor tissue sample will be taken on Cycle 2 Day 8 (± 3 days). Once the FRα status of a patient has been established, new biopsies should be taken only if, in the opinion of the Investigator, there is no concern of significant risk to the patient (Section 7.1.1).

[c] Directed physical examination is acceptable while on study treatment. A complete physical examination, including assessment 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 end of treatment.

[d] Screening labs (hematology, clinical chemistry, and urinalysis), CA125, and ECG may be performed within 14 days before the first dose before the start of Cycle 1 Day 1. Repeat testing on Cycle 1 Day 1 is not required if tests were obtained up to 4 days before dosing and are within acceptable ranges.

[e] Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol (Section 8.6).

[f] Pulmonary function tests should include spirometry, diffusion capacity, and lung volumes. Pulmonary function tests will be performed at screening and in the event of pulmonary symptoms as clinically indicated.

[g] ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days before Day 1.

[h] Day 1 laboratory assessments may be performed up to 4 days before study agent administration. Laboratory results must be reviewed before each scheduled administration of mirvetuximab soravtansine and pembrolizumab. In the event of severe toxicity, laboratory tests must be repeated as necessary until the toxicity resolves or stabilizes.

[i] The thyroid panel includes T3 or free T3, free T4, and TSH. Testing will be performed every 6 weeks during the study.

[j] For WCBP, a urine or serum pregnancy test will be performed at screening, before dosing on Day 1 of every cycle (it can be performed up to 3 days before Day 1), and at the 30-day follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.

[k] Baseline ophthalmic exams will be performed by a board-certified ophthalmologist and will include the following: visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and corneal photography (when feasible to document corneal abnormalities). A Schirmer test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination

and subsequently if clinically indicated. Ophthalmic exam may be performed within 14 days before Cycle 1 Day 1. Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms, mirvetuximab soravtansine will be stopped, and the subject will be referred to an ophthalmologist for a complete examination (detailed in full protocol). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye exams. All patients will have a complete ophthalmologic exam performed at the end of treatment visit or 30-day follow-up visit.

[l] Radiologic tumor assessment by CT scan or MRI is to be performed every 6 weeks (± 1 week) through Week 24 and then every 3 months (± 1 month) for up to 1 year after randomization, and then either every 6 months ((± 1 month) or per standard of care based upon symptoms, until the 30-day follow-up visit. CA125 will be measured every 3 weeks and at approximately the same time as radiologic assessment. Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

[m] If a patient discontinues before documentation of PD, a tumor assessment is to be performed at the end of treatment visit or 30-day follow-up visit, if not performed within the previous 6 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST Version 1.1 every 12 weeks (± 3 weeks) until documentation of PD, start of subsequent anti-cancer therapy, or for up to 1 year after Cycle 1 Day 1, whichever comes first.

[n] Single ECG will be performed at screening, end of treatment, and as clinically indicated. On-study ECGs will be performed in triplicate at each of the following 4 time points in Cycles 1 and 3: pre-dose (baseline), within 1 hour before first dose of mirvetuximab soravtansine; post-dose, end of mirvetuximab soravtansine infusion to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); post-dose, immediately after the end of infusion of the last drug in the Regimen to coincide with C_{max} and PK blood draw (within 1 hour after this blood draw); 24 ± 2 hours after infusion of mirvetuximab soravtansine to coincide with PK blood draw (Section 8.7).

[o] As clinically indicated.

[p] All AEs and SAEs from the time of informed consent are recorded.

[q] Lubricating eye drops are administered every day of the cycle. Patients should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops (Section 5.8.3).

[r] Corticosteroid eye drops will be administered on Days 1 through 8 of each cycle (Section 5.8.2).

[s] Performed before dosing.

APPENDIX D. BLOOD SAMPLE COLLECTION FOR PHARMACOKINETICS, IMMUNOGENICITY, AND BIOMARKER ASSESSMENTS – REGIMENS A, B, C, D, AND E

Regimen	Cycles 1 and 3					Cycles 2, 4, 5, and 6					End of Treatment and 30-Day Follow-up				
	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
Day 1, pre-dose[a]	●	●	●	●	●	●	●	●	●	●					
Day 1, end of mirvetuximab soravtansine infusion[b]	●	●	●	●	●	●	●	●	●	●					
Day 1, after combination infusion[c]	●	●	●	●	●	●	●	●	●	●					
Day 1, 6 hours[d]	●	●	●	●	●										
Day 2, 24 hours[e]	●	●	●	●	●										
Day 3, 48 hours[f]	●	●	●	●	●										
Day 8[g]	●	●	●	●	●										
Day 15[g]	●	●	●	●	●										
Day 22[g]			●												
Study visit[g]											●	●	●	●	●

[a] Predose samples to be collected before the start of the first infusion, and to also include a sample for the FcγR biomarker assessment. All patients will be genotyped for FcγR alleles via peripheral blood mononuclear cell analysis at Cycle 1 Day 1.

[b] Immediately after completion of mirvetuximab soravtansine infusion (+ 10 minutes).

[c] Cohorts A, B, C, and D: sample collected immediately after completion of bevacizumab/carboplatin/pegylated liposomal doxorubicin/pembrolizumab infusion (+ 10 minutes). Cohort E: samples to be collected immediately after completion of bevacizumab infusion (+ 10 minutes) and immediately after completion of carboplatin infusion (+ 10 minutes).

[d] 6 hours after completion of mirvetuximab soravtansine infusion (+ 20 minutes).

[e] 24 hours after completion of mirvetuximab soravtansine infusion (± 2 hours).

[f] 48 hours after completion of mirvetuximab soravtansine infusion (± 2 hours).

[g] A single sample collected when safety assessments are performed.

APPENDIX E. PEMBROLIZUMAB BACKGROUND

Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley 2005, Hunder 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 (cluster of differentiation 28) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald 2005, Okazaki 2001).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain–associated protein kinase, which are involved in the CD3 T-cell signaling cascade (Okazaki 2001, Chemnitz 2004, Sheppard 2004, and Riley 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins (Parry 2005, Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in EOC.

Nonclinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma. In such studies, tumor infiltration by CD8+ T cells and increased interferon γ, granzyme B, and perforin expression were observed, indicating that the mechanism underlying the anti-tumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T-cell function in vivo. Experiments have confirmed the in

vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, and in combination with chemotherapy, in syngeneic mouse tumor models.

Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose– and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W
- Clinical data showing meaningful improvement in benefit-risk, including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2,262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W with 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W with 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All of these studies demonstrated flat dose– and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W regimen provided similar responses to the highest doses studied. Subsequently, flat dose exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose, independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a physiologically based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed dosing has advantages of reduced dosing complexity and reduced potential for dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

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

Sources: Muggia 1997 and 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 G. RESPONSE DEFINITION (RECIST VERSION 1.1)

Source: 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.
- Magnetic resonance imaging 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 scan (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. If 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 < 10 mm are considered non-pathological and are not to be recorded or followed.

- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT scan or MRI) are considered non-measurable.

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

- Target lesions are to be selected on the basis of their size (lesions with the longest diameter) to represent all involved organs, and to be those that lend themselves to reproducible repeated measurements.
- On occasion, the largest lesion may not lend itself to reproducible measurement; in this case, the next-largest lesion that 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 beyond the 5 target lesions are to be identified as non-target lesions and recorded at baseline.

- Measurements of these lesions are not required, but the presence, absence, and 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 be considered for response assessment only 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 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 lesions.

Bone Lesions: Bone scan, positron emission tomography (PET) scan, and 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 scan or MRI be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

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

- There has been prior documented progression in the lesion by at least 2 sequential CT scans or MRIs performed after the completion of radiation.

OR

- There is 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 Scan or MRI: This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT scan 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. Magnetic resonance imaging is also acceptable in certain situations (eg, for body scan), except for lungs.

CA125: Tumor marker CA125 alone cannot be used to assess response or determine progression; however, it will be followed. CA125 measurements should be scheduled to approximately coincide with radiologic assessment (every 6 weeks ± 1 week). Patients whose CA125 is above the ULN at baseline will need to have their values normalize to ≤ the ULN, in addition to complete disappearance of measurable or evaluable disease, to be considered in CR.

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

Time Point Assessments

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

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

At all post-baseline evaluations, the baseline classification (target or 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 lesions, if any, are to be documented separately.

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

Time Point Response Criteria

Target Lesion Time Point Response (TPR)	
Complete response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response (PR)	At least 30% decrease in the SLD of target lesions, taking as reference the baseline SLD.
Progressive disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the smallest (nadir) SLD since and including baseline. In addition to the relative increase of 20%, the SLD 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 (NA)	No target lesions identified at baseline.
Unable to evaluate (UE)	One or more target lesions are not imaged, and the remainder of the SLD compared with the nadir SLD 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 SLD 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 ULN. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of CA125 above the normal limits if CA125 at baseline is above the ULN.
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 (NA)	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 SLD 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 not assessed or incompletely assessed for new lesion.

Determining Overall Time Point Response

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

* Patients with an overall response of CR or PR must have a repeat tumor assessment performed no fewer than 4 weeks after the criteria for response are first met.
Any = CR, PR, SD, PD, NA, or UE.
The overall response at a given time point does not depend on the overall response assigned at any prior time point.

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 at a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no fewer 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 H. GYNECOLOGIC CANCER INTERGROUP CRITERIA FOR EVALUATION OF CA125

Source: 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 studies so that response can be measured by either RECIST or CA125 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

Greater than or equal to 50% reduction in CA125 levels from baseline:

- The response must be confirmed and maintained for at least 28 days.
- The pre-treatment sample must be ≥ 2.0 times the ULN and within 2 weeks before starting treatment.
- The date of response corresponds to the date when the CA125 level is first reduced by 50%.

To calculate CA125 responses accurately, the following rules apply:

1. Intervening samples and the 30-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
2. Variations within the normal range of CA125 levels will not interfere with the response definition.

Timing of CA125 Assessments

The GCIG recommends that CA125 measurements be taken at specific time intervals:

- The first sample is collected within 2 weeks before treatment is started.
- Later samples are collected at intervals of 2 to 4 weeks during treatment and at intervals of every 2 or 3 months during follow-up.
- 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 CA125 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 CA125 response definition has been produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities for relapse (eg, surgery and chemotherapy), any CA125 response results from both treatments. CA125 cannot distinguish between the effects of each treatment. To calculate response rates in protocols, an intent-to-treat analysis should be used that includes all patients with an initial CA125 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 CA125 response and whose CA125 level falls to within the normal range.

APPENDIX I. RESPONSE DEFINITION (IMMUNE-RELATED RECIST) (REGIMEN D ONLY)

RECIST Version 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab; therefore, RECIST Version 1.1 will be used with the following adaptations:

If radiologic imaging indicates PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment as described below while awaiting radiologic confirmation of progression.

If repeat imaging shows < 20% tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed.

If repeat imaging confirms PD due to any of the scenarios list below, patients will be discontinued from study therapy (exception noted in Section 5.10.6.4.3).

In determining whether the tumor burden has increased or decreased, the site study team should consider all target lesions and non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared with nadir.
- Non-target disease resulting in initial PD is worse (qualitative).
- New lesion resulting in initial PD is worse (qualitative).
- Additional new lesion(s) since last evaluation.

In patients who have initial evidence of radiologic PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating PD
- No decline in ECOG PD
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the

observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Immune-Related RECIST Assessment of Disease

Immune-related RECIST is RECIST Version 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. Immune-related RECIST will be used by the site Investigator/local radiology review to assess tumor response and progression and make treatment decisions. These data will be collected in the clinical database.

Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST Version 1.1	Repeat imaging at > 4 weeks at site to confirm PD.	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at > 4 weeks to confirm PD per physician discretion only.	Discontinue treatment.
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required	NA
Repeat tumor imaging shows SD, PR, or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments.	Continue study treatment at the local site Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or is clinically stable per Investigator's discretion. Next tumor image should occur according to the every 3 weeks (XX ± 7 days) imaging schedule for the first year and every Y weeks (XX ± 7 days) after the first year.

- In determining whether the tumor burden has increased or decreased, local study site investigators should consider all target lesions and non-target lesions (please refer to the irRECIST Tip Sheet). Patients who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.
- For a **clinically stable** patient with first radiologic evidence of PD by RECIST Version 1.1 (ie, **unconfirmed progression of disease**), it is at the discretion of the site investigator to continue treating the patient with the assigned treatment per protocol until PD is confirmed at least 28 days after the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan, the patient will be discontinued from study treatment. If radiologic progression is not confirmed by irRECIST per the site, the patient may continue on treatment and follow the

regular imaging schedule intervals until progression is confirmed at a later time point by the site.

  - **NOTE**: If a patient has confirmed radiologic progression (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the patient is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals outlined in Appendix C.

- Any patient deemed **clinically unstable** should be discontinued from study treatment at first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.
- In patients who discontinue study therapy without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every Y weeks (XX days ± 7 days), until (1) the start of new anti-cancer treatment, (2) PD, (3) death, or (4) the end of the study, whichever occurs first.

The irRECIST data will be collected in the clinical database.

APPENDIX J. CALVERT FORMULA FOR CARBOPLATIN DOSING

The formula for calculating carboplatin dosage is based upon the patient's glomerular filtration rate (GFR; in mL/min) and carboplatin injection target area AUC (in mg/mL*min).

Calvert formula for carboplatin dosing:

Total Dose (mg) = (Target AUC) × (GFR + 25).

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m².

Calculations may be based on a patient's actual body weight subject to appropriate consideration of other comorbid conditions; however, GFR should be capped at 125 mL/min for carboplatin dosing. For more information regarding carboplatin dosing, please refer to https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf

APPENDIX K. BODY SURFACE AREA CALCULATION

To prepare the correct pegylated liposomal doxorubicin doses for administration to each patient, the body surface area must be calculated using the following formula or equivalent:

Body Surface Area (m^2) = ([Height {cm} × Weight {kg}] / 3600)½

The value calculated will be used to determine the quantity of chemotherapeutic drug to be placed in the infusion bag. The weight used for calculation of body surface area should be obtained before first treatment and thereafter should be modified only for significant (≥ 10%) changes in body weight not influenced by weight gain or loss attributed to fluid retention (exceptions may be made for institutional policies).

APPENDIX L. ADJUSTED IDEAL BODY WEIGHT CALCULATION

Adjusted Ideal Body Weight (AIBW)

$IBW^a + 0.4\ (\text{Actual Weight} - IBW^a)$,

where:

Ideal Body Weight (IBW)

$IBW^a\ (\text{Male}) = 0.9H^a - 88$, and

$IBW^a\ (\text{Female}) = 0.9H^a - 92$.

[a] H = height in cm; W = weight in kg.

APPENDIX M. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.03 GRADING FOR SELECTED ADVERSE EVENTS

Source: CTCAE Version 4.03, National Cancer Institute, 14 June 2010; NIH Publication No 09-5410.

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

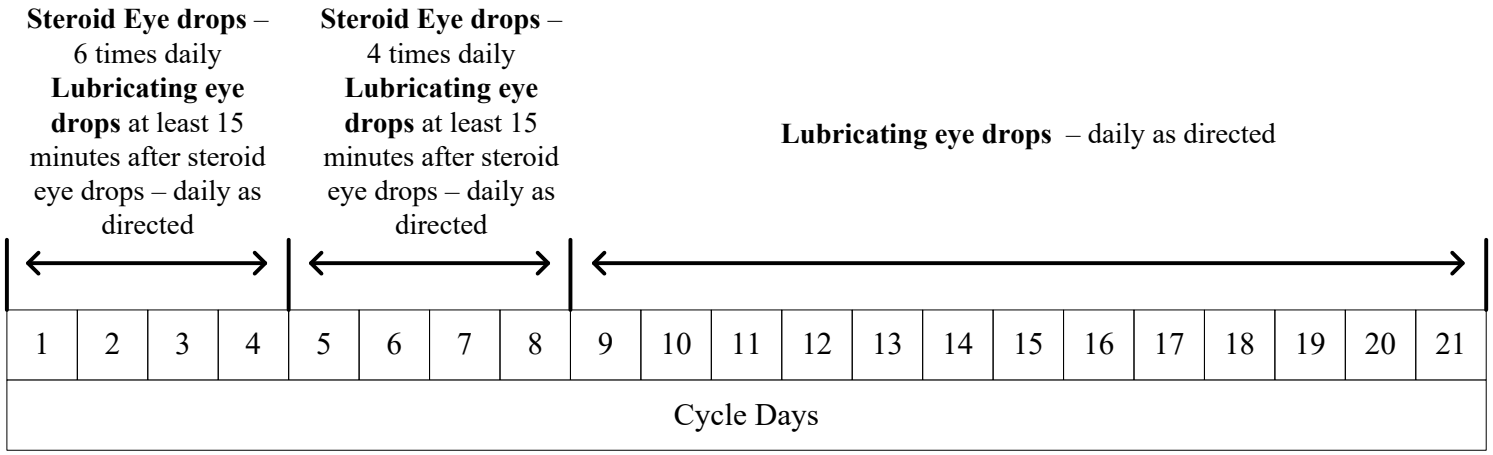
ADL = activities of daily living.

APPENDIX N. EXAMPLES OF SENSITIVE IN VIVO CYTOCHROME P450 SUBSTRATES AND CYTOCHROME P450 SUBSTRATES WITH NARROW THERAPEUTIC RANGE (28 JULY 2011)

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

Source: FDA drug development resources.
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classSub. Accessed 09 June 2016.

APPENDIX O. SCHEMA FOR ADMINISTRATION OF STUDY-REQUIRED EYE DROPS



* Lubricating drops are continued if dose is held and/or cycle is delayed.

APPENDIX P. HISTORY OF AMENDMENTS

Amendment 1 Summary of Key Changes

The primary reasons for amending the protocol were to revise the table for management of potential infusion-related reactions, to clarify drugs for premedication before mirvetuximab soravtansine infusion, and to add a section for reporting a pregnancy occurring during the study.

Amendment 1A Summary of Key Changes

The primary reasons for amending the protocol were to revise inclusion criteria for WCBP, to clarify the maximum dose of each drug administered for each regimen and dosing schedule, and to add monitoring and management guidelines for peripheral neuropathy.

The following key changes were made to Amendment 1:

1. Barrier contraceptive with spermicide and partner's latex condom were removed from the list of acceptable highly effective contraceptive methods. The length of time for the use of contraceptives after the last study dose of bevacizumab, carboplatin, or pegylated liposomal doxorubicin was changed to 6 months.
2. The maximum allowable dose of each drug is as follows: mirvetuximab soravtansine 6.0 mg/kg AIBW every 3 weeks, mirvetuximab soravtansine 6.0 mg/kg every 4 weeks, bevacizumab 15 mg/kg every 3 weeks, bevacizumab 10 mg/kg every 2 weeks, carboplatin AUC6 every 3 weeks, and pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks.
3. Monitoring and management guidelines for peripheral neuropathy were added to Section 5.9.

Amendment 1B Summary of Key Changes

The primary reasons for amending the protocol were to correct discrepancies between sections of the protocol and the Schedules of Clinical Assessments in the appendices and to clarify study assessments.

The following key changes were made in Amendment 1B:

1. The PK and immunogenicity section (Section 6) was updated to provide additional clarity on the time points for PK and immunogenicity sample collection.
2. The vital signs and ECG sections (Section 8.6 and Section 8.7) were updated to provide additional clarity on time points.
3. Study activities (Section 10) were updated. Most of the section was removed because this information is included in the Schedules of Clinical Assessments in the appendices. Information regarding screening, end of treatment, and follow-up visits remains in the section.
4. The Schedules of Clinical Assessments and pharmacokinetics (Appendix A, Appendix B, Appendix C, and Appendix D) were updated to correct discrepancies with the protocol text.

Amendment 2 Summary of Key Changes

The primary reasons for amending the protocol were to add Regimen D, to revise the time period for reporting AEs, and to clarify PK time points.

The following key changes were made to Amendment 1A:

1. Regimen D was added to the protocol. This regimen is mirvetuximab soravtansine in combination with pembrolizumab. The entire protocol was updated to include this regimen. There is a Dose Escalation part and a Dose Expansion for Regimen D.
2. The time period for reporting AEs and SAEs was updated. In this amendment, AEs and SAEs regardless of causality are recorded and reported from the time of informed consent until at least 30 days after the last dose of study medication.
3. The PK section (Section 6.1) was updated to clarify the timing of PK sample collection for each drug administered. The blood collection schedule was updated to separate each drug.
4. Adverse events of special interest were added.
5. Overdose information for pembrolizumab was added.
6. The concomitant medications section was updated to include medications metabolized by CYP3A, vaccines (Regimen D only), and systemic steroids (Regimen D only).
7. Typographical errors were corrected.

Amendment 3 Summary of Key Changes

The primary reasons for amending the protocol were to add prophylactic corticosteroid eye drops, to modify the inclusion criteria for prior therapies, and to clarify management guidelines for ocular AEs.

1. The premedication section (Section 5.8.1) was updated to include prophylactic corticosteroid eye drops. A schema for the administration schedule for eye drops was added (Appendix O). Additionally, information about lubricating eye drops was moved from the concomitant medication section (Section 5.13) to the premedication section (Section 5.8.1).
2. Inclusion criteria to define the therapies considered to be prior therapies were modified.
3. Inclusion criteria for prior therapies for Regimen A Dose Expansion were changed.
4. Exclusion criterion 12 for all patients was revised to specify that patients with a history of non-infectious pneumonitis that required steroids or who have current pneumonitis will be excluded.
5. Exclusion criterion 14 was updated to add that patients with severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients will be excluded.
6. The ocular management guidelines were updated for clarification.
7. Discontinuation criterion for carboplatin to allow for discontinuation of carboplatin after 6 cycles at the discretion of the Investigator was added.
8. Dose modification guidelines for bevacizumab were updated.

9. The AE section was updated to provide further clarification.
10. The section for patient informed consent was updated for clarification.
11. Typographical errors were corrected.

Amendment 4 Summary of Key Changes

The primary reason for this amendment was to add a cohort of patients with EOC, primary peritoneal cancer, or fallopian tube cancer who will receive a triplet dosing regimen of mirvetuximab soravtansine + carboplatin + bevacizumab. The amendment also enabled early closure, due to slow enrollment, of the bevacizumab-naïve cohort (Cohort 1) and removal of Regimen A Expansion Cohort 3 (endometrial cancer).

1. The protocol was updated for the new triplet cohort: The study title was updated to reflect the new scope of the study; a rationale for the triplet cohort was added to Section 1.10; the study objectives and endpoints were updated (Section 2); the number of patients, study design, and study schema were adjusted and new eligibility criteria added (Section 3 and Section 4); PK sample collections were added (Section 6); and the statistical analysis was updated (Section 11).
2. The number of patients to be recruited into Expansion Cohort 1 was adjusted from 35 bevacizumab-naïve patients to approximately 20 bevacizumab-naïve patients (Section 4.1.5), and the statistical analysis was updated (Section 11).
3. Clarified the procedures for tumor sample collections including the timing of the collection, and a window for the Cycle 2 Day 8 sample was added (Section 7.1.1 and Section 8.17).
4. Removed the Endometrial Expansion Cohort 3. This change was made throughout the protocol.
5. The patient FRα status for patients enrolled into the Expansion Cohorts was increased from FRα ≥ 25% to FRα ≥ 50% of tumor staining at ≥ 2 + intensity. This change was primarily made in the inclusion criteria (Section 3.1.2).
6. Reduced the scan frequency for patients receiving Regimen A and Regimen B, after they have been receiving study drug for 24 weeks, from every 6 weeks to every 12 weeks, and then reduced the frequency further to every 3 months for patients who remain on study for more than one year from randomization.
7. Provided greater clarity around the definition of *platinum sensitive* in the inclusion criteria for Regimens B and E (Section 3.1.1.2).
8. Updated the background information on pembrolizumab (Section 1.5.1 and Appendix E).
9. Updated the dose modification guidelines for pembrolizumab (Section 5.10.4.5).

Amendment 5 Summary of Key Changes

The primary reason for this amendment was to add an additional cohort (Cohort 3) to Regimen A, which will include patients with one to three prior therapies who may be either platinum resistant or platinum sensitive, and who may or may not have received prior therapy with bevacizumab. Further, the amendment includes the change of the investigational product name from IMGN853 to the International Non-proprietary Name of mirvetuximab soravtansine. The amendment also removed the alternative dosage schedule for Regimen A because it was not enrolled.

1. The protocol was updated to reflect a new Cohort (Cohort 3) in Regimen A based on clinical experience with Regimen A Cohorts 1 and 2. This includes the study title (Phase 1b/2), rationale for the new Cohort (Section 1.10), Study Objectives and Endpoints (Section 2), Study Population/Inclusion and Exclusion Criteria (Section 3), Study Overview and Schema (including diagram) (Section 4.1.1), and Sample Size (Section 11.1).
2. The alternative dosing schedule for Regimen A was removed because this schedule did not enroll. Text was removed from (Section 4.1.3.1), and Table 2 and Appendix C were deleted.
3. The AIBW justification was removed for calculating the mirvetuximab soravtansine dose because the use of AIBW is now established and no longer needs justification (Section 5.8.4.1, Appendix L, and Appendix K).
4. The mirvetuximab soravtansine administration section was amended to include a special note to ensure that mirvetuximab soravtansine is administered first when used in combination with other study treatments (Section 5.8.4.3).
5. Monitoring of Ocular disorders was updated for safety information guidelines and clarification around study visits (Section 5.9.2.1 and Table 8).
6. Monitoring of Non-infectious Pneumonitis was updated for safety information guidelines (Section 5.9.3 and Table 11).
7. Re-treatment criteria were updated to reflect specifications for Regimen E (Section 5.10.1).
8. Pregnancy testing after study discontinuation after a CR was updated (Section 5.10.6.4.2).
9. Myocarditis was added as an AE that would cause discontinuation from pembrolizumab (Section 5.10.6.4.4 and Table 25).
10. Guidelines on reporting an overdose from any study treatment were updated (Section 5.1.4.1).
11. The methodology used to assess the tumor FRα expression levels was defined and updated (Section 7.1.1).
12. The Potential Markers of Drug Resistance section was updated to align with objectives and endpoints and to improve overall clarity (Section 7.2.1).

13. Eligibility based on FRα expression was updated to provide clear guidance on the methods used, and Regimen A Cohort 3 was added to this section (Section 8.16).
14. The safety sections were updated for consistency with program and ImmunoGen standards (Section 9.1, Section 9.1.1.1, Section 9.1.1.2, Table 29, Section 9.1.1.3, Section 9.2.1, and Section 9.2.4).
15. The sample size section was updated for the new cohort and to provide better clarity around patient numbers in Regimens D and E (Section 11.1).
16. The PK section was updated to include a description of the analysis of the PK samples, including the substances to be analyzed and indication of the parameters to be calculated from the analysis (Section 11.2).
17. The immunogenicity analysis section was updated to improve clarity around the calculation of ADA-positive results (Section 11.3).
18. The patient confidentiality section was updated to provide details on protected health information and Investigator responsibilities (Section 13.5).
19. The study procedures section and the Schedule of Clinical Assessment tables were aligned and streamlined for internal consistency. Associated footnotes were amended and updated (Section 8, Appendix A, Appendix B, and Appendix C).