Clinical Study Protocol

NCT Number: NCT06390995

Title: A phase 1/2 open-label study to evaluate the safety, tolerability, efficacy and pharmacokinetics of mirvetuximab soravtansine (TAK-853) in Japanese patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors

Study Number: TAK-853-1501
Document Version and Date: Amendment 2 / 12-JUN-2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A phase 1/2 open-label study to evaluate the safety, tolerability, efficacy and pharmacokinetics of mirvetuximab soravtansine (TAK-853) in Japanese patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors

<Short Title>

A phase 1/2 study of mirvetuximab soravtansine (TAK-853) for patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors

Sponsor:	Takeda Pharmaceutical Company Limited. 4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645
Study Number:	TAK-853-1501
EudraCT Number:	Not Applicable
Universal Trial Number:	Not Applicable
Compound:	TAK-853 (mirvetuximab soravtansine)
Date:	12 Jun 2024 **Amendment Number:** 02

Amendment History:

Date	Amendment Number
15 February 2024	Initial Protocol
22 March 2024	Amendment 01
12 June 2024	Amendment 02

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE), pregnancy, and other applicable safety reporting information is presented in the Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures may be found on the last page of this document.

[redacted] Date	[redacted] Date
Program Clinical Lead, Oncology Cell Therapy and Therapeutic Area Unit	Statistician, Statistical & Quantitative Sciences
[redacted] Date	
Clinical Pharmacology Lead, Quantitative Clinical Pharmacology	

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes and Rationale

Rationale for Amendment 02

This section describes the changes in reference to the protocol incorporating Amendment 02.

The primary reason for this substantial amendment is to establish a blinded independent central review (BICR) committee.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 02			
Summary of Changes Since the Last Version (Amendment 01) of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	2.0 STUDY SUMMARY 6.1.1 Overview of Study Design	Added that CT/MRI scans will be collected and read for sensitivity analysis by a BICR.	To hold CT/MRI scans for sensitivity analysis by a BICR
2	2.0 STUDY SUMMARY 7.1.1 Inclusion Criteria for Phase 1 part	Excluded MIRV from prior treatment with investigational compounds targeting folate receptor in the inclusion criteria 1.c.	To exclude patients who have prior treatment with MIRV
3	8.10.3.1 Monitoring and Preventive Measures	Revised “clean the eyes” to “clean the eyelid”	To clarify area of the eye to be cleaned
4	8.15 Storage, Handling, and Accountability	Added that MIRV vial is stored with protection from light.	To clarify how to store MIRV
5	9.4.1 Informed (e)Consent	Added on eConsent.	To clarify eConsent
6	9.4.10 Pregnancy Test	Revised “for 3 months” to “for 7 months” on the timing of pregnancy test after the last dose of MIRV. In addition, removed “for 6 months after the last dose of chemotherapy” of the timing for pregnancy test.	To correct an error
7	9.4.16.1 Radiological imaging	Added on the work of a central imaging vendor.	To clarify the work of a central imaging vendor
8	9.5.5.2 Response Follow-up Appendix A Table 1 (the footnote q)	Added on the timing of assessment.	To clarify the timing of assessment
9	10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Revised the procedure on SSR to the procedure on medication errors (including overdose).	To not use the procedure on SSR in the study
10	11.1 BICR committee	Added on a BICR committee.	To establish a BICR committee
11	13.1.3 Efficacy Analysis	Revised the definition of ORR and PFS associated with the addition of sensitivity analysis by a BICR. In addition, clarified that ORR, DOR and PFS assessed by investigator are endpoints in Phase 2 part.	To clarify assessment by investigator and BICR
12	Appendix A Table 2 (Including the footnote f)	The item of “FFPE Archived Tumor Tissue and/or New Biopsy” was described separately “for FRα expression” and “for exploratory biomarker”.	To clarify the tests
13	Appendix A Table 2 (the footnote k)	Revised the timing of assessment.	To clarify the timing of assessment

Abbreviations: BICR = blinded independent central review; CT = computed tomography; DOR = duration of response; FFPE = formalin-fixed, paraffin embedded; MIRV = mirvetuximab soravtansine; MRI = magnetic resonance imaging; ORR = objective response rate; PFS = progression-free survival; SSR = special situation report.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Company, Ltd.	**Compound:** mirvetuximab soravtansine (TAK-853)
Title of Protocol: A phase 1/2 open-label study to evaluate the safety, tolerability, efficacy and pharmacokinetics of mirvetuximab soravtansine (TAK-853) in Japanese patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors	**EudraCT No.:** Not Applicable
Study Number: TAK-853-1501	**Phase:** 1/2

Study Design:

This is a Phase 1/2 study. Initially, the study will start as a Phase 1 study to assess the safety of the global recommended phase 2 dose (RP2D) of mirvetuximab soravtansine (MIRV, TAK-853) 6.0 mg/kg adjusted ideal body weight (AIBW) when administered intravenously (IV) once every 3 weeks (Q3W) in Japanese patients with folate receptor alpha-positive (FRα-positive) advanced ovarian cancer or other solid tumors. After it is confirmed that the RP2D in Japanese patients is safe, a Phase 2 part will be followed; the Phase 2 part is designed to evaluate the efficacy and safety of MIRV in patients with platinum-resistant ovarian cancer (PROC) and high FRα expression. This study will be conducted under open-label in Japan. Eligible patients, who have provided informed consent and meet study entry criteria will be enrolled in the study.

Disease progression will be evaluated by the investigator using Response Evaluation Criteria in Solid Tumors RECIST v1.1 (Appendix E). CT/MRI scans will be collected and read for sensitivity analysis by a blinded independent central review (BICR).

Patients will continue to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminates the study (whichever comes first).

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

For phase 1 part, if patients discontinue study treatment for reasons other than progressive disease (PD), a tumor assessment is to be performed at the End of Study (EOS) visit or 30-day Follow up visit, if not performed within the previous 6 weeks. Additional tumor assessments may be conducted based on the investigator's decision.

For phase 2 part, patients who discontinue study treatment 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.

For phase 2 part, all patients who discontinue study drug will be followed every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or EOS, whichever comes first.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, with exception of corneal adverse events which will be also evaluated according to non-CTCAE grading as defined in the protocol.

Primary Objectives:

Phase 1 part:

To evaluate the safety and tolerability of MIRV at 6.0 mg/kg AIBW when administered IV Q3W in Japanese patients with FRα positive advanced ovarian cancer or other solid tumors.

Phase 2 part:

To determine the efficacy of MIRV in patients with PROC with high FRα expression.

Secondary Objectives:

Phase 1 part:

- To characterize the pharmacokinetics of MIRV.
- To characterize the immunogenicity of MIRV.

Phase 2 part:

- To determine the durability of response to MIRV based on investigator assessment.
- To evaluate the safety profile of MIRV.
- To characterize the pharmacokinetics of MIRV.
- To characterize the immunogenicity of MIRV.

[redacted]

Patient Population:

Phase 1 part: Patients with FRα-positive advanced ovarian cancer or other solid tumor

Phase 2 part: Patients with platinum-resistant ovarian cancer with high FRα expression, who have received 1 to 3 prior lines of therapy

Number of Patients:	**Number of Sites:**
Phase 1 part: At least 3 (up to 9) patients Phase 2 part: Approximately 22 patients	Phase 1 part: Approximately 2 sites in Japan Phase 2 part: Approximately 20 sites in Japan
Dose Level(s): Single-agent MIRV 6.0 mg/kg (AIBW) Q3W	**Route of Administration:** Intravenous
Duration of Treatment: Patients may receive study drug until disease progression, unacceptable toxicity, withdrawal of consent or permanent study discontinuation due to any other reasons specified in the study protocol.	**Period of Evaluation:** Phase 1 part: The estimated time frame for study completion (screening, study drug administration and follow-up period) is approximately 9 months. Phase 2 part: The estimated time frame for study completion (screening, study drug administration and follow-up period) is approximately 24 months.

Criteria for Inclusion:

Phase 1 part:

1. Diagnosis, allowable prior therapy, and disease measurability requirements:
    a. All patients must have a pathologically documented, following advanced solid tumor known to express FRα, that is resistant or refractory to standard treatment, for which no standard treatment is available, or the patient refuses standard therapy.
        - Ovarian cancer
        - Endometrial cancer
        - Non-small cell lung cancer (NSCLC)
        - Triple-negative breast cancer (TNBC)
        - Cholangiocarcinoma
        - Colorectal cancer (CRC)
        - Gastro-esophageal adenocarcinoma

        Note: Patients with a solid tumor type other than the above will be eligible as long as there is prior documentation of tumor FRα expression.
    b. All patients without prior documentation of tumor FRα expression by immunohistochemistry (IHC) must be 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 IHC confirmation of FRα positivity of ≥1% of viable tumor cells with membrane staining at ≥1+ intensity for entry into Phase 1 part
    c. There is no upper limit on the number of prior cytotoxic or targeted therapies the patient may have received. Patients may have received prior treatment with investigational compounds targeting folate receptor excluding MIRV.
    d. Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) according to RECIST v1.1.
2. Japanese patients aged ≥ 18 years old at the time of informed consent.
3. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
4. Time from Prior Therapy:
    - Systemic anti-neoplastic therapy: five half-lives or four weeks, whichever is shorter (6 weeks for prior nitrosoureas or mitomycin C)
    - FRα-targeted therapy: five half-lives or four weeks, whichever is longer
    - Radiotherapy: wide-field radiotherapy (e.g. affecting at least 30% of the bone marrow) completed at least four weeks, or focal radiation completed at least two weeks, prior to starting study drug
5. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
6. Major surgery must be completed four weeks prior to first dose of MIRV. Patients must have recovered or stabilized from the side effects prior to study treatment.
7. Patients must have adequate hematologic, liver and kidney function as defined by the following parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1,500/μL) without granulocyte colony stimulating factor (G-CSF) in the prior 10 days or long-acting WBC growth factors in the prior 20 days
    b. Platelet count ≥ 100.0 x 10^9/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
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance of ≥ 30 mL/minute (as calculated using the Cockcroft Gault equation),

e. AST ≤ 2.5 x ULN; ALT ≤ 2.5 x ULN (AST, ALT < 5 x ULN if liver metastases), and

f. Total bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)

8. Patients with central nervous system (CNS) disease involvement are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study Day 1 and they meet all of the following criteria:

   (1) Residual neurological symptoms ≤ Grade 1

   (2) No dexamethasone requirement, and

   (3) Follow-up MRI shows no progression of treated lesions and no new lesions appearing.

9. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements.
10. Women of childbearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must

    - Agree to use 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed (e)consent (or 14 days before the initiation of study medication for oral contraception) through 7 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

11. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study treatment.
12. Male patients must, even if he is surgically sterilized (i.e., status postvasectomy)

    - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

<u>Phase 2 part:</u>

1. Japanese female patients ≥ 18 years of age
2. Patients must have a confirmed diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
3. Patients must have platinum-resistant disease:

   a. 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 (complete response [CR] or partial response [PR]) and then progressed between > 3 months and ≤ 6 months after the last dose date of platinum

   b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum

   Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression

   Note: Patients who are primary 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 therapy

5. Patients must be 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 IHC confirmation of FRα expression (reported as "positive") as defined by the Ventana FOLR1 Assay. Tumors must be confirmed FRα-high as defined by FRα positivity of ≥75% of viable tumor cells with membrane staining at ≥2+ intensity for entry into the Phase 2.
6. Patients must have at least one lesion that meets the definition of measurable disease by RECIST v1.1 criteria (radiologically measured by the Investigator) (See Appendix E for lesions with prior local treatment).
7. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy is appropriate as the next line of treatment:
    a. Neoadjuvant ± adjuvant considered one line of therapy
    b. Maintenance therapy (e.g., bevacizumab, poly-ADP ribose polymerase [PARP] inhibitors) will be considered as part of the preceding line of therapy (i.e., not counted independently)
    c. Therapy changed due to toxicity in the absence of progression will be considered as part of the same line (i.e., not counted independently)
    d. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance
8. Patient must have an ECOG PS of 0 or 1
9. Time from prior therapy:
    a. Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)
    b. Focal radiation completed at least 2 weeks prior to first dose of study drug
10. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
11. Major surgery must be completed at least 4 weeks prior to first dose and the patient must have recovered or stabilized from the side effects of prior surgery
12. Patients must have adequate hematologic, liver, and kidney functions defined as:
    a. ANC ≥ 1.5 x 10^9/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 10^9/L (100,000/μL) without platelet transfusion in the prior 10 days
    c. Hemoglobin ≥ 9.0 g/dL without PRBC transfusion in the prior 21 days
    d. Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance of ≥ 30 mL/minute (as calculated using the Cockcroft Gault equation).
    e. AST and ALT ≤ 3.0 x ULN
    f. Total bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
    g. Serum albumin ≥ 2 g/dL
13. Patients or their legally authorized representative must be willing and able to sign the ICF and to adhere to the protocol requirements
14. WCBP, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must
    - Agree to use 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed (e)consent (or 14 days before the initiation of study medication for oral contraception) through 7 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

15. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study drug

Criteria for Exclusion:

Phase 1 part:

1. Patients with > Grade 1 peripheral neuropathy per NCI CTCAE v5.0
2. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.
3. Serious concurrent illness, including, but not limited to the following:
    a. Clinically relevant active infection including
        - Active hepatitis B or C infection (whether or not on active antiviral therapy)
        - Human Immunodeficiency Virus (HIV) infection
        - Active cytomegalovirus infection
        - Active COVID-19/SARS-CoV-2 infection. Although SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines and standards
        - Any other known concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

        Note: Testing at screening for hepatitis is required, while not required for the remaining infections above unless clinically indicated. Patients with known hepatitis B surface antigen seropositivity and/or detectable hepatitis C virus RNA will be excluded. Patients who have positive hepatitis B core antibody and/or hepatitis B surface antibody can be enrolled but must have an undetectable serum hepatitis B virus DNA. Patients who have positive hepatitis C virus antibody must have an undetectable hepatitis C virus RNA serum level. Patients will be monitored and managed according to Guideline for the prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection (The Japan Society of Hepatology 2022).

    b. Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
        - Myocardial infarction ≤ 6 months prior to first dose of study medication
        - Unstable angina pectoris
        - Uncontrolled congestive heart failure (New York Heart Association > class II)
        - Uncontrolled ≥ Grade 3 hypertension (per NCI CTCAE v5.0)
        - Uncontrolled cardiac arrhythmias
        - Severe aortic stenosis
        - ≥ Grade 3 cardiac toxicity following prior chemotherapy

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

    d. Previous clinical diagnosis of interstitial lung disease (ILD), including pneumonitis.
4. Any other concomitant anti-cancer treatment such as immunotherapy, biotherapy, radiotherapy, chemotherapy, investigative therapy, or high-dose steroids; however, low-dose steroids and Luteinizing Hormone Releasing Hormone (LHRH) at doses that have been stable for ≥ 14 days are permitted for patients with prostate cancer

5. Known hypersensitivity to previous monoclonal antibody therapy or maytansinoids, or study drugs and/or any of their excipients
6. Prior history of solid tumor malignancy within the last 3 years except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment)
7. Patients with required use of folate-containing supplements (e.g., folate deficiency)
8. Patients who have received prior allogeneic or autologous bone marrow transplants
9. Women who are pregnant or lactating

   Note: Patients who may be in the very early stage of pregnancy based on the doctor's interview with a negative pregnancy test are excluded from the study. Patients who are lactating will be eligible if they discontinue breastfeeding before the first dose of study drug.

Phase 2 part:

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumor
2. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first line platinum-containing chemotherapy
3. Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per NCI CTCAE v5.0
5. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision
6. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
   a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
   b. HIV infection
   c. Active cytomegalovirus infection
   d. Active COVID-19/SARS-CoV-2 infection. Although SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines and standards.
   e. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

   Note: Testing at screening for hepatitis (a) is required, while not required for the remaining infections above (b-e) unless clinically indicated. Patients with known hepatitis B surface antigen seropositivity and/or detectable hepatitis C virus RNA will be excluded. Patients who have positive hepatitis B core antibody and/or hepatitis B surface antibody can be enrolled but must have an undetectable serum hepatitis B virus DNA. Patients who have positive hepatitis C virus antibody must have an undetectable hepatitis C virus RNA serum level. Patients will be monitored and managed according to Guideline for the prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection (The Japan Society of Hepatology 2022).
7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
   a. Myocardial infarction ≤ 6 months prior to first dose of study medication
   b. Unstable angina pectoris
   c. Uncontrolled congestive heart failure (New York Heart Association > class II)
   d. Uncontrolled ≥ Grade 3 hypertension (per NCI CTCAE v5.0)

e. Uncontrolled cardiac arrhythmias

9. Patients with a history of hemorrhagic or ischemic stroke within six months prior to first dose of MIRV
10. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
11. Patients with a previous clinical diagnosis of ILD, including pneumonitis
12. Patients with required use of folate-containing supplements (e.g., folate deficiency)
13. Patients with prior hypersensitivity to monoclonal antibodies or maytansinoids
14. Women who are pregnant or lactating

    Note: Patients who may be in the very early stage of pregnancy based on the doctor's interview with a negative pregnancy test are excluded from the study. Patients who are lactating will be eligible if they discontinue breastfeeding before the first dose of study drug.

15. Patients with prior treatment with MIRV or other FRα-targeting agents
16. Patients with untreated or symptomatic CNS metastases
17. Patients with a history of other malignancy within 3 years prior to first dose of MIRV

    Note: does not include tumors with a negligible risk for metastasis or death (e.g., adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma *in situ* of the cervix or breast)

18. Prior known hypersensitivity reactions to study drugs and/or any of their excipients
19. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order
20. Simultaneous participation in another clinical trial

Endpoints:

Phase 1 part:

Primary:

- The number and percentage of patients with dose-limiting toxicities (DLTs) in Cycle 1.
- Adverse events including:
  - The number and percentage of patients with treatment-emergent adverse events (TEAEs).
  - The number and percentage of patients with Grade 3 or higher TEAEs.
  - The number and percentage of patients with serious TEAEs
  - The number and percentage of patients with TEAEs leading to drug discontinuation.
  - The number and percentage of patients with TEAEs leading to infusion interrupted.
  - The number and percentage of patients with TEAEs leading to dose delayed.
  - The number and percentage of patients with TEAEs leading to dose reduction.
  - The number and percentage of patients with AEs of Clinical Interest (AECIs).

Secondary:

- PK parameters for intact ADC, total Ab, DM4 and S-methyl DM4:
  maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), terminal half-life ($t_{1/2}$), total clearance (CL), volume of distribution at steady state (V_{ss}), time of first occurrence of C_{max} (t_{max}) as applicable
- Incidence of immunogenicity of MIRV.

[redacted]

[redacted]

[redacted]

Phase 2 part:

Primary:

- ORR based on the investigator's assessment using RECIST v1.1

Secondary:

- Duration of response based on the investigator's assessment, defined as the time from the first assessment of either CR or PR until progressive disease.
- Intact ADC, total Ab, DM4 and S-methyl DM4 concentration
- Incidence of immunogenicity of MIRV

Safety:

- Adverse events including:
  - The number and percentage of patients with TEAEs after study drug administration.
  - The number and percentage of patients with Grade 3 or higher TEAEs.
  - The number and percentage of patients with serious TEAEs
  - The number and percentage of patients with TEAEs leading to drug discontinuation.
  - The number and percentage of patients with TEAEs leading to infusion interrupted.
  - The number and percentage of patients with TEAEs leading to dose delayed.
  - The number and percentage of patients with TEAEs leading to dose reduction.
  - The number and percentage of patients with AECIs.
- Laboratory values
- Vital signs

[redacted]

Statistical Considerations:

Phase 1 part

The safety of global RP2D of 6.0 mg/kg AIBW will be evaluated through the 3+3+3 rule using the data collected in the Phase 1 part. Dose-limiting toxicities (DLTs) in Cycle 1 and AEs will be summarized for patients who received at least one dose of MIRV.

Phase 2 part

The primary endpoint of phase 2 part is ORR, defined as the proportions of patients with a confirmed CR or PR assessed by the investigator using RECIST v1.1. The analysis of ORR is based on the full analysis set, defined as patients who received at least one dose of MIRV. Estimates of ORR will be presented with the 90% exact confidence interval (CI).

Sample Size Justification:

Phase 1 part

The study will follow a 3+3+3 design. 6.0 mg/kg AIBW is the only dose level to be evaluated in this trial. Patients will be enrolled and treated at the dose level 6.0 mg/kg AIBW with 3 patients in each cohort. The number of evaluable patients is planned to be 3 to 9.

Phase 2 part

Approximately 22 patients will be enrolled and a total of 20 patients will be evaluated for efficacy analysis, assuming a dropout rate of 10%. This will allow the study to have over 80% power to detect a difference in ORR of 26% (42% vs 16%) with a 1-sided alpha of 0.05. These results assume that the ORR is 16% under the null hypothesis and 42% under the alternative hypothesis.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the protocol annex. The vendors identified in the protocol annex will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol and the study medication, expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-HT_3	serotonin receptor subtype 3
Ab	antibody
ADA	anti-drug antibodies
ADC	antibody drug conjugate
ADCC	antibody dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
AECI	adverse event of clinical interest
AIBW	adjusted ideal body weight
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
BCVA	best corrected visual acuity
BICR	blinded independent central review
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
CxDy	Cycle x Day y
CEC	clinical endpoint committee
CI	confidence interval

CL	total clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DM4	N2'-deacetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOS	End of Study
EOT	End of Treatment
EPO	erythropoietin
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDA	[United States] Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FOLR1	folate receptor 1
FRα	folate receptor α
[redacted]	[redacted]
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GPSP	Good Post-marketing Study Practice
HIV	human immunodeficiency virus
IB	investigator's brochure
IBW	ideal body weight
IC_{50}	half maximal (50%) inhibitory concentration
IC Chemo	investigator's choice chemotherapy
ICF	informed consent form (including electronic consent where applicable)
ICH	International Council for Harmonisation

IEC	independent ethics committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
J-non-IMP	Japan Drug, Product, or Device Used in the Clinical Trial other than IMP
LHRH	Luteinizing Hormone Releasing Hormone
mAb	monoclonal antibody
MDR1	multidrug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIRV	mirvetuximab soravtansine (TAK-853)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
Pac	paclitaxel
PARP	poly-ADP ribose polymerase
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PFT	pulmonary function test
PI	principal investigator
PK	pharmacokinetic(s)
PLD	pegylated liposomal doxorubicin
PLT	platelets
PMDA	Pharmaceuticals and Medical Devices Agency
PO	orally
PR	partial response
PRO	patient-reported outcome
PRBC	packed red blood cell
PROC	platinum-resistant ovarian cancer
PT	prothrombin time

Q3W	once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time of first occurrence of maximum observed concentration
TNBC	triple-negative breast cancer
Topo	topotecan
ULN	upper limit of normal
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WCBP	women of childbearing potential
WHO	World Health Organization

3.4 Corporate Identification

Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC Americas	Takeda Development Center Americas, Inc
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Japan	Takeda Development Center Japan

4.0 INTRODUCTION

4.1 Background

4.1.1 Target Background

Folate receptor α (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (FOLR1) gene. FRα internalizes folate, which is an essential co-factor for one-carbon transfer reactions that are required for DNA and RNA synthesis, cell growth and proliferation. Marked upregulation of FRα occurs during neonatal development and in cancer, suggesting that the receptor functions primarily under conditions of high folate demand. In contrast, normal adult tissues generally lack FRα expression and employ alternative transporters such as folate receptor β, reduced folate carrier and proton-coupled folate transporter for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004, Kelemen 2006, Investigator's brochure).

Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly serous and endometrioid ovarian cancers and serous and endometrioid endometrial cancers (Garin-Chesa 1993, Kalli 2008, Crane 2012, Dainty 2007, Jones 2008, Ab 2015, and Allard 2007). IHC results obtained from patients screened or enrolled in the Phase 1 Study IMGN853-0401 and Phase 3 Study IMGN853-403 are generally consistent with the literature (Investigator's brochure). While assessing the FRα distribution in the platinum-resistant ovarian cancer (PROC) expansion cohort, approximately 40% of patients had high expression.

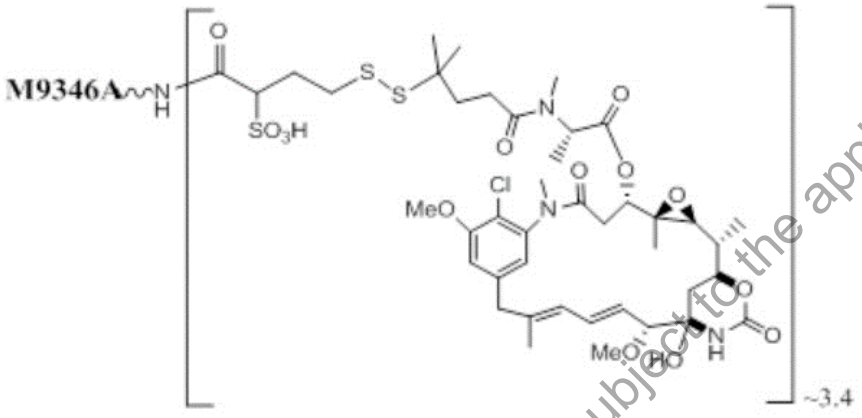
Several additional studies have further validated FRα as a target in serous epithelial ovarian cancer (EOC). First, quantitative polymerase chain reaction studies show ubiquitous FRα mRNA expression in serous EOC (Hanker 2012, Hoskins 1998, and Hough 2001) and high levels of FRα mRNA correlate with poor response to chemotherapy and decreased disease free survival (Chen 2012). Second, both Kalli et al and Crane et al have demonstrated that recurrent tumors retain FRα expression comparably to primary tumors as shown by serial biopsy sampling and IHC (Kalli 2008, Crane 2012). Third, studies with FRα-specific imaging agents have demonstrated real-time FRα expression at primary and metastatic tumor sites (Fisher 2008, Garcia 2013, Garin-Chesa 1993, and van Dam 2011). Finally, a truncated form of FRα has been detected in ascites and blood of EOC patients (Basal 2009, Mantovani 1994), further confirming expression in this disease and suggesting that the receptor may serve as a circulating biomarker. Collectively, these data suggest that FRα is a promising target in solid tumors, particularly EOC.

4.1.2 Mirvetuximab Soravtansine

Because of its tumor-specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a promising target for antibody drug conjugate (ADC) therapy. ADCs combine the specificity of monoclonal antibody (mAb) to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target proliferating cells. mirvetuximab soravtansine (MIRV) is an ADC designed to target FRα. It consists of the humanized anti-FRα mAb M9346A attached via a cleavable disulfide

linker to the cytotoxic maytansinoid, DM4 (Figure 4.a). MIRV is a recombinant drug of which the antibody is produced by Chinese hamster ovary cells.

Figure 4.a Mirvetuximab Soravtansine Structure



DM4 is ~2% by weight relative to mAb.

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

In vitro, MIRV binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against tumor cells expressing FRα. Cytotoxic effects of MIRV in vitro is related to level of cell-surface expression of FRα (Ab 2015). MIRV additionally demonstrates significant activity against FRα positive xenografts, with partial and complete remissions observed in ovarian models (Ab 2015). Together with the selective upregulation of FRα in solid tumors, these results provide the rationale for exploring the clinical utility of MIRV.

MIRV received accelerated approval in the U.S. in November 2022 for the treatment of adult patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. This approval was based on a single-arm Phase 3 SORAYA study (IMGN853-0417) with the primary endpoint of investigator-assessed objective response rate (ORR). To date, MIRV demonstrated statistically significant and clinically meaningful improvements in investigator-assessed progression-free survival (PFS), ORR, and overall survival (OS) compared to investigators' choice chemotherapy in a randomized Phase 3 MIRASOL study (IMGN853-0416) that is the

confirmatory study for the initial accelerated approval (Moore 2023). The adverse event (AE) profile of MIRV of patients with platinum-resistant high-grade EOC, primary peritoneal, or fallopian tube cancer, whose tumors expressed high level of FRα, was characterized predominantly by low-grade, reversible ocular, gastrointestinal, and neurosensory events, including blurred vision, keratopathy, dry eye, abdominal pain, fatigue, diarrhea, nausea, constipation, and peripheral neuropathy.

4.1.3 Epithelial Ovarian Cancer

Ovarian cancer is a lethal disease with 19,710 new cases and 13,270 deaths expected in 2023 in the US (SEER Cancer Statistics Factsheet 2024). In Japan, 13,388 cases were diagnosed in 2019 and 4,876 deaths occurred in 2020 (National Cancer Center, Japan 2022).The estimated number of new EOC cases in the EU (EU27) in 2022 was 40,740 with 27,699 deaths (EUCAN Cancer Fact Sheet: Ovary 2024). The overall 5-year survival for EOC patients is only 50.8% (SEER Cancer Statistics Factsheet 2024).

Recent studies indicate that ovarian, peritoneal, and fallopian tube cancers are not distinct entities, but represent a spectrum of diagnoses that originate in the Mullerian tissue. Primary fallopian tube carcinoma and peritoneal cancers are now included in the ovarian cancer staging classification (Cobb 2015, Grant 2010, Naumann 2011, and O'Shannessy 2013), and are considered to be part of EOC with the same treatment and outcomes.

Despite considerable improvements in primary therapy, 80% of the patients with advanced EOC are expected to relapse during or after treatment with platinum-containing regimens (Armstrong 2019). Disease recurring within 6 months of platinum-based chemotherapy is classified as platinum resistant, whereas, disease recurring longer than 6 months after therapy is termed platinum sensitive. Patients with platinum-resistant disease typically receive single-agent chemotherapy (e.g., pegylated liposomal doxorubicin [PLD], topotecan [Topo], gemcitabine, paclitaxel [Pac], or other) at relapse. Unfortunately, response rates (RR) are modest (~15%) and duration of response (DOR) is typically 4 to 8 months (Cannistra 2010, Matsuo 2010). Similarly, OS is poor (median OS ~11 months). Bevacizumab was approved for use in combination with chemotherapy for recurrent EOC in the platinum-resistant setting (Pujade-Lauraine 2014). Because platinum-resistant EOC (PROC) remains a significant unmet medical need, the National Comprehensive Cancer Network (NCCN) guidelines recommend that platinum resistant patients participate in clinical trials (NCCN Guidelines 2024).

Commonly used agents for PROC are Pac, Topo and PLD, all of which have modest levels of activity, which underscores the need for improved therapies.

In addition to single-agent cytotoxic chemotherapy, bevacizumab combinations and poly-ADP ribose polymerase (PARP) inhibitors (e.g., olaparib, niraparib, and rucaparib) are approved for treatment of previously treated EOC. These agents, however, are subject to treatment limitations. In particular, bevacizumab combinations are limited to patients who have received no more than 2 prior chemotherapy regimens and are not at risk for bowel perforations (recto-sigmoid involvement, bowel involvement and/or history of bowel obstruction) (Aghajanian 2012,

PujadeLauraine 2014). Those patients with PROC who receive bevacizumab + chemotherapy typically receive subsequent single-agent chemotherapy if they remain eligible for further treatment.

PARP inhibitors (e.g., olaparib and rucaparib) are approved as single-agent treatment for patients with breast cancer susceptibility gene (*BRCA*) mutated EOC (~15% of EOC) and have received ≥ 2 prior regimens (Moore 2019) based on the durable responses seen in this subset of EOC. The activity of PARP inhibitors in *BRCA* wild-type patients with PROC is negligible, with response rates of approximately 5% (Gelmon 2011, Moore 2019, Sandhu 2013).

4.1.4 Current Therapies

Current management of advanced stage disease includes surgical tumor debulking, followed by adjuvant platinum- and taxane-based chemotherapy with/out bevacizumab or PARP inhibitor as maintenance if applicable. However, the majority of the patients will recur (Garcia 2013). Patients with relapsed platinum sensitive disease are often treated with carboplatin alone or as part of a combination regimen (Pfisterer 2006, Tokunaga 2021), whereas those with platinum-resistant disease may be treated with a variety of agents, including Pac, Topo and PLD. For patients with platinum-resistant recurrence, monotherapy is the mainstay of treatment. A single agent without cross-resistance to previous treatment and the addition of bevacizumab to a cytotoxic agent is suggested in the 2020 Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (Tokunaga 2021).

4.2 Rationale for the Proposed Study

4.2.1 Rationale for the Study Plan

The design of this study is based on data obtained from Phase 1 study (IMGN853-0401) and Phase 3 MIRASOL study (IMGN853-0416), which demonstrated both statistical significance and clinically meaningful efficacy outcome for MIRV over Investigator's choice of chemotherapy (IC Chemo) in patients with high FRα expression.

This phase 1/2, open-label study is designed to evaluate the safety, tolerability, efficacy and pharmacokinetics of MIRV in patients with platinum-resistant high-grade EOC, primary peritoneal, or fallopian tube cancer, whose tumors express a high level of FRα.

4.2.2 Rationale for the Study Population

The study population for Phase 1 part in this study is based on clinical observations from a Phase 1 study of MIRV (Study IMGN853-0401). Published and unpublished studies have demonstrated FRα overexpression by IHC in various epithelial tumors, including ovarian cancer, endometrial cancer, non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), cholangiocarcinoma, colorectal cancer (CRC) and gastro-esophageal adenocarcinoma (Scaranti M 2020,).

The study population for Phase 2 part in this study is based on the results from the Phase 3 Study MIRASOL (IMGN853-0416), demonstrating that treatment with MIRV led to significant improvements in PFS, ORR, and OS in PROC, when compared with chemotherapy (Moore 2023). It is important to generate additional data to support similar benefit in the Japanese population.

This study will enroll Japanese patients with FRα-positive advanced ovarian cancer or other solid tumors in Phase 1 part, and Japanese patients with PROC and high FRα expression in Phase 2 part. The study population in the Phase 2 part is similar to that of the preceding Phase 3 study with PROC population.

Please refer to the Investigator's brochure for more details on the Ventana FOLR1 assay and the FRα expression threshold selected for this study.

4.2.3 Rationale for the Selection of Drug Dose Levels and Dosing Schedules

The selection of the MIRV dose of 6.0 mg/kg adjusted ideal body weight (AIBW) IV Q3W in this study was based on data obtained from Study IMGN853-0401, a first-in-human (FIH) study designed to establish the maximum tolerated dose (MTD) and determine the recommended phase 2 dose (RP2D) of MIRV when administered IV as a single agent in adult patients with FRα-positive solid tumors who have relapsed or are refractory to standard therapies. The appropriateness of this dose regimen in patients with PROC was further supported by the favorable risk-benefit profile achieved in the phase 3 study IMGN853-0403, IMGN853-0416 and IMGN853-0417. For more information, please see Section 4.3.2 and the Investigator's brochure.

4.3 Risks and Benefits

MIRV is currently being evaluated in this phase 1/2 study in Japanese patients with FRα-positive advanced ovarian cancer and other solid tumors.

Further details for MIRV administration, safety events, and management can be found in Section 8.0 and the Guidance for Investigator section of the Investigator's brochure.

4.3.1 Potential Effects Based on Nonclinical Studies

4.3.1.1 Correlation of FRα Expression with MIRV Activity

Studies assessing the potency and specificity of MIRV were conducted on a panel of FRα-positive cell lines with a wide range of FRα expression, as well as on FRα-negative cell lines. These studies revealed a positive correlation between the level of FRα expression on the cell surface, the amount of maytansinoid catabolites generated, and the degree of sensitivity of the cells to MIRV in vitro.

4.3.1.2 Pharmacology

Results of nonclinical pharmacology studies demonstrate the following:

- FRα has limited normal tissue expression and marked expression in solid tumors, particularly cancers of the ovary and endometrium (Investigator's brochure). In vitro studies demonstrated that MIRV binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against cells expressing FRα. MIRV-mediated cytotoxicity involves binding, internalization, and degradation of MIRV, which releases DM4. DM4 can be methylated to yield S-methyl DM4. Both DM4 and S-methyl DM4 can inhibit tubulin polymerization and microtubule assembly, causing cell death. The lipophilic molecules S-methyl DM4 and DM4 can also diffuse to neighboring cells and induce bystander killing.
- In vitro cytotoxicity studies suggest that cells sensitive to MIRV express higher levels of FRα and release 10- to 100-fold more cytotoxic maytansinoid than cells resistant to MIRV.
- MIRV retains the inherent activities of its Ab moiety, M9346A, including binding affinity (apparent affinity ≤ 0.1 nM) and selectivity for FRα, capacity for uptake, internalization and degradation by FRα-positive target cells, and ability to induce Ab dependent cell-mediated cytotoxicity (ADCC) in vitro.
- MIRV demonstrates significant activity against FRα-positive xenografts. Partial and/or complete regressions in xenograft models of EOC were seen at doses of MIRV well below its MTD.

4.3.1.3 Pharmacokinetics

Nonclinical studies with MIRV cross-reactive (monkey) and non-cross-reactive (mouse) species were conducted to define pharmacokinetic (PK) parameters and to determine the stability of the linker and impact of conjugation on Ab clearance. An additional PK study with free DM4 was conducted in monkey. PK studies demonstrated the stability of MIRV in circulation after IV administration, with a distribution phase lasting about 24 hours followed by a slower terminal elimination phase. The data indicated that the PK of MIRV were approximately dose proportional within the ranges evaluated (1 mg/kg – 10 mg/kg). These studies are further detailed in the Investigator's brochure.

4.3.1.4 Toxicology

MIRV was evaluated for toxicity after a single IV injection in cross-reactive (monkey) and noncross-reactive (mouse) species. Results of these studies supported the FIH study exploring the safety and tolerability of MIRV when administered once every three weeks to patients with advanced solid tumors. Potential risks suggested by these studies as well as clinical experience with other maytansinoid ADCs include hematologic abnormalities, electrolyte alterations, injection site reactions, infusion reactions, immunogenicity, hepatic abnormalities, and peripheral neuropathy. Toxicology studies are further detailed in the Investigator's brochure.

4.3.2 Effects Based on Clinical Studies

4.3.2.1 First-in-Human Phase 1 Clinical Trial: Study IMGN853-0401

Dose escalation in the first-in-human Phase I trial (IMNG853-0401) (NCT01609556) evaluated MIRV administered IV on Day 1 of a 21-day cycle (i.e., once every 3 weeks [Q3W]) to patients with FRα-positive solid tumors, which included individuals with ovarian, endometrial, cervical, renal, and non-small cell lung cancer (Moore 2018). A total of 44 patients were enrolled, with the first 30 receiving MIRV at escalating doses from 0.15 to 7.0 mg/kg calculated on total body weight. Dose-limiting toxicities (DLTs) of Grade 3 hypophosphatemia and Grade 3 punctate keratitis were observed in one patient each at the 5.0 and 7.0 mg/kg dose levels, respectively. A modification to dosing based on AIBW was implemented to decrease interpatient variability in drug exposure, and subsequently enrolled patients received MIRV at either 5.0 or 6.0 mg/kg AIBW (n = 7 per group). No DLT were observed and based on a collective evaluation of safety, activity, and pharmacokinetics data, dosing at 6.0 mg/kg AIBW Q3W was established as the RP2D.

4.3.2.2 Phase 3 Monotherapy Trial in Patients with Platinum-resistant EOC, Peritoneal, and Fallopian Tube Cancer: Study IMGN853-0403

MIRV monotherapy has been studied in recurrent PROC extensively to date. IMGN853-0403 (FORWARD I) (NCT02631876) was a Phase 3 study with the objective to evaluate the safety and efficacy of single-agent MIRV vs. IC Chemo in patients with platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer, and whose tumor was FRα-positive (medium or high expression) by the Ventana IHC assay. 352 patients received at least 1 dose of MIRV or IC Chemo (243 and 109, respectively). The primary endpoint, PFS, did not reach statistical significance in either the overall ITT population (p-value = 0.897; HR = 0.981) or in the pre-specified FRα-high population (p-value = 0.049; HR = 0.693). MIRV treatment in PROC patients with high FRα expression resulted in an ORR of 24% (95% CI: 17.2, 31.5) compared with 10% (95% CI: 4.1, 19.3) for patients randomized to IC Chemo (p-value = 0.014), median PFS of 4.8 months (95% CI: 4.11, 5.68) vs. 3.3 months (95% CI: 1.97, 5.59) for patients randomized to IC Chemo (p-value = 0.049; HR = 0.693). The MIRV safety profile was predominantly characterized by low-grade nausea (51%), diarrhea (40%), and blurred vision (40%). These treatment emergent AEs (TEAEs) are generally managed and mitigated with antiemetics, antidiarrheals, and lubricating/steroid eye drops.

4.3.2.3 Phase 3 Study in Patients with Platinum-resistant high-grade serous EOC, Primary Peritoneal, or Fallopian Tube Cancer: IMGN853-0417 (SORAYA)

One-hundred six patients were enrolled in a single-arm, Phase 3 SORAYA study (IMGN853-0417) (NCT04296890), which met the primary endpoint with a confirmed ORR of 32.4% and median DOR of 6.9 months per investigator assessment. In SORAYA, MIRV demonstrated meaningful antitumor activity regardless of prior lines of therapy or prior PARP inhibitor treatment and a tolerability profile consistent with that of previous studies. In terms of safety, MIRV was well-tolerated and no new safety signals were observed. The most common

treatment-related AEs were blurred vision (any grade: 41%, grade 3–4: 6%), keratopathy (29% and 9%), and nausea (29% and 0%). Accordingly, the Food and Drug Administration (FDA) granted accelerated approval to MIRV for the treatment of patients with FRα-positive, platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior lines of therapy.

4.3.2.4 Phase 3 Study in Patients with Platinum-resistant high-grade EOC, Primary Peritoneal, or Fallopian Tube Cancer: IMGN853-0416 (MIRASOL)

The confirmatory IMGN853-0416 (MIRASOL) (NCT04209855) (Moore 2023) trial designed to compare the efficacy and safety of MIRV versus IC Chemo in patients with platinum-resistant high-grade epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer whose tumors express a high level of FRα; MIRASOL enrolled a total of 453 patients with high FRα expression (≥75% of cells with PS2+) who had received 1–3 prior lines of therapy. The primary endpoint of the study was investigator-assessed PFS and secondary endpoints included ORR, OS, quality of life and safety and tolerability. At a median follow-up of 13.1 months, MIRV demonstrated a statistically significant improvement in OS vs IC Chemo (16.4 vs 12.75 months, HR 0.67, P = .0046); median PFS was 5.62 vs 3.98 months (HR 0.65, P ≤ .0001), and ORR was 42% with MIRV, compared with 16% with IC Chemo (OR 3.81, P ≤ .0001). The safety profile of MIRV was consistent with previous reports. In addition, patients receiving MIRV had lower rates of grade 3 or higher TEAEs (42% vs 54%), SAEs (24% vs 33%), and discontinuation of therapy due to treatment-related AEs (9% vs 16%) compared with those receiving IC Chemo. This trial was the first to demonstrate both a PFS and OS benefit for a therapy in PROC compared with standard chemotherapy.

4.3.2.5 Conclusion

The available safety and efficacy data from patients treated with single-agent MIRV in previous clinical studies are consistent with a positive risk benefit assessment. The potential benefit of the anti-tumor activity demonstrated by MIRV in patients with FRα-high PROC, a population with high unmet need, outweighs the risks associated with the well tolerated safety profile.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Phase 1 Objectives

5.1.1 Phase 1 Primary Objectives

The Phase 1 primary objective is:

- To evaluate the safety and tolerability of MIRV at 6.0 mg/kg AIBW when administered IV Q3W in Japanese patients with FRα-positive advanced ovarian cancer or other solid tumors

5.1.2 Phase 1 Secondary Objectives

The Phase 1 secondary objectives are:

- To characterize the pharmacokinetics of MIRV
- To characterize the immunogenicity of MIRV

5.1.3 [redacted]

[redacted]

5.2 Phase 2 Objectives

5.2.1 Phase 2 Primary Objectives

The Phase 2 primary objective is:

- To determine the efficacy of MIRV in patients with PROC and high FRα expression

5.2.2 Phase 2 Secondary Objectives

The Phase 2 secondary objectives are:

- To determine the durability of response to MIRV based on investigator assessment
- To evaluate the safety profile of MIRV when administered IV
- To characterize the pharmacokinetics of MIRV
- To characterize the immunogenicity of MIRV

5.2.3 [redacted]

[redacted]

- [redacted]

5.3 Endpoints

5.3.1 Phase 1 Endpoint

5.3.1.1 Phase 1 Primary Endpoints

The Phase 1 primary endpoints are:

- The number and percentage of patients with DLTs in Cycle 1.
- AEs including:
  - The number and percentage of patients with TEAEs.
  - The number and percentage of patients with Grade 3 or higher TEAEs.
  - The number and percentage of patients with serious TEAEs
  - The number and percentage of patients with TEAEs leading to drug discontinuation.
  - The number and percentage of patients with TEAEs leading to infusion interrupted.
  - The number and percentage of patients by Preferred Term of TEAEs leading to dose delayed.
  - The number and percentage of patients with TEAEs leading to dose reduction.
  - The number and percentage of patients with AEs of clinical interest (AECIs, see Section 10.0).

5.3.1.2 Phase 1 Secondary Endpoints

The Phase 1 secondary endpoints are:

- PK parameters for intact ADC, total Ab, DM4 and S-methyl DM4: maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), terminal half-life ($t_{1/2}$), total clearance (CL), volume of distribution at steady state (V_{ss}), time of first occurrence of C_{max} (t_{max}) as applicable.
- Incidence of immunogenicity of MIRV.

5.3.1.3 [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

5.3.2 Phase 2 Endpoints

5.3.2.1 Phase 2 Primary Endpoints

The Phase 2 primary endpoint is:

- ORR based on the investigator's assessment using RECIST v1.1

5.3.2.2 Phase 2 Secondary Endpoints

The Phase 2 secondary endpoints are:

- DOR based on the investigator's assessment, defined as the time from the first assessment of either CR or PR until progressive disease.
- Intact ADC, total Ab, DM4 and S-methyl DM4 concentration
- Incidence of immunogenicity of MIRV

5.3.2.3 Phase 2 Safety Endpoints

The Phase 2 safety endpoints are:

- AEs including:
  - The number and percentage of patients with TEAEs after study drug administration.
  - The number and percentage of patients with Grade 3 or higher TEAEs.
  - The number and percentage of patients with serious TEAEs
  - The number and percentage of patients with TEAEs leading to drug discontinuation.
  - The number and percentage of patients with TEAEs leading to infusion interrupted.
  - The number and percentage of patients with TEAEs leading to dose delayed.
  - The number and percentage of patients with TEAEs leading to dose reduction.
  - The number and percentage of patients with AECIs (see Section 10.0).
- Laboratory values
- Vital signs

5.3.2.4 [redacted]

[redacted]

6.0 INVESTIGATIONAL PLAN

6.1 Study Design

6.1.1 Overview of Study Design

This is a Phase 1/2 study. Initially, the study starts as a Phase 1 study to assess the safety of the global RP2D of 6.0 mg/kg AIBW when administered IV Q3W in Japanese patients with FRα-positive (≥1%, PS+1) advanced ovarian cancer or other solid tumors. Patients are required to be hospitalized at least Days 1 to 3 in Cycle 1 (i.e., they can be discharged on Day 4) in Phase 1 part (Note: The investigator must document the confirmation record for stable health status of the patient per standard physical examination and available data in an appropriate source record (e.g., medical records) before the patient discharge). After it is confirmed that the RP2D is safe in Japanese patients, a Phase 2 part will be initiated; the Phase 2 part is designed to evaluate the efficacy and safety of MIRV in patients with PROC and high FRα expression (≥75%, PS+2). Eligible patients, who have provided informed consent and meet study entry criteria will be enrolled in the study.

Disease progression will be evaluated by the investigator using RECIST v1.1 (Appendix E). CT/MRI scans will be collected and read for sensitivity analysis by a blinded independent central review (BICR).

Patients will continue to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminates the study (whichever comes first).

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

For phase 1 part, if patients discontinue study treatment for reasons other than PD, a tumor assessment is to be performed at the EOS visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Additional tumor assessments may be conducted based on the investigator's decision.
Phase 2 part patients, who discontinue study treatment 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.

For phase 2 part, all patients who discontinue study drug will be followed every 3 months (±1 month) until death, loss to follow-up, withdrawal of consent for survival follow-up, or EOS, whichever comes first.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, with exception of corneal AEs which will be also evaluated according to non-CTCAE grading as defined in the protocol. DLTs are defined in Section 8.3.

The dose and schedule of study treatment are outlined in Table 6.a.

Table 6.a Study Drug Doses and Schedules of Administration

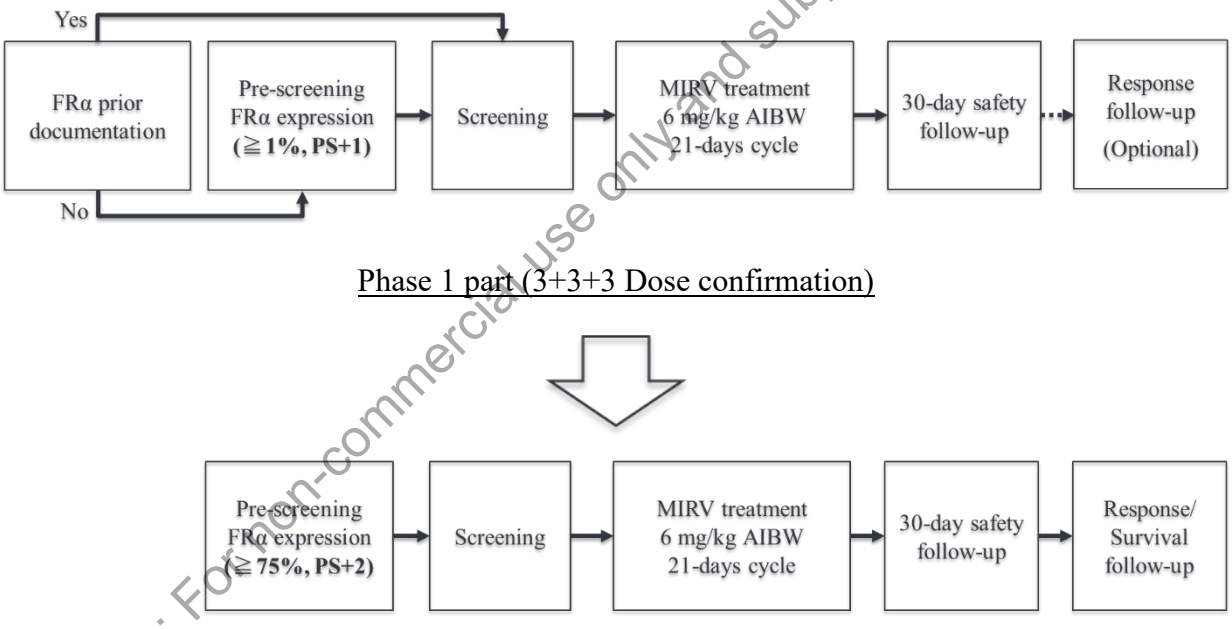
Drug	Dose and Route of Administration	Dosing Schedule
MIRV (TAK-853)	6.0 mg/kg AIBW IV	Day 1 of a 3-week cycle

Abbreviations: MIRV (TAK-853) = mirvetuximab soravtansine; AIBW = adjusted ideal body weight
IV = intravenous

A schematic of study design in is included as Figure 6.a. The treatment schedule of MIRV of Phase 1 and Phase 2 parts are provided in Figure 6.b and Figure 6.c, respectively.

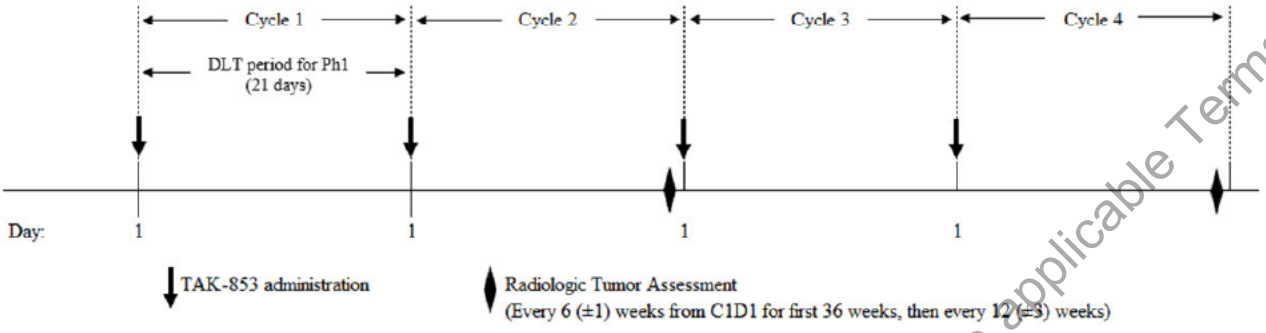
The schedule of assessments for the Phase 1 part is listed in Appendix A and the schedule of assessments for the Phase 2 part is listed in Appendix A, respectively.

Figure 6.a Schematic of Study Design (Phase 1 and Phase 2 parts)



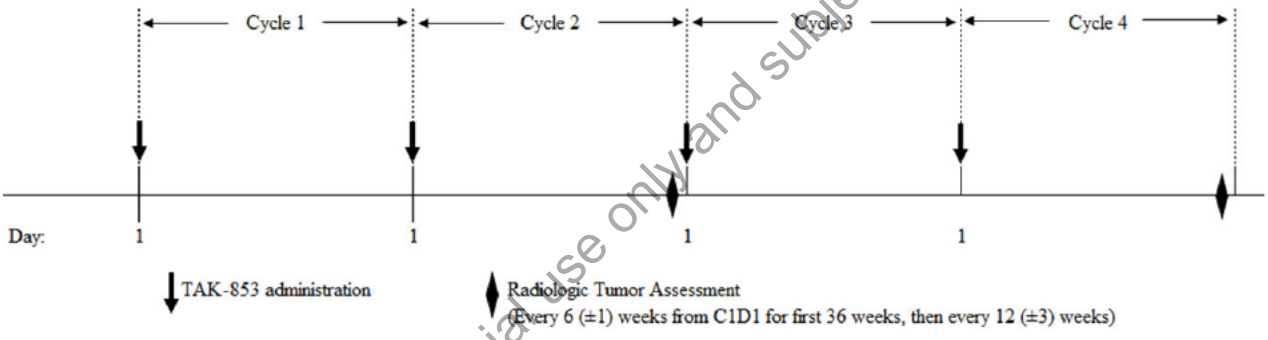
Abbreviations: AIBW = adjusted ideal body weight; FRα = folate receptor α; MIRV = mirvetuximab soravtansine

Figure 6.b Treatment schedule of MIRV (Phase 1 part)



Abbreviations: DLT = dose-limiting toxicity; MIRV = mirvetuximab soravtansine

Figure 6.c Treatment schedule of MIRV (Phase 2 part)



Abbreviations: MIRV = mirvetuximab soravtansine

6.2 Number of Patients

Phase 1 part: At least 3 (up to 9) patients will be enrolled in this study from approximately 2 study centers in Japan.

Phase 2 part: Approximately 22 patients will be enrolled in this study from approximately 20 study centers in Japan.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

For purposes of this study in both parts of Phase 1 and Phase 2, the period of safety observation extends from the time of prescreening informed consent until the 30-day Follow-up safety visit unless additional follow-up safety information is requested as described in Section 9.5.5 and Section 10.0.

For phase 1 part, if patients discontinue study drug without documented PD, a tumor assessment is to be performed at the EOS visit or 30-day Follow up visit, if not performed within the

previous 6 weeks. Additional tumor assessments may be conducted based on the investigator's decision.

For phase 2 part, short-term follow-up for patients who discontinue study drug without documented PD will be followed per RECIST v1.1 every 6 weeks (± 1 week) from C1D1 for the first 36 weeks then every 12 weeks (± 3 weeks) until PD, until the patient begins subsequent anticancer treatment, the patient dies, or the patient withdraws consent, whichever comes first. For phase 2 part, all patients will be followed every 3 months (± 1 month) for survival until death, loss to follow-up, withdrawal of consent for survival or until EOS, whichever comes first.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final data cutoff for the clinical study report will occur after all patients have discontinued treatment or been transferred to a long-term safety study or a similar program (Section 6.4). The data cutoff for primary analyses in phase 2 part will occur after all patients enrolled in the study have had the opportunity to undergo radiographic tumor assessment at least twice or discontinued treatment prematurely.

Patients previously discontinued from study treatment will undergo the End of Treatment (EOT) visit.

For phase 1 part, patients will be followed by 30-day Follow-up visit.

For phase 2 part, patients will continue to be followed every 3 months (± 1 month) from the EOT visit as described in Section 9.11 unless patients experience PD or withdrawal.

Definition of End-of-Study:

The clinical trial will continue until completion of the OS follow-up for all subjects or the time of marketing approval of MIRV for the phase 2 part indication(s), whichever occurs first. In case there will be on-treatment subjects at marketing approval of MIRV, the clinical trial will continue until the marketed MIRV can be available on prescription to all subjects in phase 2 part.

Note: If a marketing approval of MIRV is obtained in Japan before the study completion/withdrawal, this study will be continued as a post-marketing clinical study in compliance with the GCP and the Good Post-marketing Study Practice (GPSP).

Study completion:

The estimated time frame for study completion is 9 months for phase 1 part and 24 months for phase 2 part.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.b for disclosures information for all primary and secondary endpoints.

Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Phase1 part		
Primary:		
• Number and percentage of patients with DLTs in Cycle 1.	The number and percentage of patients with DLTs in Cycle 1 in the safety analysis set.	Prior to administration on Cycle 2 Day 1.
• The number and percentage of patients with TEAEs.	The number and percentage of patients with TEAEs in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with Grade 3 or higher TEAEs.	The number and percentage of patients with Grade 3 or higher TEAEs in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with serious TEAEs	The number and percentage of patients with serious TEAEs in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with TEAEs leading to drug discontinuation.	The number and percentage of patients with TEAEs leading to drug discontinuation in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with TEAEs leading to infusion interrupted.	The number and percentage of patients with TEAEs leading to dose infusion interrupted in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with TEAEs leading to dose delayed.	The number and percentage of patients with TEAEs leading to dose delayed in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with TEAEs leading to dose reduction.	The number and percentage of patients with TEAEs leading to dose reduction in the safety analysis set.	Approximately 1 year
• The number and percentage of patients with AECI.	The number and percentage of patients with AECI in the safety analysis set.	Approximately 1 year
Secondary:		
PK parameters for intact ADC, total Ab, DM4 and S-methyl DM4: C_{max}, AUC, $t_{1/2}$, CL, V_{ss}, t_{max} as applicable.	PK parameters for intact ADC, total Ab, DM4 and S-methyl DM4 in the PK analysis set: C_{max}, AUC, $t_{1/2}$, CL, V_{ss}, t_{max} as applicable.	Approximately 1 year
Incidence of immunogenicity of MIRV.	Incidence of immunogenicity of MIRV in the safety analysis set.	Approximately 1 year
Phase 2 part		
Primary:		Approximately 2 years
• ORR based on the investigator's assessment using RECIST v1.1	The proportion of patients who are confirmed to have achieved CR or PR in the FAS.	

Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Secondary:		Approximately 2 years
• Duration of response based on the investigator's assessment, defined as the time from the first assessment of either complete or partial response until progressive disease.	Duration of response based on the investigator's assessment, defined as the time from the first assessment of either complete or partial response until progressive disease in the FAS.	
• Intact ADC, total Ab, DM4 and S-methyl DM4 concentration.	Intact ADC, total Ab, DM4 and S-methyl DM4 concentration in the PK analysis set.	Approximately 2 years
• Incidence of immunogenicity of MIRV.	Incidence of immunogenicity of MIRV in the safety analysis set.	Approximately 2 years

Abbreviations: ADC = antibody-drug conjugate; AUC = area under the plasma concentration-time curve; CL = total clearance; C_{max}= maximum observed plasma concentration; DLT = dose-limiting toxicity; FAS = full analysis set; ORR = objective response rate; PK = pharmacokinetics; TEAE = treatment emergent adverse event; t_{max} = time of first occurrence of maximum observed concentration; $t_{1/2}$ = terminal half-life; V_{SS} = volume of distribution at steady state.

6.3.4 Total Study Duration

Phase 1 part:

It is anticipated that patient enrollment (for 3 patients) will be completed within approximately 1 month from the enrollment of the first patient into the study.

It is anticipated that this study will last for approximately 9 months.

Phase 2 part:

It is anticipated that patient enrollment will be completed within approximately 8 months from the enrollment of the first patient into the study.

It is anticipated that this study will last for approximately 24 months.

6.4 Posttrial Access

Posttrial access to MIRV is not planned for this study. Please also refer to Section 6.3.2.

6.4.1 Duration of Posttrial Access

Not applicable.

7.0 STUDY POPULATION

Phase 1 part: Patients with FRα-positive (*) advanced ovarian cancer or other solid tumor (* denotes ≥1% of viable tumor cells with membrane staining at ≥1+ intensity or prior documentation of tumor FRα expression)

Phase 2 part: Patients with platinum-resistant ovarian cancer with high FRα expression (**), who have received 1 to 3 prior lines of therapy (** denotes ≥75% of viable tumor cells with membrane staining ≥2+ intensity, performed at the central laboratory)

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

7.1.1 Inclusion Criteria for Phase 1 part

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

   a. All patients must have a pathologically documented, following advanced solid tumor known to express FRα, that is resistant or refractory to standard treatment, for which no standard treatment is available, or when the patient refuses standard therapy.

      - Ovarian cancer
      - Endometrial cancer
      - Non-small cell lung cancer (NSCLC)
      - Triple-negative breast cancer (TNBC)
      - Cholangiocarcinoma
      - Colorectal cancer (CRC)
      - Gastro-esophageal adenocarcinoma

      Note: Patients with a solid tumor type other than the above will be eligible as long as there is prior documentation of tumor FRα expression.

   b. All patients without prior documentation of tumor FRα expression by IHC must be 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 IHC confirmation of FRα positivity of ≥1% of viable tumor cells with membrane staining at ≥1+ intensity for entry into the Phase 1 part.

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

   d. Patients must have measurable or non-measurable disease (such as large abdominal masses that cannot be accurately measured) according to RECIST v1.1.

2. Japanese patients aged ≥ 18 years old at the time of informed consent.
3. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
4. Time from Prior Therapy:
    - Systemic anti-neoplastic therapy: five half-lives or four weeks, whichever is shorter (6 weeks for prior nitrosoureas or mitomycin C)
    - FRα-targeted therapy: five half-lives or four weeks, whichever is longer
    - Radiotherapy: wide-field radiotherapy (e.g. affecting at least 30% of the bone marrow) completed at least four weeks, or focal radiation completed at least two weeks, prior to starting study drug.
5. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities.
6. Major surgery must be completed at least 4 weeks prior to first dose of MIRV. Patients must have recovered or stabilized from the side effects of prior surgery.
7. Patients must have adequate hematologic, liver and kidney function as defined by the following parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1,500/μL) without granulocyte colony stimulating factor (G-CSF) in the prior 10 days or long-acting WBC growth factors in the prior 20 days
    b. Platelet count ≥ 100.0 x 10^9/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
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance of ≥ 30 mL/minute (as calculated using the Cockcroft Gault equation),
    e. AST ≤ 2.5 x ULN; ALT ≤ 2.5 x ULN (AST, ALT < 5 x ULN if liver metastases), and
    f. Total bilirubin ≤ 1.5 x UNL (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
8. Patients with central nervous system (CNS) disease involvement are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study Day 1 and they meet all of the following criteria:
    (1) Residual neurological symptoms ≤ Grade 1
    (2) No dexamethasone requirement, and
    (3) Follow-up MRI shows no progression of treated lesions and no new lesions appearing.

9. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements
10. Women of childbearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must
    - Agree to use 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed (e)consent (or 14 days before the initiation of study medication for oral contraception) through 7 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
11. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study treatment.
12. Male patients must, even if he is surgically sterilized (i.e., status postvasectomy),
    - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

7.1.2 Inclusion Criteria for Phase 2 part

1. Japanese female patients ≥ 18 years of age
2. Patients must have a confirmed diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
3. Patients must have platinum-resistant disease:
    a. 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 last dose date of platinum
    b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum

    Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression

Note: Patients who are primary 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 therapy
5. Patients must be 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 IHC confirmation of FRα expression (reported as "positive") as defined by the Ventana FOLR1 Assay. Tumors must be confirmed FRα-high as defined by FRα positivity of ≥75% of viable tumor cells with membrane staining at ≥2+ intensity for entry into the Phase 2.
6. Patients must have at least one lesion that meets the definition of measurable disease by RECIST v1.1 criteria (radiologically measured by the Investigator) (See Appendix E for lesions with prior local treatment).
7. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy is appropriate as the next line of treatment:
    a. Neoadjuvant ± adjuvant considered one line of therapy
    b. Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered as part of the preceding line of therapy (i.e., not counted independently)
    c. Therapy changed due to toxicity in the absence of progression will be considered as part of the same line (i.e., not counted independently)
    d. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance
8. Patient must have an ECOG PS of 0 or 1
9. Time from prior therapy:
    a. Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)
    b. Focal radiation completed at least 2 weeks prior to first dose of study drug
10. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
11. Major surgery must be completed at least 4 weeks prior to first dose and have recovered or stabilized from the side effects of prior surgery
12. Patients must have adequate hematologic, liver, and kidney functions defined as:
    a. ANC ≥ 1.5 x 10^9/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 10^9/L (100,000/μL) without platelet transfusion in the prior 10 days
    c. Hemoglobin ≥ 9.0 g/dL without PRBC transfusion in the prior 21 days

d. Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance of ≥ 30 mL/minute (as calculated using the Cockcroft Gault equation).

e. AST and ALT ≤ 3.0 x ULN

f. Total bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)

g. Serum albumin ≥ 2 g/dL

13. Patients or their legally authorized representative must be willing and able to sign the ICF and to adhere to the protocol requirements

14. WCBP, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must

- Agree to use 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed (e)consent (or 14 days before the initiation of study medication for oral contraception) through 7 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

15. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study drug

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

7.2.1 Exclusion Criteria for Phase 1 part

1. Patients with > Grade 1 peripheral neuropathy per NCI CTCAE v5.0
2. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.
3. Serious concurrent illness, including, but not limited to the following:

a. Clinically relevant active infection including

- Active hepatitis B or C infection (whether or not on active antiviral therapy)
- Human Immunodeficiency Virus (HIV) infection
- Active cytomegalovirus infection

- Active COVID-19/SARS-CoV-2 infection. Although SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines and standards
- Any other known concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

Note: Testing at screening for hepatitis is required, while not required for the remaining infections above unless clinically indicated. Patients with known hepatitis B surface antigen seropositivity and/or detectable hepatitis C virus RNA will be excluded. Patients who have positive hepatitis B core antibody and/or hepatitis B surface antibody can be enrolled but must have an undetectable serum hepatitis B virus DNA. Patients who have positive hepatitis C virus antibody must have an undetectable hepatitis C virus RNA serum level. Patients will be monitored and managed according to Guideline for the prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection (The Japan Society of Hepatology 2022).

b. Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
   - Myocardial infarction ≤ 6 months prior to first dose of study medication
   - Unstable angina pectoris
   - Uncontrolled congestive heart failure (New York Heart Association > class II)
   - Uncontrolled ≥ Grade 3 hypertension (per NCI CTCAE v5.0)
   - Uncontrolled cardiac arrhythmias
   - Severe aortic stenosis
   - ≥ Grade 3 cardiac toxicity following prior chemotherapy

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

d. Previous clinical diagnosis of interstitial lung disease (ILD), including pneumonitis.

4. Any other concomitant anti-cancer treatment such as immunotherapy, biotherapy, radiotherapy, chemotherapy, investigative therapy, or high-dose steroids; however, low-dose steroids and Luteinizing Hormone Releasing Hormone (LHRH) at doses that have been stable for ≥ 14 days are permitted for patients with prostate cancer
5. Known hypersensitivity to previous monoclonal antibody therapy or maytansinoids, or study drugs and/or any of their excipients

6. Prior history of solid tumor malignancy within the last 3 years except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment)
7. Patients with required use of folate-containing supplements (e.g., folate deficiency)
8. Patients who have received prior allogeneic or autologous bone marrow transplants
9. Women who are pregnant or lactating

   Note: Patients who may be in the very early stage of pregnancy based on the doctor's interview with a negative pregnancy test are excluded from the study. Patients who are lactating will be eligible if they discontinue breastfeeding before the first dose of study drug.

7.2.2 Exclusion Criteria for Phase 2 part

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumor
2. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first line platinum-containing chemotherapy
3. Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per NCI CTCAE v5.0
5. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision
6. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
   a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
   b. HIV infection
   c. Active cytomegalovirus infection
   d. Active COVID-19/SARS-CoV-2 infection. Although SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines and standards.
   e. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

Note: Testing at screening for hepatitis (a) is required, while not required for the remaining infections above (b-e) unless clinically indicated.
Patients with known hepatitis B surface antigen seropositivity and/or detectable hepatitis C virus RNA will be excluded. Patients who have positive hepatitis B core antibody and/or hepatitis B surface antibody can be enrolled but must have an undetectable serum hepatitis B virus DNA. Patients who have positive hepatitis C virus antibody must have an undetectable hepatitis C virus RNA serum level. Patients will be monitored and managed according to Guideline for the prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection (The Japan Society of Hepatology 2022).

7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
    a. Myocardial infarction ≤ 6 months prior to first dose of study medication
    b. Unstable angina pectoris
    c. Uncontrolled congestive heart failure (New York Heart Association > class II)
    d. Uncontrolled ≥ Grade 3 hypertension (per NCI CTCAE v5.0)
    e. Uncontrolled cardiac arrhythmias
9. Patients with a history of hemorrhagic or ischemic stroke within six months prior to first dose of MIRV
10. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
11. Patients with a previous clinical diagnosis of ILD, including pneumonitis
12. Patients with required use of folate-containing supplements (e.g., folate deficiency)
13. Patients with prior hypersensitivity to monoclonal antibodies or maytansinoids
14. Women who are pregnant or lactating

    Note: Patients who may be in the very early stage of pregnancy based on the doctor's interview with a negative pregnancy test are excluded from the study. Patients who are lactating will be eligible if they discontinue breastfeeding before the first dose of study drug.

15. Patients with prior treatment with MIRV or other FRα-targeting agents
16. Patients with untreated or symptomatic CNS metastases
17. Patients with a history of other malignancy within 3 years prior to first dose of MIRV

Note: does not include tumors with a negligible risk for metastasis or death (e.g., adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma *in situ* of the cervix or breast)

18. Prior known hypersensitivity reactions to study drugs and/or any of their excipients
19. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order
20. Simultaneous participation in another clinical trial

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

8.0 STUDY DRUG

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

8.1 Assignment of Patient Number

Patient numbers are assigned in sequential order as patients sign the pre-screening informed consent to participate (For phase 1 part, for patients who have prior documentation of FRα expression, patient numbers are assigned at the time of signing main ICF).

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

8.2 Japan Drugs, Products and/or Devices Used in the Clinical Trial other than Investigational Medicinal Product (J-non-IMP)

Not applicable.

8.3 Definitions of DLT (For Phase 1 part only)

Toxicity will be evaluated according to the NCI CTCAE, v5.0. DLT will be defined as any of the events of Table 8.a that are considered by the investigator to be at least possibly related to therapy with MIRV and that occur during Cycle 1.

If a patient experiences a DLT as outlined in Table 8.a, the study treatment must be stopped and the toxicity(ies) in question must be followed until resolution or stabilization. Investigators should confer with the sponsor regarding retreatment of the subject with MIRV. If treatment is to be resumed after discussion with the sponsor, then retreatment criteria must be met (Section 8.5.3) and administration must be resumed at one lower dose level (Section 8.5.4).

The decision of DLT or not for Grade 3 or higher anemia and anemia requiring red blood cell transfusion will be discussed and agreed on the End of Cohort meeting. Tolerability will be evaluated in consideration of all safety information including AEs that occurred in patients who were excluded from DLT evaluation for reasons other than DLT.

Table 8.a Definition of DLT

TOXICITY	DLT DEFINITION CRITERIA
Dose delays	Failure to meet re-treatment criteria (Section 8.5.3) within 14 days Note: Exception for eye pain or reduction in visual acuity: Within 21 days as defined in the Non-hematologic and other DLTs below.
Hematology	• NCI CTCAE Grade 4 neutropenia ≥ 7 days. • NCI CTCAE Grade 3 or 4 neutropenia with single temperature reading ≥ 38.3°C or sustained temperature reading of > 38°C for > 1 hour • NCI CTCAE Grade 3 thrombocytopenia, associated with clinically significant bleeding that requires transfusion therapy • NCI CTCAE Grade 4 thrombocytopenia
Non-hematologic and other DLTs	• ≥ NCI CTCAE Grade 3 nausea or vomiting despite the use of optimal antiemetic treatments • ≥ NCI CTCAE Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments • Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of study drugs due to participant intolerance • Eye pain or reduction in visual acuity that does not respond to topical ophthalmic therapy and does not improve to Grade 1 within 21 days of initiation of topical ophthalmic therapy • Other non-hematologic toxicities of NCI CTCAE ≥ Grade 3 except for the following: – AEs related to underlying disease – Alopecia – NCI CTCAE Grade 3 fatigue – Lymphopenia is not considered DLT unless accompanied by clinically-significant infection – Isolated, asymptomatic Grade 3 abnormalities in biochemistry laboratory values that last for ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention.

For any dose limiting hepatic toxicity that does not resolve to baseline within 7 days, an abdominal CT scan must be performed to assess whether it is related to disease progression.

To the extent possible, administration of coronavirus disease 2019 (COVID-19) vaccinations should be avoided during the Cycle 1 DLT window; however, vaccination timing remains at the discretion of the investigator following the guidance in Section 8.6.

8.4 Dose Confirmation Rules (For Phase 1 part only)

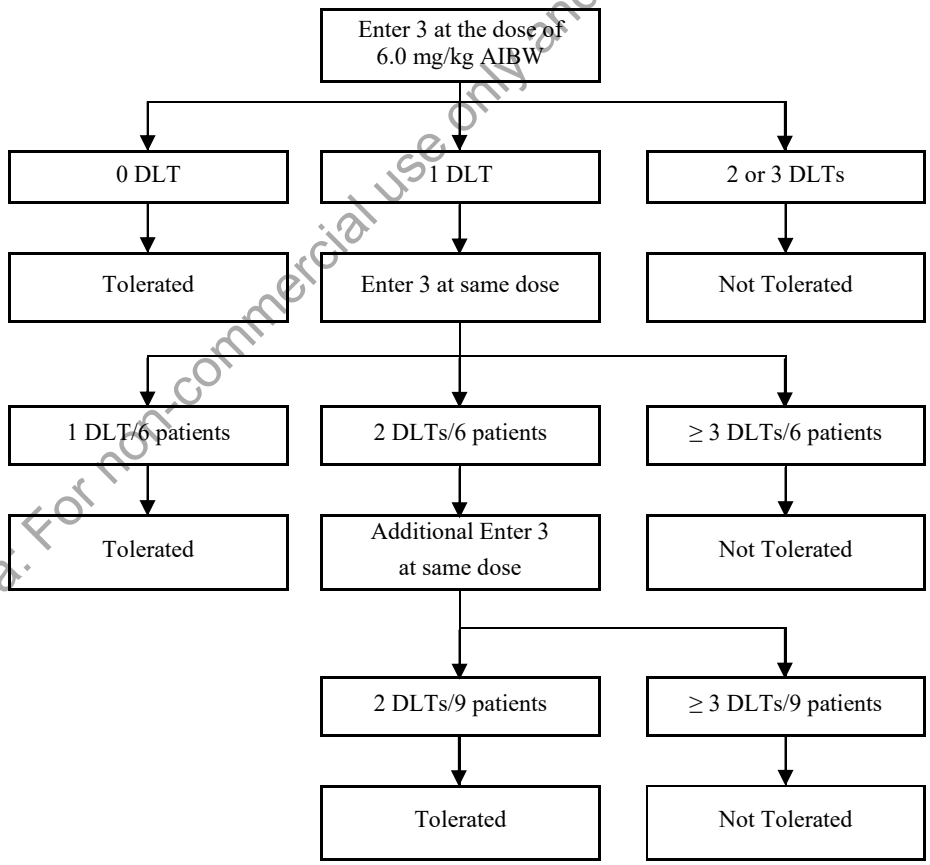
The dose intervals will follow the 3+3+3 confirmation rules, starting with the treatment of 3 patients at a planned dose level:

- Initially, 3 patients will be enrolled at dose level 6.0 mg/kg.
- If none of the 3 patients experiences a DLT during the first cycle, this dose will be considered tolerable and used for Phase 2 part.

- If 2 or more of the 3 patients experience a Cycle 1 DLT, this dose level will be considered not tolerated.
- If 1 of the 3 patients exhibits a DLT in the first cohort, then that cohort will be expanded to a total of 6 patients.
  - If no more than 1 patient of the 6 total patients has a Cycle 1 DLT, this dose will be considered tolerable and used for Phase 2 part.
  - If 3 or more of the 6 patients experience a Cycle 1 DLT, this dose level will be considered not tolerated.
  - If 2 of the 6 patients have a Cycle 1 DLT, 3 additional patients will be enrolled. If any of those 3 additional patients have a Cycle 1 DLT, this dose will be considered not tolerated and the trial will be stopped. If none of the 3 additional patients have a Cycle 1 DLT, this dose may be considered tolerable and used for Phase 2 part.

Figure 8.a is a diagrammatical representation of these rules.

Figure 8.a DLT Evaluation Algorithm



Abbreviations: AIBW = adjusted ideal body weight; DLT= dose-limiting toxicity.

8.5 Dose Modification Guidelines

Detailed MIRV dose modification guidelines are described below.

8.5.1 MIRV (TAK-853, mirvetuximab soravtansine)

8.5.1.1 Mirvetuximab Soravtansine-related Adverse Events

Dose modifications for MIRV-related AEs are described in Table 8.b.

Table 8.b Dose Modifications for MIRV-related Adverse Events

Severity Grade (NCI CTCAE v5.0)	Dose Modifications for MIRV [a]
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is ≥ 1.5 x10^9 /L (1,500 /µL) and resume at the same dose level
Grade 4	Hold drug until ANC is ≥ 1.5 x10^9 /L (1,500 /µL) and then resume at one lower dose level
Febrile neutropenia Grade 3 or 4 (with a single temperature reading ≥ 38.3°C or a sustained temperature of > 38°C for > one hour)	Hold drug until ANC is ≥ 1.5 x10^9 /L (1,500 /µL) and then resume at one lower dose level
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until PLT count is ≥ 100 x 10^9 /L (100,000/µL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until PLT count is ≥ 100 x 10^9 /L (100,000/µL) and then resume at one lower level
Non-hematological	
Nausea and Vomiting	
Grade 3 (despite use of optimal antiemetics)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue
Diarrhea	
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue
Ocular Disorders	Refer to Section 8.10.3
Noninfectious Pneumonitis	Refer to Section 8.10.4
Infusion-related Reactions	Refer to Section 8.10.6
All Other Non-hematological Toxicities (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemistry laboratory abnormalities that last for < 7 days including electrolyte abnormalities that respond to medical intervention)	
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 seven days, an abdominal CT scan must be performed to assess whether it is related to disease progression.
≥ Grade 3 Cardiac events (excluding Grade 3 hypertension)	Permanently discontinue
Grade 4 non-hematological toxicities	Permanently discontinue

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; NCI CTCAE = national cancer institute common terminology criteria for adverse events; PLT = platelets.

[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will results in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

8.5.2 Intrapatient Dose Escalation

Not applicable.

8.5.3 Criteria for Beginning a Subsequent Treatment Cycle

In the absence of a TEAE that requires dose modification (as specified in the management guidance for a particular toxicity, see Section 8.5.1.1), a patient must meet the following criteria to receive study drug at any cycle:

- ANC must be ≥ 1.5 x 10^9 /L (1,500/µL)
- Platelet count must be ≥ 100 x 10^9 /L (100,000/µL)
- All non-hematologic toxicities which are related to study drug, must be ≤ Grade 2 or returned to baseline; the exceptions to this rule being:
  - Treatment-emergent ocular disorders, which must have recovered to ≤ Grade 1 or baseline
  - Treatment-emergent pneumonitis, which must have recovered to ≤ Grade 1

8.5.4 Criteria for Dose Reduction

MIRV dose reduction will be as described in Table 8.c.

Table 8.c Mirvetuximab Soravtansine Dose Reduction Dose Levels

If the patient was receiving MIRV at:	Dose should be reduced to:
6.0 mg/kg AIBW	5.0 mg/kg AIBW
5.0 mg/kg AIBW	4.0 mg/kg AIBW
4.0 mg/kg AIBW	Permanently discontinue
Reduction of MIRV below 4.0 mg/kg will not be permitted. Dose re-escalation is not permitted.	

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine.

8.5.5 Criteria for Discontinuation of MIRV 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 8.5.1.1)
- ≥ Grade 3 pneumonitis event (Section 8.10.4)
- Non-hematologic events of Grade 4 severity (Section 8.5.1.1)
- Ocular events of Grade 4 severity (Section 8.10.3)
- Failure to meet re-treatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity unless otherwise specified in the management guidance for a particular toxicity. In such cases, continuation of MIRV may be considered for those patients who have experienced clinical benefit if agreed upon between the sponsor and the investigator.

8.6 Prohibited Concomitant Medications and Procedures

Phase 1 part

- Any investigational agent other than MIRV
- Prophylactic use of erythropoietic and granulocyte growth factors in Cycle 1
- Administration of G-CSF and long-acting WBC growth factors is NOT permitted within 10 and 20 days, respectively, prior to screening test.
  1) Folate-containing supplements should not be taken during the study.
  2) All non-study related antineoplastic therapy including but not limited to cytotoxic, immunotherapy, and vascular endothelial growth factor (VEGF)-targeted therapy, is prohibited while on study drug.
- Palliative radiotherapy for local peripheral metastases not being used as target lesions is allowed. However, the need for such therapy may be an indication of disease progression and should be discussed with the Sponsor prior to implementation. Radiotherapy for central metastases (e.g. vertebral) will not be allowed; the need for such radiotherapy while on study will be seen as an indication of disease progression and the patient should be withdrawn from the study.
- To the extent possible, administration of coronavirus disease 2019 (COVID-19) vaccinations should be avoided during the Cycle 1 DLT window; however, vaccination timing remains at the discretion of the investigator.

Phase 2 part

- Any investigational agent other than MIRV
- Administration of G-CSF and long-acting WBC growth factors is NOT permitted within 10 and 20 days, respectively, prior to screening test.
  1) Folate-containing supplements should not be taken during the study.
  2) All non-study related antineoplastic therapy including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy, is prohibited while on study drug.
- Palliative radiotherapy during study treatment is not allowed.

8.7 Discouraged Concomitant Medications and Procedures

Strong CYP3A4 inhibitors and inducers, if clinically feasible, should be avoided as concomitant medications for at least 14 days before the start of treatment and throughout the study. If strong CYP3A4 inhibitors and inducers cannot be avoided, closely monitor toxicities (Appendix G). Grapefruits, grapefruit juice, Seville oranges, pomelos, and starfruits should also be avoided.

8.8 Permitted Concomitant Medications and Procedures

1) Antiemetic and Antidiarrheal Medications

   An antiemetic (e.g., serotonin receptor subtype 3 [5-HT_3] serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) medication is recommended before each MIRV dose. Additional antiemetics and/or antidiarrheal (e.g., loperamide) medications may be used any time at the discretion of the treating physician.

2) Hematopoietic Growth Factors

   Patients receiving recombinant erythropoietin (EPO) or darbepoetin-α before study start may continue to receive pretreatment doses.

   The use of erythropoietic and granulocyte growth factors in accordance with clinical guidelines may be implemented at the discretion of the treating physician. **However, prophylactic use of those growth factors is not allowed in Cycle 1 during Phase 1.** They should not be used in this study in a manner that would help establish eligibility for the study.

3) Anticoagulants

   The use of anticoagulant agents is allowed. Please see the next 4). if using apixaban and rivaroxaban due to CYP3A interaction potential.

4) Medications that are MDR1 inhibitors, CYP3A4 sensitive substrates and CYP3A4 substrates with narrow therapeutic index

   Both DM4 and S-methyl DM4 are substrates for multidrug resistance 1 (MDR1) efflux transporter. Their exposure could potentially increase in the presence of MDR1 efflux transporter inhibitors. In vitro metabolism data also indicates that DM4 is a time-dependent inhibitor of CYP3A4. The risk of a significant in vivo drug-drug interaction caused by inhibition of CYP3A4 is unknown. If MDR1 inhibitors, CYP3A4 sensitive substrates and CYP3A4 substrates with narrow therapeutic index are used, AEs should be closely monitored (Appendix G).

5) Other Concomitant Medications

   Medications for the treatment of AEs or cancer symptoms (e.g., PRBC and pain medications), are allowed. Prophylactic use of steroids and/or antihistamines will be considered if needed to alleviate mild-moderate infusion reactions. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry including antiemetics and antidiarrheals will be allowed to continue.

8.9 Precautions and Restrictions

It is not known what effects MIRV has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or avoid

impregnating a partner. Patients of reproductive potential should use effective methods of contraception through defined periods during and after study treatment as specified below.

Reproductively female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR

  If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing the ICF (or 14 days before the initiation of study medication for oral contraception) through 7 months after the last dose of study drug,

Highly Effective Methods approved or certificated in Japan	**Other Effective Methods (Barrier Methods) approved or certificated in Japan**
Intrauterine device (IUD) Hormonal (birth control pills/oral contraceptives[a])	Male condom

[a] Only progestin/estrogen mixed preparation for inhibition of ovulation is acceptable and available in Japan.

  OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Reproductively male patients in the phase 1 part of the study, even if surgically sterilized (i.e., status postvasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Before starting treatment, patients should be advised to seek counseling on sperm or egg storage.

8.10 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed below, please refer to Section 8.5.

8.10.1 Nausea or Vomiting

Treatment-related nausea (46% all grade; 1% Grade 3+) and vomiting (16% all grade; 1% Grade 3+) have been reported in patients treated with MIRV, despite premedication with

dexamethasone (IMGN853-0403). Therefore, it is recommended that an antiemetic (e.g., 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) medication is provided before each MIRV dose (Section 8.8). Additional antiemetics may be used any time at the discretion of the treating physician, according to institutional or other practice guidelines American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and NCCN. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea.

8.10.2 Diarrhea

Mild to moderate diarrhea has been reported in patients treated with MIRV. Patients should be advised to contact their treating physician at the first sign of diarrhea. Patients may then be treated according to standard institutional practice.

8.10.3 Ocular Disorders

Changes in visual acuity resulting from reversible keratopathy have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker (Younes 2012). Patients receiving MIRV in the Phase 1 and 3 trials (IMGN853-0401, IMGN853-0403, IMGN853-0416, and IMGN853-0417) reported ocular AEs consistent with reversible keratopathy/corneal epitheliopathy. At the 6.0 mg/kg AIBW Q3W dose level, Grade 3 TEAEs of dry eye, keratopathy, vision blurred, eye pain, and photophobia were reported in Phase 3 Studies.

8.10.3.1 Monitoring and Preventive Measures

In early dose escalation, there was a relationship between MIRV plasma exposure with increased likelihood of an ocular event as well as with response. Exposure-response modeling suggested that a dose of 6.0 mg/kg AIBW provided adequate exposure for response while also maintaining overall exposure within a range that decreased the potential for ocular AEs. Due to the observation of ocular disorders consistent with reversible keratopathy/corneal epitheliopathy in patients treated with MIRV, ocular function will be carefully monitored. Ocular symptom assessments will be performed at baseline and at Day 1 of every cycle thereafter (Appendix A). Complete ophthalmologic examinations will be performed in all patients at baseline and every other cycle for the first 8 cycles. They will be also performed every other cycle if there is a TEAE reported.

Patients are advised to avoid using contact lenses while on MIRV. Baby shampoo and a soft cloth may be used to clean the eyelid, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface. Please refer to Section 8.12.2 for details on the prophylactic use of steroid eye drops and lubricating artificial tears. The use of UVA/UVB sunglasses is recommended in full daylight during the study. If patients report signs or symptoms of ocular disorders, including, but not limited to, blurred vision or eye irritation, the management and dose modification guidelines outlined in Table 8.d should be followed.

8.10.3.2 Management and Dose Modification Guidelines

If a patient develops new NCI CTCAE > Grade 1 ocular symptoms (refer to non-CTCAE grading in Table 10.a for corneal AEs), MIRV will be held until the patient undergoes a complete examination by an eye care professional. If a patient is found to have confluent superficial keratitis, a cornea epithelial defect, or a 3-line or more loss in best corrected visual acuity (BCVA), MIRV dosing must be interrupted until findings improve to nonconfluent keratitis, prior baseline, or complete resolution or asymptomatic status. Uveitis must improve to Grade 1 or better or prior baseline. Treatment with MIRV may resume if the ocular event improves as above within 28 days of the next scheduled MIRV dose (refer to Table 8.d and Table 8.e for details). Ocular AEs of any severity should be followed to complete resolution, pre-treatment baseline, or are deemed to be irreversible according to the eye care professional. Findings of keratopathy require initiation of corticosteroid eye drops as secondary prophylaxis for patients receiving MIRV; see Section 8.12.2. For 2 or more overlapping ocular AEs (ocular disorders/corneal adverse reactions), dose modification should be based on the ocular AE of greater severity. Any other ocular AEs not specifically noted in Table 8.d or Table 8.e will be managed at the discretion of the treating physician in consultation with their eye care professional.

Subsequent eye examinations will be scheduled to occur in every other cycle going forward from the time that the corneal AE was initially reported until resolution of the corneal toxicity to patient's prior baseline or complete resolution or until it is deemed irreversible even if the results of the patient's ocular symptom assessment show no obvious clinical findings. For patients with ongoing keratitis/keratopathy, a cornea epithelial defect, or a 3-line or more loss in BCVA at the 30-Day Safety Follow-up visit, an ophthalmic examination should be done every 30 days until complete resolution, stabilization without likelihood of improvement in the opinion of the eye care professional, or return to pre-treatment baseline. Ocular symptoms (e.g., blurred vision) should also be assessed at this time.

A complete ophthalmic examination will be performed at baseline, before Cycles 3, 5, and 7 prior to dosing for all patients regardless of reporting symptoms (see Appendix A), and at the 30-Day Safety Follow-up visit (+ 2 weeks). Patients requiring an ophthalmologic examination due to symptoms prior to cycle 2 or 4 will then proceed to every-6-week examinations as indicated by findings and do not require the routine, asymptomatic examinations prior to Cycles 3, 5, and 7 in addition.

Management of treatment-emergent ocular AEs with inflammatory characteristics or other noncorneal/visual acuity ocular AEs should include measures as indicated by an eye care professional.

Recommended dosage modifications for corneal adverse reactions should be based on both corneal examination findings, using the system outlined in Table 8.d, and changes in BCVA. Dose modification for noncorneal ocular AEs other than uveitis (Table 8.e) is at the discretion of the treating physician, in collaboration with an eye care professional.

Note: Table 8.d describes the management of corneal adverse reactions with regard to MIRV dosing. Corneal AEs will be described and classified on the ocular case report form to enter and record this data in the electronic database for the study. Due to limitations of NCI CTCAE grading in adequately capturing these toxicities, severity of corneal AEs should be assessed with NCI CTCAE grading as well as grading according to Table 8.d, which is not based on NCI CTCAE (see Section 10.1.5 Classification of Corneal AEs).

Table 8.d Management of Corneal Adverse Reactions (Keratitis/Keratopathy)

Ocular Exam Finding[a]	Management	Guidelines for MIRV Dose Modifications
Nonconfluent superficial keratitis[b] or nonconfluent keratopathy[c]	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Patients should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to pre-treatment baseline or nonconfluent superficial keratitis or better or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed	Monitor to complete resolution or return to pre-treatment baseline or asymptomatic status. Continue MIRV dosing.
Confluent superficial keratitis[b] or confluent keratopathy[c], cornea epithelial defect (+Sodium Fluorescein [NaFl] staining), or ≥3-line loss in BCVA	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Patients should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to pre-treatment baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Hold MIRV dosing until AE has resolved to pre-treatment baseline, asymptomatic status or nonconfluent superficial keratitis/keratopathy or better. Patients with corneal adverse reactions lasting < 14 days may be allowed to resume MIRV at the same dose level. Recurrence of toxicity on subsequent cycles despite best supportive care will require a dose reduction to one lower dose level. Patients with corneal adverse reactions lasting ≥ 14 days but no more than 28 days may resume MIRV at one lower dose level. If findings persist > 28 days, continuation at reduced dose level is at the discretion of the investigator in consultation with the sponsor.
Corneal ulcer or clinically significant stromal opacity or BCVA 20/200 or worse	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Patients should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Hold MIRV dosing. Patients may be allowed to resume MIRV at one lower dose level after AE has resolved to nonconfluent keratitis or better or to pre-treatment baseline or asymptomatic status within 28 days. If findings persist > 28 days, continuation at reduced dose level is at the discretion of the investigator in consultation with the sponsor.
Corneal perforation	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Patients should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Permanently discontinue MIRV dosing. Must be reported as a SAE.

Abbreviations: AE = adverse event; BCVA = best corrected visual acuity; MIRV = mirvetuximab soravtansine; SAE = serious adverse event.

[a] Normal = clear cornea, no epithelial defects.

[b] Positive NaFl staining; including punctate epithelial erosion, epithelial erosion, or epithelial defect.

[c] Including corneal epithelial microcysts, microcyst-like corneal epithelial deposits, microcystic epithelial change, punctate epithelial keratopathy, or subepithelial inclusion cyst.

Table 8.e Management of Uveitis

(Refer to Table 8.d for corneal adverse reactions)

Severity Grade (NCI CTCAE v5.0 Grade)	Management	Guidelines for MIRV Dose Modifications
Grade 1	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Monitor for worsening symptoms.	Monitor to complete resolution, return to pre-treatment baseline, asymptomatic status or are deemed to be irreversible. Continue MIRV dosing.
Grade 2	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Repeat complete examination as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold MIRV dosing until AE has resolved to Grade 1 or better. Dose continuation or reduction is at the discretion of the treating physician in consultation with an eye care professional. Monitor to complete resolution, return to pre-treatment baseline, asymptomatic status or are deemed to be irreversible.
Grade 3	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Repeat complete examination as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold MIRV dosing until AE has resolved to Grade 1 or better. Dose continuation is at the discretion of the treating physician in consultation with an eye care professional. If MIRV is continued, dose reduction of one level is required. Monitor to complete resolution, return to pre-treatment baseline, asymptomatic status or are deemed to be irreversible.
Grade 4	Complete eye examination as outlined in Schedule of Assessments (Appendix A). Repeat complete examination as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed irreversible by the investigator.	Permanently discontinue MIRV. Monitor to complete resolution, return to pre-treatment baseline, asymptomatic status or are deemed to be irreversible.

Abbreviations: AE = adverse event; MIRV = mirvetuximab soravtansine; NCI CTCAE = national cancer institute common terminology criteria for adverse events.

8.10.4 Monitoring for Non-infectious Pneumonitis

Non-infectious pneumonitis has been observed after the administration of MIRV. Non-infectious pneumonitis may result in fatigue, shortness of breath, cough or respiratory distress. Drug-induced pneumonitis may be immediately life threatening. If a patient presents with signs or

symptoms consistent with pneumonitis and/or other clinically meaningful signs or symptoms of pulmonary toxicity, the patient should be immediately evaluated. Patients are advised to notify their treating physician immediately if they experience new or worsening shortness of breath, cough or respiratory distress. Patients who are asymptomatic may continue dosing of MIRV with close monitoring.

The management and treatment guidelines outlined in Table 8.f should be followed.

Table 8.f Management of Non-infectious Pneumonitis

NCI CTCAE v5.0 Grade	NCI CTCAE v5.0 Definition	Medical Management of Pneumonitis	Guidelines for Dose Modifications[a]
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• 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	Symptomatic; medical intervention indicated; limiting instrumental ADL	• 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. • MIRV may be resumed at same dose level or one dose level lower after discussion with the sponsor.
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated	• 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 MIRV.
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)		

Abbreviations: ADL = activities of daily living; CT = computed tomography; MIRV = mirvetuximab soravtansine; NCI CTCAE = national cancer institute common terminology criteria for adverse events.

[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will results in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

8.10.5 Management of Electrolytes Imbalance

Prompt attention should be given to the correction of potential electrolytes imbalance, especially hypokalemia and hypomagnesemia.

8.10.6 Potential Infusion-related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (IRR) (see NCI CTCAE v5.0). The signs and symptoms may vary and include for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (e.g., epinephrine, inhaled beta agonists, antihistamines, and corticosteroids), and other required resources to treat anaphylaxis must be readily available. In general, investigators should manage acute allergic or hypersensitivity reactions according to institutional practices. General guidelines for the management of acute IRRs and for subsequent retreatment are provided in Table 8.g. Delayed IRRs may occur; therefore, patients should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Table 8.g Management Guidelines for Potential Infusion-related Reactions

Infusion Reaction NCI 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. • Promethazine (or equivalent) 150 mg PO per day (Q4h) prn for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Methylprednisolone (or equivalent) 125 mg IV prn
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine (or equivalent) 150 mg PO per day (Q4h) prn for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Acetaminophen (or equivalent) 650 mg PO prn • Methylprednisolone (or equivalent) 125 mg IV prn • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, patients should be pre-medicated with dexamethasone (or equivalent) 8 mg PO BID the day before drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 min before dosing.
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 OR **Grade 4**: Life-threatening consequences; urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient. • Administer diphenhydramine (25-50 mg) IV (or equivalent) • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5 mg/kg Q 6h) to treat ongoing reaction and prevent recurrence • Administer bronchodilators (nebulized albuterol/salbutamol, 2.5-5 mg in 3 mL of saline or equivalent) as medically indicated • Administer normal saline as medically indicated • Administer epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the IRR. • Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE (see Section 10.2). • Permanently discontinue study medication treatment

Abbreviations: BID = twice a day; IM = intramuscular; IRR = infusion related reaction; IV = intravenously; NCI CTCAE = national cancer institute common terminology criteria for adverse events; PO = orally; prn = as needed; Q4h = every 4 hours; Q6h = every 6 hours; SAE = serious adverse event; SQ = subcutaneous.

8.11 Blinding and Unblinding

This is an open-label study.

8.12 Study Drug Administration

8.12.1 Premedication for Study Treatment

All patients receiving study drug must receive 325-650 mg of acetaminophen (orally [PO] or IV), 10 mg IV dexamethasone, and 25-50 mg diphenhydramine (IV or PO) (equivalent drugs of similar drug classes are also acceptable) approximately 30 to 90 minutes before each infusion of study drug. If individual patients require more intensive treatment to prevent IRRs, investigators may modify the regimen accordingly. An antiemetic medication (e.g., 5-HT_3 serotonin receptor antagonists such as palonosetron, granisetron, or ondansetron or appropriate alternatives) is recommended before each study drug dose and may be used any time at the discretion of the treating physician.

8.12.2 Prophylactic use of Eye Drops

1) Lubricating Artificial Tears

Patients receiving study drug will be mandated to use lubricating artificial tears on a daily basis (as directed by the product label or the treating physician but not less than 4 times per day throughout the treatment cycle). Preservative-free lubricating drops are strongly recommended.

2) Corticosteroid Eye Drops

Patients found on slit lamp examination to have signs of suspected MIRV-related keratopathy (including but not limited to microcystic epithelial change, punctate epithelial keratopathy, and subepithelial inclusion cyst) should start secondary prophylactic corticosteroid eye drops for the remaining cycles of MIRV unless the patient's eye care professional documents that the risks outweigh the benefits of such therapy. Patients with keratopathy need to have complete eye examinations prior to every other cycle of MIRV until the findings have resolved or returned to the patient's prior baseline.

8.13 Preparation and Administration of MIRV

8.13.1 Calculation for Adjusted Ideal Body Weight

The total dose of drug is calculated based on each patient's AIBW using the following formula.

Adjusted Ideal Body Weight (AIBW)

AIBW = IBW + 0.4× (Actual weight [kg] – IBW)

Where:

Ideal Body Weight (IBW)

IBW (female) = 0.9×Height [cm] – 92
IBW (male)* = 0.9×Height [cm] – 88

*: Phase 1 part only

The weight used for calculation should be obtained before study drug administration on C1D1 (within 14 days) and thereafter should only be modified for significant (≥ 10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention). If required per institutional policy, it is acceptable to recalculate AIBW at each cycle using the patient's current weight. Sites must clearly document the weight used to calculate dose at each cycle.

8.13.2 Description of Investigational Agents

The investigational study drug, MIRV, will be provided by the sponsor, at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution. The further information is detailed in the Investigator's brochure.

8.13.3 Preparation, Reconstitution, and Dispensation

1) Preparation

MIRV is an experimental anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. The desired amount of drug should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the Pharmacy Manual.

Note: MIRV is incompatible with saline (0.9% sodium chloride). Therefore, dilutions should be made using 5% dextrose. Infusion bags must be labeled with the protocol number, patient number, storage temperature, dose, and volume of MIRV filtered into the bag, or labeled according to institutional protocol. Once the solution is prepared, the infusion bag should be stored at room temperature protected from direct sunlight, and the infusion must be completed within eight hours of preparation. Please refer to Pharmacy Manual for further details.

If necessary, study drug from different drug lots may be mixed in a single-dose administration.

2) Administration

MIRV is administered at 6.0 mg/kg AIBW as an IV infusion following preparation as outlined in the Pharmacy Manual. Details on required and compatible infusion materials are also included in the Pharmacy Manual.

At C1D1 MIRV study drug should be administered at a rate of 1 mg/min; after 30 min, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after 30 min at 3 mg/min, the MIRV infusion rate may be increased to 5 mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. After infusion, the IV line should be flushed with 5% dextrose prn to ensure delivery of the full dose.

Administration should always be performed on schedule; however, if extenuating circumstances prevent a patient from beginning treatment on a particular dosing day, a ±3 day window is allowable for all cycles.

Patients are carefully observed during each infusion and vital signs are taken as outlined in the Schedule of Assessments (Appendix A). Patients will remain in the clinic under observation for four hours after the first infusion, and for at least one hour after each subsequent infusion. While in the treatment area, patients are closely monitored for AEs.

3) MIRV Study Treatment Compliance

The MIRV supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

If necessary, MIRV from different drug lots may be mixed in a single-dose administration.

Under no circumstances is the investigator allowed to release study drug supplies to any physician not named in regulations allow or equivalent form, or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the Principal Investigator (PI [i.e., hospital pharmacy, satellite pharmacy]), it is the responsibility of the PI to ensure that all study drug is stored and administered as described (refer to Pharmacy Manual for instructions).

8.14 Packaging and Labeling

MIRV will be provided in a 20 mL glass, single-use vial with 20 mL deliverable volume. The study medication will be provided in a labeled glass vial and packaged in an appropriately labeled carton with a single-panel label that will contain, but will not be limited to, the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, and storage conditions. A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

Additional details are provided in the Pharmacy Manual.

8.15 Storage, Handling, and Accountability

All investigational supplies are to be kept in a secure area with controlled access.
Vials of MIRV are to be stored at 2°C to 8°C with protection from light.

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

Accountability and shipping documents for MIRV must be maintained by the PI or designee (e.g., the study pharmacist, contract research organization representative, or auditor). The PI or designee must maintain an accurate record of all MIRV received, stored, dispensed, destroyed, and used in an Investigational Product Dispensing/Accountability Log or equivalent. These records must always be available for inspection, and a copy will be supplied to TAKEDA on request. Information recorded on the Accountability Log will include dates and quantities of drug received, dates and quantities of drug dispensed, patient number and initials to whom drug is administered, lot number of drug administered, the recorder's initials, and dates and quantities of drug destroyed or returned. Upon receipt, vials should be visually inspected for vial integrity (i.e., cracks or leaks) and a record of any damaged or suspect drug should be kept on the Accountability Log.

Upon completion of the study, all MIRV dispatched to a site must be accounted for and unused supplies returned to depot (refer to Pharmacy Manual). The original drug reconciliation records shall be maintained at the site and a copy collected and sent to the sponsor or designee once a representative of the company has confirmed the drug accountability. The clinical trial database shall also record details of MIRV administration such as date and time of administration. Drug accountability will be monitored.

8.15.1 J-non-IMP Drugs and/or Products Used in the Clinical Trial at Japanese Sites

Not applicable.

8.16 Other Protocol-Specified Materials

Information on supplies required by the site for drug administration is provided in the Pharmacy Manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the Study Manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the contract research organization, other vendors participating in the study, and the list of investigators can be found in the protocol annex.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Treatment Group Assignments

Not applicable.

9.4 Study Procedures

Refer to the schedule of events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. Procedures will be applied for both Phase 1 and Phase 2 parts unless specified.

9.4.1 Informed (e)Consent

Each patient must provide written or electronic informed consent before any protocol-directed procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patients consenting electronically (eConsent, including informed consent process that is conducted remotely), where available, will electronically sign consent forms.

eConsent provides the same information as written consent forms. eConsent does not replace the important discussion between the study participant and site staff or investigator. Regardless of the consent format, the investigational site is responsible for the consenting process.

9.4.2 Confirmation of Disease Diagnosis

At Screening, disease diagnosis, and current disease status are confirmed from information in the source record (Appendix A).

9.4.3 Mutation Status

Known mutation status (e.g., *BRCA* for ovarian cancer, anaplastic lymphoma kinase [*ALK*] for NSCLC) from prior testing (information in the source record) will be recorded (Appendix A). For example, patients with a *BRCA* mutation (germline mutation or somatic mutation in tumor tissue) are classified as positive and patients who were tested and shown to not have a *BRCA* mutation will be classified as negative. Patients without known *BRCA* mutation status in the source record are classified as unknown.

9.4.4 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening (Appendix A).

9.4.5 Medical History

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

9.4.6 Physical Examination, Weight, and Height

Physical examination (PE), height (Screening only) and weight must be performed as indicated in the Schedule of Assessments (Appendix A). A complete PE, including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system, will be completed at Screening and the 30-day Follow-up Visit. Symptom-directed PEs will be completed at additional time points as specified in the Schedule of Assessments (i.e., while on study drug and the EOT visit).

9.4.7 Vital Signs

Vital signs include blood pressure, heart rate, and body temperature. Pulse oximetry must be added only in Phase 1 part. These signs are measured as outlined in Appendix A.

9.4.8 Pulmonary function tests (Phase 1 part only)

Pulmonary function tests (PFTs) should include spirometry, diffusion capacity, and lung volume tests. PFTs will be performed within 14 days prior to Cycle 1 Day 1 and in the event of pulmonary symptoms as clinically indicated (Appendix A).

9.4.9 Ocular Symptom Assessment and Ophthalmic Examination

9.4.9.1 Ocular Symptom Assessment

Ocular symptom assessment will be performed at screening. Ocular symptom assessment will be performed before the start of each cycle for patients by the treating physician or other qualified individual. For patients reporting > NCI CTCAE Grade 1 ocular symptoms, study drug will be

held until the patient is evaluated by an ophthalmologist for a complete examination. The ocular symptom assessment will also be performed at EOT and the 30-day Follow-up (Appendix A).

9.4.9.2 Ophthalmic Examination

An ophthalmic examination will be performed at Screening (within 14 days prior to first dose of study drug) by an ophthalmologist and will include the following: manifest refraction, BCVA, intraocular pressure measurement (IOP), slit lamp examination, and indirect fundoscopy. All patients, regardless of reporting symptoms, are required to have ophthalmological examinations including manifest refraction, BCVA, IOP, and slit lamp examination before Cycles 3, 5 and 7. Patients who experience ocular TEAEs while on study will have an ophthalmologic examination performed at the emergence of the symptoms and at every other cycle thereafter until resolved to baseline or deemed irreversible in the opinion of the eye care professional. All patients will have a complete ophthalmologic examination including indirect fundoscopy performed at 30-day follow-up visit (Appendix A).

9.4.10 Pregnancy Test

All WCBP will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test within 4 days before the first dose of study drug and urine or serum pregnancy tests within 4 days prior to Day 1 of each cycle and at the 30-day Follow-up visit. It is recommended to perform monthly pregnancy tests for 7 months after the last dose of MIRV. Additional testing may be performed in accordance with institutional requirements. Pregnancy tests must be negative for the patient to be enrolled and to continue to receive the study drug (Appendix A).

If a patient becomes pregnant or suspects pregnancy while participating in this study, the investigator and sponsor must be informed immediately (Section 10.4) and the patient will discontinue the study drug. See Section 10.4 for more details.

9.4.11 Concomitant Medications and Procedures

All concomitant medications and supportive therapies taken within four weeks of Cycle 1, Day 1 and through 30 days after last study treatment or prior to the start of a new anti-cancer treatment whichever comes first must be recorded on the appropriate electronic case report form (eCRF). The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the eCRF.

See Section 8.6, Section 8.7 and Section 8.8 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.12 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the schedule of events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.13 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug. Patients who are issued a patient number, but who do not successfully complete the screening process will be considered screen failures. Patient numbers for patients who screen fail will not be re-issued. Procedures for completing enrollment information are described in the Study Manual.

9.4.14 Electrocardiogram (ECG)

A standard, single 12-lead ECG will be performed at the time points specified in the Schedule of Events in Appendix A.

9.4.15 Clinical Laboratory Evaluations

Local laboratories will be used for the analysis of scheduled hematology, biochemistry, coagulation and other tests collected as part of safety monitoring. Screening labs (Table 9.a) will be performed within 14 days of first dose. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 4 days of dosing and are within acceptable ranges. Repeat testing will be performed as outlined in the Schedule of Assessments (Appendix A) and as clinically indicated.

Note that before each administration of study drug, laboratory results must be reviewed to evaluate for potential toxicity.

9.4.15.1 Clinical Chemistry, Hematology, and Urinalysis

A list of clinical laboratory tests may be found in Table 9.a.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (Screening only)	Coagulation (Screening only for Phase 2 part)
• Hematocrit • Hemoglobin • WBC (with 5-part differential) • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN or Urea • Calcium • Chloride • Creatinine • Glucose • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin	• pH • Ketones • Protein • Glucose • Occult blood • Leukocyte esterase • Nitrite	• PT-INR and 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.

If creatinine clearance is to be estimated, the Cockcroft Gault formula will be employed as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) * Weight\ (kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

For transgender patients, use the sex at birth for patients not using hormone therapy or for patients who have used hormone therapy for <6 months; use the current gender for patients who have used hormone therapy for ≥6 months.

9.4.15.2 Krebs von den Lungen-6 and surfactant protein D (Phase 1 part only)

Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) will be tested as specified in the schedule of events (Appendix A).

9.4.15.3 Viral serology

Viral serology on hepatitis B and C will be tested as specified in the schedule of events (Appendix A). Patients with known hepatitis B surface antigen seropositivity and/or detectable hepatitis C virus RNA will be excluded. Patients who have positive hepatitis B core antibody and/or hepatitis B surface antibody can be enrolled but must have an undetectable serum hepatitis B virus DNA. Patients who have positive hepatitis C virus antibody must have an

undetectable hepatitis C virus RNA serum level. Patients will be monitored and managed according to Guideline for the prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection (The Japan Society of Hepatology 2022).

9.4.16 Disease Assessment

9.4.16.1 Radiological imaging

Radiologic tumor evaluation by contrast enhanced (unless contraindicated) 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 weeks) thereafter (Appendix A).

For phase 1 part, if patients discontinue study treatment for reasons other than PD, a tumor assessment is to be performed at the EOS visit or 30-day Follow up visit, if not performed within the previous 6 weeks. Additional tumor assessments may be conducted based on the investigator's decision.

For phase 2 part, patients who discontinue study treatment 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. The same method of radiographic assessment used at Screening must be used at all subsequent radiographic evaluations. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Deidentified copies of all imaging scans (including those from screening and any unscheduled scans) must be collected and transferred to a central imaging vendor (See the Imaging Manual). The central imaging vendor will assess the quality of the images and an independent review will be performed for a sensitivity analysis of data collected by the investigator sites.

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.

Note: It is very important that the same method of radiologic assessment be used throughout the study and that the same lesions are followed.

[redacted]

9.4.17 Biomarker, Pharmacodynamic, and Pharmacokinetic Samples

9.4.17.1 Pharmacokinetic sample

Blood samples for PK analysis will be collected at the time points specified in Appendix A. Samples will be analyzed for plasma concentrations of intact ADC, total Ab, DM4 and S-methyl DM4 (see Section 13.1.4).

PK samples may also be obtained as feasible at any time during the treatment period for assessment of treatment-related SAEs if deemed appropriate by the investigator and sponsor.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Laboratory Manual.

9.4.17.2 Immunogenicity sample

Blood samples for the assessment of MIRV antibodies (ADA) will be collected at the time points specified in Appendix A. The potential impact of immunogenicity on PK will be explored (see Section 13.1.5).

PK sample is collected when ADA sample is taken. Details regarding the preparation, handling, and shipping of the ADA samples are provided in the Laboratory Manual.

9.4.17.3 Biomarker assessment

[redacted]

9.4.18 Sample Retention

Banked and fresh tumor tissue biopsy samples, blood and plasma samples for biomarker pharmacodynamic measurements, and blood samples for DNA measurements will be stored up to 15 years after the date of study completion as identified in the clinical study report and will be destroyed by a third-party vendor per company standard operating procedures (SOP). If a patient withdraws consent and requests that samples be destroyed, samples will be discarded following the local procedure (ie, where the sample resides at the time of withdrawal and the investigator needs to inform the sponsor patient's intent to withdraw immediately).

9.4.19 Eastern Cooperative Oncology Group Performance Status

ECOG PS (Appendix D) will be assessed during Screening and at other times specified in the Schedule of Assessments (Appendix A). An assessment is not necessary on Day 1 of Cycle 1 if the Screening assessment was obtained within the prior 4 days.

9.5 Study Activities

All study visits and assessments that must be performed during the study and follow-up are included in Appendix A.

9.5.1 Period of Observation

Period of observation is provided in Section 6.3.1.

9.5.2 Pre-screening

Prior to the pre-screening procedure, the investigator must obtains consent from each patient utilizing pre-screening informed consent.

For Phase 1 part, patients who don't have prior documentation of FRα are required to submit tumor tissue to confirm FRα expression via IHC during pre-screening period. Patients who have prior documentation of FRα do not need to re-confirm FRα expression during pre-screening period and can move on to screening period directly.

For Phase 2 part, all the patients are required to confirm FRα expression during pre-screening.

Refer to Section 9.4.17.3.

9.5.3 Screening Visit

The investigator is responsible for keeping a record of all patients screened for entry into the study, including those who are subsequently excluded. The reason(s) for exclusion must be recorded.

9.5.3.1 Standard of Care Assessments

In some cases, clinical assessments performed before obtaining informed consent may be used to qualify the patient for the study if performed within the screening window. These include radiologic tumor assessment, PEs, hematology results, serum chemistry results, coagulation results, urinalysis, or other assessments which may be considered part of standard of care. In these cases, repeat assessments may not be necessary before enrollment, unless individual parameters require further study or confirmation and are clinically appropriate.

Note that safety blood tests, and PE do not need to be repeated if normal and conducted within 4 days prior to C1D1.

9.5.4 End of Treatment Visit

Patients may voluntarily withdraw from the study drug at any time for any reason, and without prejudice to further treatment. In addition, patients may be withdrawn by the investigator if they do not feel the patient is deriving clinical benefit or because the patient is experiencing unacceptable toxicity. The reasons for which a patient may be prematurely discontinued are listed in Section 9.8 and Section 9.9.

Patients who withdraw or are removed from the study treatment will have an EOT visit within 7 days of the decision to discontinue study drug.

Additionally, these patients will undergo a 30-day follow-up safety visit. The eCRF will capture reasons for withdrawal.

If discontinue decision is made more than 14 days after the last dose of MIRV, EOT visit will be optional and the 30-day follow-up safety visit can serve as EOT visit as well.

9.5.5 Follow-up Assessments

9.5.5.1 Safety Follow-up

A safety follow-up visit will occur 30 days (+14 days) after last dose of study drug.

In some cases, nonserious AE observations may continue beyond the safety visit. All ocular AEs will be followed until resolution, stabilization, or return to baseline. In these instances, additional information may be requested by the sponsor to adequately categorize the nature of the toxicity.

All SAEs will be followed until they resolve, stabilize or return to baseline, regardless of time from last dose or last visit.

9.5.5.2 Response Follow-up

For phase 1 part, if patients discontinue study treatment for reasons other than PD, a tumor assessment is to be performed at the EOS visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Additional tumor assessments (i.e., radiologic tumor assessment and [redacted]) may be conducted based on the investigator's decision until documentation of PD or the start of a new anticancer therapy, whichever comes first.

For phase 2 part, patients who discontinued study treatment 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 (See Section 9.11). Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) 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.

9.5.5.3 Survival Follow-up (Phase 2 part only)

All patients who discontinue study treatment for any reason will be followed for survival after disease progression as per investigator, or after start of anticancer therapy (See Section 9.4.11).

All patients will be followed for survival every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up or until EOS, whichever comes first.

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they discontinue MIRV for any of the reasons outlined in Section 9.8.1.

Treatment will continue until PD, unacceptable toxicities, or withdrawal due to other reasons.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study when they complete an EOT visit and posttreatment follow-up, as applicable, and discontinue from the study for any of the reasons outlined in Section 9.9.

9.8 Discontinuation of the Patients from the Study or Study Treatment

9.8.1 End of Treatment

Patients will continue to receive study drug until they present with PD per RECIST v1.1, as assessed by study investigator, unacceptable toxicity, withdraw consent, or death, whichever comes first, or until the sponsor terminates the study.

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse Event
- Protocol Deviation.
- Progressive Disease.
- Symptomatic Deterioration.
- Unsatisfactory Therapeutic Response.
- Pregnancy (patient must be discontinued).
- Study Terminated by Sponsor.
- Withdrawal by Patient.
- Loss to Follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the schedule of events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Any AEs experienced up to the point of discontinuation and 30 days thereafter must be documented on the AE eCRF. All SAEs, and those AEs assessed by the investigator as at least

possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

In phase 2 part, patients will continue to be followed for response/survival, after discontinuing study drug (Section 9.5.5.2 and 9.5.5.3).

9.8.2 End of Study

Discontinuation from participation in the study will be documented on the EOS eCRF. Reasons for EOS include withdrawal of consent, lost to follow-up, death, or study termination by sponsor (Section 9.9).

9.8.3 Withdrawal of Consent

The patient or legally authorized representative acting on behalf of the patient is free to withdraw consent to study treatment and/or participation in the study at any time irrespective of the reason.

The investigator must make every effort (e.g., by telephone, email, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued, and no further assessments conducted. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up. If the patient or legally authorized representative withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before withdrawal of consent. All biological samples that have been already collected will be retained and analyzed at a later date. The patient or legally authorized representative may request destruction of any samples, and the investigator must document this in the site study records. Patients who have withdrawn from the study cannot be re-treated in the study and their inclusion and patient number must not be reused.

9.8.4 Loss to Follow-up

A study patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The investigator should make all efforts to contact the patient and to determine the patient's health status, including at least her vital status (in accordance with applicable regulations related to privacy and confidentiality). A patient should not be considered lost to follow-up until due diligence has been completed and documented. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason being "loss to follow-up".

9.9 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Loss to Follow-up.
- Study Terminated by Sponsor.
- Withdrawal by Patient.
- Death.
- Progressive Disease.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.10 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Tests and procedures should be performed on schedule; however, unless otherwise specified, occasional changes are allowable within number of days shown in Appendix A window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor. Allowable windows on dosing days are described in Section 8.13.

9.11 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival for Phase 2 part only)

Only in the phase 2 part, Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits (Section 9.5.5.2). The PFS follow-up visit should be conducted at the site every 12 weeks (±3 weeks) from the EOT visit until the occurrence of PD, the patient withdraws consent for further follow-up, or the start of subsequent anticancer therapy.

Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) 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 subsequent anticancer therapy.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits (Section 9.5.5.3). The OS visits should be conducted 3 months (± 1 month) after documented PD or after the start of subsequent anticancer therapy.

Survivor information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (e.g., Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

The EOS visit is to be completed when the patient discontinues from the follow-up period. See the schedule of events (Appendix A) for appropriate assessments during follow-up.

Note: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has provided informed (e)consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at

home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, v5.0, effective 27 November 2017 (ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Adverse Events of Clinical Interest

An AE of clinical interest (serious or nonserious) is one of scientific and medical concern specific to the MIRV, for which ongoing monitoring. Such events may require further investigation to characterize and understand them.

AECIs for MIRV include:

- Ocular AEs
- Pneumonitis
- Peripheral neuropathy
- Infusion related reactions

10.1.5 Classification of Corneal Adverse Events

With the exception of corneal AEs (Table 10.a; for management see Table 8.d), all AEs will be evaluated according to NCI CTCAE v5.0. Corneal AEs will be also graded according to Table 10.a, in addition to NCI CTCAE v5.0. If the AE is not listed in Table 10.a or the NCI CTCAE v5.0, it should be graded based on the description given in Table 10.b. Severity and extent of corneal AEs will be documented as on the ocular examination and symptom assessment form provided.

Table 10.a Grading (non-CTCAE) for Corneal Adverse Events

Ocular Exam Finding	Corneal AE Grade Assigned
Clear Cornea (no findings)	0
Keratitis (with +NaFl staining) (superficial keratitis, superficial punctate keratitis, epithelial erosion)	
Nonconfluent keratitis	1
Confluent keratitis	2
Keratopathy (microcystic epithelial change, punctate epithelial keratopathy, subepithelial inclusion cyst)	
Nonconfluent keratopathy	1
Confluent keratopathy	2
Cornea epithelial defect (+NaFl staining, non-punctate focal loss of epithelial cells)	2
Corneal ulcer (without perforation)	3
Cornea stromal opacity (clinically significant)	3
Corneal perforation	4

Abbreviations: NaFl: sodium fluorescein; NCI CTCAE = national cancer institute common terminology criteria for adverse events

Table 10.b Adverse Event Severity (for terms not included in CTCAE v5.0)

Severity	Definition
Grade 1 (Mild)	No limitation of usual activities
Grade 2 (Moderate)	Some limitation of usual activities
Grade 3 (Severe)	Inability to carry out usual activities
Grade 4 (Life-threatening)	Immediate risk of death
Grade 5 (Fatal)	Resulting in death

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, PE, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a

facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; e.g., surgery was performed earlier or later than planned.

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, v5.0.

Relationship of the event to study drug administration (i.e., its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed (e)consent through 30 days after administration of the last dose of study drug or prior to the start of a new anti-cancer treatment whichever comes first and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed (e)consent through 30 days after administration of the last dose of study drug or prior to the start of a new anti-cancer treatment whichever comes first and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are

resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient becomes pregnant or suspects pregnancy while participating in this study, the patient must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a patient impregnates a partner during participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product, device, or combination product. Individuals who identify a potential product complaint situation should immediately report this via the contact information provided in the study manual.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this to the study monitor and record it in applicable eCRF form.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.6 Procedures for Reporting Malfunctions in Regenerative Medicine Products in Japan

Not applicable.

10.7 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited

report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data monitoring committee, or clinical endpoint committee will be used in this study.

11.1 Blinded Independent Central review (BICR) committee

For the Phase 2 part, a blinded independent central review (BICR) committee with no knowledge of the patients' assessment status will evaluate all images collected during the study for a sensitivity analysis of data collected by the investigator sites. An independent review charter defines the procedures used by the committee.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an informed (e)consent.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed (e)consent forms, patient authorization forms regarding the use of personal health information (if separate from the ICFs), copies of all paper CRFs and query responses/electronic copies of eCRFs, including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation

printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility.

The investigator and the head of the institution are required to retain essential relevant documents until the later of:

- The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification that investigation was discontinued.)
- The day 3 years after the date of early termination or completion of the study.

Should the sponsor request a longer retention period, the head of the institution should discuss how long and how to retain those documents with the sponsor. In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

When proceeding to a local post-marketing study, the investigator and the head of the institution are required to retain essential relevant documents until the later of the end of the re-examination or re-evaluation. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

Phase 1 Part

- Safety analysis set
  The safety population is defined as all patients who receive at least 1 dose of MIRV. The safety analysis set will be used for safety analysis.
- PK analysis set
  The PK analysis set is defined as all patients for whom there are sufficient dosing and MIRV concentration-time data to reliably estimate the PK parameter(s). This population will be used for analyses of PK parameters and population PK analyses.
- Response-Evaluable Population
  The response-evaluable population is defined as patients who have radiographic assessment at baseline, receive at least 1 dose of MIRV, and have at least 1 post-baseline tumor assessment or died or clinically progressed within 105 days of last dose. The response-evaluable population will be used for efficacy analysis.

[redacted]

Phase 2 Part

- Full analysis set
  All patients who receive at least 1 dose of MIRV. The full analysis set will be used for efficacy analysis.
- Safety analysis set
  The safety population is defined as all patients who receive at least 1 dose of MIRV. The safety analysis set will be used for safety analysis.
- PK analysis set
  The PK analysis set is defined as patients who receive at least 1 dose of MIRV and have at least 1 plasma concentration data after administration of MIRV. This population will be used for PK analyses and population PK analyses.

[redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and therapies, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

13.1.3 Efficacy Analysis

The efficacy endpoints include ORR, DOR, PFS, OS and [redacted].

ORR: The ORR is defined as the proportion of patients who achieved a confirmed PR or confirmed CR during the study using RECIST v1.1.

DOR: DOR is defined as the time from the date of the first response (CR or PR), whichever occurs first, to the date of PD or death from any cause, whichever occurs first. DOR Responders without documentation of progressive disease will be censored at the date of last response assessment that is SD or better.

PFS: Defined as the time from the date of first dose administration until PD or death from any cause, whichever occurs first.

OS: Defined as the time from the date of first dose administration to the date of death due to any cause.

[redacted]

Phase 1 part

Investigator assessed ORR using RECIST v1.1 will be evaluated. The estimate of the ORR will be presented with 2-sided 95% exact binomial confidence intervals.

Phase 2 part

Investigator assessed ORR is the primary endpoint for Phase 2, estimates of ORR will be presented with the 90% exact confidence interval (CI).

Investigator assessed DOR is the secondary endpoint for Phase 2, the median time to event with 95% CI will be analyzed using estimated by the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of patients who had the event or were censored will also be reported. Investigator assessed DOR will be summarized in patients with a confirmed CR or PR only.

Analysis for time to event endpoints like PFS assessed by investigator and OS, the median time to event with 95% CI will be analyzed using the Kaplan-Meier method for the full analysis set. A Kaplan-Meier survival curve will be generated. The number and percentage of patients who had the event or were censored will also be reported.

[redacted]

Further details of the analyses of the efficacy endpoints, including sensitivity analyses, censoring rules etc., will be prespecified in the SAP.

13.1.4 Pharmacokinetic Analysis

13.1.4.1 PK Noncompartmental Analysis

Phase 1 part

PK parameters (C_{max}, AUC_{last}, AUC_{∞}, t_{max}, $t_{1/2}$, CL, V_{ss} and Accumulation ratio as applicable) for Cycle 1 and Cycle 3 will be derived from plasma concentrations of intact ADC, total Ab, DM4 and S-methyl DM4 using the actual sampling times. Concentration data and all PK parameters will be listed per patient and summarized descriptively. Standard algorithms of the non-compartmental pharmacokinetic analysis program, WinNonlin software, will be used for these analyses.

Individual plasma concentration vs. actual time profiles for each patient and analyte, as well as the mean (+/- S.D.) plasma concentration vs. scheduled time profiles for each analyte, will be presented graphically.

Phase 2 part

PK parameters will not be calculated due to the sparse sampling scheme in this part. Summary statistics of the concentration of intact ADC, total Ab, DM4 and S-methyl DM4 at each time point (nominal time) will be presented. Graphical presentation of the data may also be completed using nominal time.

13.1.4.2 PK Sampling Intended for Population PK Analysis

The PK data collected in this study are intended to contribute to future population PK analyses of MIRV. These population PK analyses may additionally include data collected in other MIRV clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

13.1.5 Immunogenicity Analyses

The proportion of subjects with positive ADA (incidence and titer) during the study will be summarized. The effect of immunogenicity on PK will be examined, if possible.

13.1.6 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patient's vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs are defined as AEs after administration of the first dose of study drug, and through 30 days after the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.

AEs will be coded using the latest MedDRA version and summarized per system organ class (SOC), preferred term (PT) and NCI CTCAE grade.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Serious TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (i.e., those reported by ≥10% of all patients).
- Treatment-emergent SAEs (related and regardless of relationship).
- TEAEs leading to study drug modification and discontinuation.
- AECIs.

The incidence of DLTs will be tabulated for Phase 1 part.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG Performance Scores will be presented in data listings. Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value.

All concomitant medications will be collected and classified to preferred terms according to the WHO Drug Dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MIRV.

13.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned in the study.

13.3 Determination of Sample Size

Phase 1 part

The study will follow a 3+3+3 design. 6.0 mg/kg AIBW is the only dose level to be evaluated in this trial. Patients will be enrolled and treated at the dose level 6.0 mg/kg AIBW with 3 patients in each cohort. The number of evaluable patients is planned to be 3 to 9.

Phase 2 part

Approximately 22 patients will be enrolled and a total of 20 patients will be evaluated for efficacy analysis, assuming a dropout rate of 10%. This will allow the study to have over 80% power to detect a difference in ORR of 26% (42% vs 16%) with a 1-sided alpha of 0.05. These results assume that the ORR is 16% under the null hypothesis and 42% under the alternative hypothesis.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Alternative approaches such as remote source data review via phone or video may be used to ensure data quality and integrity and patient safety. Additional details are in the monitoring plan. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study patients, without prior written agreement with the sponsor or prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the United States [US] FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (herein "patients") according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's brochure, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, i.e., before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed (e)Consent, and Patient Authorization

Written and electronic consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the patient is not capable of rendering adequate written or electronic informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be (e)signed and dated by the patient, or the patient's legally acceptable representative, at the time of (e)consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also (e)sign and date the ICF and patient authorization (if applicable) at the time of (e)consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once (e)signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be provided to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed (e)consent. The date the revised (e)consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed (e)consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, e.g., patient name, address, and other identifier fields not collected on the patient's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table 1 Schedule of Assessments for Phase 1 part

Activity	Pre-Screening	Screening	Cycle 1[a]			Cycle 2		Cycle 3			Cycles ≥4	EOT	30-day Follow-up (+14 Days)	Response Follow-up (Optional)
			Day 1	Day 2	Day 8±1, Day 15±1	Day 1 [b]	Day 8±3, Day 15±3	Day 1 [b]	Day 2	Day 8±3, Day 15±3	Day 1 [b]			
Pre-screening Informed Consent	●													
Study Informed consent		●[c]												
Eligibility (Sections 7.1.1 and 7.2.1)		●[c]	●[d]											
Demographics		●[c]												
Medical History		●[c]												
Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation		●[c]												
Record Baseline Signs and Symptoms		●	●											
Confirm patient meets retreatment criteria (Section 8.5.3)						●		●			●			
12-Lead ECG (Section 9.4.14)		●[e, f]	●					●				●	(●)[g]	
Coagulation (PT-INR and aPTT)		●[f]	●[h]			●[h]		●[h]			●[h]		●	
Urinalysis		●[f]	●[h]			●[h]		●[h]			●[h]		●	
FFPE Archived Tumor Tissue and/or New Biopsy (Section 9.4.17.3)[i]	●													
Physical Examination [j]		●[f]	●		●	●	●	●			●	●	●	
Height		●[c]												

Table 1 Schedule of Assessments for Phase 1 part

Activity	Pre-Screening	Screening	Cycle 1[a]			Cycle 2		Cycle 3			Cycles ≥4	EOT	30-day Follow-up (+14 Days)	Response Follow-up (Optional)
			Day 1	Day 2	Day 8±1, Day 15±1	Day 1 [b]	Day 8±3, Day 15±3	Day 1 [b]	Day 2	Day 8±3, Day 15±3	Day 1 [b]			
Weight		●[f]	●			●		●			●	●	●	
Vital signs [k]		●[f]	●	●		●		●	●		●	●	●	
Pulmonary Function Test [l]		●												
ECOG PS		●[f]	●			●		●			●	●	●	
Hematology and Chemistry		●[f]	●[h]		●	●[h]	●	●[h]		●	●[h]	●	●	
KL-6 and SP-D (Section 9.4.15.2)		●[c]				●		●			Every other cycle after Cycle 3			
Viral serology (Section 9.4.15.3)		●[c]												
Pregnancy Test (urine or Serum) [m]		●[f]	●			●		●			●		●[m]	
Ophthalmic examinations [n]		●	Every other cycle for the first 8 cycles and as clinically indicated										●	
Ocular Symptom Assessment [o]		●	●			●		●			●	●	●	
Radiologic tumor assessments		●[c]	Every 6 weeks (± 1 week) from C1D1 for first 36 weeks, then every 12 weeks (±3 weeks)[p]										●[q]	(●[q])
[redacted]		●[f]	Every 6 weeks (± 1 week) from C1D1 for first 36 weeks, then every 12 weeks (±3 weeks)[p]										●[q]	(●[q])
MIRV Infusion			●			●		●			●			
Lubricating Eye Drops (Section 8.12.2)			All patients will self-administer lubricating eye drops.											
AE and SAE assessments[s]	●[t]	●	Collected continuously while patients are on study											

Table 1 Schedule of Assessments for Phase 1 part

Activity	Pre-Screening	Screening	Cycle 1[a]			Cycle 2		Cycle 3			Cycles ≥4	EOT	30-day Follow-up (+14 Days)	Response Follow-up (Optional)
			Day 1	Day 2	Day 8±1, Day 15±1	Day 1 [b]	Day 8±3, Day 15±3	Day 1 [b]	Day 2	Day 8±3, Day 15±3	Day 1 [b]			
Record concomitant medications		●[f]	Collected continuously while patients are on study											
Molecular pathology (e.g. *BRCA*, ALK) documentation			●											
Blood Sample for PK/Immunogenicity			(See Table 3)											

1 cycle = 3 weeks

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; aPTT = activated partial thromboplastin time; *BRCA* = breast cancer susceptibility gene; C = cycle; CA = cancer antigen; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; FFPE = formalin-fixed, paraffin embedded; INR = international normalized ratio; KL-6 = Krebs von den Lungen-6; MIRV = mirvetuximab soravtansine; PK = pharmacokinetics; PT = prothrombin time; SAE = serious adverse event; SP-D = surfactant protein D.

[a] Patients are required to be hospitalized at least Days 1 to 3 in Cycle 1 (i.e., They can be discharged at Day 4) (Note: The investigator must document the confirmation record for stable health status of the patient per standard physical examination and available data in an appropriate source record (e.g., medical records) before the patient discharge).

[b] A window of ± 3 days around scheduled dosing on Day 1 (D -3 through D4) of any given cycle is permitted without protocol deviation for convenience of scheduling.

[c] Within 28 days prior to the start of C1D1

[d] Confirm before first dose.

[e] ECGs may be performed predose at C1D1 if not performed previously during screening.

[f] Within 14 days prior to the start of C1D1

[g] 12-led ECG is necessary (not optional) if EOT is combined with 30-day Follow-up visit.

[h] Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of MIRV. In the event of severe toxicity, repeat laboratory tests should be performed as necessary until the toxicity resolves or stabilizes. For a complete list of laboratory assessments, refer to Section 9.4.15.

[i] All patients who do not have archival tumor tissue to submit for FRα expression and without prior documentation of tumor FRα expression will be required to undergo tumor biopsy during the screening period in order to confirm eligibility.

[j] Directed physical examination is acceptable while on study treatment. Full examination is required at screening and the 30-day Follow-up visit.

[k] Vital signs (blood pressure, heart rate, body temperature, and pulse oximetry) will be measured before start of infusion; post infusion vital signs should be collected as clinically indicated for potential infusion related reaction.

Table 1 Schedule of Assessments for Phase 1 part

Activity	Pre-Screening	Screening	Cycle 1[a]			Cycle 2		Cycle 3			Cycles ≥4	EOT	30-day Follow-up (+14 Days)	Response Follow-up (Optional)
			Day 1	Day 2	Day 8±1, Day 15±1	Day 1 [b]	Day 8±3, Day 15±3	Day 1 [b]	Day 2	Day 8±3, Day 15±3	Day 1 [b]			

[l].Pulmonary function tests (PFTs) should include spirometry, diffusion capacity, and lung volume tests. PFTs will be performed within 14 days of receiving the first dose of study treatment (C1D1) and as clinically indicated.

[m] For women of childbearing potential (WCBP), a urine or serum pregnancy test will be performed within 4 days prior to Day 1 of each cycle and at the 30-day Follow-up visit. It is recommended to perform monthly pregnancy tests for 7 months after the last dose of MIRV.

[n] Ophthalmic examinations will be performed in all patients by an ophthalmologist, optometrist, or other qualified health care provider ("eye care professional") within 14 days before C1D1 (baseline), before Cycle 3, 5, 7, at the 30-day Follow-up visit (+ 14 days) and as clinically indicated. They will include the following: manifest refraction, best corrected visual acuity, intra-ocular pressure assessment, fundoscopy (baseline and 30-day Follow-up only), and slit lamp examination. Patients requiring an ophthalmological examination due to symptoms prior to Cycle 2 or 4 will then proceed to every-6-week examinations as indicated by findings and do not require the routine, asymptomatic exams at Cycle 3, 5, and 7 in addition.

[o] Ocular symptoms assessment will be performed by the treating physician or other qualified individual before the start of each cycle. For patients reporting > NCI CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

[p] Radiographic tumor assessment by CT scan is to be performed every 6 weeks (± 1 week). Patients [redacted] must have a confirmatory test performed at least 28 days after initial response is documented. Refer to Section 9.4.16 for details.

[q] If a patient discontinues prior to documentation of PD, a tumor assessment is to be performed at the End of Study visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Additional tumor evaluation may be conducted based on the investigator's decision until documentation of PD or the start of a new anticancer therapy, whichever comes first.

[redacted]

[s] Only AEs and SAEs attributed to study procedures are recorded.

[t] Only AEs/SAEs which are considered related to a study procedure (i.e. blood draw or fresh tumor biopsy) will be captured during the Pre-screening period, i.e. 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.

Table 2 Schedule of Assessments for Phase 2 part

Activity	Pre- screening	Screening	Cycle 1		Cycles ≥2	EOT	30-day Follow-up	Response/ Survival Follow-up
			Day 1	Day 8±3	Day 1[a]	≤ 7 days from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Pre-screening Informed Consent	●							
Study Informed Consent		●[b]						
Eligibility (Sections 7.1.2 and 7.2.2)		●[b]	●[c]					
Demographics		●[b]						
Medical History		●[b]						
Confirm Disease Diagnosis/Current Stage		●[b]						
Record Baseline Signs and Symptoms		●	●					
Confirm patient meets retreatment criteria (Section 8.5.3)					●			
12-Lead ECG (Section 9.4.14)		●[d, e]						
Coagulation (PT-INR and aPTT)		●[d]						
Urinalysis		●[d]						
FFPE Archived Tumor Tissue and/or New Biopsy (Section 9.4.17.3) [f] for FRα expression	●							
FFPE Archived Tumor Tissue and/or Biopsy at baseline (Section 9.4.17.3) for exploratory biomarker			Baseline tissue samples for exploratory analysis will be collected only from enrolled patients					
Physical Examination [g]		●[d]	●[h]			●	●	
Height		●[d]						
Weight		●[d]	●		●	●	●	
Vital Signs [i]		●[d]	●		●	●	●	
ECOG PS		●[d]	●[h]		●	●	●	
Hematology and Chemistry [j]		●[d]	●[h]		●	●	●	

Table 2 Schedule of Assessments for Phase 2 part

Activity	Pre- screening	Screening	Cycle 1		Cycles ≥2	EOT	30-day Follow-up	Response/ Survival Follow-up
			Day 1	Day 8±3	Day 1[a]	≤ 7 days from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Viral serology (Section 9.4.15.3)		●[b]						
Blood Sample for Soluble FRα			●					
Blood sample for circulating biomarkers (e.g. ctDNA) [k]			●		●	●		
Pregnancy Test (urine or Serum) [l]		●[l]	●[h]		●		●	
Ophthalmic Exam [m]		●[d]	Every other cycle for the first 8 cycles and as clinically indicated				●	
Ocular Symptom Assessment [n]		●[d]	●		●	●	●	
Radiologic Tumor Assessment [o]		●[b]	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±3) weeks			●[p]	●[p]	(●[p])
[redacted]		●[d]	Collect at each radiologic tumor assessment (±4 days)			●[p]	●[p]	(●[p])
MIRV Infusion			●		●			
Lubricating Eye Drops (Section 8.12.2)			All patients will self-administer lubricating eye drops.					
Record AE/SAEs and Con-meds	●[r]	●	Collected continuously while patients are on study					●[s]
Documentation of *BRCA* mutation status			●					
Blood Sample for PK/Immunogenicity			(See Table 4)					
Survival Phone Screen, Including New Anticancer Therapy [t]								●

1 cycle = 3 weeks

Table 2 Schedule of Assessments for Phase 2 part

Activity	Pre- screening	Screening	Cycle 1		Cycles ≥2	EOT	30-day Follow-up	Response/ Survival Follow-up
			Day 1	Day 8±3	Day 1[a]	≤ 7 days from discon.	30 (+14) days from last dose	Every 3±1 month from EOT

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; *BRCA* = breast cancer susceptibility gene; C = cycle; CA = cancer antigen; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; FFPE = formalin-fixed-paraffin-embedded; INR = international normalized ratio; MIRV = mirvetuximab soravtansine; PK = pharmacokinetics; PT = prothrombin time; SAE = serious adverse event.

[a] A window of ± 3 days around scheduled dosing on Day 1 (D -3 through D4) of any given cycle is permitted without protocol deviation for convenience of scheduling.

[b] Must be within 28 days before C1D1.

[c] Confirm before first dose.

[d] Must be within 14 days before C1D1.

[e] ECGs may be performed predose at C1D1 if not performed previously during screening.

[f] Testing for FRα expression at Pre-screening 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 during the Pre-Screening period to confirm eligibility. If the archival tumor tissue does not meet FRα criteria, a new biopsy tumor sample may be submitted and used to meet this criterion.

[g] Full physical examination (PE) is required at Screening and the 30-day Follow-up visit. Symptom-directed PEs while on study drug.

[h] ECOG, PE, pregnancy, hematology, and chemistry labs (if all parameters are within normal range) do not need to be repeated at C1D1 if performed within the previous 4 days during Screening.

[i] Vital signs (blood pressure, heart rate and body temperature) will be measured before start of infusion; post infusion vital signs should be collected as clinically indicated for potential infusion related reaction.

[j] Hematology and chemistry labs may be performed up to 4 days prior Day 1 of each cycle, and as clinically indicated while on treatment, with results reviewed before each drug administration. In the event of severe toxicity, laboratory tests must be repeated as clinically necessary until the toxicity resolves or stabilizes to baseline level.

[k] A blood sample will be collected for evaluation of circulating biomarkers, such as circulating tumor DNA and/or cytokines. Timepoints include C1D1 pre-dose, C2D1 pre-dose, C3D1 pre-dose, C4D1 pre-dose, C5D1 pre-dose, then pre-dose every 4 cycles, and PD or EOT.

[l] For women of childbearing potential (WCBP), a urine or serum pregnancy test will be performed within 4 days prior to Day 1 of each cycle and at the 30-day Follow-up visit. It is recommended to perform monthly pregnancy tests for 7 months after the last dose of MIRV. Additional testing may be performed in accordance with institutional requirements or local regulation.

Table 2 Schedule of Assessments for Phase 2 part

Activity	Pre- screening	Screening	Cycle 1		Cycles ≥2	EOT	30-day Follow-up	Response/ Survival Follow-up
			Day 1	Day 8±3	Day 1[a]	≤ 7 days from discon.	30 (+14) days from last dose	Every 3±1 month from EOT

[m] Ophthalmic examinations will be performed in all patients by an ophthalmologist, optometrist, or other qualified health care provider ("eye care professional") within 14 days before C1D1 (baseline), before Cycle 3,5,7, at the 30-day Follow-up visit (+ 14 days) and as clinically indicated. They will include the following: manifest refraction, best corrected visual acuity, intra-ocular pressure assessment, fundoscopy (baseline and 30-day Follow-up only), and slit lamp examination. Patients requiring an ophthalmological examination due to symptoms prior to Cycle 2 or 4 will then proceed to every 6-week examinations as indicated by findings and do not require the routine, asymptomatic exams at Cycle 3, 5, and 7 in addition.

[n] Ocular symptoms assessment will be performed by the treating physician or other qualified individual before the start of each cycle. For patients reporting > NCI CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

[o] Radiologic tumor assessment by CT/MRI scan. Refer to section 9.4.16 for details.

[p] If a patient discontinues before documentation of PD, a tumor assessment and [redacted] will be assessed at the EOT visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and [redacted] will continue to be performed. Patients who discontinue study treatment for reasons other than 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 C1D1), assessments should occur every 6 weeks (± 1 week) 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, death, the start of new anticancer therapy, or patient's withdrawal of consent (whichever comes first).

[redacted]

[r] Only AEs/SAEs which are considered related to a study procedure (i.e. blood draw or fresh tumor biopsy) will be captured during the Pre-screening period, i.e. 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.

[s] All ocular AEs will be followed until resolution, stabilization, or return to baseline.

[t] Survival Follow-up assessments will occur every 3 months (±1 month) until death, the patient is lost to Follow-up or withdraws of consent for Survival Follow-up, or EOS, whichever comes first. These assessments may be conducted by telephone. Information on initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) should be collected. Additional Survival Follow-up calls may occur periodically if needed.
Note: A patient's *BRCA* mutational status (germline or somatic mutation in tumor tissue) will be collected as part of her medical history if available. Patients without a known mutation will be classified as unknown.

Table 3 Pharmacokinetic/Immunogenicity Sampling Time Points for Phase 1 part

Visit	Time Point	Pharma cokinetic	Immunogenicity
C1D1	Before dosing	●	●
	Within 10 minutes of infusion completion	●	
	2 hours after end of MIRV infusion (± 10 minutes)	●	
	4 hours after end of MIRV infusion (± 10 minutes)	●	
	6 hours after end of MIRV infusion (± 10 minutes)	●	
C1D2	24 hours after end of MIRV infusion (± 2 hours)	●	
C1D3	48 hours after end of MIRV infusion (± 2 hours)	●	
C1D4	Anytime during visit	●	
C1D5	Anytime during visit	●	
C1D8	Anytime during visit	●	
C1D15	Anytime during visit	●	
C2D1	Before dosing	●	●
	After end of MIRV infusion	●	
C3D1	Before dosing	●	
	Within 10 minutes of infusion completion	●	
	2 hours after end of MIRV infusion (± 10 minutes)	●	
	4 hours after end of MIRV infusion (± 10 minutes)	●	
	6 hours after end of MIRV infusion (± 10 minutes)	●	
C3D2	24 hours after end of MIRV infusion (± 2 hours)	●	
C3D3	48 hours after end of MIRV infusion (± 2 hours)	●	
C3D4	Anytime during visit	●	
C3D5	Anytime during visit	●	
C3D8	Anytime during visit	●	
C3D15	Anytime during visit	●	
C4D1	Before dosing	●	●
	After end of MIRV infusion	●	
C5D1	Before dosing	●	●
C6D1	Before dosing	●	
EOT	Anytime during visit	●	●

Abbreviations: C = cycle; D = day; EOT = End of Treatment.

Unscheduled visit:

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

Procedures for collection, storage and shipment of samples are provided in the applicable Laboratory Manual.

Table 4 Pharmacokinetic and Immunogenicity Sampling Time Points for Phase 2 part

Visit	Time Point	Pharmacokinetic	Immunogenicity
C1D1	Before dosing	●	●
	≤ 1 hour after end of MIRV infusion	●	
C1D8	Anytime during visit	●	
C2D1	Before dosing	●	●
C3D1	≤ 1 hour after end of MIRV infusion	●	
C3D8	Anytime during visit	●	
C4D1	Before dosing	●	●
EOT	Anytime during visit	●	●

Abbreviations: C = cycle; D = day; EOT = End of Treatment.

Unscheduled visit:

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

Procedures for collection, storage and shipment of samples are provided in the applicable Laboratory Manual.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each patient who participates in the study, and document the date of (e)consent in the patient's medical chart. Valid informed (e)consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, 1982 (Oken et al. 1982).

Appendix E Response Definitions (RECIST v1.1)

(Eisenhauer 2009)

DEFINITIONS

Baseline: Baseline is defined as the most recent assessment performed before the first dose of study treatment. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable Lesions: Except for lymph nodes (described below), measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Non-measurable Lesions: all other lesions (or sites of disease) including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable.

- Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed.
- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target Lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at baseline.

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

- Target lesions will be measured at each assessment (longest axis for non-nodal lesions, shortest axis for measurable malignant nodal lesions).

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

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

Special Considerations

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

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

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

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

Lesions with Prior Local Treatment: Lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable; however, if they meet the following criteria, they may be considered for study:

- there has been prior documented progression in the lesion by at least 2 sequential CT or MRI scans performed after the completion of radiation, or
- histopathological evidence of progression

Additionally, if such lesions meet the criteria for measurability, they may be considered target lesions.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesion at baseline should be used during each follow-up assessment. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam (referring to biopsy-proven visible lesions(s) at the vaginal apex).

Chest X-ray: Lesions that are identified on chest X-ray must be confirmed and followed by CT scan. If there is/are pre-existing chest lesion(s) before the baseline tumor assessment, a chest X-ray is not necessary to assess those lesions. The pre-existing chest lesion(s) must be assessed at baseline and followed by CT scans.

Conventional CT or MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scan) except for lung.

[redacted]

Time Point Assessments

Patients will have tumor measurements 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 weeks) thereafter.

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

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

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

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

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

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

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

Time Point Response Criteria

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10mm.
Partial Response (PR)	At least 30% decrease in the sum of diameters (SoD of target lesions, taking as reference the baseline SoD
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesion, taken as reference the smallest (nadir) SoD since and including baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Applicable (N/A)	No target lesions identified at baseline
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	
Non-target Lesion TPR	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level if tumor marker at baseline is above the upper normal limit. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of [redacted] above the normal limits if [redacted] at baseline is above the upper normal limit
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (N/A)	No non-target lesions identified at baseline
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	
New Lesion TPR	
Yes	Lesion present at follow-up visit either for the very first time or reappearing (i.e., lesion was present at baseline, disappeared at a follow-up visit and re-appeared later).
No	No new lesions present at follow-up
Unable to Evaluate (UE)	Patient non assessed or incompletely assessed for new lesion

Determining Overall TPR

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

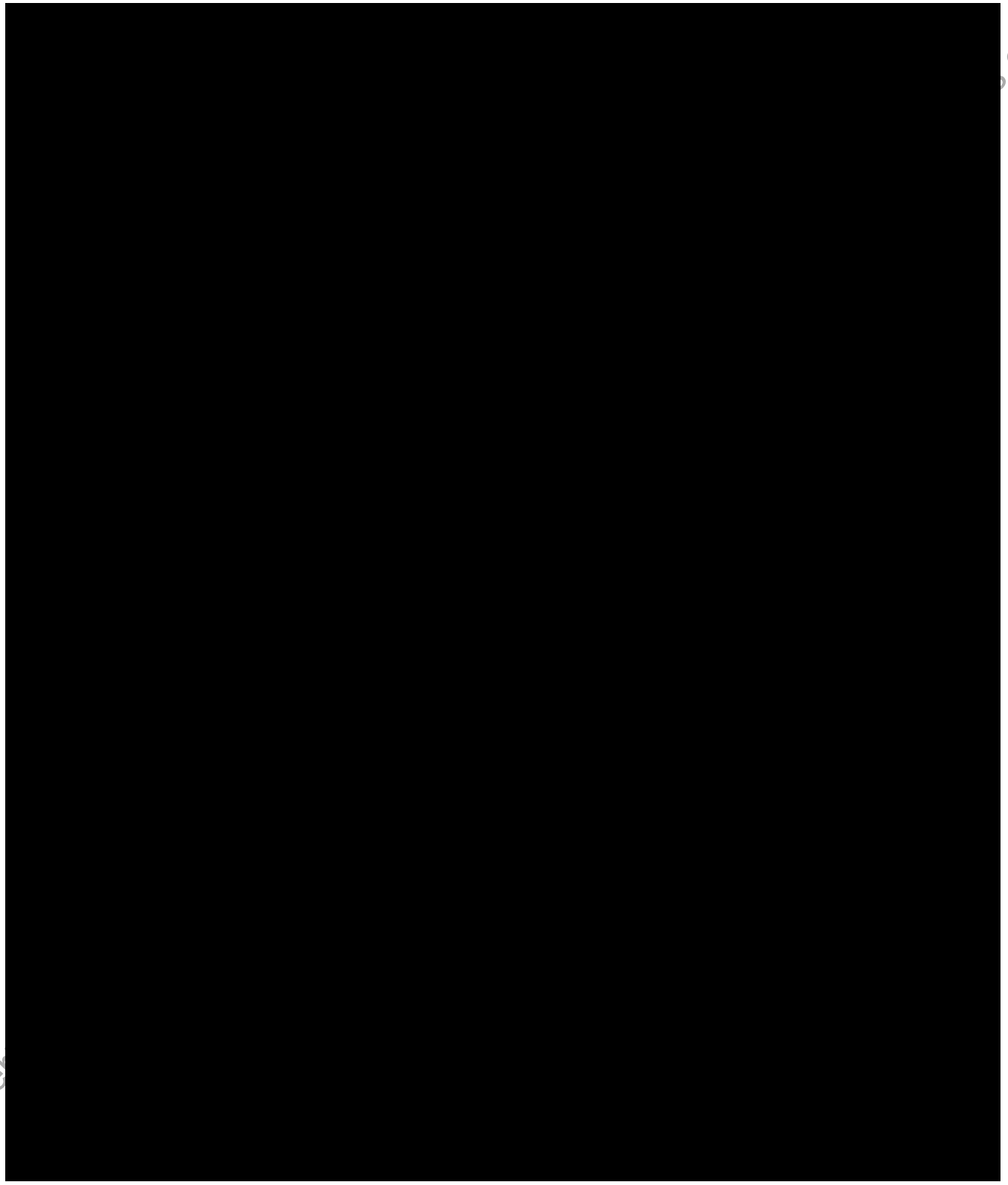
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UE, unable to evaluate; NA, not applicable (no such lesions at Screening); Any, CR, PR, SD, PD, NA or UE.

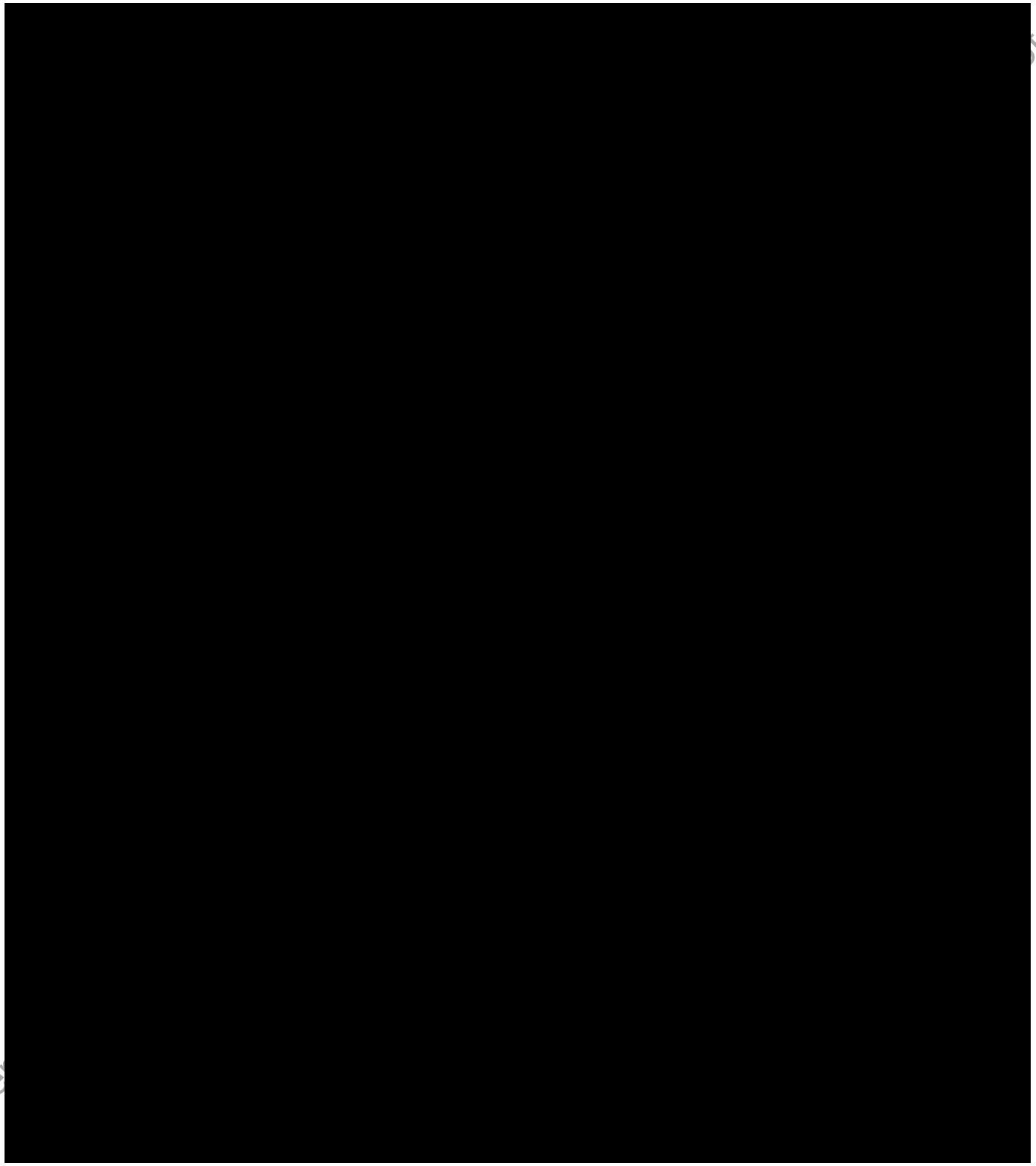
The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

*Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met.

Confirmation: The main goal of confirmation of objective response is to avoid overestimating the observed response rate. For patients with an overall response of PR or CR a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Best Overall Response: Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at any time point.





Appendix G List of Concomitant Medications Requiring Careful Monitoring

CYP Enzymes	Strong inhibitors	Strong inducers	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP3A4	Ceritinib, clarithromycin, cobicistat, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telithromycin, tipranavir and ritonavir, voriconazole	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor and ivacaftor, mitotane, phenytoin, rifampin, St. John's wort	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

Source: FDA drug development resources:
(http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classSub) (Cited 20/Dec/2023)

Appendix H Protocol History

Amendment History

Date	Amendment Number	Amendment Type	Region
15 February 2024	Initial Protocol	Not applicable	Japan
22 March 2024	Amendment 01	Non-Substantial	Japan
12 June 2024	Amendment 02	Substantial	Japan

Rationale for Amendment 01

This section describes the changes in reference to the protocol incorporating Amendment 01.

The primary reason for this non-substantial amendment is to clarify statements including the procedure to ensure safety of subjects.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 01			
Summary of Changes Since the Last Version (initial) of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	2.0 STUDY SUMMARY 7.2.1 Exclusion Criteria for Phase 1 part	Added exclusion criterion to exclude patients with known hypersensitivity to study drug and/or any of their excipients.	To be required as an exclusion criterion to ensure safety of subjects.
2	4.1.2 Mirvetuximab Soravtansine	Added that MIRV is a recombinant drug of which the antibody is produced by Chinese hamster ovary cells.	To clarify that MIRV is a drug of which the antibody is produced by Chinese hamster ovary cells.
3	6.1.1 Overview of Study Design Appendix A Schedule of Events, Table 1, footnote (a)	Added provisions regarding assessment prior to patient discharge, and that the confirmation records are kept in medical records, etc.	To clarify a procedure on ensuring safety of subjects.
4	8.3 Definitions of DLT (For Phase 1 part only)	Added that the tolerability will be evaluated in consideration of all safety information including AEs that occurred in patients who were excluded from DLT evaluation for reasons other than DLT (including considerations for Grade 3 or higher anemia and anemia requiring red blood cell transfusion).	To clarify evaluation of tolerability.
5	9.4.3 Mutation Status	Provided examples of mutation status to be collected from prior testing (e.g., BRCA for ovarian cancer, ALK for NSCLC)	To clarify mutation status to be collected.

Protocol Amendment 01			
Summary of Changes Since the Last Version (initial) of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6	2.0 STUDY SUMMARY 7.2.1 Exclusion Criteria for Phase 1 part 7.2.2 Exclusion Criteria for Phase 2 part 9.4.15.3 Viral serology	Added that hepatitis B surface antibody measurements will be performed at screening.	To clarify viral serology test for hepatitis B.
7	9.4.17.3 Biomarker assessment	Added that the results of the exploratory biomarker test (including genetic tests) will not be disclosed to subjects. Added provisions for processing and shipping samples.	Those tests are exploratory and the clinical meaning of the results have not been established. To clarify handling of samples.
8	9.4.18 Sample Retention	Added provisions regarding the storage period, storage method, and disposal of samples.	To clarify handling of samples at the consent withdraw.

Abbreviations: AE = adverse event; *ALK* = anaplastic lymphoma kinase; *BRCA* = breast cancer susceptibility gene; DLT = dose-limiting toxicity; MIRV = mirvetuximab soravtansine; NSCLC = non-small cell lung cancer.

Signature Page for TAK-853-1501-Protocol-v3-2024-06-12-JP-E

Title: A phase 1/2 open-label study to evaluate the safety, tolerability, effica

Approval	Shinichi Fukunaga shinichi.fukunaga@takeda.com Clinical 14-Jun-2024 06:06:16 GMT+0000

Approval	Shuuji Sumino shuuji.sumino@takeda.com Statistics 14-Jun-2024 08:33:48 GMT+0000

Approval	Xiaofei Zhou Xiaofei.Zhou@takeda.com Clinical 15-Jun-2024 12:27:35 GMT+0000

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