Clinical Trial Protocol

Clinical Trial Protocol Number	EMR200647-001
Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
Phase	I
CCI	CCI
EudraCT Number	2015-004366-28
Coordinating Investigator	PPD
Sponsor	For all countries except the USA and Japan: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in Japan: Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) PPD For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA
Clinical Trial Protocol Version	22 June 2021 / Version 7.2-BE-ES-IT-FR

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List of Abbreviations

ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from the time of dosing extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from the time of dosing to the time of the last observation
β-HCG	β-human chorionic gonadotropin
BOR	best overall response
CA-125	cancer antigen 125
C_{max}	maximum serum concentration observed postdose
C_{min}	minimum serum concentration observed postdose
CR	complete response
CRO	Contract Research Organization

CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
C_{trough}	trough concentration
DCR	disease control rate
DLT	dose-limiting toxicity
EC_{50}	effective concentration exerting 50% effect
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-BN20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Brain Module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument
EORTC QLQ-CX24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module
EORTC QLQ-HCC18-M	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma Module – Modified
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Module
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Module
FACS	fluorescence-activated cell sorter
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration

FFPE	formalin fixed, paraffin embedded
FHSI-8	FACT Hepatobiliary Symptom Index – 8 questions
FISH	fluorescence in situ hybridization
FOLFOX	oxaliplatin, 5-fluorouracil, and folinic acid
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HAHA	human antihuman antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HPV	human papillomavirus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	Investigational Medicinal Product

INR	international normalized ratio
IPMP	Integrated Project Management Plan
irAE	immune-related adverse event
iRANO	immune-related RANO
IRB	Institutional Review Board
CCI	[redacted]
IRC	Independent Endpoint Review Committee

CCI [redacted]

IWRS	interactive web response system
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MAHA	mouse antibody against human antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MDSCs	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MoA	mechanism of action

CCI	[redacted]
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NBF	neutral-buffered formalin
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
CCI [redacted]	
Ph Eur	European Pharmacopeia
PK	pharmacokinetic(s)
PR	partial response
pSMAD	phosphorylated SMAD
PT	prothrombin time

CCI	[redacted]
RECIST	Response Evaluation Criteria in Solid Tumors
RF	rheumatoid factor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma head and neck
SD	stable disease
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
T4	free thyroxine
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor-beta
TGFβRII	transforming growth factor-beta receptor II
t_{max}	time to reach maximum concentration
TMTB	total measured tumor burden
TNBC	triple-negative breast cancer
TNM	Tumor Node Metastasis Classification of Malignant Tumors (UICC)
Treg	regulatory T-cells
TSH	thyroid-stimulating hormone
TTP	time to progression
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
USP	United States Pharmacopeia

WBC	white blood cell
λ_z	terminal elimination rate constant

1 Synopsis

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Trial Phase	I
IND Number	CCI [redacted]
FDA covered trial	Yes
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Trial centers/countries	Approximately 220 enrolling sites in Asia Pacific, the European Union, Canada, and the USA (up to 60 sites).
Planned trial period (first subject in-last subject out)	First subject in: Q3, 2015 Last subject out: Q4, 2021

Trial Registry	ClinicalTrials.gov, EudraCT, and all other required registries

Objectives:

Primary objectives

The primary objective of the dose escalation part of the study is to determine the safety, tolerability, and the maximum-tolerated dose (MTD) of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

Except for the glioblastoma cohort, the primary objective of the efficacy expansion cohorts is to assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). For glioblastoma, the primary objective is to assess the disease control rate (DCR) according to Response Assessment in Neuro-Oncology (RANO).

Secondary objectives

The secondary objectives are:

- To characterize the pharmacokinetic (PK) profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure
- Determine the safety and tolerability of MSB0011359C in subjects with metastatic or locally advanced solid tumors (expansion cohorts)
- To assess the BOR according to RECIST 1.1.

CCI [redacted]

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Methodology:

This is a Phase I, open-label, dose-escalation trial with consecutive parallel-group expansion in selected solid tumor indications.

Dose escalation

The current trial is composed of a standard dose escalation "3 + 3" cohort design, for which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of dose-limiting toxicities (DLTs), followed by a consecutive parallel-group expansion in selected solid tumor indications.

Cohorts of 3 subjects with metastatic or locally advanced solid tumors, for which no standard effective therapy exists or standard therapy has failed, will receive MSB0011359C at escalating dose levels. The starting MSB0011359C dose is 1 mg/kg; the highest envisaged dose in the dose escalation part is 20 mg/kg, but this may be expanded based on the study safety data. The dose range and schedule for this trial were developed based on safety considerations as well as on preclinical PK / CCI [redacted] and experience with the parent avelumab antibody currently under clinical development.

Dose escalation (3 + 3 design) will be performed at the following dose levels

- 1 mg/kg
- 3 mg/kg
- 10 mg/kg
- 20 mg/kg
- 30 mg/kg
- 2400 mg flat dose

The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48-hour intervals between subjects. A DLT is defined as any Grade $\geq$ 3 adverse event (AE) assessed to be related to investigational medicinal product (IMP) by the Investigator and / or Sponsor occurring in the DLT evaluation period (21 days after first administration of MSB0011359C) confirmed by the Safety Monitoring Committee (SMC) to be relevant for the IMP treatment. The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT.

At each dose level, subjects will receive MSB0011359C as a 1-hour intravenous (IV) infusion (120 minutes for the 30 mg/kg and 2400 mg flat-dose cohorts) once every 2 weeks until progressive disease (PD) has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the IMP as outlined in this protocol. In order to mitigate potential infusion-related reactions, premedication with an antihistamine

and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions, after which premedication is optional and at the discretion of the Investigator. Steroids as premedication are not permitted.

As the 20 mg/kg cohort in the dose escalation portion has cleared SMC evaluation, an additional cohort at the 30 mg/kg dose level will be initiated, in parallel to the ongoing expansion cohorts. The 30 mg/kg cohort will be enrolled in a 3 + 3 design with SMC evaluation after the first 3 subjects and no more than 6 evaluable subjects to be enrolled. This cohort should provide additional insight into dose proportionality of PK and CCI parameters and support safety considerations at higher exposures than the expansion-phase dose of 1200 mg once every 2-weeks.

With the safety of the 30 mg/kg cohort established, a fixed dose cohort of 2400 mg once every 2 weeks will be enrolled in a 3 + 3 design with SMC evaluation after the first 3 subjects and no more than 6 evaluable subjects to be enrolled. This cohort should support safety considerations at higher exposures than the current expansion phase dose of 1200 mg once every 2 weeks, including those for alternative dosing regimens in Phase II and Phase III studies.

For PK / CCI purposes, after at least the first 2 cohorts have been evaluated with acceptable safety and for exploratory PK / CCI relationships, a decision will be made to initiate up to 2 cohorts of 3 subjects each, one at 0.1 mg/kg and one at 0.3 mg/kg, which will increase on the second dose and all subsequent doses to a 1200 mg/infusion flat dose dependent upon SMC clearance and only if the Sponsor and Coordinating Investigator have determined a meaningful dose for the intrasubject escalation. After the MTD has been reached or the 20 mg/kg cohort has been declared by the SMC as the highest non-MTD dose assessed, then further PK analyses may be performed. If deemed necessary, the 1, 3, 10, and 20 mg/kg cohorts may each enroll up to an additional 10 subjects (up to 40 total) for the purpose of establishing the PK / CCI relationship. On the second dose and all subsequent doses, the 1 mg/kg cohort may increase to a 1200 mg/infusion flat dose. No DLT evaluations will be performed in these supplemental cohorts.

Expansion

After determination of the MTD, a MSB0011359C dose for further investigation will be selected and enrollment in expansion cohorts in selected tumor indications will be opened to determine the safety and clinical activity of MSB0011359C. The indications were chosen since they offer the potential for transformative treatment with ability to establish an initial proof of principle of antitumor activity of MSB0011359C with good feasibility.

The selected dose of MSB0011359C for the expansion cohorts will be infusions of 1200 mg for all expansion cohorts except for the second-line NSCLC cohort. The second-line NSCLC cohort will be randomized to 1 of 2 dose levels 500 mg (40 subjects) and 1200 mg (40 subjects). These doses will be administered as "flat" doses independent of the body weight as 1-hour IV infusions once every 2 weeks until PD has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the IMP as outlined in this protocol.

In the dose-escalation part of the study, premedication with an antihistamine and with paracetamol (acetaminophen) has been mandatory in order to mitigate potential

infusion-related reactions. Based on an initial safety assessment in the dose-escalation cohorts at dose levels of 1, 3, 10, and 20 mg/kg with a cutoff date of 04 May 2016, no subject was reported with a treatment-emergent adverse event (TEAE) with a Preferred Term of infusion-related reaction; however using a post-reporting analysis according to criteria outlined in the Statistical Analysis Plan, 3 subjects were reported with TEAEs that were classified as "infusion-related reactions," with the Preferred Terms of abdominal pain, pyrexia, and back pain (Note: these events are undergoing further review). Based on the above observations and in order to further investigate the potential for infusion-related reactions, for subjects in the NSCLC biomarker cohort being treated at the United States (US) National Cancer Institute (NCI), premedication will be optional. This approach in the limited number of subjects enrolled in the NSCLC biomarker cohort and under close surveillance of experienced Investigators at the NCI investigational site appears to be justified. For all other escalation and expansion cohorts, premedication is mandatory for at least the first 2 infusions, and thereafter, optional at the discretion of the Investigator. If Grade ≥ 2 infusion reactions are seen during the first two infusions premedication should not be stopped. Based on safety data for subjects treated with premedication for only the first 2 infusions, the protocol might be amended at a later time point to allow dosing without premedication for all subject infusions.

Response to treatment

Subjects from either the dose-escalation or the expansion portions of the trial who have experienced stable disease (SD), a partial response (PR), or a complete response (CR) should be treated through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in this protocol. If there is further evidence of PD thereafter, trial treatment should be discontinued; however continued treatment is possible in consultation with the Medical Monitor. For subjects who achieve SD, a CR or PR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Responsible. The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available.

Subjects will be monitored and assessed for safety and efficacy parameters at regular intervals throughout the trial.

Planned number of subjects:

Dose escalation: from 3 to 82 subjects.

Expansion: Up to approximately 566 subjects.

Primary endpoints:

The primary endpoints for the dose-escalation part of the trial are the:

- Number, severity, and duration of TEAEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03

- Number, severity and duration of treatment-related adverse events (AEs) for all dose groups / indications according to CTCAE v4.03
- Occurrence of DLTs during the first 3 weeks (21 days) of treatment in the dose-escalation part of the trial

Except for the glioblastoma cohort, the primary efficacy endpoint for the dose-expansion part of the trial is the confirmed BOR according to RECIST 1.1 as adjudicated by the Independent Endpoint Review Committee (IRC) and will be evaluated by confirmed objective response rate (ORR). For glioblastoma, the primary endpoint will be disease control according to RANO as adjudicated by the IRC.

Secondary endpoints:

The secondary endpoints for the dose-escalation part of the trial are the:

- MSB0011359C PK profile (for dose escalation), including area under the concentration-time curve (AUC), maximum serum concentration observed postdose (C_{max}), minimum serum concentration observed postdose (C_{min}), and terminal half-life ($t_{1/2}$)
- Serum titers of antiMSB0011359C antibodies
- BOR according to RECIST 1.1 per Investigator assessment.

The secondary endpoints for the expansion part of the trial are the:

- MSB0011359C PK profile (for dose escalation), including AUC, C_{max}, C_{min}, and $t_{1/2}$
- Serum titers of antiMSB0011359C antibodies
- Number, severity, and duration of TEAEs and treatment-related TEAEs according to the NCI-CTCAE v4.03
- BOR according to RECIST 1.1 per Investigator assessment.

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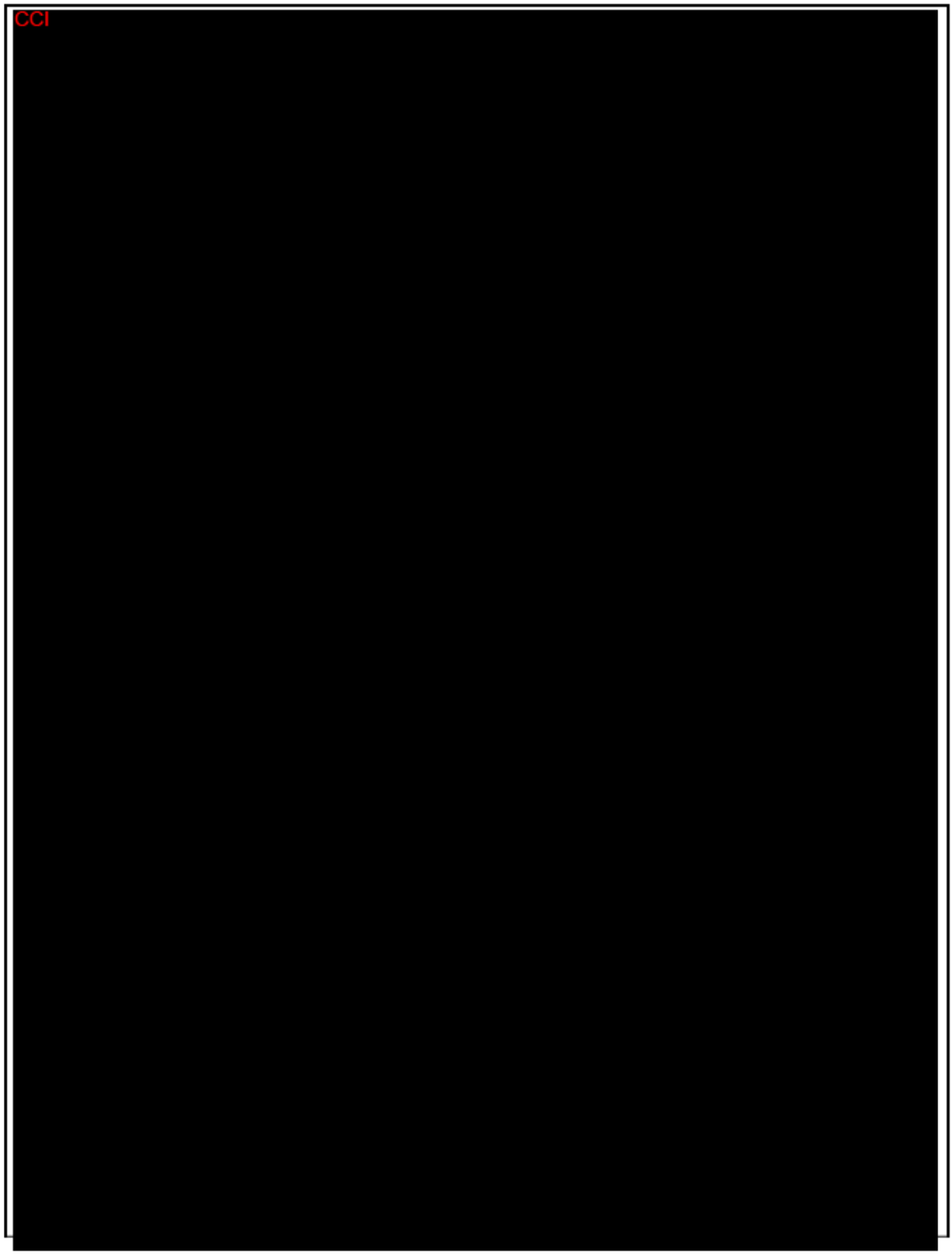
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Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria for the dose escalation include:

1. Ability to understand the purpose of the study, provide signed and dated informed consent, and able to comply with all procedures
2. Male or female subjects aged ≥ 18 years
3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no effective standard therapy exists or standard therapy has failed
4. Life expectancy ≥ 12 weeks as judged by the Investigator
5. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 at trial entry
6. Must have evaluable or measurable disease at baseline
7. Adequate hematological function defined by white blood cell (WBC) count ≥ 3×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 120×10^9/L, and hemoglobin ≥ 9 g/dL
8. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal range (ULN), an aspartate aminotransferase (AST) level ≤ 2.5 × ULN, and an alanine aminotransferase (ALT) level ≤ 2.5 × ULN. For subjects with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 × ULN is acceptable
9. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection

Key inclusion criteria for expansion cohorts include:

1. Ability to understand the purpose of the study, provide signed and dated informed consent, and able to comply with all procedures. In Japan, if a subject is < 20 years, the written informed consent from his/her parent or guardian will be required in addition to the subject's written consent
2. Male or female subjects aged ≥ 18 years
3. Availability of fresh tumor biopsies (excluding bone biopsies) is mandatory for eligibility in the NSCLC biomarker expansion, NSCLC anti-PD-1/PD-L1 failure and melanoma anti-PD-1/PD-L1 failure cohorts (it is preferable to not biopsy a target lesion; however, if

only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility). The biopsy or surgical specimen must have been collected within 28 days prior to the first IMP administration. For other expansion cohorts, availability of either tumor archival material or fresh biopsies within 28 days is acceptable (excluding bone biopsies) with one of these being mandatory (where possible fresh biopsies are preferred). If no archival material is available and only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility. CCI

4. Life expectancy ≥ 12 weeks as judged by the Investigator
5. Subjects must have one of the following:

- CCI

For ascending dose-portion and dose-expansion portion:

Uninfected, HCV, and HBV-infected subjects are eligible. If medically indicated, subjects infected with HBV must be treated and on a stable dose of antivirals (eg, entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance. Subjects on active HCV therapy at study entry must be on a stable dose without documented clinically significant liver function test or hematologic abnormalities (must meet criteria below) and with planned monitoring and management according to appropriate labeling guidance.

Additional criteria for all HCC subjects include:

- Child-Pugh A or B7
- ECOG PS 0 or 1
- Albumin $\geq$ 2.8 g/dL
- International normalized ratio (INR) < 1.7
- Adequate hematological function defined by WBC count $\geq 2.5 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 50 \times 10^9$/L, and hemoglobin $\geq$ 9 g/dL
- Subjects with no allergies to contrast and able to tolerate computed tomography (CT) or magnetic resonance imaging (MRI) contrast in the opinion of the Investigator

- **NSCLC, second line:** Histologically confirmed Stage IIIb/IV or recurrent NSCLC. Must not have received checkpoint inhibitor previously (consult with Medical Monitor if necessary). Must have experienced disease progression after an acceptable therapy defined as follows:
  - Subjects must have progressed during or after a minimum of 2 cycles of 1 course of a platinum-based combination therapy administered for the treatment of metastatic disease. A history of continuation (use of a non-platinum agent from initial combination) or switch (use of a different agent) maintenance therapy is permitted provided there was no progression after the initial combination. A switch of agents during treatment for the management of toxicities is also permitted provided there was no progression after the initial combination

  OR

  - Subjects must have progressed within 6 months of completion of a platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for locally advanced disease

  Subjects with non-squamous cell NSCLC of unknown mutational status will require testing (local laboratory, or central laboratory if local testing is not available). Subjects with known EGFR mutation and / or ALK translocation are eligible if they have received at least 1 line of tyrosine kinase inhibitor therapy. Subjects with ROS1 rearrangement must have received tyrosine kinase inhibitor therapy if locally approved. These subjects

do not require prior treatment with systemic chemotherapy. Subjects with large cell neuroendocrine cancer of the lung are not eligible

- **NSCLC, anti-PD-1 / anti-PD-L1 failure:** Subjects with histologically confirmed Stage IV (metastatic) or recurrent NSCLC (per 7th International Association for the Study of Lung Cancer classification) who have exhausted standard treatment options in the opinion of the Investigator are to be enrolled. At a minimum, subjects need to have received and failed platinum-based chemotherapy and must have received anti-PD-1 or anti-PD-L1 as monotherapy and failed with disease progression. In addition, subjects should have exhausted other indicated driver mutation therapy, as appropriate
- **Melanoma, anti-PD-1 / anti-PD-L1 failure:** Subjects with unresectable Stage III or metastatic (Stage IV) melanoma who have exhausted standard treatment options in the opinion of the investigator are to be enrolled. At a minimum, subjects need to have received anti-PD-1 or anti-PD-L1 as mono- or combination therapy and failed with disease progression. Also must have failed appropriate systemic therapies including BRAF inhibitor if BRAF V600 mutation positive
- **Pancreatic adenocarcinoma, second line or greater:** Histologically confirmed pancreatic adenocarcinoma (subjects with endocrine or acinar pancreatic carcinoma are not eligible). Must have unresectable or locally advanced or metastatic disease
  - Prior therapy with ≥ 1 systemic chemotherapy regimen for unresectable or metastatic pancreatic cancer or unwilling / unable to receive systemic chemotherapy. Subjects must not have received previous radiotherapy for measurable lesions
  - Disease progression while receiving or after discontinuing palliative chemotherapy
- **Colorectal cancer (CRC), third line or greater:** Histologically confirmed adenocarcinoma of the colon or rectum
  - Subjects must have progressed during or after a second-line of systemic treatment
  - Prior failed therapy must have included at least a fluoropyrimidine, oxaliplatin, irinotecan (single or in combination) and bevacizumab (where approved). For subjects who had wild-type RAS tumors, cetuximab or panitumumab treatment must have occurred
- **TNBC, second-line or greater:** Tumor must be confirmed negative for estrogen receptors, progesterone receptors, and HER2
  - ER negative defined by: ER IHC < 1% reactive cells
  - PR negative defined by: PR IHC < 1% reactive cells
  - HER-2 negative defined by one of four situations below:
    1. HER2 Breast IHC = 0
    2. HER2 Breast IHC = 1+
    3. HER2 Breast IHC = 2+ AND FISH-negative (non-amplified)
    4. FISH non-amplified

- Subjects must have progressed during or after first-line of chemotherapy

- **Ovarian cancer, platinum resistant or refractory, previously treated systemically:** Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (subjects with non-epithelial tumor, including malignant mixed Müllerian tumors without high grade serous component, or ovarian tumors with low malignant potential [ie, borderline tumors] are not eligible)
  - Must not be a candidate for surgical resection with curative intent
  - Must have platinum resistant / refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-based therapy (refractory), or progression on / after last non-platinum-based chemotherapy
  - Treatment history of at least 2 prior systemic regimens, including prior exposure to platinum and taxane agents.
  - BRCA status must be reported if known
- **Esophageal adenocarcinoma, post-platinum, second line or greater:** Histologically confirmed recurrent or metastatic esophageal adenocarcinoma. Must have unresectable (Stage III or IV) disease
  - Must have received at least one previous platinum-containing chemotherapy regimen. Subjects with HER2-positive tumors must have received prior trastuzumab
- **Glioblastoma, post-temozolomide / radiation, second line:** Histologically confirmed Grade IV malignant glioma (subjects with extracranial metastatic or leptomeningeal are not eligible)
  - Previous treatment with radiotherapy and temozolomide
  - Tolerance to gadolinium
  - An interval of at least 12 weeks after the end of prior radiotherapy is required unless there is either histolopathologic confirmation of recurrent tumor or new enhancement on MRI outside of the radiotherapy treatment field
  - First recurrence of glioblastoma
  - Karnofsky Performance Status ≥ 70
  - Subjects must not have received prior bevacizumab or other anti-vascular endothelial growth factor or antiangiogenic treatments
- **SCCHN, second line or greater:** Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
  - Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting

- Subjects may have received prior cetuximab
- Human papillomavirus tumor testing must be reported if known

- **Cervical cancer, second line or greater:** Histologically confirmed recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix following standard of care treatment with systemic therapy for advanced disease (typically doublet cytotoxic chemotherapy and bevacizumab, where approved)
  - Human papillomavirus tumor testing must be reported if known

6. ECOG PS of 0 to 1 at trial entry
7. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1

Key exclusion criteria (applicable to all subjects, including all expansion cohorts)

1. Concurrent treatment with non-permitted drugs and other interventions
2. Except for the anti-PD-1 / anti-PD-L1-experienced NSCLC and melanoma expansion cohorts, prior therapy with any antibody / drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4 antibody) is not allowed (consult with Medical Monitor as needed), inclusive of intrahepatic, localized administration of such agents
3. Anticancer treatment within 28 days before the start of trial treatment, for example cytoreductive therapy, radiotherapy (with the exception of palliative radiotherapy delivered in a normal organ-sparing technique), immune therapy, or cytokine therapy (with the exception of sorafenib for subjects with HCC, which must have been stopped within 14 days)
4. Major surgery within 28 days before the start of trial treatment (prior diagnostic biopsy is permitted)
5. Systemic therapy with immunosuppressive agents within 7 days before the start of trial treatment; or use of any investigational drug within 28 days before the start of trial treatment (**Note:** for subjects with glioblastoma, steroid use is allowed according to standard of care and local guidelines)
6. Previous malignant disease (other than the target malignancy to be investigated in this trial) within the last 3 years. Subjects with a history of cervical carcinoma in situ, superficial or non-invasive bladder cancer, or basal cell or squamous cell carcinoma in situ previously treated with curative intent are NOT excluded. Subjects with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor
7. Rapidly progressive disease which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or trial procedures
8. Subjects with active central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do

not require continued steroid therapy. Subjects with CNS metastases incidentally detected during Screening which do not cause clinical symptoms and for which standard of care suggests no therapeutic intervention is indicated should be discussed with the Sponsor Medical Responsible

9. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (eg, corneal transplant, hair transplant)

Additional exclusion criteria for subjects in the HCC cohort include:

- Clinical ascites (that is, not per radiological assessment only) within past 6 months not adequately controlled with medical therapy; history of variceal bleeding within past 3 months; history of uncontrolled hepatic encephalopathy in the past 3 months; or history of obstructive jaundice not amenable to stenting in the past 3 months
- Hepatitis D virus (HDV) co-infection with hepatitis B virus (HBV; if HBV surface antigen or HBV DNA positivity at Screening then must check for HDV status)
- Chemoembolization or radioembolization within 28 days prior to IMP administration

Investigational Medicinal Product: dose/mode of administration/ dosing schedule:

For the dose-escalation cohorts (except for the 2400 mg flat-dose cohort), the dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration.

Following safety and PK analysis of the Escalation cohorts, a flat dose of 1200 mg/infusion was chosen for all expansion cohorts, except for the NSCLC second-line cohort, in which 40 subjects will receive 500 mg/infusion and 40 subjects will receive 1200 mg/infusion.

MSB0011359C will be administered once every 2 weeks as a 1-hour (-10 / +20 minutes, that is, over 50 to 80 minutes) IV infusion. Subjects enrolled in the 30 mg/kg and 2400 mg flat-dose cohorts may have a total infusion time of up to 120 minutes.

In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion (premedication is optional for all infusions for subjects in the NSCLC biomarker cohort being treated at the US NCI). If Grade $\geq$ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

Reference therapy: dose/mode of administration/dosing schedule:

Not applicable.

Planned trial and treatment duration per subject:

Subjects will receive MSB0011359C until progression has been confirmed by a subsequent scan, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs as outlined in this protocol.

In the case of SD, PR, or CR, subjects should continue treatment through the end of 12 months, although additional treatment is possible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in this protocol. If there is further evidence of PD thereafter, trial treatment should be discontinued; however, continued treatment is possible in consultation with the Medical Monitor.

Statistical methods:

The sample size for the dose-escalation part of the trial is not based on any statistical assumptions; rather, it follows the "3 + 3 rule", a well-established methodology in the design of dose-finding trials in oncology.

This trial plans for 6 cohorts (1, 3, 10, 20, and 30 mg/kg, and 2400 mg flat dose) of 3 subjects to be treated at each escalating dose level and with typical DLT driven expansions to 6 subjects and at the MTD. Additional cohorts at low-dose levels for PK profile and PK / PharmDyn modeling may be enrolled as well as HCC. Accordingly, the expected total sample size in the dose-escalation part of the trial will be between 3 and 82 subjects.

Except for the glioblastoma cohort, the primary efficacy endpoint for the dose-expansion part of the trial is the confirmed BOR according to RECIST 1.1 as adjudicated by the IRC. For glioblastoma, the primary endpoint will be disease control according to RANO as adjudicated by the IRC.

CCI [redacted]

HCC, ascending-dose cohort: Up to 36 subjects will be enrolled for the purpose of tolerability and safety assessment.

There will be one planned interim analysis for internal planning purposes. There is no multiplicity adjustment applied to the interim analysis. The interim analysis will occur when the first 30 subjects treated at the MTD or dose level selected for investigation in the expansion cohorts are evaluable for response assessment at 12 weeks (that is, have either completed the first tumor reassessment at Week 12 or discontinued the study before Week 12).

HCC, second-line or sorafenib-intolerant cohort: Up to 70 subjects will be enrolled in the HCC expansion cohort at the dose selected by the SMC during the dose-escalation part of the trial, for the purpose of assessing additional safety data and efficacy based on the BOR. An initial enrollment of 30 subjects will occur if > 6 of 30 subjects in the HCC 1200 mg flat-dose ascending-dose cohort have a response (that is an ORR of at least 20%). The primary analysis for this cohort will include the 30 subjects from the HCC 1200 mg flat-dose ascending-dose cohort and 30 subjects from the HCC second-line or sorafenib-intolerant cohort (assumes a similar target population as per the inclusion criteria). An additional 40 subjects may subsequently be enrolled in order to gather additional safety data.

With 60 subjects treated (30 subjects from the HCC 1200 mg flat-dose ascending-dose cohort and 30 subjects from the HCC second-line or sorafenib-intolerant cohort), the study has approximately 88% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 35% with 1-sided 0.1 alpha.

NSCLC, anti-PD-1 / anti-PD-L1 failure cohort: 80 subjects will be enrolled to characterize the tolerability, safety profile, and for preliminary evaluation of antitumor activity for previously anti-PD-1 / anti-PD-L1 treated subjects. With 80 enrolled subjects, the study has 92% power to rule out a 5% ORR when the true ORR is 15% with 1-sided 0.05 alpha.

There will be one planned interim analyses for internal planning purposes. There is no multiplicity adjustment is applied to the interim analysis. The interim analysis will occur when the first 40 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

Melanoma, anti-PD-1 / anti-PD-L1 failure cohort: 30 subjects will be enrolled to characterize the tolerability, safety profile, and for preliminary evaluation of antitumor activity for previously anti-PD-1 / anti-PD-L1 treated subjects. With 30 subjects who were treated with prior anti-PD-1 / anti-PD-L1 therapy, the study has 87% power to rule out a 5% ORR when the true ORR is 20% with 1-sided 0.1 alpha.

There will be one planned interim analysis for internal planning purposes. There is no multiplicity adjustment applied to the interim analysis. The interim analysis will occur when the 30 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

NSCLC, second-line cohort: Up to 80 subjects will be enrolled (randomized in a 1:1 ratio to receive either 500 or 1200 mg/infusion) to characterize the tolerability, safety profile, for preliminary evaluation of antitumor activity, and to support the overall PK data to characterize the exposure-response relationship. With 30 subjects who received 1200 mg/infusion were treated with prior platinum-based therapy, the study has 82% power to rule out a $\leq$ 20% ORR when the true ORR is 40% with 1-sided 0.1 alpha.

There will be one planned interim analysis for internal planning purposes. There is no multiplicity adjustment is applied to the interim analysis. The interim analysis will occur when the 30 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12). If $\leq$ 4 responders are observed at the interim analysis, no further subjects will be enrolled into the NSCLC second-line cohort.

Pancreatic adenocarcinoma, CRC, and cervical cancer cohorts: Up to 30 subjects will be enrolled in each cohort. One interim analysis is planned for each cohort when the 30th subject from each cohort is evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

With 30 subjects treated, the study has approximately 79% power to rule out a $\leq$ 10% ORR (null hypothesis) when the true ORR is 25% with 1-sided 0.1 alpha.

Ovarian cancer, TNBC, and esophageal adenocarcinoma cohorts: Up to 30 subjects will be enrolled in each cohort. One interim analysis is planned for each cohort when the 30th subject from each cohort is evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

With 30 subjects treated, the study has approximately 87% power to rule out a ≤ 15% ORR (null hypothesis) when the true ORR is 35% with 1-sided 0.1 alpha.

Glioblastoma cohort: Up to 30 subjects will be enrolled to characterize the tolerability, safety profile, and for preliminary evaluation of antitumor activity. One interim analysis is planned when the 30 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

With 30 subjects treated, the study has approximately 97% power to rule out a ≤ 50% DCR (null hypothesis) when the true DCR is 80% at the 5% type I error rate (1-sided).

SCCHN cohort: Up to 30 subjects will be enrolled to characterize the tolerability, safety profile, and for preliminary evaluation of antitumor activity. One interim analysis is planned when the 30 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12).

With 30 subjects treated, the study has approximately 87% power to rule out a ≤ 15% ORR (null hypothesis) when the true ORR is 35% at the 10% type I error rate (1-sided).

The total sample size for the study (dose escalation and dose expansion) is expected to be up to approximately 642 subjects.

Statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. The results of the safety evaluations will be tabulated and displayed by dose level / expansion cohort. Only exploratory statistical analysis will be performed. Descriptive statistics will be examined for indications of dose-related toxicity.

Listings will be produced upon completion of each dose-escalation cohort of subjects and the decision as to whether to proceed with dose-escalation, dose-reduction or to enroll another cohort at the same dose level will be determined by reviewing these data. Full details of the planned analyses will be described in the trial Statistical Analysis Plan, separately for the dose-escalation part and the expansion part.

Schedule of Assessments

Table 1 Schedule of Assessments – Dose Escalation Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
	Day -28 to First Treatment	V1 W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D44-50[a]	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment	Every 12 Weeks (± 2 weeks)
Written informed consent	X																
Inclusion / exclusion criteria	X	X															
Medical history	X																
Cancer disease history	X																
Prior anticancer drug / radiotherapy / procedures	X																
Other prior medications	X																
Demographic data	X																
HBV and HCV testing	X																
Ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity[f]	X																
Physical examination[f]	X	X	X	X	X	X	X	X		X	X	X	6-weekly	X	X	X	
Dermatological assessment[g]	X				X		X	X		X	X	X	6-weekly	X	X	X	
12 lead ECG[h]	X	X/X[h]	X	X	X/X[h]		X/X[h]	X				X	6-weekly normal ECGs		X	X	
Vital signs including weight and height (height at Screening only)[i]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	X	X	X	
ECOG PS[j]	X	X[j]	X	X	X		X	X		X	X	X	2-weekly	X	X	X	
Enrollment (if eligible)[k]	X	X[k]															

Table 1 Schedule of Assessments – Dose Escalation Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
	Day -28 to First Treatment	V1 W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D44-50[a]	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment	Every 12 Weeks (± 2 weeks)
Hematology / hemostaseology[l]	X	X	X	X	X	X	X	X		X	X	X	2-weekly	X	X	X	
Core serum chemistry[m]		X	X	X		X	X			X	X		2-weekly				
Full serum chemistry[m]	X				X			X				X	6-weekly	X	X	X	
Serum electrophoresis	X											X			X		
Urinalysis[n]	X				X			X				X	6-weekly	X	X	X	
β-HCG pregnancy test (if applicable)[o]	X	X			X		X	X			X		4-weekly		X	X	
Tumor evaluation / staging (CT Scan / MRI / other)[c,p,q]	X							X				X	6 weekly up to 12 months / then 12 weekly		X		X[c]
Documentation of AEs, concomitant medications, and procedures	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	X	X[b]	X[b]	X[b]
Free T4 and TSH	X				X			X				X	6-weekly		X	X	
ACTH (except backfill cohorts)	X																
ANA and RF	X							X					6-weekly	X			
PK sampling	See Table 3																
ADA sampling	See Table 3																
PD-L1 target occupancy	See Table 3																
Immunomonitoring	See Table 3																
Soluble factors	See Table 3																

Table 1 Schedule of Assessments – Dose Escalation Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10					
	Day -28 to First Treatment	W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13		On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment	Every 12 Weeks (± 2 weeks)
		D1	D2	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression				
TGFβ1, 2 and 3	See Table 3																
pSMAD2/3 (except backfill, 30 mg/kg, and 2400 mg flat-dose cohorts)	See Table 3																
CCI [redacted]											[redacted]						
[redacted]											[redacted]						
[redacted]	[redacted]																
Premedication and IMP administration[s,t]		X			X		X	X		X	X	X	2-weekly				
Hospitalization first 2 doses[t]		X			X												
DLT assessment[u]		X	X	X	X	X											

ACTH = adrenocorticotropic hormone; ADA = antidrug antibody; AE = adverse events; ANA = antinuclear antibody; β-HCG = β-human chorionic gonadotropin; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EoT = End-of-Treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Hgb = hemoglobin; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; pSMAD2/3 = phosphorylated SMAD2/3; RANO = response assessment in neuro-oncology; RECIST = Response Evaluation Criteria in Solid Tumors; RF = rheumatoid factor; TGFβ = transforming growth factor beta; TSH = thyroid-stimulating hormone; T4 = free thyroxine.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all procedures (except Day 2 and the Day 44-50 visit). The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. If any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications. The Day 44-50 visit is to accommodate collection of tumor biopsy material and associated PK and CCI [redacted] sampling (see Table 3); the Day 44-50 visit is only to occur if the tumor biopsy and associated PK sampling cannot be performed at the Day 43 visit.

b See Section 7.4.1.3 for definition of the AE Reporting period and Section 7.4.1.6 for monitoring of subjects with AEs.

c Subjects without progressive disease at 28-Day Safety Follow-up visit will be followed up for disease progression (CT / MRI scans every 12 weeks with the first assessment 12 weeks after the previous tumor assessment [scheduled time point]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The

survival follow-up will continue until 1 year after the last subject receives the last dose of trial drug (see Section 7.1.4.3 for details). After completion of the Follow-up period the appropriate electronic Case Report Form section for Trial Termination must be completed.

d All subjects must undergo an End-of-Treatment visit after discontinuation of IMP for any reason. This visit should be performed within 7 days after the decision to discontinue trial treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

e Tumor evaluation at the 28-Day Safety Follow-up visit should only be performed if no disease progression has been documented previously. If another antineoplastic therapy is administered before the end of the 28-day period, the 28-Day Safety Follow-up visit should be conducted before the start of new therapy if possible. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

f Screening, Day 1, 28-Day Safety Follow-up, and 10-Week Safety Follow-up visits should include a full physical exam. All other visits should have a focused physical examination. Eye signs and symptoms should be checked at each visit. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

g Assessments for skin lesions or rash with biopsy of suspicious lesions. Dermatological consults should be requested as needed. See Section 6.5.4.5.

h ECG to be taken within 4 hours before dosing and as soon as possible after completion of the infusion. If only a single "X", then only ECG before dosing is required. All ECGs up to and including Week 13 (Visit 10) are to be taken in triplicate with digital uploading for centralized analysis. All ECGs after Week 13 are single ECGs obtained according to local procedure and will NOT be digitally uploaded.

i Vital signs should be assessed predose (within 15 minutes of start of infusion), then every 15 (± 2) minutes after the start of infusion (15, 30, 45, 60 [end infusion] minutes after start of infusion), and 15 (± 5), 30 (± 5), 60 (± 5), 120 (± 10), and 360 (± 15) minutes after the end of infusion for the first 2 infusions. Subjects should remain in the clinic for observation during this time period. If there were no clinically significant changes in vital signs during the first 2 infusions, then the vital signs schedule for subsequent infusions will be predose (within 15 minutes of start of infusion), 15 (± 2) and 30 (± 2) minutes after the start of infusion, and 30 (± 5) and 60 (± 5) minutes after the end of infusion.

j If the Screening ECOG PS was performed within 3 days prior to Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1.

k Enrollment will be done after the confirmation of fulfilling all Screening inclusion criteria without matching any exclusion criterion. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered.

l Hematology (including complete blood count) and hemostaseology assessments are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be drawn and reviewed within 48 hours prior to dose administration. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value, especially Hgb < 8 g/dL, routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly.

m Full chemistry (which includes core chemistry) and core serum chemistry samples are detailed in Table 11. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration.

n A full urinalysis is required at Screening and the 28-Day Safety Follow-up visit and basic urinalysis (protein content only) at each visit indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated (see Table 11 for details).

o β-HCG must be determined from serum at Screening and from either urine or serum sample thereafter at each indicated visit. Results of the most recent pregnancy test should be available prior to next dosing.

p Tumor Evaluations during Screening must be performed within 28 days prior to Cycle 1 Day 1 in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions (see Section 7.3). Subsequent tumor evaluations have a time window of 5 days prior to dosing (-5 days). In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1 no sooner than 4 weeks (preferably at the scheduled 6-week interval) after the initial documentation (see Section 7.3). For subjects continuing treatment beyond 12 months (in consultation with the Medical Monitor) tumor evaluations should take place every 12 weeks.

q Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms. A bone scan should be done at Screening and beyond as clinically indicated. Bone metastases detected at Screening need to be followed at the subsequent tumor evaluation visits.

r [redacted]

s In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions and then optional and at the discretion of the Investigator. Steroids as premedication are not permitted. MSB0011359C should be administered at the cohort prescribed dose by IV infusion over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes). Subjects enrolled in the 30 mg/kg and 2400 mg flat-dose cohorts may have a total infusion time of up to 120 minutes. The first 2 doses of MSB0011359C for any subject will be accompanied by overnight evaluation of at least 24 hours in an in-patient setting. Subsequent doses will require at least 2 hours observation in a clinic setting after the end of infusion.

t In-patient admission with periodic ECG and vital sign monitoring for a minimum of 24 hours.

u The observation period for DLTs refers to the first 21 days of IMP treatment in the dose-escalation part for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD (see Section 5.1.3 and subsections). Additional subjects enrolled in the dose-escalation part for PK evaluation will have AEs collected but will not have a specific DLT observation period.

Table 2 Schedule of Assessments – Expansion Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
	Day -28 to First Treatment	V1 W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D44-50[a]	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment[e]	Every 12 Weeks (± 2 weeks)
Written informed consent	X																
Inclusion / exclusion criteria	X	X															
Medical history	X																
Cancer disease history	X																
Prior anticancer drug / radiotherapy / procedures	X																
Other prior medications	X																
Demographic data	X																
Randomization (NSCLC second-line only: ≤ 4 days prior to first dose)	X																
Patient-reported outcomes (subjects in HCC, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC [second-line and anti-PD-1/PD-L1 failure] cohorts)[f]	X	X			X		X	X		X	X	X	2-weekly up to Week 25	X	X		
HBV and HCV testing	X																
Ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity[g]	X																
Full physical examination[g]	X	X													X	X	

Table 2 Schedule of Assessments – Expansion Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10					
	Day -28 to First Treatment	W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13		On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment[e]	Every 12 Weeks (± 2 weeks)
		D1	D2	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression				
Focused physical examination[g]					X		X			X		X	6-weekly	X			
Dermatological assessment[h]	X						X			X		X	6-weekly	X	X	X	
NSCLC biomarker cohort 12-lead ECG[i]	X	X/X[i]	X	X	X/X[i]		X/X[i]	X				X	6-weekly normal ECGs		X	X	
Other expansion cohorts: 12 lead ECG[i]	X	X						X				X	6-weekly normal ECGs		X	X	
Vital signs including weight and height (height at Screening only)[j]	X	X			X		X	X	X	X	X	X	2-weekly	X	X	X	
ECOG PS[k]	X	X			X		X	X		X	X	X	4-weekly	X	X	X	
Enrollment (if eligible)[l]	X	X[l]															
Hematology / hemostaseology[m]	X	X			X		X	X		X	X	X	4-weekly	X	X	X	
Core serum chemistry[n]		X					X			X	X		4-weekly				
Full serum chemistry[n]	X				X			X				X	8-weekly	X	X	X	
Urinalysis[o]	X				X			X				X	8-weekly	X	X	X	
β-HCG pregnancy test (if applicable)[p]	X	X			X			X			X		4-weekly		X	X	
Tumor evaluation / staging (CT Scan / MRI / photographs of skin lesions / other)[c,q,r,s]	X							X				X	6-weekly up to 12 months / then 12-weekly		X		X

Table 2 Schedule of Assessments – Expansion Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10					
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13					
	Day -28 to First Treatment	D1	D2	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment[e]	Every 12 Weeks (± 2 weeks)
Documentation of new anticancer therapies																X	X
Documentation of AEs, concomitant medications, and procedures	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	X	X[b]	X[b]	X[b]
Survival follow-up																	X
Free T4 and TSH	X				X			X				X	8-weekly		X	X	
ANA and RF	X							X					8-weekly		X	X	
PK sampling	See Table 3																
ADA sampling	See Table 3																
Soluble factors	See Table 3																
TGFβ1, 2 and 3	See Table 3																
Tumor biopsy surgical specimen / paired biopsy	See Table 3																
CCI [redacted]	[redacted]																
[redacted]	[redacted]																
[redacted]	[redacted]																
Premedication and IMP administration[u]		X			X		X	X		X	X	X	2-weekly				

Table 2 Schedule of Assessments – Expansion Phase

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												EoT Visit	Safety Follow-up		Long-term Follow-up[b,c]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10					
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13					
	Day -28 to First Treatment	D1	D2	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue[d]	28 Days (± 5 days) after Last Treatment[e]	10 Weeks (± 2 weeks) after Last Treatment[e]	Every 12 Weeks (± 2 weeks)

ADA = antidrug antibody; AE = adverse events; ANA = antinuclear antibody; β-HCG = β-human chorionic gonadotropin; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-BN20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Brain Module; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument; EORTC QLQ-CX24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; EORTC QLQ-OES18 = Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Module; EORTC QLQ-HCC18-M = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma Module – Modified; EORTC QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Module; EoT = End-of-Treatment; FHSI-8 = FACT [Functional Assessment of Cancer Therapy] Hepatobiliary Symptom Index – 8 questions; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD = progressive disease; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RF = rheumatoid factor; SMC = Safety Monitoring Committee; TGFβ = transforming growth factor beta; TSH = thyroid-stimulating hormone; T4 = free thyroxine.

After at least 50 subjects across the dose escalation and all expansion cohorts have been evaluated for safety by the SMC, with appropriate SMC safety recommendation and if the Sponsor considers PK characterization adequate, then Day 2, 8, and 22 visits may be skipped. Also, the Safety Follow-up visit (10 weeks after the last dose) may be conducted by phone without the scheduled assessments.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all procedures (except Day 2 and the Day 44-50 visit). The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. If any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications. The Day 44-50 visit is to accommodate collection of tumor biopsy material and associated PK and CCI sampling (see Table 3); the Day 44-50 visit is only to occur if the tumor biopsy and associated PK sampling cannot be performed at the Day 43 visit.

b See Section 7.4.1.3 for definition of the AE Reporting period and Section 7.4.1.6 for monitoring of subjects with AEs.

c Subjects without progressive disease at 28-Day Safety Follow-up visit will be followed up for disease progression (CT / MRI scans every 12 weeks with the first assessment 12 weeks after the previous tumor assessment [scheduled time point]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of trial drug (see Section 7.1.4.3 for details). After completion of the Follow-up period the appropriate electronic Case Report Form section for Trial Termination must be completed.

d All subjects must undergo an End-of-Treatment visit after discontinuation of IMP for any reason. This visit should be performed within 7 days after the decision to discontinue trial treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

e Tumor evaluation at the 28-Day Safety Follow-up visit should only be performed if no disease progression has been documented previously. If another antineoplastic therapy is administered before the end of the 28-day period, the 28-Day Safety Follow-up visit should be conducted before the start of new therapy if possible. If another antineoplastic therapy is administered before

the end of the 10-weeks period, the 10-weeks Safety Follow-up visit might be conducted as a phone call without physical or laboratory assessments. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

f Patient-reported outcomes (PGIS, FHSI-8, EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-BN20, EORTC QLQ-HCC18-M, EORTC QLQ-OES18, EORTC QLQ-OV28, and/or NSCLC-SAQ) should be completed by subjects in the HCC, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC cohorts, prior to any study-related procedures at the indicated visits.

g Screening, Day 1, 28-Day Safety Follow-up, and 10-Week Safety Follow-up visits should include a full physical exam. All other visits should have a focused physical examination. Eye signs and symptoms should be checked at each visit. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

h Assessments for skin lesions or rash with biopsy of suspicious lesions. Dermatological consults should be requested as needed.

i ECG to be taken before dosing and as soon as possible after completion of the infusion. If only a single "X", then only ECG before dosing is required. For the NSCLC biomarker cohort, all ECGs up to and including Week 13 (Visit 10) are to be taken in triplicate with digital uploading. For the NSCLC biomarker cohort, all ECGs after Week 13 are single ECGs obtained according to local procedure and will NOT be digitally uploaded. For all other expansion cohorts, ECGs are to be performed according to local procedures and will NOT be digitally uploaded.

j Vital signs should be assessed predose (within 15 minutes of start of infusion), then every 15 (± 5) minutes after the start of infusion (15, 30, 45, 60 [end infusion] minutes after start of infusion), and 15 (± 10), 30 (± 10), 60 (± 10), 120 (± 10), and 360 (± 15) minutes after the end of infusion for the first 2 infusions. Subjects should remain in the clinic for observation during this time period. If there were no clinically significant changes in vital signs during the first 2 infusions, then the vital signs schedule for subsequent infusions will be predose (within 15 minutes of start of infusion), 15 (± 5) and 30 (± 5) minutes after the start of infusion, and 30 (± 10) and 60 (± 10) minutes after the end of infusion.

k If the Screening ECOG PS was performed within 3 days prior to Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1.

l Enrollment will be done after the confirmation of fulfilling all Screening inclusion criteria without matching any exclusion criterion. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered with the guidance of Medical Monitor.

m Hematology (including complete blood count) and hemostaseology assessments are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be drawn and reviewed within 48 hours prior to dose administration according to the schedule in the above table. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value, especially Hgb < 8 g/dL, routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly.

n Full chemistry (which includes core chemistry) and core serum chemistry samples are detailed in Table 11. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration according to the schedule in the above table.

o A full urinalysis is required at Screening and the 28-Day Safety Follow-up visit and basic urinalysis (protein content only) at each visit indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated (see Table 11 for details).

p β-HCG must be determined from serum at Screening and from either urine or serum sample thereafter at each indicated visit. Results of the most recent pregnancy test should be available prior to next dosing. If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening.

q Tumor Evaluations during Screening must be performed within 28 days prior to Cycle 1 Day 1 in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions and secondarily using mRECIST for subjects in the HCC cohort (see Section 7.3). For subjects in the glioblastoma cohort, the assessment will be made according to RANO. Subsequent the tumor evaluations have a time window of 5 days prior to dosing (-5 days). In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1 no sooner than 4 weeks (preferably at the scheduled 6-week interval) after the initial documentation (see Section 7.3). For subjects continuing treatment beyond 12 months (in consultation with the Medical Monitor) tumor evaluations should take place every 12 weeks.

r Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms. A bone scan should be done at Screening and beyond as clinically indicated. Bone metastases detected at Screening need to be followed at the subsequent tumor evaluation visits.

s For subjects with melanoma, if skin lesions at certain size are chosen as target lesions, photographs of the skin lesions at the Baseline as well as on treatment should be collected. If a subject has already been enrolled without baseline photographs taken, on-treatment photographs should NOT be taken as it may be misinterpreted as new lesions after treatment started.

t CCI [redacted]

u Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is optional and at the discretion of the Investigator after the second infusion (premedication is optional for all infusions for subjects in the NSCLC biomarker cohort being treated at the US National Cancer Institute). If Grade ≥ 2 infusion reactions are seen during the first two infusions premedication should not be stopped. Steroids as premedication are not permitted. MSB0011359C should be administered by IV infusion over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes). Subjects must be observed for at least 2 hours after the end of infusion.

Table 3 Schedule of Assessments – Pharmacokinetic Sampling, CCI Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											EoT Visit	Safety Follow-up	
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b]	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 days) after Last Treatment[c]	10 Weeks (± 2 weeks) after Last Treatment
Dose Escalation																
PK sampling[d,e]		X/X/X/X[d]	X/X[b]	X/X[b]	X/X/X[e]		X/X/X[e]	X/X/X[e]	X[f]	X[e]	X[e]	X[e]	X 6-weekly up to/including Week 25, then every 12 weeks		X	X
ADA sampling (HAHA on the CRF)	X				X		X	X		X	X	X			X	X
PD-L1 target occupancy and CCI		X	X[b]		X			X	X			X				
Immunomonitoring		X			X			X				X	6-weekly up to/including Week 25		X	
Soluble factors		X	X[b]	X	X			X				X			X	
TGFβ1, 2 and 3		X	X[b]	X	X			X	X			X			X	
pSMAD2/3[g]		X	X[b]	X	X			X	X			X			X	
Tumor biopsy or archived surgical specimen (optional)[h]	X								X[i]						X if PD (optional)[i]	
CCI		[redacted]	[redacted]	[redacted]	[redacted]			[redacted]				[redacted]			[redacted]	
NSCLC biomarker expansion																
PK sampling[d,e]		X/X/X[d]	X[b]	X	X/X/X[e]		X	X/X/X[e]	X[f]			X/X/X[e]	X 6-weekly up to/including Week 25, then every 12 weeks		X	X
ADA sampling (HAHA on the CRF)	X				X		X	X				X			X	X

Table 3 Schedule of Assessments – Pharmacokinetic Sampling, CCI Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											EoT Visit	Safety Follow-up	
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b]	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 days) after Last Treatment[c]	10 Weeks (± 2 weeks) after Last Treatment
Immunomonitoring (optional)		X			X			X				X	6-weekly up to/including Week 25		X	
Soluble factors		X	X[b]	X	X			X				X			X	
TGFβ1, 2 and 3		X	X[b]	X	X			X	X			X			X	
Tumor biopsy surgical specimen / paired biopsy[j] (both mandatory)	X				X[i]									X if PD[i]		
CCI																
NSCLC second line, pancreatic adenocarcinoma, CRC, TNBC, ovarian cancer, esophageal adenocarcinoma, SCCHN, glioblastoma, and cervical cancer																
PK sampling[d,e]		X/X/X[d]	X[b]	X	X/X/X[e]		X	X/X/X[e]	X[f]			X/X/X[e]	X		X	X
ADA sampling (HAHA on the CRF)	X				X		X	X				X	6-weekly up to/including Week 25, then every 12 weeks		X	X
Soluble factors		X	X[b]	X	X										X	
TGFβ1, 2 and 3		X			X			X				X	6-weekly up to/including Week 25			
EGFR mutation / ALK translocation / ROS1 rearrangement status[k]	X															

Table 3 Schedule of Assessments – Pharmacokinetic Sampling, CCI Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											EoT Visit	Safety Follow-up	
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b]	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 days) after Last Treatment[c]	10 Weeks (± 2 weeks) after Last Treatment
CA-125[l]	X	X						X				X	6-weekly up to/including Week 25, then every 12 weeks		X	X
HPV[m]	X															
PD-L1 expression	X															
Tumor biopsy surgical specimen / paired biopsy (archived sample mandatory, fresh Baseline and D44-50 optional)[h]	X								X[i]					X if PD[i]		
CCI		[redacted]	[redacted]	[redacted]	[redacted]									[redacted]		
HCC second line: Ascending dose and dose expansion																
PK sampling[d,e]		X/X/X[d]	X[b]	X	X/X/X[e]		X	X/X/X[e]	X[f]			X/X/X[e]	X		X	X
ADA sampling (HAHA on the CRF)	X				X		X	X				X	6-weekly up to/including Week 25, then every 12 weeks		X	X
Soluble factors		X	X[b]	X	X										X	
TGFβ1, 2 and 3		X			X			X				X	6-weekly up to/including Week 25			

Table 3 Schedule of Assessments – Pharmacokinetic Sampling, CCI Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											EoT Visit	Safety Follow-up	
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b]	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 days) after Last Treatment[c]	10 Weeks (± 2 weeks) after Last Treatment
Viral load testing (HBV, HCV)[n]	X	X			X			X				X	6-weekly up to/including Week 25, then every 12 weeks		X	X
Alpha-fetoprotein		X			X			X				X	6-weekly up to/including Week 25, then every 12 weeks		X	
Tumor biopsy surgical specimen / paired biopsy (archived sample mandatory, fresh Baseline and D44-50 optional)[h]	X								X[i]					X if PD[i]		
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]									[redacted]		
NSCLC / Melanoma anti-PD-1 / anti-PD-L1 failure																
PK sampling[d,e]		X/X/X[d]	X[b]	X	X/X/X[e]		X	X/X/X[e]	X[f]			X/X/X[e]	X		X	X
ADA sampling (HAHA on the CRF)	X				X		X	X				X	6-weekly up to/including Week 25, then every 12 weeks		X	X
Soluble factors		X	X[b]	X	X										X	

Table 3 Schedule of Assessments – Pharmacokinetic Sampling, CCI Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											EoT Visit	Safety Follow-up	
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b]	D8	D15	D22	D29	D43	D44-50[a]	D57	D71	D85	Until Progression	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 days) after Last Treatment[c]	10 Weeks (± 2 weeks) after Last Treatment
TGFβ1, 2 and 3		X			X			X				X	6-weekly up to/including Week 25			
Tumor biopsy surgical specimen / paired biopsy[j] (archived sample if available, fresh Baseline mandatory, and D44-50 mandatory unless impossible)	X				X[i]									X if PD[i]		
CCI		[redacted]	[redacted]	[redacted]	[redacted]									[redacted]		

ADA = antidrug antibody; ALK = anaplastic lymphoma kinase; CA-125 = cancer antigen 125; CRC = colorectal cancer; CRF = case report form; EoT = End-of-Treatment; EGFR = epidermal growth factor receptor; HAHA = human antihuman antibody; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HPV = human papillomavirus; NSCLC = non-small cell lung cancer; PD = progressive disease; PK = pharmacokinetics; pSMAD2/3 = phosphorylated SMAD2/3; TGFβ = transforming growth factor beta; TNBC = triple-negative breast cancer.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all procedures (except Day 2 and the Day 44-50 visit). The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. If any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications. The Day 44-50 visit is to accommodate collection of tumor biopsy material and associated PK and CCI sampling (see Table 3); the Day 44-50 visit is only to occur if the tumor biopsy and associated PK sampling cannot be performed at the Day 43 visit.

b The Day 2 PK and biomarker samples must be drawn at least 24 hours after the Day 1 end of infusion, preferably > 30 hours after end of infusion. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn. In the backfill cohorts an additional sample can optionally be drawn at 3 to 5 days after the initiation of the infusion and 1 optional PK sample can be taken any time during days 10 to 12. The exact time must be recorded.

c If another antineoplastic therapy is administered before the end of this 28-day period, the 28-Day Safety Follow-up visit should be conducted, if possible, prior to the start of this new therapy. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

d Blood samples for PK analysis should be drawn on Day 1 prior to dosing, immediately after completion of the infusion, and 4 hours after the start of the infusion. A sample to be taken at 8 to

12 hours after the start of the infusion is optional in the backfill cohorts. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn.

e Samples for PK analysis to be taken before infusion (as close to the start of the infusion as possible), immediately after the completion of infusion, and 2 to 8 hours after the end of infusion (the later the better). If only 1 blood sample is scheduled at a visit, this is to be taken prior to the IMP administration. This pre-dose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn.

f A PK sample should be collected as close as possible to the time of mandatory / optional on-treatment biopsy as possible (that is, same day).

g Samples for pSMAD2/3 will not be collected for the backfill or 30 mg/kg and 2400 mg flat-dose dose-escalation cohorts.

h Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suited. Fine needle aspiration biopsies are not suited. Biopsies are optional in the dose escalation cohort. Availability of suitable (see Section 7.6 for details) tumor biopsies (excluding bone biopsies) is mandatory for eligibility in the expansion cohorts (see Section 5.3.1.2). Availability of fresh tumor biopsies (excluding bone biopsies) is mandatory for eligibility in the NSCLC biomarker expansion, NSCLC anti-PD-1 / PD-L1 failure, and melanoma anti-PD-1 / PD-L1 failure cohorts. The biopsy or surgical specimen must have been collected within 28 days prior to the first IMP administration. For other expansion cohorts availability of either tumor archival material or fresh biopsies within 28 days is acceptable (excluding bone biopsies) with one of these being mandatory (where possible fresh biopsies are preferred). For subjects with glioblastoma, archival biopsy should be made available, if possible.

i A mandatory on-treatment biopsy should be performed at Week 3 within 7 days after the Week 3 IMP administration for the NSCLC biomarker cohort (mandatory). A mandatory Week 7 biopsy should be performed within 7 days after the Week 7 IMP administration for the NSCLC anti-PD-1 / PD-L1 failure (if possible) and the melanoma anti-PD-1 / PD-L1 failure cohort (if possible). An on-treatment biopsy is optional for all other expansion cohorts. A PK sample should be collected as close as possible to the time of the on-treatment biopsy (that is, same day). A "progression biopsy" is optional for subjects who had achieved at least SD for ≥ 12 weeks but who subsequently discontinued study treatment due to an assessment of PD. The optional "progression biopsy" will be used to evaluate the potential mechanisms of tumor escape. Results from the optional "progression biopsy" will be made available. CCI [redacted]

k Subjects with non-squamous cell NSCLC of unknown EGFR mutational status will require testing (local laboratory, or central laboratory if local testing is not available [see Section 5.3.1.2]).

l Subjects with ovarian cancer will require testing for CA-125 (local laboratory, or central laboratory if local testing is not available).

m Subjects with cervical cancer and SCCHN to provide documentation of tumor sample testing for HPV if available.

n Subjects who are HBV positive should be tested for HBV viral load assessed according to the HCC Schedule. Subjects with a previous history of HCV infection who have sustained viral response should have HCV viral load assessed at the Investigator's discretion according to the HCC schedule. Subjects who are HCV antibody positive at Screening should have HCV viral load assessed according to the HCC schedule.

2 Sponsor, Investigators, and Trial Administrative Structure

The Sponsor of this clinical trial with MSB0011359C is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in USA and Merck KGaA, Darmstadt, Germany, in rest of world. In addition, Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) sponsors this clinical trial in Japan.

For trial organization in Japan, refer to the Study Organization in Japan supporting document.

A contract research organization CCI [redacted] will undertake the operational aspects of this trial. In Japan, CCI [redacted] will undertake the operational aspects. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP) maintained by CCI [redacted] The IPMP will be prepared by the CCI [redacted] Clinical Project Manager in cooperation with other CCI [redacted] Operational Team Leads.

2.1 Investigational Sites

The trial will be conducted in approximately 220 enrolling sites in Asia Pacific, the European Union, Canada, and the USA (up to 60 sites).

2.2 Trial Coordination / Monitoring

The Sponsor will coordinate the trial and will provide the support of Contract Research Organizations (CRO) for some activities of the trial. Sponsor functional groups will perform oversight of the activities performed by the CROs.

The Sponsor will supply trial medication of MSB0011359C to the sites. Packaging and distribution of clinical supplies will be performed by the Clinical Trial Supplies department of the Sponsor and the contracted manufacturing organization.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetic (PK), CCI [redacted]

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs) and serious AEs (SAEs).

Quality assurance of the trial conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses), which will be outsourced to a CRO.

The Coordinating Investigator, CCI [redacted] represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for

Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix 3.

The trial will appear in ClinicalTrials.gov, EudraCT, and all other required registries.

2.2.1 Safety Monitoring Committee

To ensure subjects' safety during the dose-escalation part of the trial as well as the expansion part, a Safety Monitoring Committee (SMC) will review the safety data on a regular basis. The SMC consists of permanent core members from the Sponsor and CRO (at least the Medical Responsible, the Global Drug Safety Product Leader, and the Biostatistician for the expansion part), the Coordinating Investigator, and an external expert with expertise in the management of cancer patients. During the dose-escalation portion of the trial, the SMC will evaluate the safety and PK data and will decide on dose-limiting toxicities (DLTs) relevant for the treatment and will advise on dose escalation or suspension of enrollment, with the final adjudication being a Sponsor prerogative. During the dose-ascension phase of the hepatocellular carcinoma (HCC) cohort, the SMC will evaluate the safety data of each cohort prior to opening enrollment to each subsequent cohort. During the enrollment phase of the expansion part of the trial (see Section 3.4.1), the SMC will monitor on an ongoing basis (for example, when 40, 120, 200, 290, 380, and 480 subjects have been enrolled and treated for at least 4 weeks), all safety information of the participating subjects and will decide by consensus on continuation, modification, or suspension of the trial or of a particular expansion cohort. The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the trial. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

2.2.2 Central Reader and Independent Endpoint Review Committee

A central facility may read and interpret all radiographic scans for subjects enrolled in the expansion cohorts (for dose escalation, radiographic scans will be read locally; however, a central review may occur at Sponsor request). The data for all images will be transferred from trial sites to the central reading center for evaluation. Scans will be evaluated at the central facility in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1, Eisenhauer 2009) or Response Assessment in Neuro-Oncology (RANO) for subjects in the glioblastoma cohort (Wen 2010) and additionally using immune-related RECIST (irRECIST), modified immune-related RANO (iRANO; Okada 2015) for subjects in the glioblastoma, and modified RECIST (mRECIST) for subjects in the HCC cohort (see Lencioni 2010). The imaging data will be transferred to the Sponsor or designee at regular intervals. A manual from the vendor will be provided to each trial site. The results of the central read will not be available in real time and will not be used for trial subject management. Local interpretation of radiographic scans will be used by the Investigator for real-time trial subject management decisions.

For subjects enrolled in the expansion cohorts, an Independent Endpoint Review Committee (IRC) will perform a blinded determination as to whether the criteria for tumor response or progression according to RECIST 1.1 or RANO have been met. The role of the IRC will be to review radiographic image findings and physical findings for the determinatio CCI [redacted] The full membership, mandate, and processes of the IRC will be detailed in the IRC charter. The results from the IRC will not be available in real-time and will not be used for trial subject management. The Investigator will determine tumor response or progression according to RECIST 1.1 for real-time trial subject management decisions. For subjects in the HCC cohorts and glioblastoma, the Investigator will determine tumor response or progression according to mRECIST and RANO, respectively, for real-time trial subject management decisions.

3 Background Information

3.1 Investigational Medicinal Product

The Investigational Medicinal Product (IMP) for the present trial is M7824 (MSB0011359C).

MSB0011359C is a bifunctional fusion protein that combines an anti-programmed death ligand 1 (PD-L1) antibody and the soluble extracellular domain of transforming growth factor beta (TGFβ) receptor type II as a TGFβ neutralizing "trap," into a single molecule. This anti-PD-L1 / TGFβ-Trap molecule is designed to target 2 major mechanisms of immunosuppression in the tumor microenvironment. The anti-PD-L1 moiety of MSB0011359C is identical to avelumab, except for three amino acid substitutions in the heavy chain constant regions, which result in a different human IgG1 allotype, and one amino acid substitution in the heavy chain for antibody stability. Avelumab (international non-proprietary name for MSB0010718C) is currently in Phase II / III clinical development by the Sponsor.

The programmed death 1 (PD-1) / PD-L1 axis is an important mechanism for tumor immune evasion (Hotchkiss 2014). Effector T-cells chronically sensing antigen take on an exhausted phenotype marked by PD-1 expression, a state under which tumor cells engage by upregulating PD-L1. Blocking the axis restores the effector function in these T-cells. Additionally, in the tumor microenvironment, myeloid cells, macrophages, parenchymal cells, and T-cells upregulate PD-L1.

TGFβ has growth inhibitory effects on normal epithelial cells, functioning as a regulator of epithelial cell homeostasis, and it acts as a tumor suppressor during early carcinogenesis. As tumors progress toward malignancy, the growth inhibitory effects of TGFβ on the tumor are lost via mutation in one or more of the TGFβ pathway signaling components or through oncogenic reprogramming (Lebrun 2012). Upon loss of sensitivity to TGFβ inhibition, the tumor continues to produce high levels of TGFβ, which then serve to promote tumor growth (Lebrun 2012). The TGFβ cytokine is overexpressed in various cancer types with correlation to tumor stage (Lebrun 2012, Wrzesinski 2007). Many types of cells in the tumor microenvironment produce TGFβ, including the tumor cells themselves, immature myeloid cells, regulatory T-cells, and stromal fibroblasts; these cells collectively generate a large reservoir of TGFβ in the extracellular matrix. TGFβ signaling contributes to tumor progression by promoting metastasis, stimulating

angiogenesis, and suppressing innate and adaptive antitumor immunity (Lebrun 2012). As a broadly immunosuppressive factor, TGFβ directly down regulates the effector function of activated cytotoxic T-cells and natural killer (NK) cells and potently induces the differentiation of naïve CD4+ T-cells to the immunosuppressive regulatory T-cells (Treg) phenotype (Wrzesinski 2007). In addition, TGFβ polarizes macrophages and neutrophils to a wound-healing phenotype that is associated with production of immunosuppressive cytokines (Hao 2012). As a therapeutic strategy, neutralization of TGFβ activity has the potential to control tumor growth by restoring effective antitumor immunity, blocking metastasis, and inhibiting angiogenesis.

MSB0011359C also binds TGFβ (all isoforms), an inhibitory cytokine produced in the tumor microenvironment by cells including apoptotic neutrophils, myeloid-derived suppressor cells, T-cells, and tumor (Hotchkiss 2014, Souza-Fonseca-Guimaraes 2013). Inhibition of TGFβ by soluble TGFβRII reduced malignant mesothelioma tumors in a manner that was associated with an increase in CD8+ T-cell antitumor effects (Suzuki 2004). CCI [redacted]

CCI [redacted] Concomitant PD-1 and TGFβ blockade can restore pro-inflammatory cytokines (Topalian 2012a). In a murine model of hepatocellular carcinoma, TGFβ appeared to increase the expression of PD-L1 in dendritic cells, which in turn promoted T-cell apoptosis and increased percentage of CD25+, Foxp3+ T regulatory cells (Song 2014). Higher levels of circulating myeloid-derived suppressor cells (MDSCs), a significant source of TGFβ, are associated with failure to respond to anti-PD-1 therapy (Weber 2014).

CCI [redacted]

Translational evidence for immune dysfunction in non-small cell lung cancer (NSCLC) has been shown such that PD-L1 is upregulated and is associated with poor prognosis (Mu 2011). In that study, dendritic cells were also implicated, suggesting a complex immune suppression mechanism related to PD-L1 (Mu 2011). The role of TGFβ is more complex in NSCLC since it can function as both a tumor suppressor and pro-proliferative factor (Jeon 2010). There is some evidence for TGFβ-mediated suppressive effects on antitumor responses in NSCLC. Plasma levels of TGFβ in NSCLC patients correlated directly with peripheral regulatory T-cell levels and that intratumor TGFβ co-stained with the FOXP3 Treg marker (Baratelli 2010). Additionally, levels of TGFβ positive tumor-infiltrating lymphocytes had prognostic significance in NSCLC (Sterlacci 2012).

CCI [redacted]

Strong clinical activity has been reported with anti-PD-1 and anti-PD-L1 antibodies (Brahmer 2012, Robert 2015) with two anti-PD-1 drugs, nivolumab and pembrolizumab, having recently been approved for the treatment of refractory melanoma and nivolumab for NSCLC. For anti-PD-L1, a Phase I, dose-ranging trial of a monoclonal antibody showed objective response rates (ORRs) of 6% to 17%, with good durability, in a variety of heavily pretreated tumor types (Brahmer 2012). Internally, recent preliminary results for the anti-PD-L1 antibody, avelumab, in a Phase I expansion population of heavily pretreated NSCLC showed an ORR of 12% (refer to the current avelumab Investigator's Brochure [IB] for most recent details). This result is similar to the response rate reported for nivolumab (OPDIVO) in squamous cell lung cancer (15%), an indication for which it was recently approved (OPDIVO USPI). Refer to the current IB for additional avelumab efficacy updates in other tumor types.

Recently, nivolumab has shown clinical activity in HCC (out of 39 evaluable subjects, 2 subjects experienced complete response [CR] and 7 experienced partial response [PR]) with an acceptable safety profile (El-Khoueiry 2015).

A Phase II study of a small molecule kinase inhibitor of TGF signaling, LY2157299, revealed a subgroup of alpha-fetoprotein (AFP) responders in sorafenib failures or sorafenib ineligible HCC subjects who had a substantial and significant increase in overall survival (OS) compared with the non-AFP responders, with median OS of 93.1 weeks versus 29.6 weeks, respectively, suggesting possible clinical activity of a TGF inhibitor in HCC (Faivre 2014).

MSB0011359C, is comprised of an extracellular domain of the human TGFβ receptor TGFβRII covalently joined via a glycine / serine linker to the C terminus of each heavy chain of the fully human IgG1 anti-PD-L1 antibody, avelumab. Given the emerging picture for PD-1 / PD-L1 class, in which responses are apparent but with room for increase in effect size, it is assumed that cotargeting a complementary immune modulation step will improve tumor response. A similar TGF-targeting agent, fresolimumab, which is a monoclonal antibody targeting TGFβ1, 2, and 3, showed initial evidence of tumor response in a Phase I trial in subjects with melanoma. The objective response was observed in 1 of 28 subjects with 6 subjects showing stable disease (Morris 2014). CCI [redacted] Given the preclinical and clinical evidence of both pathways, it is anticipated that MSB0011359C may have enhanced antitumor activity compared with avelumab.

A reasonable safety profile is anticipated when targeting these pathways. The safety of the PD-1 / PD-L1 class continues to emerge but appears to be substantially less adverse compared with the CTLA-4 class of T-cell checkpoint inhibitors (Dolan 2014, Sznol 2015). Two TGFβ inhibiting biologics have been administered in clinical trials and showed an acceptable human safety profile in humans that did not include immune-related events. Fresolimumab was studied in Phase I trial in subjects with cancer (28 with melanoma, 1 with renal cell carcinoma). No DLTs

were observed and 15 mg/kg, the highest dose tested, was determined to be safe (Morris 2014). The major AE was emergent skin tumors and hyperkeratosis. In a small trial of idiopathic pulmonary fibrosis, the most common AE was fatigue (Lonning 2011). In a study of 16 subjects with focal segmental glomerulosclerosis, the only AE was pustular rash in 2 subjects (Trachtman 2011). TβM1, an antibody inhibiting the TGFβII receptor, was well tolerated when studied at doses as high as 240 mg with diarrhea as the only DLT event (Cohn 2014). Notably, one event of low hemoglobin (Hgb) was observed in the high-dose group. Importantly, the preclinical profile of MSB0011359C is predominantly benign and highly comparable to that of avelumab. Overall, evidence suggests non-overlapping toxicity profiles for anti-PD-L1 and anti-TGFβ agent classes. There is a theoretical potential of immune-related adverse events (irAEs) that would be the consequence of a double blockade of negative regulatory loops of the immune system; however, taken together, the preclinical profile of MSB0011359C and clinical evidence of each pathway suggests a low risk of synergistic toxicity stemming from the dual-functionality of MSB0011359C.

The safety profile is described in the IB for avelumab and is briefly summarized here (refer to the current avelumab IB). As of a cutoff date of 05 November 2014, overall 558 subjects have received at least 1 dose of avelumab. In general, the safety analysis suggests an acceptable safety profile with most events either in line with those expected in subjects with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1 / PD-L1 axis. Infusion-related reactions including hypersensitivity and irAEs / autoimmune disorders have been identified as important risks for avelumab and thus considered potential risks for MSB0011359C. Management algorithms include steroids, other immune-suppressants, study drug interruption / discontinuation, and supportive management. Anti-PD-L1 has shown an overall rate of infusion reactions of approximately 10% (Grade 3 / 4 approximately 0.4% [fell to 0.2% with mandatory premedication]; no Grade 5).

A brief summary of safety experience with the PD-1 inhibitors nivolumab (Opdivo®) and pembrolizumab (Keytruda®) is given here, based on prescribing information (refer to current label information for updated information). For pembrolizumab the section on Warnings and Precautions includes adverse reactions of immune-mediated pneumonitis (2.9%), immune-mediated colitis (1%), immune-mediated hepatitis (0.5%), immune-mediated hypophysitis (0.5%), renal failure (0.5%) and immune-mediated nephritis (0.7%), immune-mediated hyperthyroidism (1.2%) and hypothyroidism (8.3%), and a variety of other immune-mediated adverse reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided. For nivolumab the section on Warning and Precautions includes adverse reactions of immune-mediated pneumonitis (2.2%) with fatal immune-mediated pneumonitis in 0.9% (5/574), immune-medicated colitis (2.2%), immune-mediated hepatitis (1.1%), immune-mediated nephritis and renal dysfunction (0.7%), immune-mediated hyperthyroidism (3%) and hypothyroidism (8%) and a variety of other immune-mediated adverse reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided.

Safety experience with various TGFβ targeting agents described in the literature suggests no overlapping immune-related profile with compounds of the anti-PD-1 / anti-PD-L1 class. In Phase I trials, the experience with a molecule with a highly similar mechanism to the

MSB0011359C TGFβ trap moiety, the anti-TGFβ-1 and 3 antibody fresolimumab, showed no dose-limiting toxicity up to 15 mg/kg and no immune related events (Morris 2014). There were no DLTs and the only major AEs were skin lesions, mainly keratoacanthomas, some with atypical features, one event of squamous cell carcinoma, plus hyperkeratosis of the skin. Immune events were not reported. A syndrome known as Ferguson-Smith disease is caused by mutations in TGFβ is associated with the formation of keratoacanthomas, similar to the findings described for fresolimumab (Goudie 2011). Therefore, it is plausible that skin tumors observed during fresolimumab treatment may be related to TGFβ inhibition. A neutralizing antibody against TGFβ-1, TβM1, was well tolerated when studied as high as 240 mg with diarrhea as the only DLT event. Notably, one event of low Hgb was observed in the high-dose group. This is notable since the only preclinical finding associated with MSB0011359C was decreased Hgb. Trabedersen, an antisense oligonucleotide that inhibits TGFβ2 expression, was associated with thrombocytopenia that was moderate (Oettle 2011). Finally, TGFβ is known to play a role in wound repair (Leask 2004).

CCI [redacted] These decreases were reversible during the recovery period; thus, anemia is considered a potential risk of the compound. Due to the involvement of TGFβ in repair of skin and other tissue injuries, alterations in wound healing or repair of tissue damage is considered a potential risk. Overall, evidence suggests non-overlapping toxicity profiles for anti-PD-L1 and anti-TGFβ agent classes. CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

demonstrated by a two-step binding assay. MSB0011359C potently attenuated TGFβ signaling in cell assays and enhanced interleukin-2 production by T-cells stimulated with a super antigen, Staphylococcal enterotoxin A. MSB0011359C is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro, but at a significantly reduced level compared with the parental avelumab antibody. MSB0011359C was shown to be internalized by PD-L1-expressing cells in vitro with kinetics similar to those of the parental avelumab antibody. In summary, the dual functionalities of MSB0011359C were confirmed by in vitro studies: the fusion protein retains the biological activities of the parental anti-PD-L1 avelumab antibody but possesses the added modality of effective TGFβ binding and neutralization.

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Furthermore, the dominant role of $CD8^+$ T-cells in maintaining long-term protective immunity following MSB0011359C induced tumor eradication has been demonstrated.

The therapeutic potential of MSB0011359C was explored in combination with various standard-of-care therapies. In combination with the core components of the FOLFOX chemotherapy regimen (oxaliplatin, 5-fluorouracil and oxaliplatin), an additive enhancement in efficacy was demonstrated against MC38 colorectal carcinoma. In combination with fractionated, localized radiotherapy, a highly synergistic antitumor effect was achieved with only a single low dose of MSB0011359C in the MC38 tumor model. CCI [redacted] These data suggest that MSB0011359C can be explored as a combination partner in different clinical settings for the treatment of cancer patients.

Refer to the Investigator's Brochure for full details of the preclinical pharmacology of MSB0011359C.

3.2.2 Pharmacokinetics / CCI [redacted]

CCI [redacted]

A brief summary of PK and PK / CCI [redacted] is as follows:

- The predicted human terminal half-life ($t_{1/2}$) for MSB0011359C is approximately 6 days
- Simulations predict that a 1 mg/kg dose will provide an average exposure of approximately 7 µg/mL in humans
- Based on PK / CCI [redacted] modeling and human projections:
  - At a human dose of 0.1 mg/kg, 95% PD-L1 total occupancy at maximum serum concentration observed postdose (C_{max}) is expected in PBMCs, providing approximately 60% total occupancy in tumor
  - At a human dose of 1.0 mg/kg, more than 95% of PD-L1 total occupancy at C_{max} is expected in PBMCs and tumor
  - At a human dose of 1.0 mg/kg, 20% effect is projected in tumor regression in the PK / CCI [redacted] model compared with 95% at 7.5 mg/kg

- Human pr[PPD]s indicate a dose of 7.5 mg/kg and higher (range 4 to 20 mg/kg), on a biweekly schedule is needed to achieve full efficacy [CCI]
- [CCI]

3.2.3 Toxicology

[CCI]

[CCI]

[CCI]

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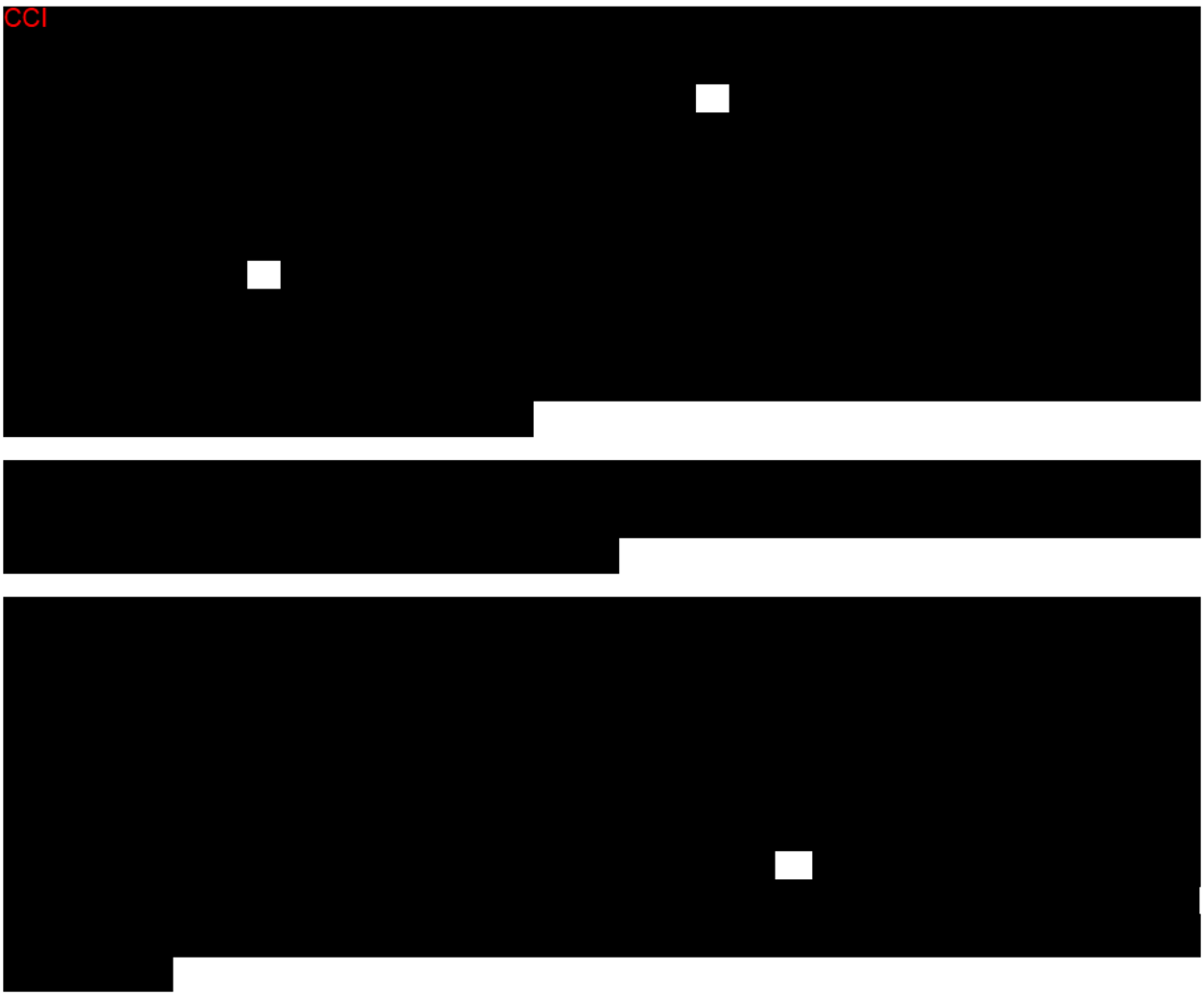
[redacted]



3.3 Brief Summary of the Clinical Findings for MSB0011359C

As of 04 May 2016, 12 subjects had enrolled in the dose-escalation part of the study with 3 subjects treated at each dose level of MSB0011359C: 1, 3, 10, and 20 mg/kg, once every 2 weeks. Median age was 56 years (range: 34 to 78). All had ECOG PS 0 or 1, with a median of 4 prior therapies (range: 2 to 7).

No subject experienced a DLT and no subject was discontinued from treatment for drug-related treatment-emergent adverse events (TEAEs). No subject was reported with a TEAE with a Preferred Term of infusion-related reaction; however, using a post-reporting analysis according to criteria outlined in the Statistical Analysis Plan, 3 subjects were reported with TEAEs that were classified as "infusion-related reactions", with the Preferred Terms of abdominal pain, pyrexia, and back pain (Note: these events are undergoing further review).

Overall, 5 of 12 subjects (41.7%) had drug-related TEAEs. All drug-related TEAEs were Grade 1 or 2: mouth hemorrhage (2 subjects, 16.7%), dry mouth, epistaxis, influenza-like illness, maculopapular rash, pruritis (1 subject, 8.3% each).

To date, 1 subject with pancreatic cancer (3 mg/kg cohort) has been reported with a confirmed PR according to RECIST (ongoing at 6 months). In addition, SD has been reported 5 subjects (41.7%), including 1 subject in the 1 mg/kg cohort, and 2 subjects in each of the 3 and 10 mg/kg cohorts. Five subjects (41.7%) were reported with a BOR of PD. At the time of the data cutoff, 8 subjects (66.7%) remained on treatment.

All subjects from the first 3 dose levels were evaluable for PK analysis showing at 3 and 10 mg/kg dose-linear pharmacokinetics and an approximate $t_{1/2}$ of 150 hours. Subjects from the 1, 3, 10, and 20 mg/kg dose levels were evaluable for PD-L1 target occupancy.

At 3 mg/kg and above, PD-L1 target occupancy was high throughout the entire dosing interval (from C_{max} through C_{min}). All subjects from the first 3 dose levels were evaluable for TGFβ1, 2, 3 plasma concentrations. After MSB0011359C infusion, TGFβ1 and 3 concentrations were undetectable in all subjects at all doses and remained suppressed throughout the dosing interval. TGFβ2 suppression was also evident in all subjects but its degree was dependent on dose and drug concentrations. These data indicate that full pharmacological activity of both modes of action of MSB0011359C is generally achieved in peripheral blood at the dose of 3 mg/kg.

CCI [redacted]

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[redacted]

3.5 Summary of the Overall Benefit and Risk

The risk-benefit ratio has been carefully considered in the planning of the trial. Based on the preclinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the MSB0011359C as specified in this clinical trial protocol. A SMC is planned for the ongoing assessment of the risk-benefit ratio. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit ratio and would render continuation of the trial unjustifiable.

Adverse Events of Special Interest (AESI) for MSB0011359C are: immune-related adverse events (irAEs), infusion-related reactions (IRRs), TGF-β inhibition mediated skin reactions, anemia and bleeding adverse events (AEs). Other safety topics of interest include impaired wound healing and embryofetal toxicity. Immune-related adverse events (immune-related pneumonitis, immune-related hepatitis, immune-related colitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, Type 1 Diabetes mellitus, pituitary disorders], immune-related rash and other irAEs [myositis, myocarditis, encephalitis]), TGF-β inhibition mediated skin reactions, anemia and bleeding adverse events have been identified as important identified risks for MSB0011359C. Respective risk mitigation measures have been implemented in the protocol (see Section 6.5.4).

The specifics of the risk categories are further described in this section and in the Investigator's Brochure (refer to IB for details).

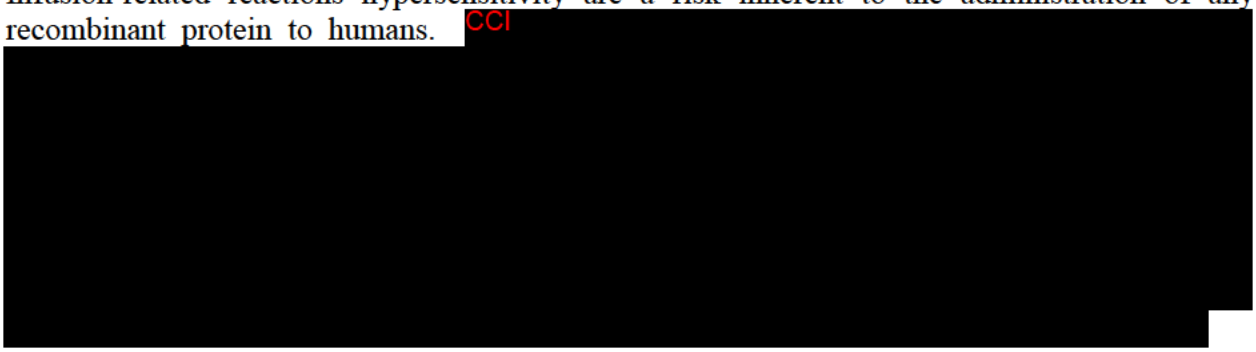
Respective safety measures that comprise inclusion / exclusion criteria for participation in clinical trials with MSB0011359C, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study treatment interruption or discontinuation.

See Section 3.3 for a summary of clinical safety findings from the ongoing dose-escalation part of the study.

3.5.1 Infusion-related Reactions / Hypersensitivity

Infusion-related reactions, including hypersensitivity, are defined in this section. Infusion-related reactions are AESIs and identified risks for MSB0011359C.

Infusion-related reactions hypersensitivity are a risk inherent to the administration of any recombinant protein to humans. CCI



As of 05 November 2014, from the EMR100070-001 trial with the parent avelumab antibody, 1 subject (2.0%) in the dose-escalation cohort reported an infusion-related reaction event (Grade 2) and 49 (10.2%) of the 480 subjects in the expansion cohorts experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 subjects, 1.7%) or Grade 2 (36 subjects, 7.5%) in intensity, and Grade 3 (3 subjects, 0.6%) or Grade 4 events (2 subjects, 0.4%) were less frequent. No Grade 5 events have been reported. Most of the infusion-related reaction events had an onset after the first (30 subjects, 6.3%) or second (16 subjects, 3.3%) avelumab infusion. In 8 subjects (1.7%), avelumab treatment was discontinued because of infusion-related reaction events.

Risk mitigation measures for potential infusion-related reactions / hypersensitivity include:

- Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C was mandatory for subjects in the dose-escalation part of the study. Based on an initial safety assessment in the dose escalation cohorts at dose levels of 1, 3, 10, and 20 mg/kg, no TEAEs with a Preferred Terms of infusion-related reaction occurred (see Section 3.3). Based on the above observations and in order to further investigate the potential for infusion-related reactions, for subjects in the NSCLC biomarker cohort being treated at the US National Cancer Institute (NCI), premedication will be optional. This approach in the limited number of subjects enrolled in the NSCLC biomarker cohort and under close surveillance of experienced Investigators at the NCI investigational site appears to be justified. For all other escalation and expansion cohorts, premedication is mandatory for at least the first 2 infusions, and thereafter,

optional at the discretion of the Investigator. If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Based on safety data for subjects treated with premedication for only the first 2 infusions, the protocol might be amended at a later time point to allow dosing without premedication for all subject infusions

- Special precautions for monitoring of subjects and management of infusion-related reactions / hypersensitivity as described in Sections 6.5.4.1 and 6.5.4.2
- Infusion-related reactions / hypersensitivity (any grade) are considered as AESI requiring expedited reporting from the Investigator to the Sponsor. For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used (see Section 7.4.1.4).

3.5.2 Immune-related Adverse Events / Autoimmune Disorders

Immune-related AEs are AESIs.

The following irAEs are important identified risks for MSB0011359C.

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders)
- Immune-related rash
- Other immune-related events (myositis, myocarditis, encephalitis)

The following irAEs are important potential risks for MSB0011359C:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

Immune-related AEs / autoimmune disorders are events that are related to the pharmacology of checkpoint inhibitors and can be explained by an immune-phenomenon after other etiologies have been ruled out. Relevant clinical safety experience has been generated with the parent anti-PD-L1 avelumab antibody.

- As of 05 November 2014, a cumulative review revealed 56 cases of potential irAEs out of 480 subjects (11.7%) treated in the dose-expansion part of Trial EMR 100070-001 and 4 cases out of 50 subjects (8.0%) treated in the dose-escalation part of Trial EMR 100070-001. A

customized Medical Dictionary for Regulatory Activities (MedDRA) query was used for data retrieval from the clinical database with predefined Preferred Terms of potential irAEs.

- Of 69 potential irAEs reported, 13 were SAEs (18.8%) and 56 were nonserious AEs (81.1%). In the majority of the cases, there was a plausible temporal association between the event onset and the drug administration. Of these 69 events, 46 events (66.7%) were assessed as treatment-related by the Investigator and 23 events (33.3%) were assessed as not treatment-related by the Investigator.
- Twenty-six events were assessed as Grade 1, 29 events as Grade 2, 11 events as Grade 3, 2 events as Grade 4, and 1 event (pneumonitis) as Grade 5 (note: 2 more events of autoimmune hepatitis had a fatal outcome; however, they were assessed as Grade 3 with a subsequent fatal liver failure).
- Based on the irAE cases that have been observed with avelumab, all trial Investigators will be trained to be made aware of the frequency and severity of the observed events and to proactively administer steroid treatment for any suspicion of irAEs.

Based on clinical experience with avelumab and with other agents blocking the PD-1 / PD-L1 pathway, irAEs / autoimmune disorders are an important potential risk for MSB0011359C. Risk management measures similar to the lead program include:

- Instructions for trial treatment discontinuation or interruption in case of irAEs / autoimmune disorders (see Section 6.5.4.3).
- Guidance for the medical management of irAEs / autoimmune disorders including specific guidance with regard to the affected organ / body system (see Section 6.5.4.3).
- irAEs / autoimmune disorders (any grade) are considered as AESIs requiring expedited reporting from the Investigator to the Sponsor. For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used.
- Regular laboratory tests on parameters indicative for autoimmune disorders will be performed as detailed in the Schedules of Assessments (see Table 1 and Table 2).
- To help monitor for autoimmune effects, baseline ophthalmology examination including slit lamp inclusive of the anterior segment and including visual acuity. If clinically relevant eye signs or symptoms during the study, appropriate ophthalmology examination within 2 days including slit lamp inclusive of the anterior segment and including visual acuity.

3.5.3 TGFβ Inhibition Mediated Skin Reactions

Skin AEs, possibly due to TGFβ inhibition, including hyperkeratosis, KA, and/or cSCC, are AESIs and important identified risks for MSB0011359C. The distribution of lesions tends to be in sun exposed areas.

For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used (see Section 7.4.1.4).

See Section 6.5.4 for risk management measures for TGFβ inhibition mediated skin reactions.

3.5.4 Anemia

Anemia is an AESI and important identified risk for MSB0011359C. Notably, there are many reasons for anemia in patients with advanced cancer, therefore a thorough investigation of new anemia cases of unspecified etiology is requested.

CCI [redacted]

Risk management measures are provided in Section 6.5.4.4. The amount of blood drawn during the study for non-essential biomarkers will be carefully considered, especially given the preclinical finding of reduced Hgb levels.

3.5.5 Bleeding Adverse Events

Mucosal/Non-tumor Bleeding

Bleeding AEs are AESIs and considered important identified risk. Participants treated with MSB0011359C were commonly reported with mild to moderate mucosal AEs such as epistaxis, hemoptysis, gingival bleeding and hematuria. In general, these reactions resolve without discontinuation of treatment. See Section 6.5.4 for risk management measures.

Tumor Bleeding

Participants treated with MSB0011359C were reported in lower frequencies, with Grade ≥ 3 hemorrhages including tumor bleeding.

3.5.6 Alterations in Wound Healing or Repair of Tissue Damage

Alternations of wound healing and tissue damage repair are considered a potential risk given the TGFβ mechanism. Management should be discussed with the Medical Monitor on a case-by-case basis.

3.5.7 Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1 / PD-L1 targeting class. Animal models link the PD-1 / PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Based on its mechanism of action (MoA), MSB0011359C may cause fetal harm when administered to a pregnant female. An appropriate contraception warning is provided in this clinical protocol. Subjects with pregnancy or in lactation period are prohibited from being enrolled in clinical trials.

3.5.8 Potential Benefit

A direct benefit is considered unlikely for participants in this Phase I trial, especially in the low doses of the dose-escalation part; therefore, only subjects with malignancies for which no standard effective therapy exists or subjects having experienced a failure of standard therapy are eligible for this part of the trial. However, preliminary results from the EMR100070-001 trial with the parent avelumab antibody demonstrate promising clinical antitumor activity. Given the preclinical models demonstrating that MSB0011359C possesses superior antitumor activities relative to monotherapy with either PD-L1 blockade or TGFβ sequestration, clinical benefit might be expected at similar or lower doses than those seen with avelumab.

As of 04 May 2016, 1 subject with pancreatic cancer (3 mg/kg cohort) has been reported with a confirmed PR according to RECIST (ongoing at 6 months). In addition, SD has been reported 5 subjects (41.7%), including 1 subject in the 1 mg/kg cohort, and 2 subjects in each of the 3 and 10 mg/kg cohorts. Five subjects (41.7%) were reported with a BOR of PD. At the time of the data cutoff, 8 subjects (66.7%) remained on treatment.

In conclusion, the risk-benefit ratio of treatment with MSB0011359C in the targeted trial population appears positive given the poor prognosis of subjects with advanced malignancies with no standard treatment options.

This clinical trial will be conducted in compliance with the clinical trial protocol, the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law in Japan; and the "Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product" (Good Clinical Practice [GCP]) in Japan, GCP (ICH Topic E6), and the applicable national regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objective of the dose escalation part of the study is to determine the safety, tolerability, and the maximum-tolerated dose (MTD) of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

Except for the glioblastoma cohort, the primary objective of the efficacy expansion cohorts is to assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). For glioblastoma, the primary objective is to assess the disease control rate (DCR) according to RANO.

4.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure

- Determine the safety and tolerability of MSB0011359C in subjects with metastatic or locally advanced solid tumors (expansion cohorts)
- To assess the best overall response (BOR) according to RECIST 1.1 (Eisenhauer 2009).

CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, open-label, dose-escalation trial with consecutive expansion in various expansion cohorts (see Figure 1).

5.1.1 Overall Trial Design

5.1.1.1 Dose Escalation

The current trial is composed of a standard dose escalation "3 + 3" cohort design, for which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of DLTs (see Section 5.1.3.3), followed by various expansion cohorts (see Figure 1). The dose-escalation part of the trial will be conducted in the USA only.

Cohorts of 3 subjects with metastatic or locally advanced solid tumors, for which no standard effective therapy exists or a standard therapy has failed, will receive MSB0011359C at escalating dose levels (see Section 5.1.3.2). The starting MSB0011359C dose is 1 mg/kg; initially, the highest envisaged dose in the dose-escalation part was 20 mg/kg. CCI [redacted]

At each dose level, subjects will receive MSB0011359C as a 1-hour IV infusion (120 minutes for the 30 mg/kg and 2400 mg flat-dose cohorts) once every 2 weeks until progressive disease (PD) has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the investigation medicinal product (IMP; see Section 5.5).

Subjects who have experienced SD, a PR, or CR should be treated through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. For subjects who achieve SD, a PR or CR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Responsible (see Section 5.1.6). The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available.

Besides determination of the MTD / maximum feasible dose, it is the intention to establish PK / CCI [redacted] correlations based on PD-L1 receptor occupancy that may provide guidance for the dose to be used in expansion cohort. The MoA of MSB0011359C in humans will be investigated through monitoring the activation status of the immune system (that is, leukocyte subsets phenotypes, PD-1 signaling pathway, ADCC, and cytokines profiling). Furthermore, explorations of specific antitumor immune responses and evaluations of potential predictive / prognostic biomarker candidates are planned in this trial.

Assessment of safety parameters will focus on potential acute side effects that include allergic reactions / hypersensitivities during and immediately following infusion, in the worst-case anaphylaxis, which could develop as consequence of an immunogenicity response and might be pronounced due to the immunostimulatory properties of MSB0011359C, promoting an immune response against itself.

Evaluation of safety will also include the incidence and severity of potential irAEs, which may manifest after weeks of treatment (Attia 2005, Calabro 2010, Di Giacomo 2011, Kaehler 2010, Phan 2003, Wolchok 2010). Such immune-mediated adverse events may include pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and thyroiditis (hypo or hyperthyroidism).

The identified and potential risks are further described (see Sections 3.5 and 6.5.4).

All DLTs will be monitored centrally, and the decision to escalate to the next dose level will be determined by the SMC as outlined in Section 2.2.1.

After the 1 and 3 mg/kg cohorts have completed the DLT evaluation period, a preliminary PK analysis will be performed. Depending on the results of this analysis, including PK linearity, a decision will be made to initiate up to 2 cohorts of 3 subjects each, one at 0.1 mg/kg and one at 0.3 mg/kg, which will increase on the second dose and all subsequent doses to a 1200 mg/infusion flat dose, dependent upon SMC clearance and only if the Sponsor and Coordinating Investigator have determined a meaningful dose for the intrasubject escalation. No DLT evaluations will be performed in these flexible cohorts.

After the MTD has been reached or the 20 mg/kg cohort has been declared by the SMC as the highest non-MTD dose assessed, then further PK analyses may be performed. If deemed necessary, the 1, 3, 10, and 20 mg/kg cohorts may each enroll up to an additional 10 subjects (up to 40 total) for the purpose of PK profile and possible PK / CCI modeling if there has been SMC clearance at the higher or same (20 mg/kg) dose level. On the second dose and all subsequent doses, the 1 mg/kg cohort may increase to a 1200 mg/infusion flat dose. No DLT evaluations will be performed in these supplemental cohorts. These lower dose cohort expansions for PK profile and PK / CCI purposes may proceed in parallel with the expansion cohorts if deemed appropriate by the Sponsor and Coordinating Investigator based on the MTD alone.

In the cohorts receiving 0.1 mg/kg and 0.3 mg/kg and in the additional subjects enrolled for the purpose of PK profile and possible PK / CCI modeling, it is intended to intensify the PK analysis by taking 3 additional PK samples during the first treatment cycle. These samples are scheduled to be taken at 8 to 12 hours, 3 to 5 days, and 10 to 12 days after the initiation of the first infusion of the study drug. The samples are to be taken at any time during these intervals. Exact sampling time must be recorded. These samples are labelled as optional in the Schedule of Assessments (Table 3) but they are highly important to allow a sufficiently detailed analysis and description of the MSB0011359C PK profile.

As the 20 mg/kg cohort in the dose escalation portion has cleared SMC evaluation, additional cohorts at 30 mg/kg and 2400 mg flat dose will be initiated, in parallel to the ongoing expansion cohorts. The 30 mg/kg and the 2400 mg flat-dose cohorts will be enrolled in a 3 + 3 design with SMC evaluation after the first 3 subjects and no more than 6 evaluable subjects to be enrolled. These cohorts should provide additional insight into dose proportionality of PK and CCI parameters and support safety considerations at higher exposures than the current expansion phase dose of 1200 mg once every 2 weeks.

5.1.1.2 Expansion Cohorts

The dose for the expansion cohorts was determined by the Sponsor based on the safety observations and PK / CCI data from the dose escalation part of the trial. The flat doses for extension part will be implemented after clearance of 20 mg/kg escalation cohort by the SMC. Except for the second-line NSCLC cohort, all subjects in expansion cohorts will be receiving 1200 mg (flat dose) every 2 weeks. Subjects in the second-line NSCLC cohort will be randomized to receive either 500 or 1200 mg every 2 weeks (see Section 3.4.1.1 for rationales).

Subjects in the expansion cohorts will receive MSB0011359C as a 1-hour IV infusion once every 2 weeks until PD has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the IMP (see Section 5.5).

Subjects who have experienced SD, PR, or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1. If there is further evidence of PD thereafter, trial treatment should be discontinued; however, continued treatment is possible in consultation with the Medical Monitor. For subjects who achieve SD, a CR or PR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Responsible (see Section 5.1.6). The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available.

For subjects in the melanoma, SCCHN, and TNBC cohorts only, symptom severity will be assessed using 2 patient-reported outcomes questionnaires:

- Patient Global Impression of Severity (PGIS)
- Select items from the EORTC QLQ-C30

For subjects in the esophageal adenocarcinoma cohort only, symptom severity will be assessed using 3 patient-reported outcomes questionnaires:

- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the EORTC QLQ-OES18

For subjects in the glioblastoma cohort only, symptom severity will be assessed using 2 patient-reported outcomes questionnaires:

- PGIS

- Select items from the EORTC QLQ-BN20

For subjects in the ovarian cancer cohort only, symptom severity will be assessed using 3 patient-reported outcomes questionnaires:

- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the EORTC QLQ-OV28

For subjects in the NSCLC second-line and anti-PD-1/PD-L1 failure cohorts only, symptom severity will be assessed using 2 patient-reported outcomes questionnaires:

- PGIS
- NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ)

For subjects in the HCC expansion cohort only, symptom severity will be assessed using 2 patient-reported outcomes questionnaires:

- PGIS
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma Module – Modified (EORTC QLQ-HCC18-M)

For subjects in the cervical cancer cohort only, symptom severity will be assessed using 3 patient-reported outcomes questionnaires:

- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module (EORTC QLQ-CX24).

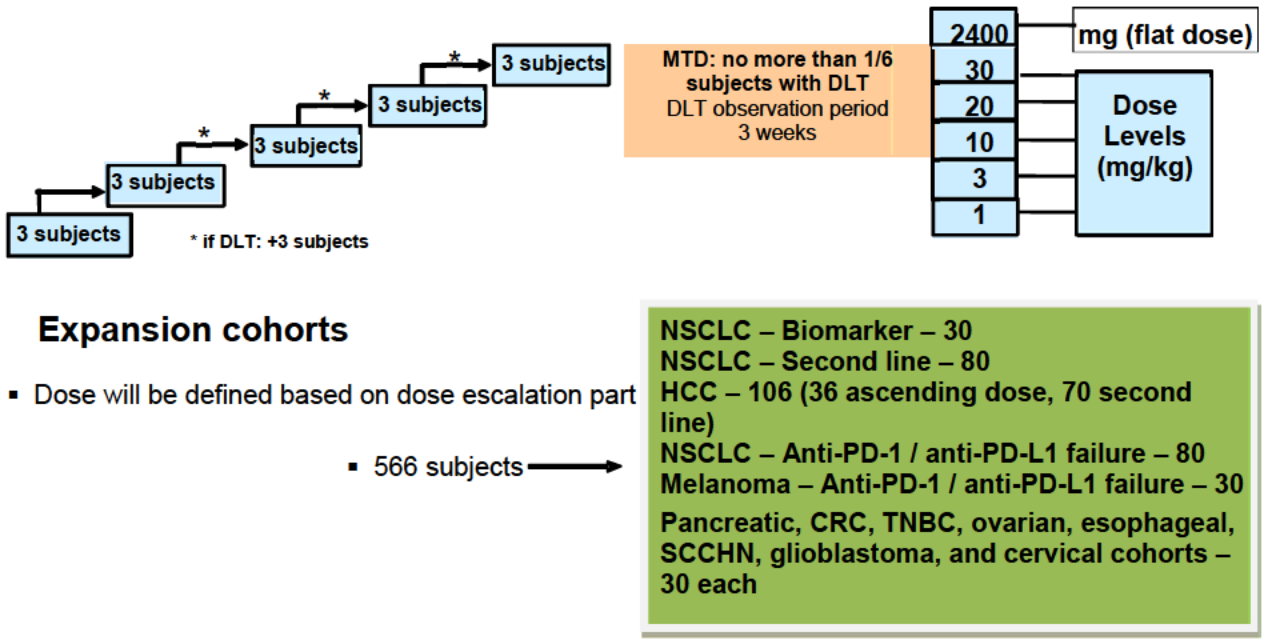
Ascending Dose HCC

After the 3 mg/kg cohort in the dose escalation portion has cleared SMC evaluation, the 3 mg/kg HCC cohort may initiate. Once the 20 mg/kg dose-escalation cohort has been cleared and deemed safe by the SMC, an HCC ascending 1200 mg flat-dose cohort will be initiated.

For subjects in the HCC 1200 mg ascending-dose cohort only, symptom severity will be assessed using 2 patient-reported outcomes questionnaires:

- PGIS
- Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index – 8 questions (FHSI-8).

Figure 1 Schematic of Trial Design



CRC = colorectal cancer; DLT = dose-limiting toxicity; HCC = hepatocellular carcinoma; MTD = maximum-tolerated dose; NSCLC = non-small cell lung cancer; SCCHN = squamous cell carcinoma head and neck; TNBC = triple-negative breast cancer.

5.1.2 Trial Medication Administration and Schedule

Subjects will receive IV infusion of MSB0011359C over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) once every 2 weeks. Subjects enrolled in the 30 mg/kg and 2400 mg flat-dose cohorts may have a total infusion time of up to 120 minutes. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions and is optional and at the discretion of the Investigator after the second infusion (premedication is optional for all infusions for subjects in the NSCLC biomarker cohort being treated at the US NCI). If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

The trial treatment schedules are provided in the Schedules of Assessments (see Table 1 and Table 2).

The formulation and packaging information of MSB0011359C is provided in Sections 6.1 and 6.6.

5.1.3 MSB0011359C Dose Escalation

The dose-escalation part of the trial is expected to enroll between 3 and 82 subjects. Eligible subjects will be patients with metastatic or locally advanced solid tumors who have failed standard therapies or who have no standard effective therapy available.

5.1.3.1 Starting Dose

The starting dose of MSB0011359C will be 1 mg/kg.

5.1.3.2 Dose Escalation

The dose escalation will use a standard 3 + 3 scheme with the following planned doses (once every 2 weeks):

- 1 mg/kg
- 3 mg/kg
- 10 mg/kg
- 20 mg/kg
- 30 mg/kg
- 2400 mg flat dose

The DLT period is defined as 21 days after the start of therapy. The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Thereafter, within each cohort 48 hours must pass before a new subject can initiate dosing. Once the 3 or 6 subjects have passed the 21-day DLT evaluation period the SMC will review the safety and available PK data to decide upon further dose escalation. Pharmacokinetic data from the previous cohort will be required for SMC review (for example, when the SMC is reviewing safety data from the 10 mg/kg cohort, available PK data from the 3 mg/kg cohort); however, PK data from the cohort under review will not be required.

The criteria for moving from 1 dose level to another do not allow escalation to the next cohort in cases where $\geq$ 2 of 3 or 6 subjects in a cohort experience a DLT. If 1 DLT in 3 subjects is observed, this cohort will be automatically expanded to 6 subjects with SMC meeting after the 6th subject completes the DLT evaluation period. Likewise, if at the highest dose level (30 mg/kg) no DLTs occurred in the first 3 subjects, the cohort may be expanded to 6 subjects with SMC meeting after the 6th subject completes the DLT evaluation period.

The MTD is defined as the highest dose where fewer than 2 of 6 subjects experience a DLT. Thus, the MTD cohort should accrue a total of 6 subjects. If 1 of 6 subjects has experienced a DLT at a dose below 10 mg/kg, dose escalation will be modified (Table 4).

The DLT criteria will not apply to any of the expansion cohorts.

Table 4 Modification of Dose Escalation Based on DLT Observations

Dose Escalation Schedule Scenarios	Dose of MSB0011359C (mg/kg)	
Dose Levels	No DLT at Dose Level	DLT at Level 1 (1 mg/kg) or DLT at Level 2 (3 mg/kg)
Level 1	1 mg/kg	1
Level 2	3 mg/kg	3
Level 3	10 mg/kg	7[a]
Level 4	20 mg/kg	10
Level 5	30 mg/kg	20
Level 6	2400 mg	No modification

DLT = dose-limiting toxicity.
a If 1 of 6 subjects has a DLT at dose level 1 or 2.

5.1.3.3 Dose-Limiting Toxicity

A DLT is defined as any Grade ≥ 3 AE assessed as related to the IMP by the Investigator and / or Sponsor (that is, Grade ≥ 3 ADR; grading according to the NCI-Common Terminology Criteria for Adverse Events version v4.03 [CTCAE v4.03]) occurring in the DLT evaluation period (21 days after first administration of MSB0011359C) confirmed by the SMC to be relevant for the IMP treatment. The SMC recognizes that in the absence of prior human experience with MSB0011359C, a conservative approach will be adopted in ascribing the relevance of the treatment-related toxicity to IMP. Treatment-related SAEs will be ascribed as related to drug except where a clear relationship to the underlying disease or recognized comorbidities is evident.

A DLT is specifically defined as the following:

Any Grade ≥ 3 adverse event that is related to MSB0011359C, occurring during the DLT evaluation period (21 days after first administration of MSB0011359C), **except** for those listed below. Also, elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times the upper limit of normal (ULN) range and a concomitant elevation of bilirubin 2 times the ULN attributable to study drug constitutes a DLT.

- Grade 3 infusion-related reactions resolving within 6 hours from the end of infusion and controlled with medical management.
- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1.
- Grade 3 Hgb decrease (< 8.0 g/dL) that resolves to at least 9 g/dL within 14 days or changes in associated red blood cell parameters during such a Hgb decrease that resolve within 14 days without blood transfusion or erythroid growth factor use.
- Malignant skin lesion that is local and can be resected with negative resection margin.

Dose-limiting toxicities that require treatment discontinuation are described in Section 5.1.7.2.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced.

5.1.4 Expansion Cohorts

After an MSB0011359C dose for further investigation is established, enrollment of several expansion cohorts will be opened to determine the safety and clinical activity of MSB0011359C in specific indications (see Section 3.4.2 for details).

Following safety and PK analysis of the escalation cohorts, a flat dose of 1200 mg/infusion was chosen for all expansion cohorts, except for the NSCLC second-line cohort, in which 40 subjects will receive 500 mg/infusion and 40 subjects will receive 1200 mg/infusion.

5.1.5 Planned Number of Subjects

The planned number of the evaluable subjects for this trial is derived from the dose-escalation "3 + 3" design and the expansion cohort sizes:

- Dose-escalation phase: 3 to 82 subjects.
- Expansion cohorts: Up to approximately 566 subjects.

The final sample size, however, may vary depending on the total number of dose levels to be escalated and tested, and the subject replacement for DLT evaluations if applicable.

In the event that rapid recruitment in the expansion phase impacts supply of IMP, the screening of new subjects for any cohort may be temporarily paused with 24 hours' notice to Investigators.

5.1.6 Planned Treatment Duration

The trial duration for a subject is estimated to be up to 2 years. This includes a 28-day Screening period (decision will be made in this period for subjects' trial inclusion if all eligibility criteria are met), a treatment duration until confirmed PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5) and a 28-Day Safety Follow-up visit 4 weeks after the last dose of MSB0011359C administration.

Subjects who have experienced SD, PR, or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1.

For subjects who achieve SD, a PR or CR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is

allowed at the discretion of the Investigator and agreement of the trial Medical Responsible. A discussion between the Investigator and Sponsor should take place. The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to permanent treatment discontinuation of the initial MSB0011359C therapy, unless the toxicity is deemed to be manageable and the potential benefit outweighs the risk of re-exposure. Prior to re-initiation of the trial treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the Schedules of Assessment for the Expansion portion of the trial starting at Week 1, Day 1 (see Table 2).

Moreover, any ADRs should be followed until they resolve, return to Baseline, or are irreversible (see Section 7.1.4 for details).

Planned first subject in: Q3, 2015.

Planned date last subject out (dose escalation, including follow-up): Q3, 2019.

Planned date last subject out (after expansion and follow-up): Q4, 2021.

5.1.7 Dose Modification and ADRs Requiring Treatment Discontinuation

5.1.7.1 Dose Modification

For the dose-escalation cohorts (except for the 2400 mg flat-dose cohort), the dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration.

Each subject will stay on the MSB0011359C dose level assigned in the trial unless treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in Sections 5.1.7.2 and 6.5.4 and subsections. There are no dose reductions.

5.1.7.2 Adverse Drug Reactions Requiring Treatment Discontinuation

Certain ADRs, defined as an AE assessed as related to MSB0011359C by the Investigator and / or Sponsor, may require permanent treatment discontinuation of MSB0011359C (listed below). For certain ADRs assessed to be immune-related, Table 7 criteria may supersede this section. These criteria may allow the subject to continue on study if medically indicated after consultation with Medical Monitor.

Any Grade 4 ADRs require permanent treatment discontinuation except for single laboratory values out of normal range that do not have any clinical correlate and resolve to Grade ≤ 1 or Baseline grade within 7 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or Baseline grade.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. The Study Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities. If the amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis has not resolved to Grade ≤ 1 within the subsequent 2 cycles (28 days), the subject should permanently discontinue treatment with MSB0011359C unless approved to continue by Medical Monitor after specific request from site Investigator.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use does not require treatment discontinuation. During the 21-Day-DLT period, a Grade 3 Hgb decrease (< 8.0 g/dL) requires treatment discontinuation, unless it resolves to at least 9 g/dL within 14 days or changes in associated red blood cell parameters during such a Hgb decrease that resolve within 14 days without blood transfusion or erythroid growth factor use.
- Increases in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 that resolves to ≤ 2 by Day 1 of the next cycle (infusions should not be given if the ECOG PS is ≥ 3 on the day of IMP administration and should be delayed until ECOG PS ≤ 2).
- Keratoacanthoma and squamous cell carcinoma of the skin. Any suspicious skin lesion should be biopsied and be surgically removed. The Study Medical Monitor should be consulted.
- Grade 3 or 4 dermatological irAEs, treatment should be delayed and treatment started according to Table 7, if condition improves to Grade 1, treatment may be resumed. If ≥ 2 consecutive doses are missed, the Medical Monitor should be consulted.
- Grade 3 or 4 symptomatic endocrinopathies (eg, thyroiditis or hypophysitis), treatment should be delayed and treatment started according to Table 7, if condition improves to Grade 1, treatment may be resumed. If ≥ 2 consecutive doses are missed, the Medical Monitor should be consulted
- Other immune-related ADRs, see Table 7.

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle but it is manageable and / or not clinically relevant, the ADR should be discussed with the Medical Monitor and based upon discussion it is possible the infusion will be given on the following cycle. If at the end of the following cycle, the event has not resolved to Grade 1, discussion should be had with the Medical Monitor about permanently discontinuing treatment with MSB0011359C.
- Upon the second occurrence of the same Grade 2 ADR in the same subject (except for fatigue and hormone insufficiencies that can be managed by replacement therapy), continuation of treatment with MSB0011359C has to be discussed with the Medical Monitor and might be permanently discontinued.
- Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the guidelines provided in Sections 6.5.4.1 and 6.5.4.2, respectively.
- Anemia should be handled according to the guidelines provided in Section 6.5.4.4.
- If immune-related ADR, see Table 7.

5.1.8 Analysis Cutoff Dates

After the end of the dose-escalation part of the trial, a full analysis for safety and PK / [redacted] data will be performed. The data cutoff date will be 6 weeks after the last subject of the escalation part has received his /her first administration of MSB0011359C. At the time of this amendment when adding the 2400 mg flat-dose cohort, the full analysis for the dose-escalation part of the trial had been completed. For the 2400 mg flat-dose cohort, an analysis will be performed at least 6 weeks after last subject first dose.

For the HCC ascending-dose cohort, an interim analysis will be conducted 12 weeks after the 30th subject in the 1200 mg ascending-dose portion received the first dose.

For the NSCLC anti-PD-1 / anti-PD-L1 failure cohort, an interim analysis will be conducted 12 weeks after the 40th subject in the cohort started treatment.

For the melanoma anti-PD-1 / anti-PD-L1 failure cohort, NSCLC second-line, pancreatic adenocarcinoma, CRC, TNBC, ovarian cancer, esophageal adenocarcinoma, SCCHN, glioblastoma, and cervical cancer cohorts, an interim analysis for that cohort will be conducted 12 weeks after the 30th subject in the cohort started treatment.

The primary data cutoff for the analysis of each expansion cohort separately will be 24 weeks after the last subject in that cohort started treatment (60th subject for the HCC cohort).

Final data cutoff will be after subjects are either enrolled into a roll-over trial or withdrawn after completing at least the Safety Follow-up visit at 10 Weeks (± 2 weeks) after Last Treatment (see Table 1).

5.2 Discussion of Trial Design

This is a Phase I, open-label, dose-escalation trial with planned expansion cohorts. An open-label, unblinded design is appropriate for a dose-escalation trial with consecutive expansion cohorts in advanced cancer subjects since subjects have exhausted treatment options.

In this trial, the assessment of the safety and tolerability of the IMP with the determination of the MTD (in the dose-escalation part only) is set to be the primary objective. The determination of the MTD is one of the first major steps in the development of a compound entering early clinical development because it might be determined that the highest tolerable dose is important in future clinical development in order to achieve the best efficacy to risk ratio for subjects. The MTD will be determined using a standard "3 + 3 subjects" dose-escalation design based on DLT assessments, which is commonly used in first-in-man oncology trials (Crowley 2006). The aim of this design is to maximize the protection to subjects and reduce the chances of more subjects to be exposed to possible drug toxicities. All these assessments will be correlated to PK / CCI parameters to potentially aid selection of the most meaningful dose for the expansion cohorts or future studies.

The enrichment of dose-escalation cohorts below the MTD are reasonable for immunotherapeutic anticancer compounds (which is in contrast to most chemotherapies, that are typically given at the MTD), as the optimal biological effects might not be exclusively observed at the MTD level (Topalian 2012b) and since it may facilitate characterization of the PK and PK / CCI profiles. The inclusion of low-dose intrasubject escalation cohorts is reasonable since it facilitates characterization of the PK profile and accounts for escalation to a meaningful dose level.

A reasonably safe starting dose of 1 mg/kg has been chosen taking also into account the information from the clinical experience with the parent monoclonal antibody, avelumab, and the predicted lack of overlapping immune-related safety profile with TGFβ inhibition, as previously discussed. Initial dose setting follows the principle that the starting dose should be pharmacologically active but also reasonably safe to use. This initial dose estimation algorithm is proposed in Guideline ICH S9 (EMEA/CHMP/ICH/646107/2008) and applicable for an end-stage cancer population. In the current study, the 1 mg/kg starting dose is projected to have approximately 20% of full antitumor activity and therefore achieves an appropriate balance of potential for therapeutic activity as well as reasonable fraction of biologic activity, which might have safety implications. In addition, preclinical evidence did not suggest immune-related toxicities.

In addition to determining the MTD, the trial will serve to explore biologic and clinical parameters after exposure to MSB0011359C. Due to a limited understanding of the interaction of the immune system and tumors in cancer subjects, there can be no certainty that the doses to be examined will be associated with relevant antitumor activity, although preliminary results with the parent avelumab antibody suggest promising clinical antitumor activity. The selection of the dose to be used for further clinical evaluation will be based on the best current scientific knowledge.

The target population for the dose-escalation part comprises subjects with metastatic or locally advanced solid tumors who have exhausted standard treatment options. Based on the clinical literature, NSCLC has some responsiveness to the anti-PD-1 / PD-L1 class (Gettinger 2014) and to avelumab (refer to current avelumab IB) and is therefore justified here for both the anti-PD-1 /

anti-PD-L1 naïve and experienced subgroups in the setting of post-platinum doublet progression and, as appropriate, driver mutation therapy. In order to obtain a trend of biological / clinical activity, to assess target engagement based on tumor biopsy samples and to collect further safety data, a treatment expansion at a meaningful dose level to be identified during the dose-escalation part to ensure further development in selected settings is justified. Furthermore, the requirement of baseline and on-treatment tumor biopsies in the expansion phase is justified since the biologic goal is to assess target engagement to aid future development. Data from the expansion cohorts will allow exploration of whether the expression of tumor or peripheral PD-L1 pathway biomarkers or TGFβ pathway biomarkers are associated with clinical response to MSB0011359C and whether PD-L1 expression or markers related to TGFβ might serve as markers for patient selection in the future development program of MSB0011359C.

The tests and analyses to examine the biologic effects of MSB0011359C dosing will include the assessment of markers of immune activation known to show typical changes after treatment with therapies blocking immune checkpoints. These details and other markers of interest are specified in Section 7.6.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled.

5.3.1.1 Inclusion Criteria for Dose Escalation

1. Ability to understand the purpose of the study, provide signed and dated informed consent, and able to comply with all procedures
2. Male or female subjects aged ≥ 18 years
3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no effective standard therapy exists or standard therapy has failed
4. Life expectancy ≥ 12 weeks as judged by the Investigator
5. ECOG performance status of 0 to 1 at trial entry
6. Must have evaluable or measurable disease at baseline

7. Adequate hematological function defined by white blood cell (WBC) count $\geq 3 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 120 \times 10^9$/L, and Hgb ≥ 9 g/dL
8. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ ULN, an AST level $\leq 2.5 \times$ ULN, and an ALT level $\leq 2.5 \times$ ULN. For subjects with liver involvement in their tumor, AST $\leq 5.0 \times$ ULN, ALT $\leq 5.0 \times$ ULN, and bilirubin $\leq 3.0 \times$ ULN is acceptable
9. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection
10. **Highly** effective contraception (that is, methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix 2 or as stipulated in national or local guidelines). **Highly** effective contraception must be used 30 days prior to first trial treatment administration, for the duration of trial treatment, and at least for 4 months after stopping trial treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.

5.3.1.2 Inclusion Criteria for Expansion Cohorts

1. Ability to understand the purpose of the study, provide signed and dated informed consent, and able to comply with all procedures. In Japan, if a subject is < 20 years, the written informed consent from his/her parent or guardian will be required in addition to the subject's written consent
2. Male or female subjects aged ≥ 18 years
3. Availability of fresh tumor biopsies (excluding bone biopsies) is mandatory for eligibility in the NSCLC biomarker expansion, NSCLC anti-PD-1/PD-L1 failure and melanoma anti-PD-1/PD-L1 failure cohorts (it is preferable to not biopsy a target lesion; however, if only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility). The biopsy or surgical specimen must have been collected within 28 days prior to the first IMP administration. For other expansion cohorts, availability of either tumor archival material or fresh biopsies within 28 days is acceptable (excluding bone biopsies) with one of these being mandatory (where possible fresh biopsies are preferred). If no archival material is available and only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility. Tumor biopsies and tumor archival material must be suitable for biomarker assessment as described in the Laboratory flowchart
4. Life expectancy ≥ 12 weeks as judged by the Investigator
5. Subjects must have one of the following:
   - **NSCLC biomarker cohort:** Subjects must have histologically or cytologically confirmed Stage IIIb or IV NSCLC with relapsed, refractory or progressive disease on or after a single line of platinum-based chemotherapy. In addition, subjects should have exhausted other

indicated treatment options such as driver mutation therapy. Previous treatment with combination immunotherapy is prohibited. Subjects with non-squamous cell NSCLC of unknown mutational status will require testing (local laboratory, or central laboratory if local testing is not available). Those subjects with epidermal growth factor receptor (EGFR) mutation and / or anaplastic lymphoma kinase (ALK) translocation must have received prior tyrosine kinase inhibitor therapy and those with ROS1 rearrangement must have received prior tyrosine kinase inhibitor therapy if locally approved. Prior platinum-based chemotherapy is not required in these subjects. Subjects with large cell neuroendocrine cancer of the lung are not eligible for this cohort.

Enrollment will additionally be as follows:

a. Subjects who are naïve to the anti-PD-1 / anti-PD-L1 class – 15 subjects with paired biopsies

b. Subjects who have relapsed, refractory, or progressive disease following an anti-PD-1 or anti-PD-L1 agent – 15 subjects with paired biopsies

- **HCC, second line or sorafenib intolerant:** Histologically confirmed HCC. Must be unresectable or advanced disease not amenable to curative resection. Must have had progression following 1 line of prior sorafenib therapy (must have received at least 14 days of sorafenib at least 400 mg per day) or previously considered to be sorafenib intolerant

  The HCC cohort will be composed of 2 portions, an ascending-dose portion and an expansion portion:

  For the ascending-dose portion:

  1) 3 mg/kg dose cohort, up to N = 6
  2) 1200 mg flat-dose cohort, up to N = 30

  For ascending-dose portion and dose-expansion portion:

  Uninfected, HCV, and HBV-infected subjects are eligible. If medically indicated, subjects infected with HBV must be treated and on a stable dose of antivirals (eg, entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance. Subjects on active HCV therapy at study entry must be on a stable dose without documented clinically significant liver function test or hematologic abnormalities (must meet criteria below) and with planned monitoring and management according to appropriate labeling guidance.

  Additional criteria for all HCC, second-line cohort subjects include:

  - Child-Pugh A or B7
  - ECOG 0 or 1
  - Albumin $\geq$ 2.8 g/dL
  - International normalized ratio (INR) < 1.7

- Adequate hematological function defined by WBC count $\geq 2.5 \times 10^9$/L with ANC $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 50 \times 10^9$/L, and hemoglobin ≥ 9 g/dL
- Subjects with no allergies to contrast and able to tolerate computed tomography (CT) or magnetic resonance imaging (MRI) contrast in the opinion of the Investigator

- **NSCLC, second line:** Histologically confirmed Stage IIIb/IV or recurrent NSCLC. Must not have received checkpoint inhibitor previously (consult with Medical Monitor if necessary). Must have experienced disease progression after an acceptable therapy defined as follows:
  - Subjects must have progressed during or after a minimum of 2 cycles of 1 course of a platinum-based combination therapy administered for the treatment of metastatic disease. A history of continuation (use of a non-platinum agent from initial combination) or switch (use of a different agent) maintenance therapy is permitted provided there was no progression after the initial combination. A switch of agents during treatment for the management of toxicities is also permitted provided there was no progression after the initial combination

  OR

  - Subjects must have progressed within 6 months of completion of a platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for locally advanced disease

  Subjects with non-squamous cell NSCLC of unknown mutational status will require testing (local laboratory, or central laboratory if local testing is not available). Subjects with known EGFR mutation and / or ALK translocation are eligible if they have received at least 1 line of tyrosine kinase inhibitor therapy. Subjects with ROS1 rearrangement must have received tyrosine kinase inhibitor therapy if locally approved. These subjects do not require prior treatment with systemic chemotherapy. Subjects with large cell neuroendocrine cancer of the lung are not eligible

- **NSCLC, anti-PD-1 / anti-PD-L1 failure:** Subjects with histologically confirmed Stage IV (metastatic) or recurrent NSCLC (per 7th International Association for the Study of Lung Cancer classification) who have exhausted standard treatment options in the opinion of the Investigator are to be enrolled. At a minimum, subjects need to have received and failed platinum-based chemotherapy and must have received anti-PD-1 or anti-PD-L1 as monotherapy and failed with disease progression. In addition, subjects should have exhausted other indicated driver mutation therapy, as appropriate

- **Melanoma, anti-PD-1 / anti-PD-L1 failure:** Subjects with unresectable Stage III or metastatic (Stage IV) melanoma who have exhausted standard treatment options in the opinion of the investigator are to be enrolled. At a minimum, subjects need to have received anti-PD-1 or anti-PD-L1 as mono- or combination therapy and failed with disease progression. Also must have failed appropriate systemic therapies including BRAF inhibitor if BRAF V600 mutation positive

- **Pancreatic adenocarcinoma, second line or greater:** Histologically confirmed pancreatic adenocarcinoma (subjects with endocrine or acinar pancreatic carcinoma are not eligible). Must have unresectable or locally advanced or metastatic disease
  - Prior therapy with ≥ 1 systemic chemotherapy regimen for unresectable or metastatic pancreatic cancer or unwilling / unable to receive systemic chemotherapy. Subjects must not have received previous radiotherapy for measurable lesions
  - Disease progression while receiving or after discontinuing palliative chemotherapy
- **Colorectal cancer (CRC), third line or greater:** Histologically confirmed adenocarcinoma of the colon or rectum
  - Subjects must have progressed during or after a second-line of systemic treatment
  - Prior failed therapy must have included at least a fluoropyrimidine, oxaliplatin, irinotecan (single or in combination) and bevacizumab (where approved). For subjects who had wild-type RAS tumors, cetuximab or panitumumab treatment must have occurred
- **Triple-negative breast cancer (TNBC), second line or greater:** Tumor must be confirmed negative for estrogen receptors, progesterone receptors, and HER2 defined as follows:
  - ER negative defined by: ER IHC < 1% reactive cells
  - PR negative defined by: PR IHC < 1% reactive cells
  - HER-2 negative defined by one of four situations below:
    1. HER2 Breast IHC = 0
    2. HER2 Breast IHC = 1+
    3. HER2 Breast IHC = 2+ AND fluorescence in situ hybridization (FISH)-negative (non-amplified)
    4. FISH non-amplified
  - Subjects must have progressed during or after first line of chemotherapy
- **Ovarian cancer, platinum resistant or refractory, previously systemically treated:** Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (subjects with non-epithelial tumor, including malignant mixed Müllerian tumors without high grade serous component, or ovarian tumors with low malignant potential [ie, borderline tumors] are not eligible)
  - Must not be a candidate for surgical resection with curative intent
  - Must have platinum resistant / refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-based therapy (refractory), or progression on / after last non-platinum-based chemotherapy
  - Treatment history of at least 2 prior systemic regimens, including prior exposure to platinum and taxane agents

- BRCA status must be reported if known

- **Esophageal adenocarcinoma, post-platinum, second line or greater:** Histologically confirmed recurrent or metastatic esophageal adenocarcinoma. Must have unresectable (Stage III or IV) disease
  - Must have received at least one previous platinum-containing chemotherapy regimen. Subjects with HER2-positive tumors must have received prior trastuzumab
- **Glioblastoma, post-temozolomide / radiation, second line:** Histologically confirmed Grade IV malignant glioma (subjects with extracranial metastatic or leptomeningeal are not eligible)
  - Previous treatment with radiotherapy and temozolomide
  - Tolerance to gadolinium
  - An interval of at least 12 weeks after the end of prior radiotherapy is required unless there is either histolopathologic confirmation of recurrent tumor or new enhancement on MRI outside of the radiotherapy treatment field
  - First recurrence of glioblastoma
  - Karnofsky Performance Status (KPS) ≥ 70
  - Subjects must not have received prior bevacizumab or other anti-vascular endothelial growth factor or antiangiogenic treatments
- **Squamous cell carcinoma head and neck (SCCHN), second line or greater:** Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
  - Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.
  - Subjects may have received prior cetuximab
  - HPV tumor testing must be reported if known
- **Cervical cancer, second line or greater:** Histologically confirmed recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix following standard of care treatment with systemic therapy for advanced disease (typically doublet cytotoxic chemotherapy and bevacizumab, where approved)
  - HPV tumor testing must be reported if known

6. ECOG performance status of 0 to 1 at trial entry
7. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1.
8. Adequate hematological function defined by white blood cell (WBC) count $\geq 3 \times 10^9$/L with ANC $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 120 \times 10^9$/L, and Hgb ≥ 9 g/dL

9. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN. For subjects with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 is acceptable
10. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection
11. **Highly** effective contraception (that is, methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix 2 or as stipulated in national or local guidelines). **Highly** effective contraception must be used 30 days prior to first trial treatment administration, for the duration of trial treatment, and at least for 4 months after stopping trial treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.

5.3.2 Exclusion Criteria (Applicable to All Subjects, Including All Expansion Cohorts)

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Concurrent treatment with non-permitted drugs and other interventions (see Section 6.5.2 and Section 6.5.3, respectively).
2. Except for the anti-PD-1 / anti-PD-L1-experienced NSCLC expansion and melanoma expansion cohorts, prior therapy with any antibody / drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody (consult Medical Monitor if necessary) is not allowed (consult with Medical Monitor as needed), inclusive of intrahepatic, localized administration of such agents
3. Anticancer treatment within 28 days before the start of trial treatment, for example, cytoreductive therapy, radiotherapy (with the exception of palliative radiotherapy delivered in a normal organ-sparing technique), immune therapy, or cytokine therapy (with the exception of sorafenib for subjects with HCC, which must have been stopped within 14 days)
4. Major surgery within 28 days before the start of trial treatment (prior diagnostic biopsy is permitted)
5. Systemic therapy with immunosuppressive agents within 7 days before the start of trial treatment; or use of any investigational drug within 28 days before the start of trial treatment (**Note:** for subjects with glioblastoma, steroid use is allowed according to standard of care and local guidelines)
6. Previous malignant disease (other than the target malignancy to be investigated in this trial) within the last 3 years. Subjects with a history of cervical carcinoma in situ, superficial or no-invasive bladder cancer, or basal cell or squamous cell carcinoma in situ previously treated

with curative intent are NOT excluded. Subjects with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor

7. Rapidly progressive disease which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or trial procedures

8. Subjects with active central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy. Subjects with CNS metastases incidentally detected during Screening which do not cause clinical symptoms and for which standard of care suggests no therapeutic intervention is indicated should be discussed with the Sponsor Medical Responsible

9. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (eg, corneal transplant, hair transplant)

10. Significant acute or chronic infections including, among others:

    - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
    - Except for the HCC cohort, HBV or HCV infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive HCV antibody with reflex to positive HCV RNA)
    - Subjects with active tuberculosis (history of exposure or history of positive tuberculosis test; plus, presence of clinical symptoms, physical or radiographic findings)

11. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

    - Subjects with diabetes type I, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
    - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses $\leq$ 10 mg of prednisone or equivalent per day
    - Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade $\geq$ 3 NCI-CTCAE v4.03) or recent, within 5 months, history of uncontrolled asthma (ie, 3 or more features of partially controlled asthma)

13. Persisting toxicity (except alopecia and vitiligo) related to prior therapy Grade > 1 NCI-CTCAE v4.03; however, sensory neuropathy Grade ≤ 2 is acceptable

14. Pregnancy or currently in lactation

15. Known alcohol or drug abuse

16. Clinically significant cardiovascular / cerebrovascular disease as follows: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia

17. Clinically relevant diseases (for example, inflammatory bowel disease) and / or uncontrolled medical conditions, which, in the opinion of the Investigator, might impair the subject's tolerance or ability to participate in the trial

18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent

19. Legal incapacity or limited legal capacity

20. Vaccine administration within 4 weeks of IMP administration. Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines)

Additional exclusion criteria for subjects in the HCC cohort include:

21. Clinical ascites (that is, not per radiological assessment only) within past 6 months not adequately controlled with medical therapy; history of variceal bleeding within past 3 months; history of uncontrolled hepatic encephalopathy in the past 3 months; or history of obstructive jaundice not amenable to stenting in the past 3 months

22. Hepatitis D virus (HDV) co-infection with hepatitis B virus (HBV; if HBV surface antigen or HBV DNA positivity at Screening then must check for HDV status)

23. Chemoembolization or radioembolization within 28 days prior to IMP administration

5.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria without matching any exclusion criterion.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal From Trial Treatment

Subjects will be withdrawn from trial treatment for any of the following reasons:

- Confirmed PD per RECIST 1.1 or RANO for subjects with glioblastoma: Subjects should continue treatment beyond the initial determination of PD, through their next tumor assessment, provided:
  a. There are no new Grade 2 or greater symptoms or significant worsening of existing symptoms.
  b. There is no decrease in ECOG PS.
  c. In the opinion of the Investigator, the subject does not require new anticancer therapy.

  Subjects should be discontinued from treatment thereafter if further evidence of PD; however, continued treatment is possible in consultation with the Medical Monitor
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and / or Sponsor
- Therapeutic failure requiring urgent additional cancer therapy
- Occurrence of Grade ≥ 3 ADRs or repetitive Grade 2 ADRs except as allowed as defined in Section 5.1.7.2
- Occurrence of AEs, at the Investigator's discretion
- Pregnancy
- Use of prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP
- Non-adherence / non-compliance to the trial protocol or trial requirements (see Section 6.9)
- Withdrawal of consent
- Participation in any other trial.

For subjects who miss ≥ 2 consecutive doses for medical reasons, the Medical Monitor should be consulted.

In the dose-escalation phase, the only subjects that may be replaced are those that do not complete the 21-day DLT observation period for reasons other than a DLT.

5.5.2 Withdrawal From the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial.

A subject must be withdrawn if any of the following occur during the trial:

- Withdrawal of the subject's consent
- Participation in any other therapeutic trial during the treatment duration of this trial; however, subjects will continue to be followed for survival

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of withdrawal from the trial, the assessments scheduled for the last visit (28-Day Safety Follow-up visit) should be performed (see Section 7.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate 28-Day Safety Follow-up electronic case report form (eCRF) visit must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy. After completion of the Follow-up period or after the End-of-Treatment visit, whatever is applicable, the appropriate eCRF section for Trial Termination must be completed.

If a subject is withdrawn prior to disease progression for any reason in the expansion part of the trial, the subject will not be replaced. In the dose-escalation part, the only subjects that may be replaced are those that do not complete the 21-day DLT observation period for reasons other than a DLT.

After primary analyses are completed, subjects may enroll into a roll-over trial before planned end of the trial or withrawn after they have at least completed the Safety Follow-up at 10 Weeks (± 2 weeks) after Last Treatment.

5.6 Premature Termination of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, for example, due to
  - evidence of inefficacy of the IMP,
  - occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - other unfavorable safety findings.

  (Note: Evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, for example, toxicology.)
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's IMP

Health Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

5.7 Definition of End of Trial

If the trial is not terminated for a reason given in Section 5.6, the end of the trial is defined as when subjects are either enrolled into a roll-over trial or withdrawn after completing at least the Safety Follow-up visit at 10 Weeks (± 2 weeks) after Last Treatment.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form. The only IMP used in this trial is MSB0011359C.

6.1 Description of the Investigational Medicinal Product

MSB0011359C drug product is provided as either a sterile freeze-dried or a sterile liquid formulation.

Each vial of Powder for Concentrate for Solution for Infusion (freeze-dried formulation) is packaged in United States Pharmacopeia (USP) and European Pharmacopeia (Ph Eur) type I glass vials. Each vial is filled with 45 mg of MSB0011359C (45 mg/vial) as preservative-free powder containing histidine, trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). The vials are closed with a rubber stopper in lyophilization format complying with USP and Ph Eur and sealed with an aluminum plastic crimping cap. Only excipients that conform to the current USP and / or Ph Eur are used for MSB0011359C drug product.

The Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The vials are closed with rubber stoppers with the same composition as used for freeze-dried formulation, but in serum format complying with USP and Ph Eur with an aluminum crimp seal closure.

The liquid formulation, compared with the freeze-dried formulation, has the same composition in terms of excipients, qualitatively and quantitatively, except for the addition of water. Of note, there is no change to the drug substance process.

For applications in clinical studies, the freeze-dried formulation must be reconstituted with 4.5 mL water for injection and further diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. The liquid formulation is diluted directly with 0.9% saline solution.

The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable. For subjects requiring doses that would exceed the maximum allowable concentration in 250 mL (eg, subjects in the 30 mg/kg cohort), MSB0011359C may be diluted in 0.9% sodium chloride to a total volume of 500 mL provided the final concentration range is 0.16 mg/mL to 9.6 mg/mL. Detailed information on infusion preparation and administration are provided in the protocol and manual of preparation.

Subjects who received the freeze-dried formulation before the introduction of the liquid formulation will remain on the freeze-dried formulation.

6.2 Dosage and Administration

Subjects will receive IV infusion of MSB0011359C over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) once every 2 weeks as detailed in the Schedules of Assessments (see Table 1 and Table 2). Subjects enrolled in the 30 mg/kg and the 2400 mg flat-dose cohorts who require a drug volume of 500 mL may have a total infusion time of up to 120 minutes in the absence of any history of infusion reaction. Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions and is optional and at the discretion of the Investigator after the second infusion (premedication is optional for all infusions for subjects in the NSCLC biomarker cohort being treated at the US NCI). If Grade $\geq$ 2 infusion reactions are seen during the first two infusions premedication should not be stopped. Steroids as premedication are not permitted. Special precautions for monitoring of subjects and management of infusion-related reactions / hypersensitivity including modifications of the infusion rate and stopping of trial drug are described in Section 6.5.4 and subsections.

The starting dose of MSB0011359C in the dose-escalation portion is 1 mg/kg (dose-escalation according to 3 + 3 design up to 30 mg/kg is intended) and the treatment cycle will be 2 weeks (14 days). The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48-hour intervals between subjects. The dose of MSB0011359C in the expansion will be determined from the dose-escalation portion of the trial.

For the dose-escalation cohorts (except for the 2400 mg flat-dose cohort), the dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration. Subjects will receive MSB0011359C once every 2 weeks until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced SD, PR, or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible.

Following safety and PK analysis of the Escalation cohorts, a flat dose of 1200 mg/infusion was chosen for all expansion cohorts, except for the NSCLC second-line cohort, in which 40 subjects will receive 500 mg/infusion and 40 subjects will receive 1200 mg/infusion.

For subjects who achieve SD, a PR or CR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Responsible (see Section 5.1.6). The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available. Subjects re-initiating treatment should be assessed according to the Schedules of Assessment for the Expansion portion of the trial starting at Week 1, Day 1 (see Table 2).

6.3 Assignment to Treatment Groups

The Investigator or delegate will assign a unique subject identifier number to eligible subjects in chronological order at the time of informed consent signature. Subject identifiers will be comprised of digits representing the trial number, the site number, and the subject number, which is allocated sequentially. Subject enrollment will be managed manually during the escalation phase and for the NSCLC biomarker cohort. Enrollment for other expansion cohorts will utilize an interactive web response system (IWRS).

NSCLC second-line cohort

Once the subject has provided a signed Informed Consent Form (ICF) and meets all inclusion and no exclusion criteria, the Investigator or delegate will request the dose group assignment using the IWRS. Qualified subjects will be randomized in a 1:1 ratio to receive either 500 or 1200 mg/infusion of MSB0011359C. The cohort is fully controlled by the IWRS, which assigns treatment individual (unique) vial numbers for each subject. The vial number is linked via the Good Manufacturing Practice qualified system to the corresponding treatment as well as to the subject. Allocation of subjects will not be stratified.

6.4 Noninvestigational Medicinal Products to be Used

In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions and is optional and at the discretion of the Investigator after the second infusion (premedication is optional for all infusions for subjects in the NSCLC biomarker cohort being treated at the US NCI). If Grade $\geq$ 2 infusion reactions are seen during the first two infusions premedication should not be stopped. This regimen may be modified based on local treatment standards and guidelines as appropriate. Steroids as premedication are not permitted.

As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock. MSB0011359C should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Infusion of MSB0011359C will be stopped in case of Grade $\geq$ 2 infusion-related, allergic, or anaphylactic reactions. Following MSB0011359C infusions, subjects must be observed for a minimum of 2 hours post end of infusion for potential infusion-related reactions, except note that during the first 2 doses in the escalation phase there will be a minimum 24-hour inpatient observation. Please see the guidelines for handling of infusion-related reaction in Section 6.5.4.1.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity reaction according to the NCI are found in Section 6.5.4.

Further precautions are provided in Section 6.5.4. For prophylaxis of flu-like symptoms, a non-steroidal anti-inflammatory drug (NSAID) for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of MSB0011359C IV infusion.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions (other than vitamins) and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of anaphylactic reactions, infusion-related reactions, and severe hypersensitivity reactions / flu-like symptoms and irAEs are described in Sections 5.1.7.2, 6.4, and 6.5.4.

Palliative radiotherapy delivered in a normal organ-sparing technique may be administered during the trial. The assessment of PD will not be based on the necessity for palliative radiotherapy.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had chemotherapy, radiotherapy (other than palliative radiotherapy delivered in a normal organ-sparing technique as described in Section 6.5.1), major surgery, or received another investigational agent within 28 days before the start of trial treatment.

The following treatments must not be administered during the trial:

- Immunotherapy including interferon, immunosuppressive drugs (for example, chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions, endocrine replacement therapy at low-dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short-term steroid use), or other experimental pharmaceutical products. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (that is, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. **Note:** for subjects with glioblastoma, steroid use is allowed.
- Adefovir.
- Prophylactic use of corticosteroids for infusion-related reactions is prohibited.
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).
- Blood transfusions and erythroid growth factors are not allowed during the 21-day DLT window during the escalation phase.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Medical Monitor may be contacted to discuss whether the IMP must be discontinued).

Medications other than those specifically excluded in this trial (as outlined in this section) may be administered for the management of symptoms associated with the administration of MSB0011359C as required. These might include analgesics, anti-emetics, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

6.5.3 Other Interventions

The following non-drug therapies must not be administered during the trial (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy)
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)
- Subjects should not abuse alcohol or other drugs during the trial.

6.5.4 Special Precautions

For subjects enrolled in this study prior to the declaration of the MTD or the dose to be used in the expansion phase of the study (in the case MTD is not reached), in-house observation in a hospitalized setting for at least 24 hours will occur for the first 2 doses administered to each subject (Table 5). To facilitate PK and biomarker sampling, subjects may remain in-house through an additional 24 hours if necessary. A nurse, nurse practitioner / physician's assistant, or physician will communicate with the first subject of each cohort after the first treatment to assess for any side effects on or after Day 5 but before enrolling a subsequent subject. Cohorts at a dose that has been cleared by the SMC will require a minimum of 48 hours between the first dose administration in the first subject and first dose in subsequent subjects.

Once the MTD / dose to be used in the expansion phase of the study has been declared there is no waiting period between dosing of subjects.

Table 5 Wait Periods Between Dosing of Subjects Within a Dose / Expansion Cohort

	Before MTD/Phase II Dose Declaration / Before Dose Clearance	Before MTD/Phase II Dose Declaration / After Dose Clearance[a]	After MTD/Phase II Dose Declaration
In-house (hospitalization) observation	24 hours	None	None
Wait period between first subject first dose and subsequent subjects in a cohort	5 days	48 hours	None

HCC = hepatocellular carcinoma; MTD = maximum-tolerated dose; SMC = Safety Monitoring Committee.

a Subjects in the HCC ascending-dose cohort may begin enrolling prior to declaration of the MTD / dose to be used in the expansion phase of the study by the SMC; however, the SMC must have cleared the starting dose for the HCC cohort as safe in the dose-escalation phase of the study.

As a routine precaution, subjects all enrolled in this trial (that is, both the dose-escalation and the expansion cohorts) must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents. At all times during MSB0011359C treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of MSB0011359C will be stopped in case of Grade $\geq$ 2 hypersensitivity, inflammatory response, or anaphylactic reaction. The treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI are outlined in Sections 6.5.4.1 and 6.5.4.2, respectively.

Investigators should also monitor subjects closely for potential irAEs, which may become manifest after several weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

6.5.4.1 Infusion-related Reactions

Infusion-related reactions, including hypersensitivity, are defined in this section.

A. Symptoms:
- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

B. Management (see Table 6)

Table 6 Treatment Modification for Symptoms of Infusion-related Reactions Caused by MSB0011359C

NCI-CTCAE Grade	Treatment Modification for MSB0011359C
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the MSB0011359C infusion rate by 50% and monitor closely for any worsening. • The total infusion time for MSB0011359C should not exceed 120 minutes
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop MSB0011359C infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and / or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the MSB0011359C infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately from MSB0011359C treatment and must not receive any further MSB0011359C treatment

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Additional Modifications for Subjects With Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion of IMP should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2-blocker antihistamines (for example, famotidine or ranitidine), in addition to premedication, for select subjects. However, prophylactic steroids are NOT permitted. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, with or without the addition of further medication to premedication, the infusion should be stopped and the subject removed from MSB0011359C treatment.

6.5.4.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

A. Symptoms
- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale / clammy skin
- Cyanosis.

B. Management
1. Epinephrine injection and IV dexamethasone
2. Patient should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
3. Alert intensive care unit for possible transfer if required.

For prophylaxis of flu-like symptoms, a NSAID, for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of MSB0011359C IV infusion.

6.5.4.3 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur.

Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 7.

Table 7 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue MSB0011359C therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay MSB0011359C therapy Symptomatic treatment	If improves to Grade 1: Resume MSB0011359C therapy If persists > 5 to 7 days or recur: 0.5 to 1 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue MSB0011359C therapy per protocol 1 to 2 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis Permanently discontinue IMP

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue MSB0011359C therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Consider delaying MSB0011359C therapy Consider 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life-threatening consequences	Delay or discontinue MSB0011359C therapy Consider skin biopsy Dermatology consult 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume MSB0011359C therapy (except in cases of Toxic Epidermal Necrolysis or Stevens-Johnson Syndrome)
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of MSB0011359C therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay MSB0011359C therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume MSB0011359C therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4 Permanently discontinue IMP

Grade of Pneumonitis (NCI-CTCAE v4.03)	Management	Follow-up
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue MSB0011359C therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) Permanently discontinue IMP
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue MSB0011359C therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay MSB0011359C therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume MSB0011359C therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy
For subjects with liver involvement at Baseline (Baseline AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0)	Continue MSB0011359C therapy	Continue liver function monitoring If worsens: Treat as Grades 3 to 4
Grades 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue MSB0011359C therapy Increase frequency of monitoring to every 1 to 2 days	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds:

For subjects with liver involvement at Baseline (Baseline AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0)	1 to 2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted Delay MSB0011359C therapy Increase frequency of monitoring to every 3 days	Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines Permanently discontinue IMP If returns to Baseline: Resume routine monitoring, consider resuming MSB0011359C therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy. If does not improve in > 3 to 5 days, worsens or rebounds: Discontinue MSB0011359C therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines Permanently discontinue IMP

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, creatine kinase-MB, brain natriuretic peptide) or cardiac imaging abnormalities suggestive of myocarditis	Withhold MSB0011359C therapy. Hospitalize. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.[a] Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start MSB0011359C therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue MSB0011359C. Guideline based supportive treatment as appropriate as per cardiology consult.[a] Methylprednisolone 1 to 2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).

a Local guidelines, or eg, European Society of Cardiology or American Heart Association guidelines

European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

American Heart Association guidelines website:

http://professional heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue MSB0011359C therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal laboratory / pituitary scan: Delay MSB0011359C therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal laboratory / pituitary MRI scan but symptoms persist: Repeat laboratories in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume MSB0011359C therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue MSB0011359C therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	
Renal irAEs		
Renal Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2	Repeat renal function laboratory tests / urine sediment every 2 to 3 days Stop treatment until return to baseline	
Renal dysfunction / immune-related nephritis	Evaluate renal function Consider biopsy to confirm nephritis and immune-related inflammatory process	If returns to Grade 2: Taper steroids over at least 1 month

	Discontinue subject from MSB0011359C therapy 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections	If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; IV = intravenous; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

6.5.4.4 TGFβ Inhibition Mediated Skin Reactions

Skin assessments are performed at Screening period and every 6 weeks for all subjects per Schedule of Activities (see Table 1**Error! Reference source not found.**).

Skin AEs, possibly due to TGFβ inhibition, including hyperkeratosis, KA, and/or cSCC, are AESIs and important identified risks for MSB0011359C. The distribution of lesions tends to be in sun-exposed areas.

Management guidelines for potential TGFβ inhibition mediated skin reactions are:

1. Discontinuation or interruption is not required in most cases. Continuation of treatment should be evaluated by the Investigator.
2. Emollients may continue to be used.
3. Diagnostic and treatment plan should be developed in collaboration between Investigator and dermatologist. In general, treatment of TGFβ mediated skin lesions such as hyperkeratosis, KA and cSCC should be based on local guidelines/SoC. Lesion evaluation should include excision biopsy of one representative lesion to confirm diagnosis.
4. Treatment and Follow-up for KA and cSCC will depend on number and localization of lesions.
   - For single lesions: Full excision may be recommended.
   - In case of multiple lesions or location not suitable for full excision, other treatment options may be offered by the dermatologist, such as:
     - Mohs surgery, cryotherapy, or other standard treatment options depending on the pathology
     - Use of retinoids, if recommended by dermatologist, may be considered after discussion with Medical Monitor.
5. Close clinical Follow-up for re-evaluation, resolution, or potential recurrence should be implemented.

6. Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing MSB0011359C.

Consult with study Medical Monitor, as needed, for management of TGFβ mediated skin lesions.

6.5.4.5 Anemia

Risk management measures in addition to routine laboratory tests will include:

- Subjects must enter the study with Hgb values at least 9 g/dL
- Routine monitoring of Hgb, red blood cells, and hematocrit will be performed every week up to Week 5 and then every 2 weeks thereafter (prior to treatment)
- Instructions for study treatment discontinuation or modification in case of anemia will be provided, briefly described here:
  - During the 21-Day-DLT period, a grade 3 Hgb decrease (< 8.0 g/dL) requires treatment discontinuation, unless it resolves to at least 9 g/dL within 14 days or changes in associated red blood cell parameters during such a Hgb decrease that resolve within 14 days without blood transfusion or erythroid growth factor use. However, if after the 21-Day-DLT period the subject experiences a Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use, this does not require treatment discontinuation
  - Especially if Hgb < 7 g/dL, the Investigator should consider blood transfusion
  - In case of any Hgb < 8 g/dL, the Investigator should use discretion to initiate anemia work up, including Coombs, haptoglobin, indirect bilirubin and peripheral smear, and prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR); Hgb, red blood cells, and hematocrit are to be closely monitored
- If a subject experiences significant anemia, then the amount of blood to be drawn may be reduced by not taking blood at selected time points for PD-L1 target occupancy, immunomonitoring, soluble factors, and TGFβ. The decision to reduce the time points for these biomarkers will be taken by the Investigator in consultation with the Medical Monitor. This will be documented. Blood will continue to be taken as scheduled for safety analyses, PK, and ADAs.

6.5.4.6 Bleeding Adverse Events

Mucosal/Non-tumor Bleeding

If a Grade 2 treatment-related TEAE improves to Grade ≤ 1 or completely resolves by the day before the next infusion, study intervention may be continued.

If a Grade 2 treatment-related non-tumor bleeding does not improve to Grade ≤ 1 or completely resolve by the day before the next infusion, but it is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.

For Grade 3 non-tumor bleeding, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.). In case of alternative explanations for the Grade 3 bleeding event, study treatment should be held until the event recovers to Grade ≤ 1.

For Grade 4 non-tumor bleeding, treatment must be permanently discontinued if no alternative explanation is identified.

Tumor Bleeding

For Grade ≥ 2 tumor bleeding, study treatment must be held until the event recovers to Grade ≤ 1. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

6.5.4.7 Alterations in Wound Healing or Tissue Damage Repair

Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed.

6.5.4.8 Dose Interruptions for Adverse Events Not Related to Study Drug

In case of Grade 3 and Grade 4 AEs not study drug related, the study treatment may be interrupted based on the Investigator assessment and the subject will be medically treated for the event.

If the AE reduces to a lower tolerable grade the study treatment might be resumed in the subsequent cycle. If the AE remains the same in spite of medical treatment until the next treatment (second cycle after the AE occurred) a discussion with the Medical Monitor should occur and consideration of a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment should be considered.

If upon the resumed study treatment the subject experiences the same AE this should be rediscussed with the Medical Monitor to assess permanent withdrawal from the study treatment.

Grade 3 and 4 laboratory abnormalities that do not have clinical significance do not require dose interruption.

6.6 Packaging and Labeling of the Investigational Medicinal Product

MSB0011359C freeze-dried formulation is presented at a concentration of 45 mg/vial in USP and Ph Eur type I glass vial closed with a rubber stopper and sealed with an aluminum crimping cap. MSB0011359C liquid formulation is presented at a 10 mg/mL concentration in a USP / Ph Eur type I 50R vial closed with a rubber stopper and sealed with an aluminum crimp seal closure. The stopper is made of elastomer complying with USP and Ph Eur. Vials are filled with 61.2 mL of drug product solution in order to allow an extractable volume of 60 mL.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. MSB0011359C will be packed in boxes containing a suitable number of vials. The information on the medication will be in accordance with approved submission documents.

MSB0011359C will be shipped in transport cool containers CCI [redacted] are monitored with temperature control devices.

6.7 Preparation, Handling, and CCI [redacted] of the Investigational Medicinal Product

MSB0011359C drug product should be stored CCI [redacted] until use. MSB0011359C must not be frozen and should be stored in the original packaging.

Additional instructions for the preparation, handling, storage, and disposal of MSB0011359C will be provided in the Pharmacy Manual.

MSB0011359C must not be used for any purpose other than the study. The administration of IMPs to subjects who have not been enrolled into the study is not covered by the study insurance.

The contents of the MSB0011359C vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

6.8 Investigational Medicinal Product Accountability

The Investigator (in Japan, head of the study site) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records. In Japan, the head of the study site can delegate the control of and accountability for the IMP to an investigational product storage manager.

- Upon receipt of IMP, the responsible person (in Japan, the head of the study site or the investigational product storage manager) will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the site.
  - The use of each dose by each subject.

- The disposition (including return, if applicable) of any unused IMP.
- Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled. In Japan, the head of the study site should maintain records that all IMPs provided were fully reconciled.

Unused IMP must not be used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

The Sponsor's Monitor will periodically collect and review the IMP accountability forms and where applicable, will check all returns (both unused and used containers) before arranging for their return or authorizing their destruction by the trial site.

At the conclusion or termination of this trial, trial site personnel and the Clinical Trial Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the Investigator / pharmacist / head of the study site or the investigational product storage manager.

It must be ensured at each trial site that the IMP is not used

- after the expiry date, and
- after the retest date unless the IMP is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

Destruction of used and unused study intervention(s) should be performed at site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible.

Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive IMP (MSB0011359C IV infusions) at the investigational site. Well-trained medical staff will monitor and perform the IMP administration. The information of each IMP administration including the date, time, and dose of IMP will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding IMP administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 1 administration of trial treatment for nonmedical reasons. If 1 treatment administration was missed and the interval between the subsequent treatment and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the Medical Monitor.

6.10 Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose 5% greater than the highest dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or nonserious), must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the Serious Adverse Event Paper Report Form following the same timelines as SAE reporting in addition to entering the Overdose in the AE section of the eCRF (see Section 7.4.1.4).

There are no known symptoms of MSB0011359C overdose to date. The Investigator should monitor closely for AEs should an overdose occur and use his or her clinical judgment in providing symptomatic / supportive care as medically indicated. There is no known antidote for MSB0011359C.

6.13 Medical Care of Subjects After End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs.

Upon withdrawal from the trial, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival and AEs as specified in Section 7.1.4.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete schedule of assessments for the dose-escalation phase of the trial is provided in Table 1 and for the expansion phase in Table 2. Sample collection for PK, CCI [redacted] provided in Table 3.

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2.

7.1.1 Screening and Baseline Procedures and Assessments

There is a 28-day washout / recovery period for prior anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative radiotherapy delivered in a normal organ-sparing technique], immune therapy, or cytokine therapy except for erythropoietin) and major surgery before the start of trial treatment (Section 5.3.2). Hematology, hemostaseology and chemistry laboratory samples must be drawn and reviewed within 48 hours prior to dose administration.

During the Screening period and before any trial-related investigations and assessments are started, the subjects will be asked to sign the relevant ICFs. The subjects' information that will be documented during Screening includes the demographic information (birth date, sex, ethnicity, and race) and the complete medical history, including the history of the tumor disease and prior anticancer therapies, previous medications (prior 30 days to signing of ICF), concomitant medications, and baseline medical condition (the information of concomitant medications and AEs will be monitored throughout the trial treatment period). Moreover, an Emergency Medical Support card will be handed out at the baseline assessments visit.

During Screening, subjects will undergo a complete physical examination, dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions), recording vital signs, including body weight and height (height only at Screening), 12-lead electrocardiogram (ECG), ophthalmology examination including slit lamp inclusive of the anterior segment and including visual acuity, and a determination of the ECOG PS (Appendix 1).

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, serum electrophoresis (dose escalation only), and full urinalysis. Adrenocorticotropic hormone (dose-escalation cohorts only with the exception of the backfill cohorts), antinuclear antibody (ANAs), rheumatoid factor (RF), free thyroxine (T4), and TSH will also be assessed at Screening.

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of child bearing potential and blood HBV and HCV testing will be performed for all Screening subjects as these conditions are trial entry exclusion criteria (except for subjects in the HCC expansion cohort, see Section 5.3.1.2). A female is considered of childbearing potential (that is fertile) following menarche and until becoming postmenopausal

unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral tubal occlusion or salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level (> 40 mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy.

The tumor evaluation (type / staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory [for trial sites in countries with radiation exposure control for subjects, only MRI may be used]; for subjects in the HCC cohort, contrast is mandatory) as well as tumor markers or any other established methods (see Section 7.2.5 for details). Bone scans should be performed as clinically indicated. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

Collection of tumor biopsies or archived surgical specimen will also be done during this period, if applicable (optional for the dose-escalation phase). Subjects in the expansion cohorts are required to provide tumor tissue samples, see Section 5.3.1 and Section 7.6.2.3 for details.

Baseline samples for ADAs (the term for ADA on the CRF is human-antihuman antibodies [HAHA]) and PGt (including changes in gene expression through gene expression evaluation should be collected [see Table 3]).

For subjects in the HCC 1200 mg ascending-dose cohort, HCC expansion cohort, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC second-line and anti-PD-1/PD-L1 failure cohorts, subject-reported outcomes / symptom severity assessments (PGIS, FHSI-8, EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-BN20, EORTC QLQ-HCC18-M, EORTC QLQ-OES18, EORTC QLQ-OV28, and/or NSCLC-SAQ) will be administered and completed by the subjects at Screening to collect baseline data about their symptom severity.

For subjects in the NSCLC second-line cohort, once a subject has been determined to meet all inclusion and no exclusion criteria, the subject will be randomized as described in Section 6.3. Study treatment should start ≤ 4 days after randomization.

7.1.2 Treatment Period

For this protocol, a cycle is defined as 14 days. In this trial, the treatment will be given until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a SD, PR, or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1.

For subjects who achieve SD, a PR or CR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation

course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor. The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. Moreover, for subjects in which BOR was SD, the Investigator should confirm no other reasonable treatment options are available. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to permanent treatment discontinuation of the initial MSB0011359C therapy. Prior to re-initiation of the study treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory samples must be drawn and results available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the Schedule of Assessment for the Expansion portion of the trial starting at Week 1, Day 1 (see Table 2).

Subjects will be asked to visit the investigational site according to the Schedules of Assessments (see Table 1 and Table 2). A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all study procedures (except on Day 2 and the Day 44-50 visit). In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days). Furthermore, if any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications.

7.1.2.1 Dose-Escalation Phase Treatment Period

For the dose-escalation phase, in-house observation in a hospitalized setting for at least 24 hours will occur for the first 2 MSB0011359C doses administered to each subject. The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48-hour intervals between subjects.

During the treatment period, the following assessments will be performed (see Table 1 and Table 3 for the detailed schedule):

- DLTs will be assessed during the first 21 days of trial treatment for each dose level of the dose-escalation part (see Section 5.1.3.2)
- AEs and concomitant medications will be documented at each study visit
- ECOG PS will be assessed prior to trial treatment on Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and according to Table 1 thereafter
- Physical examination will be performed prior to trial treatment on Day 1 (Week 1), Day 2, Day 8, and then prior to trial treatment according to Table 1
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days

- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions according to Table 1)
- Vital signs including body weight, will be assessed prior to trial treatment according to Table 1
- The 12-lead ECG will be assessed prior to and as soon as possible after infusion according to Table 1
- The laboratory hematology and hemostaseology tests will be assessed prior to trial treatment according to Table 1. Complete blood count results must be drawn and reviewed within 48 hours prior to dose administration
- Full serum chemistry (includes core chemistry) and core serum chemistry will be assessed prior to trial treatment according to Table 1. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration
- Samples for ANAs and RF according to Table 1
- Serum electrophoresis at Week 13 (Visit 10)
- A basic urinalysis will be performed prior to trial treatment according to Table 1
- A serum HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed according to Table 1. Results of the most recent pregnancy test should be available prior to next dosing (if applicable)
- The tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks, with a tumor assessment visiting time window of 5 days prior to dosing. For subjects continuing treatment beyond 12 months (in consultation with the Medical Monitor), tumor evaluations should take place every 12 weeks
- PK samples will be drawn as detailed in Table 3
- Free T4 and TSH will be measured prior to trial treatment according to Table 1
- ADA samples will be drawn as detailed in Table 3. The term for ADA on the CRF is human-antihuman antibodies (HAHA)
- PD-L1 target occupancy samples will be drawn as detailed in Table 3 (see Section 7.6.1)
- The immunomonitoring and soluble factors will be performed as detailed in Table 3 and as described in Section 7.6.1.2
- Samples for TGFβ1, 2 and 3 determination and quantification of phosphorylated SMAD2/3 (pSMAD2/3) will be drawn as detailed in Table 3 (note: Samples for pSMAD2/3 will not be collected in the backfill, 30 mg/kg, or 2400 mg flat-dose dose-escalation cohorts)
- Blood samples for gene expression evaluation will be collected according to Table 3 (prior to study drug administration where applicable)
- For subjects undergoing the optional Week 7 biopsy, the biopsy should be performed within 7 days after the Week 7 IMP administration (Table 3).

7.1.2.2 Expansion Phase Treatment Period

During the treatment period, the following assessments will be performed (see Table 2 and Table 3 for the detailed schedule):

- For subjects in the HCC 1200 mg ascending-dose cohort, HCC expansion cohort, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC second-line and anti-PD-1/PD-L1 failure cohorts, subject-reported outcomes / symptom severity assessments (PGIS, FHSI-8, EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-BN20, EORTC QLQ-HCC18-M, EORTC QLQ-OES18, EORTC QLQ-OV28, and/or NSCLC-SAQ) will be completed prior to any study-related procedures as indicated in Table 2
- AEs and concomitant medications will be documented in each study visit

  For any biopsies or other procedures resulting in tissue acquisition, official pathology reports must be filed and available for review if requested
- ECOG PS will be assessed prior to trial treatment on Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and according to Table 2 thereafter
- Physical examination will be performed prior to trial treatment on Day 1 (Week 1) and then prior to trial treatment according to Table 2
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions according to Table 2)
- Vital signs, including body weight, will be assessed prior to trial treatment according to Table 2
- The 12-lead ECG will be assessed according to Table 2
- The laboratory hematology and hemostaseology tests will be assessed prior to trial treatment according to Table 2. Complete blood count results must be drawn and reviewed within 48 hours prior to dose administration. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value, especially Hgb < 8 g/dL, routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly
- Full serum chemistry (includes core chemistry) and core serum chemistry will be assessed prior to trial treatment according to Table 2. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration
- A basic urinalysis will be performed prior to trial treatment every according to Table 2
- Samples for ANAs and RF according to Table 2
- A serum HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed according to Table 2. Results of the most recent pregnancy test should be available prior to next dosing (if applicable)

- The tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks, with a tumor assessment visiting time window of 5 days prior to dosing. For subjects continuing treatment beyond 12 months (in consultation with the Medical Monitor), tumor evaluations should take place every 12 weeks
- Mandatory on-treatment biopsy should be performed at Week 3 within 7 days after the Week 3 IMP administration for the NSCLC biomarker cohort. A mandatory Week 7 biopsy should be performed within 7 days after the Week 7 IMP administration for the NSCLC anti-PD-1 / PD-L1 failure (if possible) and the melanoma anti-PD-1 / PD-L1 failure cohort (if possible), as detailed in Table 3
- PK samples will be drawn as detailed in Table 3
- Free T4 and TSH will be measured prior to trial treatment according to Table 2
- ADA samples will be drawn as detailed in Table 3. The term for ADA on the CRF is human-antihuman antibodies (HAHA)
- The immunomonitoring and soluble factors will be performed as detailed in Table 3 as described in Section 7.6.1.2
- Samples for TGFβ determination will be drawn as detailed in Table 3
- Samples will be collected for viral load testing (HBV, HCV) and alpha-fetoprotein from subjects in the HCC second-line cohort (both ascending dose and expansion) as detailed in Table 3
- CCI [redacted]

Note: After at least 50 subjects across the dose escalation and all expansion cohorts have been evaluated for safety by the SMC, with appropriate SMC safety recommendation and if the Sponsor considers PK characterization adequate, then Day 2, 8, and 22 visits may be skipped.

7.1.3 End of Treatment

7.1.3.1 End-of-Treatment Visit

All subjects must undergo an End-of-Treatment visit after discontinuation of IMP for any reason. This visit should be performed on the day of or within 7 days after the decision to discontinue trial treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier (see Table 1 and Table 2). If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit. For all these subjects, the discontinuation visit consists of:

- For subjects in the HCC 1200 mg ascending-dose cohort, HCC expansion cohort, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC second-line and anti-PD-1/PD-L1 failure cohorts, subject-reported outcomes / symptom severity assessments (PGIS, FHSI-8, EORTC QLQ-C30, EORTC QLQ-CX24,

EORTC QLQ-BN20, EORTC QLQ-HCC18-M, EORTC QLQ-OES18, EORTC QLQ-OV28, and/or NSCLC-SAQ) will be completed prior to any study-related procedures as indicated in Table 2

- Documentation of AEs and concomitant medication
- Physical examination including vital signs and body weight
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions)
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis
- Samples for ANAs and RF (Escalation phase)
- ECOG performance status will be assessed
- Blood samples for gene expression evaluation (expansion cohorts only)
- Optional "progression biopsy" for subjects who had achieved at least SD for ≥ 12 weeks but who subsequently discontinued study treatment due to an assessment of PD. The optional "progression biopsy" will be used to evaluate the potential mechanisms of tumor escape.

7.1.4 Post-Treatment Follow-up

7.1.4.1 28-Day Safety Follow-up Visit

A Safety Follow-up visit is scheduled 4 weeks (28 ± 5 days) after the last administration of MSB0011359C but before any new therapy is started, if possible, whichever occurs earlier. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit. The 28-Day Safety Follow-up visit will comprise a full assessment for safety, immunogenicity, and tumor response as appropriate, which will include the following (refer to Table 1, Table 2, and Table 3):

- For subjects in the HCC 1200 mg ascending-dose cohort, HCC expansion cohort, esophageal adenocarcinoma, glioblastoma, melanoma, ovarian cancer, SCCHN, TNBC, cervical cancer, and NSCLC second-line and anti-PD-1/PD-L1 failure cohorts, subject-reported outcomes / symptom severity assessments (PGIS, FHSI-8, EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-BN20, EORTC QLQ-HCC18-M, EORTC QLQ-OES18, EORTC QLQ-OV28, and/or NSCLC-SAQ) will be completed prior to any study-related procedures as indicated in Table 2
- AEs, concomitant medications
- Vital signs and body weight

- Physical examinations
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions)
- The 12-lead ECG
- The laboratory hematology, hemostaseology, full serum chemistry, serum electrophoresis tests (dose escalation only), and full urinalysis
- ECOG performance status will be assessed
- The urine β-HCG pregnancy test (in females of childbearing potential)
- The tumor evaluation (only to be performed, if no disease progression was documented previously)
- Free T4 and TSH
- Samples for ANAs and RF (Expansion cohorts)
- PK sample
- ADA sample (see Section 7.7.1). The term for ADA on the CRF is human-antihuman antibodies (HAHA)
- The immunomonitoring and soluble factors will be performed as described in Section 7.6.1.2 and Section 7.6.2.2 and Table 1, Table 2, and Table 3
- Samples for TGFβ determination and pSMAD2/3 (dose-escalation phase only; note: Samples for pSMAD2/3 will not be collected in the backfill or 30 mg/kg dose-escalation cohorts) quantification as described in Table 3
- Samples for viral load testing (HBV, HCV) and alpha-fetoprotein (HCC second-line cohort, both ascending dose and expansion)
- Blood samples for gene expression evaluation for subjects with PD (dose-escalation cohorts only).

7.1.4.2 Safety Follow-up Visit

All subjects will have a subsequent visit scheduled 10 weeks (± 2 weeks) after the last administration of MSB0011359C. If another antineoplastic therapy is administered before the end of the 10-weeks period, the 10-Week Safety Follow-up visit might be conducted as a phone call without physical or laboratory assessments. Otherwise, the visit will include the following full assessment of safety parameters (refer to Table 1, Table 2, and Table 3):

- AEs that are deemed attributable to trial drug by the Investigator and concomitant medications (including further anti-cancer therapy) will be documented

- Vital signs and body weight will be measured
- Physical examination will be performed
- Eye signs and symptoms should be checked. If clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days
- Dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions)
- ECOG performance status will be assessed
- 12-lead ECG will be assessed
- Laboratory testing consisting of the following will be assessed:
  - Hematology, hemostaseology, full serum chemistry, and urinalysis
  - T4, and TSH levels
- Samples for ANAs and RF (Expansion cohorts)
- PK sample will be collected
- ADA sample. The term for ADA on the CRF is human-antihuman antibodies (HAHA)
- Samples for viral load testing (HBV, HCV; HCC second-line cohort, both ascending dose and expansion)
- A urine β-HCG pregnancy test (in women of child bearing potential) will be conducted.

Note: After at least 50 subjects across the dose escalation and all expansion cohorts have been evaluated for safety by the SMC, with appropriate SMC safety recommendation the 10-Week Safety Follow-up visit may be conducted by phone without the scheduled assessments.

7.1.4.3 Long-term Follow-up / Trial Termination

All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". In addition, all trial drug-related SAEs occurring after 28-Day Safety Follow-up visit and ongoing at the Safety Follow-up visit have to be followed up in the same manner.

Subjects without PD at the 28-Day Safety Follow-up visit will be followed up for disease progression (CT / MRI scans every 12 weeks with the first assessment 12 weeks after the previous tumor assessment [scheduled time point]) until PD.

After the 28-Day Safety Follow-up visit, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further anticancer therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of MSB0011359C.

After completion of the Follow-up period or at discontinuation of the trial, whatever is applicable / comes first, the appropriate eCRF section for Trial Termination must be completed.

7.1.5 Blood Consumption for Clinical Assessments

The overall amount of blood to be drawn from a single subject must not exceed 120 mL/day and 550 mL in an 8-week period for safety laboratory testing, pregnancy testing, PK analyses, CCI , and antibody evaluation.

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

7.2.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier
- Date of birth
- Sex
- Ethnicity
- Race.

7.2.2 Diagnosis of Tumor

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- Detailed history of the tumor, including histopathological diagnosis, grading and staging in accordance with the Union Internationale Contre le Cancer Tumor Node Metastasis Classification **at diagnosis** (UICC TNM)
  - The M category (M0 or M1) of the tumor at the time of study entry, based on screening assessments
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy, etc)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current cancer signs and symptoms and side effects from current and / or previous anticancer treatments
- Current cancer disease status
- BRCA, tumor HPV and tumor mismatch-repair status documentation, if known
- Smoking history (for NSCLC and cervical cancer expansion cohorts only).

7.2.3 Medical History

In order to determine the subject's eligibility to the trial, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant non-malignant diseases and treatments
- All medications taken and procedures carried out within 30 days prior to Screening

For the trial entry, all the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.4 Vital Signs and Physical Examination

Vital signs including body temperature, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest), body weight and height will be recorded at study entry.

Physical examinations will be performed according to Table 1 and Table 2. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted.

The ECOG PS will be documented during the Screening phase.

7.2.5 CT or MRI Scans for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory [for trial sites in countries with radiation exposure control for subjects, only MRI may be used]; for subjects in the HCC cohort, multiphase CT with contrast is mandatory) of the chest, abdomen, and pelvis (at a minimum and other established assessments of tumor burden if CT / MRI imaging is not sufficient for the individual subject; other regions as specifically required for specific tumor indications) will be performed within 28 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions and secondarily using mRECIST for subjects in the HCC cohort (see vendor manual). For subjects in the glioblastoma cohort, the assessment will be made according to RANO. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the Screening CT / MRI does not need to be performed.

A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT / MRI scan should be done if clinically indicated by development of new specific symptoms.

A bone scan should be done at Screening as clinically indicated.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening. The ECG will be recorded after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate

the heart rate, atrial-ventricular conduction, QR, QT, and corrected QT intervals, and possible arrhythmias.

The dose escalation and NSCLC biomarker cohorts must utilize digital ECGs. The ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The digital ECGs will also be electronically transferred to the central ECG laboratory to be read by a cardiologist. The result of the central read will be used for statistical evaluation of ECG data. For the NSCLC biomarker cohort, all ECGs after Week 13 are single ECGs obtained according to local procedure and will NOT be digitally uploaded. For all other expansion cohorts, ECGs are to be performed according to local procedures and will NOT be digitally uploaded.

Digital ECG uploading and central reading will not be used for the remaining expansion cohorts.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values will not be recorded as AEs unless they are the reason for discontinuation of the trial IMP due to AEs or are SAEs.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the trial, but also help to make sure that each enrolled subject fulfills all the trial entry criteria as listed in Section 5.3.1 and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3.2. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

For all subjects in all cohorts, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory [for trial sites in countries with radiation exposure control for subjects, only MRI may be used], for subjects in the HCC cohort, multiphase CT with contrast is mandatory) imaging of the chest / abdomen / pelvis (plus other regions as specifically required for specific tumor types) and other established assessments of tumor burden if CT / MRI imaging is insufficient for the individual subject. All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

A brain CT / MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter brain CT / MRI scan should be performed, if clinically indicated by development of new specific symptoms. A bone scan should be performed at Screening and beyond as clinically indicated. Skin metastasis can be used as target lesions according to RECIST 1.1 using measurements by caliper, if they fulfill RECIST 1.1 for target lesions as described below. The presence of new cutaneous lesions will be considered diagnostic of progression for RECIST 1.1, even if not imaged. For each subject, the Investigator will

designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and / or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments (refer to Table 1 and Table 2).

The foreseen treatment duration is until disease progression verified by a scan subsequent to the initial documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). **Before stopping the treatment, progressive disease should be confirmed by imaging 4 to 6 weeks (preferably 6 weeks, but not later) after progression has been diagnosed according to RECIST 1.1.** If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 6 weeks later should be considered before performing the 28-Day Safety Follow-up visit. Treatment may be continued despite progression according to RECIST 1.1 at any time if:

- There are no new symptoms or worsening of existing symptoms.
- There is no decrease in ECOG PS.
- The Investigator does not consider it necessary to administer a salvage therapy.

The treatment should be stopped immediately, if the subject does not tolerate MSB0011359C anymore or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression / deterioration.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation) and secondarily using mRECIST for subjects in the HCC cohort (see Section 7.3.2). For subjects in the glioblastoma cohort, the assessment will be made according to RANO.

- To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions according to RECIST 1.1 and secondarily using mRECIST for subjects in the HCC cohort. For subjects in the glioblastoma cohort, the assessment will be made according to RANO.

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed according to RECIST 1.1 or RANO for subjects with glioblastoma. **In the case of a PR or CR, a confirmatory CT or MRI scan must be done no sooner than 4 weeks (preferably at the scheduled 6-week interval).**

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

As outlined in Section 5.1, treatment should continue with the investigational drug and the subject may remain on study according to the Investigator's decision and in agreement with the subject in case of PD according to RECIST 1.1, mRECIST (HCC), or RANO (glioblastoma).

Subjects who have experienced SD, PR, or CR should continue treatment through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (see Section 5.1.6).

7.3.1 Immune-related Response Criteria

The irRECIST is only assessed by the independent radiology review, not as an Investigator assessment.

Below is a summary of irRECIST (for more comprehensive information, refer to Bohnsack 2014).

1. Total measured tumor burden (TMTB): Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the TMTB, and one combined assessment provided.

2. New Measurable Lesions: In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non-measurable tumor burden, but do not get measured.

3. irPR if no Target Lesions: If new measurable lesions appear in subjects with no target lesions at Baseline, irPD will be assessed. That irPD time point will be considered a new Baseline, and all subsequent time points will be compared with it for response assessment. An assessment of irPR is possible if the TMTB of new measurable lesions decreases by $\geq$ 30% compared with the first irPD documentation.

4. Non-Target Lesions: In alignment with RECIST 1.1, Baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

Example: A subject has multiple lung metastases, all smaller than 10 mm and selected as no-target lesions at Baseline. If, at a subsequent time point some of these non-target lesions increase and become > 10 mm, and 1 new lesion > 10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the Baseline selected non-target lesion that increased in size. Otherwise such an increase would make persisting non-target lesions switch into the new measurable lesion category, which would be inaccurate, as the lesion existed at Baseline.

5. irPD Based on Non-Target Lesions: In irRECIST, a substantial and unequivocal increase of non-target lesions is indicative of progression.

6. irPD Based on New Non-Measurable Lesions: According to irRECIST, the reviewer may assign irPD for the subject with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening.

7. irPD Confirmation: Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended, especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

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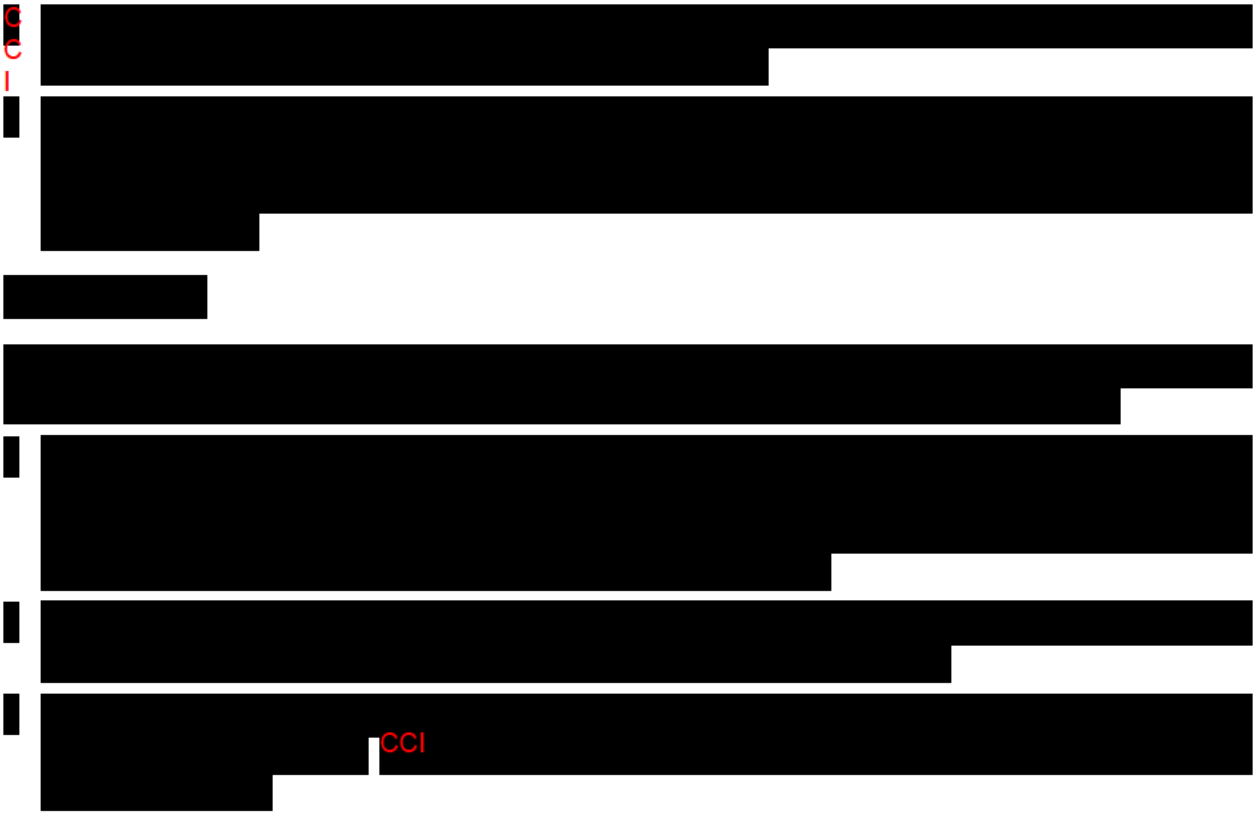

OVERALL RESPONSE ASSESSMENT

Any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

7.3.3 Response Assessment in Neuro-Oncology

The text below was obtained from Wen 2010.

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the nonenhancing component, should be performed. The product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

MEASURABLE AND NONMEASURABLE DISEASE FOR CONTRAST-ENHANCING LESIONS

Measurable disease is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. In the event the MRI is performed with thicker slices, the size of a measurable lesion at Baseline should be two times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at Baseline. In general, lesions such as a cyst or surgical cavity should be considered nonmeasurable unless there is a nodular component measuring

≥ 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

NUMBER OF LESIONS

If there are multiple contrast-enhancing lesions, a minimum of the 2 largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. A maximum of 5 of the largest lesions may be measured. In general, the largest enlarging lesion(s) should be selected; however, emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected.

For subjects who have multiple lesions of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded.

DEFINITION OF RADIOGRAPHIC RESPONSE

Radiographic response should be determined in comparison with the tumor measurement obtained at pretreatment Baseline for determination of response, and the smallest tumor measurement at either pretreatment Baseline or after initiation of therapy should be used for determination of progression. Table 9 lists the criteria for radiographic changes after therapy. In the event that the radiographic changes are equivocal and it is unclear whether the subject is stable or has developed progressive disease, it is permissible to continue treatment and observe the subject closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. All measurable and nonmeasurable lesions should be assessed using the same techniques as at Baseline. Ideally, subjects should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Table 9 Criteria for Response Assessments Incorporating MRI and Clinical Factors

Assessment	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. **Note:** Subjects with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progressive disease	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
* Stable doses of corticosteroids include subjects not on corticosteroids.

The definition of clinical deterioration is left to the discretion of the Investigator, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any Baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the ECOG PS and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

MULTIFOCAL TUMORS

For multifocal lesions, progressive disease is defined as ≥ 25% increase in the sum of products of perpendicular diameters of all measurable lesions compared with the smallest tumor measurements after initiation of therapy (Table 9). The appearance of a new lesion or unequivocal progression of nontarget lesions will also be considered progression. Partial response is defined as ≥ 50% decrease, compared with Baseline, in the sum of products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

Table 10 summarizes the radiological and clinical criteria for tumor response assessments according to RANO.

Table 10 Summary of Proposed RANO Response Criteria

Criteria	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1 gadolinium enhancing disease	None	≥ 50% decrease	< 50% decrease but < 25% increase	≥ 25% increase
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	Not applicable**
Clinical status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for response	All	All	All	Any*

FLAIR = fluid-attenuated inversion recovery; RANO = Response Assessment in Neuro-Oncology.
* Progression occurs when this criterion is present.
** Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and eyes signs and symptoms, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). Given the intended MoA, particular attention will be given to AEs that may follow the enhanced T-cell activation such as persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, uveitis and other inflammatory eye conditions, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis. Furthermore, due to the anti-TGFβ activity, particular attention will also be given to events associated with, anemia, and rash with hyperkeratosis / keratoacanthoma and squamous cell carcinoma of the skin.

The reporting period for AEs is described in Section 7.4.1.3.

The safety assessments will be performed according to the Schedules of Assessments (see Table 1 and Table 2).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of 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 product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition / illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as an AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE v4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity / intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event Grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE as per Section 7.4.1.4; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the MSB0011359C include, but may not be limited to, temporal relationship between the AE and the MSB0011359C, the known safety profile of MSB0011359C, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP. The AE could not medically (pharmacologically / clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. The AE could medically (pharmacologically / clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

7.4.1.1.1 Adverse Drug Reaction (ADR)

An ADR is defined in this trial as any AE assessed as related to MSB0011359C by the Investigator and / or Sponsor.

7.4.1.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe),
- Requires inpatient hospitalization or prolongs an existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect, or
- Is otherwise considered to be medically important.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such 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 type of new (secondary) cancer including squamous cell cancer of the skin should be considered as medically important condition.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a SAE, as described in Section 7.4.1.4.

Events That Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.4.1.1.3 Events Not to Be Considered as AEs / SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

AE / SAEs Observed in Association With Disease Progression

Progression of the disease / disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an AE / SAE, unless the subject's general condition is more severe than expected and / or unless the outcome is fatal within the AE reporting period (as defined in Section 7.4.1.3).

7.4.1.1.4 Predefined AEs of Special Interest (AESI) for Safety Monitoring

The AESIs for MSB0011359C are summarized in Section 3.5. The reporting of AESI is defined in Section 7.4.1.4.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF.

All SAEs and all nonserious AEs of special interest must be additionally documented and reported using the appropriate SAE Report Form or the AESI Report Form, respectively as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. If an AE constitutes a DLT this has to be documented accordingly.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date and time of first signature of informed consent) and continues through the trial's 28-Day Safety Follow-up visit, defined as 28 days (± 5 days) after last trial drug administration. After the 28-Day Safety Follow-up visit only AEs that are deemed attributable to trial drug by the Investigator should be documented until the 10-Week Safety Follow-up visit, defined as 10 weeks (± 2 weeks) after the last trial drug administration.

Any SAE assessed as related to MSB0011359C must be reported whenever it occurs, irrespective of the time elapsed since the last administration of MSB0011359C.

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum 24 hours after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form following specific completion instructions.

In exceptional circumstances, a SAE (or follow-up information) may be reported by telephone; in these cases, SAE Report Form must be provided immediately thereafter.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome final evaluation, other records where needed) or to any question the Sponsor or designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a ***nonserious*** Grade $\geq$ 3 AESI, the Investigator must complete the AESI Report Form and provide it to the Sponsor / designee immediately (within 24 hours) following the specific completion instructions. Serious AESIs have to be reported in an expedited manner as SAEs as outlined above. For Grade 1 and Grade 2 nonserious AESIs, the AESI Report Form should be provided to the Sponsor / designee within 5 working days following the specific completion instructions.

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT (see Section 5.1.3.3) has to be recorded in the eCRF within 24 hours after becoming aware of the event. Serious DLTs have to be reported in an expedited manner as SAEs as outlined above.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees / Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC / IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor or designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's / IRB's approval / favorable opinion to continue the trial". In particular and in line with respective regulations, the Sponsor / designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or designee will provide appropriate Safety Reports directly to the concerned lead IEC / IRB and will maintain records of

these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC / IRB of any Safety Reports provided by the Sponsor or designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs / SUSARs / Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance.

7.4.1.6 Monitoring of Subjects With Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the 28-Day Safety Follow-up visit. After the 28-Day Safety Follow-up visit, only AEs that are deemed attributable to the trial drug by the Investigator should be documented until the 10-Week Safety Follow-up visit, defined as 10 weeks (± 2 weeks) after the last trial drug administration.

All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". In addition, all trial drug-related SAEs occurring after the 28-Day Safety Follow-up visit and ongoing at the Safety Follow-up visit must be followed up in the same manner. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs; however, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page / section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must also notify the Sponsor or designee in an expedited manner of any pregnancy using the Paper Pregnancy Report Form, which must be transmitted according to the same timelines as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor or designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child / Fetus Adverse Event Report Form if the child / fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor or designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be taken from non-fasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site and relevant results must be drawn and checked before administration of MSB0011359C. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the tests listed in Table 11 will be taken from non-fasted subjects during the Screening phase, at the 28-Day Safety Follow-up visit, and during the treatment phase as specified in the Schedules of Assessments (Table 1 and Table 2). Complete blood count and core serum chemistry must be checked within 48 hours prior to each dose administration.

Serum electrophoresis, ACTH (dose-escalation cohorts only), ANA, RF, T4, TSH, and urinalysis will be assessed at the time points defined in the Schedules of Assessments (Table 1 and Table 2). If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 7.1.1.

Table 11 Required Laboratory Panel Tests

Full Chemistry	Hematology
Albumin	Absolute lymphocyte count
Alkaline phosphatase*	Absolute neutrophil count
Alanine aminotransferase *	Hematocrit
Amylase	Hemoglobin
Aspartate aminotransferase *	Platelet count
Gamma-glutamyltransferase	RBC count
Blood urea nitrogen / total urea*	White blood cell count and differential count
Calcium*	Red blood cell morphology**
Chloride*	Reticulocytes
Cholesterol	Mean corpuscular hemoglobin
Creatine kinase	Mean corpuscular volume
Creatinine*	Mean corpuscular hemoglobin concentration
C-reactive protein	
Glucose*	**Hemostaseology**
Lactate dehydrogenase	Activated partial thromboplastin time
Lipase	Prothrombin time / international normalized ratio
Phosphorus / phosphates*	
Magnesium*	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and 28-Day Safety Follow-up visits and a basic urinalysis prior to each administration of the IMP.
Potassium*	
Sodium*	
Total bilirubin / indirect bilirubin*	
Total protein	
Uric acid	Totality of binding ADAs
Triglycerides	AFP (HCC cohort only)
	ACTH (dose-escalation cohorts only), ANA, RF, TSH, and T4
Hormone Follicle-stimulating hormone (if applicable)	**Hepatitis Screening**[a] Hepatitis B surface antigen, hepatitis B core antibody Hepatitis B DNA (quantitative PCR)[a] Hepatitis C Antibody, Hepatitis C RNA (quantitative PCR) [a] Hepatitis D antibody[b]

ACTH=adrenocorticotropic hormone; ADA=antidrug antibody; ANA=antinuclear antibody; HCC = hepatocellular carcinoma; IMP=Investigational Medicinal Product; PCR = polymerase chain reaction; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; T4=free thyroxine.

* Core serum chemistries

** Only in case of anemia onset assessed as related to study treatment

a If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA (PCR); if hepatitis B core antibody positive alone, then reflex to quantitative hepatitis B DNA (PCR); if hepatitis C antibody positive, then reflex to quantitative hepatitis C RNA (PCR). If subject is positive for hepatitis B or C, then viral load will be followed by quantitative PCR according to Table 3.

b If hepatitis B surface antigen or hepatitis B DNA positivity at Screening then must check for hepatitis D status (hepatitis D antibody).

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

The ECOG PS will be assessed at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1 and Table 2) and documented in the eCRF.

Body weight will be measured at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1 and Table 2) and documented in the eCRF. Body height will be measured at Screening only.

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1 and Table 2) and documented in the eCRF (detailed description in Section 7.1). Any abnormalities arising or worsening after the signing of the ICF should be documented in the eCRF Adverse Event section (see Section 7.4.1). Abnormal findings are to be reassessed at subsequent visits.

An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

Digital 12-lead ECGs will be recorded in triplicate at Screening and at trial visits as indicated in the Schedules of Assessments (Table 1 and Table 2) until Week 13 (Visit 10). Subsequent ECGs will be obtained as single recordings. For immediate safety assessments, 1 ECG will be locally analyzed at each time point (see Section 7.2.6). All ECGs obtained in triplicate will be formally analyzed to evaluate whether MSB0011359C has any effects on cardiac electrophysiology, and in particular repolarization. Although preclinical data shows no cardiovascular signal, weekly ECG assessments with triplicates and digital recording are justified due to the need to characterize exposure / QTc relationships to facilitate future clinical rationale.

All newly diagnosed or worsening conditions, signs and symptoms observed since Screening, whether related to trial treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, serum β-HCG pregnancy test will be carried out during the Screening phase. A urine or serum β-HCG test will be performed according to Table 1 and Table 2 during the treatment phase, at the 28-Day Safety Follow-up visit, and at the Safety Follow-up visit. Results of the most recent pregnancy test should be available prior to the next dosing of IMP. Subjects who are postmenopausal (age-related amenorrhea $\geq$ 12 consecutive months and if needed FSH > 40 mIU/mL [in the postmenopausal range] as outlined in Section 7.1.1), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.

7.5 Pharmacokinetics

7.5.1 Dose Escalation Phase

Pharmacokinetic parameters include AUC from the time of dosing to the time of the last observation (AUC_{0-t}), AUC from the time of dosing extrapolated to infinity ($AUC_{0-\infty}$), terminal elimination rate constant (λ_z), C_{max}, time to reach maximum concentration (t_{max}), minimum serum concentration observed postdose (C_{min}), and $t_{1/2}$ (for definitions, see Section 8.5.3.2). Blood samples for the analysis of serum concentrations of MSB0011359C will be drawn in all subjects according to the Schedule of Assessments (Table 1).

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7.5.2 Expansion Phase

Pharmacokinetic parameters are described in Section 8.5.3.2. Blood samples for the analysis of serum concentrations of MSB0011359C will be drawn in all subjects according to the Schedule of Assessments (Table 3).

7.5.3 Body Fluid

Whole blood (3.5 mL per sample) will be collected for PK assessments. Post-infusion samples should be drawn from a site other than the infusion site (that is, the contralateral arm) on the days of infusion. If the infusion is interrupted, the reason for interruption and the exact infusion times will be documented on the eCRF.

The total amount of blood taken during the first 8 weeks of the trial will not exceed the total of 550 mL and during the first 85 days will not exceed the total of 650 mL.

Further details will be summarized in the Laboratory Manual.

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7.7 Other Assessments

7.7.1 ADA Analysis

The blood sample for Baseline ADA analysis will be collected before trial treatment start. Further serum samples for ADA analysis will be collected as indicated in the Schedules of Assessments (Table 3).

For subjects who achieve a CR on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, ADA samples will be drawn prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation.

Samples positive for ADAs will be re-analyzed to determine the titer.

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7.7.3 Health-related Quality of Life

For subjects in the melanoma, SCCHN, and TNBC cohorts only, symptom severity will be assessed using the PGIS and select items from the EORTC QLQ-C30 as indicated in the Schedule of Assessments (Table 2).

PGIS: The PGIS is an in-house questionnaire to assess how the subject rates their overall symptom severity (How would you rate the overall severity of your symptoms over the past 7 days – none, mild, moderate, severe, very severe).

EORTC QLQ-C30: The EORTC QLQ-C30 is a 30-item patient-reported outcome questionnaire created to measure broad functioning, symptoms, and health-related quality of life issues across all types of cancers (Aaronson 1991). A subset of the EORTC QLQ-C30 items have been selected for administration to reduce patient burden while allowing for key tumor-related and metastasis-related symptoms to be assessed. For melanoma and SCCHN, the selected EORTC QLQ-C30 items measure fatigue (3 items), pain (2 items), and loss of appetite (1 item). For TNBC, the selected EORTC QLQ-C30 items measure fatigue (3 items), pain (2 items), dyspnea (1 item), and loss of appetite (1 item). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the HCC 1200 mg ascending-dose cohort, symptom severity will be assessed using a generic question to assess severity of symptoms (PGIS) and a cancer-specific instrument for the assessment of hepatobiliary symptoms (FHSI-8) as indicated in the Schedules of Assessments (Table 2).

FHSI-8: The FHSI-8 is a patient-reported outcome questionnaire designed to assess symptoms in patients with pancreatic and hepatobiliary cancers (Yount 2002). It is an 8-item index pain (3 items), fatigue (2 items), weight loss, nausea, and jaundice, with each item scored on a 5-point scale (0 = not at all; 4 = very much).

For subjects in the HCC expansion cohort, symptom severity will be assessed using the PGIS and a modified version of a cancer-specific instrument for the assessment of hepatobiliary symptoms (EORTC QLQ-HCC18-M) as indicated in the Schedules of Assessments (Table 2).

EORTC QLQ-HCC18-M: The EORTC QLQ-HCC18-M is a modified version of the EORTC's HCC-specific module (Blazeby 2004). It consists of 17 patient-reported items intended provide comprehensive HCC-related symptom coverage while minimizing patient assessment burden. The EORTC QLQ-HCC18-M includes 7 items from the EORTC QLQ-C30 measuring dyspnea (1 item), fatigue (3 items), loss of appetite (1 item), and nausea and vomiting (2 items). The EORTC QLQ-HCC18-M includes an additional 10 items from the EORTC's HCC-specific module measuring sense of taste (1 item), wasting (1 item), abdominal bloating (1 item), jaundice (1 item), pruritus (1 item), shoulder pain (1 item), abdominal pain (1 item), fever (2 items), and early satiety (1 item). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the esophageal adenocarcinoma cohort only, symptom severity will be assessed using the PGIS, select items from the EORTC QLQ-C30, and select items from the EORTC QLQ-OES18 as indicated in the Schedule of Assessments (Table 2). For the esophageal adenocarcinoma cohort, the selected EORTC QLQ-C30 items measure fatigue (3 items) and pain (2 items).

EORTC QLQ-OES18: The EORTC QLQ-OES18 is an 18-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to esophageal cancer (Blazeby 2003). A subset of the EORTC QLQ-OES18 items have been selected for administration in the esophageal adenocarcinoma cohort to reduce patient burden while allowing for key tumor-related symptoms to be assessed. The selected EORTC QLQ-OES18 items measure dysphagia (3 items) and reflux pain (2 items). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the glioblastoma cohort only, symptom severity will be assessed using the PGIS and select items from the EORTC QLQ-BN20 as indicated in the Schedule of Assessments (Table 2).

EORTC QLQ-BN20: The EORTC QLQ-BN20 is a 20-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to brain cancer (Taphoorn 2010). A subset of the EORTC QLQ-BN20 items have been selected for administration in the glioblastoma cohort to reduce patient burden while allowing for key functional impacts of the primary tumor to be assessed. The selected EORTC QLQ-BN20 items measure motor dysfunction (3 items), communication deficit (3 items), and drowsiness (1 item). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the ovarian cancer cohort only, symptom severity will be assessed using the PGIS, select items from the EORTC QLQ-C30, and select items from the EORTC QLQ-OV28 as indicated in the Schedule of Assessments (Table 2). For the ovarian cancer cohort, the selected EORTC QLQ-C30 items measure fatigue (3 items), pain (2 items), and dyspnea (1 item).

EORTC QLQ-OV28: The EORTC QLQ-OV28 is a 28-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to ovarian cancer (Greimel 2003). A subset of the EORTC QLQ-OV28 items have been selected for administration in the ovarian cancer cohort to reduce patient burden while allowing for key metastasis-related symptoms to be assessed. The selected EORTC QLQ-OV28 items measure abdominal / gastrointestinal symptoms (6 items). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the cervical cancer cohort only, symptom severity will be assessed using the PGIS, select items from the EORTC QLQ-C30, and select items from the EORTC QLQ-CX24 as indicated in the Schedule of Assessments (Table 2). For the cervical cancer cohort, the selected EORTC QLQ-C30 items measure fatigue (3 items), pain (2 items), dyspnea (1 item), and loss of appetite (1 item).

EORTC QLQ-CX24: The EORTC QLQ-CX24 is a 24-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to cervical cancer (Greimel 2006). A subset of the EORTC QLQ-CX24 items have been selected for administration in the cervical cancer cohort to reduce patient burden while allowing for key metastasis-related symptoms to be assessed. The selected EORTC QLQ-CX24 items measure lymphedema (1 item) and lower back pain (1 item). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

For subjects in the NSCLC second-line and anti-PD-1/PD-L1 failure cohorts only, symptom severity will be assessed using the PGIS and the NSCLC-SAQ as indicated in the Schedule of Assessments (Table 2).

NSCLC-SAQ: The NSCLC-SAQ and a 7-item patient-reported outcome questionnaire created to measure the cardinal symptoms of NSCLC (McCarrier 2016). Items measure cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 loss). Each of these items is rated in terms of symptom severity or frequency on a 5-point response scale (1 = none or never; 5 = very severe or always).

8 Statistics

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8.1.1 Dose Escalation

The sample size for the dose-escalation part of the trial is not based on any statistical assumptions; rather, it follows the "3 + 3 rule," a well-established methodology in the design of dose-finding trials in oncology.

This trial plans for up to 6 cohorts (1, 3, 10, 20, and 30 mg/kg, and 2400 mg flat dose) of 3 subjects to be treated at each escalating dose level and with typical DLT driven expansions to 6 subjects and at the MTD. After the appearance of a single DLT, the cohort for that dose level will be expanded to 6 subjects. Therefore, the number of subjects enrolled in the dose-escalation phase of the trial will depend on the number of dose escalation steps needed to reach the MTD.

After the 1 and 3 mg/kg cohorts have completed the DLT evaluation period, a PK / CCI analysis will be performed. Depending on the results of this analysis for PBMC PD-L1 receptor occupancy, a decision will be made to initiate up to 2 cohorts of 3 subjects each, one at 0.1 mg/kg and one at 0.3 mg/kg, which will increase on the second dose and all subsequent doses to a 1200 mg/infusion flat dose. No DLT evaluations will be performed in this flexible cohort.

After the MTD has been reached or the 20 mg/kg cohort has been declared by the SMC as the highest non-MTD dose assessed, then further PK/CCI analyses will be performed. If deemed necessary, the 1, 3, 10, and 20 mg/kg cohorts may each enroll up to an additional 10 subjects (up to 40 total) for the purpose of PK / CCI modeling. On the second dose and all subsequent doses, the 1 mg/kg cohort may increase to a 1200 mg/infusion flat dose. No DLT evaluations will be performed in these supplemental cohorts.

With the safety of the 30 mg/kg cohort established, a fixed dose cohort of 2400 mg once every 2 weeks will be enrolled in a 3 + 3 design with SMC evaluation after the first 3 subjects.

Accordingly, the expected total sample size in the dose-escalation part of the trial will be between 3 and 82 subjects.

8.1.2 Expansion Cohorts

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Table 12 The 95% Exact (Clopper-Pearson) Confidence Intervals for ORR Based on 30 Enrolled Subjects

ORR	95% Exact Confidence Interval
0.20	(0.077, 0.386)
0.30	(0.147, 0.494)
0.40	(0.227, 0.594)
0.50	(0.313, 0.687)
0.60	(0.406, 0.773)
0.70	(0.506, 0.853)

HCC ascending-dose cohort

In order to further assess the tolerability and safety of MSB0011359C in subjects with HCC, up to 36 subjects may be enrolled in the ascending dose part of the HCC cohort. Six subjects will be enrolled at 3 mg/kg once the 3 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC. Thirty subjects will be enrolled at a 1200 mg flat dose once the 20 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC.

HCC second-line or sorafenib-intolerant cohort

Up to 70 subjects will be enrolled in the HCC second-line or sorafenib-intolerant cohort at the dose selected by the SMC during the dose-escalation part of the trial, for the purpose of assessing efficacy based on the BOR. An initial enrollment of 30 subjects will accrue if > 6 of 30 subjects in the HCC 1200 mg flat-dose ascending-dose cohort have a response (that is an ORR of at least 20%). The primary analysis will be 24 weeks after the 60th subject started treatment. The analysis will include the 30 subjects from the HCC 1200 mg flat-dose ascending-dose cohort and 30 subjects from the HCC second-line or sorafenib-intolerant cohort (assumes a similar target population as per the inclusion criteria). An additional 40 subjects may subsequently be enrolled in order to gather additional safety data.

With 60 subjects treated (30 subjects from the HCC 1200 mg flat-dose ascending-dose cohort and 30 subjects from the HCC second-line or sorafenib-intolerant cohort), the study has approximately 88% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 35% at the 10% type I error rate (1-sided).

NSCLC anti-PD-1 / anti-PD-L1 failure cohort

With 80 subjects treated, the study has approximately 92% and 99% power to rule out a ≤ 5% ORR (null hypothesis) when the true ORR is 15% and 20%, respectively, at the 5% type I error rate (1-sided).

Melanoma anti-PD-1 / anti-PD-L1 failure cohort

The goal of this cohort is an exploration of anti-PD-L1 retreatment and initial clinical responses as a way to show confidence in the proof-of-mechanism of the addition of TGFβ inhibition to the anti-PD-L1 mechanism. With 30 subjects who were treated with prior anti-PD-1 / anti-PD-L1 therapy, the study has 87% power to rule out a 5% ORR when the true ORR is 20% with 1-sided 0.1 alpha.

NSCLC second-line cohort

With 30 second-line subjects treated at 1200 mg/infusion, the study has approximately 82% power to rule out a ≤ 20% ORR (null hypothesis) when the true ORR is 40% at the 10% type I error rate (1-sided).

An interim analysis will occur when the 30 subjects are evaluable for response assessment at 12 weeks (that is, have either completed the second tumor reassessment at Week 12 or discontinued the study before Week 12). If ≤ 4 responders are observed at the interim analysis, no further subjects will be enrolled into the NSCLC second-line cohort.

Pancreatic adenocarcinoma, CRC, and cervical cancer cohorts

With 30 subjects treated, the study has approximately 79% power to rule out a ≤ 10% ORR (null hypothesis) when the true ORR is 25% at the 10% type I error rate (1-sided).

Ovarian cancer, TNBC, and esophageal adenocarcinoma cohorts

With 30 subjects treated, the study has approximately 87% power to rule out a ≤ 15% ORR (null hypothesis) when the true ORR is 35% at the 10% type I error rate (1-sided).

Glioblastoma cohort

With 30 subjects treated, the study has approximately 97% power to rule out a ≤ 50% DCR (null hypothesis) when the true DCR is 80% at the 5% type I error rate (1-sided).

SCCHN cohort

With 30 subjects treated, the study has approximately 87% power to rule out a ≤ 15% ORR (null hypothesis) when the true ORR is 35% at the 10% type I error rate (1-sided).

All expansion cohorts

Except for the glioblastoma cohort, the primary efficacy endpoint for the dose expansion-part of the trial is the confirmed BOR according to RECIST 1.1 as adjudicated by the Independent Endpoint Review Committee (IRC) and will be evaluated by confirmed ORR. For glioblastoma, the primary endpoint will be disease control.

For each cohort separately (except for the HCC cohort), upon continuation of the cohort up to the targeted sample size, the primary analysis will occur 24 weeks after the start of treatment in the

last subject enrolled. For the HCC cohort, the primary analysis will be after 60 subjects (including 30 subjects from the ascending dose and 30 subjects from the second line expansion cohort).

The total sample size for the expansion cohorts is expected to be up to approximately 566 subjects.

8.2 Randomization

NSCLC second-line cohort

Qualified subjects will be randomized at a 1:1 ratio to receive either 500 or 1200 mg/infusion MSB0011359C using permuted block randomization. Randomization will not be stratified. Randomization will occur upon completion of the Screening procedures and determination of subject eligibility as described in Section 6.3.

Not applicable for subjects not included in the NSCLC second-line cohort.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints for the dose-escalation part of the trial are the:

- Number, severity, and duration of TEAEs according to the NCI-CTCAE v4.03
- Number, severity and duration of treatment-related AEs for all dose groups / indications according to CTCAE v4.03
- Occurrence of DLTs during the first 3 weeks (21 days) of treatment in the dose-escalation part of the trial

Except for the glioblastoma cohort, the primary efficacy endpoint for the dose-expansion part of the trial is the confirmed BOR according to RECIST 1.1 as adjudicated by the IRC (Section 2.2.2) and will be evaluated by confirmed ORR. For glioblastoma, the primary endpoint will be disease control according to RANO as adjudicated by the IRC.

8.3.2 Secondary Endpoints

The secondary endpoints for the dose-escalation part of the trial are the:

- MSB0011359C PK profile (for dose escalation), including AUC, C_{max}, C_{min}, and $t_{1/2}$
- Serum titers of antiMSB0011359C antibodies
- BOR according to RECIST 1.1 per Investigator assessment

The secondary endpoints for the expansion part of the trial are the:

- MSB0011359C PK profile (for dose escalation), including AUC, C_{max}, C_{min}, and $t_{1/2}$
- Serum titers of antiMSB0011359C antibodies

- Number, severity, and duration of TEAEs and treatment-related TEAEs according to the NCI-CTCAE v4.03
- BOR according to RECIST 1.1 per Investigator assessment

[redacted]

[redacted]

8.3.4 Safety Endpoints

Besides the endpoints specified as primary and secondary variables the following endpoints will be evaluated:

- Laboratory parameters

- Eye signs and symptoms
- Vital signs
- ECG parameters.

8.4 Analysis Sets

The following analysis sets will be defined separately for the dose-escalation part and the expansion cohorts in this trial, as applicable:

- **DLT Analysis Set (dose-escalation part):** All subjects with data used for implementing the dose-escalation schedule. These subjects will have received all study treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.
- **Safety Analysis Set:** All subjects who receive at least 1 dose of trial treatment.
- **Full Analysis Set:** All subjects who receive at least 1 dose of trial treatment. For the NSCLC second-line cohort, the Full Analysis Set includes all subjects randomized.
- **PK Analysis Set:** All subjects who complete at least 1 infusion of IMP, and who provide at least 1 sample with a measurable concentration of MSB0011359C.
- **Immunogenicity Analysis Set:** All subjects who complete at least 1 infusion of IMP, and who have provided the blood sample prior to any MSB0011359C treatment and at least one post-treatment serum sample.
- CCI [redacted]

8.5 Description of Statistical Analyses

Full details of the planned analyses will be described in the trial Statistical Analysis Plan (SAP), separately for the dose-escalation and the expansion part of the trial.

8.5.1 General Considerations

All data recorded during the study will be presented in individual data listings performed on the Safety Analysis Set. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified in the SAP. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be performed.

Descriptive statistics will be used to summarize the trial results, that is, statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Unless otherwise specified, the calculation of proportions will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The DLT Analysis Set is the underlying data set for the MTD determination. Safety analyses will be performed on the Safety Analysis Set. Baseline summaries and efficacy analyses will be performed on the Full Analysis Set. Analyses of PK variables will be performed on the PK Analysis Set. Analysis of serum titers of Anti-MSB0011359C Antibodies (ADA) will be performed on the Immunogenicity Analysis Set. CCI [redacted]

The estimation of PK parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher, or R, Version 2.10.1 or higher.

Unless otherwise specified, the endpoint analyses described in the following will be performed separately for both the dose-escalation part and the expansion part of the trial.

8.5.2 Analysis of Primary Endpoints

8.5.2.1 Maximum-Tolerated Dose Determination

For determination of the MTD, individual subject data from the dose-escalation part will be reported.

In addition, for the final statistical analysis, the following will be analyzed:

- At each dose level, the number and proportion of subjects in the DLT Analysis Set who experience a DLT during the DLT evaluation period.
- At each dose level, the number and proportion of TEAEs experienced by subjects in the DLT Analysis Set during the DLT evaluation period.

The MTD will be determined according to the dose-escalation plan described in Section 5.1.3.2. The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT.

8.5.2.2 Best Overall Response

Except for the glioblastoma cohort, the primary efficacy endpoint for the dose-expansion part of the study is the confirmed BOR according to RECIST 1.1 as adjudicated by the IRC and will be evaluated by the confirmed ORR. For glioblastoma, the primary endpoint will be disease control according to RANO as adjudicated by the IRC.

Except for the glioblastoma cohort, the he primary efficacy parameter in the expansion part is the BOR according to RECIST 1.1 as adjudicated by the IRC (Section 2.2.2) and will be evaluated by confirmed ORR. For glioblastoma, the primary efficacy parameter will be disease control according to RANO as adjudicated by the IRC.

The primary analysis of the BOR will be conducted in the Full Analysis Set. The number and proportion of BOR (defined as CR + PR) will be tabulated. For the glioblastoma cohort, the proportion of BOR of CR, PR, or SD $\geq$ 12 weeks according to RANO will be tabulated. The 2-sided 95% Clopper-Pearson CI will be constructed.

For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) or RANO for subjects with glioblastoma (Wen 2010) will be required for the final analysis. The interim analysis will be based on unconfirmed response. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The ORR, defined as the proportion of subjects with BOR of PR or CR, will be tabulated for each cohort.

8.5.3 Analysis of Other Endpoints

8.5.3.1 Efficacy Parameters

Clinical efficacy parameters will be analyzed descriptively in the Full Analysis Set.

For the dose escalation part of the trial, the secondary efficacy endpoint is BOR according to RECIST 1.1 per Investigator assessment. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) will be required. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The ORR, defined as the proportion of subjects with BOR of PR or CR, will be tabulated by dose level.

For the dose-expansion part of the trial, the following secondary efficacy endpoints will be assessed:

- Duration of response, according to RECIST 1.1 and adjudicated by the IRC, will be calculated for each subject with a confirmed response and will be analyzed using the Kaplan-Meier method
- DCR, defined as the proportion of subjects with BOR of CR, PR, or SD for $\geq$ 12 weeks will be tabulated within each expansion cohort
- PFS and TTP time (according to RECIST 1.1 and adjudicated by the IRC) and OS time will be presented in listings and analyzed using the Kaplan-Meier method in each expansion cohort separately if the cohort enrolls the full planned number of subjects

8.5.3.2 Pharmacokinetic Profile

Plasma concentrations of MSB0011359C will be determined by a validated method at the times listed in Schedules of Assessments (refer to Table 1 and Table 2).

The following PK parameters will be estimated and reported in the PK Analysis Set:

- AUC_{0-t} (dose escalation portion, HCC, and NSCLC biomarker cohorts only): Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).
- $AUC_{0-\infty}$ (dose escalation portion, HCC, and NSCLC biomarker cohorts only): Area under the concentration-time curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using $C_{last}/\lambda z$).
- λ_z (dose escalation portion, HCC, and NSCLC biomarker cohorts only): Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of log (concentration) vs. time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time, and (iii) the correlation coefficient (r) of regression must be ≥ 0.95.
- C_{max}: Maximum serum concentration observed postdose.
- C_{min}: Minimum serum concentration observed postdose.
- t_{max} (dose escalation portion, HCC, and NSCLC biomarker cohorts only): Time at which the C_{max} occurs.
- $t_{½}$ (dose escalation, HCC, and NSCLC biomarker cohorts only): Elimination half-life, determined as $0.693/\lambda_z$.

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation.

8.5.3.3 Serum Titers of Anti-MSB0011359C Antibodies (ADA)

Immunogenicity testing strategy will be implemented and conducted in line with:

- Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006).
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (European Medicines Agency [EMA]/CHMP/BMWP/86289/2010).
- Food and Drug Administration (2009, draft) Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins.

A qualified method that uses an acid dissociation step to detect ADAs in the presence of excess drug in human serum will be applied. Removal of drug after acid treatment is not required. The ADA titers of positive samples will be determined.

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8.5.4 Analysis of Safety

The extent of exposure to MSB0011359C will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), and number of dose delays.

Safety analyses will be performed on the Safety Analysis Set. The safety endpoints will be tabulated by dose-level or cohort, using descriptive statistics.

Safety assessments will be based on review of the incidence of AEs, including AEs of special interest, treatment-related AEs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology and serum chemistry).

8.5.4.1 Adverse Events

Adverse events will be coded according to MedDRA. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

The incidence of treatment-emergent AEs regardless of attribution and AEs defined as related to MSB0011359C will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to MSB0011359C. Adverse events (serious and nonserious) will be considered treatment-emergent adverse events when emerging in the on-treatment period defined as the time from the first trial drug administration to the last drug administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. All premature terminations will be summarized by primary reason for treatment withdrawal.

8.5.4.2 Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-trial grades after the first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as within or above normal limits. Only subjects with post-Baseline laboratory values will be included in these analyses.

8.5.4.3 Physical Examination, Including Vital Signs and 12-lead Electrocardiogram

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure), eye signs and symptoms based on System Organ Class of "eye disorders", and 12-lead ECG recorded according to the Schedules of Assessments (refer to Table 1 and Table 2) will be presented.

Further details will be provided in the SAP based on current safety experience applying the latest MedDRA version.

8.6 Interim and Additional Planned Analyses

Enrollment of expansion cohorts will not be stopped for the purpose of conducting their respective interim analyses but will stop if futility is met as specified.

Dose Escalation Part

In the dose-escalation part, the trial data will be evaluated before decision is made to go to the next dose level or to start with treatment in the expansion part.

Expansion Part

For all expansion cohorts except glioblastoma cohort, the endpoints in these interim analyses are ORR (confirmation is not required). For glioblastoma, the endpoint in the interim analysis will be DCR. There is no multiplicity adjustment is applied to the interim analyses. The decision rules at the interim analyses serve as guidance and are non-binding. In the absence of a control arm, outcomes in this single arm study have to be interpreted with caution, both at interim and final analyses.

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HCC ascending-dose cohort

An interim analysis will be conducted 12 weeks after the final subject in the ascending-dose portion received their first dose.

If ≤ 6 responses are observed in the 30 subjects at the interim analysis, the enrollment into HCC second-line or sorafenib-intolerant cohort will be stopped. This decision criterion has 39% probability of rejecting the null hypothesis if the true response rate is 20% and 6% probability of rejecting the alternative hypothesis if the true response rate is 35%.

Enrollment of HCC second-line or sorafenib-intolerant cohort will not be stopped for the purpose of conducting this interim analysis but will stop if futility is met as specified.

HCC second-line or sorafenib-intolerant cohort

No interim analysis is planned.

NSCLC anti-PD-1 / anti-PD-L1 failure cohort

One interim analysis is planned for this cohort 12 weeks after the 40th subject in this cohort started treatment.

- If ≤ 2 responses are observed in the 40 subjects at the interim analysis, the enrollment will be stopped. This decision criterion has 32% probability of rejecting null hypothesis if the true response rate is 5% and 5% probability of rejecting alternative hypothesis if the true response rate is 15%.
- If 3 to 4 responses are observed at the interim analysis, the enrollment will be temporarily stopped until the first 40 subjects have completed tumor assessment at Week 24. After a review of the totality of data, including duration of response, DCR, and safety, the Sponsor will make a decision as to whether to resume the accrual.
- If ≥ 5 responses are observed at the interim analysis, an additional 40 subjects will be enrolled. With 5 responses and using Bayesian principal, the posterior probability of true ORR being above 15% (alternative hypothesis) is approximately 41% and the posterior probability of true ORR being below 5% (null hypothesis) is approximately 2%.

Melanoma anti-PD-1 / anti-PD-L1 failure cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

NSCLC second-line cohort

There is one planned interim analysis. The primary objective of the interim analysis is to assess the tolerability, safety, and preliminary antitumor activity.

The planned interim analysis will occur 12 weeks after the 30th subject in the cohort started treatment. If ≤ 4 responders are observed at the interim analysis, no further subjects will be enrolled into the NSCLC second-line cohort.

Pancreatic adenocarcinoma second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

CRC third-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

SCCHN second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

TNBC second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

Ovarian post-platinum second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

Esophageal post-platinum second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

Glioblastoma second-line cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

Cervical cohort

One interim analysis is planned for this cohort 12 weeks after the 30th subject in the cohort started treatment.

Additional Interim Analyses

In general, interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law in Japan; and the "Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product" (GCP) in Japan, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial. Throughout this clinical trial protocol, Investigator refers to both the principal investigator and any subinvestigators.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. In Japan, when a subject is < 20 years of age, the written informed consent must be obtained from the subject's parent or guardian in addition to the subject's voluntary written consent. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with Japan GCP and ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject or the subject's legal representative and the Investigator.

For all trial sites, the signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion manually for the dose escalation and NSCLC biomarker cohorts and by the IWRS system for other expansion cohorts. The subject number will be assigned immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

Blood and tumor tissue samples for PGt and biomarkers will be stored for up to 10 years after trial completion. During this time, the samples may be reanalyzed for newly identified markers or with new or improved technology. After 10 years, the samples will be destroyed or fully anonymized or a new IEC / IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified and the tumor tissue will be returned to the site upon request. If the site does not request the return of the tumor tissue, it will be destroyed.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour toll-free contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

In Japan, the Sponsor is entirely responsible for AEs that are associated with this study and impair the health of the subjects, except for AEs caused by an intentional and / or significant deviation on the part of the Investigator, the study site, and / or the subject. The Sponsor will provide insurance to fulfill this responsibility.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (such as the ICF) to the responsible IEC / IRB for its favorable opinion / approval. The written favorable opinion / approval of the IEC / IRB will be filed in the Investigator Site File, and a copy will be filed with the CRO.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion / approval from the concerned IEC / IRB. The IEC / IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion / approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion / approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC / IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC / IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Electronic Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data standards of the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. All PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Sex
- Race
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Tumor disease information
- Trial identification (EMR200647-001)
- Date of subject's inclusion into the trial (that is, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial and must be safely archived for at least 15 years (or longer, in accordance with the local requirements of Japan GCP or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor / designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

In Japan, the head of the study site must retain all records, including documents and data, which relate to the clinical study in accordance with Japan GCP. The head of the study site must retain the records at the site (hospital, research institute, or practice) for the longest possible time permitted by Japan GCP, and / or as per ICH GCP guidelines, whichever is longer. In any case, the head of the study site should ensure that no destruction of medical records is performed without the written approval of the Sponsor. The Investigator must retain records, including documents and data, which relate to the clinical study in accordance with the instructions from the head of the study site.

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC / IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC / IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, or completion of a particular cohort or cohorts if applicable, a clinical trial report according to ICH Topic E3 will be written by the Sponsor or the designated CRO in consultation with the Investigator.

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites that participated in the dose-escalation part of the trial.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor.

The Sponsor will not suppress or veto publications but maintains the right to delay publication in order to protect intellectual property rights.

10.7 Record Retention in Japan

The head of the study site and the Investigator will retain all records as described in Section 10.3. The Sponsor and any person who establishes an IEC / IRB must retain all records, including documents and data, which relate to the clinical trial for the required period in accordance with Japan GCP.

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12 Appendices

Appendix 1 Eastern Cooperative Oncology Group Performance Status

ECOG PS[a]	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 2 Guidance on Contraception

Birth control methods considered as highly effective

Aligned with the Clinical Trials Facilitation Group (CTFG 2014) "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2,3])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,4]
- sexual abstinence[5]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods in the context of this guidance are considered to have low user dependency

[3] Not approved in Japan

[4] Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

[5] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Abstinence needs to be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 3 Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
IND Number:	CCI
EudraCT Number:	2015-004366-28
Clinical Trial Protocol Date / Version:	22 June 2021 / Version 7.2-BE-ES-IT-FR

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Biopharma Co. Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany)
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Trial Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
IND Number	CCI [redacted]
EudraCT Number	2015-004366-28
Clinical Trial Protocol Date / Version	22 June 2021 / Version 7.2-BE-ES-IT-FR

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD [redacted]
Function / Title:	PPD [redacted]
Institution:	PPD [redacted]
Address:	PPD [redacted]
Telephone number:	PPD [redacted]
Fax number:	PPD [redacted]
E-mail address:	PPD [redacted]

Signature Page – Principal Investigator

Trial Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
IND Number	CCI [redacted]
EudraCT Number	2015-004366-28
Clinical Trial Protocol Date / Version	22 June 2021 / Version 7.2-BE-ES-IT-FR
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws, and in Japan, the Declaration of Helsinki, the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law in Japan; and the "Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product" (Good Clinical Practice) in Japan.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons Not Named on the Cover Page

Name, academic degree	PPD
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Institution	Merck KGaA
Address	Frankfurter Strasse 250, 64293 Darmstadt, Germany
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Institution	Merck Biopharma Co., Ltd.
Address	PPD
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Appendix 4 Protocol Amendments and List of Changes

Previous Protocol Amendments

Amendment Number	Substantial (Yes/No)	Date	Region or Country	Included in the current document (Y/N)
Amendment 1.0	Yes	16 June 2015	Global	Yes
Amendment 2.0	Yes	17 July 2015	Global	Yes
Amendment 3.0	Yes	29 October 2015	Global	Yes
Amendment 3.1	No	12 January 2016	Belgium, Germany, Italy, Spain, and United Kingdom	Yes
Amendment 3.2	No	09 February 2016	Belgium, Germany, Italy, Spain, and United Kingdom	No
Amendment 3.3	Yes	18 April 2016	All countries except VHP-participating countries (Belgium, Germany, Italy, Spain, and United Kingdom)	Yes
Amendment 3.4	No	25 August 2016	All countries except VHP-participating countries (Belgium, Germany, Italy, Spain, and United Kingdom)	Yes
Amendment 3.5	Yes	25 August 2016	VHP-participating countries (Belgium, Germany, Italy, Spain, and United Kingdom)	Yes
Amendment 3.6	Yes	12 August 2016	Japan	No
Amendment 4.0	Yes	14 December 2016	Global	Yes
Amendment 4.1	Yes	14 December 2016	Japan	No
Amendment 5.0	Yes	22 February 2017	Global	Yes
Amendment 5.1	Yes	22 February 2017	Japan	No
Amendment 5.2	No	15 June 2017	France	Yes
Amendment 5.3	Not applicable	31 August 2017	United States	Yes
Amendment 5.4	Not applicable	09 July 2018	United States	Yes
Amendment 6.0	Yes	31 January 2019	Global	Yes
Amendment 6.1	Yes	04 June 2019	VHP-participating countries (Belgium, France, Germany, Italy, Spain, and United Kingdom))	Yes

The main purpose of this protocol amendment (Version 7.2-BE-ES-IT-FR, 22 June 2021) is to update the risk classification and risk minimization measures. The end of trial is also revised.

List of Changes

Main changes to the clinical trial protocol text are presented in the table below. Minor typographical, grammatical or other changes not affecting the trial conduct are not included.

Changes from Version 7.1 to Version 7.2 included in the Amendment:

Section # and Name	Description of Change	Brief Rationale
Title page	Deletion of Medical Monitor name and "replaced versions"	CCI [redacted]
Synopsis 5.1.6, Planned Teatment Duration	Updated planned date for last subject out from Q4 2020 to Q4 2021	CCI [redacted]
3.5, Summary of Overall Benefit and Risk	Updated the risk categories	CCI [redacted]
3.5.1, Infusion-related Reactions / Hypersensitivity	Clarified that infusion-related reactions, including hypersensitivity, are defined in the current section and that infusion-related reactions are AESIs and identified risks for MSB0011359C.	
3.5.2, Immune-related Adverse Events / Autoimmune Disorders	Clarified that immune-related AEs are AESIs. Added a list of irAEs and clarified that they are important identified or important potential risks for MSB0011359C	CCI [redacted]
3.5.3, TGFβ Inhibition Mediated Skin Reactions	Deleted previous Section 3.5.5 Rash with Hyperkeratosis / Ke ratoacanthoma / Squamous Cell Carcinoma of the Skin Added new section describing skin AEs and clarified that they are AESIs and important identified risks for MSB0011359C.	
3.5.4, Anemia	Clarified that anemia is an AESI and is an important identified risk for MSB0011359C	
3.5.5 Bleeding Adverse Events	Added a new section to describe mucosal/non-tumor bleeding events and clarified that bleeding AEs are AESIs and are an important identified risk for MSB0011359C	
5.1.1.1 Dose Escalation	Remove the text describing other potential risks of the compound, and added a reference to Sections 3.5 and 6.5.4 for details on identified and potential risks.	CCI [redacted]
5.1.8, Analysis Cutoff Dates	Revised the final data cutoff to state that it will be after all possible subjects are enrolled into the rollover study or all	CCI [redacted]

Section # and Name	Description of Change	CCI
	subjects have completed the Safety Follow-up visit.	
5.5.2, Withdrawal from the Trial	Text moved from Section 5.6 and clarified that after primary analyses are completed, subjects may be offered to enroll into the rollover study before the planned end of trial, or before they have withdrawn after completing the Safety Follow-up visit	CCI
5.7, Definition of End of Trial	End of trial definition updated to when subjects are either enrolled into the roll-over trial or have completed at least the Safety Follow-up visit at 10 weeks (±2 weeks) after Last Treatment	CCI
6.5.4.1, Infusion-related Reactions	Added text to clarify that infusion-related reactions, including hypersensitivity, are defined in the section	
6.5.4.4, TGFβ Inhibition Mediated Skin Reactions	Deleted previous Section 6.5.4.5 Rash With Hyperkeratosis / Keratoacanthoma / Squamous Cell Carcinoma of the Skin. Section added to describe the risk minimization measures for TGFβ Inhibition Mediated Skin Reactions	CCI
6.5.4.6 Bleeding Adverse Events	Section added to describe risk minimization measures for bleeding events.	
7.4.1.1.4 Predefined AEs fo Special Interest (AESI) for Safety Monitoring	Description of AESIs has been moved to Section 3.5, and a cross reference added to that section	
Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes made in the protocol or to add further clarity and precision.		