Novella CLINICAL

IMMUNOGEN, INC.

ImmunoGen, Inc.
Protocol #: 0401

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

Statistical Analysis Plan

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ADA	Anti-drug antibody
AIBW	Adjusted Ideal Body Weight
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the time-concentration curve
BAC	Bronchioloalveolar carcinoma
BOR	Best Overall Response
CA-125	Cancer Antigen 125, a marker for certain cancers
CM	Concomitant medication
C_{max}	Maximum plasma drug concentration
CR	Complete response/remission
CRC	Cohort Review Committee
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DOR	Duration of Response
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOC	Epithelial Ovarian Cancer
FACT/GOG	Functional Assessment of Cancer Therapy, Gynecologic Oncology Group
FIH	First in Human
FOLR1	Folate receptor 1
IHC	Immunohistochemistry
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
MMA	Methylmalonic acid
MTD	Maximum Tolerated Dose
NE	Not Evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Relapsed/progressive disease
Pd	Pharmacodynamic
PFS	Progression-Free Survival
PgP	P-glycoprotein
PK	Pharmacokinetics
PR	Partial Response/remission
Q3W	Administration every 3 weeks
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
$t_{1/2}$	Terminal half life
TBL	Total Bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time at which C_{max} occurs
TTP	Time-to-Progression
TTR	Time to Response
ULN	Upper Limit of Normal
Vss	Volume of distribution at steady state
WHO Drug	World Health Organization drug dictionary

1. INTRODUCTION

1.1. Background

IMGN853 0401 is an open label, non-randomized, first-in-human (FIH), dose-escalation and dose-expansion Phase 1 study. It is designed to identify the maximum tolerated dose (MTD) of IMGN853 when administered intravenously as a single agent in adult patients with relapsed or refractory epithelial ovarian cancer (EOC) and other FOLR1-positive solid tumors (dose escalation) and enable further evaluation of the recommended Phase 2 dose (RP2D). The safety, tolerability, pharmacokinetics (PK), pharmacodynamics (Pd), immunogenicity, and preliminary anti-tumor activity of IMGN853 will be characterized.

During dose escalation two dosing schedules were evaluated: Schedule A (IMGN853 administered on Day 1, with cycles repeating every 21 days (Q3W)) and Schedule B (IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days). Dose expansion began once the Schedule A MTD was identified and a dose was selected for further exploration. Schedule B evaluation was stopped prior to identifying the MTD

The purpose of this Statistical Analysis Plan (SAP) is to outline the statistical principles which will be used to analyze and present the data from this study. This SAP includes a description of the study endpoints, stopping rules, and analysis populations. Table, Figure, and Listing shells will be supplied in a separate document. The SAP may be modified until the time of data base lock. Any deviations from the SAP, including any deviations after the time of database lock, will be documented in the study report.

The protocol for IMGN853 0401 describes the general approach to analysis of data from the study. This Statistical Analysis Plan is based on Amendment 10 of Clinical Study Protocol IMGN853 0401. A brief history of the protocol amendments is presented in Table 1.

Table 1: History of Protocol and Amendments to the Protocol

Version	Approval Date	Changes Expected to Impact the SAP
Protocol	01Mar2012	
Amendment 1	13Apr2012	Lowered starting dose, added additional escalation cohort
Amendment 2	18Oct2012	Endometrioid endometrial cancer was added to the list of tumors that could be enrolled without proof of FOLR1+.
Amendment 3	07Mar2013	Secondary endpoints PFS, TTP, and DoR added.
Amendment 4	13May2013	Assay for Circulating Tumor Cells (CTCs) and other Pd assessments added
Amendment 5	18Oct2013	FLT-PET was removed from the protocol Additional expansion cohort added for patients with endometrial cancer. Dosing procedure modified to employ adjusted ideal body weight. Collection of CTCs in selected patients added.

Table 1: History of Protocol and Amendments to the Protocol (Continued)

Version	Approval Date	Changes Expected to Impact the SAP
Amendment 6	27Nov2013	Additional dosing schedule added (Schedule B). Pd/Biomarker studies revised. Increased number of patients. Data capture of Ocular symptom assessments separated from Ophthalmic exams.
Amendment 7	13Aug2014	Estimated number of patients has been increased. Size of MTD expansion cohorts was revised. Circulating Tumor Cell analyses have been removed from the study. Assessment of objective response rate for expansion cohorts has been added to the protocol.
Amendment 8	26Aug2014	None
Amendment 9	25Feb2015	Updated exploratory objectives and endpoints. Updated the number of patients to be enrolled in Dose Expansion Cohort 1. Estimated number of patients planned therefore has increased. Added language to allow for selection of a less frequent dosing regimen for Schedule B if dosing is deemed sub-optimal. Removed requirement for confirmation of the objective responses. Use of lubricating eye drops made mandatory. Increased requirements for eye exams.
Amendment 10	02Sep2015	Schedule B dosing discontinued. A total of five specific dose expansion cohorts were defined: Cohort 1:Platinum resistant EOC Cohort 2:Advanced or recurrent uterine cancer Cohort 3: Relapsed ovarian cancer amendable to biopsy Cohort 4: Relapsed/refractory NSCLC adenocarcinoma or BAC Cohort 5: Relapsed EOC, using corticosteroid eye drops

2. STUDY DESIGN

2.1. Protocol Objectives

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

2.1.1. Primary

- Determine MTD and RP2D of IMGN853 when administered intravenously

2.1.2. Secondary

- 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

2.1.3. Exploratory

- 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 disease progression
  - Changes in the numbers of tumor infiltrating immune cells after treatment with IMGN853
  - Mechanism of relapse or treatment emerging resistance to IMGN853

2.2. Study Endpoints

2.2.1. Primary

The primary endpoints:

- MTD
- RP2D.

2.2.2. Secondary

Secondary endpoints include:

- Treatment-emergent adverse events (TEAEs) 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 (Vss), T_{max}, AUC
- Number of patients with RECIST 1.1 criteria (see Protocol Appendix E) clinical responses and/or number of patients with GCIG Cancer Antigen 125 (CA-125) criteria clinical responses (see Protocol 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-Drug Antibody (HADA) and Human Anti-Human Antibody (HAHA) levels

2.2.3. Exploratory

Exploratory endpoints include:

- Evaluate FOLR1 expression by immunohistochemistry (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. P-glycoprotein (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 Day 8) 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

2.3. Study Overview

IMGN853 0401 is an open label, non-randomized, FIH, dose-escalation and dose-expansion Phase 1 study. It is designed to identify the MTD of IMGN853 when administered intravenously as a single agent in adult patients with relapsed or refractory EOC and other FOLR1-positive solid tumors (dose escalation) and enable the selection and further evaluation of a RP2D (dose escalation and dose expansion). The safety, tolerability, PK, Pd, immunogenicity, and preliminary anti-tumor activity of IMGN853 will be characterized.

2.3.1. Dose Escalation

During dose escalation, 2 dosing schedules (Schedule A and Schedule B) were evaluated. Initially patients received IMGN853 using Schedule A. After the introduction of Schedule B (Protocol Amendment 6) patients received IMGN853 either using Schedule A or Schedule B. Following the enrollment of 4 of the Schedule B dose escalation cohorts, Schedule B escalation was closed (Protocol Amendment 10).

2.3.1.1. Schedule A

IMGN853 dosed on Day 1 of a 21-day cycle.

The first 4 escalation cohorts were single patient cohorts. Subsequent escalation cohorts used a standard 3+3 design, with each cohort consisting of 3 or 4 to 6 patients. The initial planned doses for Schedule A dose escalation are shown in Table 2, exploration of intermediate doses was allowed following CRC review of all available data.

Patients initially had their doses calculated based on their actual body weight, from Protocol Amendment 5 onwards patients have had their doses calculated based on their adjusted ideal body weight (AIBW). When the MTD for Schedule A was identified and a RP2D selected for further evaluation, enrollment into the Expansion Cohorts began.

Table 2: Initial Planned Dose Levels for Schedule A

Dose Level	Dose (mg/kg)[a]	Percent Increase From Previous Dose Level	Number of Patients (Planned)
1	0.15	N/A1/20 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

Table 2: Initial Planned Dose Levels for Schedule A (Continued)

Dose Level	Dose (mg/kg)[a]	Percent Increase From Previous Dose Level	Number of Patients (Planned)
6	5.0	52%	3 or 4-6
7	7.0	40%	3 or 4-6
8	9.0	28%	3 or 4-6

[a] Patients enrolled under Amendment 5 or later were dosed based on AIBW. Patients enrolled prior to Amendment 5 were dosed based on actual body weight.

2.3.1.2. Schedule B

IMGN853 administered on Days 1, 8, and 15, with cycles repeating every 28 days.

The starting dose of IMGN853 for Schedule B was 1.1 mg/kg, which was 1/3 the 3.3 mg/kg dose level deemed clinically safe in 9 patients dosed at that level in Schedule A. All patient doses were calculated according to AIBW. Patients were enrolled in cohorts of 3 to 6 patients.

The initial planned doses for Schedule B dose escalation are shown in Table 3. If additional dose exploration was required to define the MTD then dose escalation could proceed at increments ≤ 25%. The CRC determined the magnitude of the dose escalation increments following review of available clinical and PK data from patients treated in the current cohort.

Table 3: Initial Planned Dose Levels for Schedule B

Dose Level	Dose (mg/kg)[a]	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

[a] Patients were dosed based on AIBW

2.3.2. Study Population

2.3.2.1. Dose Escalation

Patients with a pathologically documented, definitively diagnosed, advanced solid tumor that is either refractory to standard treatment, or for which no standard treatment is available, or the patient refuses standard therapy.

Enrollment without prior documentation of tumor FOLR1 expression was limited to a set of histologic subtypes which were likely to have a high incidence of FOLR1 positivity, as described in Section 3.1.A of the protocol.

2.3.2.2. Dose Expansion

Patients were enrolled into 1 of the following 5 expansion cohorts:

- Cohort 1 -patients with platinum-resistant EOC
- Cohort 2 - patients with advanced or recurrent uterine cancer
- Cohort 3 - patients with relapsed or refractory EOC
- Cohort 4 - patients with relapsed/refractory non-small cell lung cancer (NSCLC) adenocarcinoma or bronchioloalveolar carcinoma (BAC)
- Cohort 5 - patients with EOC which has relapsed following platinum-based therapy and who will receive prophylactic corticosteroid eye drops

Further details for the Criteria for Selection of Patient Population are described in Section 3.1 of the protocol.

2.3.2.3. Enrollment

Patients who received at least one dose of IMGN853 will be considered enrolled. Patients who were issued a patient number, but who did not successfully complete the screening process and who did not receive a dose of IMGN853 will be considered screen failures. Patient numbers were not re-issued.

2.3.3. Sample Size

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

2.3.3.1. Dose Escalation

Ascending doses of IMGN853 were evaluated to identify the MTD for both dosing schedules. In Schedule A, single patient was enrolled into the first 4 cohorts and then 3 or 4 to 6 patients into the following cohorts dependent on the incidence of DLTs and all other emerging data. In Schedule B, 3, or 4 to 6 patients were enrolled into each of the cohorts dependent on the incidence of DLTs and all other emerging data. The actual number of patients accrued during this phase was determined by the evaluation of all patient data.

2.3.3.2. Dose Expansion

Following identification of the MTD for Schedule A and the selection of a dose for further evaluation there was an expansion phase. The number of patients to be enrolled into each of the expansion cohorts were:

- Cohort 1 - 40 patients
- Cohort 2 - 20 patients
- Cohort 3 - 20 patients
- Cohort 4 - 20 patients
- Cohort 5 - 40 patients

If the true DLT rate at the MTD is 10-20%, there is a 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 4).

Table 4: 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

2.3.4. Treatment Randomization

No randomization will be performed in this study.

2.3.5. Schedule of Assessments

See Protocol Appendix A and Appendix B.

2.4. Interventions

2.4.1. Clinical Trial Material

2.4.1.1. Schedule A

Patients will receive an infusion of IMGN853 as a single agent on Day 1 of a planned 21 day cycle. For logistical reasons such as holidays, delays in the scheduled study treatment of up to 3 days may be allowed. Additionally, shifts in the start of a new cycle by -1 or +3 days will be permitted in Cycles ≥3.

2.4.1.2. Schedule B

Patients received infusions of IMGN853 as a single agent on Days 1, 8, and 15 of each planned 28-day cycle. A delay of 1 day in the doses received on Days 8 and 15 was permitted; if a delay occurred, each subsequent dose in that cycle was shifted by 1 day. Intervals of <7 days between each dose were not permitted. The start of the next cycle remained the same.

2.5. Study Procedures

Secondary and exploratory objectives include characterization of PK, Pd, immunogenicity, FOLR1 levels, and other potential biomarkers in blood, tumor tissue, and biologic fluids that might predict response to IMGN853. Full profiles of blood samples for PK measurements were taken in Cycles 1 and 3 for all patients. Additionally, a single sample was collected pre-dose and following completion of the infusion in Cycles 2, 4, 5 and 6 for PK. A single blood sample for analysis of HADA and HAHA was taken on Day 1 of Cycles 2, 4, and 5

and at EOT and 28 day follow up visits, and three hours and 1 week following the onset of an IMGN853 infusion-related reaction. If PK sampling were performed concurrently, the HADA and HAHA samples were taken from the PK sample tube.

Ki67 IHC staining was assessed as a marker of cell proliferation on fresh biopsy samples from patients in Expansion Cohort 3.

All patients were genotyped for FcγR alleles via Peripheral Blood Mononuclear Cell (PBMC) analysis at screening.

Samples for FcγR were taken at screening. P-glycoprotein (PgP) IHC staining will be assessed in archived tumor tissues and on fresh biopsy samples obtained from patients in the expansion cohorts.

FOLR1 expression via a homocysteine-dependent upregulation of FOLR1 mRNA translation and plasma total homocysteine levels will be assessed in all patients at baseline, during Cycle 2, and at the end of treatment visit. Plasma methylmalonic acid (MMA) will be analyzed in parallel with plasma total homocysteine to differentiate folate and B12 status.

Exploratory biomarkers were collected pre-dose on the first day of each cycle and at other noted time points. Details can be found in Sections 6 and Section 7 of the study protocol.

3. GENERAL ANALYTICAL CONSIDERATIONS

3.1. Data Sources

All data is to be collected via eCRFs through remote data entry, or through electronic transfers. Section 13 of the study protocol provides additional details regarding data recording and handling.

3.2. Definition of Baseline

Cycle 1, Day 1 (Study Day 1) was designated as the first day a patient receives IMGN853. For most measurements, baseline labs were taken pre-dose on Day 1. If pre-dose assessments on Day 1 are not available, the screening result closest to (prior to dosing on) Day 1 will be substituted.

3.3. Missing Data

TEAE onset dates will be reported in listings as collected. Every effort will be made to query missing dates. If exploratory analyses require imputed dates, the following procedure will be employed:

- TEAE onset dates with missing year will be assumed to occur on Study Day 1.
- TEAE dates with missing month will be assumed to occur on the first day of the non-missing year, except for TEAEs occurring in the first year of dosing, in which case the date will be the first day of dosing.

- TEAE dates with non-missing month and missing day will be assumed to occur on the first day of the non-missing month, except for TEAEs occurring in the first month of dosing, in which case the date will be the first day of dosing.

All other data will be reported as they are collected. No imputation methods will be used to replace missing data.

3.4. Outliers

No adjustments for outliers will be made.

3.5. Multiple Study Centers

No adjustment for stratification by the study centers is planned.

3.6. Interim Analyses or Timing of Analyses

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.

3.7. Analysis Populations

Three analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used (Table 5).

Table 5: Analysis Populations

Analysis Population	Analysis				
	Baseline	**Patient Disposition**	**Efficacy**	**Safety**	**DLT**
Safety	X	X		X	X
Response-Evaluable			X		
CA-125-Evaluable			CA-125 only		

3.7.1. Safety Population

The Safety Population will consist of all patients who received at least one dose of study drug.

3.7.2. Response-Evaluable Population

To meet the definition of response-evaluable, patients must have

EITHER:

- received a radiographic assessment at baseline,
- received at least one dose of IMGN853, and

- have had at least one post-dose tumor assessment;

OR

- have died within 105 days of receiving their first dose, or
- have clinically progressed within 105 days of receiving their first dose.

3.7.3. CA-125 Evaluable Population

To meet the definition of CA-125 evaluable, patients must have a baseline CA-125 value ≥2xULN, received at least one dose of IMGN853, and must have had at least one post-dose CA-125 assessment. This population will be used in CA-125 response analysis only.

3.8. Data Display Characteristics

Data displays produced for this study will include data listings, summary tables, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow. Final delivery of tables, listings, and figures will have numbering in compliance with the ICH E3 guideline. Prior to compilation of the clinical study report, Novella standard TREF, FREF, and LREF reference numbers will be used.

Data listings will simply list the data recorded in the eCRF or derived for each patient. They will be ordered by phase (escalation or expansion), cohort, patient number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Summary tables will display summary statistics calculated for each of the dose cohorts or treatment groups, unless described otherwise in following sections. See shell tables for specific formats.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. 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. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

4. PATIENT ACCOUNTABILITY

4.1. Patient Characteristics

Patient characteristics will be summarized and listed for the Safety population.

4.1.1. Demography

Demography will include age, race, ethnicity, gender, ECOG performance status, and cancer stage at study entry.

Age will be calculated as (First Dose Date – Birth Date + 1)/365.25, rounded down to the nearest whole number. This corresponds to the typical calculation of age a person would use in conversation.

4.1.2. Height and Body Weight

Height, weight, and AIBW at baseline will be summarized.

4.1.3. Cancer History

Cancer history will summarize: stage of cancer at diagnosis; prior radiation therapy (yes/no); prior cancer systemic therapy (number of regimens), prior cancer-related surgery (yes/no).

Cancer histories will be summarized for the Safety population as the numbers and percentages of patients with histories significant for each of the cancer history elements.

4.1.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1 or later), associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. All medical history information will be provided in listings.

4.2. Patient Disposition

A summary of patient disposition will show the total number of patients who were treated and the number of patients treated in each relevant treatment group. The reasons for discontinuation will be summarized by categories included on the End of Study form as listed below, the summary will include the total number and percentage of patients per category and the number of patients and percentage of patients in each relevant treatment group. Percentages of patients will be calculated using all members of the relevant population in the relevant treatment group for the denominator.

End of Study form categories for discontinuation are:

- One year post treatment without PD or subsequent therapy
- Adverse Event
- Disease progression
- Clinical Progression
- Began new anti-cancer therapy
- Study Terminated by Sponsor
- Withdrawal from Study
- Investigator decision

- Lost to follow up
- Death
- Other

End of Treatment information, including reason for discontinuation of IMGN853, will also be summarized.

4.2.1. Protocol Deviations and Population Inclusions

Protocol deviations will be summarized by the categories used in the protocol deviation log as follows:

- Patients who were enrolled into the study even though they did not satisfy all of the entry criteria
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients who received the wrong treatment or incorrect dose
- Patients who received an excluded concomitant treatment

A listing of all deviations will also be presented.

5. EFFICACY ANALYSES

Efficacy analyses will use data from the Response-Evaluable population unless otherwise specified. Unless stated otherwise, patients will be analyzed in the following groups: Escalation Schedule A, Escalation Schedule B, EOC Expansion Cohorts, Endometrial Expansion Cohort.

5.1. Efficacy Outcomes

5.1.1. Best Overall Response

Best overall response (BOR) for a patient is the best response designation as assessed by the investigator, recorded between the date of the first dose of study treatment and the date of objectively documented progression per RECIST v1.1 or the date of treatment discontinuation, whichever occurs first. The BOR will be categorized as a complete response/remission (CR), a partial response/remission (PR), a stable disease (SD), or a relapsed/progressive disease (PD). Patients who cannot be evaluated for response will be categorized as Not Evaluable (NE). Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks (28 days) after the criteria for response are first met. Patients with an overall response of SD must have a minimum duration of 35 days (6 weeks – 1 week window = 35 days). The confirmatory scan is valid following treatment discontinuation as long as the patient has not started a new anti-cancer therapy. BOR will be reported in listings for all patients and summarized for each of the expansion cohorts.

5.1.2. Objective Response Rate

The objective response rate (ORR) will be calculated as the number of subjects with a BOR of CR or PR divided by the number of subjects in the Response-Evaluable population. Subjects without at least one post-baseline RECIST assessment will be treated as non-responders. ORR with 95% confidence intervals will be reported for each group.

5.1.3. Progression Free Survival (PFS)

PFS is defined as the time from the date of the first dose of study drug until the date of progressive disease or death from any cause, whichever occurs first. PFS is defined based on radiological assessments and determined by the investigator. Clinical progression is not considered a progression endpoint. PFS will be calculated using the following:

- Patients who did not die or have PD will be censored at the date of their last radiological assessment.
- Patients who had PD or death after missing two or more consecutive radiological assessments (PD or death date – last radiological assessment date +1 >=105 days) will be censored at the last adequate radiological assessment.
- Patients who had no baseline or post-baseline radiological assessment(s) will be censored on Day 1 unless the patient died within 105 days of Day 1; in that case, the patient will be considered as having an event at the date of death.
- Patients who started a new anti-cancer therapy prior to documented PD or death will be censored at the last radiological assessment prior to initiation of new anti-cancer therapy.
- When an analysis cutoff date is implemented, only data (deaths and radiological assessments) occurring on or prior to the cutoff date will be used for analysis.

5.1.4. Duration of Response

Duration of response (DOR) is defined as the time from the date of the first response (CR or PR), whichever is recorded first, to the date of progressive disease (PD). Duration of response is only defined for patients who have a best overall response of CR or PR using the method of Kaplan-Meier. Confirmation of the response must be performed no less than 4 weeks (28 days) after the criteria for response are first met. The first date at which a CR or PR response was noted will be used to calculate DOR, not the date of the confirmatory tumor assessment.

5.1.5. Time to Progression

Time to progression (TTP) is defined as the time from the date of the first dose of study drug until the date of progressive disease. TTP is defined based on radiological assessments and determined by the investigator. Clinical progression is not considered a progression endpoint. TTP will be censored as follows:

- Patients who did not have PD will be censored at the date of their last radiological assessment.

- Patients who had PD after missing two or more consecutive radiological assessments (PD date – last radiological assessment date +1 >=105 days) will be censored at the last adequate radiological assessment.
- Patients who had no baseline or post-baseline radiological assessment(s) will be censored on Day 1.
- Patients who started a new anti-cancer therapy prior to documented PD will be censored at the last radiological assessment prior to initiation of new anti-cancer therapy.
- When an analysis cutoff date is implemented, only radiological assessments occurring on or prior to the cutoff date will be used for analysis.
- Patients who died prior to PD will be censored at the last radiological assessment.

5.1.6. Time to Response

Time to response (TTR) is defined as the time from the date of the first dose of study treatment until the date of the first observed CR or PR. TTR is only defined for subjects who have confirmed CR or PR. TTR will be reported in listings for all patients and summarized for each of the expansion cohorts with medians and 95% confidence intervals for the medians will be presented for TTR for the expansion cohorts.

5.1.7. CA-125 Response

A CA-125 response is defined as a ≥ 50% reduction in CA-125 levels from baseline. The response must be confirmed and maintained for at least 28 days. The baseline sample must be ≥ 2.0 times the upper limit of normal (ULN) and within two weeks prior to starting treatment. The date of response corresponds to the date when the CA-125 level is first reduced by 50%. The summary table for CA-125 will be based on CA-125 evaluable population for the expansion cohorts only.

5.1.8. Overall Survival

Overall survival (OS) is defined as the time from the date of the first dose of study treatment until the date of death from any cause. Patients who are still alive at the time of the analysis will be censored at the last known time alive.

5.2. Analysis of Efficacy Outcomes

5.2.1. ORR

Responses will be tabulated separately for each group with medians and 95% confidence intervals.

5.2.2. PFS

The PFS will reported in listings and tabulated separately for each group with medians and 95% confidence intervals.

5.2.3. DOR

DOR will be reported in listings for all patients and will be tabulated separately for each group with medians and 95% confidence intervals.

5.2.4. TTP

TTP will be reported in listings for all patients and will be tabulated separately for each group with medians and 95% confidence intervals.

5.2.5. TTR

TTR will be reported in listings for all patients and will be tabulated separately for each group with medians and 95% confidence intervals.

5.2.6. OS

OS will be reported in listings for all patients and will be tabulated separately for each group with medians and 95% confidence intervals.

5.2.7. Subgroup Analysis of Efficacy Outcomes in EOC Expansion Cohorts

Efficacy outcomes will be analyzed for EOC expansion cohorts (1, 3, and 5) on the following patient subgroups:

- Patients who are platinum resistant in EOC expansion cohorts 1, 3, and 5.
- Patients who are platinum resistant in EOC expansion cohorts 1, 3 and 5 by number of prior regimens (1-3 vs >3).
- Patients who are platinum resistant in EOC expansion cohorts 1, 3 and 5 by FRa percent staining at intensity 2+ (PS2) (25-49%, 50-74%, 75-100%, and 50-100%).
- Patients who are platinum resistant in EOC expansion cohorts 1, 3, and 5 by number of prior regimens and FRα percent staining at intensity 2+ (1-3 priors and PS2>=50%, 1-3 priors and PS2 is 25-49%, >3 priors and PS2>=50%, >3 priors and PS is 25-49 %).

Kaplan-Meier plots for PFS will be generated for the above subgroup analyses.

5.2.8. Efficacy Data Listings

Efficacy data listings will include:

- All lesion assessments (target lesion, non-target lesion, new lesion)
- Investigator's RECIST assessments
- CA-125 results
- derived parameters for CA-125 response, BOR, PFS, TTP, DOR, TTR and OS
- censoring for time-to-event variables

6. SAFETY ANALYSES

Safety analyses will use data from the Safety population. Patients will be analyzed according to the actual study treatment received.

6.1. Exposure

Exposure to IMGN853 will be summarized with descriptive statistics for the number of doses received, the number of cycles received, duration of dosing (weeks, calculated as [date of last dose – date of first dose + 21]/7 for Schedule A, and [date of last dose – date of first dose + 14]/7 for Schedule B), total cumulative dose (mg), dose intensity (mg/kg AIBW Q3W, calculated as [total cumulative dose (mg) / {baseline AIBW (kg) * duration of dosing (weeks)/3}]), and relative dose intensity (%, calculated as [dose intensity/ 6] *100).

The number of infusions with dose decreased, infusions interrupted, and dose delayed will also be summarized by cohort. The number of infusions with the rate of infusion decreased will also be summarized by cohort.

Listings will be provided with the information from all of the study drug administration eCRFs. A further listing reporting the exposure measures above will be provided.

6.2. Adverse Events

Adverse event (AE) data are available to ImmunoGen from two sources, the eCRFs and the serious adverse event (SAE) forms. While SAE reconciliation will be performed, the production of data summaries and listings will be based on the data collected on the eCRF.

Treatment-emergent adverse events (TEAEs) are defined as adverse events with an onset date on or after the first dose of study drug, and within 28 days of the last dose of study drug. The adverse events will be coded using MedDRA (version 18.1 or later), associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. The tables will display the counts and percentages of patients who reported at least one TEAE in each system organ class represented in the AE data. Within each system organ class, the tables will display the counts and percentages of patients reporting at least one TEAE as designated by the preferred terms.

The following TEAEs are of special interest:

- Ocular TEAEs
  - This subset includes TEAEs meeting criteria for the following terms: keratopathy and blurred vision. A list of preferred terms for keratopathy will be provided and finalized by the Sponsor before the final database lock.
- Peripheral Neuropathy
  - A list of preferred terms for peripheral neuropathy will be provided and finalized by the Sponsor before the final database lock.
- Pneumonitis

The following AE tables will be produced:

- An Overall Summary of Safety will summarize the numbers of patients with TEAEs by cohort and CTCAE grade and the number of patients who died during the study or within 28 days of last dose.
- All TEAEs
- TEAEs related to IMGN853. This table will include TEAEs with a drug relationship of "Possibly Related" or "Definitely Related." It will also include TEAEs with missing drug relationships. An AE reported by a patient more than once will be included in this table if at least one of the drug association grades is one of the grades listed here.
- Serious TEAEs
- Serious, Related TEAES. This subset includes all serious TEAEs with a drug relationship of "Possibly Related" or "Definitely Related." It will also include serious TEAEs with missing drug relationships. An AE reported by a patient more than once will be included in this table if at least one of the drug association grades is one of the grades listed here.
- Grade 3 or above TEAEs
- Treatment related ≥Grade 3 TEAEs
- TEAEs leading to drug withdrawal. This subset includes TEAEs with an Action Taken of "Drug Permanently Discontinued."
- Related TEAEs leading to drug withdrawal.
- TEAEs leading to dose delay.
- TEAEs leading to dose reduction.
- TEAEs leading to dose delay or dose reduction.
- Related TEAEs leading to dose delay.
- Related TEAEs leading to dose reduction.
- Related TEAEs leading to dose delay or dose reduction.
- All deaths as well as deaths on Study or within 28 Days of the Last Dose
- Treatment related TEAEs leading to death on study or within 28 days of Last Dose
- Ocular TEAEs
  - Incidence and CTCAE grade of ocular TEAEs
  - Time to first onset of ocular TEAEs
  - Action taken (none, interruption, dose reduction or delay, discontinuation) due to ocular TEAEs
- Peripheral Neuropathy

Subgroup analyses of TEAEs for the patients in EOC expansion cohorts (cohorts 1, 3, and 5) will be performed on the following patient subgroups:

- Patients in EOC expansion cohorts 1, 3, and 5 by platinum resistant status (platinum resistant vs platinum sensitive).
- Patients who are platinum resistant in EOC expansion cohorts 1, 3, and 5 by number of prior regimens (1-3 vs >3).
- Patients who are platinum resistant in EOC expansion cohorts 1, 3, and 5 by FRα percent staining at intensity 2+ (PS2) (25-49%, 50-74%, 75-100%, 50 – 100%).

In addition, TEAEs and related TEAEs will be summarized for patients in EOC expansion cohorts (1, 3, and 5) who are platinum resistant and who have received 1-3 prior lines of therapy and whose FRα percent staining at intensity 2+ (PS2) is 50-100%.

The following AE listings will be produced:

- All pre-treatment AEs will be listed.
- All AEs, sorted by cohort and chronologically within patient. This listing includes system organ class, preferred term, onset and end dates, and other relevant information.
- Serious TEAEs, sorted by cohort and chronologically within patient.
- TEAEs leading to drug withdrawal. This subset includes TEAEs with an Action Taken of "Drug Permanently Discontinued."
- TEAEs related to study drug. This listing will include TEAEs with a drug relationship of "Possibly Related" or "Definitely Related." It will also include TEAEs with missing drug relationships.
- Serious TEAEs related to study drug. This listing will include serious TEAEs with a drug relationship of "Possibly Related" or "Definitely Related." It will also include serious TEAEs with missing drug relationships.
- TEAEs resulting in death. This listing includes TEAEs with a Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade of "Grade 5 (Death)".
- Ocular TEAEs
- Neuropathy TEAEs
- Pneumonitis TEAEs

6.3. Dose Limiting Toxicities (DLTs)

DLTs 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 retreatment. DLTs will be considered related to the study treatment unless there is clear evidence of an alternative explanation and this attribution is agreed to by the CRC.

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.

A listing of DLTs will be provided.

6.4. Clinical Laboratory Results

Laboratory test results (including hematology, coagulation, serum chemistry, and urinalysis) and abnormal laboratory values will be presented in data listings. CTCAE v4.03 lab grades will also be presented for those tests which have associated grading criteria. CTCAE grades will be derived based on laboratory results, and will not factor in clinical evaluations.

Shift tables summarizing the changes from baseline in severity of lab grades will be provided for lab parameters that are graded according to the CTCAE v4.03. Summaries of actual values and changes from baseline will be presented by treatment group for each assessment time point, beginning with the first post-baseline assessment. Grade 3 or above lab values will also be summarized based on the worst grade observed on study.

For the liver function tests, a summary of clinically significant values in liver function tests will be reported by the following categories using the maximum value while on treatment. The denominator for the summaries will be the number of patients who had at least one non-missing value during treatment. Note the categories for each test are not mutually exclusive:

- Aspartate Aminotransferase (AST)
  - >3xULN
  - >5xULN
  - >10xULN
  - >20xULN
- Alanine Aminotransferase (ALT)
  - >3xULN
  - >5xULN
  - >10xULN
  - >20xULN
- AST or ALT
  - >3xULN
  - >5xULN
  - >10xULN
  - >20xULN

- Total Bilirubin (TBL)
  - >1.5xULN
  - >2xULN
- Alkaline Phosphatase (ALP)
  - >1.5xULN
- (AST or ALT) and TBL
  - AST or ALT >3xULN and TBL >1.5xULN
  - AST or ALT >3xULN and TBL >2xULN
- (AST or ALT) and ALP and TBL
  - AST or ALT >3xULN and ALP <2xULN and TBL ≥2xULN

Results from pregnancy tests will be provided in data listings.

6.5. Immunogenicity

The potential immunogenicity against IMGN853 or DM4 will be assessed at various time points in Cycles 1 through 6, as outlined in Protocol Section 6.3 and Protocol Appendix C. Exploratory analyses will be completed to evaluate the potential impact of immunogenicity on PK, safety, and efficacy.

6.6. Vital Signs and Pulse Oximetry

Vital signs (including temperature, pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate and weight, pulse oximetry) will be presented in data listings. Summaries of actual values and changes from C1D1 pre-dose baseline at each time point will be presented.

6.7. Electrocardiograms

Electrocardiograms (ECG) results (Rhythm, Heart Rate, PR Interval, RR Interval, QRS Interval, QT Interval, QTcF Interval, and classification of Within Normal Limits, Abnormal, Not Clinically Significant, and Abnormal, Clinically Significant will be presented in data listings. If a different correction for QT is captured in the eCRF, that QTc will also be reported in the listing for that patient along with QTcF.

The number and percent of patients in the following non-mutually exclusive categories will be summarized by visit:

- QTc >450 ms
- QTc >480 ms
- QTc >500 ms
- QTc change from baseline >30 ms
- QTc change from baseline >60 ms

Note that dosing ECGs are collected in triplicate; analyses for replicated results will be based on the average of the replicate results. The QTcB and QTcF collected on eCRF will not be used in this summary table. Instead, for this summary table, QTcB and QTcF will be derived from QT and RR:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

$$QTcB = \frac{QT}{\sqrt{RR}}$$

Where QT and RR are both measured in seconds.

For the overall ECG result (Within Normal Limits, Abnormal, Not Clinically Significant, and Abnormal, Clinically Significant) summaries will be provided for baseline and each post-baseline assessment time point. Note that dosing ECGs are collected in triplicate and analyses for the overall ECG result will be based on the worst-case result (i.e. if any one of the triplicate results is Abnormal, Clinically Significant then the value for the time point will be Abnormal, Clinically Significant). The hierarchy for the worst-case assessment is: Abnormal, Clinically Significant will be considered the worst value, with Abnormal, Not Clinically Significant being considered worse than Within Normal Limits.

6.8. Concomitant Medications

All medications and supportive therapy taken within four weeks prior to 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.

Prior and concomitant medications will be coded using the September 2015 or later version of World Health Organization drug dictionary (WHO Drug). Separate summary tables will be provided for prior and concomitant medications. Summary tables will be organized to display the anatomical main class of each coded medication (ATC level 1 term) and, within that, the pharmacological subgroup (ATC level 3 term) of the coded medication. The summary table will display counts and percentages of patients who reported using at least 1 medication in each represented pharmacological subgroup. If a patient has more than one medication in the subgroup, they will be counted only once. A complete listing will be generated as well.

6.9. Concomitant Procedures

All procedures within four 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). Concomitant procedures will be coded using MedDRA (version 18.1 or later), associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. Complete listings of these data will be generated.

6.10. Ophthalmic Examinations

Results of the Ophthalmic Examinations will be presented in data listings.

6.11. Ocular Symptom Assessments

Results of the Ocular Assessments will be presented in data listings.

6.12. Transfusions

All blood product transfusions recorded on the concomitant procedure or concomitant medication eCRF will be presented in data listings.

6.13. Physical Examination

Physical Examination results will be presented in data listings.

6.14. Pulmonary Function Tests

Pulmonary Function Test results will be presented in data listings.

6.15. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Eastern Cooperative Oncology Group performance status (ECOG PS) results will be presented in data listings.

6.16. FACT/GOG Neurotoxicity Questionnaire

Data from the Functional Assessment of Cancer Therapy, Gynecologic Oncology Group (FACT/GOG) Questionnaire will be reported in data listings.

7. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The PK analyses for this study will be covered by a separate, independent analysis plan prepared by the PK analysis vendor in collaboration with ImmunoGen.

8. EXPLORATORY BIOMARKER ANALYSES

The exploratory biomarker analyses will be covered by a separate, independent Exploratory Biomarker analyses plan.

IMMUNOGEN

IMGN853 0401

Pharmacokinetic and Immunogenicity Analysis Plan

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

Report Number	QPK28-001
Facility	**qPharmetra** **9 Nollet Drive** **Andover, MA 01810**
Report Date	07 December 2017
Report Author	**Name:** [redacted] **Title:** [redacted] **Department:** [redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

N/A

ABBREVIATIONS

ADA	Anti-Drug Antibody
ASCII	American Standard Code for Information Interchange
AUC	Area Under the Time-Concentration Curve
BQL	Below the Quantifiable Limit
CI	Confidence Interval
C_{max}	Maximum Plasma Drug Concentration
CRC	Cohort Review Committee
CRO	Clinical Research Organization
CV	Coefficient of Variance
DM4	N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
ELISA	Enzyme Linked Immunosorbent Assay
EOC	Epithelial Ovarian Cancer
FIH	First in Human
FOLR1	Folate Receptor 1
K_2EDTA	Potassium Ethylenediaminetetraacetic Acid
LC-MS	Liquid Chromatography – Mass Spectrometry
LLOQ	Lower Limit of Quantification
Max	Maximum
Min	Minimum
MTD	Maximum Tolerated Dose
N	Number of Observations
NC	Not Calculated
NSCLC	Non-Small Cell Lung Cancer
PK	Pharmacokinetics
Q3W	Administration Every 3 Weeks
SAE	Severe Adverse Event
SD	Standard Deviation
$t_{1/2}$	Terminal Half-Life
TAB	Total Antibody
T_{max}	Time at Which C_{max} Occurs
V_{ss}	Volume of Distribution at Steady State
Wx3Q4W	Dosing on Day 1, 8, 15, with Cycles Repeating Every 28 Days

1. OVERVIEW AND INVESTIGATIONAL PLAN/PURPOSE

This analysis plan provides a description of the strategy and techniques to be used to analyze pharmacokinetic (PK) and immunogenicity data for the mirvetuximab soravtansine (IMGN853) 0401 study.

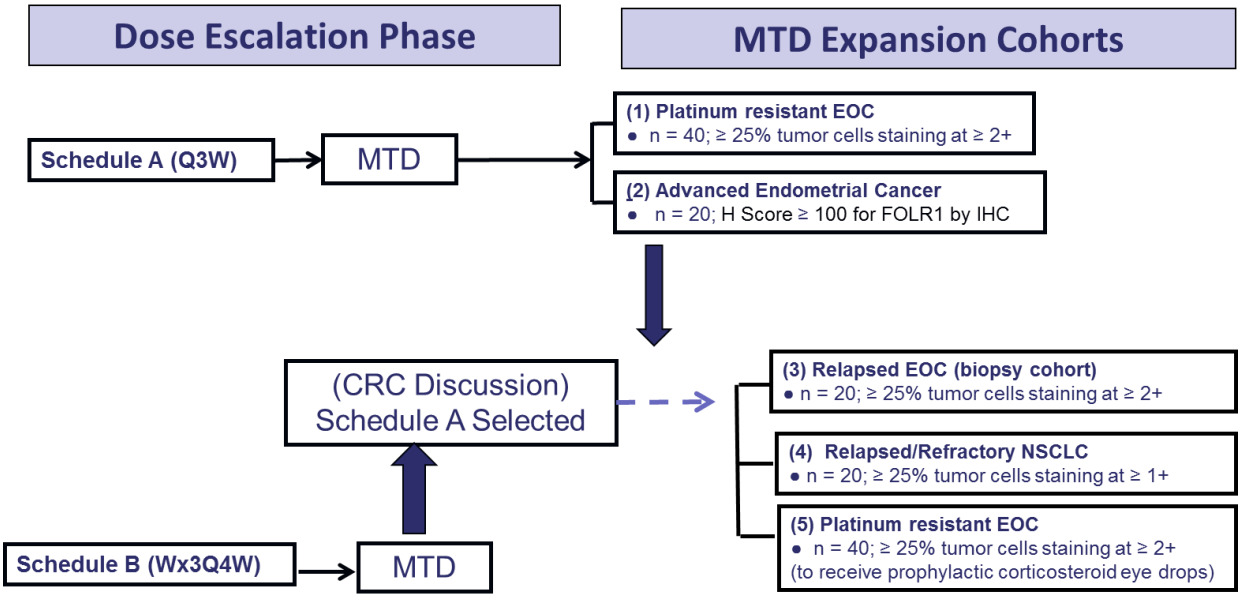
1.1. Study Design

This was an open label, Phase 1, non-randomized, first in human (FIH) study of IMGN853 in adult patients with FOLR1-positive solid tumors that have relapsed, or are refractory to standard therapies. Two dosing schedules were evaluated in this study:

Schedule A: IMGN853 administered on Day 1, with cycles repeating every three weeks (Q3W)

The dose escalation phase initially enrolled 1 patient each at the first four dose levels. Patients were enrolled in subsequent cohorts using a standard 3+3 design, with each cohort consisting of 3 or 4 up to 6 patients.

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



1.2. Pharmacokinetic and Immunogenicity Analysis Objectives

The objective of this analysis is to characterize the PK and immunogenicity of IMGN853.

1.3. PK Sampling Schedule

1.3.1. Schedule A

Blood samples for PK measurements were taken at the following time points:

Cycles 1 and 3:

Day 1 – Pre-dose, immediately following completion of infusion (+10 minutes), 2 hours (±10 minutes) following the completion of infusion, 4 hours (±10 minutes) following the completion of infusion, 6 hours (±10 minutes) following the completion of infusion and 8 hours (±10 minutes) following the completion of infusion

NOTE: 8 hours and 6 hours following the completion of infusion were not required for all patients

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

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

Day 4 or 5 – a single blood sample for PK (±24 hours)

Day 8– a single blood sample for PK (±24 hours)

Day 15 – a single blood sample for PK (±24 hours)

Cycles 2 and 4 through 6:

Day 1 – Pre-dose and immediately following completion of infusion (+10 minutes)

End of Treatment

28 Day Follow Up

1.3.2. Schedule B

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

Cycles 1 and 3:

Day 1 – Pre-dose, immediately following completion of infusion (+10 minutes), 2 hours (±10 minutes) following the completion of infusion, and 4 hours (±10 minutes) following the completion of infusion

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

Day 8 – Pre-dose and immediately following completion of infusion (+10 minutes)

Day 15 – Pre-dose, immediately following completion of infusion (+10 minutes), 2 hours (±10 minutes) following the completion of infusion, and 4 hours (±10 minutes) following the completion of infusion

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

Day 22 – a single blood sample for PK (±24 hours)

Cycles 2 and 4 through 6:

Day 1 – Pre-dose and immediately following completion of infusion (+10 minutes)

End of Treatment

28 Day Follow Up

1.3.3. Additional Samples

Per study protocol, any patient who experienced a Grade 2 or greater infusion reaction during the administration of IMGN853 had blood drawn within 3 hours of the onset of the reaction and one week later for determination of drug concentration and antibodies to IMGN853.

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

1.3.4. Bioanalysis of PK Samples

The following table summarizes the bioanalytical methodology used to quantitate IMGN853, total antibody, and free payload (DM4 and s-methyl DM4).

Analyte	Method	Lower Limit of Quantitation	CRO Validation Report Number
IMGN853	ELISA	75.0 ng/mL	REYB2, REGD2
Total Antibody	ELISA	500 ng/mL	REYN2, REGE2
DM4, S-methyl-DM4	LC-MS	0.100 ng/mL	REGC2

ELISA, enzyme linked immunosorbent assay; LC-MS, liquid chromatography-mass spectrometry.

1.4. Immunogenicity Assessments

Assessments for immunogenicity against IMGN853 were performed on plasma samples collected for PK assessments. This included samples collected prior to infusion on Day 1 of Cycles 1, 2, 4, and 5, at the End of Treatment and at Follow-up visits. The current analysis will evaluate the potential impact of immunogenicity on PK of IMGN853 and total M9346A antibody, specifically comparing IMGN853 and total antibody exposure between the immune positive and immune negative populations.

1.4.1. Bioanalysis of Immunogenicity Samples

An electrochemiluminescent method was used for the detection of anti-IMGN853 antibodies in plasma from samples collected into either sodium heparin or K_2EDTA tubes (respective validation reports: REYO2 and REGG2). The qualitative assay was designed to detect anti-IMGN853 antibodies in human plasma. Samples with a signal response above the fixed cut point were classified as potentially positive, while those below the cut point were classified as negative. Potentially positive samples were confirmed in the Tier 2 screening assay, where conjugate was added as an inhibition solution. Samples were confirmed positive if the percent inhibition was $\geq$ 29.1% for sodium heparin samples and 30.2% for K_2EDTA samples. In Tier 3, the confirmed positive samples were titered until a negative response was obtained and the sample titer was reported as the reciprocal of the last dilution that produced a response above the cut point.

2. METHODS

2.1. PK Analysis

2.1.1. PK Population

The PK population includes all patients who received at least one infusion of IMGN853 and have evaluable PK data. All patients who received IMGN853 and had samples collected with no major deviations related to administration of study drug will be included in the PK population.

2.1.2. Data Handling

Analysis-ready PK datasets will be constructed from audited and locked clinical databases. The data and dosing information will be formatted for PK analysis and saved in ASCII format using R software, Version 3 or higher (R Core Team 2015). All data manipulation programs will be documented and archived to maintain an audit trail, and will be subject to quality review.

Individual data for all PK subjects will be tabulated by patient and summarized by time point, dose level, and cycle, unless stated otherwise.

2.1.3. Data Presentation

The number of significant digits displayed for the individual values of plasma concentrations will be based on the number of significant figures in the source data. The following descriptive statistics will be reported for each nominal sampling point and PK parameter: number of observations (N), mean, geometric mean, standard deviation (SD), minimum (min), median, maximum (max), coefficient of variation (CV) (CV = SD/mean, expressed as %), and 95% confidence interval (CI) of the mean. The number of significant digits given for the descriptive statistics will generally exceed that of the source data by one. The min and max will have the same number of significant digits as the source data, and CV% will be quoted to one decimal place. If the mean, geometric mean, or median are below the lower limit of quantification (LLOQ), these statistics will be reported as below the quantifiable limit (BQL) and ignored in the calculation of geometric mean. The SD, CV%, and 95% CI will not be calculated (NC) when less than three individual values are available. The other descriptive statistics will be determined when at least one value is reported. Descriptive statistics will be calculated using R software.

2.1.4. Analysis of PK Data

All the PK analyses will be performed using the PK population, and will be conducted similarly for the Schedule A, Schedule B, and Dose Expansion cohorts. Initially, individual and mean concentrations for IMGN853, total antibody (TAb), DM4, and s-methyl-DM4 will be plotted vs. time by dose level for data collected in Cycles 1 and 3. The PK parameters listed in Table 1 will be calculated from these data via standard non-compartmental methods (Gabrielsso 2016), and the results will be tabulated and summarized by Cycle and dose level. The PK data will be evaluated for dose proportionality and accumulation of each analyte will be assessed.

The observed concentrations for end of infusion in Cycles 2, 4, 5, and 6, as well as end of treatment and follow-up will be summarized and tabulated, but will not be analyzed further.

Table 1: PK Parameters to be Calculated from Data Collected in Cycles 1 and 3

PK Parameter	Definition
C_{max}	Maximum plasma concentration observed
C_{last}	Final observed plasma concentration above LLOQ
AUC_{∞}	Area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{last}	Areas under the plasma concentration versus time curve from time of dose until T_{last}
T_{max}	Observed first time to reach C_{max}
T_{last}	Time corresponding to the last concentration above the limit of quantification
$t_{1/2}$	Terminal half-life
CL	Clearance, i.e. volume of plasma that is completely cleared of the drug per unit time
V_{ss}	Volume of distribution at steady-state

2.1.5. Statistical Analysis

PK parameters will be summarized using descriptive statistics by Cycle and dose level. No hypothesis testing between dose-levels will be performed. Examinations of dose proportionality will be conducted according to the method of Smith (2000).

2.1.6. Additional Analyses

Additional analyses may be performed to determine the effect of CYP3A inhibitors or inducers on PK as well as the effect of FRα levels on PK.

2.2. Immunogenicity Analysis

2.2.1. Immunogenicity Population

The immunogenicity population includes all patients who received at least one infusion of IMGN853 and have evaluable immunogenicity data.

2.2.2. Analysis of Immunogenicity Data

Anti-IMGN853 seroconversion refers to the development of detectable antibodies which bind to IMGN853 and is based upon positive results in both screening and confirmatory assays. If a patient tests negative at all visits (no seroconversion), then the patient will be classified as seronegative. If the patient is positive at one or more visits (seroconversion), then the patient will be classified as seropositive. Percentage of patients who screen positive for anti-drug antibodies (ADA), percentage of patients who confirm positive, and antibody titer data will be summarized by time point using descriptive statistics. All data will be presented in listings for each patient.

Time to seroconversion will be calculated for the patients who have confirmed positive ADAs during the study. A table of time to seroconversion will be provided. Additionally, a table of ADA titer over time, and a table for last titer will be provided, as well as the supporting listing.

Peak titer value is defined as the maximum titer value experienced by a patient during the study. A table of peak titer and time to peak titer will be provided, including summary statistics, specifically, median, mean peak tiers and minimum, maximum titers by dose level.

2.2.3. Exploratory Analyses

Exploratory analyses may be performed to elucidate the relationship between IMGN853 PK and ADA titers. Analyses and presentation of data may be done using pooled data and/or by dose cohort, dosing schedule or tumor type as appropriate. For each assessment, raw observed measures and change and percentage change from baseline data will be tabulated and summarized.

3. REFERENCES

R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Gabrielsson J, and Weiner D, Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 5th ed. Stockholm: Apotekarsocieten, 2016.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, and Forgue ST (2000). Confidence interval criteria for assessment of dose proportionality. Pharm Res; 17(10):1278-1283.

4. APPENDIX LISTING

N/A