CLINICAL STUDY PROTOCOL

Study Title:	FORWARD 1: A Randomized, Open Label Phase 3 Study to Evaluate the Safety and Efficacy of Mirvetuximab Soravtansine (IMGN853) Versus Investigator's Choice of Chemotherapy in Women with Folate Receptor α–positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer
Study Number	0403
Study Phase:	3
Product Name:	Mirvetuximab soravtansine (IMGN853)
IND Number:	111,915
Indication:	Folate Receptor α–positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer
Investigator/Trial Location:	Multinational, Multicenter trial
Sponsor:	ImmunoGen, Inc. 830 Winter Street Waltham, MA 02451 USA
Sponsor Contact:	Karim Malek, MD. Medical Director, Clinical Development Phone: (781) 895-0263 E-mail: Karim.Malek@Immunogen.com
Original Protocol Date:	18 August 2015
Amendment No. and Date:	Amendment 1: 01 September 2015 Amendment 2: 23 September 2015 Amendment 3: 20 October 2015 Amendment 4: 01 February 2016 Amendment 4A: 05 April 2016 Amendment 5: 17 August 2016 Amendment 6: 19 September 2016 Amendment 7: 04 November 2016 Amendment 8: 08 May 2017

Sponsor Contact List

	PRIMARY CONTACTS
Primary Medical Monitor	Karim Malek, MD Tel: (781) 895-0263 Karim.Malek@immunogen.com
Clinical Scientists	Binaifer Balsara Phone: (781) 895-0164 Binaifer.Balsara@immunogen.com
Trial Management	Donna-Lee Destouche Tel: (781) 895-0219 Donna-Lee.Destouche@immunogen.com

SPONSOR SIGNATURE PAGE

Karim S Malek, MD
Karim S Malek, MD (May 8, 2017)

May 8, 2017

Karim Malek, MD
830 Winter Street
Waltham, MA 02451
United States of America
Tel: (781) 895-0263
FAX: (781) 895-0612

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for mirvetuximab soravtansine. I have read the ImmunoGen Protocol #0403 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 of Investigator

_____
Signature of Investigator

_____
Date

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIBW	Adjusted ideal body weight
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC_{0-24}	Area under the time-concentration curve from time 0 to 24 hours
BIRC	Blinded independent review committee
BRCA	Breast cancer susceptibility gene
BSA	Body Surface Area
BUN	Blood urea nitrogen
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response/remission
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
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
DNA	Deoxyribonucleic acid
DOR	Duration of response

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOC	Epithelial Ovarian Cancer
EORTC	European organization for research and treatment of cancer
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FIH	First-In-Human
FOLR1, FRα	Folate receptor 1/Folate receptor alpha
FOSI	Fact-ovarian symptom index
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HFS	Hand-Foot Syndrome
HIV	Human Immunodeficiency Virus
IA	Interim analysis
IC	Investigator's choice
IC_{50}	Half maximal (50%) inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMGN	ImmunoGen
IND	Investigational New Drug
INR	International Normalized Ratio

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA scan	Multigated Acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next Generation Sequencing
nM	Nanomolar
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PET	Positron Emission Testing
PFS	Progression-free Survival
PFS2	Time to Second Disease Progression
PFT	Pulmonary Function Tests
PgP	P-Glycoprotein
PK	Pharmacokinetics
PLD	Pegylated Liposomal Doxorubicin
PR	Partial Response/remission
PRO	Patient-reported Outcomes
PS	Performance Status
PT	Prothrombin Time
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QoL	Quality of Life
QTc	Corrected QT interval

Abbreviation or Specialist Term	Explanation
RBC	Red Blood Cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SoD	Sum of Diameters
SOC	Standard of Care
SOP	Standard Operating Procedure
SSC	Schedule Selection Committee
SC	Steering Committee
STD	Severely Toxic Dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TPR	Time Point Response
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell (count)
WCBP	Woman of Child Bearing Potential
WHO	World Health Organization
WHO-DD	World Health Organization –Drug Dictionary

PROTOCOL SYNOPSIS

Title of Study: FORWARD1: A Randomized, Open Label Phase 3 Study to Evaluate the Safety and Efficacy of Mirvetuximab Soravtansine (IMGN853) Versus Investigator's Choice of Chemotherapy in Women with Folate Receptor α–positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer

Number of Patients (planned): Approximately 333 patients

Study Center(s): approximately 130 centers globally

Studied Period (months): Approximately 42 months (including follow up): First patient enrolled: 02-Mar-2016 (amendment 4) First patient dosed: 03-Mar-2016 First patient enrolled in Phase 3: 24-Jan-2017	**Phase of Development:** 3

Purpose/Rationale:

Mirvetuximab soravtansine (IMGN853) is a specific, targeted antibody drug (maytansinoid) conjugate (ADC) that binds with high affinity to folate receptor alpha (FRα), a glycosylphosphatidylinositol-linked protein, which is highly expressed on the surface of solid tumors, particularly epithelial ovarian cancer (EOC), endometrial cancer, and non-small cell lung carcinoma (NSCLC). IMGN853 consists of a humanized anti-FRα monoclonal antibody attached via a disulfide containing linker to the cytotoxic maytansinoid, N2'-[4-[(3-carboxypropyl) dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine (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, IMGN853 binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against tumor cells expressing folate receptor 1 (FOLR1). IMGN853 additionally demonstrates significant activity against FRα-positive xenografts, with partial and complete remissions observed in ovarian cancer and NSCLC models. Together with the selective upregulation of FRα in solid tumors, these results provide the rationale for exploring the clinical utility of IMGN853.

EOC patients often present with advanced disease, and have limited prognosis. Despite considerable improvements in primary therapy, 80% of the patients with advanced EOC are expected to relapse during or after treatment with platinum-containing regimens (Ledermann 2010). Treatment of patients with recurrent EOC is less standardized than treatment of newly diagnosed patients.

A recent retrospective study demonstrated that progression-free survival (PFS) and overall survival (OS) decrease by more than 50% as patients move from the first to the fifth relapse (Hanker 2012). Therefore, there is a clear need for new therapies that can improve the outcomes of this patient population, even though several agents are approved for platinum-resistant EOC, including pegylated liposomal doxorubicin (PLD), topotecan, paclitaxel, and more recently bevacizumab in combination with chemotherapy

IMGN853 has a 44% confirmed overall response rate [95% confidence interval (CI): 20% to 70%] and median PFS of 6.7 months (95% CI: 3.9 to 11 months) in the subset of 16 patients

with FRα–positive (medium/high expression) platinum-resistant EOC with one to three prior regimens treated as part of a 46 patient expansion cohort in the Phase 1 study (IMGN853 study 401) (Moore 2016). Adverse events occurring in > 20% of patients in this cohort included diarrhea, blurred vision, fatigue, nausea, vomiting, and peripheral neuropathy, and were mostly low grade. Blurred vision is likely related to corneal keratopathy, transient microcysts that form on the cornea, causing temporary astigmatism. In the initial part of the expansion cohort, blurred vision occurred in 54.5% of patients and was mostly Grade 2, data presented at ASCO 2015 (Moore 2015). The latter half expansion cohort was associated with lower frequency (38.5%) and grade of blurred vision, mostly Grade 1. This improvement may be explained by the use of more effective management procedures, and implementation of concomitant use of preservative-free lubricating eye drops that was first recommended in September 2014 then mandated in April 2015 (Section 1.7.1). Following the implementation of these improved management procedures, the rate of blurred vision in the platinum-resistant EOC expansion cohort is now near the 35% that was targeted by the primary objective of exploring an every four-week dosing schedule in the Phase 2 trial (Section 1.7.1 and Appendix K). Based on these findings the every four-week dosing schedule was not explored further.

Objectives:

Primary Objective:

- To compare the progression free survival (PFS) of patients randomized to IMGN853 versus selected standard of care chemotherapy, as assessed by the blinded independent review committee (BIRC), in the intent to treat (ITT) population (defined as all randomized patients) and in the high FRα subgroup (≥ 75% of tumor staining at ≥2+ intensity)

Key Secondary Objectives:

- To compare the ORR of patients randomized to IMGN853 versus selected standard of care chemotherapy
  - Primary analysis of ORR will be based on BIRC assessments. ORR based on investigator's assessment will be analyzed as sensitivity analysis
- To compare the primary patient-reported outcome (PRO) endpoint using QLQ-OV28 assessments from patients randomized to IMGN853 versus selected standard of care chemotherapy as described in Section 11.7
- To compare the OS of patients randomized to IMGN853 versus selected standard of care chemotherapy

Other Secondary Objectives:

- To compare the safety and tolerability of IMGN853 with that of selected standard of care chemotherapy
- To compare the duration of response (DOR) of patients randomized to IMGN853 versus selected standard of care chemotherapy
  - Primary analysis of DOR will be based on BIRC assessments. DOR based on investigator's assessment will be analyzed as sensitivity analysis
- To compare the CA-125 response rate per Gynecologic Cancer Intergroup (GCIG)

CA-125 criteria of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)

- To compare the PFS of patients randomized to IMGN853 versus selected standard of care chemotherapy, as assessed by the investigator
- To evaluate the pharmacokinetics (PK) of IMGN853
- To assess the immunogenicity of IMGN853 (Anti-drug antibodies, ADA)
- To assess PRO using the EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L, and eight-item FACT-ovarian symptom index (FOSI) questionnaires

Exploratory Objectives:

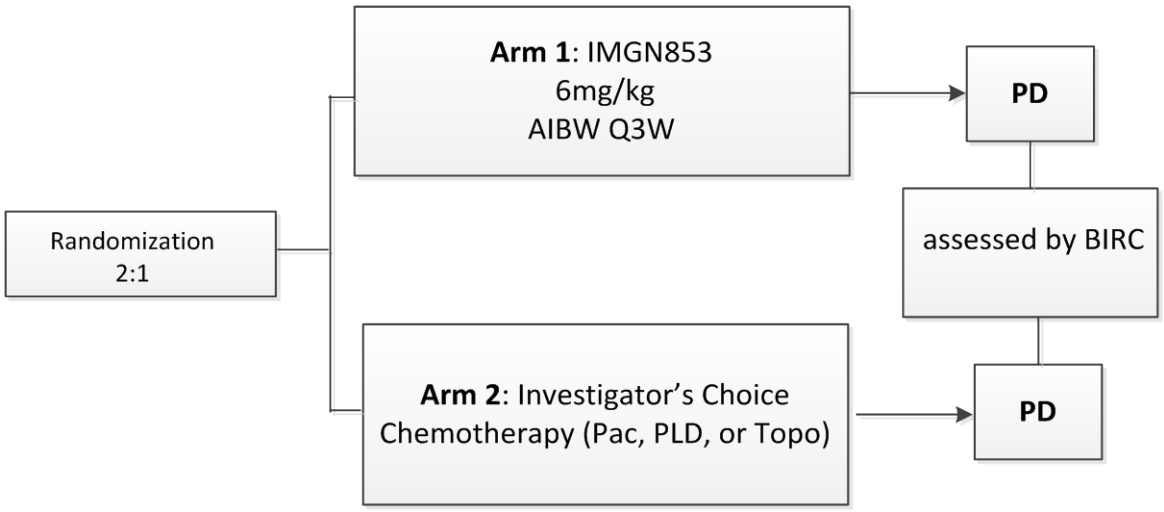
- To evaluate potential biomarkers in blood and tumor tissue that might predict response to IMGN853
- To compare the time to second disease progression (PFS2) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)

Study Design Overview and Schema:

This Phase 3, open label, randomized study is designed to compare the efficacy of IMGN853 to that of selected standard of care chemotherapy (Investigator's choice) in patients with FRα–positive advanced EOC, primary peritoneal cancer or fallopian tube cancer.

In this study, patients are randomized 2:1 to Arm 1: IMGN853 6 mg/kg AIBW Q3W; or Arm 2: Investigator's choice (IC) chemotherapy: weekly paclitaxel every four weeks, PLD administered once every four weeks; or topotecan administered either on Days 1, 8, and 15 every four weeks or for five consecutive days every three weeks. Patients are stratified according to the number of prior lines of therapy (1 or 2 vs. 3), FRα levels (high, defined as ≥ 75% of tumor staining at ≥2+ intensity, vs. medium, defined as ≥ 50% and < 75% at ≥ 2+ intensity), and IC chemotherapy (Paclitaxel, PLD, or Topotecan).

Study Schema:



Abbreviations: Pac: paclitaxel; PLD: pegylated liposomal doxorubicin; Topo: topotecan; BIRC: Blinded Independent Review Committee

Patients enrolled in Arm 1 (IMGN853) receive study drug at 6 mg/kg AIBW Q3W whereas

patients enrolled in Arm 2 (IC chemotherapy) receive paclitaxel, PLD, or topotecan as determined by the investigator prior to randomization. Paclitaxel is administered at 80 mg/m^2 as a 1-hour intravenous (IV) infusion on Days 1, 8, 15 and 22 of a four-week cycle. PLD is administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a four-week cycle. After Cycle 1, if tolerated, PLD can be delivered as a one-hour infusion. Topotecan will be administered at 4 mg/m^2 as a 30 min IV infusion on Days 1, 8 and 15 of a four-week cycle. Alternatively, a 1.25 mg/m^2 dose can be administered over 30 minutes on Days 1–5 of a three-week cycle.

Patients will continue to receive study treatment until they present with progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, (as assessed by the BIRC), develop unacceptable toxicity or withdraw consent, whichever comes first, or until the Sponsor terminates the study.

Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans are performed at Screening and subsequently every six weeks for the first 36 weeks then every twelve weeks until PD, death or the initiation of subsequent anti-cancer therapy, whichever occurs first. All patients who discontinue study treatment for any reason are followed every three months until death, lost to follow-up or withdrawal of consent for survival follow-up.

Study Eligibility (Refer to Section 3.1 for complete eligibility criteria):

Key Inclusion Criteria

- Patients must have been diagnosed with Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer.
- Patients must have platinum-resistant ovarian cancer, defined as progression within 6 months from completion of a minimum of four cycles of platinum-containing therapy. This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.
- Patients must have at least one lesion that meets the definition of measurable disease by RECIST v1.1.
- Patients must have received at least one but no more than three prior systemic lines of anti-cancer therapy and for whom single agent chemotherapy is appropriate as the next line of treatment.
  - Adjuvant±Neoadjuvant will be considered as one line of therapy
  - Maintenance therapy (example: bevacizumab, PARP inhibitors) will be considered as part of the preceding line of therapy (i.e., not counted independently)
- Patients must be willing to provide an archival tumor tissue block or slides, or fresh biopsy collected using a non-significant risk procedure.
- Patients must meet threshold of FRα positivity criteria by the Ventana IHC test.
- Female patients ≥ 18 years of age with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.

- Patients must have adequate hematologic, liver, cardiac, and kidney function.

Key Exclusion Criteria:

- Patients with clear cell, mucinous or sarcomatous histology, or low grade ovarian cancer
- Patients with primary platinum-refractory disease as defined by those who progressed during or within four weeks of completion of first platinum-based chemotherapy (Friedlander 2011)
- Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow
- Patients with uncontrolled bleeding disorders or inadequate coagulation parameters
- Patients with > Grade 1 peripheral neuropathy
- Patients with active or chronic ocular disorders
- History of neurological conditions, or concurrent neurological condition that would confound assessment of treatment-emergent neuropathy
- History of hemorrhagic or ischemic stroke within the prior six months
- Women who are pregnant or lactating or women of childbearing potential (WCBP) not protected by highly-effective contraceptive methods

Investigational Product, Dosage and Mode of Administration:

Patients randomized to IMGN853 receive a dose of 6 mg/kg AIBW on Day 1, with cycles repeating every three weeks. IMGN853 doses are calculated according to AIBW.

Duration of Study Participation:

The duration of study participation extends from the time the patient signs study consent until the final follow-up study visit. Patients continue to receive study treatment until they present with PD per RECIST 1.1, as assessed by the BIRC, develop unacceptable toxicity or withdraw consent, whichever comes first, or until the Sponsor terminates the study. Patients who discontinue study drug for reasons other than PD continue with tumor assessments until documentation of PD or start of new anti-cancer therapy. All patients are followed for PFS2 and survival until one year after final analysis for the primary endpoint of PFS.

Statistical Methods:

This is a Phase 3 study designed to evaluate the efficacy of IMGN853 compared with that of standard of care chemotherapy in women with epithelial ovarian cancer (EOC), primary peritoneal cancer or fallopian tube cancer.

Sample Size Estimation:

Primary endpoint for the study is PFS as assessed by BIRC in all randomized patients and PFS as assessed by BIRC in the FRα high expression subgroup. The study is designed to test the null hypothesis that the survival function for PFS is the same between IMGN853 arm and the IC chemotherapy arm versus the alternative hypothesis that the survival function for PFS is different between IMGN853 and IC chemotherapy arm. The Hochberg procedure will be used to control the study-wise type I error (Appendix I). Approximately 333 patients will be

randomized 2:1 (222 in IMGN853 arm: 111 in IC arm) over a period of approximately 21 months. The final analysis will be conducted when at least 236 PFS events are observed. An interim futility analysis will be conducted when at least 80 PFS events have occurred. The study will be terminated for futility at interim analysis (IA) if the observed hazard ratio is greater than 1 in both, all randomized patients as well as in the FRα high expression subgroup. The study will have 91% power to detect a hazard ratio of 0.583 in the FRα high expression subgroup and 96% power in all randomized patients at a study-wise alpha level of 5% and the study will have a 39% probability of stopping for futility at interim analysis under the null hypothesis. Sample size and power was determined by simulations using SAS® software with the following assumptions:

- median PFS for the IC arm is 3.5 months
- median PFS for the IMGN853 arm is 6 months
- exponential distribution for both event and censoring processes
- ratio of FRα high to FRα medium is 2:1
- annual censoring rate is 20% in both arms

Statistical Analyses: Sample size calculations were based on efficacy assumptions.

An interim futility analysis will be conducted when at least 80 PFS events, as assessed by the BIRC, have been observed. If the observed hazard ratio is greater than 1 in all randomized patients as well as in the FRα high expression subgroup, the study will be terminated for futility.

If the study continues to full enrollment of 333 patients, the final analysis will be conducted when at least 236 PFS events have been observed. The Hochberg procedure will be used to control the study-wise type I error.

Demographics and baseline characteristics will be summarized using descriptive statistics (n, mean, standard deviation, median, and range) for continuous variables and n (%) for discrete variables.

Efficacy Analyses:

Endpoints		Statistical Analysis Methods
Primary	PFS as assessed by BIRC	Kaplan-Meier method for survival function estimate Stratified Cox proportional hazard regression for hazard ratio estimate Stratified log-rank test for hypothesis testing **Stratification factors:** FRα expression level (medium vs. high), IC chemotherapy (paclitaxel vs. PLD vs. topotecan), and Number of prior lines of therapy (1 or 2 vs. 3) Unstratified analysis will be conducted as sensitivity analysis

Key secondary	ORR as assessed by BIRC and by investigator	Stratified Cochran-Mantel-Haenszel (CMH) test for treatment comparison Clopper-Pearson method for 95% CI estimation
	Primary PRO endpoint	As described in Section 11.7
	OS	Same as primary analysis

Safety data such as treatment-emergent adverse events (TEAEs), laboratory parameters, vital signs, etc., will be summarized and presented in tables. TEAEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and concomitant medications will be coded using the latest version of WHO-DRUG.

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

All analyses will be carried out using SAS and/or WinNonlin software.

A Statistical Analysis Plan (SAP) will fully describe the planned analyses for this study.

Study Committees:

- Steering Committee (SC)
- Independent Data Monitoring Committee (IDMC)
- Blinded Independent Review Committee (BIRC)

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1. INTRODUCTION

1.1. Target Background

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

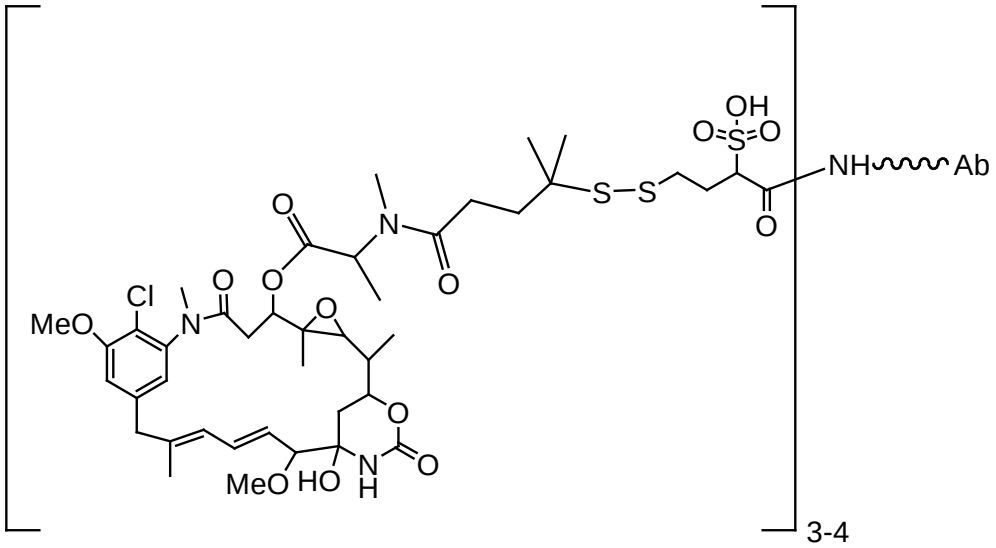
Published studies have demonstrated FRα over expression by immunohistochemistry (IHC) in various epithelial tumors, particularly serous and endometrioid ovarian cancers, and serous and endometrioid endometrial cancers (Scorer 2010, Garin-Chesa 1993, Kalli 2008, Crane 2012, Dainty 2007, Jones 2008, Ab 2015, and Allard 2007). IHC results obtained from patients screened or enrolled in the Phase 1 Study (IMGN853 study 0401) are generally consistent with the literature (Investigator's Brochure). While assessing the FRα distribution in the platinum-resistant EOC expansion cohort, 81.8. % patients had high/medium FRα expression, (high, defined as ≥ 75% of tumor staining at ≥2+ intensity, vs. medium, defined as ≥ 50% and < 75% at ≥ 2+ intensity) (Borghei 2015).

Several additional studies have further validated FRα as a target in serous ovarian cancer. First, quantitative polymerase chain reaction studies show ubiquitous FRα mRNA expression in serous ovarian cancer (Hanker 2012, Hoskins 1998, Hough 2001) and high levels of FRα mRNA correlate with poor response to chemotherapy and decreased disease free survival (Chen 2012). Second, both Kalli et al and Crane et al have demonstrated that recurrent tumors retain FRα expression comparably to primary tumors as shown by serial biopsy sampling and IHC (Kalli 2008, Crane 2012). Third, studies with FRα -specific imaging agents have demonstrated real-time FRα expression at primary and metastatic tumor sites (Fisher 2008, Garcia 2013, Garin-Chesa 1993, and van Dam 2011). Finally, a truncated form of FRα has been detected in ascites and blood of ovarian cancer patients (Basal 2009, Markman 2000, 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 ovarian cancer.

1.2. IMGN853

Because of its tumor specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a promising target for ADC therapy. ADCs combine the specificity of monoclonal antibodies to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target proliferating cells. IMGN853 is an ADC designed to target FRα. It consists of the humanized anti- FRα monoclonal antibody M9346A attached via a cleavable disulfide linker to the cytotoxic maytansinoid, DM4 (Figure 1).

Figure 1: IMGN853 Structure



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

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

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

1.3. Epithelial Ovarian Cancer (EOC)

EOC is a lethal disease with 21,290 new cases and 14,180 deaths expected in 2015 (Surveillance Cancer Statistics Factsheet 2015). The estimated number of new ovarian cancer cases in European Union (EU27) in 2012 was 44,149 with 29,758 deaths (EUCAN "Cancer Fact Sheet: Ovary" 2012). The overall 5-year survival for ovarian cancer patients is only 44% (Cannistra 2004, Baldwin 2012).

Despite considerable improvements in primary therapy, 80% of the patients with advanced EOC are expected to relapse during or after treatment with platinum-containing regimens (Ledermann 2010). Disease recurring within six months of platinum-based chemotherapy is classified as *platinum resistant*, whereas, disease recurring greater than 6 months after therapy is termed *platinum sensitive.* Patients with platinum resistant disease typically receive single agent chemotherapy (e.g. liposomal doxorubicin, topotecan, gemcitabine, paclitaxel, or other) at relapse. Unfortunately, response rates associated with these treatments range from

~10 to 20 percent, and duration of response is typically 4-8 months (Cannistra 2010, Matsuo 2010). Similarly, overall survival rates are poor with a median overall survival rate of ~11 months. Recently, bevacizumab was approved for use in combination with chemotherapy for recurrent ovarian cancer in the platinum resistant setting (Pujade-Lauraine 2014). Because platinum resistant ovarian cancer remains a significant unmet medical need, the National Comprehensive Cancer Network (NCCN) guidelines recommend that platinum resistant patients participate in clinical trials (NCCN Guidelines 2015).

Commonly used agents for platinum resistant EOC are paclitaxel, topotecan and pegylated liposomal doxorubicin, all of which have modest levels of activity. In a single-agent Phase 2 study of liposomal doxorubicin in patients who progressed following previous paclitaxel and platinum-based regimens, the response rate was 27% and PFS was 5.7 months. In a number of Phase 2 studies, response rates between 10 and 15% were reported (Gordon 2000; Markman 2000). Modest results associated with these single-agent salvage regimens underscore the need for improved therapies.

1.4. Current Therapies

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

1.4.1. Paclitaxel

Paclitaxel is a taxane that can stabilize microtubules to inhibit cell division. The drug was approved for treatment of recurrent EOC when response rates (RR) of 25% to 37% were observed in multiple Phase 2 trials testing the 3-weekly schedule (McGuire 1989, Thigpen 1994, Rowinsky 1995). In the study by Thigpen et al, a median PFS of 4.2 months and an OS of 16 months were observed. A Phase 2 trial showed that weekly dosing could lead to a 20.9% RR in platinum- and paclitaxel-resistant EOC patients (Gynecologic Oncology Group 2006). This alternative weekly dosing schedule for paclitaxel was studied in many trials in refractory, persistent, or recurrent EOC patients, as reviewed by Baird et al. (Baird 2010). A randomized Phase 3 study comparing weekly versus 3-weekly paclitaxel in recurrent EOC patients (of whom half were platinum-resistant) showed no difference in RR, PFS, or OS. However, the weekly schedule had a better safety profile than the 3-weekly schedule, as considerably less neutropenia, neuropathy, and myalgia were observed (Rosenberg, 2002). Of note, the occurrence of neutropenia was also reduced when paclitaxel was infused over 3 hours instead of 24 hours (Eisenhauer 1994). A recent randomized Phase 2 clinical trial (CARTAXHY) tested the efficacy of weekly paclitaxel as a single agent, or in combination with carboplatin, or weekly topotecan in patients with platinum-resistant EOC. The results showed that the combination treatments increased hypersensitivity reactions, febrile neutropenia, and anemia, and did not improve RR or median PFS when compared to single agent weekly paclitaxel (Lortholary 2012).

1.4.2. Topotecan

Topotecan's mechanism of action is different from that of paclitaxel, as it does not directly block cell division, but instead induces irreversible DNA damage. Topotecan inhibits

topoisomerase 1, leading to both single and double stranded DNA breaks that eventually promote apoptosis. Topotecan (administered once daily 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 RR 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, Markman 2000). For example, one Phase 2 trial tested the effect of the "standard" dosing of topotecan (1.5 mg/m^2, daily the first 5 days of 21-day cycles) compared with an alternative dosing regimen (1.75 mg/m^2, once a week for 4 weeks, repeated every six weeks) in patients with recurrent EOC. The alternative dosing regimen led to a lower RR (9.6% compared with 22.6% in the standard dosing arm), but also decreased myelotoxicity (52% of patients had Grade 3 or 4 granulocytopenia in comparison with 94% in the standard dosing arm) (Hoskins 1998). A subsequent Phase 2 trial tested the effect of yet another dosing schedule (1.5 mg/m^2, daily the first three days of 21-day cycles) (Markman 2000). Compared to historical controls, this alternative dosing regimen seemed to decrease the toxicity of 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).

1.4.3. Pegylated Liposomal Doxorubicin (PLD)

PLD is another standard chemotherapy regimen used for treating platinum-resistant EOC. The active component of this drug (doxorubicin) is an anthracycline that intercalates DNA, leading to inhibition of replication and, subsequently, the inhibition of proper cell division. Efficacy of PLD in platinum-resistant EOC has been confirmed in several Phase 2 trials. In detail, the trial by Muggia et al reported a 26% RR, median PFS of 5.7 months, and OS of 11 months (Muggia 1997). A subsequent trial showed a 17% RR and median PFS of 4.5 months (Gordon 2000). Of note, a Phase 3 trial testing topotecan treatment versus PLD treatment showed a trend toward a higher RR in the platinum-resistant EOC patients subset treated with PLD, although there was no improvement of PFS or OS (Gordon 2001, Gordon 2004).

1.5. Non-Clinical Studies of IMGN853

1.5.1. Impact of FRα Expression

Studies assessing the potency and specificity of IMGN853 were conducted on a panel of FRα-positive cell lines with a wide range of FRα expression, as well as on FRα-negative cell lines (Investigator's Brochure). These studies revealed a positive correlation between the level of FRα expression on the cell surface, the amount of maytansinoid catabolites generated, and the degree of sensitivity of the cells to IMGN853 *in vitro*. IMGN853 is not active against low and negative FRα expressing cells.

1.5.2. Pharmacology

Results of nonclinical pharmacology studies demonstrate the following:

- FRα has limited normal tissue expression and marked expression in solid tumors, particularly cancers of the ovary and endometrium (Investigator's Brochure). In vitro studies demonstrated that IMGN853 binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against cells expressing FRα. IMGN853-mediated cytotoxicity involves binding, internalization, and degradation of IMGN853, which releases DM4. DM4 can be methylated to yield S-methyl-DM4. Both DM4 and S-methyl-DM4 can inhibit tubulin polymerization and microtubule assembly, causing cell death. The lipophilic molecules S-methyl DM4 and DM4 can also diffuse to neighboring cells and induce bystander killing.
- In vitro cytotoxicity studies suggest that cells sensitive to IMGN853 express higher levels of FRα and release 10- to 100-fold more cytotoxic maytansinoid than cells resistant to IMGN853.
- IMGN853 retains the inherent activities of its antibody moiety, M9346A, including binding affinity (apparent affinity ≤ 0.1 nM) and selectivity for FRα, capacity for uptake, internalization and degradation by FRα-positive target cells, and ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.
- IMGN853 demonstrates significant activity against FRα -positive xenografts. Partial and/or complete regressions in xenograft models of epithelial ovarian cancer were seen at doses of IMGN853 well below its maximum tolerated dose (MTD).

1.5.3. Pharmacokinetics

Nonclinical studies with IMGN853-cross reactive (monkey) and non-cross reactive (mouse) species were conducted to define pharmacokinetics (PK) parameters and to determine the stability of the linker and impact of conjugation on antibody clearance. An additional PK study with free DM4 was conducted in monkey. PK studies demonstrated the stability of IMGN853 in circulation following IV administration, with a distribution phase lasting about 24 hours followed by a slower terminal elimination phase. The data indicated that the PK of IMGN853 were approximately dose proportional within the ranges evaluated (1 mg/kg – 10 mg/kg). These studies are further detailed in the Investigator's Brochure.

1.5.4. Toxicology

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

1.6. Clinical Studies of IMGN853

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

The FIH Phase 1 study is evaluating the safety, pharmacokinetics and pharmacodynamics of single-agent IMGN853 in patients with EOC and other FRα -positive tumors. The recommended Phase 2 dose (RP2D) for single agent IMGN853 administered once every three weeks was determined to be 6.0 mg/kg AIBW. Data from this study, including PK and TEAEs reported by patients enrolled in the dose escalation cohorts are detailed in the Investigator Brochure.

As of 31 January 2017, 206 patients have been dosed. At least one TEAE was reported by 205 patients (>99%). TEAEs of Grade 1 or 2 were most common (102 patients, 50%), 86 patients (42%) reported Grade 3 TEAEs, 10 patients (5%) reported Grade 4 and seven patients (3%) experienced a Grade 5 TEAE.

The most common TEAEs, reported in ≥ 20% of patients included diarrhea (94 patients, 46%); fatigue (91 patients, 44%); nausea (84 patients, 41%); blurred vision (72 patients, 35%); neuropathy peripheral (47 patients, 23%); headache (55 patients, 27%); vomiting (54 patients, 26%); abdominal pain (47 patients, 23%); decreased appetite and aspartate aminotransferase (AST) increased (46 patients, 22%). Safety data are further detailed in the IMGN853 Investigator Brochure.

1.6.2. Phase 1b Combination Trial: Study 0402

A Phase 1b study is ongoing to evaluate the safety, tolerability and pharmacokinetics of IMGN853 in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin or pembrolizumab in adults with FRα -positive advanced epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer, or endometrial cancer.

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

1.7.1. IMGN853: Rationale for 6 mg/kg AIBW Q3W Dosing Schedule

IMGN853 will be administered at 6 mg/kg, with the dose calculated using AIBW. The use of AIBW to calculate the dose of IMGN853 has been shown to reduce intra-cohort variability in C_{max} and AUC_{0-24} (Moore 2014).

IMGN853 administered at 6 mg/kg AIBW once every three weeks was found to be the RP2D in the FIH study (Phase 1 study, 0401). As of 29 April 2016, data from the 46 patients (treated at 6mg/kg AIBW Q3W) in the platinum-resistant EOC expansion cohort of the Phase 1 study was analyzed for safety profile, tumor response, FRα expression, prior therapies and drug exposure. Adverse events occurring in > 20% of patients in this cohort included diarrhea, blurred vision, fatigue, nausea, vomiting, and peripheral neuropathy, and were mostly low grade.

Blurred vision is likely related to corneal keratopathy, characterized by transient microcysts that form in the corneal epithelium, causing temporary astigmatism. In the initial part of the expansion cohort, blurred vision occurred in 54.5% of patients and was mostly Grade 2 (data presented at ASCO 2015, Moore 2015). The latter half expansion cohort was associated with lower frequency (38.5%) and grade of blurred vision, mostly Grade 1. This improvement may be explained by the use of more effective management procedures such as exclusion of

patients with active or chronic corneal disorders or other active ocular conditions requiring ongoing treatment/monitoring, and patients experiencing eye disorders are advised to use baby shampoo and soft cloth to clean the eyes, and warm compress at bedtime. Additionally, recommendation of daytime use of UVA/UVB sunglasses, avoidance of contact lenses and use of preservative-free lubricating eye drops are recommended for all patients during active study treatment. These management guidelines were first recommended in September 2014 then mandated in April 2015. Following implementation of these guidelines, the rate of blurred vision in the platinum resistant EOC expansion cohort is now near the 35% that was targeted by the goal of exploring a once every four weeks dosing schedule in the Phase 2 study. Safety data from study 0401 showed a 29% reduction in the rate of blurred vision (38.5% versus 54.5%). (For details, refer to Appendix K). Additionally, increased investigator awareness of expected ocular events may have improved the evaluation and management of ocular treatment emergent adverse events (TEAEs) in these patients. Preliminary data from study 0401 suggest further reduction in the intensity and frequency of ocular AEs with the prophylactic use of corticosteroid eye drops.

Based on these findings, the sponsor determined that it is not essential to explore the once every four weeks dosing schedule as per the study design in the original Phase 2 study protocol. The data were presented to the Independent Data Monitoring Committee (IDMC) and the Schedule Selection Committee (SSC), and both committees supported this assessment. The SSC approved the decision to use 6 mg/kg AIBW Q3W for patients randomized to IMGN853.The Phase 2 study was amended to a Phase 3 study (Appendix K). For study treatment and clinical assessment guidelines for the four patients enrolled on the Phase 2 versions of the study, please refer to Appendix K.

1.7.2. Chemotherapeutic Agents in the Investigator's Choice (IC) Arm

Three drugs most commonly used in the setting of platinum resistance are pegylated liposomal doxorubicin, paclitaxel and topotecan (Ledermann 2013 (ESMO Guidelines), NCCN Guidelines 2014 and Luvero 2014). The ability of patients to tolerate the bone marrow suppressive effects of cytotoxic chemotherapy is less than that of patients receiving initial therapy. Modified doses and administration schedules (outside of the label for first line or second-line EOC) are therefore, typically used to treat ovarian cancer in such settings.

1.7.2.1. Paclitaxel

The approved schedule of paclitaxel every 3 weeks for second-line treatment of ovarian cancer is associated with a high rate of myelosuppression, particularly neutropenia, and peripheral neuropathy. Investigators therefore developed interest in evaluating the antitumor activity and tolerability of a weekly schedule. The weekly schedule is associated with similar efficacy and an improved toxicity profile, with less bone marrow suppression and neuropathy. Supporting evidence for the 80 mg/m^2 weekly dosing schedule has been reported for several Phase 2 and Phase 3 studies (Rosenberg 2002, Markman 2002, Gynecologic Oncology Group 2006, and Baird 2010) as described in Section 1.4.1.

1.7.2.2. Topotecan

The approved topotecan dosing for relapsed ovarian cancer is 1.5 mg/ m^2/d, administered on days 1 to 5 of a 3-week schedule. However, reduced doses (i.e., 1.25 mg/m^2/d) are associated with decreased toxicity and similar outcome, thereby being widely used in routine clinical practice (Sehouli 2009). Results from several studies suggest that women with relapsed ovarian cancer may benefit from similar effectiveness but significantly lower hematologic

toxicity if topotecan is administered in a weekly schedule. A Phase 2 trial of the North-Eastern German Society of Gynaecology Oncology Ovarian Cancer Study Group, has compared weekly schedule versus the conventional 5-day schedule, reporting comparable OS rates and a favorable toxicity profile for weekly 4.0 mg/m^2/week topotecan, making it another viable option in platinum resistant ovarian cancer (Sehouli 2011). Based on this evidence from the literature, a conventional (1.25 mg/m^2/d, on days 1 to 5 of a 3-week schedule) and an alternative (4.0 mg/m^2/week, days 1, 8, and 15 of a 4 week cycle) schedules of topotecan were selected for the study.

1.7.2.3. Pegylated Liposomal Doxorubicin (PLD)

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

1.8. Rationale for the Study Plan

This Phase 3, open label, randomized study is designed to compare the efficacy of IMGN853 to that of selected standard of care chemotherapy (Investigator's choice (IC)) in women with platinum- resistant, advanced EOC, primary peritoneal cancer or fallopian tube cancer.

This study will compare the safety and efficacy of IMGN853 administered at 6 mg/kg AIBW Q3W with IC standard of care chemotherapy (paclitaxel, PLD or topotecan). Patients will be enrolled 2:1 into one of two arms as follows:

- ***Arm1:*** IMGN853 6mg/kg AIBW Q3W
- ***Arm 2:*** IC chemotherapy

1.8.1. Rationale for the Study Population

Preliminary results from the FIH study of IMGN853 suggest that higher FRα levels correlate with response to treatment (Martin 2015). Therefore, this study will enroll patients who meet the FRα eligibility criterion of ≥50% of tumor staining at ≥2+ intensity. Additionally, a more stringent stratification cut-off of ≥75% of tumor staining at ≥2+ intensity will be evaluated.

Results from 46 patients from the platinum-resistant EOC expansion cohort of the Phase 1 study, also suggest that the response rate correlates with the number of prior therapies. IMGN853 has a 44% confirmed overall response rate (95% CI: 20% to 70%) and a median PFS of 6.7 months (95% CI: 3.9 to 11 months) in the subset of 16 patients with FRα–positive (medium/high expression) platinum-resistant EOC with one to three prior regimens treated as part of a 46 patient expansion cohort in the Phase 1 study (Moore 2016). These data suggest that patients with medium to high FRα expression who have received no more than three prior therapies are more likely to respond to IMGN853. Based on the above observations, the

current study will enroll patients who have received one to three prior therapies and who meet the FRα eligibility criterion (≥50% tumor staining at ≥2+ intensity).

1.8.2. Crossover to IMGN853 after Progressive Disease as Assessed by BIRC (Patients Enrolled Under Amendment 6 Only)

Patients who consented to this study under Amendment 6 and who discontinue IC chemotherapy for BIRC-confirmed, RECIST-defined PD will be given the option to crossover to the IMGN853 arm (Arm 1). Patients who choose to crossover to IMGN853 must meet entry criteria (Appendix L) prior to treatment with IMGN853. The EOT visit will be completed before crossing over to the IMGN853 arm. The schedule of events for patients who crossover is located in Appendix A. Patients will continue to receive study treatment until they present with PD per RECIST 1.1, as assessed by investigator, develop unacceptable toxicity or withdraw consent, whichever comes first, or until the Sponsor terminates the study (Section 5.6.1.10, Section 5.7.2, Section 5.7.3, and Section 5.7.4). Study treatment and/or participation in the study may be discontinued at any time at the discretion of the Investigator. The Crossover End of Treatment (CO-EOT) visit will be performed when the patient discontinues study treatment. Follow-up assessments as per Section 10.3 will be followed.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To compare the progression free survival (PFS) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC), as assessed by the blinded independent review committee (BIRC), in the intent to treat (ITT) population (defined as all randomized patients) and in the high FRα subgroup (≥ 75% of tumor staining at ≥2+ intensity)

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Objectives

- To compare the objective response rate (ORR) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)
  - Primary analysis of ORR will be based on BIRC assessments. ORR based on investigator's assessment will be analyzed as sensitivity analysis
- To compare the primary PRO endpoint using QLQ-OV28 assessments from patients randomized to IMGN853 versus selected standard of care chemotherapy (IC) as described in Section 11.7
- To compare the overall survival (OS) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)

2.1.2.2. Other Secondary Objectives

- To compare the safety and tolerability of IMGN853 with that of selected standard of care chemotherapy (IC)
- To compare the DOR of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)
  - Primary analysis of DOR will be based on BIRC assessments. DOR based on investigator's assessment will be analyzed as sensitivity analysis
- To compare the CA-125 response rate per Gynecologic Cancer Intergroup (GCIG) CA-125 criteria of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)
- To compare the progression free survival (PFS) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC), as assessed by the investigator
- To evaluate the pharmacokinetics of IMGN853
- To assess the immunogenicity of IMGN853(Anti-drug antibodies, ADA)
- To assess PRO using the EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L, and eight-item FOSI questionnaires

2.1.3. Exploratory Objectives

- To evaluate potential biomarkers in blood and tumor tissue that might predict response to IMGN853
- To compare the time to second disease progression (PFS2) of patients randomized to IMGN853 versus selected standard of care chemotherapy (IC)

2.2. Endpoints

2.2.1. Primary Endpoints

- Progression-free survival (PFS): the time from the date of randomization until the time of death or PD, as assessed by the BIRC
  - In all patients randomized to the study
  - In patients with high FRα level (≥ 75% of tumor staining at ≥2+ intensity)

2.2.2. Secondary Endpoints

2.2.2.1. Key Secondary Endpoints

- Objective response rate (ORR) per RECIST 1.1 criteria as assessed by BIRC
- Primary PRO endpoint using the QLQ-OV28 questionnaire as described in Section 11.7
- Overall survival (OS): the time from the date of randomization until the date of death

2.2.2.2. Other Secondary Endpoints

- Treatment-emergent adverse events and laboratory test results, physical examination, ECGs or vital signs
- Gynecologic Cancer Intergroup (GCIG) CA-125 criteria (Appendix F) clinical response rate
- Time to event endpoints:
  - PFS as assessed by investigator
  - Duration of response (DOR)：the time from first objective response (CR/PR) to the time of PD among those who have achieved a PR or CR
- PK parameters of IMGN853
- Immunogenicity of IMGN853: ADA
- Patient scores on EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L and eight-item FOSI questionnaires

2.2.3. Exploratory Endpoints

- Evaluate association of breast cancer susceptibility gene (BRCA) mutation status in tumor tissue and FRα expression level with anti-tumor activity of IMGN853
- Evaluate the association of anti-tumor activity and/or safety with the following:
  - Mutational status as well as other genomic alterations in tumor samples
  - Activation status of oncogenic pathways in tumor samples
  - Expression of drug transporters such as MDR1 (i.e. P-Glycoprotein [PgP]) as well as other proteins that may influence anti-tumor activity or safety
  - Blood-based biomarkers (such as soluble FRα)
  - Genotyping of Fc gamma receptor (FcγR)
- PFS2 as assessed by investigator: the time from randomization to the time of second PD or death

3. STUDY POPULATION

3.1. Criteria for Selection of Patient Population

3.1.1. Inclusion Criteria

1. Patients must have one of the following pathologically documented, definitively diagnosed tumor types:
   a. Advanced EOC
   b. Primary peritoneal cancer
   c. Fallopian tube cancer
2. Patients must have platinum-resistant ovarian cancer, defined as progression within 6 months from completion of a minimum of four cycles of platinum-containing therapy.

This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

3. Patients must have at least one lesion that meets the definition of measurable disease by RECIST v1.1.
4. Patients must have received at least one but no more than three prior systemic lines of anti-cancer therapy and for whom single agent chemotherapy is appropriate as the next line of treatment.
    a. Adjuvant±Neoadjuvant will be considered as one line of therapy
    b. Maintenance therapy (examples: bevacizumab or PARP inhibitors) will be considered as part of the preceding line of therapy (i.e., not counted independently)
5. Patients must be willing to provide an archival tumor tissue, or fresh biopsy collected using a non-significant risk procedure. Patients who do not have archival tissue and for whom the only sites of disease would require biopsy procedure considered to be of significant risk must not be enrolled in the study. These significant risk procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel.
6. Patients must have confirmation of FRα positivity by Ventana IHC test (≥ 50% of tumor staining at ≥2+ intensity) in archival or fresh biopsy tumor sample. If the archival tumor tissue does not meet FRα criteria, a fresh biopsy tumor sample may be submitted and if positive, it may be used to meet this criterion.
7. Female patients ≥ 18 years of age
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
9. Time from prior therapy:
    a. Systemic anti-neoplastic therapy: five half-lives or four weeks, whichever is shorter
    b. Focal radiation completed at least two weeks, prior to starting study drug
10. Patients must have stabilized or recovered (Grade 1 or baseline) from all therapy-related toxicities.
11. Major surgery (not including placement of vascular access device or tumor biopsies) must be completed four weeks prior to Day 1. Patients must have recovered or stabilized from the side effects prior to study treatment
12. Patients must have adequate hematologic, liver and kidney function as defined by the following parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1,500/μL)
    b. Platelet count ≥ 100 x 10^9/L (100,000/μL); no transfusion within previous 10 days
    c. Hemoglobin ≥ 9.0 g/dL
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or 24-hour creatinine clearance of ≥ 60 mL/minute
    e. AST ≤ 3.0 x ULN; ALT ≤ 3.0 x ULN
    f. Serum bilirubin ≤ 1.5 x ULN (Patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
    g. Serum albumin ≥ 2 g/dL

13. Patients must be willing and able to sign the informed consent form, and to adhere to the study visit schedule and other protocol requirements.
14. Women of childbearing potential (WCBP) are defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). WCBP must agree 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 twelve weeks after the last dose of IMGN853 and for at least six months after the last dose of paclitaxel, PLD or topotecan (Refer to Section 5.9.6).
15. WCBP must have a negative pregnancy test prior to the first dose of study treatment.

3.1.2. Exclusion Criteria

1. Male patients
2. Patients with clear cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low grade ovarian cancer
3. Patients with primary platinum-refractory disease as defined by those who progressed during or within four weeks of completion of first platinum-based chemotherapy (Friedlander 2011).
4. Patients who have received prior wide-field radiotherapy affecting at least 20% of the bone marrow
5. Patients with uncontrolled bleeding disorders or inadequate coagulation parameters:
   a. Activated partial thromboplastin time (aPTT))>1.5 x ULN, unless related to lupus anticoagulant. Patients receiving unfractionated heparin must have aPTT between 1.5 and 2.5 x ULN or within a range determined by their physician.
   b. International normalized ratio (INR)>1.5. Patients receiving warfarin must have an INR between 2.0 and 3.0 or within a range determined by their physician.
6. Patients with > Grade 1 peripheral neuropathy
7. Active or chronic corneal disorders such as Sjogren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, active ocular conditions requiring on-going treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision.
8. Serious concurrent illness or clinically-relevant active infection, including, but not limited to the following:
   a. Known active hepatitis B or C whether or not on active antiviral therapy
   b. Known Human Immunodeficiency Virus (HIV) infection
   c. Varicella-zoster virus (shingles)
   d. Cytomegalovirus infection
   e. Any other known concurrent infectious disease, requiring IV antibiotics within 2 weeks of starting study treatment
9. Clinically-significant cardiac disease including any one of the following:

a. Recent myocardial infarction (≤ 6 months prior to day 1)
b. Unstable angina pectoris
c. Uncontrolled congestive heart failure (New York Heart Association > class II)
d. Uncontrolled hypertension (≥ CTCAE v4.03 Grade 3)
e. If the choice of chemotherapy agent is PLD for patients randomized to the IC chemotherapy arm, LVEF (measured by Echocardiography (ECHO) or Multigated Acquisition (MUGA) scan) that is below the institutional limit of normal
f. Prior history of hypertensive crisis or hypertensive encephalopathy
g. Uncontrolled cardiac arrhythmias
h. Clinically-significant vascular disease (e.g. aortic aneurysm, or dissecting aneurysm)
i. Severe aortic stenosis
j. Clinically significant peripheral vascular disease, or ≥ Grade 3 cardiac toxicity following prior chemotherapy
k. Corrected QT (QTc) >470 msec using on-screening ECG

10. History of neurological condition, or concurrent neurological condition that would confound assessment of treatment-emergent neuropathy
11. History of multiple sclerosis or other demyelinating disease and/or Eaton-Lambert syndrome (para-neoplastic syndrome)
12. History of hemorrhagic or ischemic stroke within the last 6 months
13. History of cirrhotic liver disease
14. Previous clinical diagnosis of non-infectious interstitial lung disease, including non-infectious pneumonitis.
15. Required use of folate –containing supplements (e.g. folate deficiency)
16. Prior hypersensitivity to monoclonal antibodies
17. Women who are pregnant or lactating
18. Patients with known hypersensitivity to any of the standard of care (SOC) chemotherapy agents included in the study (paclitaxel, PLD, or topotecan) are excluded from receiving that particular medicinal product, but can receive one of the other chemotherapy agents included in the study.
19. Untreated CNS disease or symptomatic CNS metastasis
20. Prior treatment with IMGN853 or prior treatment on the study
21. History of other clinically active malignancy within 3 years of enrollment, except for tumors with a negligible risk for metastasis or death, such as adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix or breast.

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

4. INVESTIGATIONAL PLAN

4.1. Study Design

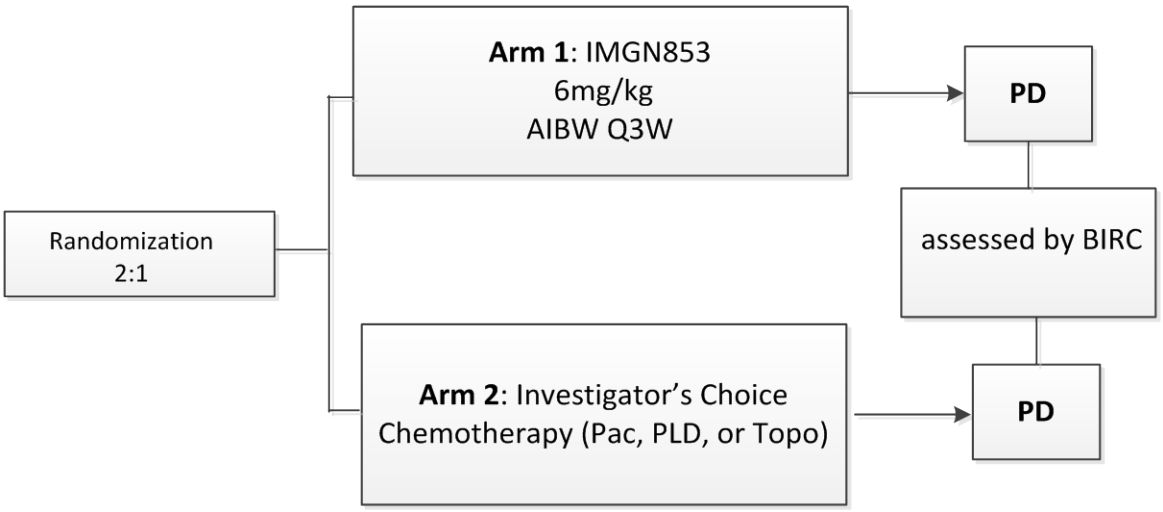
4.1.1. Overview and Schema

This Phase 3, open label, randomized study is designed to compare the efficacy of IMGN853 to that of selected standard of care chemotherapy (Investigator's choice) in women with advanced EOC, primary peritoneal cancer or fallopian tube cancer.

Patients will be stratified by number of prior lines (1 or 2 vs. 3), FRα levels (≥ 75% tumor staining at ≥ 2+ intensity vs. ≥ 50% and < 75% tumor staining at ≥ 2+ intensity) and IC chemotherapy (paclitaxel, PLD or topotecan). Patients will be randomized 2:1 into one of two arms as follows:

- ***Arm1:*** IMGN853 6mg/kg AIBW Q3W
- ***Arm 2:*** IC chemotherapy (weekly paclitaxel every four weeks, PLD administered once every four weeks, or topotecan administered either on Days 1, 8, and 15 every four weeks or for five consecutive days every three weeks).

Figure 2: Study Design Schema



Abbreviations: Pac: paclitaxel; PLD: pegylated liposomal doxorubicin; Topo: topotecan; BIRC: Blinded Independent Review Committee

The study consists of a Screening period, a Treatment period, and a Follow-up period.

Patients will continue to receive study treatment until they develop PD per RECIST 1.1, (as assessed by the BIRC), experience unacceptable toxicity or withdraw consent, whichever comes first, or until the Sponsor terminates the study.

Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans will be performed at Screening and subsequently every six weeks for the first 36 weeks then every twelve weeks until PD per RECIST 1.1, death or the initiation of subsequent anti-cancer therapy, whichever occurs first. All patients will be followed every three months (± 2 weeks) for survival until death, lost to follow-up, withdrawal of consent for survival, or until End of Study, whichever comes first.

4.1.2. Dosing and Dosing Schedules for IMGN853 and Chemotherapeutic Agents

In this Phase 3 study, patients enrolled in Arm 1 will receive IMGN853 at 6 mg/kg AIBW administered IV on Day 1 of a three-week cycle. Patients in Arm 2 will receive paclitaxel, PLD or topotecan. Paclitaxel will be administered at 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15 and 22 of a four-week cycle. PLD will be administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a four-week cycle. After Cycle 1, if tolerated, PLD can be administered as a one-hour infusion. Topotecan will be administered at a 4 mg/m^2 dose over 30 minutes on days 1, 8 and 15 of a four-week cycle. Alternatively, topotecan can be administered at a 1.25 mg/m^2 dose over 30 minutes on days 1–5 of a three-week cycle. The dose of chemotherapeutic agents will be calculated using body surface area (BSA). Institutional conventions can be used to calculate BSA.

For logistical reasons such as holidays, delays in the scheduled study treatment for up to three 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.

Table 1: Dose and Dosing Schedules

Randomization 2:1			
Group	**Drug**	**Dose**	**Dosing Schedule**
Arm 1	IMGN853	6 mg/kg AIBW	Day 1, of a 3-week cycle
Arm 2	Paclitaxel	80 mg/m^2	Days 1, 8, 15 and 22 of a 4-week cycle
	PLD	40 mg/m^2	Day 1 of a 4-week cycle
	Topotecan (4 week cycle)	4 mg/m^2	Days 1, 8 and 15 of a 4-week cycle
	Topotecan (3 week cycle)	1.25 mg/m^2	Days 1 through 5 of a 3-week cycle

5. STUDY TREATMENT

5.1. IMGN853

The investigational study drug, IMGN853, will be provided by ImmunoGen, at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution.

5.1.1. IMGN853 Packaging

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

5.1.1.1. IMGN853 Storage, Handling and Accountability

Specific details regarding storage and handling of IMGN853 can be found in the Pharmacy Manual.

Accountability and shipping documents for IMGN853 must be maintained by the Principal Investigator or designee (e.g., the study pharmacist). The Investigator or designee must maintain an accurate record of the receipt and dispensing of IMGN853 in a drug accountability log or equivalent. These records must always be available for inspection, and a

copy will be supplied to ImmunoGen on request. Information recorded on 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.

Any investigator site-to-site transfers (e.g., investigator satellite sites) of the study drug must follow local laws. At a minimum, the originating site and the receiving site should document the transfer and receipt of the study drug in their respective drug accountability logs; the originating site must ensure proper packing (e.g., cold packs to maintain the temperature control) of the study drug during the transport (refer to Pharmacy Manual).

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

Drug accountability will be monitored regularly.

5.1.1.1.1. IMGN853 Study Treatment Compliance

The IMGN853 supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

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

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

5.2. Investigator's Choice Chemotherapeutic Agents

Since the type of IC chemotherapy received is one of the stratification factors, it is required that the choice of the chemotherapy agent, paclitaxel or PLD or topotecan, be made prior to randomization. Paclitaxel, PLD and topotecan are supplied as commercially available formulations. Refer to the prescribing information or Summary of Product Characteristics for complete information.

A separate Investigational Product Dispensing/Accountability Log or equivalent should be maintained for paclitaxel, PLD, and topotecan. Vials should be visually inspected for vial integrity (i.e., cracks or leaks) and a record of any damaged or suspect drug should be kept on the Investigational Product Dispensing/Accountability Log or equivalent.

5.3. Assignment of Patient Number

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

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

5.3.1. Enrolled Patient Definition

Patients who have consented to the study and randomized, are considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and are not randomized will be considered screen failures. Patient numbers for patients who screen fail will not be re-issued.

5.3.2. Patient Assignment to Dosing Regimens

Eligible patients will be randomly assigned 2:1 to IMGN853 6 mg/kg AIBW Q3W (Arm 1) or IC chemotherapy (Arm 2; paclitaxel, PLD or topotecan).

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

Patients will be stratified as follows:

- FRα levels (≥ 75% of tumor staining at ≥2+ intensity vs. ≥ 50% and <75% of tumor staining at ≥ 2+ intensity)
- Number of prior therapies (1 or 2 vs. 3)
- IC of chemotherapy (paclitaxel, PLD, or topotecan)

5.4. Blinding Methods

Not applicable as this is an open-label study.

5.5. Study Treatment Administration

5.5.1. Premedication for Study Treatment

5.5.1.1. IMGN853

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

5.5.1.1.1. Prophylactic use of Corticosteroid Eye Drops

Patients receiving IMGN853 will be mandated to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighs the benefit as per the ophthalmologist/physician. All patients enrolled will be instructed to self-administer 1% prednisolone (Pred Forte® or generic equivalent) six times daily on Days 1-4 and four times daily on Days 5-8 of each cycle during the study. For individual patients who cannot tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops may be substituted (e.g. difluprednate 0.05%; Durezol®) and administered on Days 1-8 of each cycle at a frequency prescribed by the ophthalmologist.

5.5.1.1.2. Lubricating Artificial Tears

Patients receiving IMGN853 will be mandated to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician). Patients should be advised to wait at least 15 minutes following corticosteroid eye drop administration before instilling lubricating eye drops.

5.5.1.2. IC Chemotherapy

Patients receiving paclitaxel, PLD or topotecan may receive premedication at the discretion of the investigator or according to institutional guidelines.

5.5.2. Preparation and Administration of IMGN853

5.5.2.1. Calculation for Adjusted Ideal Body Weight

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

Adjusted Ideal Body Weight (AIBW)

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

Where:

Ideal Body Weight (IBW)

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

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

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

5.5.2.1.1. Preparation

IMGN853 is an experimental anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. The desired amount of drug should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the Pharmacy Manual. **Note: IMGN853 is incompatible with saline (0.9% sodium chloride). Therefore, dilutions should be made using 5% dextrose.** Infusion bags must be labeled with the protocol number, patient number, storage temperature, dose, and volume of IMGN853 filtered into the bag, or labeled according to institutional protocol. Once the solution is prepared, the infusion bag should be stored at ambient temperature protected from direct sunlight, and the infusion must be completed within eight hours of preparation. Please refer to Pharmacy Manual for further details.

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

5.5.2.1.2. Administration

IMGN853 is administered at 6 mg/kg (Table 1) as an IV infusion following preparation as outlined in the Pharmacy Manual. Details on required and compatible infusion materials are also included in the Pharmacy Manual. Initially the study drug should be administered at a

rate of 1 mg/min; after 30 minutes, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after 30 minutes at 3 mg/min, the IMGN853 infusion rate may be increased to 5 mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. Following infusion, the IV line should be flushed with 5% dextrose as needed to ensure delivery of the full dose.

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

5.5.3. Preparation and Administration of IC Chemotherapy

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

5.5.3.1. Preparation and Administration of Paclitaxel

Paclitaxel will be prepared as described in the prescribing information and administered IV at 80 mg/m^2 (Table 1). Body weight at Cycle 1 Day 1 (-14 days) is to be used to calculate BSA in order to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.5.3.2. Preparation and Administration of Pegylated Liposomal Doxorubicin

PLD will be prepared as described in the prescribing information and administered IV at 40 mg/m^2 (Table 1). Body weight at Cycle 1 Day 1 (-14 days) is to be used to calculate BSA in order to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.5.3.3. Preparation and Administration of Topotecan

Topotecan will be prepared as described in the prescribing information and administered IV at 4 mg/m^2 (Table 1). Alternatively, topotecan will be administered at 1.25 mg/m^2. Body weight at Cycle 1 Day 1 (-14 days) is to be used to calculate BSA in order to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.6. Dose Modification Guidelines

Detailed IMGN853 and chemotherapy-specific dose modification guidelines are described below.

5.6.1. IMGN853

5.6.1.1. Treatment Criteria

In the absence of a TEAE that requires dose modification, a patient must meet the following criteria in order to receive study treatment:

- ANC must be ≥ 1.5x10^9/L (1,500/μL)
- Platelet count must be ≥ 100 x 10^9/L (100,000/μL)

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

5.6.1.2. IMGN853-Related Adverse Events

Dose modifications for IMGN853 related adverse events are described in Table 2.

Table 2: Dose Modifications for IMGN853 Related Adverse Events

Severity Grade (CTCAE v4.03)	**Dose Modifications for IMGN853**
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and resume at the same dose level
Grade 4	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and then resume at a lower dose level
Febrile neutropenia Grade 3 or 4 (with a single temperature reading ≥ 38.3°C or a sustained temperature of > 38°C for > one hour)	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and then resume at a lower dose level
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until Platelet count is ≥ 100 x 10^9/L (100,000/μL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until Platelet count is ≥ 100 x 10^9/L (100,000/μL) and then resume at a lower level
Non-hematological	
Nausea and Vomiting	
Grade 3 (despite use of optimal anti-emetics)	Hold drug until resolved to ≤ Grade 1, then resume at lower level
Grade 4	Permanently discontinue
Diarrhea	
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold drug until resolved to ≤ Grade 1, then resume at lower level
Grade 4	Permanently discontinue
Ocular Disorders	Refer to Section 5.6.1.6
Non-infectious Pneumonitis	Refer to Section 5.6.1.7
Infusion-related Reactions	Refer to Section 5.6.1.9

Severity Grade (CTCAE v4.03)	**Dose Modifications for IMGN853**
All Other Non-hematological Toxicities (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemistry laboratory abnormalities that last for < 7 days including electrolyte abnormalities that respond to medical intervention)	
Grade 3	Hold drug until resolved to ≤ Grade 1, then resume at lower level For any Grade 3 hepatic toxicity that does not resolve to baseline within seven days, an abdominal CT scan must be performed to assess whether it is related to disease progression.
≥ Grade 3 Cardiac events	Permanently discontinue
Grade 4 non-hematological toxicities	Permanently discontinue

5.6.1.3. IMGN853 Dose Reduction Dose Levels

IMGN853 dose reduction will be as described in Table 3.

Table 3: IMGN853 Dose Reduction Dose Levels

If the patient was receiving IMGN853 at:	**Dose should be reduced to:**
6.0 mg/kg AIBW	5.0 mg/kg AIBW
5.0 mg/kg AIBW	4.0 mg/kg AIBW
Reduction of IMGN853 below 4.0 mg/kg will not be permitted.	

5.6.1.4. Monitoring and Management of Nausea and Vomiting

Nausea and vomiting have been reported in patients treated with IMGN853. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea. Patients should be treated according to the ASCO Clinical Practice Guidelines for the use of antiemetics (Basch 2011) outlined in Table 4.

Table 4: Management of Nausea and Vomiting

Severity Grade (CTCAE v4.03 Grade)	**Management**
Grade 1	Administer a single 8-mg dose of dexamethasone before therapy.
Grade 2	Administer a 5- HT_3 receptor antagonist on Day 1 (e.g. palonosetron, granisetron, or ondansetron) in combination with dexamethasone on days 1-3 or treat as per institutional guidelines. Aprepitant may be added to the combination.
Grades 3 and 4	Administer a neurokinin 1 receptor antagonist (e.g. aprepitant on Days 1-3 or fosaprepitant on 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 as per institutional guidelines.

5.6.1.5. Monitoring and Management of Diarrhea

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

5.6.1.6. Ocular Disorders

Changes in visual acuity resulting from reversible keratopathy have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker (Younes 2012). Patients receiving IMGN853 in the Phase 1 trial (IMGN853 study 0401) reported ocular adverse events consistent with reversible keratopathy/corneal epitheliopathy. At the 6 mg/kg AIBW Q3W dose level, 46% of patients reported Grade 1 or 2 blurred vision. Grade 1 and Grade 2 keratopathy was reported in 26% of patients. There were no Grade 3 ocular adverse events reported at this dose level.

5.6.1.6.1. Monitoring and Preventative Measures

In early dose escalation, there was a relationship between IMGN853 plasma exposure with increased likelihood of an ocular event as well as with response. Exposure-response modeling suggested that a dose of 6.0 mg/kg AIBW provided adequate exposure for response while also maintaining overall exposure within a range that decreased the potential for ocular adverse events. Due to the observation of ocular disorders consistent with reversible keratopathy/corneal epitheliopathy in patients treated with IMGN853, ocular function will be carefully monitored. Ocular symptom assessments will be performed at baseline and at Day 1 of every cycle thereafter (Appendix A and Appendix B). Complete ophthalmologic exams will be performed in all patients at baseline and every other cycle thereafter if there is a TEAE reported (Appendix A and Appendix B).

Patients are strongly advised to avoid using contact lenses while on IMGN853. Baby shampoo and a soft cloth should be used to clean the eyes, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface. Please refer to Section 5.5.1.1.1 for details on the prophylactic use of steroid eye drops and lubricating artificial tears. The use of UVA/UVB sunglasses is recommended in full daylight during the course of the study. The use of temporary lower punctal plugs to increase lubrication of the eyes is optional if lubricating artificial tears and corticosteroid eye drops are not sufficient. If patients report signs or symptoms of ocular disorders, including, but not limited to, blurred vision or eye irritation, the management and dose modification guidelines outlined in Table 5 should be followed.

5.6.1.6.2. Management and Dose Modification Guidelines

If a patient develops ocular symptoms of any grade, the patient is required to have a complete examination by an ophthalmologist. If a patient develops ≥ CTCAE Grade 2 ocular symptoms, treatment with IMGN853 will be interrupted. Treatment should not be interrupted solely for Grade 2 ocular signs (e.g. Grade 2 keratopathy) unless they are also associated with Grade 2 ocular symptoms. Therapy may resume if ocular symptoms improve to Grade 1 or baseline within 28 days of the next scheduled IMGN853 dose (refer to Table 5 for details). Subsequent eye examinations will be scheduled to occur in every other cycle going forward, from the time that the AE was initially reported, and at either the End of Treatment visit or

30-day follow-up visit following treatment discontinuation, even if the results of the patient's ocular exam shows no obvious clinical findings. Management of treatment-emergent ocular AEs with inflammatory characteristics should include corticosteroid eye drops and/or other measures as indicated by an ophthalmologist.

Table 5: Management of Ocular Disorders

Severity Grade (CTCAE v4.03 Grade)	Management	Guidelines for IMGN853 Dose Modifications
Grade 1	• Complete eye exam as outlined in schedule of clinical assessments (Appendix A and Appendix B). • Monitor for worsening symptoms	Continue IMGN853 dosing
Grade 2 Symptoms	• Complete eye exam as outlined in schedule of clinical assessments (Appendix A and Appendix B). • Repeat complete exam as clinically indicated • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator	• Hold IMGN853 dosing until AE has resolved to Grade 1 or better. • Patients with ocular symptoms lasting < 14 days may be allowed to resume IMGN853 at the same dose level • Patients with ocular symptoms lasting ≥ 14 days but no more than 28 days may resume IMGN853 at a lower dose level
Grade 3	• Complete eye exam as outlined in schedule of assessments (Appendix A and Appendix B). Repeat complete exam as clinically indicated. • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	• Hold IMGN853 dosing. • Patients may be allowed to resume IMGN853 at a lower dose after AE has resolved to Grade 1 or better within 28 days.
Grade 4	• Complete eye exam as outlined in schedule of assessments (Appendix A and Appendix B). Repeat complete exam as clinically indicated. • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to Grade 1 or baseline or are deemed irreversible by the investigator.	• Permanently discontinue IMGN853

5.6.1.7. Monitoring of Non-Infectious Pneumonitis

Non-infectious pneumonitis has been observed following the administration of IMGN853. Non-infectious pneumonitis may result in fatigue, shortness of breath, cough or respiratory

distress. Drug-induced pneumonitis may be immediately life threatening. If a patient presents with signs or symptoms consistent with pneumonitis and/or other clinically meaningful signs or symptoms of pulmonary toxicity, the patient should be immediately evaluated. Patients are advised to notify their treating physician immediately if they experience new or worsening shortness of breath, cough or respiratory distress.

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

Table 6: Management of Non-Infectious Pneumonitis

Severity Grade (CTCAE v4.03 Grade)	Medical Management of Pneumonitis	Guidelines for Dose Modifications
Grade 1	• Radiologic 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.	• Hold dosing until symptoms resolve to ≤ Grade 1. • IMGN853 may be resumed at same dose level after discussion with the Sponsor.
Grade 3	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	• Permanently discontinue IMGN853.
Grade 4	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	• Permanently discontinue IMGN853.

5.6.1.8. Management of Electrolytes Imbalance

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

5.6.1.9. Potential Infusion-Related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (see CTCAE Version 4.03). The signs and symptoms may vary and include for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (e.g. epinephrine, inhaled beta agonists, antihistamines, and corticosteroids), and other required resources to treat anaphylaxis must be readily available. In general, Investigators should manage acute allergic or hypersensitivity reactions according to Institutional practices. General guidelines for the management of acute infusion-related reactions and for subsequent retreatment are provided in Table 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 ≥ Grade 2 infusion-related reaction during or immediately following administration of IMGN853 will have blood drawn for determination of drug concentration and antibodies to IMGN853 (ADA). The sample should be obtained within three hours of the onset of the reaction and one week later. Such patients should undergo all scheduled efficacy and safety evaluations.

Table 7: Management Guidelines for Potential Infusion-related Reactions

Infusion Reaction CTCAE v4.03 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below. • Promethazine (or equivalent) 150 mg PO per day (Q4h) prn for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Methylprednisolone (or equivalent) 125 mg IV prn
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine (or equivalent) 150 mg PO per day (Q4h) prn for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Acetaminophen (or equivalent) 650 mg PO prn • Methylprednisolone (or equivalent) 125 mg IV prn • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, patients should be pre-medicated with dexamethasone (or equivalent) 8 mg PO BID the day prior to drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 minutes prior to dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient. • Administer diphenhydramine (25-50 mg) IV (or equivalent) • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to treat ongoing reaction and prevent recurrence • Administer bronchodilators (nebulized albuterol/salbutamol, 2.5-5 mg in 3 mL of saline or equivalent) as medically indicated • Administer normal saline as medically indicated • Administer epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the infusion-related reaction. • Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as a serious adverse event (see Section 9.1.1.2). • Permanently discontinue study medication treatment

5.6.1.10. Discontinuation of IMGN853 Due to Toxicity

IMGN853 should not be resumed in the case of the following treatment-related events:

- ≥ Grade 3 cardiac event

- Non-hematologic events of Grade 4 severity
- Failure to meet re-treatment criteria within one cycle following the missed dose due to insufficient recovery from a treatment-related toxicity. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

5.6.2. Paclitaxel

Label warnings, manufacturer's recommendations and standard clinical practice should be followed. Guidelines for dose interruptions and dose modifications are described in Table 8.

Table 8: Paclitaxel Dose Modification Guidelines

Severity Grade (CTCAE v4.03 Grade)	Dose Modification
Hematological Toxicities	
Grade 1	No action
Grade 2 & 3	Hold paclitaxel until ANC and platelet levels meet the following criteria: **Day 1:** ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) **Day 8, 15 & 22:** ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) *Retreat at same dose level.*
Grade 4	Hold paclitaxel until ANC and platelet levels meet the following criteria: **Day 1:** ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) **Day 8, 15 & 22:** ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) *Dose reduce by 1 level*
For febrile neutropenia and/or severe bleeding, permanently discontinue paclitaxel	
Non-hematological Toxicities	
Grade 1	No action
Grade 2	No action; for patients experiencing neurotoxicity, dose reduce by 1 level.
Grade 3	Dose reduce by 1 level
Grades 3 and 4	Hold paclitaxel until the event resolves or improves to Grade 1. Dose reduce by 1 level.

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

5.6.2.1. Dose Reduction Dose Levels

Paclitaxel dose reduction will be as described in Table 9.

Table 9: Paclitaxel Dose Reductions

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

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

5.6.2.2. Criteria for Permanent Discontinuation of Paclitaxel

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

5.6.3. Topotecan

Label warnings, manufacturer's recommendations and standard clinical practice should be followed. Guidelines for dose interruptions and dose modifications are described in Table 10.

Table 10: Topotecan Dose Modification Guidelines

Severity Grade (CTCAE v4.03 Grade)	Dose Modification
Hematological Toxicities	
Grade 1	No action required.
Grades 2 or 3	Hold topotecan until ANC and platelet levels meet the following criteria: **Day 1:** ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) **Day 8, & 15:** ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) *Retreat at same dose level.*
Grade 4 or any grade neutropenia complications (fever, infection)	Hold topotecan until ANC and platelet levels meet the following criteria: **Day 1:** ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) **Day 8, & 15:** ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) *Dose reduce by one level.*
Non-hematological Toxicities	
Grade 1	No action required.
Grade 2	No action required.
Grades 3 or 4	Hold topotecan until the event improves to Grade 1 or resolves. Dose reduce by one level.

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

Patients who receive topotecan and develop a TEAE requiring an interruption of topotecan may resume treatment at a reduced dose level as shown in Table 11.

5.6.3.1. Dose Reduction Dose Levels

Topotecan dose reduction will be as described in Table 11 and Table 12.

Table 11: Topotecan Dose Reductions (Weekly Schedule)

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

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

Table 12: Topotecan Dose Reductions (Five Days Schedule)

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

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

5.6.3.2. Criteria for Permanent Discontinuation of Topotecan

Treatment should be permanently discontinued according to the guidelines shown in Table 13, in case the observed TEAE is unmanageable despite dose reductions.

Table 13: Adverse Events Requiring Permanent Discontinuation of Topotecan

Severity Grade (CTCAE v4.03 Grade)	Adverse Event
Hematological Toxicities	
Grade 4	ANC < 0.5 x 10^9/L for more than two weeks
Grade 4	Thrombocytopenia for more than 2 weeks
Non-hematological Toxicities	
Grade 3 or 4	Mucositis
Grade 3 or 4	Neurotoxicity
Grade 3 or 4	Toxicities (except nausea, vomiting, and alopecia) lasting for more than three weeks

5.6.4. Pegylated Liposomal Doxorubicin (PLD)

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

5.6.4.1. Hematological Toxicities

Patients receiving PLD are at risk of bone marrow suppression. Leukopenia is usually transient; hematological AEs may require dose delays or reductions as indicated in Table 14.

Table 14: Pegylated Liposomal Doxorubicin (PLD) Dose Modification Guidelines for Hematological Adverse Events

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

5.6.4.2. Non-hematological Toxicities

5.6.4.2.1. Hand-Foot Syndrome

Hand-Foot syndrome (HFS) is a disease characterized by palmar-plantar skin eruptions with swelling, pain, erythema and, for some patients, desquamation of the skin of the hands and feet. HFS has been observed in patients receiving PLD at doses of 50 mg/m^2 and, with less frequency, in those receiving PLD at 30 mg/m^2. If patients present with symptoms/signs consistent with HFS, the dose of PLD should be modified as indicated in Table 15.

Table 15: PLD Dose Modification Guidelines for Hand and Foot Syndrome and Mucositis

Severity Grade (CTCAE v4.03 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 PLD, unless previous Grade 3 or 4 HFS. In case of previous Grade ¾ 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 PLD until resolved to Grade 1 or baseline. If after 2 weeks there is no resolution, PLD should be discontinued. If no prior Grade 3-4 HFS, resume at the dose prior to the event. If previous HFS Grade 3-4 toxicity, decrease dose by 25%.
Grade 3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing.	Painful erythema, edema, or ulcers; cannot eat	Hold PLD until resolved to Grade 1 or baseline. Decrease dose by 25%. If after 2 weeks there is no resolution, PLD should be discontinued.
Grade 4	Diffuse or local process causing infectious complications, a bed ridden state, or hospitalization.	Requires parenteral or enteral support	

If patients receiving PLD experience a TEAE, their PLD dose should be reduced as indicated in Table 16. Patients who require dose reductions below 20 mg/m^2 should discontinue their PLD treatment.

5.6.4.2.2. Cardiac Toxicity

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

5.6.4.3. Criteria for Permanent Discontinuation of PLD

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

5.6.4.4. Dose Reduction Dose Levels

PLD dose reduction will be as described in Table 16.

Table 16: PLD Dose Reductions

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

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

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

5.7.1. End of Treatment (EOT)

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

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

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

5.7.2. End of Study (EOS)

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

5.7.3. Withdrawal of Consent

The patient or legal guardian acting on behalf of the patient is free to withdraw consent to study treatment and/or participation in the study at any time irrespective of the reason. The investigator must make every effort (e.g., telephone, email, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. Further attempts to contact the patient are not allowed unless safety findings require communication or follow up. If the patient or legal guardian withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before withdrawal of consent. All biological samples that have been already collected will be retained and analyzed at a later date. The patient or legal guardian

may also request destruction of any samples taken and not tested, and the investigator must document this in the site study records. The statistical analysis plan will specify how early withdrawals from treatment will be accounted for in the analyses of efficacy endpoints. Patients who have withdrawn from the study cannot be re-treated in the study. Their inclusion and patient number must not be reused.

5.7.4. Lost to Follow up

A study participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The Investigator should make all efforts to contact the patient (e.g., contacting patient's family or private physician, reviewing available registries or health care databases), and to determine the patient's health status, including at least his/her vital status. A patient should not be considered lost to follow up until due diligence has been completed. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

5.8. Period of Observation

For purposes of this study, the period of safety observation extends from the time of informed consent until the 30-day follow-up safety visit unless additional follow up safety information is requested as described in Section 9.1 and Section 10.3.1. Short-term follow-up for patients who discontinue study treatment without documented progressive disease will be followed per RECIST 1.1 every 12 weeks (± 3 weeks) until PD, until the patient begins subsequent anti-cancer treatment, or until the patient dies, whichever comes first. All patients will be followed every three months (± 2 weeks) for survival until death, lost to follow-up, withdrawal of consent for survival or until End of Study, whichever comes first.

5.9. Concomitant Medications and Procedures

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

5.9.1. Antiemetic and Antidiarrheal Medications

Antiemetic (e.g. 5-HT_3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) and antidiarrheal (e.g. loperamide) medications may be used at the discretion of the treating physician, but they are not to be used prophylactically.

5.9.2. Folate-Containing Supplements

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

5.9.3. Antineoplastic Therapy

Chemotherapy (other than agents specified for patients enrolled in Arm 2 of the study), and other investigational agents, or biologic therapy will not be permitted during the study.

Palliative radiotherapy during study treatment should be discussed with the Sponsor prior to 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.

5.9.4. Hematopoietic Growth Factors

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

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

5.9.5. Anticoagulants

The use of the following anticoagulant agents is allowed: Warfarin (prophylactic or therapeutic), Unfractionated Heparin (prophylactic or therapeutic), Low Molecular Weight Heparins (prophylactic or therapeutic), Fondaparinux (prophylactic or therapeutic), Dabigatran and Edoxaban. Please see Section 5.9.8 if using Apixaban and Rivaroxaban due to CYP3A interaction potential.

5.9.6. Contraception

5.9.6.1. Acceptable Methods of Contraception

- Single method (one of the following is acceptable)
- Intrauterine Device (IUD)
- Vasectomy of a female patient's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- 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: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study WCBP must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up and for at least twelve weeks after the last dose of IMGN853 and for at least six months after the last dose of paclitaxel, topotecan and pegylated liposomal doxorubicin. If there is any question that a WCBP will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.9.7. Other Concomitant Medications

Medications for the treatment of adverse events or cancer symptoms (e.g. packed red blood cells and pain medications), are allowed. Prophylactic use of steroids and/or antihistamines will be considered if needed to alleviate mild-moderate infusion 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.

5.9.8. Medications that are CYP3A Substrates or CYP3A Substrates with Narrow Therapeutic Index

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

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

5.10. Overdose and Medication Error

5.10.1. Overdose

There is no known treatment/antidote available for IMGN853. For IC chemotherapy agents, please follow management guidelines for overdose as described in the prescribing

information and/or institutional guidelines. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug.

5.10.2. Medication Error

The Sponsor must be immediately notified in the event of error in prescribing, dispensing, administering and/or use of any study drug, and the event must be reported on the eCRF. If an error resulted in a serious adverse event, a Serious Adverse Event form must be submitted within 24 hours of the event (see Section 9.2.1).

6. PHARMACOKINETIC (PK) AND IMMUNOGENICITY ASSESSMENTS

6.1. PK Assessments – IMGN853

The PK properties of IMGN853 and possibly its metabolites will be evaluated following IV administration, as outlined in Appendix C. Plasma samples will be collected to determine the PK of IMGN853 (conjugate, total M9346A antibody, free DM4, DM4-Me and possibly other metabolites).

Blood samples for PK measurements will be taken as follows (Appendix C):

Cycles 1 and 3:

Day 1 – pre-dose, and immediately following the completion of the IMGN853 infusion (+5 minutes)

Day 8 – single blood sample

Day 15 – single blood sample

Cycles 2 and 4

Day 1– pre-dose, and immediately following the completion of the IMGN853 infusion (+5 minutes).

Unscheduled visit: Any patient who experiences a ≥ Grade 2 infusion-related reaction during the administration of IMGN853 will have blood drawn within three hours of the onset of the reaction and one week later for determination of drug concentration, antibodies to IMGN853.

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

End of Treatment visit: A blood sample for PK analysis will be collected at the End of Treatment Visit.

30-day follow up visit: A blood sample for PK analysis will be obtained if feasible.

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

6.2. Immunogenicity Assessments – IMGN853

The potential immunogenicity against IMGN853 will be assessed in Cycles 1 through 6, as outlined in Appendix C. The potential impact of immunogenicity on PK, safety, and efficacy of IMGN853 and total M9346A antibody will be explored.

The sample for ADA analysis is taken from the PK tube on Day 1 Pre-Dose for Cycles 1, 2, and 4 and at the End of Treatment and 30-day Follow-up visits. An additional blood draw for ADA is required on Day 1 Pre-Dose for Cycle 6.

7. BIOMARKER RESEARCH STUDIES

Several biomarkers, including FRα, are evaluated as potential biomarkers of clinical response to IMGN853. These will help guide further clinical development of IMGN853.

7.1. Evaluation of FRα Expression in Tumor Tissue

FRα expression varies with tumor histology, as reported in the literature and demonstrated in pre-clinical studies (Section 1.1 and Investigator's Brochure). FRα expression in tumors will be analyzed using an IHC based Investigational Use Only assay co-developed by ImmunoGen and Ventana Medical Systems Inc. This assay will be conducted at a central lab for testing of patient samples. All patients must submit tumor tissue, or formalin-fixed, paraffin embedded (FFPE) slides for analysis of FRα expression by IHC prior to enrollment.

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

The required FRα expression level is ≥ 50% of tumor staining at ≥2+ intensity. A stratification cut-off of ≥75% at ≥2+ will also be implemented.

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

7.2. Exploratory Biomarker Studies

Studies in tumor tissue and blood will be performed to explore potential markers of IMGN853 sensitivity and resistance. The sections below describe activities that are planned, but other additional biomarkers/biological pathways may be investigated based on emerging data.

7.2.1. Potential Predictive Markers of Drug Response

Cancer is a disease driven by molecular level changes, which include mutations, DNA rearrangements and copy number changes, as well as changes in gene expression of key oncogenic pathways. Many of these changes determine or influence the aggressiveness of the disease, how the cancer responds to standard of care and/or novel therapeutic agents, and development of resistance to treatment. To evaluate how these molecular changes are associated with response to IMGN853, we are planning to characterize the genomic profile of archival tumor samples using a fit for purpose technology such as the Foundation Medicine's next generation sequencing (NGS) panel, including BRCA1, BRCA2, and other oncogenes and tumor suppressors. We are also planning to study oncogenic pathway activation using a fit for purpose technology such as the NanoString gene expression Pan Cancer panel. New assays for candidate biomarkers associated with sensitivity or resistance to IMGN853,

identified in the current study or earlier studies, may also be developed and tested on patient samples.

IMGN853 retains the ADCC activity of the parental M9346A antibody. FcγR is the principle leukocyte receptor that mediates ADCC and FcγR polymorphisms modulate leukocyte ADCC activity. Therefore, all patients will be genotyped for FcγR alleles using peripheral blood mononuclear cells on Cycle 1 Day 1. Potential associations between FcγR genotype and clinical response will be examined.

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 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.

8. STUDY PROCEDURES

8.1. Informed Consent

Each patient or legally authorized representative sign an IRB/IEC-approved informed consent form before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care (Appendix A and Appendix B).

8.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are assessed during Screening (within 28 days prior to the first dose of any study drug on Cycle 1, Day 1). All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the patient's routine clinical management and obtained before signing an informed consent form may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the timeframe defined in the schedule of assessments. A patient is considered enrolled when randomized to a study treatment (Appendix A and Appendix B).

8.3. Confirmation of Disease Diagnosis

At Screening, disease diagnosis, and current disease status are confirmed from information in the source record (Appendix A and Appendix B).

8.4. BRCA Mutation Status

The BRCA mutation status from prior testing (information in the source record) will be recorded (Appendix A and Appendix B). Patients with a BRCA mutation (germline mutation or somatic mutation in tumor tissue) are classified as positive and patients without a known mutation will be classified as negative. Patients without known BRCA mutation status in the source record are classified as unknown. If a patient with unknown status is tested and is found to have a BRCA mutation, this patient is considered BRCA mutation positive in analyses.

8.5. Demographic/Medical History

The age, race, and gender of the patient are to be recorded during Screening for all patients who consent to the study (Appendix A and Appendix B).

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

8.6. Physical Examination, Weight, and Height

Physical examination, height (Screening only) and weight must be performed as indicated in the Schedule of Clinical Assessments (Appendix A and Appendix B). A complete physical examination - including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system - will be completed at Screening and End of Treatment. Directed physical examinations will be completed at additional time points as specified in the Schedule of Clinical Assessments.

8.7. Vital Signs

Vital signs include body temperature, blood pressure, pulse measurements, and the respiratory rate. These signs are measured as outlined in Appendix A and Appendix B.

8.8. Electrocardiogram (ECG)

A standard, single 12-lead electrocardiogram (ECG) will be performed within 14 days prior to first dose to determine study eligibility and at EOT or 30-day follow-up safety visit and as clinically indicated.

8.9. Pulmonary Function Tests

Pulmonary function tests (PFT) should include spirometry, diffusion capacity, and lung volumes. PFT will be performed at Screening and as clinically indicated (Appendix A and Appendix B).

8.10. Ocular Symptom Assessment and Ophthalmic Examination

8.10.1. Ocular Symptom Assessment

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

8.10.2. Ophthalmic Examination

An ophthalmic examination will be performed at Screening (within 14 days prior to first dose of study drug) by an ophthalmologist and will include the following: distant visual acuity, best corrected visual acuity, slit lamp examination, intraocular pressure measurement, Schirmer's test and indirect fundoscopy. Patients who experience ocular TEAEs while on study will have a complete ophthalmologic exam performed at the emergence of the symptoms and at every other cycle thereafter. All patients will have a complete ophthalmologic exam performed at the End of Treatment visit or 30-day follow-up visit (Appendix A and Appendix B).

8.11. Laboratory Assessments

A central laboratory will be used for the analysis of scheduled hematology, biochemistry and other tests collected as part of safety monitoring. Patients should be in a seated or supine position during blood collection. Screening labs (Table 17) will be performed within 14 days of first dose. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within four days of dosing and are within acceptable ranges. Repeat testing will be performed as outlined in the Schedule of Clinical Assessments (Appendix A and Appendix B) and as clinically indicated.

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

The site does not need to wait for the results of centrally analyzed laboratory assessments when an immediate clinical decision needs to be made and in those cases locally, unscheduled testing may be performed. Details on collection, shipment of samples and reporting of results by central laboratory are provided in the laboratory manual.

8.11.1. Clinical Laboratory Panels

A list of clinical laboratory tests may be found in Table 17.

Table 17: Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation Tests	Urinalysis
• Hematocrit • Hemoglobin • WBC (w/5-part differential) • RBC • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN • Calcium • Carbon dioxide • Chloride • Creatinine • Glucose • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin	• 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 beyond trace)

WBC, white blood cell count; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, International Normalized Ratio; PT, Prothrombin time; aPTT, Activated partial thromboplastin time

8.12. Pregnancy Screen

All patients of child-bearing potential will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test not more than 3 days before the first dose of

IMGN853; this test must be negative for the patient to be enrolled and to receive the study treatment (Appendix A and Appendix B).

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

8.13. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (Appendix D) will be assessed during Screening and at other times specified in the Schedule of Clinical Assessments (Appendix A and Appendix B). An assessment is not necessary on Day 1 of Cycle 1 if the Screening assessment was obtained within three days prior to Day 1.

8.14. ECHO/MUGA Scan

ECHO or MUGA scans will be performed only in patients receiving PLD (Appendix B). ECHO 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.

8.15. Tumor Response Assessment

8.15.1. Radiological Imaging

Radiographic tumor evaluation by computed tomography (CT) or MRI of chest, abdomen, and pelvis will be performed within 28 days prior to first dose of study treatment and every six weeks (±1 week) for the first 36 weeks on study and every 12 weeks (±1 week) thereafter (Appendix A and Appendix B). The same method of radiographic assessment used at Screening must be used at all subsequent radiographic evaluations. Copies of all imaging scans must be obtained and sent to a central imaging vendor designated by ImmunoGen as outlined in the Imaging Manual. The central imaging vendor will assess the quality of the images. The imaging vendor will be responsible for the formation and management of the BIRC.

Tumor response will be assessed by the investigator and by the BIRC using RECIST 1.1 (Eisenhauer 2009). Response as determined by the investigator will be recorded in the eCRFs. The BIRC assessment will be used for the primary endpoint analysis.

All time points without investigator determined progression will be assessed by BIRC in a non-expedited manner. Results of these assessments will not be communicated to the sites.

For time points with investigator-determined progression, the BIRC will perform an expedited review. While the images are assessed by the BIRC, patients should continue on the study treatment as planned if it is clinically acceptable. If the BIRC confirms disease progression, the patient must be discontinued from study treatment. If the BIRC does not confirm disease progression, the patient should continue receiving the study treatment unless there is a medical need (i.e., rapid progression or clinical deterioration) that requires an immediate change in therapy. Although progression may be determined by the investigator based upon clinical deterioration, every effort should be made to document progression using radiographic methods. The basis for determination of progression per clinical deterioration should be documented in the eCRFs.

The central imaging vendor will ensure that the central radiologists remain blinded to the local assessment from the investigator and other unblinding information. This and all other

imaging procedures will be documented in an independent review charter agreed upon between ImmunoGen and the imaging vendor before initiation of any BIRC reviews. BIRC assessment of disease progression will be used for the primary end point analysis.

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. CA-125

Serum CA-125 assessments will be performed within 14 days prior to the first dose of study treatment, at day 1 (± 1 week) of each cycle and at each radiologic tumor evaluation thereafter (Appendix A and Appendix B). CA-125 should be assessed by the same laboratory throughout the study.

8.16. Quality of Life - EORTC QLQ-C30, EORTC QLQ-OV28, eight-item FOSI and EQ-5D-5L Questionnaires

Quality of life questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, eight-item FOSI and EQ-5D-5L (Greimel 2003, Osoba 1994, and King 2014) will be used in this trial. The questionnaires should be given to the patient and completed during their Screening visit and at other times specified in the Schedule of Clinical Assessments (Appendix A and Appendix B). The patient should not be sent home with the questionnaires to complete and return at their next visit. An assessment is not necessary on Cycle 1 Day 1 if the Screening assessment was completed within 14 days prior to Day 1.

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

8.17. Health-care Resource Utilization

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

9. ASSESSMENT OF SAFETY

9.1. Recording Adverse Events and Serious Adverse Events

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

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

The Investigator should 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, in order to ensure the safety of the patients. This may mean that observations continue beyond the last planned visit per protocol and that additional investigations may be requested by the Sponsor.

9.1.1. Definition of Adverse Events

9.1.1.1. Adverse Event (AE)

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

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

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

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

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

9.1.1.2. Serious Adverse Event (SAE)

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

- Death
- Is life-threatening
- Requires inpatient hospitalization

- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Pneumonitis is an AESI; any symptom or sign potentially suggestive of pneumonitis should be promptly reported as a SAE

Note that hospitalization is defined as admission to treat a clinical adverse event. 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 (e.g., a homeless patient) or admission not associated with a precipitating clinical adverse event (e.g., elective ore pre-planned surgery, or in-patient administration of subsequent chemotherapy, etc.).

9.1.1.3. Adverse Events of Special Interest (AESI)

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

9.1.1.3.1. IMGN853

IMGN853 has one AESI: pneumonitis.

Any symptom or sign potentially suggestive of pneumonitis should be promptly reported as per Section 9.2.1 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's appearance

9.1.2. Classification of Adverse Events

All AEs will be evaluated according to the NCI CTCAE version 4.03 (effective 14 June 2010). If the AE is not listed in the CTCAE version 4.03, it should be graded based on the description given in Table 18.

Table 18: Adverse Event Severity

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

Relationship of an AE or SAE to study medication is to be determined by the Investigator based on the definitions in Table 19.

Table 19: Adverse Event Causal Relatedness

Relationship to Product(s)	Definition
Not Related	No relationship between the event, including laboratory test abnormality, and the administration of study drug. There is no temporal relationship and there is unambiguous evidence supporting another cause.
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on study drug withdrawal may be lacking or unclear.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. The association of the clinical event, including laboratory test abnormality, must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	A clinical event, including laboratory test abnormality occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

9.2. Adverse Events

9.2.1. Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medication, which occurs in a patient from the time of informed consent until 30 days after the last study treatment, must be recorded by the clinical site on an SAE report form. The SAE must also be recorded on the patient's AE

eCRF, including the Investigator's assessment regarding the relationship of the SAE to the study treatment (IMGN853, PLD, paclitaxel or topotecan). The Investigator will promptly supply all information requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

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

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

- The underlying diagnosis or syndrome should be reported as the primary SAE term, rather than the signs or symptoms (signs and symptoms may be described in the narrative).
- An event term of "Death" should not be reported as an SAE, but rather be recorded as an outcome of a specific SAE term. Initially, the event term of "death" can be used until the actual cause of death is known. If an autopsy was performed, the autopsy report should be provided.
- Pneumonitis is an AESI; any symptom or sign potentially suggestive of pneumonitis should be promptly reported as a SAE.

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

The Investigator (or Sponsor or designee) must promptly report all SUSARs to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for review in accordance with national regulations. IRB/IEC notification of the SUSAR may take the form of a submission of a copy of the CIOMS/MedWatch report or other format accepted by the IRB/IEC. A copy of the CIOMS/MedWatch report and notification to IRB/IEC should be retained in the site's study files.

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

9.2.1.1. Reporting of Disease Progression

Disease progression and/or progression of the disease under study are anticipated occurrences in oncology drug development. They are not adverse events unto themselves.

"Progression of disease" should not be used as an AE term per se. However, any medical event/condition that is untoward in the context of disease progression 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 CRF page(s) pertaining to death should be completed immediately in order to record the disease progression/death.

9.2.2. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. Women of child bearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., 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 at least twelve weeks after the last dose of IMGN853 and for at least six months after the last dose of paclitaxel, topotecan and pegylated liposomal doxorubicin.

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

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

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

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

10. STUDY ACTIVITIES

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

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.

10.1.1. Standard of Care Assessments

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

Note that safety blood tests, and physical examination do not need to be repeated if normal and conducted within four days prior to Cycle 1, Day 1.

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 they do not feel the patient is deriving clinical benefit or because the patient is experiencing unacceptable toxicity. The reasons for which a patient may be prematurely discontinued are listed in Section 5.6.1.10, Section 5.6.2.2, Section 5.6.3.2, and Section 5.6.4.3.

Patients who withdraw or are removed from the study treatment will have an End of Treatment (EOT) visit within seven days of the decision to discontinue study treatment.

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

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.

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

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

10.3.2. Response Follow-up

Patients who have discontinued study treatment for reasons other than PD will continue tumor assessments every 12 weeks (+/- 3 weeks) until documentation of PD, withdrawal of consent or until the patient starts subsequent anti-cancer therapy, whichever comes first.

10.3.3. PFS2 and Survival Follow-up

All patients who discontinue study treatment for any reason will be followed for survival after disease progression as per BIRC, or after start of anti-cancer therapy. All patients will be followed for survival every three months (± 2 weeks) until death, lost to follow-up, withdrawal of consent for survival follow-up or until End of Study, whichever comes first.

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

11. STATISTICAL METHODS

This is a Phase 3 study designed to evaluate the efficacy of IMGN853 compared with that of standard of care chemotherapy in women with advanced EOC, primary peritoneal cancer or fallopian tube cancer.

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

A SAP will fully describe the planned analyses for this trial and will be finalized prior to database lock. The safety analyses will be based on patients who receive at least one dose of IMGN853 or investigator choice chemotherapy. The primary efficacy analyses will be performed on the intent-to-treat (ITT) population. The ITT population is defined as all randomized patients.

11.1. Sample Size

The primary endpoint for this Phase 3 study is PFS as assessed by BIRC in all randomized patients and PFS as assessed by BIRC in the FRα high expression subgroup. The study is designed to test the null hypothesis that the survival function for PFS is the same between IMGN853 arm and IC chemo arm versus the alternative hypothesis that the survival function for PFS is different between IMGN853 and IC chemo arm. The Hochberg procedure will be used to control the study-wise type I error (Appendix I). Approximately 333 patients will be randomized 2:1 (222 IMGN853 arm: 111 IC arm) over a period of approximately 21 months. The final analysis will be conducted when at least 236 PFS events are observed. An interim futility analysis will be conducted when at least 80 PFS events have been observed. The study will be terminated for futility at interim analysis if the observed hazard ratio is greater than 1 in all randomized patients as well as in the FRα high expression subgroup. The study will have 91% power to detect a hazard ratio of 0.583 in the FRα high expression subgroup and 96% power in all randomized patients at a study-wise alpha level of 5% and the study will have a 39% probability of stopping for futility at interim analysis under the null hypothesis. Sample size and power was determined by simulations using SAS® software with the following assumptions:

- median PFS for the IC arm is 3.5 months
- median PFS for the IMGN853 arm is 6 months
- exponential distribution for both event and censoring processes
- ratio of FRα high to FRα medium is 2:1
- annual censoring rate is 20% in both arms

11.2. Stratification

Randomization will be stratified by:

- Number of prior lines of therapy (1 or 2 vs. 3)
- FRα levels (≥ 75% of tumor staining at ≥2+ intensity vs. ≥ 50% and < 75% at ≥ 2+ intensity)
- IC chemotherapy (paclitaxel, PLD or topotecan)

The required FRα expression level is ≥ 50% of tumor staining at ≥2+ intensity. A stratification cut-off of ≥75% at ≥2+ will also be implemented to evaluate anti-tumor activity of IMGN853 based on higher levels of FRα expression.

Since the type of IC chemotherapy received is one of the stratification factors, it is required that the choice of the chemotherapy agent, paclitaxel or PLD or topotecan, be made prior to randomization.

11.3. Pharmacokinetic Analyses

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

11.4. Safety Analyses

Safety analyses will be based on patients who receive at least one dose of IMGN853 or investigator choice chemotherapy.

Adverse events and concomitant medication will be listed.

Adverse events will be coded using the latest MedDRA version and summarized per system organ class and preferred term.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD; June 1, 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 per 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 (patients receiving PLD), 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 ADA.

11.5. Efficacy

Efficacy analyses will be performed on an ITT basis. The ITT population is defined as all randomized patients.

An interim futility analysis will be conducted when at least 80 PFS events, as assessed by the BIRC, have been observed. If the observed hazard ratio is greater than 1 in both all randomized patients and FRα high expression subgroup, the study will be terminated for futility.

If the study continues to full enrollment of 333 patients, final analysis will be conducted when at least 236 PFS events have been observed. Hochberg procedure will be used to control the study-wise type I error.

The primary endpoint of PFS, as assessed by BIRC, will be estimated using Kaplan-Meier method. Comparison between treatment arms will be conducted using Cox proportional hazard regression and log rank test, stratified by FRα expression level (for ITT analysis only, high vs. medium), IC chemo (paclitaxel vs. PLD vs. topotecan), and number of prior lines of therapy (1 or 2 vs. 3). Unstratified analysis will also be conducted as sensitivity analysis.

The secondary endpoint of ORR (objective response = complete response [CR] + partial response [PR]) will be estimated along with a 95% CI. The ORR of the IMGN853 arm and that of the IC arm will be compared using appropriate statistics tests; all results will be presented in a table.

The secondary endpoints of overall survival (OS), duration of response (DOR), and PFS (as assessed by the investigator) will be estimated using Kaplan-Meier method. Comparison between treatment arms will be conducted using Cox proportional hazard regression and log rank test.

For ORR and DOR, the primary analysis will be based on BIRC assessment. ORR and DOR as assessed by the investigator will be summarized as sensitivity analysis.

CA-125 response will be determined using the GCIG criteria (see Appendix F). CA-125 response per GCIG criteria will be determined programmatically (see Appendix F).

Duration of Response (DOR) – DOR defined as the time from initial response until progressive disease, will be estimated for all patients who achieve a confirmed objective response (PR or CR).

Progression Free Survival (PFS) – PFS defined as the time from date of randomization until progressive disease or death whichever occurs first. Results will be summarized by arm.

Time to Second Disease Progression (PFS2) – PFS2 defined as the time from date of randomization until second disease progression or death whichever occurs first. Results will be summarized by arm.

Overall Survival (OS) – OS is defined as the time from the date of randomization until the date of death. Patients who do not experience the event of death will be censored at their last date known to be alive.

11.6. Interim Analysis

Safety analysis data will be monitored by the IDMC (Section 13.5.2) as described in the IDMC charter. An interim futility analysis will be conducted when at least 80 PFS events as assessed by BIRC have been observed. The study will be terminated for futility at interim analysis if the observed hazard ratio is greater than 1 in all randomized patients as well as in the FRα high expression subgroup. No alpha spending is planned for this futility. The SAP describes the planned IA in greater detail.

Under the enrollment assumptions (Appendix I), the interim analysis will occur when approximately 160-180 patients have been randomized. This is expected to occur approximately one year after the first patient is randomized.

11.7. Patient-Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-OV28, eight-item FOSI and the EQ-5D-5L questionnaires will be used to collect data on the patient's functioning, health-related quality of life, disease symptoms and health status.

The primary PRO endpoint is the number of patients achieving at least a 15% (≥15-point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale (items 31-36) at week 8/9 assessment (Stockler 2014). Patients with missing week 8/9 questionnaires will be included as unimproved.

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

11.8. Multiple Comparisons

11.8.1. Multiple Comparisons for Primary Efficacy Endpoints

For the primary endpoint of PFS as assessed by BIRC

- in all patients randomized to the study (intent-to-treat or ITT population) and
- in patients with high FRα level (≥ 75% of tumor staining at ≥2+ intensity)
- the Hochberg procedure (Appendix I) will be used to control the overall type I error

11.8.2. Multiple Comparisons for Key Secondary Efficacy Endpoints

For the key secondary endpoints, a hierarchical testing procedure will be used to control the overall type I error, only if the primary endpoint is statistically significant in both ITT population and FRα high subgroup. The hierarchical testing procedure will be carried out in the following order:

- Objective response rate (ORR) per RECIST 1.1 criteria as assessed by BIRC
- Primary PRO endpoint as described in Section 11.7.
- Overall survival (OS): the time from the date of randomization until the date of death

This procedure will stop at the first test not significant at a two-side alpha level of 0.05.

12. QUALITY CONTROL AND ASSURANCE

12.1. Recording of Data and Data Quality Assurance

Data will be captured using validated, electronic data capture (EDC) systems. Data will be documented in various source documents (e.g. the patient medical chart) and then manually entered into the eCRF by study site personnel. Clinical sites will be monitored by ImmunoGen or its designee to ensure the accuracy of data against source documents. If necessary, the study site will be contacted for corrections or clarifications.

Adverse events will be coded using the latest MedDRA version. Concomitant medications will be coded using the (WHO-DD; June 1, 2012 or later version. Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals (e.g., 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 or safety database in accordance with Code of Federal Regulations (CFR) 21 Part 11 compliance. The database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password protected environment. All missing data will be explained.

13. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1. Ethical and Regulatory

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and sub-Investigator(s), in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

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

13.1.1. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) 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 prescreening ICF (latter ICF is applicable for sites requesting permission to prescreen for FRα positivity prior to performing any additional study related tests). This approval must refer to the ICF(s) and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year or as per institutional guidelines. The IRB/IEC must be notified of completion of the study and a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor or designee. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs, which are subject to expedited reporting to the FDA or other regulatory agencies (SUSARs), must be submitted promptly to the IRB/IEC.

13.1.2. Patient Information and Consent

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 ICF that includes information about the study will be prepared and given to the patient, or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements. The ICF must be in a language understandable to the patient or the patient's legally authorized representative(s) and must specify who informed the patient or the patient's legally authorized representative.

After the patient has been given ample time to read and ask questions regarding the informed consent form 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 13.3.

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

A model of the prescreening and the main study ICF will be provided to the sites separately for this protocol. The main study consent can be used to confirm a patient's consent to all study procedures and all study-specific screening tests. The prescreening ICF can be used to prescreen patients for FRα status prior to performing any additional study related tests. If patient is eligible based on FRα expression level, the patient will be provided the main study

consent and only after signing the main study ICF will additional study-specific screening tests be performed. Alternatively, patient can be consented on both prescreening and main study ICF at the same time; and FRα testing and study-specific screening assessments can be carried out in parallel.

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

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

13.3. Patient Confidentiality

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

13.4. Study Monitoring

ImmunoGen personnel and the designee (CRO) will review the protocol and the eCRFs with the Investigator and the site staff at a site initiation visit. Monitoring procedures that comply with current GCP guidelines will be followed. On-site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor). On-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. During the monitoring visits the field monitor will check the progress of enrollment, and ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel from the site must be available to assist the field monitor during these visits. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (e-mail, letter, telephone, and facsimile).

The investigator must maintain source documents for each patient in the study, consisting of all visit notes, laboratory data, electrocardiograms, and the results of any other tests or assessments. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs is required. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

13.5. Study Committees

13.5.1. Steering Committee (SC)

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

13.5.2. Independent Data Monitoring Committee (IDMC)

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

13.6. Case Report Forms and Study Reports

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

13.7. Critical Documents

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

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable

- Approval/favorable opinion from the IRB/IEC clearly identifying the document and document revision reviewed, including but not limited to: the protocol, any protocol amendments, Investigator's Brochure, Patient Information/Informed Consent Form, and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form/any other written information/advertisement
- List of IRB/IEC Committee members/constitution or equivalent compliance statement
- Study and Financial agreement(s)
- Completed Form FDA 1572
- Completed Financial Disclosure Form

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.

13.8. Protocol Adherence

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

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

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

Prospective waivers or exemptions are not permitted.

13.9. End of Study

End of Study is defined as one year after the final analysis for the primary endpoint of PFS is conducted.

13.10. 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 due to an unacceptable

patient risk, the study must be terminated after appropriate consultation between ImmunoGen and the Investigators. In addition, a decision on the part of ImmunoGen to suspend or discontinue development of the test material may be made at any time.

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

13.11. Site Termination

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

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

Study or center termination and follow up will be performed in compliance with the conditions set forth in 21 Code of Federal Regulations (CFR) Section 312 and in compliance with the principles set forth in International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

13.12. Access to Source Documentation

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.13. Audits and Inspections

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

crosschecking with source documents, and clarification of administrative matters will be performed.

13.14. Data Generation and Analysis

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

13.15. Retention of Data

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

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

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

13.16. Financial Disclosure

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

13.17. Insurance Compensation

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

13.18. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the

information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Information obtained during the conduct of this study will be used by ImmunoGen in connection with the development of the study drug. The study Investigator is obliged to provide ImmunoGen with complete test results and all data developed in this study. The Sponsor has full ownership of the original case report forms completed as part of the study. This information may be disclosed to other physicians who are conducting similar studies and to the FDA 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 ARM 1 (IMGN853) AND ARM 2 (IC: TOPOTECAN) – 3 WEEK CYCLE

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4		EOT	30-Day Follow-up (+14 Days)
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8		
Informed consent	●[a]													
Demography	●[a]													
Medical History	●[a]													
Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation	●[a]													
Review and document I/E	●													
Confirm patient continues to satisfy I/E Criteria		●												
Height	●[a]													
Physical Examination[b]	●[c]	●[f]	●	●	●[f]	●	●	●[f]	●	●	●[f]		●	●
Weight	●[c]	●			●			●			●		●	●
Vital signs[d]	●[c]	●[d]	●	●	●[d]	●	●	●[d]	●	●	●[d]		●	●
Pulmonary Function Tests[e]	●[a]													
ECOG PS	●[c]	●			●			●			●		●	●
Hematology and Chemistry[o]	●[c]	●[f]	●	●	●[f]	●	●	●[f]	●	●	●[f]	●	●	●

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4		EOT	30-Day Follow-up (+14 Days)
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8		
Coagulation (PT/INR/aPTT)	●[c]	●[f]			●[f]			●[f]			●[f]			●
Urinalysis	●[c]	●[f]			●[f]			●[f]			●[f]			●
Pregnancy Test (urine or Serum)[g]	●	●			●			●			●			●
Documentation of BRCA mutation status[p]	●[a]													
Ophthalmic examinations[h]	●[c]	Every other cycle (from point at which treatment-emergent eye disorder was first reported)[h]											●[h]	●[h]
Ocular Symptom Assessment[i]	●[c]	●			●			●			●		●	●
Radiologic tumor assessments	●[a]	Every 6 weeks (± 1 week) for first 36 weeks then every 12 weeks (± 1 week)[j]											●[k]	●[k]
CA-125	●[c]	At day 1 of each cycle (± 1 week) and at every 6 weeks (± 1 week) for first 36 weeks then every 12 weeks (± 1 week)[j]											●[k]	●[k]
12-Lead ECG	●[c]												●[m]	●[m]
Quality of Life (QoL) assessment EQ-5D-5L	●[c]	●			●			●			●		●[n]	
Quality of Life (QoL) assessment EORTC QLQ-C30, EORTC QLQ-OV28 Eight-item FOSI	●[c]	●	Every 9 weeks (± 1 week) until disease progression as assessed by BIRC										●	
IMGN853 Administration Arm 1		●			●			●			●			

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4		EOT	30-Day Follow-up (+14 Days)
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8		
Topotecan Administration Arm 2		●[1]			●[1]			●[1]			●[1]			
AE and SAE assessments	●	●	●	●	●	●	●	●	●	●	●		●	●
Record concomitant medications	●	●	●	●	●	●	●	●	●	●	●		●	●

NOTE: This schedule of assessments will also be used for patients enrolled on amendment 6 of the protocol, who will crossover to the IMGN853 Arm.
EOT = End of Treatment

a. Within 28 days prior to the start of Cycle 1, Day 1.
b. Directed physical examination is acceptable while on study treatment. Full examination is required at Screening and the 30-day Follow-up visit.
c. Within 14 days prior to the start of Cycle 1, Day 1.
d. Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured predose within 10 minutes prior to start of infusion and at 10 minutes following completion of the infusion.
e. Pulmonary function tests (PFTs) should include spirometry, diffusion capacity, and lung volumes. PFTs will be performed at Screening, within 28 days prior to C1D1, and in the event of pulmonary symptoms as clinically indicated.
f. Day 1 laboratory assessments and physical exam may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled drug administration. 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, prior to dosing on Day 1 of every cycle (it can be performed up to 3 days prior to Day 1) and at the 30-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
h. Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days of first dose and will include the following: visual acuity (with/without corrective lens; whichever best reflects the patient's usual functioning), slit lamp examination, intraocular pressure measurement, Schirmer's test and indirect fundoscopy. All patients will have a complete ophthalmologic exam performed at the End of Treatment visit or 30-Day Follow-up visit.
i. Ocular symptoms assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.
j. Radiographic tumor assessment by CT/MRI scan is to be performed every 6 weeks (± 1 week) for the first 36 weeks then every 12 weeks (± 1 week). CA-125 will be measured at Day 1 of each cycle (± 1 week) and at approximately the same time they undergo radiologic assessment, in accordance with GCIG criteria (responses will be confirmed according to GCIG criteria).
k. If a patient discontinues prior to documentation of PD, a tumor assessment and CA-125 will be assessed at the End of Treatment visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed every 12 weeks (± 1 week) until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 every 12 weeks (±3 weeks) until documentation of PD, starting a subsequent anti-cancer therapy or for up to one year from Cycle 1, Day 1, whichever comes first.

l. Topotecan administered daily on Days 1-5; no assessments performed on Days 2-5.
m. ECG will be performed at EOT or 30-day follow-up visit.
n. EQ-5D-5L assessment will also be performed at the first post-progression survival follow-up visit.
o. As listed in Table 17
p. As defined in Section 8.4

APPENDIX B. SCHEDULE OF CLINICAL ASSESSMENTS – ARM 2 (IC: PLD, PACLITAXEL AND TOPOTECAN)- 4 WEEK CYCLE

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4			EOT	30-Day Follow-up (+14 Days)
		Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22		
Informed consent	●[a]														
Demography	●[a]														
Medical History	●[a]														
Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation	●[a]														
Review and document I/E	●														
Confirm patient continues to satisfy I/E Criteria		●													
Height	●[a]														
Physical Examination[b]	●[c]	●	●		●	●		●	●		●			●	●
Weight	●[c]	●			●			●			●			●	●
Vital signs[d]	●[c]	●[d]	●	●	●[d]	●	●	●[d]	●	●	●[d]	●[m]	●[n]	●	●
Pulmonary Function Tests[e]	●[a]														

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4			EOT	30-Day Follow-up (+14 Days)
		Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22		
ECOG PS	●[c]	●			●			●			●			●	●
Hematology and Chemistry[r]	●[c]	●[f]	●	●	●[f]	●	●	●[f]	●	●	●[f]	●[q]		●	●
Coagulation (PT/INR/ aPTT)	●[c]	●[f]			●[f]			●[f]			●[f]				●
Urinalysis	●[c]	●[f]			●[f]			●[f]			●[f]				●
Pregnancy Test (urine or Serum)[g]	●	●[g]			●[g]			●[g]			●[g]				●[g]
Documentation of BRCA mutation status[s]	●														
ECHO/MUGA[h] (only for patients receiving PLD)	●[a]										Every 4 cycles or as clinically indicated			●	
Ophthalmic examinations[i]	●	Every other cycle (from point at which TEAE was first reported)[i]												●[i]	●[i]
Ocular Symptom Assessment[j]	●	●			●			●			●			●	●
Radiologic tumor assessments	●[a]	Every 6 weeks (± 1 week) for first 36 weeks then every 12 weeks (± 1 week)[k]												●[l]	●[l]

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥4			EOT	30-Day Follow-up (+14 Days)
		Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22	Day 1	Days 8 & 15	Day 22		
CA-125	●[c]	At day 1 of each cycle (± 1 week) and at every 6 weeks (± 1 week) for first 36 weeks then every 12 weeks (± 1 week)[k]												●[l]	●[l]
12-Lead ECG	●[c]													●[o]	●[o]
Quality of Life (QoL) assessment EQ-5D-5L	●[c]	●			●			●			●			●[p]	
Quality of Life (QoL) assessment EORTC QLQ-C30, EORTC QLQ-OV28 Eight-item FOSI	●[c]	●	Every 8 weeks (± 1 week) until disease progression as assessed by BIRC											●	
IMGN853 Administration		●			●			●			●				
PLD administration		●			●			●			●				
Topotecan administration		●	●		●	●		●	●		●	●			
Paclitaxel administration		●	●	●	●	●	●	●	●	●	●	●	●		
AE and SAE assessments	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medications	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

NOTE: This schedule of assessments will also be used for patients enrolled to the IMGN853 Q4W schedule in amendment 3 of the protocol.

EOT = End of Treatment

a. Within 28 days prior to the start of Cycle 1, Day 1
b. Directed physical examination is acceptable while on study treatment. Full examination is required at Screening and the 30-day Follow-up visit.
c. Within 14 days prior to the start of Cycle 1, Day 1
d. Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured predose within 10 minutes prior to start of infusion and at 10 minutes following completion of the infusion on Day 1 of all Cycles.
e. Pulmonary function tests (PFTs) should include spirometry, diffusion capacity, and lung volumes. PFTs will be performed at Screening, within 28 days prior to C1D1, and in the event of pulmonary symptoms as clinically indicated
f. Day 1 laboratory assessments and physical exam may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of treatment. 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 prior to dosing on Day 1 of every cycle (it can be performed up to 3 days prior to Day 1) and at the 30-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
h. The same method of assessment technique should be used throughout the study. To be performed at Screening, every four cycles or as clinically indicated and at the End of Treatment visit. If the patient's left ventricular ejection fraction drops below normal or by at least 15% from the baseline value, study treatment should be interrupted. Discuss event with Sponsor before resuming treatment.
i. Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days of first dose and will include the following: visual acuity (with/without corrective lens; whichever best reflects the patient's usual functioning), slit lamp examination, intraocular pressure measurement, Schirmer test and indirect fundoscopy. All patients will have a complete ophthalmologic exam performed at the End of Treatment visit or 30-Day Follow-up visit.
j. Ocular symptoms assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.
k. Radiographic tumor assessment by CT/MRI scan is to be performed every 6 weeks (± 1 week) for the first 36 weeks then every 12 weeks (± 1 week). CA-125 will be measured at Day 1 of each cycle and at approximately the same time they undergo radiologic assessment, in accordance with GCIG criteria (responses will be confirmed according to GCIG criteria).
l. If a patient discontinues prior to documentation of PD, a tumor assessment and CA-125 will be assessed at the End of Treatment visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will be assessed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 every 12 weeks (±3 weeks) until documentation of PD, starting a subsequent anti-cancer therapy or for up to one year from Cycle 1, Day 1, whichever comes first.
m. Only for topotecan and paclitaxel arm
n. Only for the paclitaxel arm
o. ECG will be performed at EOT or 30-day follow-up visit.
p. EQ-5D-5L assessment will also be performed at the first post-progression survival follow-up visit.
q. On Day 8 only.
r. As listed in Table 17
s. As defined in Section 8.4

APPENDIX C. BIOMARKER, PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENTS

Activity	Screening	Cycle 1			Cycle 2	Cycle 3			Cycle 4	Cycle 6	End of Treatment	30-Day Follow-up (+14 Days)
		Day 1	Day 8	Day 15	Day 1	Day 1	Day 8	Day 15	Day 1	Day 1		
FFPE archived tumor tissue and/or fresh tumor biopsy[a]	•											
Blood sample for biomarkers		•[d]									•[d]	•[d]
Blood sample for FcγR polymorphisms (only for patients on IMGN853 treatment)		•										
Blood samples for PK[b] (only for patients on IMGN853 treatment)		•	•	•	•	•	•	•	•		•	•[e]
Blood samples for immunogenicity (ADA) assessment[c] (only for patients on IMGN853 treatment)		•			•				•	•	•	•[e]

a. Testing for FRα expression is required for all patients enrolled in the study. Patients who do not have archival tumor tissue to submit for FRα expression testing will be required to undergo tumor biopsy during the Screening period in order to confirm eligibility and undergo stratification. If the archival tumor tissue does not meet FRα criteria, a fresh biopsy tumor sample may be submitted and used to meet this criterion.
b. Blood samples for PK analysis will be taken pre-dose and within 5 minutes following IMGN853 infusion on Day 1 of Cycles 1, 2, 3, and 4; single samples will be taken on Days 8 and 15 of Cycles 1 and 3, End of Treatment and 30-Day Follow-up.
c. Blood samples for immunogenicity will be taken from the PK sample on Day 1 of Cycles 1, 2, and 4 Separate blood samples for assessment of ADA will be collected pre-dose on Day 1 of Cycle 6 (if feasible).
d. Blood sample for circulating tumor DNA will be collected pre-dose and at End of Treatment or at 30-Day Follow-up.
e. If feasible

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

(Oken 1982)

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

APPENDIX E. RESPONSE DEFINITION (RECIST 1.1)

(Eisenhauer 2009)

DEFINITIONS

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

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

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

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

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

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

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

Non-target Lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to < 15 mm short axis) and all

measurable lesions over and above the five target lesions are to be identified as non-target lesions and recorded at baseline.

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

Special Considerations

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

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

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

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

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

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

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

Imaging Methods

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

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

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

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

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

Time Point Assessments

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

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

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

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

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

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

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

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

Time Point Response Criteria

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10mm.
Partial Response (PR)	At least 30% decrease in the sum of diameters (SoD of target lesions, taking as reference the baseline SoD
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesion, taken as reference the smallest (nadir) SoD since and including baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Applicable (N/A)	No target lesions identified at baseline
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	
Non-Target Lesion TPR	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level if tumor marker at baseline is above the upper normal limit. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of CA-125 above the normal limits if CA-125 at baseline is above the upper normal limit
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (N/A)	No non-target lesions identified at baseline
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	

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

Determining Overall TPR

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

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

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

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

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

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

APPENDIX F. GYNECOLOGIC CANCER INTERGROUP (GCIG) CRITERIA FOR EVALUATION OF CA-125

(Rustin 2004)

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

Definition of response:

≥ 50% reduction in CA-125 levels from baseline

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

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

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

Timing of CA-125 assessments:

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

- The first sample would be collected within two weeks before treatment is started
- Later samples would be collected at intervals of two to four weeks during treatment and at intervals of every two or three 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 CA-125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

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

APPENDIX G. LIST OF CONCOMITANT MEDICATIONS REQUIRING CAREFUL MONITORING

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

Ref: FDA drug development resources:
(http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classSub)

APPENDIX H. ADJUSTED IDEAL BODY WEIGHT (AIBW) CALCULATION

Adjusted Ideal Body Weight (AIBW)

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

Ideal Body Weight (IBW)

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

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

APPENDIX I. SIMULATION REPORT

This section describes the assumptions, algorithms, and results of Monte-Carlo simulation studies evaluating the type I error and power under different scenarios.

Randomization and Stratification

The study will randomize 333 patients over a period of 21 months with a randomization ratio of 2:1 (222 to IMGN853 arm and 111 to IC chemo arm). The randomization will be stratified by the following factors:

- FRα expression level by IHC (≥ 75% tumor staining at ≥2+ intensity vs. ≥ 50% and < 75% tumor staining at ≥ 2+ intensity)
- Number of prior lines of therapy (1 or 2 vs. 3)
- IC chemotherapy (paclitaxel, PLD or topotecan)

Interim Futility Analysis

The study will have an interim futility analysis when at least 80 PFS events have occurred in the intent-to-treat (ITT) population. If the hazard ratio (HR, IMGN853 relative to IC chemotherapy) estimate for PFS is greater than 1 in both, ITT population and the FRα high expression subgroup, the study will be stopped for futility. Otherwise, the study will continue to full enrollment of 333 patients in the ITT population.

Primary Efficacy Endpoint

The final analysis will occur when at least 236 PFS events have occurred in the ITT population and the primary efficacy endpoint of PFS as assessed by BIRC in all randomized patients and in the FRα high expression group will be analyzed:

Hypothesis Testing

The null hypotheses are:

- H_{01}: the survival function for PFS is the same between IMGN853 arm and IC chemo arm in the ITT population, and
- H_{02}: the survival function for PFS is the same between IMGN853 arm and IC chemo arm in the FRα high expression subgroup

And the alternative hypotheses are:

- H_{a1}: the survival function for PFS is different between IMGN853 arm and IC chemo arm in the ITT population, and
- H_{a2}: the survival function for PFS is different between IMGN853 arm and IC chemo arm in the FRα high expression subgroup

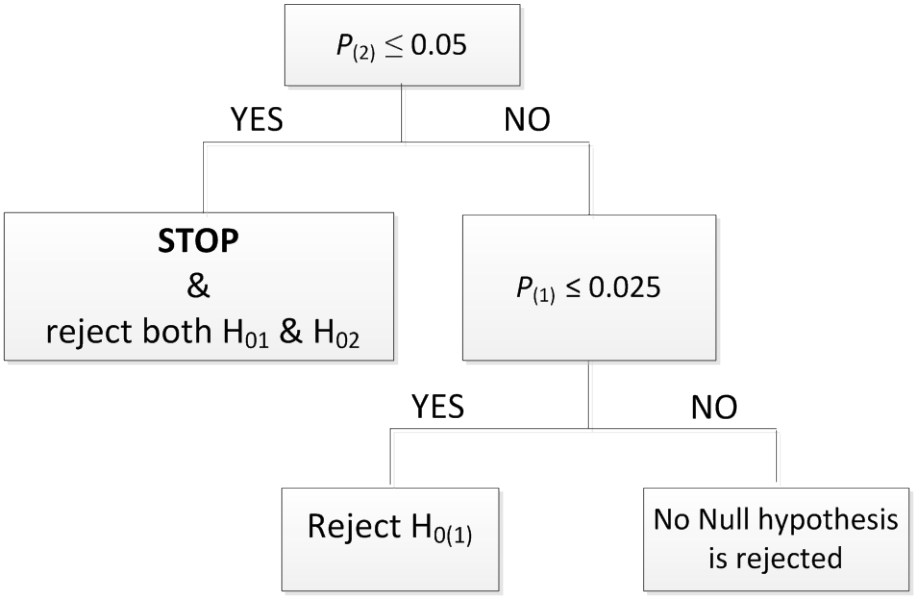
Each endpoint will be tested using stratified log-rank test (stratified by the stratification factors used in randomization).

Multiple Testing Procedure

The Hochberg procedure will be used to control the study-wise type I error. Assume the log-rank p-values for the two endpoints are $P_{(1)}$ and $P_{(2)}$ ($P_{(1)} \leq P_{(2)}$). Let $H_{0(1)}$ be the null hypothesis corresponding to $P_{(1)}$ and $H_{0(2)}$ the hypothesis corresponding to $P_{(2)}$. The Hochberg will first test $P_{(2)}$ against 0.05.

- If $P_{(2)} \leq 0.05$, then reject both H_{01} and H_{02} and claim statistical significance in both endpoints.
- If $P_{(2)} > 0.05$, then $P_{(1)}$ will be tested against 0.025.
  - If $P_{(1)} \leq 0.025$, then reject $H_{0(1)}$ and claim statistical significance for that endpoint.
  - If $P_{(1)} > 0.025$, then no null hypothesis will be rejected.

This Hochberg procedure is illustrated below (Huque 2016):



Simulation Assumptions

The following assumptions are used in the Monte-Carlo simulation studies

- Monthly enrollment rate increases linearly during first 6 months, followed by uniform enrollment during months 7-21.
- PFS follows exponential distribution for the IC chemo arm, FRα medium expression subgroup in the IMGN853 arm, and FRα high expression subgroup in the IMGN853 arm, respectively.
- Censoring process follows an exponential distribution with 1-year censoring rate of 20% for both arms.
- Ratio of number of patients between FRα high expression and medium expression is 2:1 or 1:1.
- Median PFS for IC chemo arm is 3.5 months.
- Number of trials under each scenario is 10000.

Simulation Results

Under different scenarios, the probability of stopping for futility at interim and probability of rejecting H_{01} (for ITT population) and H_{02} (for FRα high expression subgroup) are summarized in a table below. If the FRα high/medium ratio is 2:1, there is 39% probability of

stopping for futility at interim if both null hypotheses H_{01} and H_{02} are true and the overall type I error is controlled at 4.0%. Using Hochberg procedure, the study will have a 96% and 91% power to detect a median PFS of 6.0 months in the IMGN853 arm (HR=0.583) in the ITT population and FRα high expression subgroup, respectively. If the FRα high/medium ratio is 1:1, there is 37% probability of stopping for futility at interim if both null hypotheses H_{01} and H_{02} are true and the overall type I error is controlled at 3.6%. Using Hochberg procedure, the study will have a 96% and 81% power to detect a median PFS of 6.0 months in the IMGN853 arm (HR=0.583) in the ITT population and FRα high expression subgroup, respectively.

Summary of Monte-Carlo Simulations

True Median PFS (months)			**FRα High/Medium Ratio**	**Probability of Stopping for Futility at Interim Analysis**	**Probability of Rejecting**	
IC Chemo	**IMGN853 (FRα medium)**	**IMGN853 (FRα high)**			H_{01}	H_{02}
3.5	3.5	3.5	2:1	39%	2.1%	1.9%
3.5	3.5	6.0	2:1	2.1%	75%	85%
3.5	4.5	6.0	2:1	1.2%	89%	89%
3.5	5.0	6.0	2:1	0.8%	93%	90%
3.5	5.5	6.0	2:1	0.6%	95%	90%
3.5	6.0	6.0	2:1	0.5%	96%	91%
3.5	3.5	3.5	1:1	37%	1.9%	1.7%
3.5	3.5	6.0	1:1	3.4%	51%	72%
3.5	4.5	6.0	1:1	1.8%	80%	77%
3.5	5.0	6.0	1:1	1.2%	88%	79%
3.5	5.5	6.0	1:1	0.8%	93%	80%
3.5	6.0	6.0	1:1	0.5%	96%	81%

APPENDIX J. HISTORY OF AMENDMENTS

This section summarizes all amendments to the Phase 2 protocol. It is noted that amendments 1 through 4 were made prior to the enrollment of the first patient on the Phase 3 study.

Amendment 1 Summary of Key Changes

The primary reasons for amending the protocol were to revise the secondary objectives for Stage 1, revise exclusion criterion #3 to avoid inclusion of patients with pre-existing ocular conditions, update the management of ocular adverse events to align with IMGN853 program level changes, and to improve clarity and consistency between sections.

The following key changes were made to the original protocol:

- Determining the anti-tumor activity in patients with the FRα expression level ≥75% at ≥2+ intensity was removed as a secondary objective of Stage 1. Assessing the correlation between FRα level and anti-tumor activity was added as an exploratory objective in Stage 1. Study design schema was revised to reflect the same.
- Identification/evaluation of potential biomarkers in blood and tumor tissue that might predict response to IMGN853 was added as a new exploratory objective for Stage 1 and Stage 2, and relevant exploratory endpoints were included.
- Exclusion criteria 3 was revised to avoid inclusion of patients with pre-existing ocular conditions as confounding factors for the analysis.
- Stratification criteria for Stage 2 was updated to include the FRα levels, to balance the number of patients with high and low folate expression in both the arms in Stage 2.
- Number of patients planned was revised from 246 to 247 to make the total number of patients enrolled in Stage 2 divisible by 3, given the 2:1 randomization (approximately 100 patients to enroll in Stage 1; 147 patients to enroll in Stage 2).
- Management of ocular adverse events was revised to align with IMGN853 program level changes.
- Monitoring and Management of Adverse Events and for Treatment Guidelines sections were combined for easy readability and clarity.
- Dose modification guidelines for IMGN853 were tabulated for clarity and easy reference. Table 8: IMGN853 DME Definitions was replaced with Table 3: Dose modifications for IMGN853 adverse events. Table for the vital sign measurements was removed and details were outlined in Appendix A and Appendix B.
- In addition, editorial changes and text corrections were made as required.

Amendment 2 Summary of Key Changes

The primary reason for amending the protocol was to revise the table for management of potential infusion-related reactions.

Amendment 3 Summary of Key Changes

The primary reason for amending the protocol was to provide details on the rationale for the selection of dose levels and the dosing schedule for the chemotherapeutics agents in the

investigator's choice (IC) arm of Stage 2, clarification around high-risk biopsies in inclusion criteria 2, modification of the CA-125 assessment schedule and corrections for inconsistencies between sections.

The following key changes were made to amendment 3:

- Details on the rationale for the selection of dose levels and dosing schedule for paclitaxel, topotecan, PLD and gemcitabine was added.
- Inclusion criterion #4 was revised to clarify that biopsies for FRα screening be limited to procedures known to have a low risk of complications (e.g., exclusion of biopsies from brain or lung).
- Frequency of CA-125 assessments was modified from every six weeks to being assessed at day 1 of each cycle and at each radiologic tumor evaluation.
- Editorial and text corrections were made as required.

Amendment 4 Summary of Key Changes

The primary reason for amending the protocol was to add an exclusion criteria for patients with known hypersensitivity to any of the SOC drugs (gemcitabine, PLD, paclitaxel or topotecan) and revise inclusion criteria 13 regarding the use of contraception methods.

The following key changes were made to amendment 4:

- Inclusion criterion #13 was updated to exclude the use of barrier contraceptive with spermicide and partner's latex condom from the list of acceptable highly effective contraceptive methods. The length of time for the use of contraception after the last dose of SOC chemotherapy agents was added.
- Exclusion criterion #12 was added to clarify that patients with known hypersensitivity to any of the SOC chemotherapy agents are excluded from receiving that particular medicinal product but can receive one of the other possible SOC agents.

Amendment 4A Summary of Key Changes

The primary reason for amending the protocol was to add exclusion criteria for patients with inadequate coagulation parameters, untreated CNS disease or symptomatic CNS metastasis, and for women who are pregnant or lactating.

Amendment 5 Summary of Key Changes

The primary reason for amending the protocol was to close enrollment to Stage 1 of the study, and revise the trial from a Phase 2 to a Phase 3 study.

The following key changes were made:

1. The trial has been revised as a Phase 3 study in women with Folate Receptor α-positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer. The title of the study was revised to reflect these changes, and exclusion criterion #1 for male patients was added.
2. Stage 1 of the protocol was closed for enrollment. Study design schema was revised to reflect the same.
3. Dosing Schedule for Arm 1 (IMGN853) was selected to be 6mg/kg AIBW Q3W.

4. Chemotherapy agents for the IC (Arm 2) chemotherapy were updated to include only paclitaxel, PLD and topotecan.
5. Stratification factors have been revised to include, number of prior lines of therapy, FRα levels, and IC chemotherapy while BRCA mutation status has been excluded.
6. The primary endpoint was revised. Progression free survival assessed by the BIRC is the primary endpoint.
7. Secondary objectives were revised. Key secondary objectives include ORR, primary PRO endpoint using QLQ-OV28, and OS.
8. Blood-based biomarkers, such as soluble FRα was added as an exploratory end-point.
9. Patients on IC chemotherapy will have the option to crossover to the IMGN853 arm after BIRC confirmed PD. Study design schema was revised to reflect this option.
10. A window for start of treatment from randomization was added. Cycle 1 Day 1 should be within seven calendar days of randomization.
11. Inclusion criterion # 2 was added to include patients with platinum-resistant ovarian cancer
12. Inclusion criterion #4 was revised to include patients who have received at least one but no more than three prior systemic lines of therapy and for whom single agent chemotherapy is appropriate as the next line of treatment. Clarification regarding PARP inhibitor therapy considered as a prior treatment regimen while hormonal therapy not considered as a prior systemic treatment, was added.
13. If the archival tumor tissue does not meet FRα positivity by IHC (> 50% of tumor staining at >2+ intensity), a fresh biopsy tumor sample may be obtained for reassessment of FRα positivity. Inclusion criterion #6 was updated to reflect this change.
14. Inclusion criterion #12 was updated to include testing of serum albumin.
15. Exclusion criterion #3 was added to exclude primary platinum refractory patients
16. Exclusion criterion # 4 for prior radiotherapy was added.
17. Exclusion criterion # 8 was updated to specify patients with known active hepatitis B or C whether or not on active antiviral therapy are excluded.
18. Exclusion criterion # 9 was updated to exclude patients with corrected QT (QTc) >470 msec on the screening ECG
19. Exclusion criterion #10 for history of neurological condition, or concurrent neurological condition that would confound assessment of treatment-emergent neuropathy was added.
20. Exclusion criterion for patients treated with another investigational drug within four weeks of starting the study treatment was removed, as inclusion criteria #9 adequately describes the wash out period from prior therapies.
21. Exclusion criterion #20 was updated to exclude patients who have been previously treated on the study.
22. Tumor assessment schedule was revised to be performed every 6 weeks (± 1 week) for first 36 weeks and then every 12 weeks (± 1 week).

23. Quality of Life Questionnaires to be used in the study have been revised to include EORTC QLQ-C30, EORTC-OV28, eight-item FOSI and EQ-5D-5L questionnaires instead of the FACT-O questionnaire.
24. Prophylactic use of corticosteroid eye drops was mandated.
25. Collection of AEs has been revised to collect events from the time of informed consent until 30 days after patient's last study treatment.
26. Pneumonitis was added as the adverse event of special interest (AESI) for IMGN853 and reporting details were included.
27. Acceptable methods of contraception were added under Section 5.9.8.
28. Section 10 for Study Activities was revised with reference to Appendix A and Appendix B for all assessments to be performed for the respective study visits.
29. Requirement for pulse oximetry assessment was removed.
30. Requirement for post dose ECG assessments was removed. ECGs will be performed at Screening and at EOT or 30-day follow-up.
31. Requirement for triplicate ECGs as well measuring vital signs within 10 minutes following completion of ECG recording was removed.
32. Section 11 for Statistical Methods was updated with change in sample size and primary endpoint. An interim futility analysis was included with rules for study termination.
33. Statistical tests for patient reported outcomes were added.
34. Pharmacokinetic analyses were updated in view of the sparse sampling scheme to include only summary statistics of the concentration at each time point.
35. Copies of the PRO questionnaires will not be provided as part of the protocol.
36. Appendix for the CTCAE grading for the selected adverse events has been removed.
37. Simulation report describing the assumptions, algorithms, and results of Monte-Carlo simulation studies has been added under Appendix I.
38. Section on history of amendments has been moved under Appendix J.
39. Appendix K was added to provide details on the study design of the Phase 2 protocol, closing enrollment to Stage 1, revising Stage 2 of the protocol as a pivotal Phase 3 study, selection of the dosing schedule by the SSC, and how the data from the four ongoing patients from Stage 1 will be handled.

Amendment 6 Summary of Key Changes

The primary reason for amending the protocol was to correct an important typographical error in inclusion criterion # 2, which impacts the definition of the patient population under study. In the previous version of the protocol, platinum-resistant ovarian cancer was defined as disease having progressed within six months of completion of a minimum of four cycles of first-line platinum containing therapy. The descriptor "first-line" for platinum therapy was a typographical error and has been deleted.

Amendment 7 Summary of Key Changes

The primary reason for amending the protocol was to remove the option for patients on IC chemotherapy to crossover. Study schema was updated to reflect this change.

The following key changes were made:

1. The option to crossover to IMGN853 (Arm 1) after disease progression on the IC chemotherapy arm (Arm 2) was removed. The crossover option could confound overall survival, a key secondary endpoint. The study design schema and other applicable sections were revised to reflect the same.
2. Section 1.8.2 was revised to clarify that patients enrolled under amendment 6 will have the option to crossover and discontinuation of treatment for PD for these patients will be as assessed by the investigator.
3. For patients enrolled on Amendment 6, eligibility criteria to crossover to IMGN853 was moved to Appendix L.
4. Time to second disease progression (PFS2) was added as an exploratory objective and endpoint. Text was added to the statistical methods section (Section 11.5) to define PFS2.
5. Collection of information on disease progression and subsequent anti-cancer therapies during survival follow-up was added.
6. CA-125 response rate per Gynecologic Cancer Intergroup (GCIG) CA-125 criterion was added as a secondary objective for the corresponding secondary endpoint.
7. EQ-5D-5L questionnaire was added in the other secondary endpoints since it was inadvertently omitted.
8. Inclusion Criterion #4 was revised to clarify that PARP regimen given as maintenance therapy will not be counted as a prior treatment, immunotherapy such as check point inhibitors will be considered as a prior therapy, and cancer vaccines will not be considered as a prior treatment.
9. Exclusion Criterion #3 was edited to clarify the definition of primary platinum refractory epithelial ovarian cancer.
10. Exclusion Criterion #5 was edited for coagulation parameters.
11. Exclusion Criterion #9 was revised to add the LVEF parameter for patients intended to be treated with PLD if randomized to the IC chemotherapy arm. This parameter is a standard exclusion criterion for patients treated with PLD.
12. Language was added to clarify the requirement of selecting Investigator's Choice of chemotherapy agent prior to randomization.
13. Management of Ocular Disorders (Table 5) was updated with clarifications on the dose modification guidelines for Grade 2 and Grade 3 ocular TEAEs.
14. Section 8.10 on Ocular Symptom Assessment and Ophthalmic Examination was edited for clarity.
15. Justification for the prophylactic use of corticosteroid eye drops was added.
16. Text was added in the statistical methods for Quality of Life Questionnaires (patient-reported outcomes) for the analysis methods for PRO endpoints.
17. Laboratory safety assessments (Hematology and Chemistry) will also be performed on Day 8 for cycles ≥4 for patients on both treatment arms. Appendix A and Appendix B were updated to reflect the change.

18. End of Study definition was revised as one year after the final analysis for the primary endpoint of PFS has been conducted.

Amendment 8 Summary of Key Changes

The primary reason for amending the protocol was to revise inclusion criterion # 4 to include hormonal therapies and cancer vaccines as prior lines of anti-cancer therapy.

The following key changes were made:

1. Inclusion criterion #4 was revised to include hormonal therapies and cancer vaccines as prior lines of anti-cancer therapy.
2. Patients with a history of clinically active malignancy within 3 years of enrollment will be excluded. Exclusion criterion # 21 was added which provides details regarding the criterion.
3. Exclusion criterion # 8 was revised to add clarity on excluding patients with known HIV infection.
4. Synopsis was updated to reflect the revision to inclusion criterion # 4, the date of the first patient enrolled on the Phase 3 study was added and exclusion criterion # 1 was edited to be consistent with the protocol text.
5. Section 1.6.1 was revised with updates from the first-in-human Phase 1 study 0401 to align with version 6.0 of the Investigator Brochure.
6. Further clarification was added on dose modification guidelines for the ocular disorders.
7. Use of prescreening and main study ICFs was clarified.
8. Reference to QoL was changed to PRO, except when referring to the questionnaires.

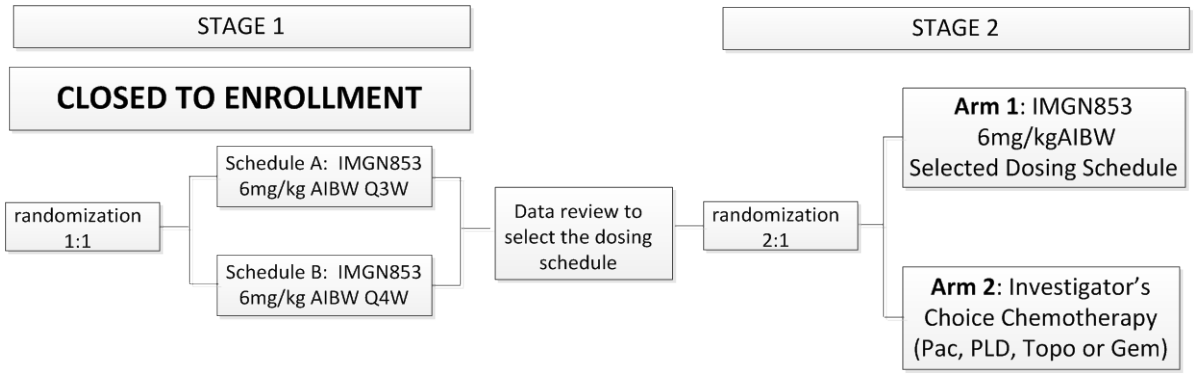
APPENDIX K. PHASE 2 STUDY PROTOCOL REVISED IN AMENDMENT 6 AS A PIVOTAL PHASE 3 STUDY

The Phase 2 study was a two-stage study, designed to select the dosing schedule for IMGN853 and to compare the efficacy of IMGN853 to that of selected standard of care chemotherapy (IC) in patients with advanced EOC, primary peritoneal cancer or fallopian tube cancer.

Stage 1 of the study was designed to test a once every four weeks dosing schedule, with the goal of reducing the occurrence of ocular TEAEs. First patient was enrolled on 02-Mar-2016 (Amendment 3) and a total of four patients were enrolled and dosed on Stage 1 of the study. Enrollment to Stage 1 is now closed. Decision to close Stage 1 was based on the recent safety data from the ongoing Phase 1, single-agent, first-in-human (FIH), study (Section 1.7.1). Safety, pharmacokinetics and anti-tumor activity data from the four patients treated on IMGN853 in Stage 1 of the study will be summarized.

The Stage 2 part of the study was revised as the current Phase 3 study.

Study Schema of the Phase 2 study:



Abbreviations: Pac: paclitaxel; PLD: pegylated liposomal doxorubicin; Topo: topotecan; Gem: gemcitabine

In Stage 1 of the study, patients were stratified by BRCA status (positive or negative/unknown) and FRα levels (≥ 75% tumor staining at ≥2+ intensity or < 75% tumor staining at ≥ 2+ intensity). Patients were randomized 1:1 into two groups as follows:

- ***Schedule A:*** IMGN853 administered at 6 mg/kg AIBW once every three weeks (Q3W)
- ***Schedule B:*** IMGN853 administered at 6 mg/kg AIBW once every four weeks (Q4W)

The primary objective for Stage 1 was to select the schedule of IMGN853 (once every three weeks versus once every four weeks) with selection based on a reduction of 15% (50% from study 0401 versus 35%) in the rate of ocular TEAEs. Safety data from study 0401 showed a 29% reduction in the rate of blurred vision (38.5% versus 54.5%) which is near the 35% that was targeted. Based on these findings, the sponsor determined that it is not essential to explore the once every four weeks dosing schedule. The data were presented to the Independent Data Monitoring Committee (IDMC) and the Schedule Selection Committee (SSC). The SSC comprised of two lead Investigators and ImmunoGen medical representatives. Both the IDMC and SSC supported this assessment, and the SSC approved

the decision to use 6 mg/kg AIBW Q3W for patients randomized to IMGN853 in this Phase 3 study.

Patients enrolled in Stage 1 of the Phase 2 study prior to the Sponsor decision will continue on the study on the respective dosing schedule to which they were assigned and follow the schedule of assessments as outlined in Appendix A (Schedule A) and Appendix B (Schedule B).

APPENDIX L. CRITERIA FOR CROSSOVER TO IMGN853 AFTER PROGRESSIVE DISEASE AS ASSESSED BY BIRC (PATIENTS ENROLLED TO AMENDMENT 6 ONLY)

Patients who discontinue IC chemotherapy for BIRC-confirmed, RECIST-defined PD will be given the option to crossover to the IMGN853 arm (Arm 1). Patients are assigned to IMGN853 after meeting the following criteria:

- ECOG performance status (PS) 0 or 1.
- Patients must complete five half-lives or four weeks whichever is shorter after the last dose of IC chemotherapy.
- Patients must have recovered from all toxicities related to reference chemotherapy to AEs Grade ≤ 1 or baseline values (CTCAE v 4.03).
- Major surgery (not including placement of vascular access device or tumor biopsies) must be completed four weeks prior to Day 1.
- Patients must have adequate hematologic, liver and kidney function and coagulation parameters (Section 3.1.1).
- Patients must fulfill exclusion criteria #4 to #14 (Section 3.1.2) and must not have untreated CNS disease or symptomatic CNS metastasis.
- Patients must crossover to the IMGN853 treatment within 56 days of BIRC-confirmed PD.
- Patients who receive non-protocol anticancer therapy after BIRC confirmed PD will not be eligible to crossover.
- Patients must complete EOT visit before crossing over to Arm 1.

A Crossover End of Treatment (CO-EOT) visit will be performed when the patients discontinue IMGN853.