Mirvetuximab Soravtansine: IMGN853 (MIRV)

Indication

Platinum Resistant Ovarian Cancers ****Only as part of the SL03-OHD-105 Clinical Trial****

Mirvetuximab Soravtansine: IMGN853 (MIRV) is an antibody-drug conjugate targeting folate receptor α (FRα) that delivers the tubulin-targeting maytansinoid DM4 directly to the tumour.

Regimen Details

DRUG	FLUID	CONCENTRATION	TIME
Mirvetuximab Soravtansine: IMGN853 (MIRV) 6mg/kg (Adjusted Ideal Body Weight)	5% Dextrose	1mg/ml (if <200mg) 2mg/ml (if >200mg)	Variable (see below)

Cycle Frequency

Every three weeks

Number of Cycles

Ongoing

Administration

IMGN853 (MIRV) is administered as an IV infusion in 5% Dextrose. The dose is made up by the aseptic team according to adjusted ideal bodyweight to 1-2mg/ml depending on total dose required.

The IMGN853 (MIRV) infusion should be administered via a 0.2 micron filter at a rate of 1 mg/min. After a continuous 30 minutes of infusion, the rate can be increased to 3 mg/min, if well tolerated. If tolerated after a continuous 30 minutes of infusion at 3 mg/min, the infusion rate may be increased to 5 mg/min. **Subsequent infusions may be delivered at the highest tolerated rate.**

Initial rate	After 30 mins (if tolerated)	After further 30 mins (if tolerated)
1mg/min	3mg/min	5mg/min

Patients should be observed for hypersensitivity reactions during infusion. After the infusion the IV line should be flushed with 5% Dextrose to ensure delivery of the full dose.

Patients will remain in the chemotherapy unit under observation for 1 hour after each IMGN853 (MIRV) infusion. For the first infusion though they will be transferred to the LCRF for a further 3 hours of observation.

Pre-Medication

Dexamethasone 10mg IV, Chlorphenamine 10mg IV, Ondansetron 8mg IV, Paracetamol 1000mg IV should be given before each infusion. This should start at -45mins and be completed by -30mins prior to infusion.

Observations

Blood pressure, Heart Rate, Temperature, Pulse Oximetry, and Respiratory Rate will be collected at baseline within 60 minutes before starting the IMGN853 (MIRV) infusion. On infusion, vital signs will be collected at 30 mins, 60mins and then hourly (more frequently if infusion reaction occurs). Post infusion vital signs should be collected if clinically indicated (eg if potential infusion-related reaction has occurred).

Emetogenicity

Mild-moderate (Grade 1-2 mostly reported). Patient to be discharged on PRN Metoclopramide or similar antiemetic.

Additional supportive medication

Subjects receiving IMGN853 (MIRV) in other trials have reported ocular effects including vision blurred, dry eye, corneal epithelial microcysts, corneal erosion, eye irritation, eye pain, limbal stem cell deficiency, visual impairment, keratitis, and punctate keratitis. A corticosteroid eye drop and a lubricating artificial tears eye drop will be used by the subjects at home (this is prescribed on iQemo). Unless directed otherwise by the treating physician, the corticosteroid eye drop should be administered six times per day on Days -1 (day before infusion) to Day 4 and four times per day (QD) on Day 5 to Day 8 of each cycle during the study.

NB – Corticosteroid eye drops to be prescribed before the Chemo visit.

Attention David Barber—to help you write prescription chart

Dexamethasone 10mg
Chlorphenamine 10mg
Ondansetron 8mg
Paracetamol 1000mg
IMGN853 (MIRV) 6m/kg AIBW
Observations (min 1 hour on Chemotherapy Unit)
TTO:
Ondansetron 1 day
Metoclopramide 1 day
Corticosteroid Eye drops; Administer one drop of ophthalmic topical steroids in each eye 6 times daily starting the day prior to each infusion until day 4; then administer one drop in each eye 4

times daily for days 5-8 of each cycle. Study protocol recommends the use of 1% Prednisolone (PredForte or equivalent if not available).
Preservative free Lubricating Eye drops: The use of lubricating eye drops (eg Minims lubricating drops) at least four times daily and as needed is recommended during treatment. Instruct patients to use lubricating eye drops. They must wait at least 15 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops.

Consider additional premedications including corticosteroids the day prior to IMGN853 (MIRV) administration for patients who experienced IRRs.

Extravasation

Pain and erythema may be noted. Management of extravasation is symptomatic.

Investigations – pre first cycle

Full blood count

Urea & Electrolytes

Liver function

Serum Magnesium

Thyroid function

Bone Profile

Random Glucose

Ca125

Ophthalmic exam including visual acuity and slit lamp exam (Arranged as part of trial screening)

Patients are advised to avoid contact lenses and use UVA/UVB sunglasses

Investigations – pre subsequent cycles

Full blood count

Urea & Electrolytes

Liver function

Bone Profile

Serum Magnesium

Random Glucose

Ca125

Ophthalmic exam including distant visual acuity, best corrected visual acuity and slit lamp exam as per protocol, every other cycle for the first 8 cycles, and as clinically indicated

Standard limits for administration to go ahead

Neutrophil count must be ≥1.5x10^9/L

Platelet count must be ≥100x10^9/L

Hb >90 g/L

Dose Modifications

The study team should always be involved in dose modifications please.

Dose reduction requires reducing the dose by 1mg/kg unless this would take it below 4mg/kg in which case IMGN853 (MIRV) should be discontinued. See trial protocol for full details. Dose reduction may be required in the following circumstances (graded where applicable by CTCAE v5.0 criteria):

Neutropenia <1.5x10^9/L

Thrombocytopenia <100x10^9/L

Nausea & Vomiting Grade 3+ (despite adequate antiemetic support)

Diarrhoea Grade 3+

Ocular disorders

Non-infectious Pneumonitis

Infusion-related Reactions

Other Adverse events of Grade 3+

General Dose Modification Guidance

Grade (Severity)	**Guideline for dose modification**
Grade 3	Hold drug until resolved to Grade ≤1, then resume at one lower level For any Grade 3 hepatic toxicity that does not resolve to baseline within 7 days, an abdominal CT scan must be performed to assess whether it is related to progressive disease.
Grade 4	Permanently discontinue

Corneal Adverse Reactions

Grade (Severity)	**Management**	**Guideline for dose modification**
Grade 1 (nonconfluent superficial keratitis)	Complete eye exam as outlined in SOA (Section 6.2). Patients should have weekly symptomatic ocular assessments to monitor for worsening symptoms and repeat eye examinations as needed.	Continue IMGN853 (MIRV) dosing.
Grade 2 (confluent superficial keratitis, a cornea defect, or 3-line or more loss in best corrected visual acuity)	Complete eye exam as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade ≤1 or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Hold IMGN853 (MIRV) dosing until AE has resolved to Grade ≤1. Subjects with corneal adverse reactions lasting Grade 1 persist >28 days, permanently discontinue IMGN853 (MIRV).
Grade 3 (corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse)	Complete eye exam as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade ≤1 or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Hold IMGN853 (MIRV) dosing. Subjects may be allowed to resume IMGN853 (MIRV) at one lower dose level after AE has resolved to Grade ≤1 within 28 days.
Grade 4 (corneal perforation	Complete eye exam as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade ≤1 or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Permanently discontinue IMGN853 (MIRV) dosing.

Ocular Adverse Events

Grade (Severity)	Management	Guideline for dose modification
Grade 1	Complete eye exam as outlined in protocol	Continue IMGN853 (MIRV) dosing
Grade 2	Complete eye exam as outlined in the study protocol. Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the Investigator until the symptoms resolve to Grade ≤1 or are deemed to be irreversible by the Investigator.	Hold IMGN853 (MIRV) dosing until AE has resolved to Grade 1 or better. Subjects with ocular symptoms lasting <14 days may be allowed to resume IMGN853 (MIRV) at the same dose level. Subjects with ocular symptoms lasting 14-28 days may resume IMGN853 (MIRV) at one lower dose level. Recurrence of Grade 2 toxicity on subsequent cycles despite best supportive care will require a IMGN853 (MIRV) dose reduction of one level.
Grade 3	Complete eye exam as outlined in the study protocol. Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the Investigator until the symptoms resolve to Grade ≤1 or are deemed to be irreversible by the Investigator.	Recurrence of Grade 3 toxicity on subsequent cycles despite best supportive care will require a IMGN853 (MIRV) dose reduction of one dose level.
Grade 4	Complete eye exam as outlined in the study protocol. Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the Investigator until the symptoms resolve to Grade ≤1 or are deemed irreversible by the Investigator.	Permanently discontinue IMGN853 (MIRV).

Noninfectious Pneumonitis

Grade (Severity)	Management	Guideline for dose modification

Grade 1	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• Continue dosing in asymptomatic patients and monitor closely.
Grade 2	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	• Hold dosing until symptoms resolve to Grade ≤1. • IMGN853 (MIRV) may be resumed at same dose level or one dose level lower after discussion with the Sponsor.
Grade 3 Grade 4	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	• Permanently discontinue IMGN853 (MIRV).

Peripheral Neuropathy

Grade (Severity)	**Guideline for dose modification**
Grade 2	Withhold dose until Grade ≤1, then reduce by one dose level
Grade 3 Grade 4	Permanently discontinue

Adverse Events

Infusion-related reactions, diarrhoea, vision blurred, aspartate aminotransferase increased, nausea, vomiting, headache, asthenia, dry eye, keratopathy, decreased appetite, ALT increased, alkaline phosphatase increased, abdominal pain, fatigue, constipation, vomiting, visual acuity reduced, peripheral neuropathy, pneumonitis, dehydration, gastroenteritis, pneumonia, UTI, organising pneumonia, leukopenia, neutropenia, anaemia, lymphopenia, reduced albumin, reduced magnesium.

• IMGN853 (MIRV) can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis. Ocular toxicities are most commonly seen around the time of the third cycle. Withhold IMGN853 (MIRV) for ocular toxicities (other than nonconfluent superficial keratitis) until improvement and resume at the same or reduced dose. Discontinue IMGN853 (MIRV) for Grade 4 ocular toxicities.

• Pneumonitis: Withhold IMGN853 (MIRV) for persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue IMGN853 (MIRV) for Grade 3 or 4 pneumonitis.

• Peripheral Neuropathy: Monitor patients for new or worsening peripheral neuropathy. Withhold dosage, dose reduce, or permanently discontinue IMGN853 (MIRV) based on the severity of peripheral neuropathy.

• Embryo-Foetal Toxicity: IMGN853 (MIRV) can cause foetal harm. Patients who are pregnant or who plan to become pregnant or breast feed while receiving treatment are excluded from the SL03-OHD-105 Clinical Trial.

• Patients may develop Cytokine Release Syndrome (CRS) as part of this treatment. Please see detailed protocol for the management of this condition.

Signs & Symptoms of progressive malignancy /Less likely to be adverse events

Intestinal obstruction, pleural effusion, ascites, metastatic neoplasm

Significant drug interactions

IMGN853 (MIRV) active ingredient is a CYP3A4 substrate. Concomitant use of IMGN853 (MIRV) with strong CYP3A4 inhibitors may increase exposure which may increase the risk of adverse reactions. Closely monitor patients for adverse reactions when used concomitantly with strong CYP3A4 inhibitors.

Patients are advised to avoid grapefruit juice.

Renal Impairment

No dosage adjustment is recommended for patients with mild to moderate renal impairment

(CrCl 30 to 90 mL/min). The effect of severe renal impairment (CrCl 15 to < 30 mL/min) or end-stage renal disease on IMGN853 (MIRV) is unknown. For the SL03-OHD-105 Clinical Trial a CrCl >30 mL/min is required for eligibility.

Hepatic Impairment

No dosage adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST). Avoid use of IMGN853 (MIRV) in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN). For the SL03-OHD-105 Clinical Trial ALT/AST ≤3x ULN and Total Bilirubin ≤1.5x ULN is required eligibility.

Additional comments

IMGN853 (MIRV) is an antibody-drug-conjugate (ADC) that is manufactured as a clear to slightly opalescent, colourless to slightly brown or slightly yellow liquid, which may contain translucent to white to off-white particles. It is used in this context only as part of the SL03-OHD-105 Clinical Trial.

The Lancashire Clinical Research Facility team will be on-site when the infusions are given. Please contact the team on 01772 522031 if any acute concerns. Additionally, it is possible to contact the Principal Investigator Dr Dennis Hadjiyiannakis for further details if required.

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Useful Links

https://www.immunogen.com/wp-content/uploads/2022/11/ELAHERE_PI.pdf

https://www.elaherehcp.com/eye-care#management

Infusion-Related Reaction

The following advice is given by the study sponsors on the management of infusion related reactions. See also UKONS protocol (https://ukons.hosting.sundownsolutions.co.uk/).

Please alert the study team in the event of a suspected infusion-related reaction.

Infusion Reaction CTCAE v5.0 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to Grade ≥2; if symptoms worsen, refer to guidelines below. • Antiemetic (eg Ondansetron 8mg IV) PRN for nausea • Chlorphenamine 10mg IV • Consider IV steroids (eg Hydrocortisone 200mg) • Perform observations every 15 minutes until resolution of acute event
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Antiemetic (eg Ondensetron) PRN for nausea • Chlorphenamine 10mg IV • Paracetamol 1g IV PRN • IV steroids (eg Hydrocortisone 200mg slow IV) • Oxygen treatment as required • After recovery from symptoms and if no further symptoms appear after 30 minutes, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • Consider the use of Pethidine for rigors • Perform observations every 15 minutes until resolution of acute event
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae	• Immediately stop infusion and disconnect infusion tubing from patient. • Chlorphenamine 10mg IV • Administer IV steroids (eg Hydrocortisone 200mg IV) to treat ongoing reaction and prevent recurrence

OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Administer bronchodilators (nebulized salbutamol, 2.5 to 5 mg in 3 mL of saline or equivalent) as medically indicated • Oxygen treatment as required • Administer normal saline as medically indicated • Administer Adrenaline (0.5 mL of a 1:1000 dilution IM) as medically indicated. • Admit patient. Patient will require Prednisolone 40-60mg OD for 3/7 (or equivalent), plus antihistamine for 3/7 (for example Chlorphenamine 4mg TDS). • Advise patient to seek emergency treatment and notify Investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Permanently discontinue study medication treatment • Consider the use of Pethidine for rigors • Perform observations every 15 minutes until resolution of acute event