SYNOPSIS

Name of Sponsor/Company: ImmunoGen, Inc. **Name of Finished Product:** mirvetuximab soravtansine	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: SORAYA: A Phase 3, single arm study of mirvetuximab soravtansine in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression		
Protocol ID: IMGN853-0417		
Study Center(s): This study enrolled patients at 39 study centers in North America, Europe, and Asia Pacific.		
Publications (reference): Not applicable		
Studied Period (years): Date first patient enrolled: 23 July 2020 Date last patient completed: Ongoing Data cutoff for primary analysis: 16 November 2021		**Phase of Development:** 3

Objectives:

Primary:

- To determine the efficacy (as determined by objective response rate [ORR]) of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer (PROC) and high folate receptor-alpha (FRα) expression

Key Secondary:

- To determine the durability of response to mirvetuximab soravtansine in patients with PROC and high FRα expression

Additional Secondary:

- To evaluate the safety and tolerability of mirvetuximab soravtansine
- To characterize the clinical activity of mirvetuximab soravtansine in patients with PROC and high FRα expression

Methodology:

This was a single-arm Phase 3 study designed to evaluate the efficacy and safety of mirvetuximab soravtansine in patients with bevacizumab-pretreated, platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer (referred to throughout as PROC), whose tumors express a high level of FRα. Patients were, in the opinion of the investigator, appropriate for single-agent therapy for their next line of therapy. FRα positivity (high FRα) was defined by the Ventana FOLR1 (FOLR1-2.1) CDx assay, hereafter referred to as Ventana FOLR1 Assay.

Tumor assessments, including radiological assessment by computed tomography (CT)/magnetic resonance imaging (MRI) scan, were performed at Screening and subsequently every 6 weeks (± 1 week) from Cycle 1 Day 1 for the first 36 weeks and then every 12 weeks (± 3 weeks) until progressive disease (PD), death, start of new anticancer therapy, or patient's withdrawal of consent, whichever occurred first.

Patients who discontinued mirvetuximab soravtansine for reasons other than PD continued with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever came first. Prior to Week 36, 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, assessments 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 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.

Number of Patients (planned and enrolled):

Planned: Up to approximately 110 patients

Analyzed: 106 patients

Diagnosis and Main Criteria for Inclusion (not all-inclusive):

- Female patients ≥ 18 years of age.
- Patients must have had a confirmed diagnosis of high-grade serous endometrial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
- Patients must have had platinum-resistant disease.
- Patients must have progressed radiographically on or after their most recent line of anticancer therapy.
- 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 confirmation of FRα positivity.
- Patient's tumor must have been positive for FRα expression as defined by the Ventana FOLR1 Assay.
- Patients must have had at least 1 lesion that meets the definition of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (radiologically measured by the investigator).
- Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line of therapy containing bevacizumab, and for whom single-agent therapy was appropriate as the next line of treatment:
    - Adjuvant ± neoadjuvant were considered 1 line of therapy.
    - Maintenance therapy (eg, bevacizumab, PARP inhibitors) were considered part of the preceding line of therapy (ie, not counted independently).
    - Therapy changed due to toxicity in the absence of progression was considered part of the same line (ie, not counted independently).
    - Hormonal therapy was counted as a separate line of therapy unless it was given as maintenance.
- Patients must have had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

- Patients must have had adequate hematologic, liver, and kidney functions.

Main Criteria for Exclusion (not all-inclusive):

- Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade/borderline ovarian tumor.
- 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.
- Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow.
- Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events.
- Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring.
- Patients with serious concurrent illness or clinically relevant active infection.
- Patients with a history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome).
- Patients with clinically significant cardiac disease.
- Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to enrollment.
- Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C).
- Patients with a previous clinical diagnosis of noninfectious interstitial lung disease, including noninfectious pneumonitis.
- Patients with untreated or symptomatic central nervous system metastases.
- Patients with a history of other malignancy within 3 years prior to enrollment.

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

Mirvetuximab soravtansine 6 mg/kg adjusted ideal body weight intravenously administered every 3 weeks

Batch Numbers: P1947918001 and P1947918002

Duration of Treatment: Patients continued to receive mirvetuximab soravtansine until PD, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came first).

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for Evaluation:

Efficacy: Tumor response was evaluated by the investigator using RECIST v1.1. CT or MRI scans were collected for sensitivity analysis by blinded independent central review (BICR).

Safety: Safety assessments included treatment-emergent adverse events (TEAEs) and clinically significant ≥ Grade 3 changes in laboratory test results, physical examination, and vital signs, and treatment-emergent ocular or pulmonary adverse events.

[redacted]

Statistical Methods:

Efficacy Endpoints and Analyses:

The primary efficacy endpoint was ORR, which included best confirmed response of CR or PR, as assessed by the investigator. The primary endpoint of ORR was calculated based on the Efficacy Evaluable population and its 95% exact confidence interval (CI) was estimated using the Clopper-Pearson method.

The key secondary endpoint was duration of response (DOR), defined as the time from initial investigator-assessed response (CR or PR) until PD or death as assessed by the investigator. The key secondary endpoint of DOR was summarized in patients with a confirmed best overall response (BOR) of CR or PR only. The distribution of DOR was summarized using the Kaplan-Meier method.

Timing of Final Analysis for the Primary Endpoint:

To allow for reasonable duration on treatment to achieve a confirmed response, the final analysis for ORR was conducted after all efficacy evaluable patients had undergone at least 4 postbaseline tumor assessments, experienced radiological disease progression, died or had clinical progression within 105 days of first dose of mirvetuximab soravtansine, or withdrawn from study for other reasons.

SUMMARY – RESULTS AND CONCLUSIONS

ANALYSIS POPULATIONS:

Safety population: 106 patients who received at least 1 dose of mirvetuximab soravtansine.

Efficacy Evaluable population: 105 patients in the Safety population who had measurable disease at Baseline by investigator assessment per RECIST v1.1.

DEMOGRAPHICS:

Among the 106 patients in the Safety population, the median age was 62 years, and all patients were female. There were no patients of childbearing potential. The majority of patients were white (96%) and not Hispanic or Latino (93%). The majority of patients enrolled (80%) had epithelial ovarian cancer, followed by primary peritoneal (11%) or fallopian tube cancer (8%). All patients (100%) had high-grade serous histology, had tumor samples that were assessed as FRα-positive, and had received prior bevacizumab. Approximately half (51%) of the patients had received 3 prior lines of therapy, and approximately half (48%) had received a prior PARP inhibitor. The platinum-free interval was 0 to 3 months in 37% of patients and > 3 to 6 months in 60% of patients. Most patients had an ECOG performance status of 0 (57%), followed by an ECOG performance status of 1 (43%).

EFFICACY RESULTS:

The confirmed ORR per RECIST v1.1 as assessed by investigator was 32.4% (95% CI: 23.6% to 42.2%). Five patients had a confirmed response of CR; 29 patients had a confirmed response of PR. The confirmed ORR as assessed by BICR was 31.6% (95% CI: 22.4% to 41.9%). Overall concordance of BOR between investigator and BICR assessments was 85% (Clopper-Pearson exact CI: 76% to 91%).

Among patients with a confirmed CR or PR by investigator assessment, the median DOR per RECIST was 5.9 months (95% CI: 5.6 to 7.7 months). The median time to response was 1.5 months (range: 1.0 to 5.6 months). At the time of the protocol-specified primary analysis, 15 of the 34 responders remained on mirvetuximab soravtansine without PD and were censored in the DOR analysis.

The Gynecologic Cancer Intergroup (GCIC) cancer antigen 125 (CA-125) response rate was 46.5%. The median progression-free survival in the investigator-assessed Efficacy Evaluable population was 4.3 months (95% CI: 3.7 to 5.1 months). With a median follow-up of 8.5 months, 31% of patients had died, and median overall survival was not reached.

SAFETY RESULTS:

Patients received a median of 6 cycles of treatment (range: 1 to 17 cycles).

Almost all patients (99%) had ≥ 1 reported TEAE. The most common TEAEs were blurred vision (46%), nausea (40%), keratopathy ([grouped term] 37%), abdominal pain ([grouped term] 33%), diarrhea (31%), constipation (30%), fatigue (30%), dry eye ([grouped term] 27%), peripheral neuropathy ([grouped term] 27%), and asthenia (21%).

The incidence of study drug–related TEAEs was 86%. The most common study drug–related TEAEs were blurred vision (41%), keratopathy ([grouped term] 36%), nausea (29%), dry eye ([grouped term] 23%), fatigue (23%), diarrhea (22%), and peripheral neuropathy ([grouped term] 21%).

The incidence of ≥ Grade 3 TEAEs was 50%. The most common ≥ Grade 3 TEAEs by System Organ Class (SOC) were Gastrointestinal disorders (21%). The most common Grade 3 or higher TEAEs by Preferred Term were keratopathy (8%), abdominal pain (7%), blurred vision (7%), increased gamma-glutamyl transferase (GGT) (5%), ascites (4%), small intestinal obstruction (4%), diarrhea (3%), and cataract (3%). The most common ≥ Grade 3 study drug–related TEAEs were keratopathy (8%), blurred vision (6%), and increased GGT (4%).

Seven patients (7%) died on study drug or within 30 days of the last dose. The primary cause of death was PD in 4 patients, TEAEs in 2 patients, and "other" (palliative sedation) in 1 patient. Of the 2 patients with fatal TEAEs, 1 patient had study drug–related respiratory failure (possibly related, without evidence of drug reaction on autopsy showing metastatic ovarian cancer in lungs, with diffuse alveolar damage in background of fibrosis with recent bronchopneumonia). The other patient had a fatal TEAE of small bowel obstruction, which was considered not related to mirvetuximab soravtansine and related to PD.

The nature and frequency of serious adverse events (SAEs) experienced were consistent with the drug's known safety profile and/or the underlying disease. Related SAEs were infrequent (a total of 15 events in 11 patients [10%]), and all occurred in single incidences.

A total of 8% of patients reported TEAEs of pneumonitis. All pneumonitis TEAEs were Grade 1 or Grade 2 in severity. The median time to onset of a first pneumonitis TEAE was 4.2 months (range: 1.2 to 5.5 months).

No events of corneal ulcer or corneal perforation occurred. Approximately half (52%) of patients reported ocular TEAEs of blurred vision and/or the grouped term of keratopathy, including 11 patients (10%) who reported maximum Grade 3 events and 1 patient who reported a maximum Grade 4 event (keratopathy). Review of ophthalmic examination reports confirmed that the Grade 4 keratopathy event reflected visual acuity change in 1 eye (left) from 20/25 to 20/200 that was accompanied by nonconfluent corneal deposits treated as dry eye syndrome with lubrication. Corneal deposits resolved and vision returned to baseline in 15 days by ophthalmic examination. The remainder of the patients reported Grade 1 (20 patients, 19%) or Grade 2 (23 patients, 22%) ocular TEAEs. The median time to onset of a patient's first ocular TEAE was 1.4 months (range: 0 to 8.4 months). Nine patients had Grade 2 or greater TEAEs that did not resolve to Grade 1 or Grade 0 at the time of the primary analysis. Five of these patients were still on study drug, including 1 patient with ongoing Grade 3 blurred vision and 4 patients with ongoing Grade 2 events. The remaining 4 patients, all of whom had ongoing Grade 2 events, discontinued mirvetuximab soravtansine due to PD but remained on study in survival follow-up.

A total of 27% of patients reported peripheral neuropathy TEAEs, including 2 patients (2%) who reported a maximum Grade 3 event and 6 patients (6%) who reported maximum Grade 2 events; the remainder of events were Grade 1 in severity. The median time to onset of a first peripheral neuropathy event was 1.4 months (range: 0.2 to 6.9 months).

One patient had an SAE of Grade 3 infusion-related reaction, which led to permanent discontinuation of study drug. Standard Medical Dictionary for Regulatory Activities (MedDRA) queries (broad and narrow) for hypersensitivity to identify potentially relevant TEAEs within 3 days of infusion revealed no additional Grade 3 events or other safety signals.

Twelve patients (11%) had ≥ 1 TEAE leading to discontinuation of study drug. Seven patients (7%) had ≥ 1 study drug–related TEAE leading to discontinuation of mirvetuximab soravtansine (thrombocytopenia [2%] and keratopathy, fatigue, infusion-related reaction, peripheral motor and sensory neuropathy, and respiratory failure [1% each]).

Forty-nine patients (46%) had ≥ 1 TEAE leading to dose delay or dose reduction; 42 patients (40%) had ≥ 1 study drug–related TEAE leading to drug dose delay or dose reduction. TEAEs leading to dose delay or reduction occurred most commonly in the SOC of Eye disorders (23 patients).

Shifts to Grade 3 or Grade 4 laboratory values were infrequent and were not associated with severe TEAEs. No significant trends in vital signs parameters were observed.

CONCLUSION:

Mirvetuximab soravtansine administration was associated with an ORR of 32.4% (95% CI: 23.6% to 42.2%), meeting the primary endpoint and rejecting the null hypothesis of 12%. The median DOR was 5.9 months (95% CI: 5.6 to 7.7 months). The clinically meaningful efficacy, as demonstrated by ORR and DOR, in biomarker-identified FRα-high patients treated with mirvetuximab soravtansine, together with a differentiated safety profile and tolerability, demonstrate a favorable benefit-risk profile in this patient population.

Date of the report:

04 March 2022

[redacted]

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 Events
Title Page & Protocol Synopsis	**SORAYA:** A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression	Addition of study name	N	No
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
Protocol Synopsis	Study Period (months): Approximately 30 months, including follow-up • First patient enrolled: February 2020 • Last patient last visit: **December 2021** ~~December 2020~~	Administrative; logistical	N	No
Protocol Synopsis, 2.1.4 Exploratory Objectives	Exploratory Objectives: • To evaluate potential blood-**based** biomarkers predictive of response to MIRV • **To evaluate potential tumor-based biomarkers predictive of response to MIRV**	An exploratory objective to examine tumor based biomarkers was added to permit analysis, as appropriate, of evolving biomarkers relevant to treatment of ovarian cancer patients such as tumor BRCA and HRD status.	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 Events
2.2.4 Exploratory Endpoints	Exploratory Endpoints: **Identification of tumor DNA mutational status and the expression level of genes and pathways involved in cancer development, progression and responsiveness to treatment**	An exploratory objective to examine tumor based biomarkers was added to permit analysis, as appropriate, of evolving biomarkers relevant to treatment of ovarian cancer patients such as tumor BRCA and HRD status.	N	No
Protocol Synopsis & 4.1.1 Overview	Number of Patients (planned): Approximately ~~100~~ **110** patients Study Design Overview: Approximately ~~100~~ **110** eligible patients will be enrolled to achieve a total of ~~91~~ **105** efficacy evaluable patients…. ….. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans will be collected ~~and held~~ **for sensitivity analysis by blinded independent central review (BICR).** Section 4.1.1 Approximately ~~100~~ **110** patients who have provide informed consent and meet study entry criteria will be enrolled to achieve at total of ~~91~~ **105** efficacy evaluable patients. **Efficacy evaluable patients include those who have measurable lesions (per RECIST 1.1) at baseline and received at least 1 dose of MIRV**. ~~Efficacy evaluable~~	The target for efficacy was revised to target a doubling of the 12% ORR in Aurelia to 24% based on feedback that 12% would be an appropriate benchmark that would need to be statistically exceeded. Based on this, the sample size was increased to enroll approximately 110 patients to obtain data from 105 efficacy evaluable patients	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	~~patients include those who have measurable disease at baseline, received at least 1 dose of MIRV, and had a least 1 post baseline tumor assessment or had PD or died before first assessment.~~			
Protocol Synopsis & 4.1.1. Overview and Schema	~~Patients who discontinue MIRV for reasons other than radiographic disease progression will continue with tumor assessments every 12±1 week until documentation of disease progression per RECIST 1.1 or the start of new anticancer therapy.~~ **Patients who discontinue MIRV 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 PD or the start of new anticancer therapy.**	Updated per FDA feedback	N	No
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	Made language consistent with other criteria and with rest of protocol	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 Events
	be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements			
Protocol Synopsis & 3.1.2. Exclusion Criteria	**1. Male patients.**	Clarified subject population	N	No
Protocol Synopsis, Table 2 (footnote m), 4.1.1 Overview and Schema, 9.3.2 Response Follow-up, 9.3.3 Survival Follow-up	Patients who discontinue ~~study treatment~~ **MIRV**…..	Administrative	N	No
Table 2	Added column C3	Include Cycle 3 Day 8 in Table 2	N	No
Table 2 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
Table 2 Footnote m	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 every 12(±~~1~~**3**) weeks until PD is documented per RECIST 1.1 or the patient starts new anticancer therapy. **Patients who discontinued**	Updated per FDA feedback	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	MIRV 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 week). After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.			
Table 2 Footnote o	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
Table 2 Footnote p	For "Blood samples for immunogenicity" removed footnote from C2+ column and 30-Day Follow-up column	Footnote within procedure title	N	No
6 – Section Title	PHARMACOKINETIC, ~~AND~~ IMMUNOGENICITY, **AND BIOMARKER** ASSESSMENTS	Section title updated to reflect new sections	N	No
6.4 Potential Predictive Markers of Drug Response, 6.4.1 Blood Biomarkers & 6.4.2 Tumor	**6.4 Potential Predictive Markers of Drug Response** **6.4.1 Blood Biomarkers** An exploratory endpoint of the study is to assess if soluble FRα levels in blood at Screening are predictive of response to MIRV.	New sections added to describe blood and tumor biomarker analyses	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
Biomarkers	**6.4.2 Tumor Biomarkers** Cancer is a disease driven by molecular level changes, which include mutations, DNA rearrangements and copy number changes, as well as changes in gene expression of key oncogenic pathways. Many of these changes determine or influence the aggressiveness of the disease, how the cancer responds to standard of care and/or novel therapeutic agents, and development of resistance to treatment. To evaluate how tumor molecular changes are associated with response to MIRV we will characterize the genomic profile (gene mutations, genomic translocations etc) as well as gene expression levels of archival tumor samples using a fit for purpose technologies such as next generation sequencing (NGS).			
4.1.1 Overview and Schema	Tumor response will be evaluated by the Investigator using RECIST v1.1. CT or MRI scans will be collected ~~and held~~ for sensitivity analysis by a BICR.	Clarification of Process	N	No
Table 9	**Coagulation** • **PT or INR/aPTT** Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; **INR = international normalized ratio; PT = prothrombin time**; WBC = white blood cell count	Consistency with Schedule of Assessments	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 Events
7.10. 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
7.13.1. 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 (±3 week) thereafter (Table 2) …… The central imaging vendor will assess the quality of the images. The imaging vendor will be responsible for the formation and management of the blinded independent central review (BICR) **which will be used as a sensitivity analysis of ORR and DOR by investigator**. Tumor response will be assessed by the Investigator using RECIST v1.1 (Eisenhauer 2009). Response as determined by the Investigator will be recorded in the clinical trial database. ~~If the primary endpoint (ORR by Investigator) is statistically significant at the final analysis, the BICR assessment will be used for a sensitivity analysis of ORR and DOR.~~	Provided clarification of analysis to be performed by BICR	N	No
8.2.2 Reporting a Pregnancy	…..The Sponsor must be immediately notified in the event of a pregnancy occurring during the study and through 30 days after a patient's last dose of study drug. **If a patient becomes pregnant the patient will be withdrawn from study drug. Pregnancy is not an AE unto itself and therefore should not be reported as an AE**.	Clarification for reporting a pregnancy	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 Events
9.3.2. 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 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
10. Statistical Method Rationale for the Study Population	…. The Efficacy Evaluable Population will include all patients who have received at least 1 dose of MIRV and • ~~undergone baseline tumor assessment and~~ **have measurable lesions at baseline** ~~who have measurable target lesions~~ **(per RECIST v1.1).** ~~and~~ • ~~undergone at least 1 post-baseline tumor assessment, OR~~ • ~~died or had clinical progression within 105 days after first dose of MIRV before any post-baseline tumor assessment~~	The definition of Efficacy Evaluable Population was revised following discussion with FDA regarding an acceptability of primary endpoint and definition of the appropriate evaluable population that would support a potential accelerated approval based on ORR.	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 Events
10.1 Sample Size	Primary endpoint is confirmed ORR per Investigator assessment. A sample size of **105** ~~91~~ efficacy evaluable patients achieves ~~90~~ **91**% power to detect a difference in ORR of ~~13~~ **12**% (~~25~~ **24**% vs. 12%) using a 1-sided binomial test. The target significance level (1sided α level) is 0.025. The actual significance level achieved by this test is **0.0242** ~~0.0221~~. These results assume that the ORR is 12% under the null hypothesis and ~~25~~ **24**% under the alternative hypothesis. Patients who have received at least 1 dose of MIRV but are not efficacy evaluable will be included in Safety Analysis Population. However, these patients will not be included in the Efficacy Evaluable Population and will be replaced for the purpose of sample size determination. A total of approximately ~~100~~ **110** patients will be enrolled to achieve ~~91~~ **105** efficacy evaluable patients.	The target for efficacy was revised to target a doubling of the 12% ORR in Aurelia to 24% based on feedback that 12% would be an appropriate benchmark that would need to be statistically exceeded. Based on this, the sample size was increased to enroll approximately 110 patients to obtain data from 105 efficacy evaluable patients	N	No
10.5 Interim Analysis	There are no planned interim analyses for this study. Efficacy data generated **in** ~~throughout~~ the MIRV program in patients with FRα high expression (by the PS2+ scoring method), ~~which~~ includes a 44% Investigator-assessed ORR in the 27 patients in IMGN853-0401 and a 38% Investigator-assessed ORR in the 116 patients in IMGN853-0403 (Moore 2019). **In addition, an analysis of patients derived from both Study 0401 and Study 0403 who are eligible for this study (n=70), revealed an ORR by investigator of 31.4% with a DOR of 7.8 months. Thus,** an interim analysis for futility in	Further data to support the rationale for no planned interim analysis	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 Events
	the current study in **the same or a very similar population** is not warranted.			
12.2. Investigators and Study Administrative Structure	Before initiation of the study, the Investigators 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
12.12. 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

[redacted]

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 Events
Title Page and Page Headers	Updated protocol version number and version date	Administrative	N	N
Investigator Statement	Updated Investigator Statement to include reference to Ventana Assay: I have received and read the Investigator Brochure for mirvetuximab soravtansine **which also contains information related to the investigational VENTANA FOLR1 (FOLR1-2.1) CDx Assay.** I have read the ImmunoGen Protocol IMGN853-0417 and agree to conduct the study as outlined and in conformance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) and applicable regulatory requirements. **I acknowledge that protocol IMGN853-0417 utilizes an investigational in vitro diagnostic, VENTANA FOLR1 (FOLR1-2.1) CDx Assay, to determine the FRα expression status of my patient's tumor specimen, an inclusion criterion for the study. I acknowledge that I am responsible for procurement of an epithelial ovarian cancer tumor specimen for each patient and providing the specimen to a diagnostic laboratory in Belgium for analysis of FRα expression, the result of which will be used to determine the patient enrollment eligibility for Study IMGN853-0417.**	Per discussion with BfArM on 08June 2020; Investigator statement to be updated to include acknowledgement of the use of an investigational IVD and the responsibilities of the investigator as it relates to the investigational IVD.	N	N

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
4.1.1. Overview and Schema	Added reference to Appendix F: Ventana Assay Diagnostic Protocol and Plan	Administrative	N	N
Appendix F	New Appendix added APPENDIX F. DIAGNOSTIC PROTOCOL TO DETERMINE FRα EXPRESSION LEVEL	Per discussion with BfArM on 08June 2020; Sponsor to amend diagnostic plan to the protocol for Study 0417.	N	N

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 Events
Schedule of Events; Footnote i	[i] For women of childbearing potential (WCBP), a urine or serum pregnancy test must be performed within the 4 days prior to D1 of each cycle and at the 30-Day Follow-up visit. **After the 30-day follow-up visit it is recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV**	Added recommendation to perform monthly pregnancy test in WCBP for 3 months after last dose of MIRV	N	No
Section 5.8.6 Methods of Contraception	**5.8.6 ~~Acceptable~~ 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. **A Woman of Childbearing Potential is a woman who is considered fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.** **The following birth control methods may be considered highly effective (failure rate of less than 1% per year):** **~~5.8.6.1 Single Method~~** **~~One of the following is acceptable:~~** • **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:**	Revise contraception language to be in accordance 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 Events
	– **Oral** – **Intravaginal** – **Transdermal** • **Progestogen-only hormonal contraception associated with inhibition of ovulation:** – **Oral** – **Injectable** – **Implantable** • Intrauterine Device (IUD) • **Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • Vasectomi**sed**~~y of a female patient's male~~ partner • **Sexual abstinence** ~~**5.8.6.1.2 Combination Method**~~ ~~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)~~			

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	• ~~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~~ Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Board/Independent Ethics Committee (IECs /IRBs). Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods, etc) and withdrawal are not acceptable methods of contraception. If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region. Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study WCBP must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days before the			

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	initiation of study medication for oral contraception) through the duration of study treatment and for at least 3 months after the last dose of MIRV. If there is any question that a WCBP will not reliably comply with the requirements for contraception, that patient should not be entered into the study.			
Section 7.11 Pregnancy Screen	All WCBP will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test not more than 14 days before the first dose of study drug and urine or serum pregnancy tests within 4 days of each study drug administration and at the 30-Day Follow-up visit. **After 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. Pregnancy tests must be negative for the patient to be enrolled and to continue to receive the study drug (Table 2).If a patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Sponsor must be informed immediately (Section 8.2.2) and the patient will be withdrawn from study drug. See Section 8.2.2 for more details.	Added recommendation to perform monthly pregnancy test in WCBP for 3 months after last dose of MIRV	N	No

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 Events
Global	Minor changes in spelling/use of abbreviations revised	Minor revisions throughout to improve document flow, readability, and consistency.	N	No
Title Page, Protocol Synopsis Title of Study	SORAYA: A Phase 3, Single Arm Study of Mirvetuximab Soravtansine 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	1 (18 December 2019) **1.1 (18 June 2020) Germany** **1.2 (22 July 2020) Czech Republic, Germany, and United Kingdom** **2.0 (XX September 2020)**	Addition of Amendment numbers and dates for comprehensiveness.	N	No
Protocol Synopsis Studies Period	• ~~First patient enrolled: February 2020~~ • ~~Last patient last visit: December 2021~~	Enrollment details removed for consistency with other protocols within the MIRV program.	N	No
Protocol Synopsis Study Design, 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 the first 36 weeks then every 12 **weeks** ~~(~~± 3 weeks) until disease progression, death, ~~or~~ the start of new	Ending of tumor assessment details revised to include 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 Events
	anticancer therapy, **or patient's withdrawal of consent** (whichever occurs first).			
Protocol Synopsis Study Design, 4.1.1. Overview and Schema, 9.3.3. Survival Follow-up	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)~~. All patients who discontinue MIRV will be followed for survival every 3~~± 1~~ months **(± 1 month)** until death, lost to follow-up, withdrawal of consent for survival follow-up, or end of study (EOS) (whichever comes first).	Discontinuation of MIRV and assessment/follow-up details revised for accuracy.	N	No
Protocol Synopsis Inclusion Criteria, 3.1.1 Inclusion Criteria	3. Patients must have platinum-resistant disease ~~(defined as progression within 6 months from completion of a minimum of 4 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 of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum** ~~a.~~**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~~; patients who are platinum refractory during front-line treatment are excluded (see exclusion criteria)~~	Inclusion criteria updated providing further details regarding previous use of platinum-based therapies, disease progression, and hematological parameters to provide clarity.	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 Events
	Note: Patients who are platinum refractory during front-line treatment are excluded (see exclusion criteria) 4. Patients must have progressed **radiographically** on or after their most recent line of anticancer therapy ~~Note: Progression must be determined radiographically and/or by CA-125 GCIG progression 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 c. Hemoglobin ≥ 9.0 g/dL **without packed red blood cell (PRBC) transfusion in the prior 21 days**			
Protocol Synopsis Exclusion Criteria, 3.1.2 Exclusion Criteria	3. 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 7. 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)	Exclusion criteria updated providing further details regarding non responders to platinum-based therapies, infections and testing requirements, and drug hypersensitivity language added to provide clarity and a	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 Events
	b. Human immunodeficiency virus (HIV) infection c. ~~Cytomegalovirus~~**Active cytomegalovirus** infection d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to the first dose of MIRV **Note: Testing at screening is not required for the above infections unless clinically indicated** **19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients**	more comprehensive study exclusion.		
Schedule of Assessments	Table 2 updated as follows: • Pre-screening column added • Pre-screening Informed Consent row added • FFPE archived tumor tissue and/or new biopsy timepoint moved to Pre-screening • Blood sample for Biomarkers timepoint added at Pre-screening • CA-125 row and timepoints/details/associated footnotes updated • Record AE/SAEs and concomitant medications row and timepoints/details/associated footnote "o" added • Footnote "d" updated: Testing for FRα expression is required for all patients. Those who do not have archival tumor tissue to submit will be required to undergo procedures to obtain a new biopsy using a low-risk, medically routine procedure during the	Schedule of Assessments revised to accurately reflect anticipated assessments throughout the study.	Y	Yes

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	~~Screening~~**Pre-screening** period to confirm eligibility. • Footnote "i" updated: For women of childbearing potential (WCBP), a urine or serum pregnancy test must be performed within the 4 days prior to D1 of each 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. • Footnote "m" updated: If a patient discontinues before documentation of PD, a tumor assessment and CA-125 will be assessed at the EOT or 30-Day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed every 12 (± 3) weeks until PD is documented per RECIST 1.1 or the patient starts new anticancer therapy. Patients who discontinue MIRV 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 PD ~~or~~**, death,** the start of new anticancer therapy**, or patient's withdrawal of**			

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	consent (whichever occurs first). • Footnote "n" updated: CA-125 will be measured ~~prior to dosing on D1~~**at the time** of every ~~cycle~~**tumor assessment (± 4 days)** (responses will be confirmed according to GCIG criteria Appendix C) • Footnote "o" added: **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.** • Footnote "r" updated: Survival follow-up assessments will occur every 3~~±1~~ months **(±1 month)** until death, the patient is lost to follow-up or withdrawal of consent for survival follow-up, or EOS (whichever comes first). These assessments may be conducted by telephone. Information on the start of new anticancer therapy (including start date, therapy type/name, and response on treatment) should be collected. Additional survival follow-up calls may occur periodically if needed for regulatory requests or at time of database lock for either primary or final analysis.			
1.6.3 Conclusion	**The available safety and efficacy data from the 455 patients treated with single-agent mirvetuximab**	Conclusion section added to summarize the	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 Events
	soravtansine in previous clinical studies are consistent with a positive risk benefit assessment. The potential benefit of the anti-tumor activity demonstrated by mirvetuximab soravtansine 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.	risk benefit of mirvetuximab soravtansine.		
5.1.3 Mirvetuximab Soravtansine Study Treatment Compliance, 5.4.3.1.1 Preparation	**If necessary,** MIRV from ~~two~~ different drug lots ~~cannot~~**may** be mixed in a single-dose administration. 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
Section 5.2. 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
5.5.1. Treatment Criteria	In the absence of a TEAE that requires dose modification **(as specified in the management guidance for a particular toxicity, see Section 5.5.1.1.),** a patient must meet the following criteria to receive MIRV at any cycle:	Reference link and language to management guidance of toxicities added for improved clarity.	N	No
5.5.1.1 Mirvetuximab	Footnote "a": Failure to meet retreatment criteria within 1	Language added to	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 Events
Soravtansine-Related Adverse Events (Table 3), 5.5.3 Monitoring of Noninfectious Pneumonitis (Table 6), 5.5.6. Discontinuation of Mirvetuximab Soravtansine Due to Toxicity	cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation~~.~~ **unless otherwise specified in the management guidance for a particular toxicity.**	provide clarity of criteria for drug discontinuation per toxicity management guidance.		
5.5.2.2. 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 5 for details). **If ocular symptoms last longer than 28 days, resumption of MIRV, with or without dose reduction, 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 continuing drug with ocular symptoms.	N	No
5.5.2.2. Management and Dose Modification Guidelines (Table 5)	Table title revised: Management of Ocular ~~Disorders~~**Symptoms** Heading revised: Guidelines for MIRV Dose Modifications* Severity Grade: Grade 2 ~~Symptoms~~ Guidelines for MIRV Dose Modifications (Grade 2):	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 Events
	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" removed: ~~Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment related toxicity will result in treatment discontinuation.~~			
5.5.4. Management of Electrolytes Imbalance	Section moved below Table 6	Content moved to improve document flow.	N	No
5.5.5. Potential Infusion-related Reactions	Section moved below Table 6	Content moved to improve document flow.	N	No
5.5.6. Discontinuation of Mirvetuximab Soravtansine Due to Toxicity	MIRV should be discontinued in the case of the following treatment-related events: • ~~≥~~Grade ≥ 3 cardiac event (excluding Grade 3 hypertension) **(Section 5.5.1.1)** • **Grade ≥ 3 pneumonitis event (Section 5.5.3)** • Non-hematologic events of Grade 4 severity **(Section 5.5.1.1)**	Treatment-related adverse events triggering the discontinuation of MIRV updated to include pneumonitis and ocular events as well as reference links	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 Events
	• **Ocular events of Grade 4 severity (Section 5.5.2.2)**	provided for improved document flow.		
5.6.3. Withdrawal of Consent	"legal guardian" replaced with "legally authorized representative" throughout section.	Updated for clarity and consistency.	N	No
5.6.4 Lost to Follow-Up, 12.1.2. Patient Information and Consent	"participant" replaced with "patient" throughout section.	Updated for clarity and consistency.	N	No
5.7 Period of Observation	Short-term follow-up for patients who discontinue study drug without documented PD will be followed per RECIST 1.1 every ~~12±1 weeks~~ **6 weeks (± 1 weeks) from C1D1 for the first 36 weeks then every 12 weeks (± 3 weeks)** until PD, until the patient starts new anticancer treatment, the patient dies, or the patient withdraws consent, whichever comes first. All patients will be followed every 3~~± 1~~ months **(± 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
5.8.3. 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
5.8.6. Methods of	Title Change: ~~Acceptable~~ Methods of Contraception	Women of childbearing	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 Events
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. **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.**	potential defined for clarity.		
5.8.6.1 Single Method	Section revised merged into parent section 5.8.6: ~~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 Events
	• ~~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			
5.8.8. 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**	CYP3A4/MRD1 interaction language updated for accuracy.	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 Events
	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** 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).			
6.3. 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**	Analysis methods of FRα expression updated as well as PS2+ scoring language added for clarity and accuracy.	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 Events
	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.			
7.1 Informed Consent	**Patients will sign a pre-screening ICF to allow testing of fresh or archival tumor tissue by the assay required for study inclusion. 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
7.10.1 Clinical Laboratory Panels	Table 9 revised: • BUN **or Urea** • ~~Carbon dioxide~~ • Urinalysis **(Screening only)** • Coagulation **(Screening only)**	Updated for consistency in scheduled clinical laboratory tests.	N	No
7.11. Pregnancy Screen, 8.2.2. Reporting a Pregnancy	All WCBP will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test ~~not more than 14~~**within 4** days before the first dose of study drug and urine or serum pregnancy tests within 4 days of each study drug administration 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.**	Language regarding monthly pregnancy test following last MIRV dose added for improved safety.	N	No
7.13.1. Radiographical	Radiographic tumor evaluation by CT or MRI of chest, abdomen, and pelvis will be performed within 28 days before	Radiographical imaging timing and details	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 Events
Imaging	first dose of study drug and every 6 weeks (±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (± **3 weeks) thereafter (**Table 2~~3 week) thereafter ().~~. **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. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.**	further described for improved clarity.		
7.13.2. CA-125	Serum CA-125 assessments will be performed within 14 days ~~prior to the first dose of study drug, prior to dosing on Day 1 of every subsequent cycle~~**and at each radiologic tumor assessment (± 4 days)** (Table 2).	Serum CA-125 assessment language revised for accuracy.	N	No
8.1. Recording Adverse Events and Serious Adverse Events, 8.1.1.1. Adverse Events, 8.2.1. Reporting Serious Adverse Events	~~However,~~ **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 of the pre-screening informed consent (if one is utilized) until the time of signing of the main study informed consent, or until the patient is determined to be a screen failure. All AEs and SAEs, regardless of causality, will be captured after the main study ICF has been signed.**	Criteria for capturing and recording AEs/SAEs during the pre-screening and main study added for clarity.	N	No

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
9.3.2. 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 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks ~~(± 1 week)~~.	Language distilled regarding discontinuation of MIRV for reasons other than PD to simplify and improve clarity.	N	No
11.1. 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

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
12.1.1. 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
12.1.2. Patient Information and Consent	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 must** be recorded and dated in the **patient's** source document ~~that consent was given~~.	Language re-worked for improved readability and clarity.	N	No
12.4. 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 design and~~	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 Events
	~~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 consistency 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 consistency 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**			

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
	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 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.**			
12.8 End of Study	EOS will occur 12 months after the primary analysis for ORR. ~~Patients~~**If patients are** still receiving clinical benefit from MIRV 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 SAEs, dosing information) until they are no longer benefiting** or **patients will be given the option to rollover to** a long-term extension study .	Language and details revised for improved clarity on continuing study treatment if receiving clinical benefit.	N	No
12.14 Retention of Data	Essential documents will be retained until the following requirements are met:	Details regarding retention of data updated for accuracy	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 Events
	• 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**,	and clarity.		
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 assessments will be performed as indicated in Table 2**~~CA-125 measurements should be 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: 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~~ **3 weeks**) thereafter.	Language revised for consistency with Schedule of Assessments.	N	No

[redacted]

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 Events
Title Page and Page Headers	Updated protocol version number and version date	Administrative	N	N
Investigator Statement	Updated Investigator Statement to include reference to Ventana Assay: I have received and read the Investigator Brochure for mirvetuximab soravtansine **which also contains information related to the investigational VENTANA FOLR1 (FOLR1-2.1) CDx Assay.** I have read the ImmunoGen Protocol IMGN853-0417 and agree to conduct the study as outlined and in conformance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) and applicable regulatory requirements. **I acknowledge that protocol IMGN853-0417 utilizes an investigational in vitro diagnostic, VENTANA FOLR1 (FOLR1-2.1) CDx Assay, to determine the FRα expression status of my patient's tumor specimen, an inclusion criterion for the study. I acknowledge that I am responsible for procurement of an epithelial ovarian cancer tumor specimen for each patient and providing the specimen to a diagnostic laboratory in Belgium for analysis of FRα expression, the result of which will be used to determine the patient enrollment eligibility for Study IMGN853-0417.**	Per discussion with BfArM on 08June 2020; Investigator statement to be updated to include acknowledgement of the use of an investigational IVD and the responsibilities of the investigator as it relates to the investigational IVD.	N	N

[redacted]

Section	Key Change(s)	Rationale	Substantial Change (Y/N)	Potential Impact on Patient Safety, Study Conduct, or Expectedness of Suspected Serious Adverse Events
4.1.1. Overview and Schema	Added reference to Appendix F: Ventana Assay Diagnostic Protocol and Plan	Administrative	N	N
Appendix F	New Appendix added APPENDIX F. DIAGNOSTIC PROTOCOL TO DETERMINE FRα EXPRESSION LEVEL	Per discussion with BfArM on 08June 2020; Sponsor to amend diagnostic plan to the protocol for Study 0417.	N	N

[redacted]

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

A list of investigators and other important participants in the study is presented in Table 1 and Table 2. A summary of the number of patients enrolled at each site and in each region is provided in Table 14.1.1.1. The list of vendors and subcontractors used in the study is presented in Table 3. A list of committee charters and associated meeting minutes for this study is presented in Table 4.

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[a]	Sub-Investigator Names
003	[redacted]	Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114 United States	[redacted]
008		Tennessee Oncology, PLLC, 250 25th Avenue North, Suite 100, Nashville, TN, 37203 United States	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
	[redacted]		[redacted]
009		University of Kansas Hospital 2650 Shawnee Mission Parkway Westwood, KS 66205 United States	

[redacted]

Site No.[a]	[redacted]	Site Address[a]	[redacted]
010		Dana-Farber Cancer Institute (DFCI) 450 Brookline Ave. Boston MA 02215 United States	
012		Sarasota Memorial Health Care System 1700 S. Tamiami Trail Sarasota FL 34239 United States	
023		Center of Hope 5465 Reno Corporate Dr. Reno Nevada 89502 United States	
026		MSKCC 1275 York Avenue New York NY 10065 United States	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
	[redacted]		[redacted]

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
	[redacted]		[redacted]
028		Dr. Sudarshan K. Sharma, Ltd. 121 N. Elm Street Hinsdale IL 60521 United States	
032		Icahn School of Medicine at Mount Sinai 1 Gustave L. Levy Place Box 1170, New York, NY 10029, United States	
054		Kadlec Clinic Hematology and Oncology 7360 W. Deschutes Ave. Kennewick WA 99336 United States	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
068	[redacted]	The Blavatnik Family – Chelsea Medical Center at Mount Sinai 325 West 15th Street New York NY 10011 United States	[redacted]
071		Texas Oncology-Austin Central (main) 6204 Balcones Dr. Austin TX 78731 United States	
072		Texas Oncology - Fort Worth Cancer Center 500 South Henderson Street Fort Worth TX 76104 United States	
074		Arizona Oncology Associates, PC - HAL (main) 2222 E. Highland Avenue, Suite 400 Phoenix AZ 85016 United States	
079		Women's Cancer Center 606 W. 12th Avenue Covington LA 70433 United States	
081		MidAmerica Division, Inc., c/o Research Medical Center	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
	[redacted]	2340 E. Meyer Blvd Kansas City Missouri 64132 United States	[redacted]
126		Holy Name Medical Center 718 Teaneck Road Teaneck NJ 7666 United States	
138		Texas Oncology-McAllen South Second Street 1901 South 2nd St. McAllen TX 78503 United States	
148		Texas Oncology-Sugar Land 1350 First Colony Blvd. Sugar Land, TX 77479 United States	
151		Maryland Oncology Hematology, P.A. 9905 Medical Center Drive, Suite 200 Rockville MD 20850 United States	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
168	[redacted]	Florida Cancer Specialist Research 1309 N. Flagler Drive West Palm Beach FL 33401 United States	[redacted]
172		University of Wisconsin Carbone Cancer Center 600 Highland Avenue Madison, WI 53792 United States	
174		California Cancer Associates (cCare) 7130 N. Millbrook Ave. Fresno CA 93720 United States	
177		City of Hope 1500 E. Duarte Road Bldg 182, 2nd Floor, Rm 2251 Duarte CA 91010 United States	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
178	[redacted]	Northside Hospital, Inc. 960 Johnson Ferry Rd NE, Suite 130 Atlanta, GA 30342 United States	[redacted]
179		Stanford Sch of Med 900 Blake Wilbur Drive Palo Alto CA 94304 United States	
201		UZ Leuven Herestraat 49 Leuven 3000 Belgium	
203		UZ Gent Corneel Heymanslaan 10 Gent, Belgium 9000	
205		CUSL 10, Avenue Hippocrate Bruxelles 1200 Belgium	
206		Centre Hopsitalier de l'Ardenne Avenue de Houffalize 35, Libramont Luxembourg 6800 Belgium	
207		CHU UCL Namur Ste Elisabeth Place Louise Godin 15 Namur B5000 Belgium	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
301	[redacted]	MD Anderson Cancer Center C/ Arturo soria nº 270 Ensayos Clínicos - Planta Baja Madrid 28033 Spain	[redacted]
302		Hospital Vall Hebrón P. Vall d´Hebron 119-129 planta 12 Edificio maternal Barcelona BCN 8035 Spain	
304		Hospital La Paz Paseo Castellana 261 Madrid Castellana 28046 Spain	
309		ICO Hospitalet Av. Gran Via 199-203. Hospital Duran i Reynals. Edificio Principal. Planta 2. L'Hospitalet de Llobregat Barcelona 8908 Spain	
310		Institut Català d'Oncologia Badalona Hospital Universitari Germans Trias i Pujol Ctra. de Can Ruti, Cami de les escoles, s/n Primera planta Barcelona 8916 Spain	
311		Institut Català d'Oncología de Girona Avda Francia s/n Sotano 2 Girona 17007 Spain	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
312	[redacted]	Complejo Hospitalario Universitario A Coruna C/Xubias De Abaixo, 84, A Coruña 15006 Spain	[redacted]
313		IOR-Hospital Quiron Dexeus c/ sabino arana 5-19 planta -1 consulta - 1.1 Barcelona 08028 Spain	
317		Hospital Clínico Universitario San Carlos Pabellón B, ala sur. Planta Baja Madrid 28040 Spain	
320		Hospital Reina Sofia de Cordoba Avda Menendez Pidal, s/n, Sótano - 1 Serv. Córdoba 14004 Spain	
321		Hospital Clinico de Valencia Avda Blasco Ibañez 17 Valencia 46010 Spain	
322		Hospital Clínico Universitario Virgen de la Arrixaca Ctra. Madrid - Cartagena, s/n 4ª Planta El Palmar Murcia 30120 Spain	
332		Clinica Universidad de Navarra Calle del Marquesado de Santa Marta nº1 Planta -2 Madrid 28027 Spain	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
375	[redacted]	Complex Oncology Center 86 Demokratsia Blvd. Burgas 8000 Bulgaria	[redacted]
386		SPZOZ MSWIA Z WMCO W OLSZTYNIE Aleja Wojska Polskiego 37 Budynek A, biuro badań klinicznych, pokój nr 4 Olsztyn Warmińsko-mazurskie 10-228 Poland	
390		Instytut Centrum Zdrowia Matki Polki ul. Rzgowska 281/289 Klinika Onkologii, Instytut Centrum Zdrowia Matki Polki Łódź łódzkie 93-338 Poland	
393		Specjalistyczna Przychodnia Lekarska Medicus Ul. Lompy 4 Chorzow Silesia Province 41-500 Poland	
490		Sheba Medical Center derech sheba 2 ramat gan 52621 Israel	
491		Meir Medical Center Tchernichovsky St 59 Kefar Sava 4428164 Israel	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
492	[redacted]	Hadassah Ein Kerem Medical center Kiryat Hadassah Jerusalem 9112001 Israel	[redacted]
494	[redacted]	Ziv Medical Center Derech HaRambam Building 1, Floor 4, Room 531 Safed 13100 Israel	[redacted]
495	[redacted]	Rambam Medical center HaAliya HaShniya St 8 PO BOX 9601 - Sami Offer main building Floor -1 Haifa 3109601 Israel	[redacted]
502	[redacted]	IEO Istituto Europeo di Oncologia Via Ripamonti, 435 Milano 20141 Italy	[redacted]
504	[redacted]	Fondazione Policlinico Universitario A. Gemelli IRCCS stanza 1022 PIANO 10 ALA O Largo Agostino Gemelli 8 Roma 00168 Italy	[redacted]
508	[redacted]	Policlinico S. Orsola-Malpighi Viale Ercolani 4/2 Bologna 40138 Italy	[redacted]
510	[redacted]	Istituto Nazionale Tumori- G. Pascale Via Mariano Semmola, 53 Napoli 80131 Italy	[redacted]

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
518	[redacted]	Istituto Oncologico Candiolo Strada Provinciale 142-Km 3,95 Candiolo (Torino)10060 Italy	[redacted]
519		Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Piazzale Spedali Civili, 1 U. O. Ginecologia-oncologica Brescia 25123 Italy	
524		Osperdale Cannizzaro di Catania Via Messina, 829 Oncologia Medica Padiglione L7 Catania 95126 Italy	
700		Bon Secours Hospital College Road Cork, Ireland	
701		Mater Misericordiae University Hospital 47 Eccles Street Dublin Leinster 7 Ireland	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
702	[redacted]	University Hospital Waterford Dunmore Rd Cancer Research Department Waterford X91 ER8E Ireland	[redacted]
707		Cork University Hospital Wilton Cork Munster T12DC4A Ireland	
708		Beaumont Hospital Beaumont Road Dublin 9 Ireland	
709		St James's Hospital Dublin Leinster D8 Ireland	
802		Všeobecná fakultní nemocnice v Praze Apolinářská 18 Gynekologicko-porodnická klinika 1. LF UK a VFN Praha 2 Prague 128 51 Czech Republic	
825		Universitätsmedizin Mannheim Frauenklinik, Haus 1, Ebene 1 Theodor-Kutzer-Ufer 1-3, Mannheim Baden-Württemberg 68167 Germany	

[redacted]

Site No.[a]	Investigator Name	Site Address[a]	Sub-Investigator Names
829	[redacted]	KEM Evang. Kliniken Essen Mitte Henricistr. 92 Gyon Ambulanz Essen 45136 Germany	[redacted]
926		ICON Cancer Care Level 1, 22 Cordelia Street South Brisbane, QLD, Australia 4101	
932		St John of God Subiaco Hospital 12 Salvado Road, Subiaco, WA, Australia 6008	
934		Peninsula and South Eastern Haematology and Oncology Group Suite 7, Level 3, North Building Frankston, VIC, Australia 3199	

[a] Site list includes all sites that screened or enrolled patients.
[b] At time of clinical study (updated when available)

[redacted]