# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| Study Title: | A Phase 1, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of IMGN853 in Adults with Ovarian Cancer and other FOLR1-Positive Solid Tumors |
| Study Number | 0401 |
| Study Phase: | 1 |
| Product Name: | IMGN853 |
| IND Number: | 111,915 |
| Indication: | Relapsed or Refractory FOLR1-Positive Solid Tumors |
| Investigators: | Multicenter |
| Sponsor: | ImmunoGen, Inc.<br>830 Winter Street<br>Waltham, MA 02451 USA |
| Sponsor Contact: | [redacted]<br>Phone: [redacted]<br>E-mail: [redacted] |
| Original Protocol Date: | 01 March 2012 |
| Amendment No. and Date: | Amendment 1: 13 April 2012<br>Amendment 2: 18 October 2012<br>Amendment 3: 07 March 2013<br>Amendment 4: 07 May 2013<br>Amendment 5: 18 October 2013<br>Amendment 6: 27 November 2013<br>Amendment 7: 13 August 2014<br>Amendment 8: 26 August 2014<br>Amendment 9: 25 February 2015<br>Amendment 10: 02 September 2015 |

# SPONSOR SIGNATURE PAGE

Date

[redacted]
830 Winter Street
Waltham, MA 02451
United States of America
Tel: [redacted]
FAX: [redacted]

# INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for IMGN853. I have read the ImmunoGen Protocol #0401 and agree to conduct the study as outlined and in conformance with Good Clinical Practices (GCPs) 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 |
|---|---|
| ADC | Antibody drug conjugate |
| ADCC | Antibody-dependent cell mediated cytotoxicity |
| AIBW | Adjusted ideal body weight |
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| AMC | Antibody maytansinoid conjugate |
| ANC | Absolute neutrophil count |
| ALK-P | Alkaline phosphatase |
| aPTT | Activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under the time-concentration curve |
| BAC | Bronchioloalveolar carcinoma |
| β-hCG | beta-human chorionic gonadotropin |
| BUN | Blood urea nitrogen |
| $C_{max}$ | Maximum plasma drug concentration |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CL | Clearance |
| CR | Complete response/remission |
| CRF | Case report form |
| CRC | Cohort Review Committee |
| CRO | Contract Research Organization |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose limiting toxicity |
| DM4 | N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of Response |
| EC | Endometrial cancer |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| ECG | Electrocardiogram |
| ELISA | Enzyme-linked immunosorbent assay |
| EOC | Epithelial Ovarian Cancer |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin embedded |
| FIH | First in Human |
| FOLR1, FRα | Folate receptor 1/Folate receptor α |
| GCIG | Gynecologic cancer intergroup |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GPI | Glycophosphatedylinositol |
| HADA | Human anti-drug antibody |
| HAHA | Human anti-human antibody |
| Hct | Hematocrit |
| HED | Human Equivalent Dose |
| Hgb | Hemoglobin |
| HIV | Human Immunodeficiency Virus |
| HNSTD | Highest non-severely toxic dose |
| IBW | Ideal body weight |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMGN | ImmunoGen |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LBW | Lean body weight |
| LDH | Lactic acid dehydrogenase |
| LFT | Liver function test |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| Mab | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| MRSD | Maximum Recommended Starting Dose |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NSCLC | Non-small cell lung cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| PBMC | Peripheral blood mononuclear cell |
| PCFT | Proton-coupled folate transporter |
| PD | Progressive disease |
| Pd | Pharmacodynamic(s) |
| PET | Positron emission testing |
| PFS | Progression-free survival |
| PGP | p-glycoprotein |
| PK | Pharmacokinetics |
| PO | Per orem (by mouth) |
| PR | Partial response/remission |
| PT | Prothrombin time |
| qPCR | Quantitative real time polymerase chain reaction |
| RBC | Red blood cell (count) |
| RNA | Ribonucleic acid |
| RP2D | Recommended phase 2 dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Stable disease |
| STD | Standard Deviation |
| SGOT | Serum glutamic oxaloacetic transaminase (AST) |
| SGPT | Serum glutamic pyruvic transaminase (ALT) |
| SOC | Standard of Care |
| SOP | Standard Operating Procedure |
| SoD | Sum of the longest diameters |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| STD | Severely Toxic Dose |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{1/2}$ | Half-life |
| TBW | Total body weight |
| TTP | Time to progression |
| ULN | Upper limit of normal |
| US | United States |
| VHL | Von Hippel Lindau |
| $V_{SS}$ | Volume of distribution at steady state |
| WBC | White blood cell (count) |
| WCBP | Woman of child bearing potential |
| WHO | World Health Organization |
| WHO-DD | World Health Organization –Drug Dictionary |

# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title of Study:** A Phase 1, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of IMGN853 in Adults with Ovarian Cancer and other FOLR1-positive Solid Tumors | |
| **Study center(s):** up to 10 in the United States and 1 site in Canada | |
| **Studied period (months):** Approximately 50 months (including follow up)<br>First patient enrolled: June 28, 2012<br>First patient dosed: July 9, 2012 | **Phase of development:** 1 |
| **Purpose/rationale:** IMGN853 is a specific, targeted antibody maytansinoid conjugate (AMC) that binds with high affinity to folate receptor 1 (FOLR1), a GPI-linked protein, which is highly expressed on the surface of solid tumors, particularly epithelial ovarian cancer, endometrial cancer, NSCLC and renal cell cancer. IMGN853 consists of a humanized anti-FOLR1 monoclonal antibody (M9346A) attached via a disulfide containing linker to the cytotoxic maytansinoid, DM4. Once released within the target cell, DM4 acts as an anti-mitotic agent that inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis.<br>*In vitro*, IMGN853 binds cell surface FOLR1 with high apparent affinity (≤ 0.1 nM) and shows potent ($IC_{50}$ ≤ 1 nM) and selective cytotoxicity against tumor cells expressing FOLR1. IMGN853 additionally demonstrates significant activity against FOLR1-positive xenografts, with partial and complete remissions observed in ovarian and NSCLC models. Together with the selective upregulation of FOLR1 in solid tumors, these results provide the rationale for exploring the clinical utility of IMGN853.<br>This first-in-human (FIH) Phase 1 study is designed to establish the maximum tolerated dose (MTD) and determine the recommended Phase 2 dose (RP2D) of IMGN853 when administered intravenously as a single agent in adult patients with relapsed or refractory ovarian cancer and other FOLR1-positive solid tumors. The safety, tolerability, pharmacokinetics (PK), pharmacodynamics (Pd), immunogenicity, and preliminary anti-tumor activity of IMGN853 will be characterized. Two dosing schedules will be evaluated in this study:<br>**Schedule A:** IMGN853 administered on Day 1, with cycles repeating every 21 days (Q3W)<br>**Schedule B:** IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days (modified weekly)<br>***Amendment 10 Update:*** further evaluation of dosing Schedule B has been discontinued in this study. | |
| **Objectives:** The primary objectives of this study are to determine the MTD (dose escalation) and define the RP2D (MTD expansion) for the two dosing schedules. The secondary objectives are to evaluate the safety and tolerability of IMGN853 and to characterize the PK, Pd, immunogenicity and preliminary efficacy of IMGN853. The exploratory objectives are to determine any association between FOLR1 expression levels and clinical response and to evaluate potential biomarkers in blood and tumor tissue that might predict response to IMGN853.<br>The study objectives are detailed in Sections 2.1, 2.3, and 2.5, and corresponding study endpoints are defined in Sections 2.2, 2.4, and 2.6. | |
| **Number of patients (planned):** | |

It is estimated that 209 patients* will be enrolled into the study.

- Dose Escalation Phase: (1) **Schedule A:** 44 patients (2) **Schedule B:** 25 patients
- Dose Expansion Cohort 1: Patients with epithelial ovarian cancer (EOC) which is resistant to platinum-based therapy: 40 patients
- Dose Expansion Cohort 2***:*** Advanced or recurrent uterine cancer : 20 patients
- Dose Expansion Cohort 3 : Patients with relapsed EOC, which is amenable to biopsy: 20 patients
- Dose Expansion Cohort 4: Relapsed/refractory NSCLC adenocarcinoma or bronchioloalveolar carcinoma (BAC): 20 patients
- Dose Expansion Cohort 5: Patients with EOC which has relapsed following platinum-based therapy: 40 patients; this cohort of patients will receive prophylactic corticosteroid eye drops

***NOTE:** Every effort will be made to ensure the requisite number of patients are accrued in each cohort, and to this end, communications with the site will be monitored carefully. There are instances however, where, as a result of simultaneous screening activities, patients may qualify for the study at the same time, resulting in slight over-enrollment in individual cohorts*

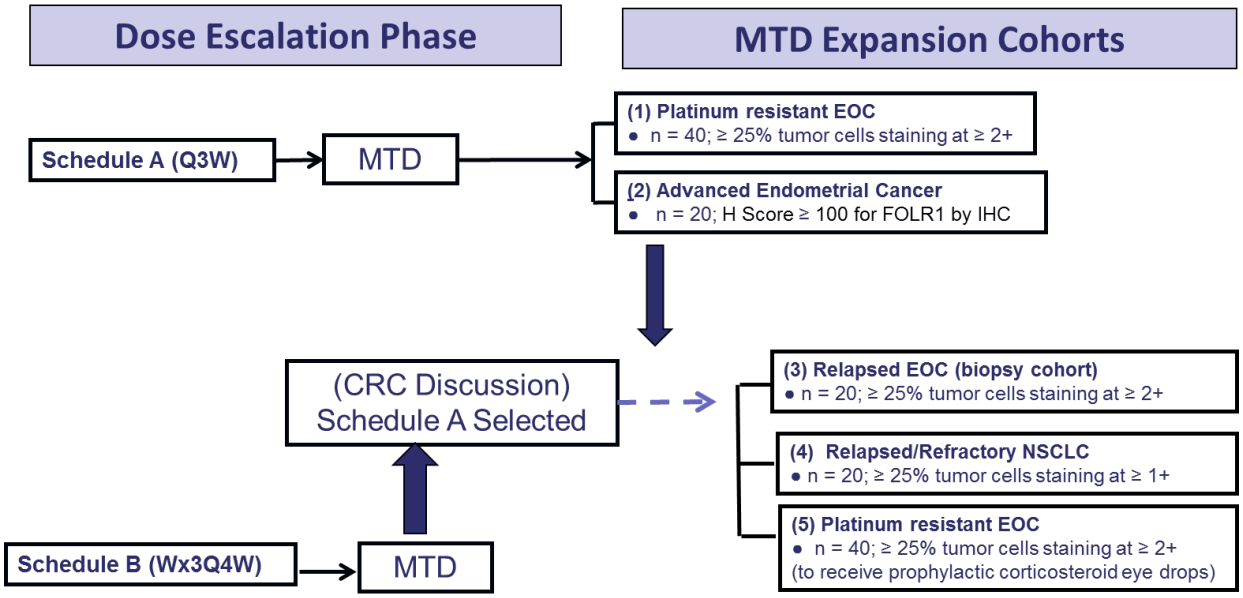
The estimated study duration is approximately 50 months for patient accrual, dosing, and follow up.

**Study Design Overview and Schema:** This is an open label, Phase 1, non-randomized, FIH study of IMGN853 in adult patients with FOLR1-positive solid tumors that have relapsed, or are refractory to standard therapies. Two dosing schedules will be evaluated in this study:

**Schedule A**: IMGN853 administered on Day 1, with cycles repeating every 21 days (Q3W)

The dose escalation phase will initially enroll 1 patient each at the first four dose levels. Patients will be enrolled to subsequent cohorts using a standard 3+3 design, with each cohort consisting of 3 or 4 to 6 patients. **Amendment 10 Update:** Dose escalation is complete and the MTD was determined to be 6 mg/kg (AIBW) and available data available to date indicate that the MTD is equal to the RP2D. Schedule A is currently being evaluated in the dose expansion cohorts.

**Schedule B:** IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days (modified weekly)




The starting dose of IMGN853 was 1.1 mg/kg, which was 1/3 the 3.3 mg/kg dose level, which was deemed clinically safe in nine patients on a Q3W schedule. All doses were calculated according to adjusted ideal body weight (AIBW). Patients were enrolled in cohorts of 3 to 6 patients and the MTD was determined to be 2.0 mg/kg (AIBW). The CRC convened to review safety, PK and efficacy data from the dose escalation cohorts, as well as available data from patients treated on Schedule A. These findings were presented at the ASCO annual meeting (Borghei 2015).

The modified weekly schedule did not provide any apparent safety or efficacy advantage. ***Based on safety and overall response data collected through May 2015, the CRC determined that all new patients will receive IMGN853 treatment according to Schedule A (Q3W) only (***Figure 2***). All new patients enrolled in the trial will receive IMGN853 at the MTD of 6 mg/kg once every three weeks. Of note, safety data that are available to date indicate that the MTD is equal to the RP2D.***

The study design and methodology is outlined in detail in Section 4.1.

**Main Criteria for Study Eligibility:**

**Diagnosis, allowable prior therapy and disease measurability:**

- **Dose Escalation Phase:**

All patients must have a pathologically documented, definitively diagnosed, advanced solid tumor that is refractory to standard treatment, for which no standard treatment is available, or the patient refuses standard therapy. Patients may have measurable or non-measurable disease. There is no upper limit on the number of prior treatment regimens the patient may have received, and prior treatment with folate receptor-targeting investigational agents is allowed.

**Enrollment (without prior documented FOLR1 expression) will be limited to the following histologic subtypes, which have a high incidence of FOLR1 positivity:**

- Serous or endometrioid EOC, primary peritoneal cancer, or fallopian tube cancer
- Serous or endometrioid endometrial cancer
- Adenocarcinoma or Bronchioloalveolar carcinoma (BAC) Non-small cell lung cancer (NSCLC)

Patients with tumor types not listed above must have confirmation of ≥ 1% tumor cells with ≥ 1 FOLR1 positivity by immunohistochemical staining (IHC) prior to enrollment (see the Laboratory Manual for IHC screening procedures). The tumor samples will be analyzed for folate receptor alpha FRα expression in the Companion Diagnostics Pharma Services CAP-accredited and CLIA-certified laboratory and Pathology Services at Ventana Medical Systems, Inc.

- **Dose Expansion Phase:**
- ***Dose Expansion Cohort 1 – patients with platinum resistant EOC***
  - Patients must have histologically-confirmed EOC, primary peritoneal cancer or fallopian tube cancer that is resistant to platinum therapy.
  - Patients must have platinum-resistant ovarian cancer, which is defined as disease that responded to primary platinum therapy and then progressed within six months or disease that progressed during or within six months of completing subsequent platinum therapy.
  - Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).
  - Patients with primary platinum refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.
  - Patients with clear cell or low grade ovarian cancer are excluded.
  - Patients should not have received more than five prior systemic treatment regimens.
  - Patients must have at least one lesion that meets the definition of measurable according to RECIST 1.1 (Appendix E).

- ***Dose Expansion Cohort 2– patients with advanced or recurrent uterine malignancies***

- Patients must have histologically-confirmed diagnosis of advanced or recurrent uterine cancer
- Patients must have confirmation of FOLR1 expression by IHC (enrollment cut-off H score ≥100).
- Patients must have received at least one platinum-based chemotherapy regimen and no more than five prior systemic treatment regimens (including cytotoxic chemotherapy, hormonal therapy, and targeted therapy, or any other investigational treatment in the adjuvant or the metastatic setting) for EC.
- The subject must have at least one lesion that is measurable on CT or MRI scan determined by investigator per RECIST Version 1.1

- ***Dose Expansion Cohort 3, relapsed ovarian cancer, which is amenable to biopsy:***
  - Patients must have relapsed EOC, primary peritoneal cancer or fallopian tube cancer; patients with primary refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.
  - Patients with clear cell or low grade ovarian cancer are excluded.
  - Patients must be willing to undergo tumor biopsy prior to the first dose of IMGN853 and on Cycle 2, Day 8±3 days.
  - Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).
  - There is no upper limit on the number of prior treatment regimens (cytotoxic and/or targeted therapies) the patient may have received.
  - Patients may have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) as defined by RECIST 1.1 (Appendix E).
- ***Dose Expansion Cohort 4, relapsed/refractory NSCLC adenocarcinoma or BAC***
  - Patients must have histologically or cytologically-confirmed NSCLC adenocarcinoma or BAC, and must be refractory to or cannot tolerate standard of care (SOC).
  - Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥1+ intensity).
  - There is no upper limit on the number of prior treatment regimens (cytotoxic and/or targeted therapies) the patient may have received.
  - Patients may have measurable or non-measurable disease (such as large masses that cannot be accurately measured) as defined by RECIST 1.1 (Appendix E).

- ***Dose Expansion Cohort 5 -*** *Patients enrolled in this cohort will receive corticosteroid eye drops as primary prophylaxis to assess whether they reduce the risk or severity of blurred vision and/or keratopathy observed following treatment with IMGN853.*

- Patients must have one of the following pathologically documented, definitively diagnosed tumor types:
  - Advanced EOC
  - Primary peritoneal cancer
  - Fallopian tube cancer
- Patients must have received at least 3 but not more than 4 prior systemic treatment regimens
- Patients must have confirmation of ≥ 2 FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).
- Patients with primary platinum refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.
- Patients with clear cell or low grade ovarian cancer are excluded.
- Patients must be willing and able to self-administer corticosteroid eye drops four times a day, for the first 10 days of each cycle, during active study treatment.
- Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) per RECIST 1.1 (Appendix E).

***Main Eligibility Criteria for All Patients:***

- Patients with CNS metastases are eligible if they meet the requirements outlined in the Inclusion Criteria (Section 3.1.1). Other standard inclusion criteria will be employed and are detailed in Section 3.1.1.
- Patients will be excluded if they have > Grade 1 peripheral neuropathy, or an active or chronic corneal disorder.
- Patients who have received prior allogeneic or autologous bone marrow transplants will not be enrolled.

**Additional exclusion criteria are detailed in Section 3.1.2.**

**Investigational product, dosage, and mode of administration:** Two IMGN853 administration schedules will be investigated:

**Schedule A:** IMGN853 administered IV on Day 1, with cycles repeating every 21 days (Q3W)

- The starting dose was 0.15 mg/kg based on total body weight.
- With amendment 5, the starting dose using adjusted ideal body weight (AIBW) was 5.0 mg/kg.

**Schedule B:** IMGN853 administered IV on Days 1, 8, and 15, with cycles repeating every 28 days (modified weekly schedule)

- The starting dose was 1.1 mg/kg, calculated using AIBW.
- The MTD was 2.0 mg/kg (AIBW). This schedule of administration will not be further evaluated in this study.

The dose of IMGN853, used in both Schedule A and Schedule B dose escalation schedules and in all expansion cohorts, will be calculated using adjusted ideal body weight (AIBW). Treatment guidelines and dose modification guidelines are detailed in Section 5.9.

**Duration of treatment:** The period of observation extends from the time the patient receives the first dose of IMGN853 until the final follow-up study visit. Patients will continue to receive IMGN853 until they develop progressive disease (PD), unacceptable toxicity, withdraw consent, or until the Sponsor terminates the study. Patients who discontinue study drug for reasons other than PD will be followed until PD or start of new anti-cancer therapy, or death, whichever occurs first.

**Statistical methods:** There will be no formal hypothesis testing. All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. 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 will be summarized. PK data will be presented descriptively and graphically.

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the Cohort Review Committee (CRC, Section 4.1.2) upon completion of each dose escalation cohort, and every 2 or 4 weeks during MTD Dose Expansion. A statistical analysis plan (SAP) will fully describe the planned analyses for this study.

**Sample Size:** Ascending doses of IMGN853 will be evaluated to identify the MTD for both dosing schedules. The actual number of patients accrued during this phase will be determined largely by the findings observed during the course of their treatment.

Following identification of the MTD for Schedule A (Q3W), there will be an expansion phase which will accrue two cohorts each at the MTD:

*(1) Dose Expansion Cohort 1:* 40 patients with platinum resistant EOC. The sample size of Schedule A Cohort 1 was increased from 20 to 40 to better define the frequency of ocular adverse events and assess the impact of the proposed toxicity management guidelines.

Given a sample size of 40 patients, the power to detect a difference of 20% (rate of Blurry vision drop from 50% to 30%) is 68% using one-sided alpha of 20% and Chi-Square test statistics.*(2) Dose Expansion Cohort 2:* 20 patients with advanced or recurrent uterine cancer.

**Amendment 10 Update:** The CRC committee met and reviewed the available safety and response data. The decision was made to proceed with Schedule A only. All new patients enrolled in the trial will receive IMGN853 at the MTD of 6 mg/kg once every three weeks. Safety data available to date indicate that the MTD is equal to the RP2D.

*(3) Dose Expansion Cohort 3:* 20 patients with relapsed ovarian cancer, which is amenable to biopsy.

*(4) Dose Expansion Cohort 4:* 20 patients with relapsed/refractory NSCLC adenocarcinoma or BAC.

*(5) Dose Expansion Cohort 5:* 40 patients with relapsed EOC. In this cohort of patients, the use of corticosteroid eye drops as part of the management plan for treatment-emergent ocular adverse events will be evaluated. Given a sample size of 40 patients, the power to detect a difference of 20% (rate of Blurry vision decrease from 50% to 30%) is 68% using one-sided alpha of 20% and Chi-Square test statistics.

Cohorts evaluated under two dosing schedules, will be referenced in clinical study documents by both cohort number and schedule (e.g. Cohort 1A).

If the true DLT rate at the MTD is 10-20%, there is a 98.5-99.9% probability of observing at least 1 dose limiting toxicity (DLT) in the 40 patient cohorts. If the true response rate at the MTD is 20%, there is a 99.9% probability of observing at least 1 response in the 40 patient cohorts.

Approximately 209 patients will be enrolled allowing for dropouts and expansion of dose escalation cohorts as needed.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# 1. INTRODUCTION

## 1.1. Target Background

Folate receptor 1 (FOLR1; aka folate receptor α, FRα) is a glycosyl phosphatidylinositol (GPI)-anchored cell surface protein that binds and internalizes folates, which are essential co-factors for one carbon transfer reactions that are required for DNA and RNA synthesis, cell growth and proliferation. Marked upregulation of FOLR1 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 FOLR1 expression and employ alternative transporters such as folate receptor β (FRβ), reduced folate carrier (RFC) and proton-coupled folate transporter (PCFT) for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004, Kelemen 2006, and IMGN853 Investigator's Brochure).

Published studies have demonstrated FOLR1 over expression by IHC in various epithelial tumors, particularly serous and endometrioid ovarian cancers, serous and endometrioid endometrial cancers, NSCLC (adenenocarcinoma or BAC histology) and clear cell renal carcinomas (Scorer 2010, Garin-Chesa 1993, Kalli 2008, Crane 2012, Franklin 1994, Dainty 2007, Jones 2008, Akram 2004, and Allard 2007). IHC results obtained at ImmunoGen are generally consistent with the literature (Table 1).

**Table 1: FOLR1 expression by IHC in epithelial ovarian cancer, endometrial cancer, NSCLC and RCC[1,2]**

| Indication | Source N positive/N tested (% positive) | | | | | |
|---|---|---|---|---|---|---|
| | IMGN[2] | | Literature Review[1] | | | |
| | ≥3 hetero[3] | Any Positivity[4] | Scorer | Garin-Chesa | Kalli | Crane |
| Epithelial Ovarian Cancer | | | | | | |
| Serous | 44/129 (34%) | 100/129 (78%) | 33/52 (63%) | 27/27 (100%) | 85/104 (82%) | 135/165 (82%) |
| Endometrioid | 15/35 (43%) | 26/35 (74%) | ND | 15/20 (75%) | 26/39 (67%) | 7/32 (22%) |
| Mucinous | 2/29 (7%) | 5/29 (17%) | 2/12 (17%) | 3/5 (60%) | 2/9 (22%) | 6/11 (55%) |
| Clear Cell | 1/5 (20%) | 3/5 (60%) | 1/7 (14%) | 3/4 (75%) | 19/30 (63%) | 4/5 (80%) |
| Transitional Cell | 0/3 | 2/3 (67%) | 2/5 (40%) | ND | ND | ND |
| **Indication** | **Source N positive/N tested (% positive)** | | | | | |
| | **IMGN[2]** | | **Literature Review[1]** | | | |
| | **≥2 hetero[5]** | **Any Positivity[4]** | **Scorer** | **Franklin** | -- | -- |
| NSCLC | | | | | | |
| Adenocarcinoma | 39/67 (58%) | 47/67 (70%) | 32/69 (46%) | 9/10 (90%) | | |
| Large Cell | 1/7 (14%) | 3/7 (43%) | 0/5 (0) | 3/5 (60%) | | |
| Squamous | 4/74 (5%) | 12/74 (16%) | 5/55 (9%) | 4/22 (18%) | | |
| Bronchoalveolar | 5/7 (71%) | 5/7 (71%) | 2/4 (50%) | 5/5 (100%) | | |

| Indication | Source N positive/N tested (% positive) | | | | | |
|---|---|---|---|---|---|---|
| | IMGN[2] | | Literature Review[1] | | | |
| | ≥2 hetero[5] | Any Positivity[4] | Scorer | Dainty | Jones | Allard |
| Endometrial Cancer | | | | | | |
| Endometrioid adenocarcinoma | 23/58 (40%) | 40/58 (69%) | 27/68 (40%) | 5/13 (38%) | 46/166 (28%) | 28/237 (12%) |
| Adenosquamous | 1/4 (25%) | 3/4 (75%) | | | | |
| Undifferentiated carcinoma | 3/4 (75%) | 3/4 (75%) | | | | |
| Squamous cell carcinoma | 0/2 | 0/2 | | | | |
| Serous/non-endometrioid | ND | ND | ND | 11/16 (69%) | 81/141 (64%) | 16/32 (50%) |

| Indication | Source N positive/N tested (% positive) | | | | | |
|---|---|---|---|---|---|---|
| | IMGN[2] | | Literature Review[1] | | | |
| | ≥2 hetero[6] | Any Positivity[4] | Scorer | -- | -- | -- |
| Clear Cell Renal Cancer | 9/34 (26%) | 29/34 (85%) | 16/67 (24%) | -- | -- | -- |

[1] Literature data reflect any positivity.
[2] IMGN data are based on an in house developed and validated IHC assay, the scoring of which is different from the CLIA validated clinical study assay. (see Investigator's Brochure)
[3] Equivalent to ≥ 25% tumor staining at ≥ 2+ by clinical study assay
[4] any positivity for IMGN data represents ≥ 1 focal IHC staining
[5] Equivalent to ≥ 25% tumor staining at ≥ 1+ by clinical study assay
[6] Equivalency to clinical study assay not yet established

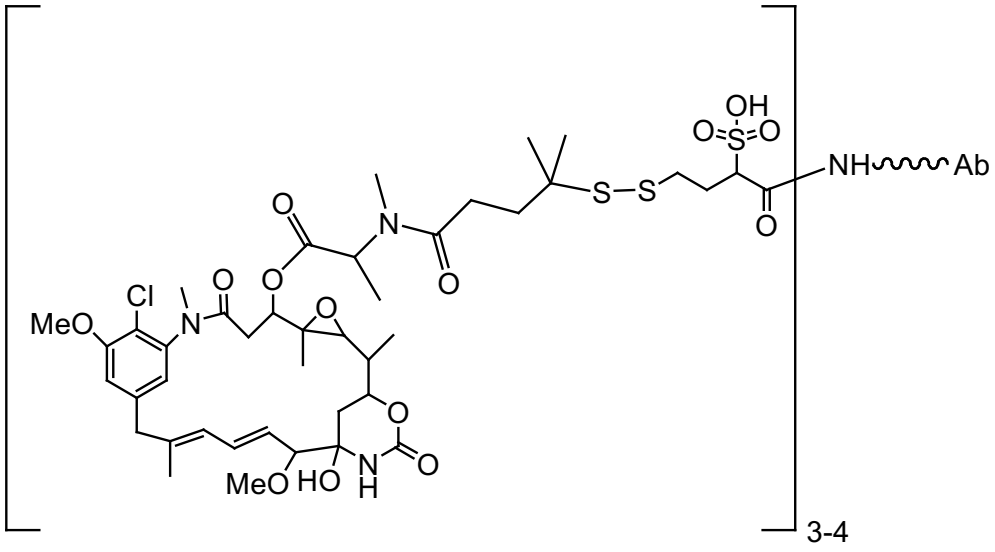
Other cancers including small cell lung cancer (SCLC; 0/13 positive), colorectal cancer (0/92 positive), pancreatic cancer (1/4 positive) and head and neck cancer (1/17 positive) tested at IMGN were largely negative for FOLR1 expression by IHC analyses (refer to Investigator's Brochure).

Several additional studies have further validated FOLR1 as a target in serous ovarian cancer. First, quantitative polymerase chain reaction (qPCR) studies show ubiquitous FOLR1 mRNA expression in serous ovarian cancer (Hough 2001) and high levels of FOLR1 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 FOLR1 expression comparably to primary tumors as shown by serial biopsy sampling and IHC (Kalli 2008, Crane 2012). Third, studies with FOLR1-specific imaging agents have demonstrated real-time FOLR1 expression at primary and metastatic tumor sites (Fisher 2008, Ghamande 2011, and van Dam 2011). Finally, a truncated form of FOLR1 has been detected in ascites and blood of ovarian cancer patients (Basal 2009, Mantovani 1994), further confirming expression in this disease and suggesting that the receptor may serve as a circulating biomarker. Collectively, these data suggest that FOLR1 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, FOLR1 has emerged as a promising target for antibody maytansinoid conjugate (AMC) therapy. AMCs 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 AMC designed to target FOLR1. It consists of the humanized anti-FOLR1 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 Mab

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

## 1.3. Epithelial Ovarian Cancer (EOC), Endometrial Cancer (EC) and NSCLC

The dose expansion phase of the study focuses on EOC, EC and NSCLC because they frequently express high levels of FOLR1and constitute significant unmet medical need.

### 1.3.1. EOC

EOC is a lethal disease with 21,990 new cases and 15,460 deaths expected in 2011. The high-grade serous subtype comprises 60 to 80% of all epithelial ovarian cancers and demonstrates the most aggressive disease course, with less than 25% of cases diagnosed in the early stages (tages I and II). This characteristic is further reflected in the poor survival statistics (Cannistra 2004). Treatment for advanced disease involves surgical de-bulking, followed by platinum/taxane-based chemotherapy. Although most patients initially respond to platinum-based chemotherapy, nearly all relapse and eventually develop drug resistant disease. Disease recurring within six months of platinum-based chemotherapy is classified as *platinum resistant*, whereas, disease recurring greater than six 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. Because platinum resistant ovarian cancer remains a significant unmet medical need, the NCCN guidelines recommend that platinum resistant patients participate in clinical trials (Morgan 2011).

### 1.3.2. NSCLC

Lung cancer is the leading cause of cancer death in the United States. Approximately 220,000 new cases of lung cancer are diagnosed in the US per year. Of these, NSCLC comprises about 75% of all lung cancers, with adenocarcinoma being the most common histology subtype. Although several chemotherapeutic agents and targeted therapies are approved for treatment of advanced lung cancer, no agents are curative and approximately 150,000 patients die each year of progressive disease. Patients with advanced disease and good performance status may benefit from platinum-based chemotherapy doublets; however, objective response rates are low and one-year survival rates remain at about 30-40% (Kelly 2001, Schiller 2002). Thus, NSCLC remains a prevalent, unmet medical need that requires new therapeutic approaches.

### 1.3.3. Endometrial Carcinoma

In the US an estimated 49,560 news cases will be diagnosed, and 8,190 deaths from endometrial cancer (EC) will occur in 2013 (American Cancer Society 2013). The 1- and 5-year relative survival rates for uterine corpus cancer are 92% and 82%, respectively. The 5-year survival rate is 95%, 67%, or 16%, if the cancer is diagnosed at a local, regional, or distant stage, respectively. Despite the generally favorable prognosis for patients with local disease, for patients with recurrent or advanced disease, there remains unmet medical need for more effective treatments. To date, there is no approved treatment for adjuvant treatment of advanced or recurrent EC. Platinum agents, paclitaxel, and doxorubicin have been investigated as single agents and in combination for primary advanced and recurrent disease. Not surprisingly, higher response rates, and greater toxicity, were observed with the combination regimens (Akram 2004, Humber 2007). The combination of paclitaxel and carboplatin is gaining favor as the preferred regimen for treating advanced and refractory EC; however, toxicity remains problematic; therefore, new treatment modalities are needed.

## 1.4. Non-Clinical Studies of IMGN 853

### 1.4.1. Pharmacology

Results of nonclinical pharmacology studies demonstrate the following:

- Marked expression of FOLR1 occurs in epithelial tumors, particularly serous and endometrioid ovarian cancers, serous and endometrioid endometrial cancers, clear cell RCC and NSCLC adenocarcinoma and BAC as assessed by IHC (Table 1 and Investigator's Brochure).
- IMGN853 shows potent ($IC_{50} \leq 1$ nM) and selective cytotoxicity towards FOLR1-positive tumor cells *in vitro* via a mechanism that involves binding to target antigen followed by IMGN853 internalization and degradation of M9346A, the antibody moiety

of IMGN853. IMGN853 processing releases the cytotoxic payload, which then kills the cell via induction of G2-M arrest and consequent apoptosis.

- *In vitro* cytotoxicity studies suggest that cells sensitive to IMGN853 express higher levels of FOLR1 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 FOLR1, capacity for uptake, internalization, and degradation by FOLR1-postive target cells, and ability to induce ADCC *in vitro*.
- IMGN853 shows significant *in vivo* efficacy against ovarian (IGROV-1, OVCAR-3, and OV-90 models) and NSCLC (NCI-H2110 model) tumor xenografts.

### 1.4.2. Pharmacokinetics

Nonclinical studies with IMGN853-cross reactive (monkey) and non-cross reactive (mouse) species were conducted to define 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. These studies are summarized here and further detailed in the IMGN853 Investigator's Brochure.

#### 1.4.2.1. Single Dose Non-GLP Studies in CD-1 Mice

IMGN853 shows biphasic pharmacokinetics upon single intravenous administration in CD-1 mice with a distribution phase that lasts about 24 hours and a terminal elimination phase that follows first-order kinetics. The elimination phase half-life of IMGN853 is about 5 days for conjugate and 10 days for the M9346A antibody component, indicating that DM4 is slowly released from IMGN853 during circulation in the mouse.

To assess the impact of conjugation on the clearance of the parental M9346A antibody component of IMGN853, PK studies were performed with radiolabeled antibody species: unconjugated M9346A[$^3$H] and IMGN853 (M9346A[$^3$H]-sulfo-SPDB-DM4). Unconjugated M9346A[$^3$H] and IMGN853 (M9346A[$^3$H]-sulfo-SPDB-DM4) show biphasic pharmacokinetics upon intravenous administration in CD-1 mice, with a distribution phase that lasts about 24 hours and a terminal elimination phase that follows first-order kinetics. The clearance-dependent pharmacokinetic parameters, $t_{1/2,}$ CL, and $AUC_{0-\infty}$, were similar for both unconjugated M9346A[$^3$H] and IMGN853 (M9346A[$^3$H]-sulfo-SPDB-DM4), indicating that conjugation of DM4 has minimal impact on the plasma pharmacokinetic properties of M9346A antibody in CD-1 mice.

#### 1.4.2.2. Single Dose Toxicokinetics of IMGN853 in Cynomolgus Monkeys

The pharmacokinetic profiles of IMGN853 and its M9346A antibody component were determined as part of a study to evaluate the toxicity of IMGN853 in cynomolgus monkeys administered as a single intravenous (slow bolus) injection. The plasma clearance of IMGN853 was measured using sandwich ELISA techniques, and showed an initial distribution phase of about 24 hours followed by a slower terminal elimination phase, with half-life of about 4 days for the conjugate. At all dose levels of IMGN853 (1, 3, 5 and 10 mg/kg), the conjugate clearance

profiles and distribution volumes were similar, and both $C_{max}$ and $AUC_{0-\infty}$ increased with increasing conjugate dose, suggesting linear pharmacokinetics. The volume of distribution at steady state ($V_{SS}$) estimated from plasma concentrations of IMGN853 assessed over time, was in the range of the expected plasma volume of the animal.

#### 1.4.2.3. PK of Free DM4 in Cynomolgus Monkeys

The plasma concentration of the maytansinoid in IMGN853, DM4, was evaluated in the cynomolgus monkey following administration of an IV dose of 0.1 mg/kg. Free maytansinoid levels were measured using a sensitive ELISA method (LLQ = 3.6 ng/mL) that utilized a murine monoclonal anti-maytansinoid antibody. The free maytansinoid concentration in plasma was about 0.56 µg/mL at 30 minutes post-infusion, falling below the limit of detection by 7 hours post infusion. The observed rapid reduction in plasma concentration for free DM4 in the monkey is consistent with the pharmacokinetic parameters reported for maytansine in mice, which are characterized by a rapid initial distribution phase, a large volume of distribution (9.8 L/kg), and a rapid terminal elimination phase ($t_{½}$ about 2h).

### 1.4.3. Toxicology

A comprehensive nonclinical toxicology program has been conducted in mice and monkeys to support the use of IMGN853 in clinical trials in humans. These studies are summarized here and further detailed in the IMGN853 Investigator's Brochure. Cynomolgus monkey was considered the most appropriate species for GLP toxicology based on preclinical work, which included sequence comparisons of FOLR1 orthologs, IHC studies of human and monkey (rhesus and cynomolgus) and binding affinity studies with rhesus monkey cell lines.

#### 1.4.3.1. Single-Dose GLP Cynomolgus Monkey Toxicology Study

A single dose GLP toxicology study was performed in cynomolgus monkeys with doses of, 1, 3, 5, or 10 mg/kg IMGN853 administered intravenously. Vehicle and IMGN853-treated animals were evaluated after a 5- or 29-day recovery period to assess the reversibility of any observed toxic effects. Test article-related effects were observed at 3, 5, and 10 mg/kg. IMGN853-related alterations were typically dose-dependent and had returned to control levels or demonstrated a significant restoration towards normal by day 29.

The principal findings included:

- Bone marrow and lymphoid toxicity (5 and 10 mg/kg groups) characterized by decreased leukocyte counts (mean WBC and lymphocyte counts), red cell mass (i.e. Red blood cell count, hemoglobin, and hematocrit), and reticulocyte counts. Bone marrow findings were characterized by generalized depletion of marrow, with decreased density of myeloid and erythroid elements. Lymphoid findings included lymphocyte depletion, germinal center loss and decreased cortical follicle size in lymph nodes and depletion of white pulp in spleen. All alterations in hematology parameters had resolved by day 7. Except for the observation of minimal bone marrow depletion in a single 10 mg/kg group male, no bone marrow and lymph node histopathology alterations were noted at the day 29 recovery necropsy.

- Transient increases in mean neutrophil count (3, 5, and 10 mg/kg groups) and fibrinogen level (10 mg/kg group) observed on study day 2 and study days 2 and 5, respectively. Both alterations resolved by study day 7.
- Injection site histopathology changes observed at the day 5 interim necropsy. These changes included superficial and perivascular inflammation, ulceration, and edema of the dermis and subcutis. Except for the observation of minimal superficial and perivascular injection site inflammation in a single 10 mg/kg group male, no injection site histopathology alterations were noted at the day 29 recovery necropsy.
- Non-adverse test article-related serum chemistry findings included lower phosphorous and potassium levels in the 3, 5, and/or 10 mg/kg group females. The lower serum levels of potassium and phosphorus did not correlate with other serum chemistry, histopathology, or clinical findings, and were considered changes of minimal toxicological or biological importance.

Although a formal *in vivo* safety pharmacology study has not been conducted with IMGN853, no treatment-related cardiovascular, respiratory, or central nervous system alterations were noted in cage-side clinical observations or veterinary physical examinations.

All laboratory abnormalities and histopathology alterations were considered non-adverse and reversible as they had returned to control levels or demonstrated a significant restoration towards normal by day 29. Based on these findings, the highest non-severely toxic dose (HNSTD) was considered 10 mg/kg.

#### 1.4.3.2. Single-Dose IV Toxicity Studies with DM4 in Mice and Monkeys

Single dose toxicity studies were performed in mice and monkeys to assess the toxicity of DM4, the cytotoxic payload of IMGN853 and to compare its toxicity with the parent maytansinoid molecule, maytansine, and the closely related chemical analogue, DM1.

In the mouse study, a single dose of DM4 (1.2-4.1 mg/kg), DM1 (1.0-3.5 mg/kg), maytansine (1.2-3.2 mg/kg) or vehicle was administered intravenously and the mice were assessed clinically daily for 15 days. Necropsy was performed at day 15 or earlier for severe morbidity. The LD50 was about 2.2 mg/kg (6.6 mg/m2) for DM4 and DM1 and 1.8 mg/kg (5.4 mg/m2) for maytansine. DM1 and DM4 showed a similar toxicity profile at all 4 tested doses. All mice survived the 1.0 mg/kg DM1 dose and only 1/8 mice died in the group treated with 1.2 mg/kg DM4, a DM4 dose equivalent to the amount of DM4 present in a ~59 mg/kg dose of IMGN853. Drug-related changes were observed in the gastrointestinal tract and bone marrow in mice terminated early due to morbidity. The incidence and severity of the tissue lesions generally increased with increasing dose. The gastrointestinal lesions were characterized by mucosal attenuation, glandular cell loss, and necrosis. Bone marrow depletion roughly paralleled the incidence of changes in the alimentary tract, and was characterized by loss of cellularity across all myeloid components. The observed changes in the alimentary tract and bone marrow were generally resolved by 15 days post-administration in the surviving animals. No compound-related histopathologic abnormalities were observed in the liver, heart, lung, or kidney at any dose level of maytansinoid tested.

In the cynomolgus monkey study, DM4 was administered at 0.1 mg/kg via intravenous infusion. Animals were assessed clinically daily and necropsies were performed on Days 5 or 29.

There were no clear DM4-related effects noted on physical examination, body temperature, electrocardiogram, indirect blood pressure, heart rate, urinalysis, or organ weight assessments.

DM4-related clinical pathology alterations included mild leucopenia primarily due to neutropenia, which corresponded microscopically to bone marrow depletion. Transient elevations in alkaline phosphatase values were noted in DM4-treated animals. Decreases in red blood cells and increases in platelets were seen in both control and treated animals.

Morphologic changes associated with administration of 0.1 mg/kg DM4 were limited to depletion of bone marrow cellular elements only at Day 5. No morphologic changes were noted at Day 29.

#### 1.4.3.3. Acute Toxicity Profile of IMGN853 (M9346A-sulfo-SPDB-DM4) and M9346A-SPDB-DM4 in Female CD-1 Mice

A study was conducted in CD-1 mice to determine the acute toxicity profile of IMGN853 which contains the novel sulfo-SPDB linker in comparison to an SPDB-DM4 conjugate for which extensive preclinical toxicity data exists. The M9346A antibody does not cross-react with the murine FOLR1 antigen, and these results represent the non-targeted tolerability profile for these conjugates. The tolerability profile and MTD (1.4 – 1.6 mg/kg based on DM4 concentration) of IMGN853 (M9346A-sulfo-SPDB-DM4) and M9346A-SPDB-DM4 were similar in CD-1 mice. The MTD of 1.4 – 1.6 mg/kg based on DM4 concentration is approximately 72-91 mg/kg based on antibody weight. A second study with additional animals (N=24/group) confirmed the results of this study (see Investigator's Brochure).

## 1.5. Rationale for the starting dose

The selection of the maximum recommended starting dose (MRSD) for this clinical trial was performed according to ICH S9 guidance. The highest non-severely toxic dose (HNSTD) observed in the GLP toxicology studies conducted in cynomolgus monkeys HNSTD was 10 mg/kg. Based on allometric scaling, the MRSD is 0.5 mg/kg, which represents 1/6 the HNSTD observed in the cynomolgus monkey toxicology study. Specifically, the value represents 1/6 of 10 mg/kg, scaled to mg/m$^2$, then calculated as a flat dose for a human with body surface area = 1.74 m$^2$ and 70 kg.

1/6 x 10 mg/kg (cyno HNSTD) x 12 (cyno conversion factor to mg/m$^2$) = 20 mg/m$^2$

20 mg/m$^2$ x 1.74 m$^2$ x 1/70 kg = 0.497 mg/kg ≈ 0.5 mg/kg

To allow an additional margin of safety, the starting clinical dose chosen was 0.15 mg/kg, which represents approximately 1/20 the HNSTD observed in the GLP toxicology study.

## 1.6. Clinical Hypothesis

A formal hypothesis will not be tested in this study. Analysis of safety, tolerability, PK, Pd, and preliminary anti-tumor activity data will help guide future development of IMGN853.

## 1.7. Rationale for the Study Plan

This is a two part Phase 1, FIH study consisting of a dose escalation phase evaluating two dosing schedules of IMGN853 administration and up to 6 dose expansion groups at the MTD. The primary aims of the dose-escalation are to evaluate the safety and tolerability of IMGN853, to

identify the MTD, and to characterize the PK profile of IMGN853 when administered IV for two dosing schedules:

**Schedule A:** IMGN853 administered on Day 1, with cycles repeating every 21 days

**Schedule B:** IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days

The patient population for the dose escalation will include patients with tumors known to express FOLR1 at high incidence (e.g. serous and endometrioid ovarian cancer, serous and endometrioid endometrial cancer, NSCLC adenocarcinoma and BAC, clear cell carcinoma) and patients with other solid tumors with detectable FOLR1 (≥1% of tumor staining at ≥1+ intensity) by IHC. Based on the favorable safety margins suggested by the non-clinical cynomolgus monkey toxicology study and to minimize patient exposure to biologically-inactive doses of IMGN853, an accelerated dose escalation will be used for the first four cohorts as detailed in Section 4.1.

**Schedule A (Q3W):** Once the MTD has been identified, enrollment to MTD dose-expansion Cohorts 1 and 2 will begin. Patients enrolled to Cohort 1 must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity) and patients enrolled to Cohort 2 will have tumors with an H score ≥ 100 for FOLR1 by IHC. The use of Schedule A in Cohort 3, 4, and 5 will be determined following review of the data for both dosing regimens, by the CRC.

**Schedule B (modified weekly):** Patients will be enrolled in cohorts of 3 to 6 patients until the MTD is defined.

**Amendment 10 Update -** The Schedule B MTD was established at 2.0 mg/kg (AIBW). The CRC to review safety, PK and efficacy results from both schedules. The modified weekly schedule did not provide any apparent safety or efficacy advantage; moreover, while the Q3W schedule PK profile analysis indicated no accumulation of IMGN853, accumulation of IMGN853 was observed using the modified weekly schedule. Based on safety and tumor response data collected and reviewed through May 2015, the CRC determined that Schedule B will not be evaluated further in the current study (Borghei 2015).

All new patients enrolled in the trial will receive IMGN853 at the MTD of 6 mg/kg once every three weeks (Figure 3). Safety data available to date indicate that the MTD is equal to the RP2D. Patients currently receiving IMGN853 study treatment according to Schedule B will continue to do so.

Safety and tolerability will be further defined for the patient populations evaluated in the Dose Expansion phase of the study. The dose expansion cohorts will additionally investigate IMGN853 Pd (MTD Expansion Cohort3), preliminary anti-tumor efficacy (MTD Expansion Cohorts 1, 2 and 4), and will assess the effectiveness of primary, prophylactic steroid eye drops in preventing or lessening ocular toxicity (Cohort 5).

a. **Expansion Cohort #1** - Patients with EOC, primary peritoneal cancer or fallopian tube cancer, which is resistant to their last platinum-based therapy, excluding those patients with primary platinum refractory disease.

b. **Expansion Cohort #2** – Patients with FOLR1-positive uterine cancer that is advanced or recurrent and has received at least one platinum-based regimen, and no more than five prior systemic treatment regimens for EC

c. **Expansion Cohort #3** – Patients with biopsy-accessible relapsed or refractory ovarian cancer, primary peritoneal cancer or fallopian tube cancer

d. **Expansion Cohort #4** – patients with relapsed and refractory NSCLC adenocarcinoma or BAC

e. **Expansion Cohort #5** - Patients with EOC, primary peritoneal cancer or fallopian tube cancer, which has relapsed following platinum-based therapy, excluding those patients with primary platinum refractory disease or low grade or clear cell ovarian cancer. *Patients enrolled in this cohort will be pre-treated with corticosteroid eye drops to assess whether prophylaxis with topical steroids prevents or lessens severity of keratopathy and blurred vision.*

Translational research studies described above and outlined in Section 7 should provide data that will help define IMGN853's mechanism of action and help guide further clinical development.

# 1.8. History of Amendments

## 1.8.1. Amendment 1 Summary of Key Changes

The following changes were made to the original protocol following FDA review according to the agency's recommendations. The key changes are noted below:

1. The starting dose was lowered to 0.15 mg/kg (1/20 HNSTD) in order to provide an extra margin of safety to study subjects.
2. The rationale for the starting dose was revised and references to the NOAEL were removed as a consequent revision as a result of the lowering of the starting dose.
3. Guidelines were added to the protocol for the management of potential IMGN853 infusion reactions.
4. AE recovery criteria for starting a new cycle of treatment have been revised.
5. Pulse Oximetry assessments were added.
6. Several corrections were made throughout the protocol to correct a number of inconsistencies noted by the FDA during protocol review.
7. Several administrative changes were made throughout the document for internal consistency and to improve readability and clarity.

## 1.8.2. Amendment 2 Summary of Key Changes

The primary reasons for amending the protocol are summarized below:

1. The conflicting instructions regarding dose escalation were removed in the Dose Escalation Guidelines section of the protocol.
2. The text describing the level of toxicity that would trigger dose expansion and reversion to 3+3 study design contained errors in the previous version. These errors were corrected.
3. Endometrioid endometrial cancer was added to the list of tumors that could be enrolled without prior documentation of FOLR1 positivity.
4. Additional guidance was provided on the reporting of SAEs including the addition of a list of events that do not meet the criteria for 'hospitalizations', defining when death is reported as an SAE vs. as an outcome, outlining what constitutes the primary event term and specifying that sites should report CIOMS/safety letters to their local IRB/IEC in accordance with their requirements.
5. Clarification was provided in the Sample Size section of the protocol, clearly stating that safety will be evaluated continuously, separately, and in aggregate in the expansion.
6. The inclusion criteria were revised to clearly state that the use of low MW heparin and low dose aspirin is permitted.
7. Guidance was added regarding those laboratory abnormalities that constitute adverse events.

8. Additional changes were made to correct typographical errors, provide minor updates (dates and contact information), correct footnote errors, and administrative corrections to improve consistency and clarity.

### 1.8.3. Amendment 3 Summary of Key Changes

The primary reasons for amending the protocol are summarized below

1. The study design was revised to allow dose escalation beyond 9.0 mg/kg; the study schema was revised accordingly.
2. The description of the patient population to be enrolled to Expansion Cohort 1 has been restricted to exclude patients with platinum-refractory disease and only focus on platinum resistant disease.
3. The enrollment estimate for the dose-escalation cohort has been increased to 30 patients; therefore, the overall enrollment estimate has been increased to 72 patients.
4. A section was added to the protocol describing clinical and PK findings to date.
5. The efficacy objectives and endpoints duration of response (DoR), progression-free survival (PFS) and time to progression (TTP) have been added. The statistics section has been updated accordingly.
6. The section of the protocol describing dosage size and vial size has been revised, as a new (larger) vial size is being made available.
7. The section of the protocol describing assignment of patient number has been updated.
8. Treatment windows have been added to allow delay in a new cycle of up to 3 days to allow patients to adjust their visit schedules in Cycles > 3.
9. A premedication regimen to prevent infusion reaction is now required for patients treated at dose levels $\geq$ 5 mg/kg. A suggested regimen is described in the protocol.
10. For patients with elevated CA125 at baseline, the schedule for obtaining samples and confirming response have been clarified.
11. Administrative changes were made for clarification purposes.

### 1.8.4. Amendment 4 Summary of Key Changes

The primary reasons for amending the protocol are summarized below

1. Guidelines have been provided in the protocol for monitoring and managing ocular toxicity. Additionally, a requirement has been added for a complete ophthalmologic examination to be performed at baseline and end of study.
2. Blood samples will be collected from patients with EOC, endometrial cancer and NSCLC to measure changes in the numbers of CTCs, and characterize FOLR1 expression on CTCs at baseline and at various time points during study participation. The protocol has been amended to add these procedures and the Exploratory Objectives section was revised accordingly (Section 1.8.7)

3. The ability to deliver the IMGN853 cytotoxic payload to tumor will be assessed by measurement of anti-maytansine in tumor specimens, using IHC methods. The protocol has been amended to add these procedures and the Exploratory Objectives section was revised accordingly.
4. The section of the protocol describing clinical experience has been updated, including the statement regarding PK findings observed to date.
5. The FOLR1 expression requirement for patients enrolled to the MTD Expansion Cohort Nos. 1 and 2 has been increased from $\geq$ 2 hetero to $\geq$3 hetero.
6. Additional Pd procedures have been added to be included for analysis of pre- and post- dose biopsy specimens (Expansion Cohort 2).
7. Cleaved caspase was removed from the Pd activity assessments.
8. A new section was added to the protocol to define "End of Study."

### 1.8.5. Amendment 5 Summary of Key Changes

1. FLT-PET procedures have been removed from the protocol.
2. The dosing regimen has been revised; an adjusted ideal body weight calculation will be employed.
3. CTCs will be collected from ovarian and endometrial cancer and NSCLC patients during dose escalation (Section 1.8.7).
4. An additional MTD expansion cohort has been added, comprised of patients with advanced or recurrent endometrial cancer.
5. Assessments of soluble FOLR1 and IMGN853 concentrations in ascites have been removed.
6. The procedures for reporting of adverse events (AEs) due to study-related procedures occurring during the screening period were clarified. The revised amendment ensures that AEs related to study procedures are captured during the screening period prior to first study drug.

### 1.8.6. Amendment 6 Summary of Key Changes

1. The study period and estimated number of patients have been updated.
2. The protocol is being amended to evaluate an additional dosing schedule: IMGN853 administered IV on days 1, 8, and 15 of each 28-day cycle.
3. The results of a PK simulation study, evaluating various multiple-dosing schedules have been added.
4. Sections of the protocol describing Pd studies have been revised for clarification and to align with objectives and endpoints.
5. The visit window for the baseline ophthalmologic examination has been increased to 7 days.

### 1.8.7. Amendment 7 Summary of Key Changes

1. The size of the MTD expansion cohorts has been increased to 20 patients each and the statistics sections of the protocol have been revised accordingly.
2. The inclusion criteria for patients enrolled to the MTD Dose Expansion#1 (Platinum-resistant ovarian cancer) have been revised.
3. The restriction excluding patients having received prior treatments with folate receptor-targeting compounds has been removed.
4. Analyses of circulating tumor cells (CTCs) have been removed.
5. Patients with RCC will be required to be pre-screened for FOLR1 positivity before being enrolled to the study.
6. The test and laboratory for the FOLR1IHC assay has been changed and threshold criteria for FOLR1 positivity have been revised. [Note: this minor change was implemented via administrative letter dated June 13, 2014.]
7. The guidelines for management of treatment-emergent eye disorders have been revised.
8. Guidelines for management of diarrhea have been added.
9. Retreatment criteria for non-hematologic criteria have been revised.
10. Lubricating, preservative-free artificial tears have been added as a daily concomitant medication for all patients.
11. The 6-hour PK time point has been removed for the Q3W PK assessments.
12. The requirement for Day 8 and Day 15 physical exams for patients treated using Schedule B, has been removed in cycles $\geq$ Cycle 4.
13. The section of the protocol describing "expectedness" of treatment-emergent adverse events has been deleted.
14. The symptom-directed physical examination has been removed from Schedule B assessments in Cycles $\geq 4$.
15. The clinical findings section of the protocol has been updated.

### 1.8.8. Amendment 8 Summary of Key Changes

1. Update the Criteria for Selection of Patient Population for Expansion Cohort #2 to clarify that patients must have measurable disease.
2. Update the Inclusion Criteria for Selection of Patient Population for Expansion Cohorts #3 and #4 to allow study participation for those patients who have received prior treatment with folate receptor-targeting compounds.
3. Clarify advised use of preservative-free, lubricating artificial tears.
4. Administrative changes were made for clarification purposes.

### 1.8.9. Amendment 9 Summary of Key Changes

1. Updated Exploratory Objectives and Endpoints.

2. The size of the MTD expansion cohort 1 has been increased to 40 patients, and the statistics sections of the protocol, the total numbers patients, and the Study Design Schema have been revised accordingly.
3. The immunohistochemistry scoring threshold that determines patient eligibility for the MTD expansion Cohort 2 (advanced endometrial cancer) was increased to an H-score of $\geq$ 100 to select the patients most likely to derive benefit from an anti-FOLR1 directed therapy.
4. An exclusion criterion was added to exclude patients with a previous clinical diagnosis of treatment-related pneumonitis.
5. An exclusion criterion referencing patients who are receiving therapeutic doses of warfarin or other anticoagulant therapy was removed.
6. The Early Clinical Safety Findings section has been replaced with a reference to the Investigator's Brochure.
7. The time for collection of the post-dose biopsy from patients enrolled in Cohort 3 has been changed to Cycle 2, Day 8±3. In addition, patients who relapsed after showing clinical benefit will be asked to provide an optional biopsy to help understand the mechanism of resistance to IMGN853.
8. A section describing the duration of the participation of the patients in the study has been added to the protocol for clarification purposes. In addition, patients who meet the RECIST criteria for PD may now be allowed to remain on study if it is determined that they receive clinical benefit as agreed upon by the Investigator and the medical monitor.
9. Sections describing the monitoring and management of infusion-related headaches, nausea and vomiting have been added to the protocol. Monitoring guidelines for pneumonitis have been added. A requirement for all patients enrolled in Schedule B to receive pretreatment with acetaminophen has been added to the protocol to align with the IB.
10. A table outlining the management and dose-modification guidelines for ocular disorders has been added for clarification purposes.
11. Update the Inclusion Criteria for Selection of Patient Population for Expansion Cohorts #2 to allow study participation for those patients who have received up to five prior systemic regimens.
12. A table outlining the IMGN853 dose modification guidelines for both Schedule A and Schedule B has been added.
13. A requirement for the use of lubricating artificial tears have been added to the Monitoring and Management of Treatment Emergent Eye Disorders and the Concomitant Medications and Procedures sections.
14. A requirement for all patients, irrespective of whether or not they display ocular treatment-emergent adverse events, to receive a complete ophthalmologic exam and ocular symptom assessment at End of Study or Follow-Up has been added. In addition, patients who experience blurred vision, but had normal eye exams are now required to have complete exams prior to Day 1 every other cycle. Appendixes A and B as well as the Study Activities section have been modified accordingly.
15. The requirement for treatment discontinuation of patients who showed clinical benefit but suffered a DLT has been removed.

16. Antiemetic and antidiarrhea medications have been added to the list of allowed concomitant medications.
17. The window for the post-dose ECG has been changed from within 10 minutes to 1 hour for logistic reasons.
18. The procedures for reporting of Serious Adverse Events have been updated.
19. Requirement for confirmation of response has been removed to align with RECIST 1.1 requirements.

Administrative changes were made for clarification purposes.

### 1.8.10. Amendment 10 Summary of Key Changes

1. The CRC decision, regarding selection of dosing schedule has been added to the protocol. As a result, Schedule B has been discontinued and all new patients enrolled in the study after implementation of this amendment will receive IMGN853 at the MTD of 6 mg/kg under Schedule A (once every three weeks). Additionally, provisional text that described actions to be taken if either Schedule A or Schedule B had been chosen has been updated for clarification purposes. Available clinical data indicates that the MTD defined for the Q3W schedule is equal to the RP2D; therefore, that statement has been added for clarification.
2. A separate cohort of patients with relapsed ovarian cancer has been added. Patients enrolled into this cohort (Cohort 5) will self-administer corticosteroid eye drops for the first 10 days of each cycle while on active study treatment. The statistics sections of the protocol, the total numbers patients, and the Study Design Schema have been revised accordingly.
3. Evaluation of effectiveness of primary, prophylactic steroid eye drops in preventing or lessening keratopathy and/or blurred vision has been added as a secondary objective, as has the corresponding endpoint.
4. The eligibility criteria for expansion cohort 2 have been broadened to include any patient with FOLR1-positive uterine cancer.
5. The wording to describe the IHC threshold positivity for the ovarian cohorts has been revised to remove the “hetero” descriptor, as it is irrelevant.
6. The eligibility criteria for expansion cohort 3 (biopsy cohort) have been revised; patients with relapsed EOC are eligible and those with primary refractory EOC are excluded.
7. An exploratory endpoint has been added. A bioinformatics approach will be used to infer the germline/somatic status of BRCA1 and BRCA2 mutations.
8. The procedure for administration of corticosteroid eye drops has been added to the protocol.
9. The procedure for administration of lubricating drops has been co-located to the section of the protocol that describes the procedure for administration of corticosteroids.
10. A table outlining the management of non-infectious pneumonitis has been added.
11. Pulmonary function tests have been added to the list of procedures that are required to be performed before Cycle 1 Day 1. The schedule of events and sections describing visits and assessments have been modified accordingly.
12. The management guidelines for nausea and vomiting have been revised to remove the requirement

for administration of dexamethasone for grade 1 nausea and/or vomiting.

13. A requirement was added to obtain a blood sample for measurement of homocysteine and methylmalonate during Cycle 2 and at the End of Treatment visit.
14. Administrative changes were made for clarification purposes.

## 1.9. Early Clinical Safety Findings

For detailed information regarding clinical safety of IMGN853, please refer to the Investigator's Brochure.

## 1.10. Clinical Pharmacology

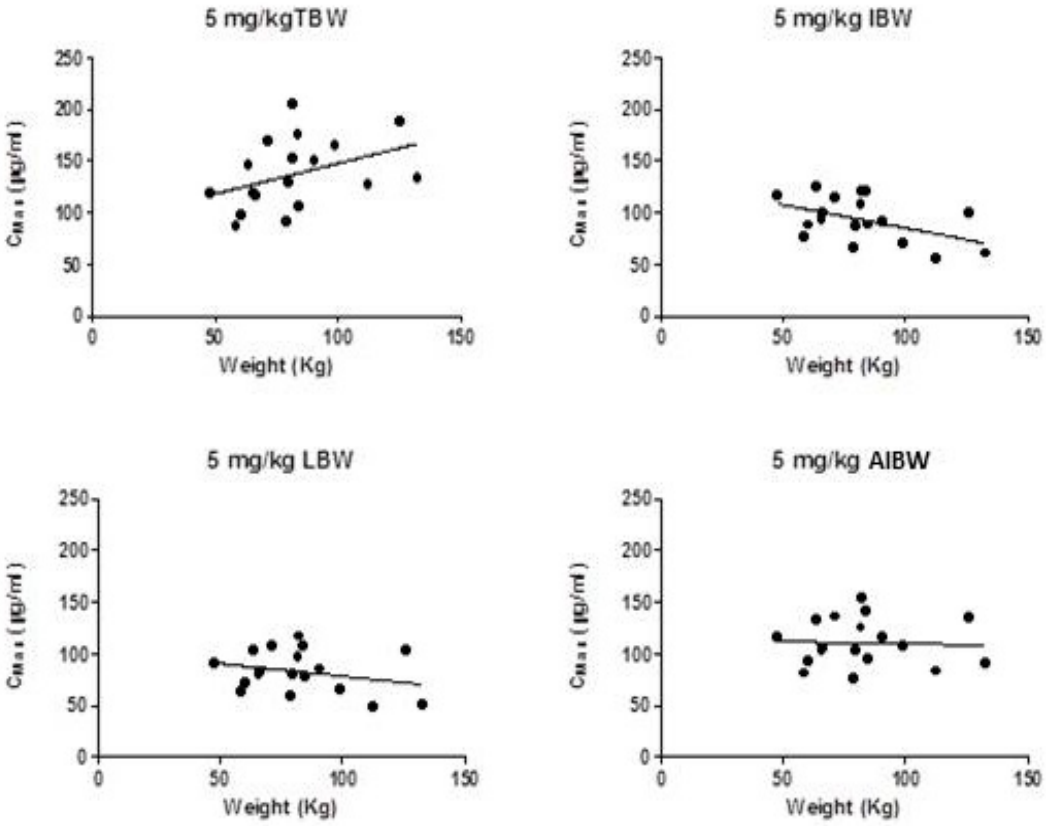
Pharmacokinetic (PK) parameters were determined for Cycle 1 dosing in each patient. The clearance of IMGN853 is shown to be rapid at low doses (CL= 1.1 mL/hr/kg) with a half-life of approximately 1.5 days. While the clearance of IMGN853 is rapid (CL= 1.1 mL/hr/kg) at the lowest dose level (0.15 mg/kg), the clearance decreases with increasing dose with a half-life of about 5 days at doses ≥ 2.0 mg/kg. The exposure (AUC) and the $C_{max}$ are shown to increase in a generally linear fashion with increasing dose of IMGN853. These data are summarized in detail in Section 5.3.1 of the Investigator's Brochure.

### 1.10.1. Rationale for Dosing Based on Adjusted Ideal Body Weight

Initial PK parameter analysis demonstrated that mean $C_{max}$ increased proportionally with the dose of IMGN853, however there was significant variability in inter-patient $C_{max}$ levels. The variability in $C_{max}$ was particularly striking in the 5 mg/kg cohort, where PK was analyzed in 10 patients with a wide range of body weights (48.2 kg – 135.8 kg). Further analysis identified a correlation between $C_{max}$ levels and the occurrence of TEAEs of ocular disorders, with higher $C_{max}$ values correlating with the occurrence of TEAEs of eye disorders. Results from these analyses are detailed in Section 5.3.3 of the Investigator's Brochure.

A number of dosing strategies were investigated in an effort to maximize IMGN853 exposure, while maintaining $C_{max}$ and $AUC_{0-24}$ levels within a range that was not associated with TEAEs of eye disorders for the great majority of patients (less than 150 µg/ml and 2785 hr*mg.ml, respectively) and with the least possible inter-patient variability in $C_{max}$. To this end, $C_{max}$ values were estimated using alternative dosing calculations for all patients treated in the 3.3 (n=3), 5.0 (n=10) and 7.0 mg/kg (n=5) dose groups. Calculated $C_{max}$ values were normalized to a 5 mg/kg dose level and compared to $C_{max}$ values observed from total body weight (TBW) dosing. Three alternate formulas were evaluated: (1) Ideal body weight (IBW), Lean Body Weight (LBW) and Adjusted Ideal Body Weight (AIBW). Of the three methods, dosing by AIBW body weight had the least total body weight dependence (Figure 2). Based on the current data, dosing by AIBW weight is expected to reduce variance in $C_{max}$ compared to dosing according to TBW for patients across a spectrum of weights. Refer to Section 5.3.3 of the Investigator's Brochure for details.

**Figure 2: Correlation Between $C_{max}$ and Total Body Weight (TBW), Ideal Body Weight (IBW), Lean Body Weight (LBW), and Adjusted Ideal Body Weight (AIBW)**




The results of the PK modeling, suggest that dosing according to adjusted ideal body weight may reduce the variation in exposure within dosing cohorts. Therefore, the adjusted ideal body weight calculation will be used to dose IMGN853 (see Section 5.8.4). For Schedule A (Q3W) a new cohort of patients will be enrolled and treated at a starting dose level of 5 mg/kg based on AIBW. In the ten patients previously treated at 5 mg/kg based on total body weight (TBW), ocular toxicity was observed in some patients, but the MTD was not exceeded and none of the ocular changes met the threshold for a DLT. Modification of the dosing method to calculate dose based on adjusted ideal body weight is predicted to reduce ocular toxicity, by minimizing peak exposure levels ($C_{max}$ and AUC 0-24hrs). The adjusted ideal body weight calculation will also be used to dose patients treated on Schedule B (modified weekly). The starting dose will be 1.1 mg/kg.

### 1.10.2. Rationale to Explore a Modified Weekly Dosing Schedule

As described in Section 1.10.1 a significant correlation between high $C_{max}$ values (≥ ~150 µg/ml) and incidence of ocular toxicity was observed across the 5 and 7 mg/kg dose levels when IMGN853 was

administered on day 1 of a 21-day cycle dosed by total body weight. Alternate dosing schedules were explored via simulation to identify the dose levels that would achieve maximal exposure with limited accumulation and a $C_{max}$ below 150 µg/ml in order to minimize ocular toxicity risk.

A population PK model based on rich and sparse (peak and trough) concentration-time profiles of IMGN853 following Q3W dosing (escalating dose) was developed. Plasma concentrations of IMGN853 were best modeled by a 3-compartment model and this model was used to simulate steady-state exposure to IMGN853 for various dosing schedules, including weekly (QW), every 2 weeks (Q2W), and weekly for 3 weeks in a 4 week cycle (modified weekly schedule).

The modified weekly dosing regimen had minimal accumulation between cycles (accumulation index of 1.06), while the QW dosing regimen resulted in the highest accumulation (accumulation index of 1.97). Comparing doses that gave equivalent $C_{max}$ levels, the modified weekly schedule allowed overall exposure increases of almost ~2-fold while limiting $C_{max}$ to levels below that observed with ocular toxicity (Table 2).

**Table 2: PK Simulation to Evaluate Fractionated Dosing Regimens**

| Schedule | Dose (mg/kg) | $C_{max}$ (µg/ml) | $C_{min}$ (µg/ml) | $C_{avg}$ (µg/ml) | $AUC_{12W}$ (h*mg/ml) |
|---|---|---|---|---|---|
| Q3W | 4.2 | 112 | 7.8 | 30 | 61 |
| Q2W | 4.1 | 119 | 18 | 44 | 89 |
| QWx3 in 4W | 3.3 | 119 | 20 | 52 | 107 |

The population PK model was also used to simulate a hypothetical population of 500 patients via Monte Carlo resampling. Descriptive statistics were derived in order to determine a dosing regimen with the percentage of subjects with $C_{max}$ < 150 µg/ml to optimize the safety profile of IMGN853. Using total body weight dosing, for the Q3W regimen, dose levels of 2.0, 3.3, and 3.8 mg/kg resulted in 99%, 95% and 90% of the population with a $C_{max}$ < ~150 µg/ml, respectively. For the modified weekly regimen, dose levels of 1.5, 2.0 and 2.5 mg/kg per dose (or 4.5, 6, and 7.5 mg/kg per cycle) resulted in 99%, 95% and 90% of the population with a $C_{max}$ < 150 µg/ml, respectively.

Results from the simulation studies suggest fractionated dosing may increase overall exposure while maintaining a lower $C_{max}$ and thus improve the toxicity profile. The schedule on which IMGN853 is administered on Days 1, 8, and 15, with cycles repeating every 28 days (modified weekly), appears to minimize accumulation while simultaneously maximizing total exposure, and maintaining $C_{max}$ levels below 150 µg/ml.

# 2. TRIAL OBJECTIVES AND ENDPOINTS

**All objectives apply to both dosing schedules and all cohorts unless otherwise noted.**

## 2.1. Primary Objectives

- Determine MTD and RP2D of IMGN853 when administered intravenously

## 2.2. Primary Endpoints

- MTD
- RP2D

## 2.3. Secondary Objectives

- Evaluate the safety and tolerability of IMGN853
- Evaluate the effectiveness of primary, prophylactic steroid eye drops in preventing or lessening keratopathy and/or blurred vision
- Characterize the PK of IMGN853 when administered intravenously
- Describe any preliminary evidence of IMGN853 antitumor activity
- Characterize the immunogenicity of IMGN853

## 2.4. Secondary Endpoints

- Treatment-emergent adverse events and clinically significant ≥ Grade 3 changes in laboratory test results, physical examination, ECGs or vital signs
- Treatment-emergent ocular adverse events
- PK parameters: $C_{max}$, AUC, terminal half-life ($t_{½}$), clearance (Cl), volume of distribution at steady state ($V_{ss}$), $T_{max}$, AUC
- Number of patients with RECIST 1.1 criteria (Appendix E) clinical responses and/or number of patients with GCIG CA-125 criteria clinical responses (Appendix F)
  - Objective response rate (ORR; MTD Expansion Cohorts # 1 and 2)
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Time to progression (TTP)
- Human-Anti-Human Antibody (HAHA) and Human-Anti-Drug Antibody (HADA) levels

## 2.5. Exploratory Objectives

- Determine the predictive value of FOLR1 expression on tumor cells as a biomarker for IMGN853 anti-tumor activity

- Explore the association of molecular alterations in oncogenic genes and pathways, and established molecular tumor subtypes (e.g. the four molecular subtypes of high grade serous ovarian cancer) with FOLR1 expression and IMGN853 antitumor activity
- Evaluate any additional tumor or blood based biomarkers that may be associated with sensitivity or resistance to IMGN853 (e.g., MDR1 expression, polymorphism)
- MTD Expansion Cohort #3 only: Characterization of post-dose biopsy samples to evaluate:
  - Presence of IMGN853 in tumor
  - Pd activity measured as changes in Ki67 from baseline, and/or other biomarkers based on emerging data
  - Changes in FOLR1 expression post-treatment and at disease progression
  - Changes in the numbers of tumor infiltrating immune cells after treatment with IMGN853
  - Mechanism of relapse or treatment emerging resistance to IMGN853

## 2.6. Exploratory Endpoints

- Evaluate FOLR1 expression by IHC (protein), qRT-PCR (mRNA) or other quantitative methods
- Establish mutational status, copy number alterations, and gene structure rearrangements in known oncogenic genes and pathways (e.g. mutations in p53, BRCA1/2 in ovarian cancer, PTEN/PIK3CA in endometrial cancer, EGFR, KRAS in NSCLC)
- Infer somatic/germline status of BRCA1/2 mutations using data generated from tumor tissue
- Analyze mRNA and/or protein expression of genes known to be over expressed or silenced in cancer, as well as genes associated with molecular cancer subtypes
- Evaluate expression and polymorphism of drug transporters such as MDR1 (i.e. PgP)
- Evaluate additional biomarkers identified in preclinical studies that may be associated with IMGN853 sensitivity or resistance
- MTD Expansion Cohort#3 Only:
  - Measure binding of IMGN853 to tumor cells in post treatment biopsy by anti-Maytansine IHC
  - Compare the number of Ki-67 positive cells in baseline biopsies with that of post-treatment biopsies using IHC
  - Compare FOLR1 expression in archival samples, baseline, and post-treatment (Cycle 2 Day8) biopsies by IHC
  - Compare the number of different types of immune cells in baseline biopsies with that of post-treatment biopsies using IHC for cell-type specific markers

- Compare FOLR1 expression and mutation status at baseline with those of biopsies taken after relapse

# 3. STUDY POPULATION

## 3.1. Criteria for Selection of Patient Population

1. Diagnosis, allowable prior therapy, and disease measurability requirements:

A. ***Dose Escalation Phase:*** All patients must have a pathologically documented, definitively diagnosed, advanced solid tumor that is refractory to standard treatment, for which no standard treatment is available, or the patient refuses standard therapy. Enrollment without prior documentation of tumor FOLR1 expression will be limited to the following histologic subtypes, which have a high incidence of FOLR1 positivity:

   a. Serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

   b. Serous or endometrioid endometrial cancer

   c. Adenocarcinoma or BAC NSCLC

   d. Additional tumor types may be eligible, but require documented expression of FOLR1 (≥1% of tumor staining at ≥1+ intensity) by IHC (see Laboratory Manual for IHC screening procedures)

   e. There is no upper limit on the number of prior cytotoxic or targeted therapies the patient may have received. Patients may have received prior treatment with investigational compounds targeting folate receptor.

   f. Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) according to RECIST 1.1 (Appendix E).

B. ***Dose Expansion Cohort 1:*** Patients must have EOC, which is resistant to platinum-based chemotherapy:

   a. Patients must have received prior platinum-based therapy for management of disease.

   b. Patients must have histologically-confirmed EOC, primary peritoneal cancer or fallopian tube cancer.

   c. Patients must have platinum-resistant ovarian cancer, which is defined as disease that responded to primary platinum therapy and then progressed within six months or disease that progressed during or within six months of completing subsequent platinum therapy.

   d. Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).

   e. Patients with primary platinum refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.

   f. Patients with clear cell or low grade ovarian cancer are excluded.

   g. Patients must not have received more than five prior systemic treatment regimens.

h. Patients must have at least one lesion that meets the definition of measurable according to RECIST 1.1 (Appendix E).

C. ***Dose Expansion Cohort 2:*** Patients must have histologically-confirmed diagnosis of advanced or recurrent uterine cancer.

a. Patients must have received at least one platinum-based chemotherapy regimen and no more than five prior systemic treatment regimens (including cytotoxic chemotherapy, hormonal therapy, and targeted therapy, or any other investigational treatment in the adjuvant or the metastatic setting) for EC.

b. Patients must have confirmation of an H score ≥100 for FOLR1 expression by IHC.

c. Patients must have at least one lesion that is measurable on CT or MRI scan determined by investigator per RECIST Version 1.1 (Appendix E).

D. ***Dose Expansion Cohort 3:*** Patients must have relapsed EOC, which is amenable to biopsy.

a. Patients must have histologically-confirmed EOC, primary peritoneal cancer or fallopian tube cancer who have progressed following completion of standard therapy.

b. Patients with primary refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.

c. Patients with clear cell or low grade ovarian cancer are excluded.

d. Patients must be willing to undergo tumor biopsy prior to the first dose of IMGN853 and on Cycle 2, Day 8±3 days.

e. Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).

f. There is no upper limit on the number of prior treatment regimens (cytotoxic and/or targeted therapies) the patient may have received.

g. Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) that can be safely biopsied. (Appendix E).

E. ***Dose Expansion Cohort 4:*** Patients must have a histologically or cytologically-confirmed diagnosis of NSCLC adenocarcinoma or BAC, and must be refractory to or intolerant of standard therapy.

a. Patients must meet the minimum requirement of FOLR1-positivity by IHC (≥25% of tumor staining at ≥1+ intensity).

b. There is no upper limit on the number or prior treatment regimens the patient may have received (cytotoxic and/or targeted therapies).

c. Patients must have measurable or non-measurable disease (such as large masses that cannot be accurately measured) per RECIST Version 1.1. (Appendix E).

F. ***Dose Expansion Cohort 5:*** Patients enrolled in this cohort will receive corticosteroid eye drops as primary prophylaxis to assess whether this treatment reduces the risk or severity of blurred vision and/or keratopathy observed in patients treated with IMGN853.

   a. Patients must have one of the following pathologically documented, definitively diagnosed tumor types:
      i. Advanced EOC
      ii. Primary peritoneal cancer
      iii. Fallopian tube cancer
   b. Patients must have received at least 3 but not more than 4 prior systemic treatment regimens.
   c. Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).
   d. Patients with primary platinum refractory disease (those who have not responded to a platinum-based regimen or experienced disease recurrence within three months of completing their first platinum-based regimen) are excluded.
   e. Patients with clear cell or low grade ovarian cancer are excluded.
   f. Patients must be willing and able to self-administer low-dose corticosteroid eye drops four times daily, for the first 10 days of each cycle, during active study treatment.
   g. Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) per RECIST 1.1 (Appendix E).

### 3.1.1. Inclusion Criteria (All Patients)

1. Patients must be willing to provide an archival tumor tissue block or slides for biomarker analysis.
2. ≥ 18 years old at the time of informed consent.
3. ECOG Performance Status 0 or 1
4. Time from Prior Therapy:
   - Systemic Anti-Neoplastic Therapy: five half-lives or four weeks, whichever is shorter (6 weeks for prior nitrosoureas or mitomycin C)
   - Radiotherapy: wide-field radiotherapy (e.g. > 30% of marrow-bearing bones) completed at least four weeks, or focal radiation completed at least two weeks, prior to starting study drug
5. Patients must have recovered or stabilized from all therapy-related toxicities.
6. 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.
7. 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 ≥ 100.0 x $10^9$/L (100,000/μL; must not have been transfused 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 ≤ 2.5 x ULN; ALT ≤ 2.5 x ULN (AST, ALT < 5 x ULN if liver metastases), and

f. Serum bilirubin ≤ 1.5 x UNL

8. Patients with CNS disease involvement are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study day 1 and they meet all of the following criteria: (1) residual neurological symptoms ≤ Grade 1 (2) No dexamethasone requirement, and (3) Follow-up MRI shows no progression of treated lesions and no new lesions appearing.
9. Patients must be willing and able to sign the informed consent form, and to adhere to the study visit schedule and other protocol requirements.
10. 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; examples include oral, parenteral, or implantable hormonal contraceptive, intra-uterine device, barrier contraceptive with spermicide, partner's latex condom or vasectomy) while on study treatment and for at least twelve weeks after the last dose of study drug.
11. WCBP must have a negative pregnancy test prior to the first dose of study treatment.
12. Male patients must agree to use a latex condom even if he has had a successful vasectomy and continue to follow these requirements for at least twelve weeks following the last dose of study drug.

### 3.1.2. Exclusion Criteria (All Patients)

1. Grade >1 neuropathy
2. Any active or chronic corneal disorder, including, but not limited to the following: Sjogren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, and also active ocular conditions requiring on-going treatment/monitoring such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, acquired monocular vision Serious concurrent illness, including, but not limited to the following:

    a. Clinically relevant active infection including known active hepatitis B or C, Human Immunodeficiency Virus (HIV) infection, varicella-zoster virus (shingles) or cytomegalovirus infection or any other known concurrent infectious disease, requiring IV antibiotics within 2 weeks of study enrollment.

    b. Significant cardiac disease such as recent myocardial infarction (≤ 6 months prior to Day 1), unstable angina pectoris, uncontrolled congestive heart failure (New York Heart

Association > class II), uncontrolled hypertension (≥ CTCAE v4.03 Grade 3), uncontrolled cardiac arrhythmias, severe aortic stenosis, or ≥ Grade 3 cardiac toxicity following prior chemotherapy.

c. History of multiple sclerosis or other demyelinating disease, Eaton-Lambert syndrome (para-neoplastic syndrome), history of hemorrhagic or ischemic stroke within the last six months, or alcoholic liver disease.

d. Previous clinical diagnosis of treatment-related pneumonitis.

3. Any other concomitant anti-cancer treatment such as immunotherapy, biotherapy, radiotherapy, chemotherapy, investigative therapy, or high-dose steroids; however, low-dose steroids and Luteinizing Hormone Releasing Hormone (LHRH) at doses that have been stable for ≥ 14 days are permitted for patients with prostate cancer
4. Known hypersensitivity to previous monoclonal antibody therapy or maytansinoids
5. Prior history of solid tumor malignancy within the last 3 years except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment)
6. Concomitant administration of folate-containing vitamins
8. Patients who have received prior allogeneic or autologous bone marrow transplants
9. WCBP who are pregnant or breast feeding

# 4. INVESTIGATIONAL PLAN

## 4.1. Study Design

### 4.1.1. Overview and Schema

This is an open label, Phase 1, non-randomized, safety, PK, and Pd study of IMGN853 in adult patients with solid tumors that have relapsed, and are refractory to standard therapies. The estimated study duration is approximately 50 months for patient accrual, dosing, and follow up. The study will be conducted in 2 stages: dose escalation and dose expansion. Two dosing schedules will be evaluated in this study:

**Schedule A:** IMGN853 administered on Day 1, with cycles repeating every 21 days (Q3W)

**Schedule B:** IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days (modified weekly schedule)

- Approximately 209 patients* will be enrolled in the study.
- **Dose Escalation Phase:** (1) **Schedule A:** 44 patients (2) **Schedule B:** 25 patients
- **Dose Expansion Cohort 1:** Patients with Epithelial Ovarian Cancer (EOC) which is resistant to platinum-based therapy – 40 patients
- **Dose Expansion Cohort 2:** Advanced or recurrent uterine cancer – 20 patients
- **Dose Expansion Cohort 3:** Patients with relapsed EOC - 20 patients
- **Dose Expansion Cohort 4**: Relapsed/refractory NSCLC adenocarcinoma or bronchioloalveolar carcinoma (BAC) 20 patients
- **Dose Expansion Cohort 5:** Patients with Epithelial Ovarian Cancer (EOC) which has relapsed following platinum-based therapy – 40 patients; patients enrolled into this cohort will self-administer daily corticosteroid eye drops to assess whether prophylaxis with topical steroids prevents or lessens severity of keratopathy and/or blurred vision.***NOTE:** *Every effort will be made to ensure the requisite number of patients are accrued in each cohort, and to this end, communications with the site will be monitored carefully. There are instances however, where, as a result of simultaneous screening activities, patients may qualify for the study at the same time, resulting in slight over-enrollment in individual cohorts*

The primary aim of the dose-escalation phase is to evaluate the safety and tolerability of IMGN853, to identify the MTD, and to characterize the PK profile of IMGN853.

**Schedule A** - once the MTD has been identified, enrollment to MTD Expansion Cohorts 1 and 2 will begin.

**Schedule B,** the starting dose of IMGN853 was 1.1 mg/kg, which was 1/3 the 3.3 mg/kg dose level, which was deemed clinically safe in nine patients on a Q3W schedule. All doses were calculated according to adjusted ideal body weight (AIBW). Patients were enrolled in cohorts of 3 to 6 patients and the MTD was determined to be 2.0 mg/kg (AIBW). The CRC to review safety, PK and efficacy data from the dose escalation cohorts, as well as available data from patients treated on Schedule A. The modified weekly schedule did not provide any apparent

safety or efficacy advantage. These results were presented at the annual ASCO meeting (Borghei 2015).

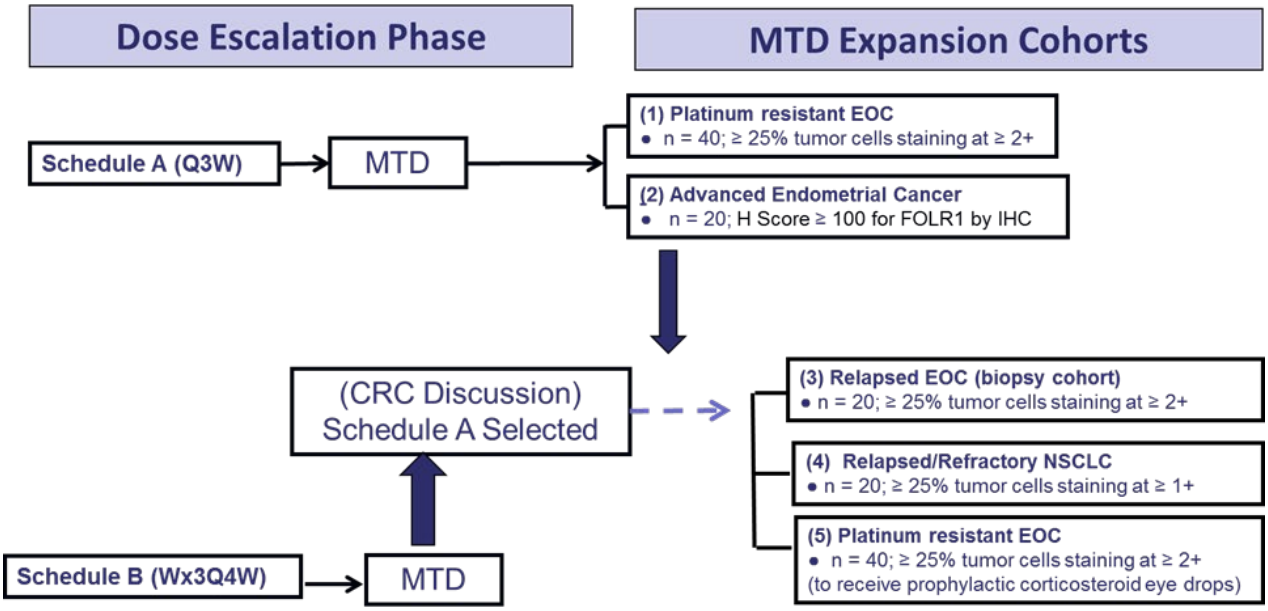
***Based on safety and overall response data collected through May 2015, the CRC determined that all new patients enrolled in the trial will receive IMGN853 at the MTD of 6 mg/kg once every three weeks. Safety data available to date indicate that the MTD is equal to the RP2D. Moving forward, Schedule B will not be evaluated any further in this study; however, patients enrolled to Schedule B prior to the CRC decision, will continue on this schedule.***

The period of observation extends from the time the patient receives the first dose of IMGN853 until the final follow-up study visit. Patients will continue to receive IMGN853 until unacceptable toxicity or withdrawal of consent, whichever comes first, or until the Sponsor terminates the study. Patients who meet the RECIST criteria for PD while on study may remain on study, provided there is evidence of clinical benefit and no unacceptable toxicity, as agreed upon by the Investigator and the medical monitor. Patients who discontinue study drug for reasons other than PD will be followed until PD, start of new anti-cancer therapy, or death, whichever occurs first.

The primary aims of the Dose Expansion phase are to further evaluate safety and tolerability and to assess IMGN853 Pd and preliminary efficacy.

CTCAE version 4.03 will be used to grade adverse events.

**Figure 3: Study Design Schema**




### 4.1.2. Cohort Review Committee

The CRC is comprised of the ImmunoGen Medical Monitor and Investigators from participating sites. Once the last patient in a given cohort has completed a cycle of study treatment, a CRC meeting will be convened to review all safety data and decide whether to continue or halt dose escalation, further expand individual dose levels to gain additional safety data, or explore lower or intermediate dose levels.

**Amendment 10 Update:** The CRC convened to review safety, PK and efficacy data from the dose escalation cohorts, as well as available data from patients treated on Schedule A. The modified weekly schedule did not provide an apparent safety or efficacy advantage; moreover, while the Q3W schedule PK profile analysis indicated no accumulation of IMGN853, accumulation of IMGN853 was observed using the modified weekly schedule (Borghaei, 2015). ***Based on safety, PK and overall response data collected through May 2015, the CRC determined that the study will proceed with IMGN853 administered under Schedule A (Q3W) only (Figure 2). All new patients enrolled in the trial will receive IMGN853 at the MTD of 6 mg/kg once every three weeks. Safety data available to date indicate that the MTD is equal to the RP2D. Patients currently being treated using Schedule B will continue to be dosed according to this schedule.***

### 4.1.3. Dose Escalation Guidelines

***Schedule A dose escalation is complete and the MTD is 6 mg/kg (AIBW); data available to date indicate that the MTD is equal to the RP2D.***

#### 4.1.3.1. Schedule A

The starting dose (Dose Level 1) for IMGN853 is 0.15 mg/kg, which is equivalent to 1/20 the HNSTD observed in the GLP cynomolgus monkey toxicology study. The planned dose levels are outlined in Table 3. IMGN853 will be given intravenously on Day 1 of every 21-day cycle. Based on the favorable safety margins suggested by the non-clinical cynomolgus monkey toxicology study and to minimize patient exposure to biologically-inactive doses of IMGN853, the dose escalation phase will initially follow an accelerated titration design. Each of the first 4 cohorts will consist of 1 patient. From cohort 5 onward, the dose escalation will proceed in a standard 3+3 design, with each cohort enrolling 3 or 4 to 6 patients.

**Table 3: Planned Dose Levels (Schedule A)**

| Dose Level | Dose (mg/kg) | Percent Increase From Previous Dose Level | Number of Patients (Planned) |
|---|---|---|---|
| 1 | 0.15 | N/A 1/20 HNSTD | 1 |
| 2 | 0.5 | 233% | 1 |
| 3 | 1.0 | 100% | 1 |
| 4 | 2.0 | 100% | 1 |
| 5 | 3.3 | 65% | 3 or 4-6 |
| 6 | 5.0 | 52% | 3 or 4-6 |
| 7 | 7.0 | 40% | 3 or 4-6 |
| 8 | 9.0 | 28% | 3 or 4-6 |
| NOTE: If additional dose exploration is required to define the MTD then dose escalation may proceed at increments ≤ 40%. The CRC will determine the magnitude of the dose escalation increments following review of available clinical and PK data from patients treated in the current cohort. | | | |

For Cohort 1, the first patient enrolled into the study will be observed for a 28 day period in Cycle 1 before the patient is retreated and before a dose escalation decision will be made. This 4 week period of observation will only apply to the first cycle for the first patient enrolled into the trial. All subsequent cycles of treatment for this patient and all other patients will be of 3 weeks duration. This additional week of observation is employed to provide an additional margin of safety to address skin findings that were improved but not completely resolved in all animals by day 28 in the GLP toxicology study. During this time period, if there are no observations of CTCAE v4.03 ≥ Grade 2 dose limiting toxicities then dose escalation to 0.5 mg/kg will proceed and will follow the rules outlined below. If a patient develops a ≥ Grade 2 toxicity for which a causal relationship to IMGN853 cannot be excluded, then 2 additional patients must be added to this dose level. If no ≥ Grade 2 TEAEs are observed, dose escalation will revert to single patient cohorts through the 2 mg/kg dose level (inclusive).

For Cohort 2 and beyond, decisions regarding dose escalation will be based on the occurrence of Cycle 1 dose limiting toxicity.

In the absence of any ≥ CTCAE Grade 2 or greater AEs observed at dose level 1 through 4, dose escalation will proceed according to the accelerated titration schema outlined in Table 3. If the patient develops a ≥ Grade 2 toxicity for which a causal relationship to IMGN853 cannot be excluded, then 2 additional patients must be added to this dose level. If no ≥ Grade 2 TEAEs are observed, dose escalation will revert to single patient cohorts through the 2 mg/kg dose level (inclusive).

The occurrence of DLT for which a causal relationship to IMGN853 cannot be excluded, will trigger a transition to the standard 3+3 dose escalation schema.

For patients enrolled to Cohorts 5 and above, dose escalation decisions will be made in accordance with a standard 3+3 design (Section 4.1.3.3).

#### 4.1.3.2. Schedule B

***Schedule B dose escalation is complete and the MTD is 2 mg/kg (AIBW). The modified weekly schedule will not be evaluated further in this study.*** In Schedule B, the starting dose of IMGN853 will be 1.1 mg/kg, which is 1/3 the 3.3 mg/kg Q3W dose level, which was deemed clinically safe in nine patients.

Patients will be enrolled in cohorts of 3 to 6 patients until the MTD is defined (Section 4.1.3.3). Planned dose levels are listed below in Table 4 and will be administered based on AIBW body weight. Based on emerging data, the CRC will decide the magnitude of the dose escalation and may determine that exploration of lower or intermediate dose levels is warranted. If at any time, the administration of IMGN853 on a weekly basis is deemed to be suboptimal or PK/ Pharmacodynamics data supports a less frequent dosing regimen, the decision may be made by the CRC to select the less frequent dosing schedule.

A patient will be deemed non-evaluable for dose escalation decisions and will not be counted toward the total cohort size if the patient did not receive a full course of treatment (i.e., all planned doses of IMGN853 for the first treatment cycle) and did not experience a DLT; or discontinued from the study prior to completing necessary safety evaluations through the end of the first cycle of treatment and did not experience a DLT. Non-evaluable patients will be replaced unless accrual to the cohort has stopped due to the occurrence of at least two patients with DLT.

**Table 4: Planned Dose Levels (Schedule B; Dosed by AIBW)**

| Dose Level | Dose (mg/kg) | Percent Increase From Previous Dose Level | Number of Patients (Planned) |
|---|---|---|---|
| 1 | 1.1 | N/A | 3 or 4-6 |
| 2 | 1.8 | 65% | 3 or 4-6 |
| 3 | 2.5 | 40% | 3 or 4-6 |
| 4 | 3.3 | 32% | 3 or 4-6 |
| NOTE: If additional dose exploration is required to define the MTD then dose escalation may proceed at increments ≤ 25%. The CRC will determine the magnitude of the dose escalation increments following review of available clinical and PK data from patients treated in the current cohort. | | | |

#### 4.1.3.3. Dose Escalation Rules (3+3 Design)

- If none of the 3 or 4 patients experience a DLT, then dose escalation to the next dose level will occur.
- If 1 of the initial 3 or 4 patients experiences a DLT, the cohort will be expanded to up to 6 patients. If no further DLT is seen, dose escalation to the next dose level may proceed.
- If at least 2 out of 2 to 6 patients or more than 33% of patients in any given cohort experience a DLT, the maximum administered dose (MAD) is reached, and no further dose escalation will occur. Enrollment into a cohort at lower dose level will be considered.
- Each dose level will be evaluated in a similar fashion.

The MTD is defined as the highest dose at which 1 or fewer among 6 patients or ≤ 33% experiences a DLT.

Once the MTD has been exceeded, the CRC will decide whether lower dose levels should be explored further or whether an intermediate dose level should be evaluated. If additional dose exploration beyond the highest dose shown in Table 3 is required to define the MTD then dose escalation may proceed at increments specified in Table 3 and Table 4. The CRC will determine the magnitude of the dose escalation increments following review of available clinical and PK data from patients treated in the current cohort.

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

### 4.1.4. Definition of Dose-Limiting Toxicity (DLT)

Dose limiting toxicity (DLT) will be defined as a TEAE or abnormal laboratory value related to study treatment (i.e., assessed as unrelated to disease, intercurrent illness, or concomitant medications), including those TEAEs and abnormal laboratory values that result in a failure to

meet the criteria for re-treatment. DLTs will be considered related to the investigational agent unless there is clear evidence of an alternative explanation and this attribution is agreed to by the CRC.

For the purposes of dose escalation and determination of the MTD, only DLTs that occur during the first cycle will be necessarily considered for decisions regarding dose escalation. Clinically significant toxicities or treatment-emergent adverse events that meet the definition of dose limiting but occurring after Cycle 1 (dose modifying events) may be considered when determining the RP2D.

If a patient experiences a DLT as outlined in Table 5, the study treatment must be stopped and the toxicity (ies) in question must be followed until resolution or stabilization. If treatment is to be resumed then retreatment criteria must be met (Section 5.9.3) and administration must be resumed at a lower dose (Section 4.1.3).

**Table 5: DLT Definitions**

| TOXICITY | DLT DEFINITION CRITERIA |
|---|---|
| Dose delays | Failure to meet re-treatment criteria within the specified timeframe |
| Hematology | • CTCAE Grade 4 neutropenia ≥ 7 days.<br>• CTCAE Grade 3 or 4 neutropenia with single temperature reading ≥ 38.3°C or sustained temperature reading of > 38°C for > 1 hour<br>• CTCAE Grade 3 thrombocytopenia, associated with clinically-significant bleeding that requires transfusion therapy<br>• CTCAE Grade 4 thrombocytopenia |
| Non-hematologic and other DLTs | • ≥ CTCAE Grade 3 nausea or vomiting despite the use of optimal anti-emetic treatments<br>• ≥ CTCAE Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments<br>• Other non-hematologic toxicities of CTCAE ≥ Grade 3 except for the following:<br>o AEs related to underlying disease<br>o Alopecia<br>o CTCAE Grade 3 fatigue<br>o Lymphopenia is not considered DLT unless accompanied by clinically-significant infection<br>o Isolated, asymptomatic Grade 3 abnormalities in biochemistry laboratory values that last for ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention. |
| For any dose limiting hepatic toxicity that does not resolve to baseline within 7 days, an abdominal CT scan must be performed to assess whether it is related to disease progression. | |

### 4.1.5. Dose Expansion Cohorts

Once the MTD is established, additional patients will be treated in a dose expansion phase that is designed to further evaluate safety and tolerability, assess preliminary efficacy at the MTD, and characterize IMGN853 Pd.

Data obtained in the dose expansion phase will help define the RP2D.

**Expansion Cohort #1** will enroll 40 patients with platinum-resistant EOC, primary peritoneal cancer or fallopian tube cancer who have tumors that meet the requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity). The size of this cohort was increased to

better define the frequency and assess the impact of the proposed management guidelines for ocular adverse events.

**Expansion Cohort #2** will enroll 20 patients with advanced, recurrent uterine cancer; eligible patients will have tumors with an H score ≥100 for FOLR1 expression by IHC.

**Expansion Cohort #3** will enroll 20 patients with relapsed EOC; eligible patients will have tumors that meet the requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity).

**Expansion Cohort #4** will enroll 20 patients with relapsed/refractory NSCLC adenocarcinoma or BAC; eligible patients will have tumors that meet the requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥1+ intensity).

**Expansion Cohort #5** will enroll 40 patients with relapsed EOC, primary peritoneal cancer or fallopian tube cancer who have tumors that meet the requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity). Patients enrolled into this cohort will self-administer corticosteroid eye drops four times daily, for the first 10 days of each cycle, to assess whether prophylaxis with topical steroids prevents or lessens severity of ocular toxicity.

In addition to FOLR1-positivity, all patients enrolled in the expansion cohorts must meet all other eligibility criteria (Section 3.1.1). Safety will be evaluated continuously, separately, and in aggregate in the expansion cohorts. If at any time ≥ 33% of patients treated in an expansion cohort experiences a Cycle 1 DLT, further enrollment to that cohort will stop and a CRC will be convened. The CRC will review all available safety data and PK data to determine how further dosing should proceed. If it is decided that a new dose should be investigated, enrollment to the cohort will begin anew.

# 5. STUDY TREATMENT

## 5.1. Description of Study Treatment

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

## 5.2. IMGN853 Packaging

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

## 5.3. Storage, Handling and Compatibility

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

All IMGN853 supplied for the study will be accompanied by accountability and shipping documents that 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. These records must always be available for inspection, and a copy will be supplied to ImmunoGen, Inc., on request. Information recorded on these accountability and shipping documents will include quantities received, dates and amount dispensed, the recorder's initials, patient number and initials to whom administered, lot number of drug administered, and drug lost, damaged or destroyed.

Upon completion of the study, all IMGN853 dispatched to a site must be accounted for and unused supplies destroyed according to the site's Standard Operating Procedures (SOPs). If the site cannot destroy onsite, return of unused supplies to ImmunoGen, Inc. can be arranged. 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.

## 5.4. 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.

Study drug 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 Form FDA 1572 or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the Principal Investigator (i.e., hospital pharmacy, satellite pharmacy),

it is the responsibility of the Principal Investigator to ensure that all study drug is maintained in the manner described.

## 5.5. Assignment of Patient Number

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

Patients are to be registered by faxing or emailing a completed eligibility checklist and enrollment form to the Clinical Manager or designee. The checklist will be verified and a dose level will be assigned as instructed by ImmunoGen, Inc. or designee. A confirmation of registration form will be faxed or emailed back to the site to complete the registration process.

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

### 5.5.1. Enrolled Patient Definition

Patients who receive at least one dose of IMGN853 will be considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and who do not receive a dose of IMGN853 will be considered a screen failure. Patient numbers for patients who screen fail will not be re-issued.

### 5.5.2. Patient Assignment to Dosing Schedules

Patients will be assigned to Schedule A or B based on eligibility criteria and slot availability.

## 5.6. Blinding

Not applicable as this is an open-label study.

## 5.7. Study Treatment Administration

### 5.7.1. Study Treatment Overview and Schedule

IMGN853 is an experimental anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation.

#### 5.7.1.1. Every 3-Week Schedule (Q3W)

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

#### 5.7.1.2. Modified Weekly Schedule (Days 1, 8 and 15, Every 28 Days)

For logistical reasons such as holidays, Day 1 delays in the scheduled study treatment for up to 3 days is permitted. Additionally, shifts in the start of a new cycle by -1 or up to +3 days will be permitted in Cycles ≥ 3. If patients do not meet retreatment criteria on Days 8 and 15 of a given cycle, the dose should be omitted. A delay of 1 day in the dosing of Days 8 and 15 is permitted; if a delay occurs, subsequent dosings on that cycle should be shifted by 1 day. Intervals <7 days between dosings are not permitted. The start of the next cycle should remain the same.

## 5.8. IMGN853 Preparation and Administration

### 5.8.1. Premedication to Prevent Infusion Reaction

#### 5.8.1.1. Schedule A

Patients should receive 10 mg IV dexamethasone, 25-50 mg diphenhydramine (IV or PO) and 325-650 mg acetaminophen (IV or PO) approximately 30 minutes prior to each infusion. If individual patients require more intensive treatment to prevent infusion reaction, investigators may modify the regimen accordingly.

#### 5.8.1.2. Schedule B

Premedication with corticosteroids will not be employed initially. For individual patients who experience signs of infusion-related reactions, the premedication regimen outlined in Section 5.8.1.1 should be administered prior to all subsequent IMGN853 infusions. All patients dosed according to Schedule B should receive 325-650 mg of acetaminophen (PO or IV) approximately 30 minutes prior to each infusion of IMGN853 to prevent infusion-related headaches.

### 5.8.2. Premedication with Corticosteroid Eye Drops (Dose Expansion Cohort#5 ONLY)

All patients enrolled into Cohort Expansion 5 will be instructed to self-administer 1% prednisolone (Pred Forte® or generic equivalent) six times daily on Days 1-5 and four times daily on Days 6-10 of each cycle during the study (Figure 4).

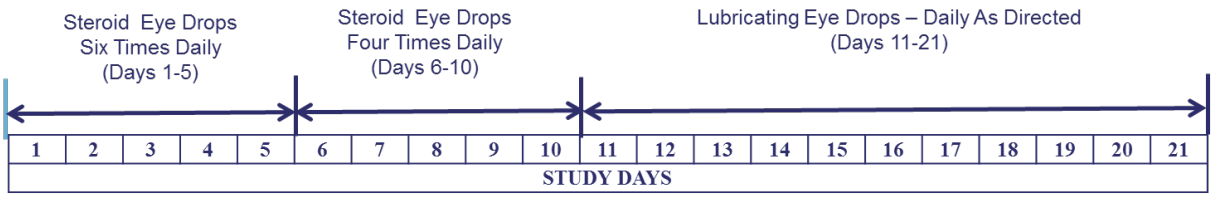
**These medications will be prescribed by the treating physician and will be sourced by the site.** Patients will record their eye drop administration in a patient diary, which will be entered on the CRF.

### 5.8.3. Lubricating Eye Drops

In order to prevent dry eye, which may predispose a patient to corneal irritation, patients will be required to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician) for the duration of their IMGN853 treatment.

**Patients in Cohort#5** will use the corticosteroid eye drops as described in Section 5.8.2 and will use the lubricating eye drops for the remainder of the cycle (Days 11 through 21 inclusive). *If patients need to use lubricating drops during Days 1-10, while steroid eye drops are being administered, they should be advised to wait at least 15 minutes following steroid administration before instilling lubricating eye drops.*

**Figure 4: Co-Administration of Steroid Eye Drops and Lubricating Eye Drops (Schema)**



As with the corticosteroid eye drops, patients will record their eye drop administration in a patient diary, which will be recorded on the CRF.

### 5.8.4. Calculation for Adjusted Ideal Body Weight

Based on the results of the PK modeling, as described in Section 1.10.1, which suggested that dosing according to adjusted ideal body weight (AIBW) may reduce the variation in exposure within dosing cohorts, the adjusted ideal body weight calculation will be used to dose IMGN853 going forward.

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

**Adjusted Ideal Body Weight (AIBW)**

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

Where:

**Ideal Body Weight (IBW)**

1. $IBW^1$ (male) = $0.9H^1$-88
2. $IBW^1$ (female) = $0.9H^1$-92

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

The weight used for calculation should be obtained prior to first treatment and thereafter should only be modified for significant (≥ 10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention). The desired amount should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the Pharmacy Manual. **Note: IMGN853 is incompatible with saline (0.9% sodium chloride).** Therefore, dilutions 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 according to institutional protocol. Once the solution is prepared, the infusion bag must not be left in direct sunlight, and the infusion must be completed within 8 hours of preparation.

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

### 5.8.5. IMGN853 Administration

During the dose escalation phase, the starting dose of IMGN853 was 0.15 mg/kg for patients enrolled to Schedule A and 1.1 mg/kg for patients enrolled to Schedule B. Following Amendment 10 implementation, IMGN853 will be administered to all patients at the MTD of 6 mg/kg every three weeks. (Note: Available safety data indicate that the MTD is equal to the RP2D). IMGN853 will be administered as an IV infusion following preparation as outlined in the Pharmacy Manual. An IV tubing administration set with a 0.22 micron in-line filter must be used for infusion. 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 5mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. Following infusion, the IV line should be flushed with 5% dextrose as needed to ensure delivery of the full dose.

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

### 5.8.6. Management of Potential IMGN853 Infusion-related Reactions

Some patients treated with IV infusions of therapeutic antibodies have experienced concurrent infusion-related reactions with signs or symptoms that can be classified as acute allergic/hypersensitivity reactions (see NCI CTCAE, Version 4.03). The signs and symptoms may include 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 hypersensitivity reactions according to Institutional practices. General guidelines for management of acute reactions and subsequent retreatment with IMGN853 are provided in Table 6 below. Due to long half-life of the antibody, the potential exists for infusion–related reactions to recur after appropriate treatment; therefore, patients should be advised to seek immediate medical treatment if symptoms recur after discharge from clinic.

Patients who experience an infusion-related reaction during or immediately following administration of IMGN853 will have blood drawn for determination of drug concentration, antibodies to IMGN853 (HADA, HAHA). The sample should be obtained within three hours of the onset of the reaction and 1 week later. Such patients should undergo all scheduled efficacy and safety evaluations.

**Table 6: Management Guidelines for Potential Infusion Reactions**

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

| Infusion Reaction CTCAE v4.03 Grade | Management |
|---|---|
| Grade 2: Moderate | • Interrupt infusion and disconnect infusion tubing from subject<br>• Promethazine (or equivalent) 150 mg PO prn nausea<br>• Diphenhydramine (or equivalent) 25-50 mg PO or IV prn<br>• Acetaminophen (or equivalent) 650 mg PO prn<br>• Methylprednisolone 125 mg (or equivalent) IV prn<br>• 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.<br>• For subsequent dosing in future cycles, subjects should be pre-medicated with Dexamethasone 8 mg PO BID the day prior to IMGN853 administration and Acetaminophen 650 mg PO and Benadryl 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 | • Stop infusion and disconnect infusion tubing from subject<br>• Administer Diphenhydramine (25-50 mg) IV<br>• Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg)SQ or IM) and bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated<br>• Consider IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to prevent recurrent or ongoing reactions<br>• Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic.<br>• Report as a serious adverse event (see Section 9.1.1.2)<br>• Investigators should confer with the sponsor regarding retreatment of the subject with IMGN853. If the investigator and sponsor agree that the subject could be rechallenged with IMGN853 then prophylaxis for an infusion-related reaction should occur in all subsequent cycles. For this, subjects should be pre-medicated with Dexamethasone 8 mg PO BID the day prior to IMGN853 administration and Acetaminophen 650 mg PO and Diphenhydramine 25-50 mg PO 30-60 minutes prior to dosing. |

| Infusion Reaction CTCAE v4.03 Grade | Management |
|---|---|
| Grade 4: Life-threatening consequences, urgent intervention indicated | • Immediately stop infusion and disconnect infusion tubing from subject<br>• Permanently discontinue study medication treatment<br>• Administer Diphenhydramine (or equivalent) 50 mg IV<br>• Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg)SQ or IM)<br>• Administer bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated<br>• Administer IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to prevent recurrent or ongoing reactions<br>• Report as a serious adverse event (see Section 9.1.1.2)<br>• Remove patient from study. |

### 5.8.7. Monitoring and Management of Infusion-Associated Headaches

Infusion-associated headaches have been shown to be common in patients receiving IMGN853 under Schedule B. Patients should be advised of the risk of headache and should inform their treating physician if they develop an infusion-associated headache, to allow for appropriate evaluation and treatment. All patients dosed according to Schedule B should receive 325-650 mg of acetaminophen (PO or IV) approximately 30 minutes prior to each infusion of IMGN853.

### 5.8.8. Monitoring and Management of Treatment-emergent Eye Disorders

#### 5.8.8.1. Monitoring - Potential 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). Due to the observation of ocular disorders in patients treated with IMGN853 at the 5.0 and 7.0 mg/kg dose levels, (Section 1.9) ocular function is being carefully monitored. Complete ophthalmologic exams and ocular symptom assessments will be performed in all patients at baseline and post-treatment as described in the following schedule:

**Table 7: Schedule for Ophthalmologic Assessments**

| Assessment | Screening | Day 1 (All Cycles) | Prior to Day 1 Dose (Every other Cycle)[4] | End of Treatment | 28-Day Follow Up |
|---|---|---|---|---|---|
| Ophthalmologic history – patients will be asked about ocular symptoms such as history of dry eye, and contact lens use | X | | | | |

| Assessment | Screening | Day 1 (All Cycles) | Prior to Day 1 Dose (Every other Cycle)[4] | End of Treatment | 28-Day Follow Up |
|---|---|---|---|---|---|
| Complete Exam[1]:<br>- Visual acuity (with/without corrective lenses; whichever best reflects the patient's usual functioning)<br>- Slit lamp examination<br>- Intraocular pressure measurement<br>- Indirect fundoscopy<br>- | X[2] | | Patients who report treatment- emergent ocular AEs | X | X |
| Schirmer's test[4] | X | | | | |
| Ocular symptom assessment (blurred vision, ocular discomfort, etc.) | X | X | | X | X |
| Prescribe 1% prednisolone (Cohort 5 Patients Only)[5] | X | | | | |

[1] Performed by a board-certified ophthalmologist

[2] Within 14 days prior to Cycle 1, Day 1

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

[4] For patients experiencing ocular symptoms, the Schirmer's test (with and without topical anaesthetic) will be repeated at the first ophthalmology exam and in subsequent ophthalmologic exams if clinically indicated.

[5] Patients enrolled to Expansion Cohort 5 will receive primary prophylaxis with 1% prednisolone six times daily on Days 1-5 of each treatment cycle, followed by four times daily on Days 6-10 of each treatment cycle.

If a subject develops ocular symptoms of any grade, the subject will be referred to an ophthalmologist for a complete examination. If a subject develops ≥ Grade 2 ocular symptoms, treatment with IMGN853 will be interrupted. In patients with clinical benefit, therapy may resume if ocular symptoms improve to Grade 1 or baseline within 21 days of the next scheduled IMGN853 dose. Subsequent 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 study or 28-day follow up visit. In the event of therapy being held for more than 14 days due to ocular symptoms, a subject showing clinical benefit prior to the onset of an ocular treatment-emergent adverse event may be allowed to resume therapy at a reduced dose after approval from the Sponsor.

### 5.8.8.2. Management Guidelines for Eye Disorders

Patients should also be firmly advised to avoid using contact lenses while on study. Baby shampoo and a soft cloth should be used to clean the eyes, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface. The use of UVA/UVB sunglasses is recommended for use outside in full daylight during the course of the study. If patients report signs or symptoms of ocular disorders, including, but not limited to, blurred

vision or eye irritation, the management and dose modification guidelines outlined in Table 8 should be followed.

Patients who have experienced study drug-related blurred vision symptoms, including those with including those with no obvious clinical findings on examination, will have a complete ophthalmic examination performed prior to the start of every other cycle and at the end of study or follow up visit following study discontinuation. Management of treatment emergent eye disorders with inflammatory characteristics should include corticosteroid eye drops and/or other measures as indicated by an ophthalmologist.

**Table 8: Management of Ocular Disorders**

| Severity Grade (CTCAE v4.03 Grade) | Management | Guidelines for IMGN853 Dose Modifications |
|---|---|---|
| Grade 1 | • Complete eye exam as outlined in Table 7.<br>• Monitor for worsening symptoms | • Continue IMGN853 dosing |
| Grade 2 | • Complete eye exam as outlined in Table 7. Repeat complete exam as clinically indicated.<br>• Patients should have weekly symptomatic ocular assessments until the symptoms resolve to grade 1 or baseline (Section 5.9.1) or are deemed to be irreversible by the investigator | • Hold IMGN853 dosing.<br>• Patients may be allowed to resume therapy at the same dose level unless there is a dosing delay > 14 days, in which case they should resume treatment at a reduced dose level (see Table 11) |
| Grade 3 | • Complete eye exam as outlined in Table 7. Repeat complete exam as clinically indicated.<br>• Patients should have weekly symptomatic ocular assessments until the symptoms resolve to grade 1 or baseline (Section 5.9.1) or are deemed to be irreversible by the investigator. | • Hold IMGN853 dosing.<br>• Patients may be allowed to resume therapy at a lower dose than the one they were receiving when their symptoms began (see Table 11). |
| Grade 4 | • Complete eye exam as outlined in Table 7. Repeat complete exam as clinically indicated.<br>• Patients should have weekly symptomatic ocular assessments until the symptoms resolve to grade 1 or baseline (Section 5.9.1) or are deemed to be irreversible by the investigator. | • Permanently discontinue IMGN853 dosing. |

### 5.8.9. Management of Non-Infectious Pneumonitis

Non-infectious pneumonitis has been observed following the administration of IMGN853 and may result in fatigue, shortness of breath, cough or respiratory distress. Drug-induced pneumonitis may be immediately life-threatening. If a patient presents with signs or symptoms consistent with pneumonitis and/or a clinically meaningful change in pulse oximetry value, the

patient should be immediately evaluated according to institutional guidelines/practice. 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 IMGN853 treatment guidelines outlined in Table 9 should be followed.

**Table 9: 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.<br>• 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.<br>• Patient must be evaluated by a pulmonary specialist.<br>• Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. | • Hold dosing until symptoms improve.<br>• 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.<br>• Patient must be evaluated by a pulmonary specialist.<br>• Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.<br>• Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed.<br>• The pneumonitis event must be followed until resolution | • Hold IMGN853 dosing until symptoms resolve<br>• IMGN853 may be resumed at a lower dose level after discussion with the Sponsor. |

| Severity Grade (CTCAE v4.03 Grade) | Medical Management of Pneumonitis | Guidelines for Dose Modifications |
|---|---|---|
| Grade 4 | • Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated.<br>• Patient must be evaluated by a pulmonary specialist.<br>• Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.<br>• Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed.<br>• The pneumonitis event must be followed until resolution | • Permanently discontinue IMGN853 dosing. |

### 5.8.10. Monitoring and Management of Diarrhea

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

### 5.8.11. Monitoring and Management of Nausea and Vomiting

Nausea and vomiting have been reported in patients treated with IMGN853 in both dosing schedules. 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 10.

**Table 10: Management of Nausea and Vomiting**

| Severity Grade (CTCAE v4.03 Grade) | Management |
|---|---|
| Grade 1 | • No premedication required as patients are already receiving 8 mg dexamethasone as part of their premedication for prevention of infusion reaction. |
| 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. |

## 5.9. Treatment Guidelines

### 5.9.1. Re-treatment Criteria

#### 5.9.1.1. To Begin a New Cycle of Treatment

In the absence of otherwise dose-limiting toxicity, for a patient to begin a new cycle of therapy, the following criteria must be met.

- ANC must be $\geq 1.5x10^9$/L (1,500/μL)
- Platelet count must be $\geq 75 \times 10^9$/L (75,000/μL)
- All non-hematologic toxicities for which a causal association to study treatment cannot be ruled out, must be ≤ Grade 2 (except alopecia) or returned to baseline; the exception to this rule is treatment-emergent ocular symptoms, which must have recovered to ≤ Grade 1 or baseline

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48-72 hours. Dosing may resume if these criteria have been met. However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related toxicity, this will be viewed as a dose-limiting event (Section 4.1.4). For patients treated on either dosing schedule, if the next cycle is delayed due to treatment-related toxicity by greater than 21 days then the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

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

#### 5.9.1.2. To Continue Treatment within a Cycle- Schedule B (modified weekly)

***Amendment 10 Update:*** *Following completion of the Schedule B Dose Escalation portion of the study, the CRC reviewed safety, PK and efficacy data from both dosing schedules and based this review, made the decision to discontinue further investigation of Schedule B dosing. While patients currently receiving IMGN853 study treatment according to Schedule B will continue to do so, new patients enrolled to the study will receive treatment according to Schedule A only.*

In the absence of otherwise dose-limiting toxicity, for a patient to continue treatment within a cycle, the following criteria must be met.

- ANC must be $\geq 1.0 \times 10^9$/L (1,000/μL)
- Platelet count must be $\geq 75 \times 10^9$/L (75,000/μL)
- All non-hematologic toxicities for which a causal association to study treatment cannot be ruled out, must be ≤ Grade 2 (except alopecia) or returned to baseline; the exception to this rule is treatment-emergent eye disorders, which must have recovered to ≤ Grade 1 or baseline
- A minimum of 7 days (~168 hours) must have elapsed between IMGN853 doses

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 72 hours. Dosing may resume if these criteria have been met. If the criteria are not met due to insufficient recovery from a treatment-related toxicity, then that week's dose will be considered "missed".

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

### 5.9.2. Follow-up for DLTs and AEs Leading to Discontinuation

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

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

### 5.9.3. Criteria for Re-Initiation of Study Treatment Following Occurrence of a DLT

Study treatment will be stopped if a patient experiences a DLT at any time during the study. It may resume, with applicable dose adjustments (Section 5.9.4.1) if the following criteria are met:

- ANC must be $\geq 1.5 \times 10^9$/L (1500 /μL)
- Platelet count must be $\geq 75 \times 10^9$/L (75,000/μL)
- All clinically-significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be ≤ Grade 1 (except alopecia) or returned to baseline

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48-72 hours. Dosing may resume if these criteria have been met. However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related toxicity, this may be viewed as a dose-limiting event (Section 4.1.4). For patients treated on either schedule, if the next cycle is delayed due to treatment-related toxicity by greater than 21 days then the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

### 5.9.4. Dose Modification Guidelines

#### 5.9.4.1. Dose Reduction Following DLT

Patients who develop DLTs or adverse events requiring holding of the study drug may resume treatment at a reduced dose level as shown in Table 11 provided the criteria outlined in Section 5.9.4.2 are met.

**Table 11: Dose Modification Guidelines**

| Dosing Schedule | If the patient was receiving IMGN853 at: | Dose should be reduced to: |
|---|---|---|
| ***Schedule A*** | 6.0 mg/kg | 5.0 mg/kg |
| | 5.0 mg/kg | 4.0 mg/kg |
| ***Schedule B**** | 2.0 mg/kg | 1.8 mg/kg |
| | 1.8 mg/kg | 1.1 mg/kg |
| **IMGN853 should be dose-reduced one dose level; a second dose reduction may be allowed as needed. Dose reductions to intermediate dose levels may be allowed based on emerging data with the approval of the Sponsor.* ***Amendment 10 Update: Schedule B will not be evaluated further in the current study.*** | | |

#### 5.9.4.2. Criteria for Re-initiation of Study Treatment Following Occurrence of a DLT

The AE reverts to baseline or ≤ Grade 1 within 14 days of the next scheduled Day 1 dose; the patient is clearly deriving clinical benefit, and the patient has an otherwise favorable risk/benefit profile.

Once a dose level reduction has occurred, patients must remain at this reduced dose.

### 5.9.5. Discontinuation of Study Treatment Due to Toxicity

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

- ≥ Grade 3 cardiac event
- other non-hematologic events of Grade 4 severity
- Failure to meet re-treatment criteria within 21 days 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.

## 5.10. Removal of the Patients from the Trial or Study Drug

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

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

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

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

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

Only patients who sign the informed consent and receive any study treatment will be considered enrolled. If an enrolled patient is discontinued from study treatment for reasons other than safety (e.g., withdrawal of consent, non-compliance, death due to disease progression) prior to the end of Cycle 1, he or she will be replaced (i.e., an additional patient will be added to the cohort). Patients who do not complete Cycle 1 due to an AE will not be replaced. Patients who are replaced will not be considered in making dose-escalation decisions, but if possible, will be followed for safety and other assessments according to the protocol.

## 5.11. Period of Observation

For purposes of this study, the period of safety observation extends from the time of first dosing until the final evaluation during the study, including the 28-day follow-up safety visit. Short-term follow-up for patients who discontinue study therapy without documented progressive disease will continue every three months until the patient's disease worsens, until the patient begins subsequent anti-cancer treatment, or until the patient dies, whichever comes first.

## 5.12. Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within 4 weeks of Cycle 1, Day 1 and through 28 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.

### 5.12.1. Lubricating Artificial Tears

Patients will be **required** to use preservative-free, lubricating artificial tears on a daily basis, as directed by the product label or the treating physician (Section 5.8.3).

### 5.12.2. Corticosteroid Eye Drops

All patients enrolled in Cohort 5 will be **required** to self-administer corticosteroid eye drops (1% prednisolone; Pred Forte® or generic equivalent) during active study treatment (Section 5.8.2). Patients will record their eye drop administration in a patient diary, which will be entered on the CRF.

### 5.12.3. 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.

### 5.12.4. Acetaminophen

All patients dosed according to Schedule B should receive 325-650 mg of acetaminophen (PO or IV) approximately 30 minutes prior to each infusion of IMGN853.

### 5.12.5. Folate-Containing Vitamins

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

### 5.12.6. Antineoplastic Therapy

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

Palliative radiotherapy for local peripheral metastases not being used as target lesions is allowed. However, the need for such therapy may be an indication of disease progression and should be discussed with the Sponsor prior to implementation. Radiotherapy for central metastases (e.g. vertebral, meditational) will not be allowed; the need for such radiotherapy while on study will be seen as an indication of disease progression and the patient should be withdrawn from therapy.

### 5.12.7. Hematopoietic Growth Factors

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

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

### 5.12.8. Anticoagulants

The use of low dose anticoagulants for maintenance of line patency is allowed. Thrombosis prophylaxis is allowed.

### 5.12.9. 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.

## 5.13. Overdose and Medication Error

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

Medication Error – The Sponsor must be immediately notified in the event of error in prescribing, dispensing, administering and/or use of IMGN853, and the event must be reported on the eCRF.

# 6. PHARMACOKINETIC (PK ASSESSMENTS)

## 6.1. Overview

Serial analyses of patient plasma will be performed to define the PK properties of IMGN853 when administered intravenously once every 3 weeks. Plasma will be analyzed for levels of IMGN853, free DM4, and total M9346A antibody to assess IMGN853 stability.

## 6.2. PK Schedule

### 6.2.1. Schedule A

Blood samples for PK measurements will be taken in Cycles 1 and 3, at the following time points:

***Day 1 –*** predose, and following completion of infusion at the following timepoints: 0-10 minutes, and 2, and 4 hours (±10 minutes)

***Day 2 –*** 24 hours after completion of infusion (±2 hours)

***Day 3 –*** 48 hours after completion of infusion (±2 hours)

***Day 4 or 5, Day 8 and Day 15 –*** a single blood sample will be drawn for PK (±24 hours)

Additionally, a single pre-dose sample will be collected before the IMGN853 infusion and following completion of the infusion in Cycles 2, 4, 5 and 6. A single blood sample for analysis of HAHA and HADA will be taken on Day 1 of Cycles 2, 4, and 5 and at the End of Treatment and Follow-up visits.

The sample for HAHA and HADA analysis will be taken from the PK tube; no additional blood draw is necessary.

### 6.2.2. Schedule B

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

**Cycle 1 & 3:**

***Day 1 –*** predose, and following completion of infusion at the following timepoints: 0-10 minutes, and 2 and 4 hours (±10 minutes)

***Day 2 –*** 24 hours after completion of infusion (±2 hours)

***Day 8*** – predose and within 10 minutes of completion of the infusion

***Day 15 –*** predose, and following completion of infusion at the following timepoints: 0-10 minutes, and 2 and 4 hours (±10 minutes)

***Day 16 –*** 24 hours after completion of infusion (±2 hours)

***Day 22 –*** a single blood sample will be drawn for PK (±24 hours)

Additionally, a single pre-dose sample will be collected before the IMGN853 infusion and following completion of the infusion in Cycles 2, 4, 5 and 6. A single blood sample for analysis

of HAHA and HADA will be taken on Day 1 of Cycles 2, 4, and 5 and at the End of Treatment and Follow-up visits.

The sample for HAHA and HADA analysis will be taken from the PK tube; no additional blood draw is necessary.

Details of sample preparation and shipping are provided in the Laboratory Manual.

### 6.2.3. Additional PK Samples

Any patient who experiences a Grade 2 or greater infusion reaction during the administration of IMGN853 will have blood drawn within 3 hours of the onset of the reaction and one week later for determination of drug concentration, antibodies to IMGN853 and factors that may be related to hypersensitivity reactions (see Section 5.8.6).

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

## 6.3. Immunogenicity Assessments

To assess for potential immunogenicity against IMGN853 or DM4, plasma samples taken for PK assessment in cycles 1 through 6 will be taken as outlined in Sections 6.2.1 and 6.2.2, using the same tube that is used for the PK assessment. The study will evaluate the potential impact of immunogenicity on PK, Pd, safety, and efficacy of IMGN853 and total M9346A antibody. Specifically, clinical characteristics such as PK, safety and efficacy of immune positive patients will be compared to the immune negative population.

# 7. TRANSLATIONAL RESEARCH STUDIES

Translational research studies will be performed to generate data that will demonstrate proof-of-mechanism and characterize pharmacodynamics and anti-tumor effects of IMGN853. In addition, several biomarkers, including FOLR1, will be evaluated as potential biomarkers of clinical response to IMGN853. These will help guide further clinical development of IMGN853.

## 7.1. Correlation between FOLR1 Expression and IMGN853 anti-tumor activity

FOLR1 expression varies with tumor histology, as reported in the literature and demonstrated in our pre-clinical studies (Sections 1.1 and Investigators' Brochure). Based on the hypothesis that tumors expressing higher levels of FOLR1 are more likely to be susceptible to anti-tumor activity of IMGN853, a threshold for FOLR1 expression was determined for each tumor histology studied in the expansion cohorts. This was done based on molecular epidemiology data generated in a number of patient samples representative of different tumor types, as well as pre-clinical efficacy data.

### 7.1.1. Evaluation of FOLR1 Expression in Tumor Tissue During Dose-Escalation and Dose Expansion

FOLR1 expression in tumors will be analyzed via IHC. All patients must submit archived tumor tissue, formalin-fixed, paraffin embedded (FFPE) slides for analysis of FOLR1 expression by IHC. For dose escalation, patients with tumors known to have high incidence of FOLR1 expression (serous and endometrioid ovarian cancer, serous and endometrioid endometrial cancer and NSCLC adenocarcinoma or BAC) may submit archived tumor tissue for retrospective analysis after enrollment. All other patients must submit archived tumor tissue for documentation of FOLR1 positivity by IHC prior to enrollment. Any level of FOLR1 expression (i.e., ≥1% of tumor staining at ≥1+ intensity) is acceptable for enrollment in the dose escalation portion of the study. If a patient does not have archival material available for analysis, the patient may alternatively undergo a biopsy to assess FOLR1 expression. The decision to biopsy will be made once patient eligibility has been determined and on the basis of tumor accessibility and patient safety.

Only patients with the required FOLR1 expression levels by IHC will be eligible to enroll in the dose expansion cohorts. If a patient wishes to enroll and does not have archival material available for analysis, he or she must undergo a biopsy to assess FOLR1 expression. In the ovarian cancer cohorts (Cohort #s 1 and 3) eligible patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity), and in the uterine cancer and NSCLC cohorts, patients will be required to have an H score ≥ 100 for FOLR1 expression in order to be eligible to enroll.

The tumor samples will be analyzed for folate receptor alpha (FOLR1) expression in the Companion Diagnostics Pharma Services CAP-accredited and CLIA-certified laboratory and Pathology Services at Ventana Medical Systems, Inc.

IHC data will be used to define any potential associations between FOLR1 expression and clinical response.

## 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 specific activities that are planned, but other additional biomarkers/biological pathways may be investigated based on emerging data.

### 7.2.1. Potential Markers of Drug Sensitivity

As IMGN853 targets proliferating cells, Ki67 IHC staining will be assessed as a marker of cell proliferation on fresh biopsy samples from patients in Expansion Cohort 3. Potential associations between Ki67 levels and clinical response will be examined.

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 via PBMC analysis at screening. Potential associations between FcγR genotype and clinical response will be examined.

### 7.2.2. Potential Markers of Drug Resistance

Drug efflux transporters and p-glycoprotein (PgP) in particular play an important role in cancer cell resistance to cytotoxic agents, including microtubule-targeting agents. Therefore, PgP IHC staining will be assessed as a marker of drug resistance in archived tumor tissues for all patients and on fresh biopsy samples obtained from patients in the Expansion Cohorts. Potential associations between PgP levels and clinical response will be examined.

### 7.2.3. Folate Pathway Markers

Preclinical studies suggest that FOLR1 is upregulated in folate deficiency and downregulated following folate repletion (Zhu 2001, Sadasivan 2002). Because folate deficiency can enhance FOLR1 expression via a homocysteine-dependent upregulation of FOLR1 mRNA translation (Antony 2004), plasma total homocysteine levels will be assessed in all patients at baseline, during Cycle 2 and at the end of treatment visit. Increased homocysteine levels correlate with low serum and RBC folate levels and suggest folate deficiency. Vitamin B12 deficiency similarly elevates homocysteine levels and also elevates plasma methylmalonate (MMA) levels. Plasma MMA will therefore be analyzed in parallel with plasma total homocysteine to differentiate folate and B12 status. Potential associations between plasma total homocysteine/MMA, FOLR1 expression, and clinical response will be examined.

## 7.3. Pharmacodynamic (Pd) and Proof of Mechanism (POM) Analyses

### 7.3.1. Pd and PoM studies in Tumor Biopsies (EOC Expansion Cohort #3 Only)

For this, patients with biopsy-accessible tumors will undergo core tumor biopsy at baseline and at Cycle 2, Day 8±3 days. The patient must sign consent to undergo the biopsy procedure. The decision to biopsy will be made once patient eligibility has been determined and on the basis of tumor accessibility and patient safety.

Biomarkers to characterize mechanisms involved in the anti-tumor activity of IMGN853 will be evaluated.

Binding of IMGN853 to FOLR1 on the surface of tumor cells results in internalization of the folate receptor. Changes in FOLR1 expression levels will be examined via pre- and post-dose tumor biopsy samples. The presence of IMGN853 will also be detected in tumor cells using IHC methods directed at the maytansinoid payload of IMGN853 (using an anti-maytansinoid antibody). Changes in Ki67 and other markers describing anti-proliferative and/or apoptotic effect of IMGN853 may also be investigated.

# 8. STUDY PROCEDURES

## 8.1. Informed Consent

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

## 8.2. Inclusion and Exclusion Criteria

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

Procedures for completion of enrollment information, and requirements to communicate with the Sponsor about enrollment, are detailed in the Study Manual.

## 8.3. Confirmation of Disease Diagnosis

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

## 8.4. Demographic/Medical History

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

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

## 8.5. Physical Examination, Weight and Height

Physical examination, height (screening only) and weight must be performed as indicated in the Schedule of Clinical Assessments (Appendix A 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 Events and Section 10.

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

## 8.6. Vital Signs

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

**Table 12: Vital Sign Measurements**

| | Screening | Day 1 of all Cycles (Predose)[a] | Every 30 Minutes During IMGN853 Infusion[b,d] | Following Completion of IMGN853 Infusion[c] | 4-hours Post End of Infusion[d] | At Same Time as ECG Assessments[e] | End of Study and FUP Visits |
|---|---|---|---|---|---|---|---|
| Blood Pressure | • | • | • | • | • | • | • |
| Pulse | • | • | • | • | • | • | • |
| Respiratory Rate | • | • | • | • | • | • | • |
| Temperature | • | • | • | • | • | | • |

[a] Within 10 minutes prior to start of infusion
[b] ± 10 minutes
[c] Within 10 minutes following completion of infusion
[d] **Cycles 1 and 2 only**. If the patient's infusion was well-tolerated, the 4-hour post infusion assessment will not be required in Cycles ≥3.
[e] Measured predose and within 10 minutes of completion of each set of triplicate ECG readings (predose, end of infusion to coincide with $C_{max}$ PK draw (+10 minute window) and 24 hrs post infusion (±2 hours) – See also Section 8.7.

## 8.7. Electrocardiogram (ECG)

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

***On study ECGs will be performed in triplicate at the following timepoints in Cycles 1 and 3:***

- Baseline ECG: Within one hour prior to the first dose
- Post Dose ECGs:
  - End-of-infusion to coincide with $C_{max}$ and PK blood draw (within one hour from this blood draw )
  - 24 ± 2 hours post infusion to coincide with PK blood draw

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

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

## 8.8. Pulse Oximetry

Pulse oximetry will be performed prior to dosing on Day 1 of every cycle and as indicated in Section 10 (Study Activities) and Appendix A and Appendix B (Schedule of Clinical Assessments for Schedules A and B, respectively).

## 8.9. Pulmonary Function Tests

Pulmonary function tests (PFTs) should include spirometry, diffusion capacity, and lung volume tests. PFTs will be performed within two weeks prior to Cycle 1 Day1 and in the event of pulmonary symptoms as clinically indicated (Appendix A).

## 8.10. Laboratory Assessments

Patients should be in a seated or supine position during blood collection. Screening labs (hematology, clinical chemistry, and urinalysis) may be performed within 14 days of first dose. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 4 days of dosing and are within acceptable ranges. Repeat testing will be performed as outlined in the Schedule of Clinical Assessments (Appendix A and Appendix B) and as clinically indicated.

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

### 8.10.1. Clinical Laboratory Panels

**Table 13: Clinical Laboratory Tests**

| Hematology | Serum Chemistry | Coagulation Tests | Urinalysis | Other |
|---|---|---|---|---|
| • Hematocrit<br>• Hemoglobin<br>• WBC (w/5-part differential)<br>• RBC<br>• Platelet count | • Albumin<br>• Alkaline phosphatase<br>• ALT<br>• AST<br>• BUN<br>• Calcium<br>• Carbon dioxide<br>• Chloride<br>• Creatinine<br>• Glucose<br>• LDH<br>• Magnesium<br>• Phosphorus<br>• Potassium<br>• Sodium<br>• Total bilirubin | • PT<br>• aPTT<br>• INR | • pH<br>• Ketones<br>• Protein<br>• Glucose<br>• Occult blood<br>• Leukocyte esterase<br>• Nitrite<br>(microscopic examination of sediment will be performed only if results of urinalysis dipstick are positive) | β-hcG<br>homocysteine<br>methylmalonate |

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

## 8.11. Pregnancy Screen

All female patients of child-bearing potential will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test (not more than 3 days before the first dose of IMGN853); this test must be negative for the patient to be enrolled and to receive the study drug.

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

## 8.12. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (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 3 days prior to Day 1.

## 8.13. Radiologic Imaging

Radiographic tumor evaluation by computed tomography (CT) or MRI of chest, abdomen, and pelvis (EOC patients only) will be performed within 28 days prior to first dose and approximately every second cycle, from the date of first dose until the 28-day Follow-up visit. The same radiographic assessment used at screening must be used at all subsequent radiographic evaluations.

## 8.14. Tumor Response Assessment

Tumor response for patients with measurable lesions should be assessed using RECIST 1.1 (Eisenhauer 2009, Appendix E). Patients with ovarian and uterine cancer will have CA125 measured at approximately the same time they undergo radiologic assessment. Patients will have a baseline tumor assessment done within the 28 days prior to Cycle 1, Day 1. Patients with measurable lesions should be assessed using CT scan approximately every second cycle, from the date of first dose until the 28-day Follow-up visit. Although progression may be determined by the investigator based upon clinical deterioration, every effort should be made to document progression using radiographic methods. The basis for determination of progression per clinical deterioration should be documented.

Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented. In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Electronic copies of radiologic images with tumor size measurements, including baselines assessment, must be sent to the sponsor within 4 weeks after PR/CR has been documented, together with a copy of the corresponding radiology report and tumor assessment worksheets. Scans must be in Digital Imaging and Communications in Medicine (DICOM) format. Electronic transfer of scan files (via FTP, HTTP, or similar means) is preferred, although transfer on physical media (such as DVD or CD) is acceptable. For digital media, one time point/patient/disk is expected. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, Good Clinical Practices (GCP), and federal, international, and/or state legal and medical requirements. ImmunoGen will retain the media for

a period of 2 years following the date a marketing application is approved or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued.

**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. Eligibility based on FOLR1 Expression

Instructions regarding processing and shipment of biopsy samples and archival tissues are detailed in the Laboratory Manual.

### 8.15.1. Dose Escalation Cohorts

Patients with serous or endometrioid ovarian cancer, uterine cancer or NSCLC adenocarcinoma or BAC, tumors known to have a high incidence of FOLR1 expression do not require IHC screening prior to enrollment (Section 1.1 and Section 7.1.1, and the Investigators' Brochure). Archival tumor tissue should be submitted for retrospective analysis of FOLR1 expression. Patients with other tumor types may be eligible, but require documented expression of FOLR1 by IHC (≥1% of tumor staining at ≥1+ intensity) on archival tissue prior to enrollment. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment. De-identified pathology reports should be included with sample shipment to ImmunoGen or designee.

### 8.15.2. Dose Expansion Cohort #1, Platinum Resistant Ovarian Cancer

Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment.

### 8.15.3. Dose Expansion Cohort #2, Advanced/Recurrent Uterine Cancer

Patients must have documented expression of FOLR1 by IHC (H score ≥ 100) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment.

### 8.15.4. Dose Expansion Cohort #3, Relapsed Ovarian Cancer

Patients must meet the minimum requirement of FOLR1 positivity by IHC (≥25% of tumor staining at ≥2+ intensity) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment.

If the patient meets all eligibility criteria and enrolls in the study, then a fresh tumor biopsy must be obtained prior to their first dose of IMGN853 and at Cycle 2 day 8±3 for pharmacodynamic analyses (Section 7.3). Patients who relapse after showing clinical benefit will be asked to undergo an optional biopsy to help understand the mechanism of resistance to IMGN853.

### 8.15.5. Dose Expansion Cohort #4, Relapsed/Refractory NSCLC Adenocarcinoma

Patients must have documented expression of FOLR1 by IHC (≥ 1 hetero - ≥25% of tumor staining at ≥1+ intensity) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment.

### 8.15.6. Dose Expansion Cohort #5, Relapsed Ovarian Cancer

Patients must have documented expression of FOLR1 by IHC ( ≥25% of tumor staining at ≥2+ intensity) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained to confirm FOLR1 expression by IHC prior to enrollment.

# 9. ASSESSMENT OF SAFETY

## 9.1. Adverse and Serious Adverse Events

Treatment-emergent AEs (including SAEs) will be documented on the AE eCRF and monitored continuously throughout the study from the time of the first dose of study treatment until 28 days after the patient's last dose of study drug or until the event has resolved, stabilized or an outcome has been reached, whichever comes first.

If the Investigator considers it necessary to report an AE in a study patient occurring after the end of study, he or she should contact the Sponsor to determine how the AE should be documented and reported. Pre-treatment AEs attributed to study procedures, including those events which occur prior to the first dose, should also be documented on the AE eCRF. Any other change in medical condition which occurs during the interval between consent and first dose will be documented on the medical history eCRF.

### 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.

Pre-treatment AEs occurring from the time of consent until the time of the first dose of study treatment, which are attributed to study procedures, must be reported on the designated AE eCRF. All treatment-emergent AEs, including AEs attributed to study procedures, occurring from the first dose of study treatment until 28 days after last study treatment or until the event has resolved, stabilized or an outcome has been reached 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 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 discontinuation or constitutes in and of itself a Serious Adverse Event, or require therapy, e.g., any hematologic abnormality that requires transfusion or cytokine 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 can be explained and the patient's safety is not at risk.

#### 9.1.1.2. Serious Adverse Event (SAE)

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

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

Note that hospitalization is defined as admission to treat a clinical 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.).

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 14.

**Table 14: 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 or disabling ) | 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 15:

**Table 15: Adverse Event Relatedness**

| Relationship to Product(s) | Definition |
|---|---|
| Not Related | No relationship between the event/laboratory abnormality and the administration of study drug. |
| Possibly Related | A clinical event/laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs/chemicals. |
| Definitely Related | A clinical event/laboratory abnormality with a reasonable time sequence to administration of study drug and follows a known response pattern to the study drug and can be confirmed with a positive re-challenge test or supporting laboratory data. |

## 9.2. Recording 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 the first dose of study treatment until 28 days after the last study treatment, should be recorded by the clinical site on an SAE form. This reporting requirement also includes SAEs that are attributed to a study procedure performed during the screening period (from the time of consent until the time of the first dose of study treatment). The SAE must be completely described on the patient's CRF, including the judgment of the Investigator as to the relationship of the SAE to the study drug. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the ImmunoGen Medical Director or designee on an SAE report form. This form must be completed and submitted within 24 hours of the Investigator's learning of the event to the contact persons listed in the Study Manual provided to each site and maintained in the Investigator study files. Any follow-up information must also be completed on an SAE form and submitted to the same contacts.

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

- The underlying diagnosis or syndrome should be reported as the primary SAE term, rather than the signs or symptoms (signs and symptoms may be described in the narrative).
- Death should not be reported as an SAE, but rather as an outcome of a specific SAE, unless the event preceding the death is unknown. In these exceptional cases, death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.

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

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

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

### 9.2.2. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. The Sponsor must be notified in the event of a pregnancy occurring during the course of the study and through 28 days after the patient's last dose of study drug. Pregnancy is not to be reported as an AE; the pregnancy reporting form should be used to report the pregnancy. The pregnancy will be followed through delivery or final outcome.

# 10. STUDY ACTIVITIES

## 10.1. Screening Visit (Days -28 to -1)

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

- Obtain written informed consent prior to the undertaking of study-specific procedures unless those procedures are performed as part of the patient's standard care
- Collect and record demographic and medical information; include all prior treatments for their disease with dates of therapy and best response, when available
- Perform complete physical examination (Appendix A and Appendix B)
- Vital signs (Section 8.6, Appendix A and Appendix B)
- Height (Appendix A and Appendix B)
- Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests – within 14 days prior to first dose (Section 8.10, Appendix A and Appendix B):
    - Serum chemistry
    - Hematology
    - Coagulation profile
    - Urinalysis
- Complete Ophthalmic Examination (performed by a board-certified ophthalmologist):
    - Schirmer test, Slit lamp examination under dilatation, visual acuity, intraocular pressure assessment, and indirect fundoscopy. (Section 5.8.8)
    - Performed within 14 days of Cycle 1, Day 1
- Pulmonary Function Tests (Section 8.9) – within 14 days prior to first dose
- Pregnancy test for WCBP (Appendix A and Appendix B)
- Radiologic imaging, disease staging, and prognostic index evaluation (Appendix A and Appendix B)
    - Confirm disease diagnosis and current disease status
    - CA125 - for patients with EOC, primary peritoneal cancer, fallopian tube cancer or uterine cancer whose baseline levels are ≥ 2.0 times the UNL – to be performed within 14 days prior to starting treatment (Appendix F)
- 12-lead electrocardiogram (a single ECG – within 14 days of first treatment)

- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness. If abnormal, an NCI CTAE grade will be recorded and if warranted a neurologist will be consulted (Appendix A and Appendix B)
    - FACT/GOG-Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G )
- Record baseline signs and symptoms (Appendix A and Appendix B)
- Record concomitant medications (Appendix A and Appendix B)
- Review and document inclusion and exclusion criteria (Appendix A)
- Record AEs and SAEs which resulted from study procedures
- PFTs (within 14 days of Cycle 1 Day 1, and as clinically indicated) (Appendix A)
- Fresh tumor biopsy (Section 7.1.1 and Appendix C)
    - Patients requiring FOLR1 documentation who do not have archival tissue available
    - All patients in MTD Expansion Cohort #3 (relapsed EOC)
- For patients with EOC, uterine cancer or NSCLC only:
    - Identify and ship fresh or archival tumor tissue (Section 8.15)

### 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. 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.

## 10.2. Cycle 1 Assessments

### 10.2.1. Cycle 1, Day 1

The following procedures must be performed or initiated as indicated prior to the start of treatment to establish the patient's baseline condition. The patient will remain in the clinical research unit/treatment area for at least 4 hours following the initial dose of IMGN853. Subsequent IMGN853 infusions require at least a 1-hour post-dose observation period (if the initial infusion is well tolerated). While in the treatment area, patients will be closely monitored for toxicity.

The following should be completed prior to dosing on Day 1 of Cycles 1 and 2 except as noted. Note that safety blood tests, and physical examination do not need to be repeated if normal and conducted within 4 days prior to Cycle 1, Day 1.

- Confirm that the patient continues to satisfy all inclusion and exclusion criteria (Appendix A and Appendix B)
- Symptom-directed physical examination (Appendix A and Appendix B)
- Vital signs (Section 8.6, Appendix A and Appendix B)
- Pulse oximetry (Section 8.8)
- Weight (Appendix A)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
    - Serum chemistry
    - Hematology
    - Coagulation profile
    - Urinalysis
- Ocular symptom assessment (Section 5.8.8)
- Pregnancy test for WCBP (Appendix A and Appendix B)
- ECG – performed in triplicate as outlined in Section 8.7 (Appendix A and Appendix B)
- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness. (Appendix A and Appendix B)
    - Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G)
- Record baseline signs and symptoms that have emerged since the screening visit (Appendix A and Appendix B)
- IMGN853 administration (Appendix A and Appendix B)
- AEs and SAEs (Appendix A and Appendix B)
- Concomitant medications (Appendix A)
- Blood sample for measurement of homocysteine and methylmalonate as outlined in Section 7.2.3 and Appendix C
- Blood sample for measurement of FcγR polymorphisms as outlined in Section 7.2.1 and Appendix C
- Record known molecular pathology data (Appendix C), for example:
    - Ovarian Cancer: BRCA1/BRCA2 status
    - NSCLC: EGFR mutation/amplification, ALK translocation, Ras mutation/amplification

- Renal Cell Carcinoma (RCC): Von Hippel Lindau (VHL) mutation

- PK sample collection as outlined in Section 6 and Appendix C
- HAHA and HADA sample collection as outlined in Section 6 and Appendix C

#### 10.2.2. Cycle 1, Day 2

- PK sample collection as outlined in Section 6 and Appendix C
- ECG performed in triplicate as outlined in Section 8.7 (also Appendix A and Appendix B)
- Vitals signs; blood pressure, pulse, temperature and respiratory rate as outlined in Section 8.6, Appendix A and Appendix B
- Pulse oximetry (Section 8.8)

#### 10.2.3. Cycle 1, Day 3 and Day 4, or 5

- **Schedule A only** - PK sample collection as outlined in Section 6 and Appendix C

#### 10.2.4. Cycle 1, Day 8 and 15

- Symptom-directed physical examination (Appendix A)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
- Pulse oximetry (Section 8.8)
- PK sample collection as outlined in Section 6 and Appendix C
- AEs and SAEs (Appendix A and Appendix B)
- Concomitant medications (Appendix A and Appendix B)
- **Schedule B Only:**
  - IMGN853 administration (Appendix A and Appendix B)

#### 10.2.5. Cycle 1, Day 16 (Schedule B only)

- PK sample collection as outlined in Section 6 and Appendix C

#### 10.2.6. Cycle 1, Day 22 (Schedule B only)

- PK sample collection as outlined in Section 6 and Appendix C

### 10.3. Cycle 2 Assessments

#### 10.3.1. Cycle 2, Day 1

- Confirm that the patient satisfies all retreatment criteria (Section 5.9.3)
- Symptom-directed physical exam (Appendix A and Appendix B)

- Vital signs (Section 8.6, Appendix A and Appendix B)
- Pulse oximetry (Section 8.8)
- Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B)
    - Serum chemistry
    - Hematology
    - Coagulation profile
    - Urinalysis
- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness. (Appendix A and Appendix B)
    - Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G)
- IMGN853 administration (Appendix A and Appendix B)
- AEs and SAEs (Appendix A and Appendix B)
- Ocular symptom assessment (Section 5.8.8)
- Concomitant medications
- PK sample collection, as outlined in Section 6 and Appendix C
- HAHA and HADA sample collection as outlined in Section 6 and Appendix C

### 10.3.2. Cycle 2, Day 8±3 Days

- Blood sample for measurement of homocysteine and methylmalonate as outlined in Section 7.2.3 and Appendix C
- Fresh tumor biopsy – Expansion Cohort #3 (Sections 7.1.1, 7.3.1 and Appendix C)
    - In addition, patients who relapse after showing clinical benefit will be asked to undergo an optional biopsy at the time of disease progression to help understand the mechanism of resistance to IMGN853

### 10.3.3. Cycle 2, Day 8 and 15

- Symptom-directed physical examination
- Vital signs (Section 8.6, Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
    - Serum chemistry
    - Hematology

- Pulse oximetry (Section 8.8)
- AEs and SAEs (Appendix A and Appendix B)
- Concomitant medications (Appendix A and Appendix B)
- Schedule B Only: IMGN853 administration (Appendix A and Appendix B) Cycle 3 Assessments

## 10.4. Cycle 3 Assessments

### 10.4.1. Cycle 3, Day 1

- Confirm that the patient satisfies all retreatment criteria (Section 5.9.3)
- Symptom-directed physical examination (Appendix A and Appendix B)
- Vital signs as outlined in Section 8.6, Appendix A and Appendix B
- Pulse oximetry (Section 8.8)
- Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
  - Coagulation profile
  - Urinalysis
- ECG – performed in triplicate as outlined in Section 8.7.
- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness (Appendix A and Appendix B).
  - Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G)
- IMGN853 administration
- AEs and SAEs (Appendix A and Appendix B)
- Ocular symptom assessment (Section 5.8.8)
- Concomitant medications
- PK sample collection as outlined in Section 6 and Appendix C
- HAHA and HADA sample collection as outlined in Section 6

### 10.4.2. Cycle 3, Day 2

- PK sample collection as outlined in Section 6 and Appendix C

- ECG – performed in triplicate as outlined in Section 8.7
- Vital signs as outlined in Section 8.6, Appendix A and Appendix B
- Pulse oximetry (Section 8.8)
- AEs and SAEs (Appendix A and Appendix B)
- Concomitant medications

#### 10.4.3. Cycle 3, Day 3 and Day 4 or 5 (Schedule A Only)

- PK sample collection as outlined in Section 6 and Appendix C

#### 10.4.4. Cycle 3, Day 8 and 15

- Clinical laboratory tests:
  - Serum chemistry
  - Hematology
- Pulse oximetry (Section 8.8)
- AEs and SAEs (Appendix A and Appendix B)
- Concomitant medications
- **Schedule B Only:**
  - IMGN853 administration (Appendix A and Appendix B)
  - PK sample collection as outlined in Section 6 and Appendix C

#### 10.4.5. Cycle 3, Day 16 (Schedule B only)

- PK sample collection as outlined in Section 6 and Appendix C

#### 10.4.6. Cycle 3, Day 22 (Schedule B only)

- PK sample collection as outlined in Section 6 and Appendix C

### 10.5. Even-Numbered Cycles (2, 4, 6, etc.), End of Cycle

- Pregnancy test (may be performed more frequently in accordance to institutional requirements) (Appendix A and Appendix B)
  - **Schedule A –** Day 18±3 days
  - **Schedule B –** Day 21±3 days
- **For patients who experience ocular toxicity and those who experience blurred vision but have normal eye examinations:** complete ophthalmic examination (Section 5.8.8); to be performed by a board-certified ophthalmologist prior to the start of every other cycle from the time it is first reported.
- Tumor assessments by CT scan (Appendix A and Appendix B)
  - **Schedule A –** Every 6 weeks±1 week

- **Schedule B –** Every 8 weeks±1 week

- CA125 - for patients with EOC, primary peritoneal cancer, fallopian tube cancer or uterine cancer (Appendix F) should be scheduled to coincide approximately with the radiographic tumor assessments

  NOTE: Patients experiencing CA125 response must have a confirmatory test performed 28 days after initial response is documented.

## 10.6. Cycles ≥ 4 Assessments

### 10.6.1. Cycles ≥4, Day 1

Within 96 hours prior to Day 1:

- Confirm patient meets retreatment criteria as outlined in Section 5.9.3.
- Symptom-directed physical examination (Appendix A and Appendix B)
- Vital signs (Section 8.6, Appendix A and Appendix B)
- Pulse oximetry (Section 8.8)
- Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests (Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
  - Coagulation profile
  - Urinalysis
- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness. If abnormal, an NCI CTAE grade will be recorded and if warranted a neurologist will be consulted (Appendix A and Appendix B)
  - Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G)
- IMGN853 administration (Appendix A and Appendix B)
- AEs and SAEs (Appendix A and Appendix B)
- Ocular symptom assessment (Section 5.8.8)
- Concomitant medications (Appendix A and Appendix B)
- Up to Cycle 6 - PK sample collection as outlined in Section 6 and Appendix C
- HAHA and HADA sample collection as outlined in Section 6 and Appendix C

### 10.6.2. Cycles ≥ 4, Day 8 and 15 (Schedule B)

- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
- Pulse oximetry (Section 8.8)
- Concomitant medications (Appendix A and Appendix B)
- IMGN853 administration (Appendix A and Appendix B)
- AEs and SAEs (Appendix A and Appendix B)

## 10.7. 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 5.10.

Patients who withdraw or are removed from the study treatment will have an end of treatment visit within 7 days of the decision to discontinue study treatment. All study evaluations described below will be performed. Additionally, these patients will undergo a 28-day follow-up safety visit. The eCRF will capture reasons for withdrawal.

The procedures listed below are to be undertaken at the end of treatment visit and documented in the eCRF:

- Symptom-directed physical examination (Appendix A and Appendix B)
- Vital signs as outlined in Section 8.6, Appendix A and Appendix B
- Pulse oximetry (Section 8.8)Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
- Blood sample for measurement of homocysteine and methylmalonate as outlined in Section 7.2.3 and Appendix C
- Ophthalmic examinations: visual acuity, fundoscopic exam, ocular symptom assessment (Section 5.8.8)
- Single, 12-lead ECG (Section 8.7)
- Radiologic imaging to monitor tumor response if PD has not been documented already (Appendix A and Appendix B)

- CA125 - for patients with EOC, primary peritoneal cancer, fallopian tube cancer or uterine cancer (Appendix F)

  NOTE: patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

- AEs and SAEs (Appendix A and Appendix B)
- Ocular symptom assessment (Section 5.8.8)
- Concomitant medications (Appendix A)
- HAHA and HADA sample collection as outlined in Section 6 and Appendix C

## 10.8. Follow-up Assessments

**Safety Follow-up:** A safety follow-up visit will occur 28 days (+ 14 days) after the last treatment. During this visit, the following assessments will be performed.

- Complete physical examination (Appendix A and Appendix B)
- Vital signs (Section 8.6, Appendix A and Appendix B)
- Pulse oximetry (Section 8.8)
- Weight (Appendix A and Appendix B)
- ECOG performance status (Appendix A and Appendix B)
- 12-Lead ECG (if clinically indicated)
- Pregnancy test for WCBP (Appendix A and Appendix B)
- Clinical laboratory tests (Section 8.10, Appendix A and Appendix B):
  - Serum chemistry
  - Hematology
  - Coagulation profile
  - Urinalysis
- Radiologic imaging to monitor tumor response if PD has not been documented already (Appendix A and Appendix B)
- For patients with EOC, uterine cancer or NSCLC only:
- CA125 - for patients with EOC, primary peritoneal cancer, fallopian tube cancer or uterine cancer (Appendix F)

  NOTE: patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

- AEs and SAEs (Appendix A and Appendix B)
- Ocular symptom assessment (Section 5.8.8)

- Complete ophthalmic examination for all patients; alternatively, the complete examination can be performed at the End of Study visit.
    - Patients experiencing an ocular treatment-emergent adverse event (Section 5.8.8.2) will continue to have examinations every 2 weeks until the condition resolves or is deemed to be irreversible by the investigator.
- Concomitant medications(Appendix A and Appendix B)
- Directed neurological examination will be performed, to include light touch, pinprick, proprioception, and deep tendon reflexes (DTRs) of the upper and lower extremities; and questioning for symptoms of paresthesia and numbness. If abnormal, an NCI CTAE grade will be recorded and if warranted a neurologist will be consulted (Appendix A and Appendix B)
    - Neurotoxicity Questionnaire (FACT/GOG NTx), Version 4.0 (Appendix G)
- HAHA and HADA sample collection as outlined in Section 6 and Appendix C

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

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

# 11. STATISTICAL METHODS

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number 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.

No formal interim analysis is planned for this study. However, a review of safety data and available preliminary PK data will be conducted by the CRC after the MTD or a RP2D for IMGN853 has been determined. Results from this data review could enable selection of dose and dosing schedule for additional studies with IMGN853, before full completion of this study.

A statistical analysis plan (SAP) will fully describe the planned analyses for this trial. All analyses will be performed for any patient that received study drug. All analyses for efficacy will use Cycle 1, Day 1 as the start time.

## 11.1. Sample Size

Ascending doses of IMGN853 are to be evaluated to identify the MTD for both dosing schedules. The actual number of patients accrued during this phase will be determined largely by the findings observed during the course of their treatment.

Following identification of the MTD for Schedule A (Q3W), there was an expansion phase which initially accrued two cohorts at the MTD: *(1) Dose Expansion Cohort 1* – 40 patients with platinum resistant EOC. *(2) Dose Expansion Cohort #2* - 20 patients with advanced or recurrent uterine cancer. Once the Schedule B MTD (modified weekly) was established, the CRC convened to review safety, PK and efficacy results from the both schedules as well as preliminary data from the Expansion Cohorts 1 and 2, with the Q3W schedule of administration. The CRC recommended use of Schedule A for all future cohorts. Three additional MTD Expansion Cohorts will enroll the following patients: *(3) Dose Expansion Cohort 3* – 20 patients with relapsed ovarian cancer, which is amenable to biopsy *(4) Dose Expansion Cohort 4* – 20 patients with relapsed/refractory NSCLC adenocarcinoma, and (5) 40 patients with platinum resistant EOC who will receive daily treatment with corticosteroid-containing eye drops.

If the true DLT rate at the MTD is 10-20%, there is an 98.5-99.9% probability of observing at least one DLT in each 40 patient cohort. If the true response rate at the MTD is 20%, there is a 99.9% probability of observing at least one response in each 40 patient cohort.

**Table 16: Probability of Observing ≥ x Events (Response or DLT) For a 40 patient Cohort**

| x (Number Observed) | True Event Rate | | |
|---|---|---|---|
| | 10% | 20% | 30% |
| 1 | 0.985 | 0.999 | 0.999 |
| 2 | 0.919 | 0.998 | 0.999 |
| 3 | 0.777 | 0.992 | 0.999 |
| 4 | 0.577 | 0.972 | 0.999 |
| 5 | 0.371 | 0.924 | 0.997 |
| 6 | 0.206 | 0.838 | 0.991 |

Given a sample size of 40 patients, the power to detect a difference of 20% (rate of Blurry vision decrease from 50% to 30%) is 68% using one-sided alpha of 20% and Chi-Square test statistics.

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

Approximately 209 patients will be enrolled in the study, allowing for dropouts and expansion of dose escalation cohorts as needed.

## 11.2. Pharmacokinetic Analyses

PK parameters ($C_{max}$, $T_{max}$, Terminal half-life ($t_{1/2}$), volume of distribution at steady state (Vss), clearance (Cl), $AUC_{0-24}$, $AUC_{0-168}$, $AUC_{inf}$) will be derived from plasma concentrations of IMGN853, total M9346A antibody and DM4 using the actual sampling times. Concentration data and all PK parameters will be listed per patient and summarized descriptively per dose. Standard algorithms of the non-compartmental pharmacokinetic analysis program, WinNonlin software, will be used for these analyses.

Individual plasma concentration vs. actual time profiles for each patient and treatment, as well as the mean (+/- STD) plasma concentration vs. scheduled time profiles for each dose level, will be presented graphically.

## 11.3. Safety Analyses

Adverse events, concomitant medication, and results from physical examination will be listed.

Adverse events will also be coded with the Medical Dictionary for Regulatory Activities (MedDRA; version 17.0 or greater) and summarized per system organ class (SOC) 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, and ECG results will be summarized by treatment. Shifts in hematology and blood chemistry from Baseline values will be summarized. Plasma also will be evaluated for the presence of humoral responses against the M9346A antibody component (HAHA) or against the DM4 component (HADA).

## 11.4. Efficacy

Objective response rate (ORR) - The best OR will be determined by the Investigator for each patient as either CR, PR, SD or relapsed disease/PD. Objective responses for patients in the dose escalation phase will be summarized by dose cohort assigned as well as the dose at which the response occurred. Responses will be tabulated separately for expansion cohorts 1-4. For each expansion cohort, the response rate will be calculated as the number of CR or PR divided by the number of response evaluable patients. To meet the definition of response-evaluable, patients must have undergone radiographic assessment at baseline, received at least one dose of IMGN853, and must have had at least one post-dose tumor assessment.

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) using the method of Kaplan-Meier. Results will be summarized by dose cohort assigned as well as the dose at which the response occurred.

Progression Free Survival (PFS) – PFS, defined as the time from initiation of study drug until progressive disease or death whichever occurs first, will be estimated using the Kaplan-Meier method. Results will be summarized by dose cohort.

Time to Progression (TTP) - TTP defined as the time from initiation of study drug until progressive disease, will be estimated using the method of Kaplan-Meier. Results will be summarized by dose cohort.

For DOR, PFS, and TTP calculations, subjects not achieving the endpoint will be censored at the time of the last endpoint assessment. Median response times and associated 95% CIs will be presented for descriptive summaries.

# 12. QUALITY CONTROL AND ASSURANCE

Clinical sites will be monitored by ImmunoGen or its designee to ensure the accuracy of data against source documents. Data will be captured using validated systems. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 or later. 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 and/or safety database in accordance with Code of Federal Regulations (CFR) 21 Part 11 compliance. The database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password protected environment. All missing data will be explained.

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

# 13. ADMINISTRATIVE CONSIDERATIONS, STUDY MONITORING AND DATA MANAGEMENT

## 13.1. Investigators and Study Administrative Structure

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

## 13.2. 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 screening ICF (latter ICF is applicable for sites requesting permission to prescreen for FOLR1 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 US Food and Drug Administration (FDA) or other regulatory agencies (SUSARs) must be submitted promptly to the IRB/IEC.

## 13.3. Ethical Conduct of the Study

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

## 13.4. Patient Information and Consent

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

elements. The ICF must be in a language understandable to the patient or the patient's legally authorized representative(s) and must specify who informed the patient or the patient's legally authorized representative.

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

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

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

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

A screening ICF may be used to confirm a patient's consent to analyze archived or fresh tumor samples for FOLR1 expression. If the IHC screening assay is positive for FOLR1, the patient will be provided the full study consent and only after signing the full study ICF will additional study-specific screening tests be performed. A model of the screening ICF will be provided to the sites separately from this protocol.

## 13.5. 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 sent to outside laboratories and/or CROs (e.g. IHC laboratory) are identified by study patient number only to ensure maintenance of confidentiality. The patient consent form will state publications resulting from this study will not refer to patient name or include any other information that might disclose the identity of the subject. The patients will be told that representatives of the 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.

## 13.6. Study Monitoring

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

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

## 13.7. Case Report Forms and Study Reports

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

## 13.8. Critical Documents

Before ImmunoGen initiates the trial (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.

## 13.9. Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement

of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

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

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

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

## 13.10. End of Study

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

## 13.11. Study termination

### 13.11.1. Study Termination

If the Sponsor, an Investigator, or Study Clinical Monitor discovers conditions arising during the study that indicate that the clinical investigation should be halted 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.

### 13.11.2. Site Termination

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

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

## 13.12. Access to Source Documentation

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

## 13.13. Data Generation and Analysis

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

## 13.14. Retention of Data

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

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

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

## 13.15. 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.

## 13.16. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product as well as any matter concerning the operation of the 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.

# 14. LIST OF REFERENCES

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

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

American Cancer Society *Cancer Facts and Figures*, 2013.

Antony AC, Tang Y-S, Khan RA, et al. Translational upregulation of folate receptors is mediated by homocysteine via RNA-heterogeneous nuclear ribonucleoprotein E1interactions. *Journal of Clinical Investigations* 113: 285-301, 2004.

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

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

Borghei H, O'Malley D, Seward S, et al. Phase 1 Study of IMGN853, a Folate Receptor Alpha (FRα)-Targeting Antibody-Drug Conjugate (ADC) in Patients (Pts) with Epithelial Ovarian Cancer (EOC) and other FRα-Positive Solid Tumors. Abstract 5558. ASCO 2015.

Buck AK, Halter G, Schirmeister H, et al. Imaging proliferation in lung tumors with PET: $^{18}$F-FLT versus $^{18}$F-FDG. *Journal of Nuclear Medicine* 44: 1426-1431, 2003.

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

Cannistra SA. Evaluating new regimens in recurrent ovarian cancer: how much evidence is good enough? *Journal of Clinical Oncology* 28: 3101-3103, 2010.

Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *Journal of Clinical Oncology* 11(3): 570-79, 1993.

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

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

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

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

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

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

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

Franklin WA, Waintrub M, Edwards D, et al. New anti-lung cancer antibody cluster 12 reacts with human folate receptors present on adenocarcinoma. *International Journal of Cancer Supplement*. 8: 89-95, 1994.

Ghamande SA, Gilber L, Penson R et al., The co-development of a folate receptor targeted diagnostic imaging agent and folate receptor targeted drug conjugate (EC145)in the treatment of ovarian cancer patients. EORTC-ASCO-NCI Meeting 2011, Abstract #93.

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

Herbst RS, Davies AM, Natale RB, et al. Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non-small cell lung cancer. *Clinical Cancer Research* 13: 6175-6181, 2007.

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

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

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

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

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

Kelly K, Crowley J, Bunn PA et al. Randomized phase 3 trial of paclitaxel plus carboplatin vs vinorelbine plus cisplatin in the treatment of patients with advanced NSCLC: a SWOG trial. *Journal of Clinical Oncology* 19: 3210-3218, 2001.

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

Matsuo K, Lin YG, Roman LD et al. Overcoming platinum resistance in ovarian cancer. *Expert Opinion on Investigational Drugs* 19:1339-1354, 2010.

Morgan RJ, Alvarez RD, Armstrong DK et al. NCCN clinical practice guidelines in oncology: epithelial ovarian cancer. *Journal of the National Comprehensive Cancer Network* 9:82-113, 2011.

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

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

Sadasivan E, Regec A and Rothenberg SP. The half-life of the transcript encoding the folate receptor α in KB cells is reduced by cytosolic proteins expressed in folate-replete and not in folate-depleted cells. *Gene* 291: 149-158, 2002.

Schiller JH, Harrington D, Belani CP, et al. Comparison of Four Chemotherapy Regimens for Advanced NSCLC. *New England Journal of Medicine* 346: 92-98. 2002.

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

Sohn H-J, Yang Y-J, Ryu J-S, et al. [$^{18}$F]fluorothymidine positron emission tomography before and 7 days after gefitinib treatment predicts response in patients with advanced adenocarcinoma of the lung. *Clinical Cancer Research* 14: 7423-7429, 2008.

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

Vesselle H, Grierson J, Muzi M, et al. In vivo validation of 3'deoxy-3'[$^{18}$F]fluorothymidine ([$^{18}$F]FLT) as a proliferation imaging tracer in humans: correlation of [$^{18}$F]FLT uptake by positron emission tomography with Ki-67 immunohistochemistry and flow cytometry in human lung tumors. *Clinical Cancer Research* 8: 3315-3323, 2002.

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

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

Yap CS, Czernin J, Fishbein MC, et al. Evaluation of thoracic tumors with $^{18}$F-fluorothymidine and $^{18}$F-fluorodeoxyglucose-positron emission tomography. *Chest* 129: 393-401, 2006.

Yamamoto Y, Nishiyama Y, Ishikawa S, et al. Correlation of $^{18}$F-FLT and $^{18}$F-FDG uptake on PET with Ki-67 immunohistochemistry in non-small cell lung cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 34: 1610-1616, 2007.

Younes A, Kim S, Romaguera J, et al. Phase I Multidose-Escalation Study of the Anti-CD19

Maytansinoid Immunoconjugate SAR3419 Administered by Intravenous Infusion Every 3 Weeks to Patients With Relapsed/Refractory B-Cell Lymphoma. *Journal of Clinical Oncology* 30:2776-2782. 2012.

Yuan Y, Nymoen DA, Dong HP, et al. Expression of the folate receptor genes FOLR1 and FOLR3 differentiates ovarian carcinoma from breast carcinoma and malignant mesothelioma in serous effusions. *Human Pathology* 40: 1453-1460, 2009.

Zander T, Scheffler M, Nogova, L, et al. Early prediction of nonprogression in advanced non-small cell lung cancer treated with erlotinib by using [$^{18}$F]fluorodeoxyglucose and [$^{18}$F]fluorothymidine positron emission tomography. *Journal of Clinical Oncology* 13:1701-1708, 2011.

Zhu WY, Alliegro MA, and Medera PW. The rate of folate receptor α (FRα) synthesis in folate depleted CHL cells is regulated by a translational mechanism sensitive to media folate levels, while stable overexpression of its mRNA is mediated by gene amplification and an increase in transcript half-life. *Journal of Cellular Biochemistry* 81:205-219, 2001.

# APPENDIX A. SCHEDULE OF CLINICAL ASSESSMENTS –SCHEDULE A (Q3W)

| Activity | Screening | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Cycles ≥4 | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 18±3 | Day 1 | Day 2 | Day 8&15 | Day 1 | | |
| Informed consent | ●[a] | | | | | | | | | | | | |
| Demography | ●[a] | | | | | | | | | | | | |
| Medical History | ●[a] | | | | | | | | | | | | |
| Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation | ●[a] | | | | | | | | | | | | |
| Record Baseline Signs and Symptoms | ● | ● | | | | | | | | | | | |
| Review and document IC/EC (Sections 3.1 and 3.1.2) | ●[c] | | | | | | | | | | | | |
| Confirm patient continues to satisfy I/E Criteria (Sections 3.1 and 3.1.2) | | ● | | | | | | | | | | | |
| Confirm patient meets retreatment criteria (Section 5.9.3) | | | | | ● | | | ● | | | ● | | |
| Height | ●[a] | | | | | | | | | | | | |
| Physical Examination[b] | ●[c] | ● | | ● | ● | ● | | ● | | | ● | ● | ● |
| Weight | ●[c] | ● | | | ● | | | ● | | | ● | ● | ● |
| Vital signs[d] | ●[c] | ● | ● | | ● | | | ● | ● | | ● | ● | ● |
| Pulse oximetry | | ● | ● | ● | ● | ● | | ● | ● | ● | ● | ● | ● |
| Pulmonary Function Test[e] | ● | | | | | | | | | | | | |
| ECOG PS | ●[c] | ● | | | ● | | | ● | | | ● | ● | ● |

| Activity | Screening | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Cycles ≥4 | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 18±3 | Day 1 | Day 2 | Day 8&15 | Day 1 | | |
| Hematology and Chemistry | ●[c] | ●[f] | | ● | ● | ● | | ● | | ● | ● | ● | ● |
| Coagulation (PT/INR/ aPTT) | ●[c] | ●[f] | | | ● | | | ● | | | ● | | ● |
| Urinalysis | ●[c] | ●[f] | | | ● | | | ● | | | ● | | ● |
| Pregnancy Test (urine or Serum)[g] | ●[c] | ● | | | | | Even-numbered cycles (2, 4, 6, etc.)[g] | | | | | | ●[g] |
| Ophthalmic examinations[h] | ● | | | | | | Every other cycle (from point at which toxicity first reported)[h] | | | | | ● | ● |
| Schirmer Test[h] | ● | For patients who experience treatment-emergent eye disorders, the Schirmer Test will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated | | | | | | | | | | | |
| Ocular Symptom Assessment[h] | | ● | | | ● | | | ● | | | ● | ● | ● |
| Radiologic tumor assessments | ●[a] | | | | | | Every 6 weeks ± 1 week)[i] | | | | | ●[j] | ●[j] |
| CA125 (Appendix F) | ●[c] | | | | | | Every 6 weeks( ± 1 week)[i] | | | | | ●[j] | ●[j] |
| 12-Lead ECG (Section 8.7)[k] | ●[c] | ● | ● | | | | | ● | ● | | | ● | ●[l] |

| Activity | Screening | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Cycles ≥4 | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 18±3 | Day 1 | Day 2 | Day 8&15 | Day 1 | | |
| Neuropathy assessment, including FACT/GOG-Neurotoxicity Questionnaire | ●[c] | ● | | | ● | | | ● | | | ● | | ● |
| IMGN853 Infusion | | ● | | | ● | | | ● | | | ● | | |
| Corticosteroid Eye Drops | | **Patients in Expansion Cohort 5 (only)** will self-administer corticosteroid eye drops as described in Section 5.8.2 | | | | | | | | | | | |
| Lubricating Eye Drops | | **All patients** will self-administer lubricating eye drops as described in Section 5.8.3 | | | | | | | | | | | |
| AE and SAE assessments | ●[n] | ● | | ● | ● | ● | | ● | ● | ● | ● | ● | ● |
| Record concomitant medications | ●[c] | ● | | ● | ● | ● | | ● | ● | ● | ● | ● | ● |

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 28-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 as outlined in Section 8.6 and 8.7.
e. Pulmonary Function Tests will be performed within 14 days of receiving the first dose of study treatment (Cycle 1 Day 1) and as clinically indicated.
f. Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN853. In the event of severe toxicity, repeat laboratory tests should be performed as necessary until the toxicity resolves or stabilizes. For a complete list of laboratory assessments, refer to Section 8.10.
g. For WCBP, a urine or serum pregnancy test will be performed at screening, prior to dosing on Day 1, every-other-cycle while on study and at the 28-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 a board-certified ophthalmologist and will include the following: indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and corneal photography. A Schirmer test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated. The baseline exam may be performed within 14 days of Cycle 1, Day 1. Ocular symptom assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms then IMGN853 will be stopped and the subject will then be referred to an ophthalmologist for a complete examination (Section 5.8.8).Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye examinations. All patients will have a complete ophthalmologic exam performed at the End of Treatment visit or 28-Day Follow Up.
i. Radiographic tumor assessment by CT scan is to be performed every 6 weeks (± 1 week). Additionally, patients with elevated CA125 at baseline will have CA125 measured at approximately the same time they undergo radiologic assessment. Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.

j. If a patient discontinues prior to documentation of PD, a tumor assessment is to be performed at the End of Study visit or 28-Day Follow up visit, if not performed within the previous 6 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 (Appendix E) every 12 weeks (±3 weeks) until documentation of PD, starting a subsequent anti-cancer therapy or for up to one year from Cycle 1, Day 1, whichever comes first.
k. ECGs will be performed as outlined in Section 8.7.
l. As clinically indicated.
m. Only AEs and SAEs attributed to study procedures are recorded.

# APPENDIX B. SCHEDULE OF CLINICAL ASSESSMENTS – SCHEDULE B (MODIFIED WEEKLY)

| Activity | Screening | Cycle 1 | | | Cycle 2 and Cycles≥4 | | | Cycle 3 | | | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 21±3 | Day 1 | Day | Day 8&15 | | |
| Informed consent | ●[a] | | | | | | | | | | | |
| Demography | ●[a] | | | | | | | | | | | |
| Medical History | ●[a] | | | | | | | | | | | |
| Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation | ●[a] | | | | | | | | | | | |
| Record Baseline Signs and Symptoms | ● | ● | | | | | | | | | | |
| Review and document IC/EC (Sections 3.1 and 3.1.2) | ●[c] | | | | | | | | | | | |
| Confirm patient continues to satisfy I/E Criteria (Sections 3.1 and 3.1.2) | | ● | | | | | | | | | | |
| Confirm patient meets retreatment criteria (Section 5.9.3) | | | | | ● | | | ● | | | | |
| Height | ●[a] | | | | | | | | | | | |
| Physical Examination[b] | ●[c] | ● | | ● | ● | Cycles 1-3 only | | ● | | ● | ● | ● |
| Weight | ●[c] | ● | | | ● | | | ● | | | ● | ● |
| Vital signs[d] | ●[c] | ● | ● | | ● | ● | | ● | ● | | ● | ● |
| Pulse oximetry | | ● | ● | ● | ● | ● | | ● | ● | ● | ● | ● |
| ECOG PS | ●[c] | ● | | | ● | | | ● | | | ● | ● |

| Activity | Screening | Cycle 1 | | | Cycle 2 and Cycles≥4 | | | Cycle 3 | | | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 21±3 | Day 1 | Day | Day 8&15 | | |
| Hematology and Chemistry | ●[c] | ●[e] | | ● | ● | ● | | ● | | ● | ● | ● |
| Coagulation (PT/INR/ aPTT) | ●[c] | ●[e] | | | ● | | | ● | | | | ● |
| Urinalysis | ●[c] | ●[e] | | | ● | | | ● | | | | ● |
| Pregnancy Test (urine or Serum)[f] | ●[c] | ● | | | | | Even-numbered cycles (2, 4, 6, etc.)[f] | | | | | ●[f] |
| Ophthalmic examinations[g] | ● | | | | | | Every other cycle (from point at which toxicity first reported)[g] | | | | ● | ● |
| Schirmer Test[g] | ● | For patients who experience treatment-emergent eye disorders, the Schirmer Test will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated | | | | | | | | | | |
| Ocular Symptom Assessment[g] | | ● | | | ● | | | ● | | | ● | ● |
| Radiologic tumor assessments | ●[a] | | | | | | Every 8 weeks ± 1 week)[h] | | | | ●[i] | ●[i] |
| CA125 (Appendix F) | ●[c] | | | | | | Every 8 weeks( ± 1 week)[h] | | | | ●[i] | ●[i] |
| 12-Lead ECG (Section 8.7)[j] | ●[c] | ● | ● | | | | | ● | ● | | ● | ●[k] |
| Neuropathy assessment, including FACT/GOG-Neurotoxicity Questionnaire | ●[c] | ● | | | ● | | | ● | | | | ● |

| Activity | Screening | Cycle 1 | | | Cycle 2 and Cycles≥4 | | | Cycle 3 | | | End of Treatment | 28-Day Follow-up (+14 Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 8&15 | Day 1 | Day 8&15 | Day 21±3 | Day 1 | Day | Day 8&15 | | |
| IMGN853 Infusion | | ● | | ● | ● | ● | | ● | | ● | | |
| AE and SAE assessments | ●[l] | ● | | ● | ● | ● | | ● | ● | ● | ● | ● |
| Record concomitant medications | ●[c] | ● | | ● | ● | ● | | ● | ● | ● | ● | ● |

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 28-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 as outlined in Section 8.6 and 8.7.
e. Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN853. In the event of severe toxicity, repeat laboratory tests should be performed as necessary until the toxicity resolves or stabilizes. For a complete list of laboratory assessments, refer to Section 8.10.
f. For WCBP, a urine or serum pregnancy test will be performed at screening, prior to dosing on Day 1, every-other-cycle while on study and at the 28-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
g. Baseline ophthalmic exams will be performed by a board-certified ophthalmologist and will include the following: indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and corneal photography. A Schirmer test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated. May be performed within 14 days of Cycle 1, Day 1. Ocular symptom assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms then IMGN853 will be stopped and the subject will then be referred to an ophthalmologist for a complete examination (Section 5.8.8). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye examinations. All patients will have a complete ophthalmologic exam performed at the End of Treatment visit or 28-Day Follow Up.
h. Radiographic tumor assessment by CT scan is to be performed every 8 weeks (± 1 week). Additionally, patients with elevated CA125 at baseline will have CA125 measured at approximately the same time they undergo radiologic assessment. Patients experiencing CA125 response must have a confirmatory test performed at least 28 days after initial response is documented.
i. If a patient discontinues prior to documentation of PD, a tumor assessment is to be performed at the End of Study visit or 28-Day Follow up visit, if not performed within the previous 8 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 (Appendix E) 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.
j. ECGs will be performed as outlined in Section 8.7.
k. As clinically indicated.
l. Only AEs and SAEs attributed to study procedures are recorded.

# APPENDIX C. PHARMACODYNAMIC, PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENTS

| Activity | Screen | Cycle 1 | | | | | | | Cycle 2 | | Cycle 3 | | | | | | | Cycles ≥ 4 | End of Study/28-Day Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Study Day | | | | | | | Study Day | | Study Day | | | | | | | Day 1 | | |
| | | 1 | 2 | 3 | 4 or 5 | 8 | 15 | 22 | 1 | 8±3 | 1 | 2 | 3 | 4 or 5 | 8 | 15 | 22 | | | |
| Fresh tumor biopsy[a] (Section 7.1.1 and 7.3.1) | ●[a,b] | | | | | | | | | ●[a,d] | | | | | | | | | ● | |
| IHC archived tumor tissue (Section 7.1.1) | ● | | | | | | | | | | | | | | | | | | | |
| Blood samples for measurement of homocysteine and methylmalonate (Section 7.2.3) | | ●[c] | | | | | | | | ● | | | | | | | | | ● | |
| Blood samples for FcγR polymorphisms (Section 7.2.1) | | ●[c] | | | | | | | | | | | | | | | | | | |
| Molecular pathology (e.g. genomic data) documentation | | ●[c] | | | | | | | | | | | | | | | | | | |
| Blood samples for PK (Cycles 1&3) and immunogenicity assessments[e] (Section 6) | | ● | ● | ● | ● | ● | ● | ● | ● | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

a. All patients in MTD Expansion Cohort 3 (relapsed EOC) will be required to undergo tumor biopsy during screening and in Cycle 2, on Day8 (±3 days). Additionally, patients enrolled to the dose escalation phase of the study who do not have serous or endometrioid ovarian cancer, serous or endometrioid endometrial cancer, NSCLC adenocarcinoma or BAC **and** who do not have archival tumor tissue to submit for FOLR1 expression, will be required to undergo tumor biopsy during the screening period in order to confirm eligibility. In addition, patients in the MTD expansion Cohort 3 who relapsed after showing clinical benefit will be asked to undergo an optional biopsy at the time of progression to help understand the mechanism of resistance.
b. Within 28 days prior to the start of Cycle 1, Day 1
c. Predose
d. Cycle 2 (Day 8±3 days) and at the end of the study. These samples will be collected for patients enrolled in Expansion Cohort 3 (relapsed ovarian cancer only).
e. Blood samples for PK analysis will be taken in Cycles 1 and 3 at the following timepoints: **Schedule A -** Day 1-predose and within 10 minutes of infusion completion and 2, and 4 hours post infusion (±10 minutes). Single samples will also be taken on Days 2 and 3 (24 and 48 hours post infusion; (±2 hours). A single blood sample will be drawn on Days 4 or 5, 8 and 15 (±24 hours post dose). **Schedule B -** Blood samples for PK analysis will be taken in Cycles 1 and 3 at the following timepoints: Days 1 & 15 -predose and within 10 minutes of infusion completion and 2 and 4 hours post infusion (±10 minutes). A single sample will be taken on Day 2, 24 hours post infusion (±2 hours). On Day 8, a sample will be taken predose and within 10 minutes of infusion completion. On Day 16, a single sample will be taken 24 hours post infusion (±2hours). On Day 22, a single sample will be drawn (+24 hours). A single pre-dose sample will be collected before the IMGN853 infusion and following completion of the infusion in Cycles 2, 4, 5 and 6. **For both schedules** - single, predose samples will be collected predose and following completion of the infusion in Cycles 2, 4, 5 and 6, and a single blood sample for immunogenicity, will be taken on Day 1 of Cycles 2, 4, and 5 and at the End of Treatment and Follow-up visits.

# 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 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at baseline.

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

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

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

**Special Considerations**

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

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

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

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

**Lesions with prior local treatment:** Lesions situated in a previously irradiated area, or in an area subjected to other 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 CA125 alone cannot be used to assess response or determine progression; however, it will be followed. CA125 measurements should be scheduled to approximately coincide with radiological assessment (every 6 weeks±1 week). Patients whose CA125 is above the upper normal limit at baseline will need to have their values normalize to ≤ upper normal limit, in addition to complete disappearance of measurable or evaluable disease, in order to be considered in complete response.

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

**Time Point Assessments**

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

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

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

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

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

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

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

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

**Time Point Response Criteria**

| Target Lesion Time Point Response (TPR) | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. |
| Partial Response (PR) | At least 30% decrease in the SoD of target lesions, taking as reference the baseline SoD |
| Progressive Disease (PD) | At least a 20% increase in the SoD of target 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 CA125 above the normal limits if CA125 at baseline is above the upper normal limit |
| Progressive Disease (PD) | Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. |
| Not Applicable (N/A) | No non-target lesions identified at baseline |
| Unable to Evaluate (UE) | One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criteria for PD |

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

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

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

## Determining Overall TPR

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

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

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

### Best Overall Response

Best overall response is determined once all the data for the patient is known. Best overall response is defined as the best response across all time-points.

# 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 2 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:**

1) Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample

2) Variations within the normal range of CA 125 levels will not interfere with the response definition.

**Timing of CA125 assessments:**

The Gynecologic Cancer Intergroup (GCIG) recommends that CA 125 measurements be taken at specific time intervals.

- The first sample would be collected within 2 weeks before treatment is started
- Later samples would be collected at intervals of 2–4 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. FACT/GOG-NEUROTOXICITY QUESTIONNAIRE, VERSION 4.0

(Cella 1993)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

| ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| I have numbness or tingling in my hands…… | 0 | 1 | 2 | 3 | 4 |
| I have numbness or tingling in my feet…… | 0 | 1 | 2 | 3 | 4 |
| I feel discomfort in my hands……. | 0 | 1 | 2 | 3 | 4 |
| I feel discomfort in my feet…… | 0 | 1 | 2 | 3 | 4 |
| I have joint pain or muscle cramps…… | 0 | 1 | 2 | 3 | 4 |
| I feel weak all over…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble hearing…… | 0 | 1 | 2 | 3 | 4 |
| I get a ringing or buzzing in my ears…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble buttoning buttons…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble feeling the shape of small objects when they are in my hand…… | 0 | 1 | 2 | 3 | 4 |
| I have trouble walking…… | 0 | 1 | 2 | 3 | 4 |