SYNOPSIS

Name of Sponsor/Company: ImmunoGen, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: mirvetuximab soravtansine (MIRV; IMGN853)		
Title of Study: MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression		
Protocol ID: IMGN853-0416		
Study Center(s): 201 centers globally, 136 of which enrolled patients		
Publications (reference): 13		
Studied Period (years): Date first patient enrolled: 03 February 2020 Date last patient completed: 22 August 2024		**Phase of Development:** 3

Objectives:

Primary Objective:

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

Key Secondary Objectives:

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

Additional Secondary Objectives:

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

Methodology:

This Phase 3 study was designed to compare the efficacy and safety of MIRV versus IC Chemo in patients with platinum-resistant, high-grade epithelial ovarian cancer (EOC), primary peritoneal, or fallopian tube cancer, whose tumors express a high level of folate receptor α (FRα). Patients were, in the opinion of the investigator, appropriate for single-agent therapy. FRα positivity was defined by the Ventana FOLR1 (FOLR1-2.1) CDx assay, hereafter referred to as Ventana FOLR1 Assay.

Eligible patients who had provided informed consent and met study entry criteria were randomized (1:1) to 1 of 2 groups:

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

Patients were stratified by

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

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

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

Abbreviations: AIBW adjusted ideal body weight; IV intravenously; Pac paclitaxel; PLD pegylated liposomal doxorubicin; Topo topotecan.

Disease progression was evaluated by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Computed tomography (CT) or magnetic resonance imaging (MRI) scans were collected and held for sensitivity analysis by a blinded independent central review (BICR).

Patients continued to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came first).

Tumor assessments, including radiological assessments by CT/MRI scans, were performed at Screening and subsequently every 6 weeks (± 1 week) from Cycle 1 Day 1 (C1D1) (for all regimens) for the first 36 weeks, and then every 12 weeks (± 3 weeks) until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurred first.

Patients who discontinued study treatment for reasons other than progressive disease (PD) continued with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever came first. Prior to Week 36 (from C1D1), assessments occurred every 6 weeks (± 1 week) as allowed by local requirements but must have occurred at an interval of no more than 12 weeks. After Week 36,

assessment occurred every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.

All patients who discontinued study drug were followed for survival every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or end of study, whichever came first. Additional survival follow-up calls may have occurred periodically if needed. All patients were followed for progression and survival.

Two interim analyses were planned: (1) an interim futility analysis (PFS only) when at least 110 PFS events had occurred, and (2) an interim analysis for OS at the time of final analysis of PFS when at least 330 PFS events had occurred. No further testing was conducted.

Number of Patients (planned and enrolled):

Planned: Approximately 430 patients

Enrolled: 453 patients

Approximately 430 patients were to be randomized 1:1, MIRV (Arm 1) to IC Chemo (Arm 2). A total of 453 patients were actually enrolled. The number of patient evaluable in each study population were

- ITT population: 227 MIRV, 226 IC Chemo
- Safety population: 218 MIRV, 207 IC Chemo
- Per-Protocol population: 217 MIRV, 204 IC Chemo
- CA-125–Evaluable population: 181 MIRV, 155 IC Chemo

Study Eligibility

Key Inclusion Criteria

1. Female patients ≥ 18 years of age
2. Patients must have had a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer
3. Patients must have had platinum-resistant disease
4. Patients must have progressed radiographically on or after their most recent line of therapy
5. Patients must have been willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy using a low risk, medically routine procedure for immunohistochemistry (IHC) confirmation of FRα positivity
6. Patient's tumor must have been positive for FRα expression as defined by the Ventana FOLR1 assay
7. Patients must have had at least one lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the Investigator)
8. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy was appropriate as the next line of treatment:
   a. Adjuvant ± neoadjuvant considered one line of therapy
   b. Maintenance therapy (e.g., bevacizumab, PARP inhibitors) was considered as part of the preceding line of therapy (i.e., not counted independently)
   c. Therapy changed due to toxicity in the absence of progression was considered as part of the same line (i.e., not counted independently)
   d. Hormonal therapy was counted as a separate line of therapy unless it was given as maintenance

9. Patient must have had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Patients must have had adequate hematologic, liver, and kidney functions

Key Exclusion Criteria

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumor
2. Patients with primary platinum-refractory disease, defined as disease that did not respond to (complete response [CR] or partial response [PR]) or had progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
3. Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
5. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring
6. Patients with serious concurrent illness or clinically relevant active infection
7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease
9. Patients assigned to PLD stratum only:
    - Left ventricular ejection fraction (LVEF) below the institutional limit of normal as measured by echocardiography (ECHO) or multigated acquisition (MUGA) scan
10. Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to randomization
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
12. Patients with a previous clinical diagnosis of non-infectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients with a history of other malignancy within 3 years prior to randomization

Test Product, Dose and Mode of Administration, Lot Number:

MIRV 6 mg/kg adjusted ideal body weight (AIBW) intravenously (IV) administered every 3 weeks

Lot Numbers: P1947918001, P1947918002, and P1947918003

Duration of Treatment:

Patients continued to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came first).

Reference Therapy, Dose, and Mode of Administration:

Pac was administered at 80 mg/m^2 as a 1-hour intravenous (IV) infusion on Days 1, 8, 15, and 22 of a 4-week cycle.

PLD was administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a 4-week cycle.

Topo was administered at 4 mg/m^2 as a 30-min IV infusion on Days 1, 8, and 15 of a 4-week cycle. Alternatively, Topo could be administered at 1.25 mg/m^2 as a 30-min IV infusion on Days 1 to 5 of a 3-week cycle.

Criteria for Evaluation:

Efficacy: Tumor response was evaluated by the investigator using RECIST v1.1. CT or MRI scans were collected and held for sensitivity analysis by a BICR.

Safety: Safety assessments included treatment-emergent adverse events (TEAEs), laboratory test results, physical examination, and vital signs.

Statistical Methods:

Efficacy Endpoints and Analyses:

The primary endpoint for Study 0416 was PFS per investigator assessment, estimated using the Kaplan-Meier method, with comparison between treatment groups conducted using Cox proportional hazard regression and log rank test. The study was designed to test the null hypothesis that the survival function for PFS was the same between the MIRV arm and the IC Chemo arm versus the alternative hypothesis that the survival function of PFS was different between MIRV and IC Chemo arms.

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

There was one interim analysis for OS at the time of the final analysis of PFS. A Lan-DeMets alpha spending function using an O'Brien-Fleming stopping boundary was used to control the overall Type I error at 2-sided alpha level of 0.05. The exact boundary of 0.01313 at the interim OS analysis was determined based on the actual number of death events. Following this hierarchical testing procedure, at the final analysis, given that the prespecified early stopping boundary at the interim analysis was reached, no additional hypothesis testing on OS was conducted.

SUMMARY – RESULTS AND CONCLUSIONS

ANALYSIS POPULATIONS:

A total of 453 patients were randomized (intent-to-treat [ITT] population), and 425 received at least 1 dose of study drug in the Safety population (MIRV or IC Chemo).

DEMOGRAPHICS:

Among the 227 patients randomized to MIRV, the median age of patients was 64.0 years, and all patients were female (100%) with 3 (1%) patients of childbearing potential. The majority of patients were White (69%) or Asian (12%) and not Hispanic or Latino (78%).

Among the 226 patients randomized to IC Chemo, the median age of patients was 62.0 years, and all patients were female (100%) with 8 (4%) patients of childbearing potential. The majority of patients were White (64%) or Asian (11%) and not Hispanic or Latino (72%).

Overall, demographic and baseline characteristics were well balanced between treatment groups.

EFFICACY RESULTS:

The patient population in this study was representative of a contemporary platinum-resistant ovarian cancer (PROC) population. The majority (80%) of patients' primary diagnoses were epithelial ovarian cancer, and almost all (452 of 453) of the enrolled patients had high-grade serous histology. Nearly half

(47%) of patients had 3 prior lines of therapy; 62% of patients had received prior bevacizumab, and 56% of patients had received a prior poly (ADP-ribose) polymerase (PARP) inhibitor.

Overall, demographics and disease characteristics were similar and well balanced between treatment groups.

In this final analysis, MIRV continued to demonstrate clinically meaningful efficacy outcomes versus IC Chemo for patients with platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers as assessed by OS with a hazard ratio (HR) of 0.68, which indicates that patients randomized to MIRV had a 32% reduction in the risk of death compared with those randomized to IC Chemo. Median OS was 16.85 months vs 13.34 months in MIRV arm and IC Chemo arm, respectively. Subgroup analyses of OS were consistent with the overall population analysis.

For other efficacy measures, MIRV also showed treatment benefit versus IC Chemo:

- The HR of PFS_{INV} was 0.63 (95% CI: 0.513, 0.785), which represents a 37% reduction in the risk of progression or death for patients randomized to MIRV over IC Chemo (median of 5.59 vs 3.98 months).
  - Both bevacizumab (BEV)-naive and BEV-pretreated subgroups demonstrated a consistent benefit with MIRV in patients with PROC with HRs of 0.67 and 0.64, respectively.
  - PFS_{BICR} was generally concordant with investigator assessment.
  - Subgroup analyses of PFS, including prior use of PARP inhibitors, were consistent with the overall population analysis.
- The ORR_{INV} in patients randomized to MIRV was more than double that of IC Chemo (41.9% vs 15.9%), with 13 CRs compared to 0 with IC Chemo.
  - ORR_{BICR} was generally concordant with investigator assessment.
  - Subgroup analyses of ORR were consistent with the overall population analysis.
- Across the PRO measures collected, trends toward meaningful improvement or stability were observed for patients randomized to MIRV while deterioration was observed for patients randomized to IC Chemo. Differences with a nominal p-value of < 0.05 were observed between treatment groups, favoring MIRV, in mean change from baseline at Week 8/9 in all European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 subscales, in Abdominal/GI and Attitude toward disease and treatment subscales of EORTC QLQ-OV28, and European Quality of Life Five Dimension (EQ-5D-5L) visual analog scale (VAS) subscale. No subscales favored IC Chemo.
- Patients randomized to MIRV who had CR or PR demonstrated a greater and clinically meaningful improvement in DOR_{INV} compared to IC Chemo.
  - Additionally, patients randomized to MIRV who had CR or PR per investigator had a shorter time to response (TTR) compared with those randomized to IC Chemo who had CR or PR per investigator (1.54 vs 2.71 months).
  - Among patients with CR or PR per BICR, the DOR_{BICR} was similar in patients randomized to MIRV versus IC Chemo; however, similar to DOR_{INV}, patients randomized to MIRV who had CR or PR per BICR had a shorter TTR compared with those randomized to IC Chemo who had CR or PR per BICR (1.74 vs 2.69 months).

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- Patients randomized to MIRV had a greater CA-125 response rate compared with those randomized to IC Chemo (58.0% vs 30.1%).
- MIRV demonstrated a greater improvement in PFS2 compared to IC Chemo, with an HR of 0.59 (95% CI: 0.480, 0.728).
  - Subgroup analyses of PFS2 were consistent with the overall population analysis.
- Due to the limited number of patients with anti-drug antibodies (ADA) against MIRV, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy.

SAFETY RESULTS:

Dosing schedules differed by treatment group. The median duration of dosing was longer in patients who received MIRV compared with IC Chemo (4.977 vs 2.957 months). Relative dose intensity among all treatment groups were similar.

The differentiated safety profile of MIRV was consistent with previous monotherapy studies as demonstrated by the following:

- TEAEs were reported in similar proportions of patients between MIRV (97%) and IC Chemo (94%) treatment groups with the following exceptions:
  - Patients treated with MIRV reported more TEAEs within the System Organ Class (SOC) of Eye disorders compared with those treated with IC Chemo.
  - A greater proportion of patients treated with IC Chemo reported events within the SOC of Blood and lymphatic system disorders compared with those treated with MIRV, with most events reported in the Pac and Topo treatment groups.
  - Similar proportions of patients reported TEAEs irrespective of geographical location.
  - Generally, the results of TEAEs by age group were consistent with the overall Safety population.
  - The most common TEAEs in all regimens were consistent with the known safety profiles of each drug.
- The most common study drug–related TEAEs by SOC and Preferred Term (PT) were consistent with the known side effect profiles of each drug. The incidence of study drug–related TEAEs was generally similar across all populations (88% vs 81% for MIRV and IC Chemo, respectively) with the following exceptions:
  - Events within the SOC of Eye disorders, which occurred more frequently in those treated with MIRV (52% vs 2%), and Blood and lymphatic system disorders, which occurred more frequently in IC Chemo–treated patients (44% vs 19%).
- Fewer patients treated with MIRV reported TEAEs ≥ Grade 3 in severity compared with IC Chemo (44% vs 55%).
- Due to the limited number of patients with ADA against MIRV, no conclusions can be drawn concerning the potential effect of immunogenicity on safety.
- Deaths occurring ≤ 30 days of last dose
- of study drug were similar across treatment groups.
  - TEAEs leading to death occurred similarly between treatment groups.

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- The nature and frequency of serious adverse events (SAE)s reported in all treatment regimens were consistent with the drugs' known safety profiles and/or underlying disease.
  - Patients treated with MIRV reported fewer SAEs than those treated with IC Chemo (25% vs 33%).
- Fewer patients treated with MIRV (11%) had TEAEs leading to discontinuation of study drug compared to those treated with IC Chemo (15%).
- The proportion of patients who had at least 1 dose modification was similar between treatment groups of MIRV (61%) and IC Chemo (59%).
- A total of 125 (57%) patients treated with MIRV reported ocular TEAEs within the SOC of Eye disorders, which was a greater proportion of patients compared with the 9% of patients treated with IC Chemo.
  - Most ocular TEAEs reported in patients treated with MIRV were ≤ Grade 2 in severity, with ≥ Grade 3 events occurring in 34 (16%) patients (IC Chemo, 0 patients, 0%).
  - The median time to onset of first ocular TEAEs when treated with MIRV was 5.43 weeks and ranged between 0.1 and 100.7 weeks.
  - The most common actions taken due to ocular TEAEs in patients treated with MIRV were no action (23%), dose reductions (18%), and dose delays (14%). Five (2%) patients were permanently discontinued from MIRV.
  - Of the 125 patients treated with MIRV who reported ocular TEAEs, 58% reported complete resolution, and an additional 34% of patients had partial improvement with most resolving to Grade 1. Of those patients that did not document resolution at the time of the database lock, 4 patients had Grade 1, 3 patients had Grade 2, and 2 patients had Grade 3 ocular adverse events (AEs).
- A total of 82 (38%) patients treated with MIRV reported peripheral neuropathy (grouped term) TEAEs, which was greater than the 23% of patients treated with IC Chemo, but less than that reported among patients treated with Pac (46%).
  - Most peripheral neuropathy (grouped term) TEAEs reported in patients treated with MIRV were ≤ Grade 2 in severity, with ≥ Grade 3 events occurring in 8 (4%) patients (Pac, 10%).
  - The most common actions taken due to events of peripheral neuropathy (grouped term) in patients treated with MIRV were no action (30%), dose reductions (6%), permanent discontinuation from MIRV (1%), and dose delays (< 1%).
  - The most common action taken due to events of peripheral neuropathy (grouped term) in patients treated with IC Chemo were no action (11%), dose reductions (7%), and permanent discontinuation from IC Chemo (all of whom were treated with Pac) and dose not given (each 2%).
  - Of the 82 patients treated with MIRV who reported peripheral neuropathy (grouped term) TEAEs, 15 (18%) patients reported complete resolution, and an additional 9 (11%) patients had partial improvement.
  - Among the 47 patients treated with IC Chemo who reported peripheral neuropathy (grouped term) TEAEs, 10 (21%) reported complete resolution, and an additional 7 (15%) patients had partial improvement.
- A total of 26 (12%) patients treated with MIRV reported pneumonitis (grouped term) TEAEs, which was a greater proportion of patients compared with 1 (< 1%) patient treated with IC Chemo.

  - Most pneumonitis (grouped term) TEAEs reported in patients treated with MIRV were ≤ Grade 2 in severity, with ≥ Grade 3 events occurring in 4 (2%) patients (1 patient reported a Grade 5 event of respiratory failure). Nine (4%) patients discontinued MIRV due to TEAEs of pneumonitis. The patient treated with IC Chemo reported a pneumonitis event that was Grade 2 in severity.
  - The median time to onset of first pneumonitis TEAEs for patients treated with MIRV was 24.14 weeks (range: 3.1 to 56.7 weeks) compared with 6.0 weeks (range: 6.0 to 6.0 weeks) for the patient treated with IC Chemo.
  - The most common actions taken due to events of pneumonitis in patients treated with MIRV were dose delays (5%), permanent discontinuation from MIRV (4%), no action taken (2%), and dose reductions (< 1%). The dose was not given in the 1 patient treated with IC Chemo who reported PTs of pneumonitis.
- Among patients treated with MIRV, 19 (9%) patients reported hypersensitivity narrow Standardized MedDRA Queries (SMQ) events within 3 days of infusion. Of these patients, 5 (2%) reported events of infusion-related reaction (IRR), none of which led to the discontinuation of study drug.
  - Of the patients treated with IC Chemo, 27 (13%) patients reported hypersensitivity narrow SMQ events within 3 days of infusion. Of these patients, 9 (4%) reported events of IRR, 1 (treated with Pac) of which led to the discontinuation of study drug.
- Shifts to Grade 3 or 4 laboratory values were generally infrequent and not associated with serious TEAEs.
- No clinically meaningful trends in vital signs parameters were observed in any treatment regimen.
- No patients were observed to meet potential for Hy's law.

CONCLUSION:

A total of 453 subjects were randomized (ITT population), and 425 patients received at least 1 dose of study drug (MIRV or IC Chemo) (Safety population).

As of the Primary Analysis CSR (data cutoff date of 06 March 2023), Study 0416 met the primary efficacy endpoint ($p<0.0001$) with a PFS_{INV} HR of 0.65 (95% CI: 0.521, 0.808). The study also met the key secondary efficacy endpoints of ORR_{INV} ($p<0.0001$) and OS ($p=0.0046$). Overall survival was significantly longer in the MIRV treatment group with a median of 16.46 months vs 12.75 months in the IC Chemo group (HR 0.67 [95% CI: 0.504, 0.885]).

In this final analysis (last patient last visit date of 22 August 2024), MIRV continued to demonstrate clinically meaningful efficacy outcomes versus IC Chemo for patients with platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers as assessed by OS with an HR of 0.68 (95% CI: 0.543, 0.840), which indicates that patients randomized to MIRV had a 32% reduction in the risk of death compared with those randomized to IC Chemo. The magnitude of OS benefit remained in keeping with the primary analysis. Median OS was 16.85 months vs 13.34 months in the MIRV and IC Chemo arms, respectively.

Together, these data demonstrate that the clinical benefit of MIRV surpasses that of previously available therapy in this patient population, for which outcomes have not substantially improved since

their initial approvals more than 20 years ago. MIRV thus provides clinically meaningful benefits in a PROC population with high unmet need.

The safety profile of MIRV in this study of patients with platinum-resistant, high-grade serous EOC, primary peritoneal, or fallopian tube cancer, whose tumors express a high level of FRα was characterized predominantly by low-grade, reversible ocular, gastrointestinal, and neurosensory events, including blurred vision, keratopathy, dry eye, abdominal pain, fatigue, diarrhea, nausea, constipation, and peripheral neuropathy, which are consistent with the known safety profile of MIRV. No new safety signals were observed since the Primary Analysis CSR.

The majority of TEAEs in the MIRV treatment group were ≤ Grade 2. TEAEs ≥ Grade 3 in severity were less frequent in patients treated with MIRV compared with IC Chemo (44% vs 55%), irrespective of causality. All-grade grouped-term AEs of interest (ocular, peripheral neuropathy, pneumonitis, and IRR TEAEs) affected 57%, 38%, 12%, and 9% of all patients treated with MIRV in Study 0416, respectively, which was proportionally higher across all parameters compared with IC Chemo, with the exception of IRRs (13%). The majority of these TEAEs of interest were mild or moderate in severity. Of the 218 total patients treated with MIRV in Study 0416, ≥ Grade 3 AEs of interest occurred in low frequency of patients overall (ocular [34 patients, 16%], peripheral neuropathy [8 patients, 4%], and pneumonitis [4 patients, 2%]), which was generally similar to patients treated with IC Chemo with the exception of ≥ Grade 3 ocular TEAEs (16% vs 0%).

Fatal AEs were similar between treatment groups and were infrequent, with 1.4% (in both MIRV and IC Chemo groups) of patients experiencing all-cause fatal AEs within 30 days of last dose of study drug.

While myelosuppression is an important safety issue with cytotoxic chemotherapies, throughout all treatment regimens, MIRV was associated with relatively low ≥ Grade 3 myelosuppression (neutropenia: < 1%; anemia: < 1%; thrombocytopenia: < 1%).

Neurotoxicity is an important safety issue with other tubulin-directed agents. MIRV, an antibody-drug conjugate with the tubulin-directed payload DM4, was associated with low study drug–related ≥ Grade 3 PTs of peripheral neuropathy (3 patients, 1%).

The clinically meaningful efficacy in biomarker-identified, FRα-high patients treated with MIRV, together with a differentiated safety profile and tolerability, demonstrate a favorable benefit-risk profile.

Date of the report:
27 November 2024

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1. SUMMARY OF CHANGES:

ImmunoGen, Inc. has updated Protocol IMGN853-0416 (dated 10 October 2019) to Amendment 1 (dated 09 December 2019).

The main elements of the protocol amendment include the following:

- Noted allowance for a patient's legally authorized representative to sign the informed consent form in the inclusion criteria, consistent with existing language in the rest of the protocol
- Documented changes to study procedures, including:
  - elimination of the Prognostic Index Evaluation at screening
  - addition of height assessment at screening
  - elimination of the requirement that vital signs be measured within 10 minutes before the start of infusion for all treatment arms
  - for comparator arms, changed the requirement that ocular symptoms assessment be performed only at screening and again as clinically indicated if symptoms appear on study
  - elimination of patient-reported outcome as procedure for Survival Follow-up
- To ensure patient safety, added mirvetuximab soravtansine (MIRV) retreatment criterion requiring that any treatment-emergent pneumonitis must have recovered to ≤ Grade 1 prior to patients receiving any additional doses. Pneumonitis has been observed with MIRV treatment, and this criterion is consistent with other clinical studies with MIRV.
- Added recommendation that patients who have discontinued study drug for reasons other than progressive disease prior to Week 36 (from Cycle 1 Day 1) and who have not received another anticancer therapy, be scanned every 6 weeks up to Week 36. This update is consistent with the frequency of disease assessments for all patients on treatment.
- Minor changes made to improve readability and for editorial consistency.

Changes made from the original protocol (10 October 2019) to Amendment 1 (09 December 2019) are summarized in the table below.

Additions are in **bold text** and deletions are designated by ~~strike through text~~.

2. SUMMARY OF ALL CHANGES

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Title Page	Indication: **Platinum-Resistant,** Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression	Provided consistency with indication under study	N	No
Title Page	~~Regulatory Agency Identifier Number:~~ [redacted]	Administrative; global study	N	No
List of Abbreviations	International Conference on Harmoni~~s~~zation	Corrected spelling	N	No
Protocol Synopsis	**Title of Study:** A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in **Platinum-Resistant**, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression	Provided consistency with indication under study		
Protocol Synopsis & 4.1.1. Overview and Schema	Patients who discontinue study drug for reasons other than ~~radiographicdisease progression~~ **progressive disease (PD)** will continue with tumor assessments ~~every 12±3 weeks (± 1 week)~~ until documentation of ~~disease progression~~**PD** ~~per RECIST 1.1~~ or the start of new anticancer therapy, **whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks (± 1 week). After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of disease progression or the start of new anticancer therapy.**	Updated per FDA feedback	N	No

[redacted]

Summary of Changes - Protocol IMGN853-0416
Amendment 1.0, 09 December 2019

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Protocol Synopsis & 3.1.1. Inclusion Criteria	1. ~~Patients~~ **Female patients** ≥ 18 years of age	Clarified subject population	N	No
Protocol Synopsis & 3.1.1. Inclusion Criteria	2. Patients ~~with~~ **must have** a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer 14. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements	Made language consistent with other criteria and with rest of protocol	N	No
Protocol Synopsis & 3.1.2. Exclusion Criteria	2. **Patients with p**~~P~~primary platinum-refractory disease, defined as disease that did not respond to or has progressed within 3 months of the last dose of first line platinum-containing chemotherapy 3. **Patients with p**~~P~~rior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow 7. **Patients with h**~~H~~istory of multiple sclerosis or other demyelinating disese and/or Lambert-Eaton syndrome (paraneoplastic syndrome) 14. **Patients with p**~~P~~rior hypersensitivity to monoclonal antibodies 15. **Patients with p**~~P~~rior treatment with MIRV **or other FRα-targeting agents**	Improved readability	N	No

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Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Schedule of Assessments (SOA)				
Table 2 Procedure	•	Removed Ocular Symptom Assessment as procedure for end of treatment and 30-day follow-up visits for mirvetuximab soravtansine treatment arm	N	No
Table 2 Footnote	[q] Blood samples for PK analysis will be taken within 1 hour after MIRV infusion on Day 1 of Cycles 1 and 3, and on Day 8 (± 24 hours) of Cycles 1 and 3. Samples will also be collected on the day of MIRV infusion prior to dosing on Day 1 of Cycles 2 and 4, EOT, and **also at** the 30-Day Follow-up **if feasible**.	Specified that PK sampling will be performed at the 30-day visit if feasible for mirvetuximab soravtansine treatment arm	N	No
Tables 2, Table 3, and Table 4 Procedure	Confirm Disease Diagnosis/Current Stage ~~and Prognostic Index Evaluation~~ [...] •	Eliminated Prognostic Index Evaluation as procedure at screening for all treatment arms Removed patient-reported outcome as procedure for Survival Follow-up for all treatment arms	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Tables 2, Table 3, and Table 4 Procedure	**Height**	Added measure of height as procedure at screening for all treatment arms	N	No
Tables 2, Table 3, and Table 4 Procedure	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±~~1~~**3**) weeks	Adjusted window for Radiologic Tumor Assessment after the first 36 weeks for all treatment arms	N	No
Tables 2, Table 3, and Table 4 Footnotes	[h] Vital signs (BP and temperature) will be measured ~~within 10 mins~~ before start of infusion; post infusion vital signs should be collected as clinically indicated for potential infusion related reaction.	Eliminated 10-minute window for vital signs measurement before start of infusion (study drug administration) for all treatment arms	N	No
Tables 2, Table 3, and Table 4 Footnotes o, p, and q, respectively	If a patient discontinues before documentation of progressive disease (PD), a tumor assessment and CA-125 will be assessed at the EOT visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed. **Patients who discontinued study treatment for reasons other than progressive disease (PD) will continue tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks (± 1**	Updated per FDA feedback	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	week). After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of disease progression or the start of new anticancer therapy~~every 12 (±3) weeks until PD is documented per RECIST 1.1 or the patient starts new anticancer therapy.~~			
Tables 2, Table 3, and Table 4 Footnotes	[s] Survival follow-up assessments will occur every 3 months (±2 weeks) until death, the patient is lost to follow-up or withdraws of consent for survival follow-up, or EOS, whichever comes first. These assessments may be conducted by telephone. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) ~~may~~**should** be collected. Additional survival follow-up calls may occur periodically if needed.	Clarified that information on other anticancer therapy should be collected for all treatment arms	N	No
Tables 2, Table 3, and Table 4 Footnotes	Note: A patient's *BRCA* mutational status (germline or somatic mutation in tumor tissue) will be collected as part of her medical history **if available**. Patients without a known mutation will be classified as unknown. Testing may be performed to support exploratory endpoints at the end of the trial; however, results will not be communicated to treating physicians or patients.	Clarified collection of *BRCA* mutational status for all treatment arms	N	No
Tables 3 and Table 4 Procedures and Footnotes	• [...] [m] Ocular symptoms assessment will be performed ~~prior to the start of each cycle~~ by the treating physician or other qualified individual **at screening and as clinically indicated if**	Removed ocular symptoms assessments for Cycle 1, Day 1; Cycle 2, Day 2; Cycle 3, Day 1; End of Treatment; and 30-day Follow-up for	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	symptoms appear on study. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.	comparator treatment arms; clarified ocular systems assessment for comparator treatment arms		
Section 1.3. Epithelial Ovarian Cancer	**Recent studies indicate that ovarian, peritoneal, and fallopian tube cancers are not distinct entities, but represent a spectrum of diagnoses that originate in the Mullerian tissue. Primary fallopian tube carcinoma and peritoneal cancers are now included in the ovarian cancer staging classification (Cobb 2015, Grant 2010, Naumann 2011, O'Shannessy 2013), and are considered to be part of EOC with the same treatment and outcomes.**	Provided additional context on epithelial ovarian cancer and the ovarian cancer staging classification	N	No
Section 1.6.1. First-in-Human Phase 1 Clinical Trial: Study IMGN853-0401	The initial antitumor activity observed with MIRV monotherapy in Study IMGN853-0401, particularly in those patients with PROC, no more than 3 prior lines of therapy and FRα medium or high expression per the original "PS2+" scoring method [defined by 2+ intensity staining of tumor cells with medium ≥50% to <75% of tumor cells and high ≥75% of tumor cells**, as detailed in the Investigator Brochure**] suggested the potential for a significant improvement over single-agent chemotherapy (Pac, PLD, or Topo).	Provided source for scoring method	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 1.9. Rationale for the Study Population	Thus, the present study will enroll a similar PROC population to the prior Phase 3 study, with the exception that patients are required to have high FRα expression by PS2+ scoring as determined by the Ventana FOLR1 (FOLR-2.1) CDx assay. **(Please see refer to the Investigator Brochure for more details on the Ventana FOLR1 assay and the FRα expression threshold selected for this study).**	Provided source for additional details on the assay and FRα expression threshold selected for this study;	N	No
Section 5.1.2. Mirvetuximab Soravtansine Accountability	The ~~electronic case report form (eCRF)~~**clinical trial database** shall also record details of MIRV administration such as date and time of administration.	Administrative	N	No
Section 5.1.3. MIRV Study Treatment Compliance	Under no circumstances is the Investigator allowed to release study drug supplies to any physician not named in the Food and Drug Administration (FDA) Form 1572 **or equivalent form** or to administer these supplies to a patient not enrolled in this study.	To allow for local regulations	N	No
Section 5.6.1.1. Treatment Criteria	In the absence of a TEAE that requires dose modification, a patient must meet the following criteria to receive study drug at any cycle: • ANC must be ≥ 1.5 x 10^9/L (1,500/μL) • Platelet count must be ≥ 100 x 10^9/L (100,000/μL)	Pneumonitis is known adverse effect of MIRV treatment, and this criterion is consistent with other studies involving MIRV and ensures greater patient safety	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	• All non-hematologic toxicities for which a causal association to study drug cannot be ruled out, must be ≤ Grade 2 or returned to baseline; the exceptions to this rule being: – Treatment-emergent ocular disorders, which must have recovered to ≤ Grade 1 or baseline – **Treatment-emergent pneumonitis, which must have recovered to ≤ Grade 1.**			
Section 5.7.1. End of Treatment	The following may be ~~justifiable~~ reasons for the Investigator to remove a patient from the study drug:	Editorial	N	No
Section 5.7.4. Lost to Follow-up	A study participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The Investigator should make all efforts to contact the patient ~~(eg, contacting patient's family or private physician, reviewing available registries or health care databases)~~, and to determine the patient's health status, including at least her vital status **(in accordance with applicable regulations related to privacy and confidentiality)**.	Clarified lost-to-follow-up procedures	N	No
Section 5.10.2. Medication Error	The Sponsor must be ~~immediately~~ notified **within 24 hours** of any error leading to the administration of either 10% more or 10% less than the intended dose; in such cases, the event must be reported on the eCRF.	Administrative	N	No
Section 7.1.	Only patients with the required FRα expression levels by	Provided source for	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Evaluation of FR-Alpha Expression in Tumor Tissue	Ventana FOLR1 (FOLR1-2.1) CDx assay are eligible to enroll in the study **(see the Investigator's Brochure for details on the assay and the FRα expression threshold selected for this study)**. [...] Instructions regarding processing and shipment of all samples for FRα ~~CDx~~ assay testing are detailed in the applicable Lab Manual.	additional details on the assay and FRα expression threshold selected for this study Administrative		
Section.7.2. Exploratory Biomarker Studies	Studies in tumor tissue and blood will be performed to explore potential **bio**markers of MIRV sensitivity and resistance.	Editorial	N	No
Section 8.10. Laboratory Assessments	Local laboratories will be used for the analysis of scheduled hematology, biochemistry, **coagulation** and other tests collected as part of safety monitoring.	Consistency with Schedule of Assessments	N	No
Section 8.10.1. Clinical Laboratory Panels, Table 21	**Coagulation** • **PT or INR/aPTT**	Consistency with Schedule of Assessments	N	No
8.14.1. Radiological Imaging	Radiographic tumor evaluation by CT or MRI of chest, abdomen, and pelvis will be performed within 28 days before first dose of study drug and every 6 weeks (±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (±1 week) thereafter (Table 2, Table 3, and Table 4). **Patients**	Updated per FDA feedback Administrative	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	who discontinued study treatment for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks (± 1 week). After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of disease progression or the start of new anticancer therapy. [...] Tumor response will be assessed by the Investigator using RECIST 1.1 (Eisenhauer 2009). Response as determined by the Investigator will be recorded in the ~~eCRFs~~**clinical trial database**.			
Section 9.1. Recording Adverse Events and Serious Adverse Events	However, ~~Sserious~~ AEs will be followed up by ImmunoGen Pharmacovigilance until resolution, stabilization or return to baseline.	Editorial	N	No
Section 10.3.2. Response Follow-up	Patients who have discontinued study treatment for reasons other than PD will continue tumor assessments every 12 weeks (± 1 week) until documentation of PD or until the patient starts subsequent anticancer therapy, whichever comes first. **Patients who discontinued study treatment for reasons other than PD will continue with tumor**	Updated per FDA feedback	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks (± 1 week). After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of disease progression or the start of new anticancer therapy.			
Section 12.1. Recording of Data and Data Quality Assurance	Data will be documented in various source documents (eg, the patient medical chart) and then manually entered into the ~~eCRF~~ **clinical trial database** by study site personnel.	Administrative	N	No
Section 13.2. Investigators and Study Administrative Structure	Before initiation of the study, the Investigators at US sites must provide the Sponsor with a completed Form FDA 1572 **or equivalent form**. Study medications must be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 **or equivalent form**.	To allow for local variations	N	No
Section 13.4. Study Monitoring	ImmunoGen personnel and the designee (ie, representative from the CRO) will review the protocol and the ~~eCRFs~~**clinical trial database** with the Investigator and the site staff at a site initiation visit. On-site review of the ~~eCRFs~~**clinical trial database** for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be	Administrative	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	performed. The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the ~~eCRF~~ **clinical trial database** entries. Additional checks of the consistency of the source data with the ~~eCRFs~~**clinical trial database** are performed according to the study-specific monitoring plan.			
Section 13.13. Audits and Inspections	On-site review of the ~~eCRFs~~**clinical trial database** for completeness and clarity, crosschecking with source documents, and clarification of administrative matters will be performed.	Administrative	N	No
Section 13.16. Financial Disclosure	The Investigator must disclose any financial interests in the Sponsor as described in 21 CFR Part 54 before beginning this study~~, at site closure,~~ and for 12 months after the study has been completed.	Administrative	N	No
Section 14. List of References	**Cobb LP, Gaillard S, Wang Y, et al. Adenocarcinoma of Mullerian origin: review of pathogenesis, molecular biology, and emerging treatment paradigms. Gynecol Oncol Res Pract. 2015;2:1.** **Grant DJ, Moorman PG, Akushevich L, et al. Primary peritoneal and ovarian cancers: an epidemiological comparative analysis. Cancer Causes Control. 2010;21(7):991-998.** **Naumann RW, Coleman RL. Management strategies for**	Added context re: ovarian cancer staging classification	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	recurrent platinum-resistant ovarian cancer. Drugs. 2011;71(11):1397-412. **O'Shannessy DJ, Somers EB, Palmer LM, et al. Serum folate receptor alpha, mesothelin and megakaryocyte potentiating factor in ovarian cancer: association to disease stage and grade and comparison to CA125 and HE4. J Ovarian Res. 2013;6(1):29.**			

Summary of Changes for Protocol IMGN853-0416

Amendment 1.1
(Belgium, Czech Republic, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom)

MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Date: 06 April 2020

[redacted]

1. SUMMARY OF CHANGES:

ImmunoGen, Inc. has updated Protocol IMGN853-0416 Amendment 1 (dated 09 December 2019) to Amendment 1.1 (dated 06 April 2020) in response to feedback provided via the Voluntary Harmonisation Procedure in the European Union pertaining to the following countries: Belgium, Czech Republic, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom.

The main elements of the protocol amendment include the following:

- CT/MRI windows added to allow flexibility around the performance of these scans and for internal document consistency.
- Added recommendations for pregnancy testing following the last doses of MIRV and chemotherapy.
- Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines.
- Added MDR1 cautionary language to be consistent with the Investigator Brochure.
- Details pertaining to FRα evaluation in tumor tissue added.
- Updated description of the end of study and continued access to patients receiving clinical benefit.
- Correct typographical errors throughout the protocol.

Changes made from Amendment 1 (dated 09 December 2019) to Amendment 1.1 (06 April 2020) are summarized in the table below.

Additions are in **bold text** and deletions are designated by ~~strike through text~~.

2. SUMMARY OF ALL CHANGES

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Title Page	Updated Amendment number and date	Updated to reflect current state	N	No
Protocol Synopsis, Study Design Overview and Schema Similar edits in: 4.1.1. Overview and Schema	Tumor assessments, including radiological assessments by CT/MRI scans will be performed at Screening and subsequently every 6 weeks **(± 1 week)** from Cycle 1 Day 1 (C1D1) (for all regimens) for the first 36 weeks then every 12 weeks **(± 3 weeks)** until disease progression, death, or the initiation of subsequent anticancer therapy, whichever occurs first.	Added time windows to show flexibility in execution of CT and MRI scans and to be consistent within the protocol	N	No
Table 2 Footnote "j" Similar edits in: 8.11. Pregnancy Screen 9.2.2. Reporting a Pregnancy	j For women of childbearing potential (WCBP), a urine or serum pregnancy test will be performed within 4 days of each study drug administration and at the 30-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation **and it is recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV**	Language added to increase patient safety and per health authority request	Y	Yes
Table 3 and 4 Footnote "k and l," respectively. Similar edits in: 8.11. Pregnancy Screen 9.2.2. Reporting a Pregnancy	k For WCBP, a urine or serum pregnancy test will be performed within 4 days of each study drug administration and at the 30-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation **and it is recommended to perform monthly pregnancy tests for 6 months after the last dose of chemotherapy.**	Language added to increase patient safety and per health authority request	Y	Yes

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
5.9.6. Acceptable Methods of Contraception	The following are considered highly effective methods of contraception.	Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines	Y	Yes
5.9.6.1. Single Method	~~One of the following is acceptable~~ • **Combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation** ☐ **Oral** ☐ **Intravaginal** ☐ **Transdermal** • **Progesterone-only hormonal contraception associated with inhibition of ovulation:** ☐ **Oral** ☐ **Injectable** ☐ **Implantable** • Intrauterine Device (IUD) • ~~Vasectomy of a female patient's male~~**Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomized** partner • ~~Contraceptive rod implanted into the skin~~ • **Sexual abstinence**	Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
5.9.6.2. Combination Method	Requires two of the following methods: • ~~Diaphragm~~ **Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action** • **Cap, diaphragm or sponge** with spermicide ~~(cannot be used in conjunction with cervical cap/spermicide)~~ ~~• Cervical cap with spermicide (nulliparous women only)~~ ~~• Contraceptive sponge (nulliparous women only)~~ • Male ~~condom~~ or female condom ~~(cannot be used together)~~ ~~Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring.~~ **with** or ~~subcutaneous (SC) contraceptive injection~~**without spermicide.** **A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.**	Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines	Y	Yes
5.9.8 Medications that are CYP3A or MDR1 Substrates or CYP3A Substrates with Narrow Therapeutic Index	Updated title of section: Medications that are CYP3A **or MDR1** Substrates or CYP3A Substrates with Narrow Therapeutic Index ~~Available~~**Both DM4 and S-methyl-DM4 are substrates for MDR1 efflux transporter. Their exposure could potentially increase** in **the presence of MDR1 efflux transporter. In** vitro metabolism data ~~suggest~~**also indicates that** DM4 ~~has~~**is** a ~~potential to inhibit CYP3A activity in vivo.~~**time-dependent inhibitor of CYP3A4**. The risk of a significant in vivo drug-drug interaction caused by ~~DM4~~ inhibition of ~~CYP3A is not currently known, therefore, treatment~~**CYP3A4 or MDR1 is unknown. Treatment**	Updated information to be accurate and added MDR1 cautionary language to be consistent with the Investigator Brochure.	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	of patients with concomitant medications that **are inhibitors of MDR1,** sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index should be carefully monitored.			
7.1. Evaluation of FRα Expression in Tumor Tissue	FRα expression varies with tumor histology, as reported in the literature and demonstrated in preclinical studies (Section 1.1 and Investigator~~'s~~ Brochure). FRα expression in tumor~~s~~ **samples** will be analyzed using the Ventana FOLR1 (FOLR1-2.1) CDx assay~~.~~**, an immunohistochemical assay developed to detect FRα in cut slide specimens of formalin fixed paraffin embedded (FFPE) epithelial ovarian cancer tissue stained on the BenchMark ULTRA automated staining instrument using the Ventana OptiView DAB IHC Detection Kit.** This assay will be conducted at a central ~~lab for testing of patient samples~~**laboratory**. All patients must submit tumor tissue, or ~~formalin-fixed, paraffin embedded (~~FFPE~~)~~ slides for analysis of FRα expression by IHC prior to enrollment. **PS2+ is the terminology used to reference a scoring method based on membrane stain intensity level of 2 or greater. The PS2+ scoring method requires the pathologist (at the central laboratory) to assess the percentage of tumor cells with moderate (2) and/or strong (3) membrane staining compared to the total number of viable tumor cells. To be considered positive for FRα expression and eligibility for the study, ≥ 75% of viable tumor cells must exhibit level 2 and/or 3 membrane staining intensity.** Only patients with the required FRα expression levels by Ventana FOLR1 (FOLR1-2.1) CDx assay are eligible to enroll in the study (see the Investigator~~'~~ Brochure **Section 5** for details on the assay and the FRα expression threshold selected for this study).	Provided additional details regarding FRα evaluation in tumor tissue	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
13.9. End of Study	EOS will occur after the final analysis of OS, which will be conducted when at least 300 deaths have occurred. It is projected that the final analysis for OS will be approximately 1 year after the final analysis of PFS. ~~Patients~~**After the final analysis of OS, the last survival follow-up visit for the last patient will be performed and the study will close. At the time of the final analysis for OS, if patients are** still receiving clinical benefit from study treatment ~~at EOS may~~**, either the study will be amended to allow those patients to** continue to receive **study** treatment ~~either on this study~~**with limited data collection (eg SAE, dosing information) until they are no longer benefiting** or **patients will be given the option to roll-over to** a long-term extension study.	Language added to clarify EOS definition and clarify continued access to patients receiving clinical benefit.	Y	Yes

[redacted]

Summary of Changes for Protocol IMGN853-0416

Amendment 2

MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Date: 04 December 2020

[redacted]

1. SUMMARY OF CHANGES

ImmunoGen, Inc. has updated Protocol IMGN853-0416 Amendment 1 (dated 09 December 2019) to Amendment 2 (dated 04 December 2020).

The main elements of the protocol amendment include the following:

- Updates to patient inclusion and exclusion criteria.
- Clarification of pre-screening ICF.
- Addition of risk benefit conclusion of mirvetuximab soravtansine.
- CT/MRI windows added to allow flexibility around the performance of these scans and for internal document consistency.
- Added recommendations for pregnancy testing following the last doses of MIRV and chemotherapy.
- Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines.
- Added MDR1 cautionary language to be consistent with the Investigator Brochure.
- Details pertaining to FRα evaluation in tumor tissue added.
- Updated description of the end of study and continued access to patients receiving clinical benefit.
- Recording of AEs/SAEs and retention of data updated.
- Study monitoring and training language updated to accommodate the existing COVID pandemic.
- Minor changes made to improve readability and for editorial consistency.

Changes made from Amendment 1 (dated 09 December 2019) to Amendment 2 (04 December 2020) are summarized in the table below.

Additions are in **bold text** and deletions are designated by ~~strike-through text~~.

2. SUMMARY OF ALL CHANGES

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Global	Minor changes in spelling/use of abbreviations revised	Minor revisions throughout to improve document flow, readability, and consistency.	N	No
Title Page	MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in **Platinum-Resistant** Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression	Clarification of study title to describe the patient population more accurately.	N	No
Title Page	Updated Amendment number and date	Updated to reflect current state	N	No
Protocol Synopsis, Studied Period	Studied Period (months): Approximately 30 months (including follow-up)~~:~~ ~~First patient enrolled: December 2019~~ ~~Last patient last visit: June 2022~~	Enrollment details removed for consistency with other protocols within the MIRV program.	N	No
Protocol Synopsis, Objectives Section 2.1.4 Exploratory Objectives	Exploratory Objectives: • To assess ~~patient-reported outcomes (~~PRO~~)~~ using the EORTC QLQ-C30~~ and~~, EuroQol-5 Dimension 5-level (EQ-5D-5L)**, and Patient Global Impression of Severity (PGIS)** questionnaires	QOL instrument added.	N	No
Protocol Synopsis, Study Design Overview and Schema 4.1.1. Overview and Schema 8.14.1 Radiological Imaging	Tumor assessments, including radiological assessments by CT/MRI scans will be performed at Screening and subsequently every 6 weeks **(± 1 week)** from Cycle 1 Day 1 (C1D1) (for all regimens) for the first 36 weeks then every 12 weeks **(± 3 weeks)** until disease progression, death, ~~or~~ the initiation of subsequent anticancer therapy, **or patient's withdrawal of consent,** whichever occurs first.	Added time windows to show flexibility in execution of CT and MRI scans and to be consistent within the protocol; clarified that tumor assessments can be ended with patient's withdrawal of consent.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Protocol Synopsis, Study Design Overview and Schema Similar edits in: Table 2, footnote "n" Table 3, footnote "o" Table 4, footnote "p" 4.1.1 Overview and Schema 8.14.1 Radiological Imaging	Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks ~~(± 1 week)~~.	Removed time window from maximum interval for tumor assessments related to progressive disease.	N	No
Protocol Synopsis, Study Design Overview and Schema Similar edits in: Table 2, footnote "t" Table 3, footnote "t" Table 4, footnote "t" 4.1.1 Overview and Schema 10.3.3 PFS2 and Survival Follow-up	All patients who discontinue study drug will be followed for survival every 3 months (~~±2 weeks~~ **1 month**) until death, lost to follow-up, withdrawal of consent for survival follow-up, or end of study (EOS) whichever comes first. Additional survival follow-up calls may occur periodically if needed. All patients will be followed for ~~PFS2~~**progression** and survival ~~until 300 deaths have occurred~~.	Revised time window for follow-up after discontinuation and removed maximum number of deaths requiring follow-up.	N	No
Protocol Synopsis, Study Eligibility, Inclusion Criteria	3. Patients must have platinum-resistant disease ~~(defined as progression within 6 months from completion of a minimum of four cycles of platinum-containing therapy)~~**:** **a.** ~~Note: This~~**Patients who have only had 1 line of platinum based therapy must have received at least 4 cycles**	Inclusion criteria updated providing further details regarding previous use of platinum-based therapies.	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Similar edits in: 3.1.1 Inclusion Criteria	**of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date last dose of platinum** **b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum** **Note: Progression** should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression. **Note:** Patients who are platinum refractory during front-line treatment are excluded (see exclusion criteria)			
Protocol Synopsis, Study Eligibility, Inclusion Criteria Similar edits in: 3.1.1 Inclusion Criteria Table 2, footnote "m" Table 3, footnote "n" Table 4, footnote "o"	4. Patients must have progressed **radiographically** on or after their most recent line of therapy ~~Note: Progression must be determined radiographically and/or by CA-125 GCIG progression criteria ()~~	Inclusion criteria updated to remove CA-125 GCIG progression criteria as part of eligibility.	Y	Yes
Protocol Synopsis, Study Eligibility, Inclusion Criteria Similar edits in: 3.1.1 Inclusion Criteria	13. Patients must have adequate hematologic, liver, and kidney functions defined as: a. Absolute neutrophil count (ANC) ≥ 1.5 x 109/L (1,500/µL) **without G-CSF in the prior 10 days or long-acting WBC growth factors in the prior 20 days** b. Platelet count ≥ 100 x 109/L (100,000/µL) without platelet transfusion in the prior 10 days	Inclusion criteria updated providing clarification for ANC and hemoglobin requirements.	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	c. Hemoglobin ≥ 9.0 g/dL **without packed red blood cell (PRBC) transfusion in the prior 21 days** d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN f. Serum bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN) g. Serum albumin ≥ 2 g/dL			
Protocol Synopsis, Study Eligibility, Exclusion Criteria Similar edits in: 3.1.2 Exclusion Criteria	2. Patients with primary platinum-refractory disease, defined as disease that did not respond to **(CR or PR)** or has progressed within 3 months of the last dose of first line platinum-containing chemotherapy	Exclusion criteria updated to clarify definition of response.	Y	Yes
Protocol Synopsis, Study Eligibility, Exclusion Criteria Similar edits in: 3.1.2 Exclusion Criteria	6. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following: a. Active hepatitis B or C infection (whether or not on active antiviral therapy) b. HIV infection c. ~~Cytomegalovirus~~**Active cytomegalovirus** infection d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug **Note: Testing at screening is not required for the above infections unless clinically indicated**	Exclusion criteria updated to clarify infections and testing requirements.	Y	Yes
Protocol Synopsis, Study Eligibility,	**19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients**	Added exclusion criteria for known hypersensitivity,	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Exclusion Criteria Similar edits in: 3.1.2 Exclusion Criteria	**20. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order** ~~19.~~**21. Simultaneous participation in another research study, in countries or localities where this is the health authority guidance**	patients who cannot express consent, and those in a simultaneous research study.		
Table 2 Similar edits in: Table 3 Table 4	**Added pre-screening column and pre-screening informed consent row.**	Revised table rows/columns.	N	No
Table 2, footnote "e" Similar edits in: Table 3, footnote "e" Table 4, footnote "f"	Those who do not have archival tumor tissue to submit will be required to undergo procedures to obtain a new biopsy during the **Pre-**Screening period to confirm eligibility ~~and undergo stratification~~	Confirmed timing of biopsy and removed erroneous stratification aspect of biopsy (not a variable for this study)	N	No
Table 2 Similar edits in: Table 2, footnote "p" Table 3 rows Table 3, footnote "q" Table 4 rows Table 4, footnote "r" 8.14.2 CA-125	CA-125[~~ao~~] Collect ~~prior to dosing on Day 1 of every cycle~~**at each radiologic tumor assessment (±4 days)** PRO ~~a~~**A**ssessment[p] ~~Every 9 (±1) weeks from C1D1 until disease progression (per Investigator)~~**Day 1 of every cycle through Week 24, then every 12 weeks until documentation of PD or start of a new anticancer therapy** [p]	Timing of assessments revised.	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Table 2 Footnote "j" Similar edits in: Table 3, footnote "k" Table 4, footnote "l" 8.11. Pregnancy Screen 9.2.2. Reporting a Pregnancy	j For women of childbearing potential (WCBP), a urine or serum pregnancy test will be performed within 4 days **prior to Day 1** of each ~~study drug administration~~**cycle** and at the 30-day Follow-Up visit. **It is recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV.** Additional testing may be performed in accordance with institutional requirements or local regulation	Language added to increase patient safety and per health authority request.	Y	Yes
Table 2 Footnote "o" Similar edits in: Table 3, footnote "p" Table 4, footnote "q"	**o CA 125 responses will be confirmed according to GCIG criteria.**	Notes reorganized to align.	Y	Yes
Table 2 Footnote "q" Similar edits in: Table 3, footnote "s" Table 4, footnote "s" 9.1 Recording Adverse Events and Serious Adverse Events 9.1.1.1 Adverse Event (AE) 9.2.1 Reporting Serious Adverse Events	**q Only AEs/SAEs which are considered related to a study procedure (ie blood draw or fresh tumor biopsy) will be captured during the Pre-screening period, ie from the time of signing the Pre-screening consent (if one is utilized) until the signing of the main study informed consent, or until the patient is determined to be a screen failure.**	Language added to clarify recording of AEs/SAEs	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Table 2 Footnote "r" Similar edits in: 9.1 Recording Adverse Events and Serious Adverse Events	Added mark for assessment of "Record AE/SAEs and Con-meds" in the to the "Response/Survival Follow-up" column. Noted that "**All ocular AEs will be followed until resolution, stabilization, or return to baseline.**"	Added footnote to clarify follow-up for ocular AEs in patients treated with mirvetuximab soravtansine.	N	Yes
Table 2 Footnote "t"	~~r~~**t** Immunogenicity will be assessed in PK samples collected prior to dosing (predose) on ~~C1D1~~, C2D1, C4D1, **and anytime** at EOT, and 30-day Follow-up. **There will be an ADA only collection prior to dosing on Day 1 of Cycle 1.**	Revised footnote to include ADA collection timing.	N	Yes
1.6.3 Conclusion	**The available safety and efficacy data from the 455 patients treated with single-agent MIRV in previous clinical studies are consistent with a positive risk benefit assessment. The potential benefit of the anti-tumor activity demonstrated by MIRV in patients with FRα high platinum resistant ovarian cancer, a population with high unmet need, outweighs the risks associated with the well tolerated safety profile, as summarized above.**	Conclusion section added to summarize the risk benefit of mirvetuximab soravtansine.	N	No
2.2.4 Exploratory Endpoints	• EORTC QLQ-C30/OV-28, ~~and~~ EQ5D-5L**, and PGIS** … • Identification of soluble FRα levels and other biomarkers, such as protein, genetic, and/or gene expression changes, related to solid malignancies and/or MIRV or IC Chemo mechanism of action. **Patient samples will only be used for exploratory research related to this trial and the development of MIRV**	QOL instrument added. and Language added to specify use of patient samples.	N	No
4.1.1 Overview and Schema	**This study will be opened/active at approximately 200 sites globally.**	Language added to specify number of sites.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
5.1.3 MIRV Study Treatment Compliance 5.5.3.1.1 Preparation	**If necessary,** MIRV from ~~two~~ different drug lots ~~cannot~~may be mixed in a single-dose administration. Under no circumstances is the Investigator allowed to release study drug supplies to any physician not named in the Food and Drug Administration (FDA) Form 1572 or equivalent form, or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the PI (ie, hospital pharmacy, satellite pharmacy), it is the responsibility of the PI to ensure that all study drug is ~~maintained in the manner~~**stored and administered as** described (refer to Pharmacy Manual for instructions).	Details revised to allow mixing of drug lots for administration to occur if necessary as well as general storage and administration language added.	N	No
5.3. Assignment of Patient Number	Patient numbers are assigned in sequential order as patients sign **the pre-screening** informed consent to participate.	Timing of informed consent signing specified to pre-screening for clarity.	N	No
5.5.2. Prophylactic use of Corticosteroid Eye Drops	**Given the lack of availability in some regions, if prednisolone eye drops cannot be obtained, alternate steroid eye drops are acceptable.**	Flexible language added for required eye drop use.	N	No
5.5.2.1.1 Lubricating Artificial Tears	Patients receiving MIRV will be mandated to use ~~preservative-free~~, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician). **Preservative-free lubricating drops are recommended.** Patients should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops.	Language for use of lubricating artificial tears clarified.	N	No
5.6.1.1 Treatment Criteria	In the absence of a TEAE that requires dose modification **(as specified in the management guidance for a particular toxicity, see Section 5.6.1.2,)**, a patient must meet the following criteria to receive study drug at any cycle:	Reference link and language to management guidance of toxicities added for improved clarity.	N	No
5.6.1.2 Mirvetuximab Soravtansine-Related	Footnote "a": Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a	Language added to provide clarity of criteria for drug	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Adverse Events (Table 6), 5.6.1.7 Monitoring of Noninfectious Pneumonitis (Table 9)	treatment-related toxicity will result in treatment discontinuation. **unless otherwise specified in the management guidance for a particular toxicity.**	discontinuation per toxicity management guidance.		
5.6.1.6.2 Management and Dose Modification Guidelines	Treatment with MIRV may resume if ocular symptoms improve to Grade 1 or baseline within 28 days of the next scheduled MIRV dose (refer to Table 8 for details). **If ocular symptoms last longer than 28 days, resumption of MIRV may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.**	Language added to provide clarity for actions to take with drug if patient experiences ocular symptoms.	N	No
5.6.1.6.2 Management and Dose Modification Guidelines (Table 8)	Table title revised: Management of Ocular ~~Disorders~~**Symptoms** Heading revised: Guidelines for MIRV Dose Modifications[a] Severity Grade: Grade 2 ~~Symptoms~~ Guidelines for MIRV Dose Modifications (Grade 2): **Recurrence of Grade 2 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level** Guidelines for MIRV Dose Modifications (Grade 3): **Recurrence of Grade 3 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level** Footnote "a" revised: ~~Failure to meet retreatment criteria within 1 cycle (21~~**If ocular symptoms last longer than 28 days) after, resumption of MIRV may be considered for those patients**	Dose reduction language added for improved guidance clarity on management of recurrent toxicity.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	who have experienced clinical benefit if agreed upon between the ~~missed dose due to insufficient recovery from a treatment-related toxicity will results in treatment discontinuation.~~**Sponsor and the Investigator.**			
5.6.1.10 Discontinuation of Mirvetuximab Soravtansine Due to Toxicity	Section moved below Table 10.	Content moved to improve document flow.	N	No
5.6.2 Paclitaxel	Section moved below Table 10	Content moved to improve document flow.	N	No
5.7.3. Withdrawal of Consent	"legal guardian" replaced with "legally authorized representative" throughout section.	Updated for clarity and consistency.	N	No
5.7.4 Lost to Follow-Up 13.1.2. Patient Information and Consent	"participant" replaced with "patient" throughout section.	Updated for clarity and consistency.	N	No
5.8 Period of Observation	For purposes of this study, the period of safety observation extends from the time of **pre-screening** informed consent until the 30-day follow-up safety visit unless additional follow-up safety information is requested as described in Section 9.1 and Section 10.3.1. Short-term follow-up for patients who discontinue study drug without documented PD will be followed per RECIST 1.1 every **6 weeks (± 1 week) from C1D1 for the first 36 weeks then every** 12 weeks (± 3 weeks) until PD, until the patient begins subsequent anticancer treatment, the patient dies, or the patient withdraws consent, whichever comes first. All patients will be followed every 3 months (± ~~2 weeks~~**1 month**) for survival until death, lost to follow-up, withdrawal of consent for survival or until EOS, whichever comes first.	Short-term follow up for patients who discontinue study drug without documented PD language revised to align with the scan period outlined in other sections of the protocol. The scan frequency of scans has not been changed for this patient population.	N	No

[redacted]

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5.9.3 Antineoplastic Therapy	All non-study related antineoplastic therapy**, including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy,** is prohibited while on study drug.	Specifics of prohibited antineoplastic drugs provided to improve clarity.	N	No
5.9.6. Methods of Contraception	Title Change: ~~Aceeptable~~ Methods of Contraception Women of childbearing potential must agree to use highly effective contraceptive method(s) while on study drug and for at least 3 months after the last dose of MIRV or at least 6 months after the last dose of Pac, PLD, or Topo. **A woman of childbearing potential is a woman who is considered fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.**	Women of childbearing potential defined for clarity.	N	No
5.9.6.1 Single Method	Section revised merged into parent section 5.9.6: ~~One of the following is acceptable:~~ **The following birth control methods may be considered highly effective (failure rate of less than 1% per year):** • **Combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation** – Oral – Intravaginal – Transdermal • **Progesterone-only hormonal contraception associated with inhibition of ovulation:** – Oral – Injectable – Implantable • Intrauterine ~~Device~~**device** (IUD)	Health Authority Request. Revised for consistency with CTFG Guidelines.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	• ~~Vasectomy of a female patient's male~~**Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomized** partner • ~~Contraceptive rod implanted into the skin~~ Section 5.8.6.2 (Combination Method) revised merged into parent section 5.8.6: ~~Requires two of the following methods:~~ • ~~Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)~~ • ~~Cervical cap with spermicide (nulliparous women only)~~ • ~~Contraceptive sponge (nulliparous women only)~~ • ~~Male condom or female condom (cannot be used together)~~ • ~~Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous (SC) contraceptive injection~~ • Sexual abstinence			
5.9.8. Medications that are CYP3A or MDR1 Substrates or CYP3A Substrates with Narrow Therapeutic Index	Title updated: Medications that are CYP3A **or MDR1** Substrates or CYP3A Substrates with Narrow Therapeutic Index ~~Available~~**Both DM4 and S-methyl DM4 are substrates for MDR1 efflux transporter. Their exposure could potentially increase** in **the presence of MDR1 efflux transporter. In** vitro metabolism data ~~suggest~~**also indicates that** DM4 ~~has~~**is** a ~~potential to inhibit CYP3A activity in vivo.~~ **time-dependent inhibitor of CYP3A4**.The risk of a significant in vivo drug-drug interaction caused by ~~DM4~~ inhibition of ~~CYP3A is not currently known.~~	CYP3A4/MRD1 interaction language updated for accuracy.	N	No

[redacted]

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	~~therefore, treatment~~**CYP3A4 or MDR1 is unknown. Treatment** of patients with concomitant medications that are **inhibitors of MDR1,** sensitive substrates of CYP3A**,** or are CYP3A substrates with a narrow therapeutic index should be used with caution and carefully monitored (Appendix D).			
7.1. Evaluation of FRα Expression in Tumor Tissue	FRα expression varies with tumor histology, as reported in the literature and demonstrated in preclinical studies (Section 1.1 and Investigator Brochure). FRα expression in ~~tumors~~**tumor samples** will be analyzed using the Ventana FOLRI Assay~~.~~**, an immunohistochemical assay developed to detect FRα in cut slide specimens of formalin-fixed, paraffin embedded (FFPE) epithelial ovarian cancer tissue stained on the BenchMark ULTRA automated staining instrument using the Ventana OptiView DAB IHC Detection Kit**. This assay will be conducted at a central ~~lab for testing of patient samples~~ **laboratory**. All patients must submit tumor tissue, or ~~formalin-fixed paraffin embedded (FFPE)~~ **FFPE** slides for analysis of FRα expression ~~by IHC~~ prior to enrollment. **PS2+ is the terminology used to reference a scoring method based on membrane stain intensity level of 2 or greater. The PS2+ scoring method requires the pathologist (at the central laboratory) to assess the percentage of tumor cells with moderate (2) and/or strong (3) membrane staining compared to the total number of viable tumor cells. To be considered positive for FRα expression and eligibility for the study, ≥ 75% of viable tumor cells must exhibit level 2 and/or 3 membrane staining intensity.**	Analysis methods of FRα expression updated as well as PS2+ scoring language added for clarity and accuracy.	N	No
7.2.1 Soluble FRα	An exploratory endpoint of the study is to assess if Soluble FRα levels in blood at **pre**-screening are predictive or prognostic of response to MIRV or IC Chemo. **The blood sample collected**	Language added to specify how sample is used.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	during pre-screening will only be used for the measurement of Soluble FRα.			
7.2.2 Potential Predictive Markers of Drug Response	The molecular characterization of ~~each~~**enrolled** patient's tumor tissue ~~and/or blood sample~~ may be conducted to determine the relationship between molecular alterations and clinical response, which may help identify patients who are most likely to benefit from treatment with MIRV or IC Chemo. Next-generation sequencing techniques may be used to evaluate somatic mutations, copy number variations, rearrangements, and expression patterns of multiple genes and/or proteins commonly altered in solid tumors.	Language clarified.	N	No
7.2.3 Future Use of Biomarker Samples	For patients who consent to it, ~~leftover~~**unused** tumor tissue ~~and blood samples~~ after biomarker testing may be used for other research purposes	Language clarified and blood sample removed from description.	N	No
8.1 Informed Consent	**Patient must be re-consented to the most current version of the ICF(s) per IRB/IEC guidelines during their participation in the study.** **Patients will sign a pre-screening ICF to allow testing of fresh or archival tumor tissue by the assay required for study inclusion and collection of a blood sample for the measurement of Soluble FRα. If patients meet entry criteria for FRα positivity (high FRα) they will sign the main study ICF and proceed with remaining screening procedures per the Schedule of Assessments. In some cases, the pre-screening ICF and main study ICF may be merged into a single ICF based on site-specific guidelines or preference.**	Paragraph added to further describe the pre-screening informed consent to allow testing of tumor tissue for FRα positivity.	N	No
8.2 Inclusion and Exclusion Criteria	All screening evaluations must be completed and reviewed **prior to first dose** to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record	Language clarified.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	details of all ~~participants~~**patients** screened and to confirm eligibility or record reasons for screening failure, as applicable.			
8.9.1 Ocular Symptom Assessment	Ocular symptom assessment will be performed before the start of each cycle **for patients in Arm 1** by the treating physician or other qualified individual.	Language clarified.	N	No
8.10.1 Clinical Laboratory Panels (Table 21)	Table 9 revised: • BUN **or Urea** • ~~Carbon dioxide~~ • Urinalysis **(Screening only)** Coagulation **(Screening only)**	Updated for consistency in scheduled clinical laboratory tests.	N	No
8.15 Quality of Life Questionnaires Similar edits in: 11.7 Patient-reported Outcomes	Quality of life (QOL) questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, ~~and~~ EQ-5D-5L, **and PGIS** (Greimel 2003, Osoba 1994) will be used in this trial. **QOL questionnaires assessments are to continue to be administered for patients in response follow-up. Assessment will occur at the time of tumor assessments approximately every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.**	QOL instrument added. Also, language added to specify follow-up assessment.	N	No
10.3.2 Response Follow-up	~~Patients who have discontinued MIRV for reasons other than PD will continue tumor assessments every 12 weeks (± 1 week) until documentation of PD or until the patient starts subsequent anticancer therapy, whichever comes first.~~ Patients who discontinued MIRV for reasons other than PD will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1	Language distilled regarding discontinuation of MIRV for reasons other than PD to simplify and improve clarity.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	week) as allowed by local requirements but must occur at an interval of no more than 12 weeks ~~(± 1 week)~~.			
11. Statistical Methods	This is a Phase 3 study designed to evaluate the efficacy of MIRV compared with that of standard of care IC Chemo in patients with in high FRα expressing, **platinum-resistant,** advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers.	Language clarified.	N	No
12.1 Recording of Data and Data Quality Assurance	~~Data will be captured using validated, electronic data capture (EDC) systems.~~ Data will be documented in various source documents (eg, the patient medical chart) and then manually entered into the clinical trial database. … Training will occur at an Investigator meeting or at the site initiation visit or both~~, and instruction~~. **Remote web-based training may be provided. Instruction** manuals (eg, laboratory manuals and pharmacy manuals) will be provided to aid consistency in data collection and reporting across sites. This clinical study will be conducted according to ICH-GCP E6(R2) guidelines. Quality oversight shall be maintained through proactive and continual risk assessment and mitigation at the operational level. GCP quality assurance audits will be conducted as **needed as** continued compliance oversight.	Details revised and updated to allow remote web-based training considering the current COVID pandemic.	N	No
13.1.1. Institutional Review Board or Independent Ethics Committee Approval	Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol, the **main** study ICF and the ~~prescreening~~**pre-screening** ICF (latter ICF is applicable for sites requesting permission ~~to prescreen~~**pre-screen** for FRα positivity **(high FRα)** before performing any additional study related tests).	Details provided to differentiate between the main study ICF and the pre-screening ICF as well as describe FRα positivity as high FRα for clarity.	N	No
13.1.2. Patient Information and	The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. ~~It should also~~**The informed consent process**	Language re-worked for improved readability and	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Consent	**must** be recorded and dated in the **patient's** source document ~~that consent was given~~. A model of the ~~prescreening~~**pre-screening** and the main study ICF will be provided to the sites separately for this protocol. The main study consent can be used to confirm a patient's consent to all study procedures and all study-specific screening tests. The ~~prescreening~~**pre-screening** ICF can be used to ~~prescreen~~**pre-screen** patients for FRα status before performing any additional study related tests**, as well as collect a blood sample for Soluble FRα**. If a patient is eligible based on FRα expression level, the patient will be provided the main study consent and only after signing the main study ICF will additional study-specific screening tests be performed. Alternatively, the patient can be consented on both ~~prescreening~~**pre-screening** and main study ICF at the same time; and FRα testing and study-specific screening assessments can be carried out in parallel.	clarity. Clarification of collection of blood sample for Soluble FRα.		
13.4 Study Monitoring	~~ImmunoGen personnel and the designee (ie, representative from the CRO) will review the protocol and the clinical trial database with the Investigator and the site staff at a site initiation visit. Monitoring procedures that comply with current GCP guidelines will be followed. On-site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor). On-site review of the clinical trial database for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. During the monitoring visits the clinical study monitor will check the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel from the site must be available to assist the clinical study monitor during these visits. The clinical study monitor will ensure that the investigation is conducted according to protocol~~	Section completely revised to accommodate the impact of the COVID pandemic and improve clarity and accuracy.	Y	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	~~design and regulatory requirements by frequent site visits and communications (e-mail, letter, telephone, and facsimile).~~ ~~The Investigator must maintain source documents for each patient in the study, consisting of (but not limited to) all visit notes, laboratory data, electrocardiograms, and the results of any other tests or assessments. The Investigator must also keep the original signed ICF (a signed copy is given to the patient). The Investigator must give the monitor access to all relevant source documents to confirm their consisteney with the clinical trial database entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs is required. Additional checks of the consisteney of the source data with the clinical trial database are performed according to the study-specific monitoring plan.~~ **Sponsor or its designee will monitor the conduct of the trial on a regular basis throughout the duration of the study, according to the monitoring plan and in compliance with ICH-GCP E6(R2). Monitoring of the study will serve to ensure: (a) The rights and well-being of human subjects are protected; (b) The reported trial data are accurate, complete, and verifiable from source documentation; and (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).** **The study monitor will train site personnel on the conduct of the trial. The monitor will assess the trial site's compliance with the protocol and will periodically review and verify a sample of the patient data recorded on CRFs against source documentation. The study monitor will also review documents that provide evidence of the proper consent and eligibility of enrolled patients, the compliant conduct of study procedures, the administration and disposition of**			

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	investigational product(s), the reporting of serious adverse events and adverse reactions, and the continued maintenance of trial records. **The Investigator will allocate adequate time to support such monitoring activities. The Investigator will also ensure that the monitor is given reasonable remote and/or on-site access to study-related documents, source documents (regardless of media) and study-related facilities (eg, investigational pharmacy, etc). Queries may be raised if any datum is unclear or contradictory. The Investigator and site personnel must address all queries in a timely manner.**			
13.9 End of Study	EOS will occur after the final analysis of OS, which will be conducted when at least 300 deaths have occurred. It is projected that the final analysis for OS will be approximately 1 year after the final analysis of PFS. ~~**Patients**~~**After the final analysis of OS, the last survival follow-up visit for the last patient will be performed and the study will close. At the time of the final analysis for OS, if patients are** still receiving clinical benefit from study treatment at EOS ~~**may**~~**, either the study will be amended to allow those patients to** continue to receive treatment ~~**either on this study**~~**with limited data collection (eg SAEs, dosing information) until they are no longer benefiting** or **patients will be given the option to roll-over to** a long-term extension study.	Language and details revised for improved clarity on continuing study treatment if receiving clinical benefit.	N	No
13.15 Retention of Data	Essential documents will be retained until the following requirements are met: • a minimum of two years (or longer, if required by local/regional regulation) has elapsed after ~~**the last**~~**an** approval of a marketing application ~~**and**~~ **which was supported by this study or**,	Details regarding retention of data updated for accuracy and clarity.	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
14. List of References	**Poveda AM, Selle f, Hilpert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol. 2015;33(32):3836-8.**	Reference added.	N	No
Appendix B. Response Definitions (RECIST 1.1) Appendix C. Gynecologic Cancer Intergroup (GCIG) Criteria for Evaluation of CA-125	Imaging Methods updated: CA-125: Tumor marker CA-125 alone cannot be used to assess response or determine progression; however, it will be followed. **CA-125 measurements will** be **performed as indicated in Table 2, Table 3, and Table 4~~scheduled to approximately coincide with radiological assessment (every 6 weeks [±1 week] from C1D1)~~.** Patients whose CA-125 is above the upper normal limit at baseline will need to have their values normalize to ≤ upper normal limit, in addition to complete disappearance of measurable or evaluable disease, to be considered in complete response. Time Point Assessments updated: Patients will have tumor measurements performed within 28 days ~~**preceding baseline**~~**before first dose of study drug** and every ~~**six**~~**6** weeks **(±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (± 3 weeks)** thereafter~~ (±1 week)~~.	Language revised for consistency with Schedule of Assessments.	N	No

[redacted]

Summary of Changes for Protocol IMGN853-0416

Amendment 2.1

MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Date: 07 June 2021

[redacted]

1. SUMMARY OF CHANGES

ImmunoGen, Inc. has updated Protocol IMGN853-0416 Amendment 2 (dated 04 December 2020) to Amendment 2.1 (dated 07 June 2021).

The main elements of the protocol amendment include the following:

- Updates to Sponsor Medical Monitor.
- Removal of exploratory objective and endpoint for biomarker analyses.
- Removal of pre-screening blood sample for biomarker assessment from Schedule of Assessments.
- Removal of description of exploratory biomarker studies to coincide with removal of endpoint.

Changes made from Amendment 2 (dated 04 December 2020) to Amendment 2.1 (dated 07 June 2021) are summarized in the table below.

Additions are in **bold text** and deletions are designated by ~~strike through text~~.

2. SUMMARY OF ALL CHANGES

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Title Page	Updated Amendment number and date	Updated to reflect current state	N	No
Title page Sponsor Signature Page & Sponsor Contact List	Updated Sponsor Contact Updated Medical Monitor	Updated to reflect current personnel	N	No
Protocol Synopsis, Objectives Section 2.1.4 Exploratory Objectives	Exploratory Objectives: • To assess PRO using the EORTC QLQ-C30, EuroQol-5 Dimension 5-level (EQ-5D-5L), and Patient Global Impression of Severity (PGIS) questionnaires • To evaluate concentrations of MIRV, total antibody (TAb), DM4 and S-methyl DM4, using sparse sampling • To assess the immunogenicity of MIRV via anti-drug antibodies (ADAs) • ~~To evaluate potential biomarkers in blood and tumor tissue predictive of response to MIRV~~	Objective removed because exploratory testing will not be part of the study conducted in sites in China.	N	No
Table 2, Table 3, and Table 4 - Schedule of Assessments Table 2 footnote "l", Table 3 footnote "m", and Table 4 footnote "n" Section 8.9.2	**If an AE of keratopathy/corneal epitheliopathy (or similar Preferred Terms) is noted during the ophthalmic examination at the 30-Day Follow-up visit, the Investigator should repeat the examination in 3 months.**	Note and text added to extend post-treatment ophthalmic examination for any ongoing keratopathy events.	N	Yes

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Ophthalmic Examination				
Table 2, Table 3, and Table 4 - Schedule of Assessments Table 2, Table 3, and Table 4 Note	Deleted row for "Blood Sample for Biomarkers" Note: A patient's *BRCA* mutational status (germline or somatic mutation in tumor tissue) will be collected as part of her medical history if available. Patients without a known mutation will be classified as unknown. ~~Testing may be performed to support exploratory endpoints at the end of the trial; however, results will not be communicated to treating physicians or patients.~~	Assessment and potential analysis removed because exploratory testing will not be part of the study conducted in sites in China.	N	No
Section 2.2.4 Exploratory Endpoints	Exploratory Endpoints: • EORTC QLQ-C30/OV-28, EQ5D-5L, and PGIS • PK parameters will not be calculated due to the use of a sparse sampling schedule. Summary statistics of intact ADC, total Ab, DM4 and S-methyl DM4 concentration data by time will be presented • Immunogenicity is defined as the presence of ADA to MIRV. Based on seroconversion status, the impact of ADA on both efficacy and safety will be evaluated • ~~Identification of soluble FRα levels and other biomarkers, such as protein, genetic, and/or gene expression changes, related to solid malignancies and/or MIRV or IC Chemo mechanism of action. Patient samples will only be used for exploratory research related to this trial and the development of MIRV~~	Objective removed because exploratory testing will not be part of the study conducted in sites in China.	N	No
Section 7 Biomarker Evaluation	Section title changed from "Biomarker Research Studies" to "Biomarker Evaluation".	Section renamed to more accurately describe the contents with the removal of	N	No

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
		the biomarker endpoint analyses and assessments		
Section 7.2 Exploratory Biomarker Studies Section 7.2.1 Soluble FRα Section 7.2.2 Potential Predictive Markers of Drug Response Section 7.2.3 Future Use of Biomarker Samples	Sections deleted	Removed sections describing biomarker endpoint analyses and assessments.	N	No
Section 8.1 Informed Consent Section 13.1.2 Patient Information and Consent	Patients will sign a pre-screening ICF to allow testing of fresh or archival tumor tissue by the assay required for study inclusion ~~and collection of a blood sample for the measurement of Soluble FRα~~.	Exploratory analysis part of the pre-screening ICF description removed.	N	No
Section 13.3 Patient Confidentiality	~~Patient~~**Any patient** blood and tissue samples, and/**or** radiographic images sent to outside laboratories and/or CROs are identified by study patient number only to ensure maintenance of confidentiality.	Sentence broadened for clarity	N	No

Abbreviations: ADA = anti-drug antibodies; ADC = antibody drug conjugate; *BRCA* = breast cancer susceptibility gene; CRO = contract research organization; DM4 = N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine; EORTC = European Organisation for Research and Treatment of Cancer; FRα = folate receptor alpha; ICF = informed consent form; MIRV = mirvetuximab soravtansine (IMGN853); PK = pharmacokinetic; PRO = patient-reported outcomes; S-methyl DM4 = methylated N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine.

Summary of Changes for Protocol IMGN853-0416

Amendment 2.2

MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Date: 23 May 2024

[redacted]

1. SUMMARY OF CHANGES

ImmunoGen, Inc. has updated Protocol IMGN853-0416 Amendment 2 (dated 04 December 2020) to Amendment 2.2 (dated 23 May 2024).

The main elements of the protocol amendment include the following:

- Updates to Sponsor Medical Monitor.
- Updates to allow patients who are receiving mirvetuximab soravtansine (MIRV) or pegylated liposomal doxorubicin (PLD) and experiencing clinical benefit the option to continue to receive MIRV or PLD after the closure of the clinical database for the study.
- Updates to reexamine patients with adverse events of keratopathy/corneal epitheliopathy (or similar preferred terms) after the 30-day safety follow-up visit as applicable.

Minor changes have been made to correct typos and enhance clarity and readability.

Changes made from Amendment 2 to Amendment 2.2 are summarized in the table below.

2. SUMMARY OF ALL CHANGES

	Description of Change	Rationale	Sections Affected
1.	Updated Amendment number and date, Sponsor contacts, and Medical Monitor.	To accurately reflect the version, date, and contact for the study protocol.	Title page Sponsor signature page Sponsor contact list Headers
2.	Added conditional language to allow patients still receiving clinical benefit from MIRV or PLD at the time the study is completed by the Sponsor may continue to receive MIRV or PLD.	To allow flexibility of continued administration of MIRV or PLD for those experiencing clinical benefit.	Synopsis: Study Design Overview and Schema Synopsis: Duration of Study Participation Section 4.1.1. Section 4.1.3. (**Added**) Section 5.7.3. (**Added**) Section 9.1. Section 9.1.1.1. Section 9.2.1. Section 13.9.
3.	Clarified that patients still receiving clinical benefit from MIRV or PLD at the time the study is completed by the Sponsor will not be followed for survival data or follow-on cancer therapy.	To provide clarity regarding survival follow-up data for these patients.	Synopsis: Study Design Overview and Schema Table 5 (**Added**) Section 4.1.3 (**Added**) Section 5.8.
4.	Added additional follow-up for patients with AEs of keratopathy/corneal epitheliopathy (or similar preferred terms) at the 30-Day Safety Follow-up Visit.	To ensure the safety of study patients.	Table 2 Table 3 Table 4 Section 8.9.2.

[redacted]

	Description of Change	Rationale	Sections Affected
5.	Added Table 5 for procedures and assessments for those patients continuing to receive MIRV or PLD treatment after the time the study is completed by the Sponsor.	To distinguish the procedures and assessments performed for these patients.	Table 5 (**Added**) Section 10
6.	Clarified that patients still receiving clinical benefit from MIRV at the time the study is completed by the Sponsor will not have blood tested for ADA.	To clarify ADA assessments for these patients.	Section 5.6.1.9. Section 6.2.
7.	Clarified that patients still receiving clinical benefit from MIRV at the time the study is completed by the Sponsor will not have additional blood drawn for PK assessment or for infusion-related reactions.	To clarify PK and infusion-related reaction assessments for these patients.	Section 6.1.
8.	Clarified that patients still receiving clinical benefit from MIRV or PLD at the time the study is completed by the Sponsor will not have BICR review of disease progression.	To clarify BIRC review of disease progression for these patients.	Section 8.14.1.
9.	Clarified that sites with patients who continue to receive MIRV or PLD treatment after the time the study is completed by the Sponsor will be trained by the Sponsor/CRO on patient oversight requirements.	To provide clarity regarding Sponsor/CRO involvement in patient oversight training of sites with these patients.	Section 12.1.

	Description of Change	Rationale	Sections Affected
10.	Added Appendix F to provide an Investigator's declaration for continued MIRV or PLD treatment for patients experiencing clinical benefit.	Form for Investigators to complete to allow patients who are experiencing clinical benefit to continue receiving MIRV or PLD treatment after the time the study is completed by the Sponsor.	Appendix F (**Added**)

Abbreviations: ADA = anti-drug antibody(ies); AE = adverse event; BIRC = blinded independent central review; CRO = Contact Research Organization; MIRV = mirvetuximab soravtansine; PK = pharmacokinetic(s); PLD = pegylated liposomal doxorubicin.

[redacted]

4. LIST AND DESCRIPTION OF INVESTIGATORS AND OTHER IMPORTANT PARTICIPANTS IN THE STUDY

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
001	[redacted]	Stephenson Cancer Center 800 NE 10th Street Oklahoma City, OK 73104 USA	[redacted]
002		OSU Wexner Medical Center OSU Gynecologic Oncology at Mill Run 3651 Ridge Mill Drive Hilliard, OH 43026 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
004	[redacted]	Fox Chase Cancer Center 333 Cottman Avenue Philadelphia, PA 19111 USA	[redacted]
008		Tennessee Oncology, PLLC 250 25th Avenue North Suite 100 Nashville, TN 37203 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
009	[redacted]	The University of Kansas Cancer Center 2650 Shawnee Mission Parkway Westwood, KS 66205 USA	[redacted]
012		Sarasota Memorial Healthcare System 1700 South Tamiami Trail Sarasota, FL 34239 USA	
013		University of Alabama Birmingham Women and Infants Center 1700 6th Avenue South Suite 10110 Birmingham, AL 35249 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
019	[redacted]	UCLA Women's Health Clinical Research Unit 10833 Le Conte Avenue CHS 24-119 Los Angeles, CA 90095 USA	[redacted]
021		Oklahoma Cancer Specialists and Research Institute, LLC 12697 East 51st Street South Tulsa, OK 74146 USA	
023		Center of Hope 5465 Reno Corporate Drive Suite 100 Reno, NV 89511 USA	
024		University of Pennsylvania Health System, Perelman Center for Advanced Medicine 3400 Civic Center Boulevard Philadelphia, PA 19104 USA	
028		Dr. Sudarshan K. Sharma, Ltd. 121 North Elm Street Hinsdale, IL 60521 USA	
029		Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
031	[redacted]	Columbia University Medical Center Herbert Irving Pavilion 161 Fort Washington Avenue Suite 4-456 New York, NY 10032 USA	[redacted]
035		Smilow Cancer Hospital at Yale - New Haven 35 Park Street New Haven, CT 06511 USA	
037		Holy Cross Hospital 1500 Forest Glen Road Silver Spring, MD 20910 USA	
038		Karmanos Cancer Institute 4100 John R Detroit, MI 48201 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
041	[redacted]	Magee Women's Hospital of UPMC 300 Halket Street Pittsburgh, PA 15213 USA	[redacted]
046		Norton Cancer Institute, St. Matthews Campus Norton Medical Plaza II 3991 Dutchmans Lane Suite 405 Louisville, KY 40207 USA	
048		Ochsner Clinic Foundation 1514 Jefferson Highway New Orleans, LA 70121 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
051	[redacted]	University of Massachusetts Memorial Medical Center 119 Belmont Street Worcester, MA 01605 USA	[redacted]
052		Women & Infants Hospital of Rhode Island 101 Dudley Street Providence, RI 02905 USA	
054		Kadlec Clinic Hematology and Oncology 7360 West Deschutes Avenue Kennewick, WA 99336 USA	
059		Moll Cancer Center Fairview Hospital 18200 Lorain Ave. Cleveland, OH 44111 USA	
060		Hirsch Cancer Center 6780 Mayfield Road Mayfield Heights, OH 44124 USA	
066		Community Health Network Cancer Center North 7979 North Shadeland Avenue Indianapolis, IN 46250 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
071	[redacted]	Texas Oncology - Austin 12221 Renfert Way Suite 300 Austin, TX 78758 USA	[redacted]
072		Texas Oncology - Fort Worth Cancer Center 500 South Henderson Street Fort Worth, TX 76104 USA	
073		Texas Oncology - Longview Cancer Center 1300/1400 North 4th Street Longview, TX 75601 USA	
074		– HonorHealth (previously Arizona Oncology Associates, PC-HAL) 19646 North 27th Avenue Suite 406 Phoenix, AZ 85027 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
075	[redacted]	Arizona Oncology Associates, PC - HOPE 1845 West Orange Grove Building 2 Tucson, AZ 85704 USA	[redacted]
081		HCA Midwest Health Research Medical Center 2340 East Meyer Boulevard Suite 546 Kansas City, MO 64132 USA	
084		Kaiser Permanente Medical Center 975 Sereno Drive Vallejo, CA 94589 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
085	[redacted]	Willis-Knighton Physicians Network/Gynecologic Oncology Associates 2600 Kings Highway Suite 420 Shreveport, LA 71103 USA	[redacted]
086		Texas Oncology - The Woodlands Gynecologic Oncology 9180 Pinecroft Drive Suite 600 The Woodlands, TX 77380 USA	
088		Kaiser Permanente Oncology Clinical Trials 3701 Broadway, 3rd Floor Oakland, CA 94611 USA	
090		Kaiser Permanente, San Francisco 2350 Geary Boulevard San Francisco, CA 94115 USA	
091		Kaiser Permanente, Walnut Creek 1425 South Main Street Walnut Creek, CA 94596 USA	
092		Kaiser Permanente, Santa Clara 710 Lawrence Expressway, Dept. 440, Rm 4986 Santa Clara, CA 95051 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
100	[redacted]	Centre Hospitalier de L'Université de Montréal (CHUM) 1051 Rue Sanguinet Montreal, Quebec H2X 3E4 Canada	[redacted]
102		Tom Baker Cancer Centre 1331 29 Street Northwest Calgary, Alberta T2N 4N2 Canada	
103		McGill University Health Centre - Glen site 1001 Decarie Boulevard D02-7228 Montreal, Quebec H4A3J1 Canada	
105		Sunnybrook Research Institute 2075 Bayview Avenue Toronto, Ontario M4N 3M5 Canada	
106		Princess Margaret Cancer Centre 610 University Avenue Toronto, Ontario M5G 2M9 Canada	

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
108	[redacted]	The Ottawa Hospital Cancer Centre 501 Smyth Road Ottawa, Ontario K1H 8L6 Canada	[redacted]
109		Cross Cancer Institute 11560 University Avenue Edmonton, Alberta T6G 1Z2 Canada	
110		CIUSSS de l'Estrie - Centre Hospitalier Universitaire de Sherbrooke (CHUS) 3001, 12e Avenue Nord Sherbrooke, Quebec J1H 5N4 Canada	
126		Holy Name Medical Center 718 Teaneck Road Teaneck, NJ 07666 USA	
127		FirstHealth Moore Regional Hospital 155 Memorial Drive Pinehurst, NC 28374 USA	
128		MetroHealth Medical Center 2500 MetroHealth Drive Cancer Care Pavilion Cleveland, OH 44109 USA	
129		Baystate Medical Center 759 Chestnut Street Springfield, MA 01199 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
130	[redacted]	Women's Care Florida / Women's Cancer Associates 2191 9th Avenue North Suite 120 St. Petersburg, FL 33713 USA - (600 Eigth Street South Suite B, St Petersburg, FL 33701)	[redacted]
132		University of Virginia Cancer Center 1240 Lee Street Charlottesville, VA 22903 USA	
133		Mayo Clinic Florida 4500 San Pablo Road Jacksonville, FL 32224 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
134	[redacted]	The University of Chicago Medical Center 5841 South Maryland Ave MC 2050 Chicago, IL 60637 USA	[redacted]
135		Tufts Medical Center 800 Washington Street North Building, Mezzanine Level Boston, MA 02111 USA	
136		The Valley Hospital - Luckow Pavilion One Valley Health Plaza Paramus, NJ 07652 USA	
137		West Virginia University 1 Medical Center Drive Morgantown, WV 26506 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
138	[redacted]	Texas Oncology, P.A. - McAllen 2121 Pease Suite 101 Harlingen, TX 78550 USA	[redacted]
139		Illinois Cancer Specialists 880 West Central Road Suite 8200 Arlington Heights, IL 60005 USA	
140		Legacy Good Samaritan Medical Center - Legacy Medical Group - Gynecologic Oncology 1130 Northwest 22nd Avenue Suite 110 Portland, OR 97210 USA	
141		Memorial Health University Medical Center 4700 Waters Avenue Savannah, GA 31404 USA	
143		Willamette Valley Cancer Institute and Research Center 845 Regent Boulevard Suite 100B Irving, TX 75063 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
144	[redacted]	Virginia Cancer Specialists, PC 845 Regent Boulevard Suite 100B Irving, TX 75063 USA	[redacted]
145		Northwest Cancer Specialists, P.C. 12123 Southwest 69th Avenue Tigard, OR 97223 USA	
146		St. Elizabeth Healthcare One Medical Village Drive Edgewood, KY 41017 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
147	[redacted]	Oncology Hematology Care, Inc. 3301 Mercy Health Boulevard Suite 100 Cincinnati, OH 45211 USA	[redacted]
148		Texas Oncology - Sugar Land 1350 First Colony Boulevard Sugar Land, TX 77479 USA	
151		Maryland Oncology Hematology, P.A. 10710 Charter Drive Suite G020 Columbia, MD 21044 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
152	[redacted]	Alaska Women's Cancer Care 3851 Piper Street Suite U264 Anchorage, AK 99508 USA	[redacted]
153		Arizona Cancer Center, University of Arizona 3838 North Campbell Avenue Tucson, AZ 85719 USA	
154		Texas Oncology - San Antonio 5206 Research Drive San Antonio, TX 78240 USA	
155		Minnesota Oncology Hematology, P.A. 11850 Blackfoot Street Northwest Suite 100 Coon Rapids, MN 55433 USA	
156		Rocky Mountain Cancer Centers 11750 West 2nd Place Suite 160 Lakewood, CO 80228 USA	
157		Columbus NCI Community Oncology Research Program (NCORP) 3535 Olentangy River Road Columbus, OH 43214 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
158	[redacted]	West Penn Hospital 4800 Friendship Avenue Pittsburgh, PA 15224 USA	[redacted]
159		University of California, San Francisco - Helen Diller Family Comprehensive Cancer Center 1825 4th Street 6th Floor San Francisco, CA 94158 USA	
160		Hoag Gynecologic Oncology 351 Hospital Road Suite 507 Newport Beach, CA 92663 USA	
161		Olive View - UCLA Medical Center 14445 Olive View Drive Department of OBGYN Sylmar, CA 91342 USA	
162		Memorial Hermann - Texas Medical Center 6400 Fannin Street Suite 2900 Houston, TX 77030 USA	
164		Trinity Health St. Joseph Mercy Ann Arbor 5301 East Huron River Drive Ann Arbor, MI 48106 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
166	[redacted]	Florida Cancer Specialists 3840 Broadway Fort Myers, FL 33901 USA	[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
167	[redacted]	Florida Cancer Specialists 560 Jackson Street Suite 220 St. Petersburg, FL 33705 USA	[redacted]

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
168	[redacted]	Florida Cancer Specialists 1309 North Flagler Drive West Palm Beach, FL 33401 USA	[redacted]
173		Mayo Clinic Hospital 5881 East Mayo Boulevard Phoenix, AZ 85054 USA	
175		Mayo Clinic Rochester 200 First Street Southwest Rochester, MN 55905 USA	
182		Florida Cancer Specialists 2351 Phillips Road Tallahassee, FL 32308 USA	
183		Kaiser Permanente, San Leandro 2500 Merced Street San Leandro, CA 94577 USA	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
184	[redacted]	Kaiser Permanente, Roseville 1600 Eureka Road Roseville, CA 95661 USA	[redacted]
185		Kaiser Permanente, San Jose 270 International Circle San Jose, CA 95119 USA	
187		Kaiser Permanente, Sacramento 501 J Street Sacramento, CA 95814 USA	
188		Zangmeister Cancer Center 3100 Plaza Properties Boulevard Columbus, OH 43219 USA	
201		Universitaire Ziekenhuizen K.U.L. - Campus Gasthuisberg (UZ Leuven) Herestraat 49 Leuven 3000 Belgium	
209		Algemeen Ziekenhuis Klina V.Z.W. Campus Klina Augustijnslei 100 Brasschaat 2930 Belgium	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
211	[redacted]	AZ St-Lucas & Volkskliniek Groenebriel 1 Gent 9000 Belgium	[redacted]
212		Onze-Lieve-Vrouw ziekenhuis Aalst (OLV Hospital Aalst) Moorselbaan 164 Aalst 9300 Belgium	
276		Amsterdam UMC Department of Oncology Meibergdreef 9 Amsterdam 1105 AZ The Netherlands	
278		Erasmus University Medical Center Dr. Molewaterplein 40 Rotterdam 3015 GD The Netherlands	
279		Radboud University Medical Center, Department of Medical Oncology Geert Grooteplein zuid 8 Nijmegen 6525 GA The Netherlands	
280		Maastricht UMC P. Debyelaan 25 Maastricht 6229 HX The Netherlands	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
310	[redacted]	Institut Català d'Oncologia Badalona Ctra de Can Ruti. Camí de les Escoles, s/n Badalona, Barcelona 08916 Spain	[redacted]
318		Centro Integral Oncologico Clara Campal (HM CIOCC) Calle Oña, 10 Madrid 28050 Spain	
322		Hospital Clínico Universitario Virgen de la Arrixaca Ctra. Madrid - Cartagena, s/n El Palmar, (Murcia) 30120 Spain	
323		Hosptial Universitari Parc Tauli de Sabadell Adva. Parc Tauli, s/n Sabadell 08208 Spain	
324		Hospital Clinico Universitario Lozano Blesa Avda. San Juan Bosco, 15 Zaragoza 50009 Spain	
325		Hospital Virgen del Rocío Av. Manuel Siurot, s/n Sevilla 41013 Spain	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
326	[redacted]	Hospital Universitario la Fe Avenida Fernando Abril Martorell, No. 106 Valencia 46026 Spain	[redacted]
327		Complejo Hospitalario Provincial de Castellón Av. Del Dr. Clarà, 19 Castellón 12002 Spain	
328		Hospital San Pedro de Alcántara Av. Pablo Naranjo S/N Cáceres 10003 Spain	
329		Hospital Universitario Infanta Sofia Paseo de Europa, 34 San Sebastián de los Reyes Madrid 28702 Spain	
330		Hospital Universatario de Jaén Avda. Del Ejército Español, 10 Jaén 23007 Spain	
331		Hospital Clínico Universitario de Santiago A Choupana, s/n Santiago de Compostela 15886 Spain	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
376	[redacted]	UMHAT Dr. Georgi Stranski Pleven, 8A Georgi Kochev str. Pleven 5800 Bulgaria	[redacted]
377		Acibadem City Clinic Tokuda Hospital EAD 51B, Nikola Vaptsarov Boulevard Sofia 1407 Bulgaria	
385		Samodzielny publiczny szpital kliniczny nr 1 w Lublinie UL Staszica 16 Lublin 20-081 Poland	
387		Wojewódzki Szpital Specjalistyczny w Olsztynie Oddzial Ginekologii Onkologicznej Ul. Zolnierska 18 Olsztyn 10-561 Poland	
388		Uniwersyteckie Centrum Kliniczne, Klinika Ginekologii Oncologicznej I Endokrynologii Ginekologicznej Ul. Smoluchowskiego 17 Gdansk 80-214 Poland	
392		Uniwersytecki Szpital Kliniczny w Poznaniu Ul. Augustyna Szmarzewskiego 84 Poznan 60-569 Poland	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
401	[redacted]	University College London Hospitals NHS Foundation Trust 250 Euston Road London NW1 3PG United Kingdom	[redacted]
404		The Royal Marsden NHS Foundation Trust The Royal Marsden Hospital Down's Road Sutton, Surrey SM2 5PT United Kingdom	
406		NHS Greater Glasgow & Clyde - Beatson West of Scotland Cancer Centre 1053 Great Western Road Clinical Trials Unit, Level 0 1053 Great Western Road Glasgow G12 0YN United Kingdom	
407		University Hospitals Coventry and Warwickshire Clifford Bridge Road Research & Development 4th Floor Rotunda, ADA40014 Coventry CV2 2DX United Kingdom	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
411	[redacted]	North West Anglia Foundation Trust Peterborough City Hospital Edith Cavell Campus, Bretton Gate Peterborough, Cambridgeshire PE3 9GZ United Kingdom	[redacted]
418		The Royal Marsden NHS Foundation Trust The Royal Marsden Hospital Down's Road Sutton, Surrey SM2 5PT United Kingdom (Operationally separate from Site 404)	
419		Royal Devon and Exeter Hospital Royal Devon & Exeter NHS Foundation Trust Barrack Road Exeter, Devon EX2 5DW United Kingdom	
420		St. Bartholomew's Hospital Barts Health NHS Trust West Smithfield London EC1A 7BE United Kingdom	
424		The Christie NHS Foundation Trust The Oglesby Cancer Research Building Wilmslow Road, Withington Manchester M20 4GJ United Kingdom	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
490	[redacted]	The Chaim Sheba Medical Center Emek HaEla St. 1 Ramat Gan 5262160 Israel	[redacted]
491		Meir Medical Center Tchernichovsky St. 59 Kfar Saba 4428164 Israel	
492		Hadassah Medical Center Kiryat Hadassah Ein Kerem Jerusalem 9112001 Israel	
494		Ziv Medical Center Derech HaRambam Street Zefat 13100 Israel	
496		Kaplan Medical Center Boris Pasternak 1 St. Rehovot 76100 Israel	
497		The Edith Wolfson Medical Center 62 Halohamim Street Holon 58100 Israel	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
502	[redacted]	IRCCS - Istituto Europeo di Oncologia (IEO) via Ripamonti 435 Milano 20141 Italy	[redacted]
504		Fondazione Policlinico Universitario, Agostino Gemelli IRCCS Ginecologia Oncologica Largo Agostino Gemelli, 8 Roma 00168 Italy	
508		Azienda Ospedaliero Universitario di Bologna - Policlinico Sant' Orsola-Malpighi SSD Oncologica Medica Viale Giambattista Ercolani, 4/2 Bologna 40138 Italy	
510		Instituto Nazionale Tumori - G. Pascale S.C. Oncologica Medica Uro-Ginecologica - Dip. Uro-Ginecologico Via Mariano Semmola, 53 Napoli 80131 Italy	
519		Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Divisione Ostetricia e Ginecologia Piazzale Spedali Civili 1 Brescia 25123 Italy	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
520	[redacted]	University of Torino, Ospedale Ordine Mauriziano Largo Turati, 62 Torino 10128 Italy	[redacted]
522		AUSL IRCCS di Reggio Emilia Unita di Oncologia Viale Risorgimento 80 Reggio Emilia 42123 Italy	
524		Ospedale Cannizzaro di Catania Ginecologia ed Ostetricia Via Messina n. 829 Catania 95126 Italy	
525		ASST di Lecco- Ospedale Alessandro Manzoni Via dell' Eremo 9/11 Lecco 23900 Italy	
526		Istituto Oncologico Veneto (IOV) UOC Oncologia Medica 2 Via Gattamelata, 64 Padova 35128 Italy	
555		Grigoriev Institute for Medical Radiology NAMS of Ukraine Pushkinska str. 82 Kharkiv 61024 Ukraine	
557		Communal non-profit enterprise "Prykarpatskyi Clinical Oncology Center of Ivano-Frankivsk Regional Council" Medychna str. 17 Ivano-Frankivsk 76018 Ukraine	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
561	[redacted]	Communal non-profit enterprise "Chernihiv Medical Center of Modern Oncology of Chernihiv Regional Council" Myru avenue 211-D Chernihiv 14029 Ukraine	[redacted]
563		Communal non-profit enterprise "Khmelnytskyi Regional Antitumor Center" of Khmelnytskoyi Regional Council Pilots'ka str. 1 Khmelnytskyi 29009 Ukraine	
575		Centro Hospitalar Universitário Lisboa Norte, EPE - Hospital de Santa Maria Avenida Professor Egas Moniz MB Lisbon 1649-028 Portugal	
576		Fundação Champalimaud Avenida Brasília Lisboa 1400-038 Portugal	
577		Hospital Beatriz Ângelo Av. Carlos Teixeira 3 Loures 2674-514 Portugal	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
579	[redacted]	Hospital da Luz Av Lusiada 100 Lisbon 1500-650 Portugal	[redacted]
601		Institut Bergonié 229 Cours de l'Argonne Bordeaux-Cedex 33076 France	
602		Institut de Cancerologie de l'Ouest (ICO) Bd Jacques Monod Saint Herblain Cedex 44805 France	
603		Hospital Cochin 27 rue du Faubourg Saint Jacques Paris 75014 France	
604		Institut Gustave Roussy 114 rue Edouard Vaillant Villejuif 94800 France	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
606	[redacted]	Institut Curie - Site St. Cloud 35, rue Dailly Saint Cloud 92210 France	[redacted]
607		Groupe Hospitalier Diaconesses Croix Saint-Simon 125 rue D' Avron Paris 75020 France	
608		Institut Claudius Regaud - IUCT-Oncopole 1, avenue Irène JoliotCurie Toulouse Cedex 9 31059 France	
609		CHRU Besançon - Hôpital Jean-Minjoz 3 bvd Alexandre Fleming Besançon 25000 France	
610		Institut de Cancérologie de l'Ouest 15 rue André Bocquel - CS10059 Angers Cedex 02 49055 France	
611		Hospices Civils de Lyon - Centre Hospitalier Lyon Sud Service Oncologie Médicale 1F 165 chemin du Grand Revoyet Pierre Bénite 69310 France	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
612	[redacted]	Centre Armoricain de Radiothérapie, Imagerie Médicale et d'Oncologie (CARIO) Hôpital Privé des Côte d'Armor 10 rue François Jacob Plerin 22190 France	[redacted]
613		Centre Oscar Lambret 3 rue Frédéric Combemale BP 307 Lille Cedex 59020 France	
614		Institut Cancérologie de Lorraine (ICL) 6 Avenue De Bourgogne Vandoeuvre les Nancy 54519 France	
615		Centre Leon Berard 28 rue Laennec Lyon Cedex 08 69373 France	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
616	[redacted]	Institut Paoli Calmettes 232 Boulevard Sainte-Margueritte BP 156 Marseille Cedex 09 13273 France	[redacted]
652		Budget Institution of Healthcare of Omsk Region Clinical Oncology Dispensary Zavertyaeva, 9 Building 1 Omsk 644031 Russia	
656		LLC "VitaMed" 10, Seslavinskaya Street Moscow 121309 Russia	
657		State Autonomous Healthcare Institution Republican Clinical Oncological Dispensary of the MoH of Republic Bashkortostan 73/1, Oktyabrya pr. Ufa 450054 Russia	
658		LLC "MedPomosch" 5/1, lit 3, Vyborg Highway Saint Petersburg 194356 Russia	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
751	[redacted]	Institute of Oncology and Radiology of Serbia Pasterova 14 Belgrade 11000 Serbia	[redacted]
760		Fudan University Shanghai Cancer Center No.270 Dongan Road, Xuhui District No.4333, Kangxin Road, Pudong New Area Shanghai 200032 China	
762		Anhui Provincial Cancer Hospital No.107 Huanhu East Road Shushan District Hefei, Anhui 230000 China	
763		Liaoning Cancer Hospital & Institute No.44 Xiaoheyan Road Dadong District Shenyang, Liaoning 110042 China	
764		Tianjin Medical University Cancer Institute & Hospital Tiyuan North Huanhu West Road Hexi District Tianjin 300060 China	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
767	[redacted]	Hubei Cancer Hospital No. 116 Zhuodaoquan South Road Hongshan District Wuhan, Hubei 430079 China	[redacted]
768		Zhongnan Hospital of Wuhan University No. 169 Donghu Road Wuchang District Wuhan, Hubei 430071 China	
769		Zhongshan Hospital Xiamen University 201-209 Hubin South Road Siming District Xiamen, Fujian 361004 China	
770		The First Affiliated Hospital of Xi'an Jiaotong University No.277 Yanta West Road Xi'an, Shanxi 710061 China	
771		Union Hospital Tongji Medical College Huazhong University of Science and Technology No. 109 Machang Road, Jianghan District No. 1277 Jiefang Avenue Wuhan, Hubei 430023 China	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
772	[redacted]	Peking University First Hospital No. 1 Xianmen Street Xicheng District Beijing 100032 China	[redacted]
773		Qilu Hospital of Shandong University No. 107 Wenhua Xilu Jinan, Shandong 250012 China	
777		Sun Yat-sen University Cancer Center No. 651 Dongfeng East Road Yuexiu District Guangzhou, Guangdong 510060 China	
780		The First Hospital of Jilin University No. 1 Xinmin Street Chaoyang District Changchun, Jilin 130021 China	
802		Všeobecná fakultní nemocnice v Praze Gynekologicko-porodnická klinika 1.LF UK a VFN, Onkogynekologické centrum Apolinářská 18 Praha 2 128 51 Czech Republic	
804		Fakultní nemocnice Ostrava Gynekologicko-porodnická klinika Onkogynekologické odděleni 17. listopadu 1790 Ostrava-Poruba 708 52 Czech Republic	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
805	[redacted]	Krajská nemocnice T.Bati a.s. Havlíčkovo nábřeží 600 Zlín 762 75 Czech Republic	[redacted]
827		Universitätsfrauenklinik Ulm Klinik für Frauenheilkunde und Geburtshilfe Prittwitzstr. 43 Ulm 89075 Germany	
831		Mammazentrum Hamburg am Krankenhaus Jerusalem Moorkamp 2-6 Hamburg 20357 Germany	
835		Universitätsklinikum Carl Gustav Carus Fetscherstr. 74 Dresden 01307 Germany	
847		Universitätsklinikum Bonn Klinik für Gynäkologie and Gynäkologische Onkologie Venusberg-Campus 1 Bonn 53127 Germany	
848		Universitätsklinikum Gießen und Marburg (UKGM) Klinikstraße 33 Giessen 35392 Germany	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
875	[redacted]	Taipei Veterans General Hospital 201 Shih-Pai Road Sec. 2 Taipei 11217 Taiwan	[redacted]
877		Far Eastern Memorial Hospital 21, Sec. 2 Nanya S. Road Banciao District New Taipei City 220 Taiwan	
925		Cabrini Malvern Hospital 183 Wattletree Road Malvern, Victoria 3144 Australia	
927		Royal North Shore Hospital Reserve Road St. Leonards, New South Wales 2065 Australia	
928		Burnside War Memorial Hospital 120 Kensington Road Toorak Gardens, South Australia 5065 Australia	
929		Newcastle Private Hospital 14 Lookout Road New Lambton Heights, New South Wales 2305 Australia	
930		Prince of Wales Hospital Barker Street Randwick, New South Wales 2031 Australia	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
931	[redacted]	Monash Health 246 Clayton Road Clayton, Victoria 3168 Australia	[redacted]
975		Asan Medical Center, University of Ulsan 88, Olympic-ro 43-gil Songpa-gu Seoul 05505 Republic of Korea	
976		Seoul National University Hospital 101, Daehak-ro Jongno-gu Seoul 03080 Republic of Korea	
977		National Cancer Center 323, Ilsan-ro, Ilsandong-gu Goyang-si, Gyeonggi-do 10408 Republic of Korea	
978		Samsung Medical Center 81, Irwon-ro, Gangnam-gu Seoul 06351 Republic of Korea	
979		Seoul National University Bundang Hospital 82, Gumi-ro 173beon-gil Bundang-gu Seongnam-si, Gyeonggi-do 13620 Republic of Korea	

[redacted]

Table 1: List and Description of Investigators and Other Important Participants in the Study that Screened or Enrolled Patients (Continued)

Site No.[a]	Investigator Name	Site Address[b]	Sub-Investigator Names
980	[redacted]	Severance Hospital, Yonsei University Health System 50-1, Yonsei-ro Seodaemun-gu Seoul 03722 Republic of Korea	[redacted]

[a] Site list includes all activated sites that were shipped IMP.
[b] At time of clinical study (updated when available).

[redacted]