Phase 1 study of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in patients with pretreated biliary tract cancer

Supplementary Information

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Full inclusion/exclusion criteria

Inclusion Criteria:

1. Able and willing to give written informed consent and has signed the appropriate written ICF, prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥20 years.
3. Subjects must have histologically or cytologically confirmed biliary tract cancer for which no standard therapy exists, or standard therapy has failed.
4. Availability of tumor (primary or metastatic) archival material or fresh biopsies within 28 days before first administration of IMP is mandatory.
5. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1.
6. ECOG PS of 0 to 1 at trial entry.
7. Life expectancy ≥12 weeks as judged by the Investigator.
8. Adequate hematological function defined by WBC count ≥3 × 109/L with ANC ≥1.5 × 109/L, lymphocyte count ≥0.5 × 109/L, platelet count ≥75 × 109/L, and Hgb ≥9 g/dL (in absence of blood transfusion).
9. Adequate hepatic function defined by a total bilirubin level ≤1.5 × ULN, an AST level≤2.5 × ULN, and an ALT level ≤2.5 × ULN.
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. Woman of childbearing potential must agree to use highly effective methods of contraception to prevent pregnancy for 4 weeks prior to registration, throughout the trial, and for 60 days after the last dose of IMP. For the purposes of this trial:
    - Woman are considered of childbearing potential unless they are postmenopausal (defined by age-related amenorrhea ≥12 consecutive months excluding the amenorrhea caused by the administration of anticancer therapy or increased FSH >40 mIU/mL or are surgically sterile.
    - Highly effective contraception is defined as use of two barrier methods (eg, female diaphragm and male condom); or one barrier method with spermicide, an intrauterine device, or hormonal contraceptives (implant [not approved in Japan] or oral).
12. Males must agree to use and to have their female partners use highly effective contraception to prevent pregnancy throughout the trial and for at least 90 days after the last IMP administration.
13. Woman of childbearing potential must have a negative serum pregnancy test at screening visit and a negative serum or urine pregnancy test at Day 1 before dosing if applicable.

Exclusion Criteria:

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

1. Concurrent treatment with non-permitted drugs, including:
    - Immunotherapy, immunosuppressive drugs (eg, 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 (ie, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are 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 (eg, inactivated influenza vaccines).

2. Prior therapy with any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody (consult Medical Monitor if necessary), or anti-4-1BB antibody is not allowed, inclusive of intrahepatic, localized administration of such agents.
3. Prior therapy with any antibody/drug targeting TGF-β/TGF-β receptor.
4. Anticancer treatment within 21 days before the start of trial treatment, eg, cytoreductive therapy, radiotherapy involving more than 30% of the bone marrow (with the exception of palliative bone directed radiotherapy), immune therapy, or cytokine therapy.
5. Anticancer treatment with antibody within 28 days before the start of trial treatment.
6. Major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy).
7. 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.
8. Previous malignant disease other than the target malignancy to be investigated in this trial with the exception of cervical carcinoma in situ and superficial or non-invasive bladder cancer (treated with curative intent) within the last 5 years or basal cell or squamous cell carcinoma in situ within the last 3 years.
9. Rapidly progressive disease which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or trial procedures.
10. Active or history of CNS metastases.
11. 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).
12. Significant acute or chronic infections including, among others:
    - 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 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)
13. 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 ≤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.

14. Interstitial lung disease or its history.
15. Known history of hypersensitivity reactions to bintrafusp alfa or its products, known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v4.03), any history of anaphylaxis, or recent (within 5 months) history of uncontrolled asthma.
16. Persisting toxicity (except alopecia and vitiligo) related to prior therapy Grade >1 NCI-CTCAE v4.03; however, sensory neuropathy Grade ≤2 is acceptable.
17. Pregnancy or currently in lactation. Subject is not eligible even if lactation is suspended.
18. Known alcohol or drug abuse.
19. 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.
20. Clinically relevant diseases (eg, 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.
21. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.
22. Legal incapacity or limited legal capacity.
23. Vaccine administration within 4 weeks of IMP administration. Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines is allowed (eg, inactivated influenza vaccines).

Biomarker analysis methods

Tumour neoantigen mutation count was measured by RNAseq by performing a total RNA extraction, random priming library preparation, and ribosomal depletion by Aspurgen (Austin, TX) from FFPE slides. The material was sequenced at 2x50 to a target of 100M read pairs on an Illumina HiSeq. Whole Exome sequencing was performed by ExpressionAnalysis (Research Triangle Park, NC, USA) from matched peripheral blood samples using an Agilent SureSelect V5 kit (Agilent Technologies, Santa Clara, CA, USA); sequencing was done on an Illumina HiSeq with a target 100X coverage. RNAseq reads were mapped to hg19 and the Ensembl gene annotations (ensGene; University of California, Santa Cruz, CA, USA) using RNA-STAR version 2.5.0b[1] and whole-exome reads were mapped to hg19 using BWA-MEM version 0.7.12.[2] Mutation calling was performed on paired BAM files (RNAseq tumor and whole exome normal) using VarDictJava version 1.4.2 and the resulting mutations annotated using the Ensembl Variant Effect Predictor version 85 to determine the type of mutation (eg, missense, silent, etc), the gene/protein, and the amino acid change.[3,4] Human leukocyte antigen (HLA) typing was performed on the RNAseq data using OptiType version 1.0.1. The HLA typing and mutation information were aggregated using a custom Python program which then ran NetMHCPan version 3.0 to determine the mutant and wild-type IC50s of peptides including the mutation site. Following filtering of neoantigens with an IC50 > 500nM, a neoantigen count was produced for each sample. Further, an expression adjusted neoantigen score was produced that weighted each neoantigen according to its expression level. Finally, the per-sample values were normalized across the dataset by inverse of the number of reads mapped to genes in each sample.

Tumor samples were used to determine immune phenotype from available immunohistochemistry data (PD-L1 stain and PD-L1–negative control) and hematoxylin and eosin stain. PD-L1 stains with clone 73-10 effectively detected immune cells in the tumor area and adjacent stroma. An exploratory classification based on the previously published Mariathasan method was used to define immune phenotypes as either immune-inflamed (immune cells in direct physical contact with tumor cells), immune-excluded (≥1% of the tumor stroma area populated by lymphocytes, immune cells possibly located in the immediate vicinity of tumor cells but not efficiently infiltrate tumor cell clusters, and very infrequent physical contact between lymphocytes and tumor cells), or immune desert (<1% of the tumor stroma area populated by lymphocytes, no dense immune cell infiltrates, and no contact of immune cells with tumor cells).[5] A pathologist who was masked to the response data scored the scanned slides and determined the corresponding immune phenotype. Microsatellite instability was measured from formalin-fixed paraffin embedded tissue sections using the Biocartis Idylla™ system (Biocartis US, Inc., Jersey City, NJ, USA).

Supplementary references

1 Dobin A, Davis CA, Schlesinger F, *et al.* STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* 2013; **29**: 15–21.
2 Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* 2009; **25**: 1754–60.
3 Lai Z, Markovets A, Ahdesmaki M, *et al.* VarDict: a novel and versatile variant caller for next-generation sequencing in cancer research. *Nucleic Acids Res* 2016; **44**: e108–e108.
4 McLaren W, Gil L, Hunt SE, *et al.* The ensembl variant effect predictor. *Genome Biol* 2016; **17**: 122.
5 Mariathasan S, Turley SJ, Nickles D, *et al.* TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* 2018; **554**: 544–8.

Redacted Trial Protocol

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

Clinical Trial Protocol

Clinical Trial Protocol Number	MS200647-0008
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 with expansion to selected indications in Asia
Trial Phase	I
Coordinating Investigator	PPD [redacted]
Sponsor	**For Japan only:** Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan **For all countries except Japan:** Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany **Medical Responsible:** PPD [redacted] Merck Serono Co., Ltd., R&D Japan, North East Asia Hub Tel: PPD Fax: PPD
Clinical Trial Protocol Version	18 April 2017/Version 5.0 including amendments 1.0 to 4.0
Replaces Version	29 September 2016/Version 4.0

- [redacted] -

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List of Abbreviations

ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
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
BTC	biliary tract cancer
CC	cholangio cell carcinoma
CI	confidence interval
CNS	central nervous system
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
DLT	dose-limiting toxicity
CCI	[redacted]
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer Module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument
EORTC QLQ-HCC18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma Module
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GBC	gallbladder cancer
CCI	[redacted]
GCP	Good Clinical Practice
HAHA	human anti-human antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCV	hepatitis C virus
HDV	hepatitis D virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irBOR	immune-related best overall response
IRC	Independent Endpoint Review Committee
irCR	immune-related complete response
irORR	immune-related objective response rate
irPD	immune-related progressive disease
irPFS	immune-related progression-free survival
irPR	immune-related partial response
irRC	immune-related Response Criteria
irSD	immune-related stable disease
LDH	lactate dehydrogenase
MAHA	mouse antibody against human antibody
MedDRA	Medical Dictionary for Regulatory Activities
MoA	mechanism of action

CCI	[redacted]
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	objective response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cell(s)
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGt	pharmacogenetics
PGx	pharmacogenomics
PharmDyn	pharmacodynamics
Ph Eur	European Pharmacopeia
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan

SMC	Safety Monitoring Committee
SpO_2	Oxygen saturation
$t_{1/2}$	terminal half-life
T4	thyroxine
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor-beta
TGFβRII	transforming growth factor-beta receptor II
Treg	regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USP	United States Pharmacopeia
VAC	carcinoma of Vater's ampular
WBC	white blood cell

1 Synopsis

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 with expansion to selected indications in Asia
Trial number	MS200647-0008
Sponsor	**For Japan only:** Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan **For all countries except Japan:** Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany
Phase	I
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial center(s)/country(ies)	**Dose Escalation Part:** CCI [redacted]. **Expansion Part:** CCI [redacted]
Planned trial period **(first enrollment-last subject out)**	**Dose Escalation Part:** CCI [redacted] **Expansion Part:** First subject in: Q4 2016 CCI [redacted] Last subject out: Q3 2019 **End of Trial:** If the trial is not terminated prematurely, the end of the trial is defined as 1 year after the last subject receives the last dose of MSB0011359C. **Analysis cut-off dates:** The primary data cut-off date for the dose escalation part is 3 months after the last subject in the dose escalation part received the first dose of MSB0011359C.

	The primary data cut-off for the analysis of each expansion cohort separately will be 6 months after the last subject in the cohort started treatment. The final data cut-off is 1 year after the last subject has received the last dose of MSB0011359C.

Trial objectives

Primary objective:

The primary objective of the trial is to determine the safety, tolerability and maximum tolerated dose (MTD) administered as monotherapy of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

Secondary objectives:

The secondary objectives are:

- To characterize the pharmacokinetics (PK) profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure
- To assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Exploratory objectives:

The exploratory objectives are:

- To assess progression-free survival time (PFS) according to RECIST 1.1
- To characterize overall survival time (OS)
- To assess the immune-related BOR (irBOR) using the modified immune-related Response Criteria (irRC), derived from RECIST 1.1
- To assess immune-related PFS (irPFS) using irRC
- To evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers

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- To assess symptom severity for subjects with CCI BTC via patient-reported outcome measures.

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Trial design and plan

This Phase I, open-label trial consists of 2 parts: a dose escalation part (Part A) and an expansion part (Part B). This trial will be conducted to investigate the safety and tolerability of MSB0011359C in subjects with metastatic or locally advanced solid tumors in Asia. This trial also has an expansion part to investigate the safety and efficacy of MSB0011359C in Asian patients with CCI biliary tract cancer (BTC), CCI .

Dose escalation (Part A):

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Expansion (Part B):

The expansion part consists of CCI cohort and other cohort indications including CCI BTC.

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After confirmation of tolerability at 20 mg/kg in the dose escalation part, the MSB0011359C dose for further investigation is 1200 mg and enrollment of CCI BTC subjects into the expansion cohorts will begin to determine the safety and clinical activity of MSB0011359C. These indications were chosen as they offer the potential for transformative treatment with ability to establish an initial proof of concept of antitumor activity of MSB0011359C with good feasibility.

Subjects in the expansion cohorts will receive MSB0011359C as a 1-hour intravenous 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 as outlined in this protocol.

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

Planned number of subjects

Dose escalation part: CCI

Expansion part: Up to CCI subjects (CCI, up to 100, CCI in the CCI, BTC, CCI, respectively).

The total sample size at the end of the trial (based on the dose escalation part and the expansion part) is expected to be up to approximately CCI subjects.

Diagnosis and key inclusion and exclusion criteria

Key inclusion criteria for the dose escalation include:

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Key inclusion criteria for the expansion cohorts are:

1. Able and willing to give written informed consent and has signed the appropriate written ICF, prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥ 20 years.
3. Subjects must have one of the following:

- **BTC, second line:** Histologically or cytologically confirmed biliary tract cancer. Must have failed or are intolerant to one line of systemic treatment. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible.

5. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1.

Key exclusion criteria:

1. Concurrent treatment with non-permitted drugs.
2. Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody (consult Medical Monitor if necessary), or anti-4-1BB antibody, is not allowed (consult with Medical Monitor as needed), inclusive of intrahepatic, localized administration of such agents.
3. Prior therapy with any antibody/drug targeting TGFβ or TGF receptor.

4. Anticancer treatment within 21 days before the start of trial treatment, eg, cytoreductive therapy, radiotherapy (with the exception of palliative bone-directed radiotherapy), immune therapy, or cytokine therapy.
5. Anticancer treatment with antibody within 28 days before the start of trial treatment.
6. Major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy).
7. 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.

Investigational Medicinal Product

Dose/mode of administration/dosing schedule:

CCI [redacted] A flat dose of 1200 mg MSB0011359C will be used for all subjects in the expansion cohort CCI [redacted] after confirming the tolerability of MSB0011359C at 20 mg/kg.

MSB0011359C will be administered once every 2 weeks as a 1-hour (-10/+20 minutes, ie, over 50 to 80 minutes) intravenous infusion.

In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous 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. If Grade 2 infusion reactions are seen during the first two infusions, then 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 complete response (CR), partial response (PR) or stable disease (SD), subjects should continue treatment through the end of 12 months at the discretion of the Investigator and in consultation with the Medical Monitor. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. For subjects who achieve a CR, PR, or SD 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. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. 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.

Primary endpoints:

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

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Secondary endpoints:

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

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

- BOR according to RECIST 1.1 as adjudicated by the Independent Review Committee (IRC)
  - BOR according to RECIST 1.1 per investigator assessments
- Duration of response according to RECIST as adjudicated by the IRC
- Disease control rate according to RECIST 1.1 as adjudicated by the IRC
  - PFS time according to RECIST 1.1 as adjudicated by the IRC
  - OS time.

Exploratory endpoints:

Exploratory endpoints for the dose escalation part of the trial are:

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Exploratory endpoints for the expansion part of the trial are:

- irBOR according to modified irRC as adjudicated by the IRC and per investigator assessments
- irPFS according to modified irRC as adjudicated by the IRC and per investigator assessments

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- Changes in blood, tumor and tumor environment biomarkers
- Potential predictive markers
- Exploratory endpoints for the CCI BTC expansion cohorts also include:

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  - Changes in symptom severity for subjects with BTC as assessed by the PGIS item and selected items from the EORTC QLQ-C30, cholangiocarcinoma and gallbladder cancer module (EORTC QLQ-BIL21), and hepatocellular carcinoma module (EORTC QLQ-HCC18).

Pharmacokinetics:

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- C_{max} observed postdose
- C_{min} observed postdose

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Biomarkers/Pharmacogenetics (for both dose escalation and expansion parts):

Biomarkers such as TGFβ concentration in plasma, soluble factors (eg, cytokine profiles) in serum, predictive biomarker candidates (eg, level of PD-L1 tumor expression, tumor infiltrating lymphocytes, TGFβ-related markers) in tumor tissue will be investigated.

Further exploratory genetic and genomic profiling exclusively related to drug effects, (patho-)biology of the tumor and the immune system, and observed AEs will be considered in blood and tumor tissue.

Statistical methods:

For the expansion cohorts of subjects with CCI BTC, the primary secondary efficacy endpoint is the BOR, as adjudicated by the IRC, and will be evaluated by confirmed objective response rate (ORR) according to RECIST 1.1 based on IRC assessment. The ORR will be determined as the proportion of patients with confirmed BOR of PR or CR.

Thirty subjects will be enrolled in each cohort. The goal of these cohorts is an exploration of initial clinical activity and viewed as hypothesis-generating, not intended as a test of a hypothesis. The sample size in these cohorts is a practical number in order to obtain preliminary estimates of efficacy. The confirmed ORR according to RECIST 1.1 as adjudicated by the IRC will be determined as the proportion of subjects with confirmed BOR of PR or CR. A 95% exact (Clopper-Pearson) confidence interval will be calculated for the ORR. The total sample size for the trial (dose escalation and expansion) is expected to be up to approximately CCI subjects.

For BTC, up to 100 subjects will be enrolled in total for the purpose of assessing additional safety data and efficacy based on the BOR, if 5 or more of first 20 BTC subjects have a response (that is an ORR of at least 25%).

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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.

CCI [redacted] 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


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Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
	Day -28 to First Treatment	V1[x] W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D43-50	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	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, HCV, and HIV testing	X															
Ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity	X															
Physical examination [s,u]	X	X	X	X	X	X	X	X		X	X	X	6-weekly[t]	x/X	X	
Dermatological assessment[e]	X				X		X	X		X	X	X	6-weekly up to/including Week 25, then every 12 weeks	x/X	X	
SpO_2	X	X			X		X	X		X	X	X	2-weekly	X	X	
12 lead ECG[f]	X	X/X	X	X	X/X		X	X				X	6-weekly normal ECGs[t]	-/X	X	

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
	Day -28 to First Treatment	V1[x] W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D43-50	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Vital signs including weight and height (height at screening only)[g]	X	X			X	X	X	X	X	X	X	X	2-weekly	x/X	X	
ECOG PS[h]	X	X	X	X	X		X	X		X	X	X	2-weekly	x/X	X	
Enrollment (if eligible)[i]	X															
Hematology/ hemostaseology[j]	X	X	X	X	X	X	X	X		X	X	X	2-weekly	x/X	X	
Core serum chemistry[k]		X	X	X		X	X			X	X		2-weekly			
Full serum chemistry[k]	X				X			X				X	6-weekly	x/X	X	
Urinalysis[l]	X				X			X				X	6-weekly[t]	x/X	X	
β-HCG pregnancy test (if applicable)[m]	X	X					X			X		X	4-weekly	-/X	X	
FSH (if applicable)	X															
Tumor evaluation/ staging (CT Scan/MRI/ other)[b, n, o, v]	X							X				X	6-weekly	-/X		X [b]
Documentation of AEs[w]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X[w]	X[w]	
Documentation of concomitant medications, and procedures	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	X
ACTH, ANA, and RF	X															
Free T4 and TSH	X				X			X				X	6-weekly	-/X	X	
EBV testing[p]	X															

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
	Day -28 to First Treatment	V1[x] W1 D1	V2 W1 D2	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D43-50	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
PK sampling	See Table 3															
ADA sampling	See Table 3															
Soluble factors	See Table 3															
TGFβ	See Table 3															
Tumor tissue or archived surgical specimen / paired biopsy	See Table 3															
Gene expression evaluation	See Table 3															
Blood sample for immune and cancer genetics[q] (optional)	X															
Pretreatment and IMP administration[r]		X			X		X	X		X	X	X	2-weekly			
Expansion: CCI BTC [y]																
Patient-reported Outcomes (PGIS and EORTC QLQ-C30, CCI [aa], QLQ-BIL21,[bb] and QLQ-HCC18 [bb])	X	X			X		X	X		X	X	X	2-weekly up to Week 25	x/X	X	

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
	Day -28 to First Treatment	V1[x]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13				
		D1	D2	D8	D15	D22	D29	D43	D43-50	D57	D71	D85				

ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AE=adverse events; ANA=anti-nuclear antibody; β-HCG=β-human chorionic gonadotropin; CT=computer tomography; DLT=dose-limiting toxicity; EBV=epstein barr virus; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument; CCI [redacted]; EORTC QLQ-BIL21=cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-HCC18= hepatocellular carcinoma module; FSH=follicle stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MRI=magnetic resonance imaging; PD=progressive disease; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; RF=rheumatoid factor; SpO_2=Oxygen saturation; TGFβ=transforming growth factor beta; TSH=thyroid stimulating hormone, T4=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 43-50 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. The Day 43-50 visit is to accommodate collection of tumor biopsy material and associated PK and biomarker sampling (see Table 3).

b Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 12 weeks) 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. After completion of the Follow-up period, the appropriate electronic Case Report Form section for Trial Termination must be completed.

c Any subject who experiences an AE that mandates discontinuation of trial treatment should have a discontinuation visit within 7 days after the decision to discontinue trial treatment.

d Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

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

f 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. All ECGs will be conducted according to local procedure and will NOT be digitally uploaded.

g Vital signs should be assessed predose (within 15 minutes of start of infusion), then every 15 (±2) minutes after the start of infusion, and 15 (±5), 30 (±5), 60 (±5), 120 (±10), and 360 (±150) minutes after the end of infusion for the first 2 infusions. 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), 30 (±5) and 60 (-5/+15) minutes after the start of infusion, and 30 (±5), 60 (±10), and 120 (±10) minutes after the end of infusion. If the subject does not have an infusion-related reaction during the first 4 injections, the 120 (±10) minutes assessment may be waived for subsequent infusions.

h 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.

i 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.

j Hematology (including complete blood count) and hemastaseology assessments are detailed in Table 8. Follicle-stimulating hormone at Screening, if applicable. 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.

k Full chemistry (which includes core chemistry) and core serum chemistry samples are detailed in Table 8. 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.

l A full urinalysis is required at Screening and the End-of-Treatment visit and basic urinalysis at each visit indicated prior to administration of trial drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.

m β-HCG must be determined from serum at Screening and from either urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to next dosing. Pregnancy testing is applied for women of childbearing potential. Woman are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea excluding the amenorrhea caused by the administration of anticancer therapy) for at least 12 months, are surgically sterile or have increased FSH levels indicating menopause.

n 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 nontarget lesions. 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 after 6 weeks.

o 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.

CCI [redacted]

q The blood sample should be collected prior to the first administration of trial treatment, ie, either during the Screening period or predose on Day 1.

r In order to mitigate potential infusion-related reactions, all subjects must receive premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of MSB0011359C (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous or oral equivalent) for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted. MSB0011359C should be administered according to the dose decided from the dose escalation part of the trial by intravenous infusion over 1 hour (-10 minutes/+20 minutes, ie, over 50 to 80 minutes). Subjects must be observed for at least 2 hours after the end of infusion.

s At each visit, 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.

t After 6 months, this will be assessed every 12 weeks and after a year, this will be assessed every 6 months.

u After Day 1, the physical examination will be a directed physical examination indicated by subject's symptoms.

v Tumor evaluation will be assessed every 12 weeks after 12 months.

w 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.

x Subjects who re-initiate treatment will continue in the trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1.

y Patient-reported outcomes should be completed prior to any study-related procedures at the indicated visits.

CCI [redacted]

bb For subjects in the BTC expansion cohort only, symptom severity also will be assessed using the EORTC QLQ-BIL21 (cholangiocarcinoma and gallbladder cancer module) and the EORTC QLQ-HCC18 (hepatocellular carcinoma module).

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, Biomarker Sampling, and Gene Expression Sampling

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

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, Biomarker Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Long-term Follow-up
	Day -28 to First Treatment	V1[j] W1 D1	V2 W1 D2[b]	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D43-50	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (±5 days) after Decision of Discontinuation/ Last Treatment[c]	10 Weeks (±2 weeks) after Last Treatment	Every 12 Weeks (±2 weeks)
CCI															
Expansion: CCI **BTC**															
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]	6-weekly up to/including Week 25, then every 12 week	- /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	

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, Biomarker Sampling, and Gene Expression Sampling

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Long-term Follow-up
	Day -28 to First Treatment	V1[i] W1 D1	V2 W1 D2[b]	V3 W2 D8	V4 W3 D15	V5 W4 D22	V6 W5 D29	V7 W7 D43	V7 W7 D43-50	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (±5 days) after Decision of Discontinuation/ Last Treatment[c]	10 Weeks (±2 weeks) after Last Treatment	Every 12 Weeks (±2 weeks)
Soluble factors		X	X[b]	X	X			X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X		
TGFβ		X														
Tumor tissue or archived surgical specimen/paired biopsy[g]	X								X[h]					- /X if PD[h]		
Gene expression evaluation[i]	X	X	X	X	X			X				X		- /X if PD		

ADA=anti-drug antibody; BTC=biliary tract cancer; CRF=case report form; CCI ; CCI ; HAHA=human antihuman antibody; HBV=hepatitis B virus; CCI ; HCV=hepatitis C virus; PD=progressive disease; PK=pharmacokinetics; TGFβ=transforming growth factor beta.

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 43-50 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.

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 or by a predose sample being drawn after start of dosing.

c If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

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.

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. 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 Week 7 biopsy as possible (ie, same day).

g Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suited. Fine needle aspiration biopsies are not suited. CCI . Availability of suitable tumor tissue is mandatory for eligibility in the expansion cohorts (See Section 7.6). The biopsy or surgical specimen must have been collected within 28 days prior to the first IMP administration. For all 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.

h A Week 7 biopsy is optional. A PK sample should be collected as close as possible to the time of the Week 7 biopsy (ie, same day). If the therapy is discontinued due to regrowth of the tumor, then a repeat biopsy is advisable.
i Sample for gene expression evaluation should be collected prior to dosing.
j Subjects who re-initiate treatment will continue in the trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1.

CCI [redacted]

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with MSB0011359C is Merck Serono Co., Ltd. (affiliate of Merck KGaA, Darmstadt, Germany) in Japan. In addition, Merck KGaA, Darmstadt, Germany, sponsors this clinical trial in Korea and Taiwan.

Trial Organization in Japan

Refer to the Trial Organization in Japan supporting document.

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

2.1 Investigational Sites

Dose escalation part: CCI

Expansion part: The trial will be conducted in CCI Japan, Korea and Taiwan.

2.2 Trial Coordination/Monitoring

The Sponsor will coordinate the trial and will provide the support of CROs for some activities of the trial. Sponsor functional groups will perform oversight of the activities performed by the CROs.

The Sponsor will supply the 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. Pharmacokinetics (PK), pharmacodynamics (PharmDyn), pharmacogenetics (PGt)/pharmacogenomics (PGx), and biomarker assessments will be performed centrally under the responsibility of the Sponsor.

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany or their designated representatives will assure drug safety monitoring, pharmacovigilance, 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, PPD , 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 4.

2.2.1 Safety Monitoring Committee

To ensure subjects' safety during the dose escalation and expansion parts of the trial, a Safety Monitoring Committee (SMC) will review the safety data on a regular basis. The SMC consists of permanent members from the Sponsor and/or 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. CCI [redacted]

During the expansion part of the trial, the SMC will monitor on an ongoing basis (eg, when 15 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 will read and interpret all radiographic scans for subjects enrolled in the expansion cohorts CCI [redacted]. 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, see Eisenhauer 2009) CCI [redacted] 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 have been met. The role of the IRC will be to review radiographic image findings and physical findings for the determination of the time point overall response and date of disease progression according to RECIST 1.1 for each subject. 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.

3 Background Information

3.1 Investigational Medicinal Product (IMP)

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 molecule contains the identical anti-PD-L1 antibody, avelumab (international nonproprietary name for MSB0010718C), currently in Phase II/III clinical development by the Sponsor. The MSB0011359C drug product is a genetic recombination drug manufactured by Chinese hamster ovary cells, transfected with an expression vector coding for this fusion protein.

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).

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.

Inhibition of TGFβ by soluble TGβRII reduced malignant mesothelioma tumors in a manner that was associated with an increase in CD8+ T cell antitumor effects (Suzuki 2004). The absence of TGFβ1 produced by activated CD4+ T cells and Treg cells has been shown to inhibit tumor growth, and protect mice from spontaneous cancer (Donkor 2012). Thus, TGFβ appears to be important for tumor immune evasion.

Combining these pathways, PD-1/PD-L1 and TGFβ, is attractive as an antitumor approach. A recent report found that blockade of TGFβ signaling in T cells or deletion of TGFβ1 from T cells in a mouse model led to diminished PD-1 expression in tumor-infiltrating CD8+ T cells (Donkor 2012). 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, a significant source of TGFβ, are associated with failure to respond to anti-PD1 therapy (Weber 2014).

Experiments demonstrate that MSB0011359C strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 antibody, avelumab, or transforming growth factor-beta receptor II (TGFβRII) control alone. Tumor rechallenge experiments in cured mice show durable protective immunity. In vivo studies showed that the

antitumor effects were mediated by CD8+ T cells and NK cells. CD8+ T-cell tumor infiltrates were observed and, overall, the CD8+ response was associated with long term protective immunity. Importantly, in the MC38 model, MSB0011359C showed significantly better efficacy than the combination of avelumab plus TGFβ Trap control, supporting the rationale of combining the 2 active moieties in 1 molecule.

Strong clinical activity has been reported with anti-PD1 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 non-small cell lung cancer. 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). Refer to the current Investigator's Brochure (IB) for additional avelumab efficacy updates in other tumor types.

CCI [redacted]

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 intolerant HCC patients 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 co-targeting 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). Internal data shows that the TGFβRII portion of MSB0011359C has dose-dependent antitumor activity in a mouse pharyngeal carcinoma xenograft model, similar to antitumor findings with soluble receptor reported elsewhere (Van Aarsen 2008). Given the nonclinical 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 cytotoxic T lymphocyte antigen-4 (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). Transforming growth factor-β1 monoclonal antibody (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 nonclinical 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 nonclinical profile of MSB0011359C and clinical evidence of each pathway suggests a low risk of synergistic toxicity stemming from the dual-functionality of MSB0011359C.

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. TβM1, a neutralizing antibody against TGFβ-1, 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 nonclinical 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]

3.2 Nonclinical Findings for MSB0011359C

CCI [redacted] please refer to the latest IB.

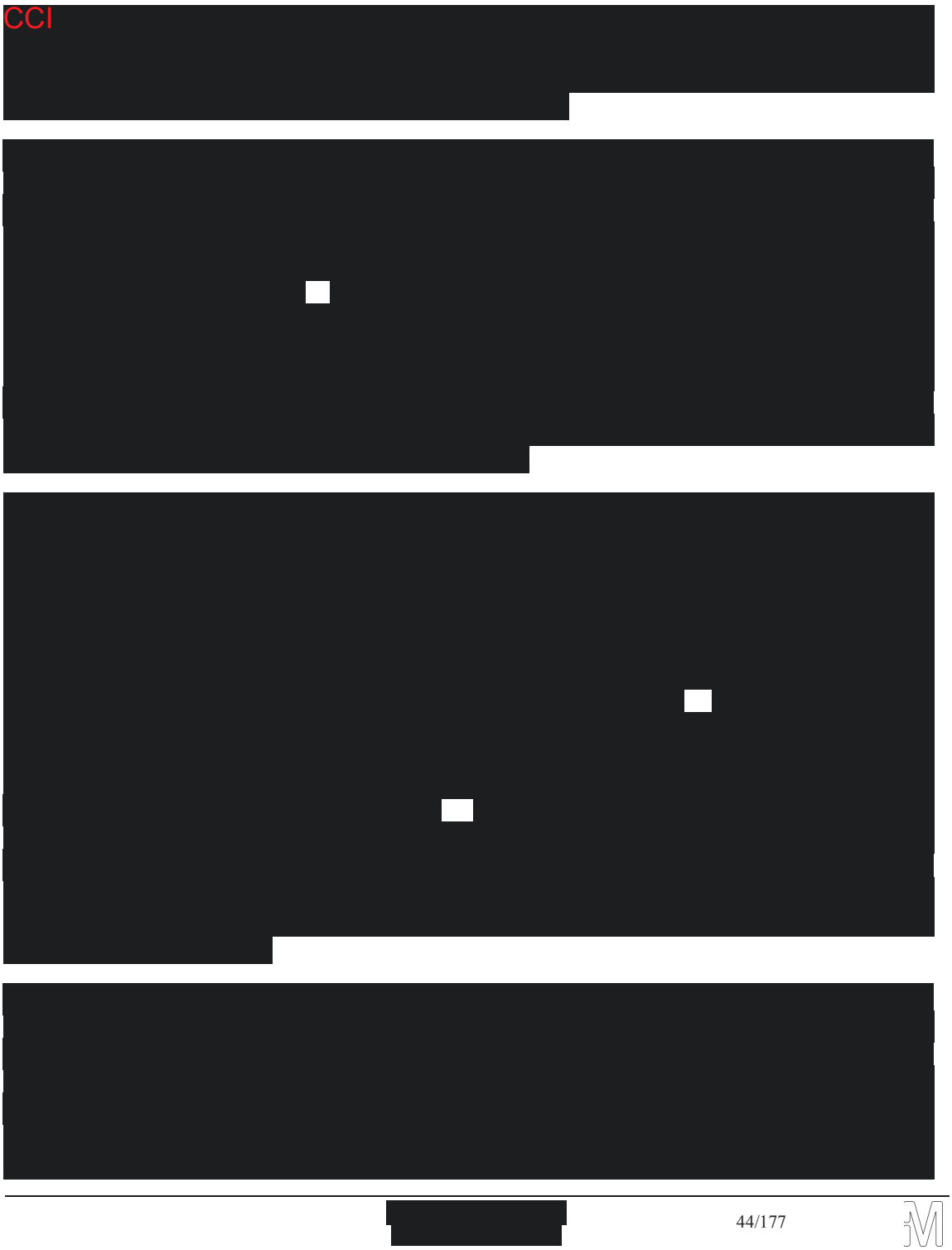
CCI [redacted]

[redacted]

[redacted] 43/177

Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008



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Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
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Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

[redacted] 47/177

Document No. CCI
Object No. CCI

3.3 Rationale for the Clinical Trial

The administration of MSB0011359C to subjects with advanced solid tumors for which no approved/established effective treatment option exists is justified by the following:

- MSB0011359C is capable of inhibiting tumor growth in vivo when applied as a monotherapy and its efficacy can be further enhanced via combination with standard-of-care therapies.
- Nonclinical models demonstrate that MSB0011359C possesses superior antitumor activities relative to monotherapy with either PD-L1 blockade or TGFβ sequestration.
- Safety experience with TGFβ-targeting agents described in the literature suggests no overlapping immune-related adverse profile with the PD-1/PD-L1 class.
- Clinical experience with the lead/parental anti-PD-L1 antibody (avelumab) and similar anti-PD-1/PD-L1 antibodies demonstrate an acceptable safety profile and encouraging clinical antitumor activity in multiple solid tumor types.

In addition, the trial will provide knowledge about safety, efficacy, biomarkers, and immune response, complementary to the global first-in-man trial, EMR200647-001.

3.3.1 Rationale for Dose Levels

CCI

[redacted]

Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

Document No. CCI
Object No. CCI

[redacted]

3.3.2 Rationale for Expansion Cohorts Dose

Clinical efficacy data are typically insufficient at this stage of clinical development to allow a clinical benefit-risk analysis as a basis for the initial dose selection; however, based on biomarker assessments in the first-in-man (FIM) study EMR200647-001, including PD-L1 target occupancy and TGFβ inhibition in the blood, it can be concluded that MSB0011359C has full pharmacological activity to achieve full and continuous target inhibition throughout most or all of the dosing interval at a dose of 3 mg/kg.

It has to be assumed that full pharmacological activity is required at the tumor site, for which no data are available though. Moreover, it is important to account for interindividual variability of the PK exposure within each dosing cohort to ensure that even patients having a lower drug exposure will have sufficient drug concentrations in order to derive the pharmacological benefits of the drug. For these reasons, and taking into account that MSB0011359C was well tolerated at all doses and no MTD was achieved in the dose escalation cohort of EMR200647-001 study, the Sponsor decided to select a dose for the majority of the expansion cohorts that will achieve an average exposure approximately 5-fold higher dose than achieved by the 3 mg/kg dose, which would amount to 15 mg/kg. The dose of 15 mg/kg is also supported by translational PK / efficacy modeling analysis based on experimental data from mouse (see Section 3.2.1)

In addition, analysis of the available PK data of the dose-escalation cohorts in both the EMR200647-001 study and this study (MS200647-0008) indicated that the clearance of MSB0011359C appeared not to be related to body weight. As a result, weight-based dosing led to higher overall exposures (as measured by area under the concentration-time curve [AUC] and C_{max}) in heavier subjects and lower exposures in lighter subjects. In order to achieve a more balanced distribution of exposures in the treated subjects, MSB0011359C will be administered in the expansion cohorts as “flat” doses, ie, not weight based. This is supported by simulation data of flat doses showing a comparable exposure across a whole weight range (in contrast to weight based administration). Taking this into account, the optimal benefit risk ratio is likely to be achieved in this clinical study if all subjects receive the same flat dose irrespective of body weight.

For all cohorts in the expansion part of this study (MS200647-0008), the flat dose of 1200 mg once every 2 weeks has been selected based on simulation to achieve an exposure that is estimated approximately 5-fold higher than the exposure that is achieved with the 3 mg/kg dose in EMR200647-001 study. After the confirmation of safety profile for 20 mg/kg cohort in the dose escalation part by the SMC for this study, the 1200 mg flat dose is implemented in this study.

3.3.3 Disease Background

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

3.3.3.3 Biliary Tract Cancer

Biliary tract cancer (BTC) is more common in East Asia and Latin America than in other continents. The incidence of BTC in 2011 was reported to be 23,606 (male: 12,250, female: 11,356) in Japan (Doi 2015). Biliary tract cancer includes gallbladder cancer (GBC), cholangio

Document No. CCI [redacted]
Object No. CCI [redacted]

cell carcinoma (CC) and carcinoma of Vater's ampular (VAC). CC is classified into intrahepatic CC and extrahepatic CC. The proportion of each cancer in BTC in Japan was reported as follows: GBC: 37.0%; CC: 48.9%; and VAC: 14.1% (Miyakawa 2009). Despite recent progress in diagnostic procedures, most cases are advanced at initial diagnosis and are treated by chemotherapy. The survival data of the unresectable patients is poor (1-year survival: GBC: 11%; CC: 25%; VAC: 38%). Even if surgery can be performed, 5-year survival rates remain low as a result of relapse (GBC: 41.6%; CC: 33.1%; VAC: 52.8%) (Miyakawa 2009). Results of several studies showed that both PD-L1 and TGFβ were related to tumor progression or malignancy of BTC. A higher tumor-related PD-1 expression was associated with a poorer histological differentiation and a more advanced primary tumor node metastasis stage in intrahepatic cholangiocarcinoma ($p < 0.05$) (Ye 2009). Another study showed that immunohistochemical TGFβ correlated with tumor progression and poor prognosis. TGFβ immune activity was significantly higher in advanced than in early GBC ($p = 0.02498$) (Kitamura 2003). These data provide a strong rationale for continuing the development of MSB0011359C in BTC.

CCI [redacted]

3.4 Summary of the Overall Benefit and Risk

The risk-benefit ratio has been carefully considered in the planning of the trial. Based on the nonclinical 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. An SMC

Document No. CCI [redacted]
Object No. CCI [redacted]

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. The following are considered potential risks of exposure to MSB0011359C:

- Infusion-related reactions including hypersensitivity
- irAEs/autoimmune disorders
- Anemia
- Rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin
- Alterations in wound healing or repair of tissue damage
- Embryofetal toxicities.

Respective safety measures 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 trial treatment interruption or discontinuation.

3.4.1 Infusion-related Reactions/Hypersensitivity

CCI

[redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

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

- Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous or oral equivalent) for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted.
- Special precautions for monitoring of subjects and management of infusion-related reactions/hypersensitivity as described in Section 6.5.4.1 and Section 6.5.4.2.
- Infusion-related reactions/hypersensitivity (any grade) are considered as adverse events of special interest (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).

3.4.2 Immune-related Adverse Events/Autoimmune Disorders

CCI [redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

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, such as thyroid stimulating hormone (TSH), 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 occur during the trial, then an appropriate ophthalmology examination should be obtained within 2 days including slit lamp evaluation inclusive of the anterior segment and with visual acuity.

3.4.3 Anemia

As the 4-week toxicology studies in cynomolgus monkeys demonstrated reversible decreases in red blood cell counts, as well as corresponding Hgb and hematocrit, anemia is considered a potential risk. Inclusion criteria for the study will require adequate entry Hgb value. Respective hematological parameters will be monitored every week up to Week 5 and then every 2 weeks thereafter. 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 nonclinical finding of reduced Hgb levels.

3.4.4 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.

3.4.5 Rash with Hyperkeratosis/Keratoacanthoma/Squamous Cell Carcinoma of the Skin

Phase I information from a TGF antibody showed excess acanthomas, some with atypical features, and one confirmed squamous cell carcinoma (Morris 2014). A genetic disorder in the TGF

pathway is also known to be associated with skin tumors (Goudie 2011). Based on this information, skin tumors are considered a potential risk. Monitoring will include skin assessments as defined in the Schedules of Assessments (see Table 1 and Table 2). Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed. Rash with hyperkeratosis/keratoacanthoma/squamous cell carcinoma of the skin are considered as AESIs requiring expedited reporting from the Investigator to the Sponsor. Any suspicious lesion should be biopsied. 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).

3.4.6 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 females. An appropriate contraception warning is provided in this clinical protocol. Subjects with pregnancy or in lactation period are prohibited from enrolling in clinical trials.

3.4.7 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 nonclinical 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.

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 study will be conducted in compliance with the clinical study protocol, standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law; and "Ministerial Ordinance on Standards for the Implementation of Clinical Studies on Pharmaceutical Product (GCP).

4 Trial Objectives

4.1 Primary Objective

The primary objective of the trial is to determine the safety, tolerability and MTD administered as monotherapy of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

4.2 Secondary Objective

The secondary objectives are:

- To characterize the PK profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure
- To assess the best overall response (BOR) according to RECIST 1.1 (Eisenhauer 2009).

4.3 Exploratory Objectives

- To assess progression-free survival time (PFS) according to RECIST 1.1
- To characterize OS time
- To assess the immune-related BOR (irBOR) using the modified immune-related response criteria (irRC), derived from RECIST 1.1 (see Section 7.3.1)
- To assess immune-related PFS (irPFS) using irRC
- To evaluate biological response or predictive markers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers

CCI [redacted]

- To assess symptom severity for subjects with CCI [redacted] BTC via patient-reported outcome measures.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, open-label, dose escalation trial to investigate the safety, tolerability, PK, biological and clinical activity of MSB0011359C (M7824) in subjects with metastatic or locally advanced solid tumors with expansion cohorts in selected indications (CCI [redacted], BTC CCI [redacted]) in Asia (see Figure 1).

5.1.1 Overall Study Design

5.1.1.1 Dose Escalation

CCI

[redacted]

Document No. CCI
Object No. CCI

CCI [redacted]

[redacted]

[redacted]

5.1.1.2 Expansion Cohorts

After determination of the MTD in the dose escalation part, an MSB0011359C dose for further investigation will be selected and enrollment in the expansion cohorts of CCI [redacted] BTC will begin (Figure 1).

CCI [redacted]

Subjects in the expansion cohorts will receive MSB0011359C as a 1-hour intravenous 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 CR, PR or SD should continue treatment through the end of 12 months after confirmation, 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. 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 a CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the study, 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 (see Section 5.1.6).

CCI [redacted]

[redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

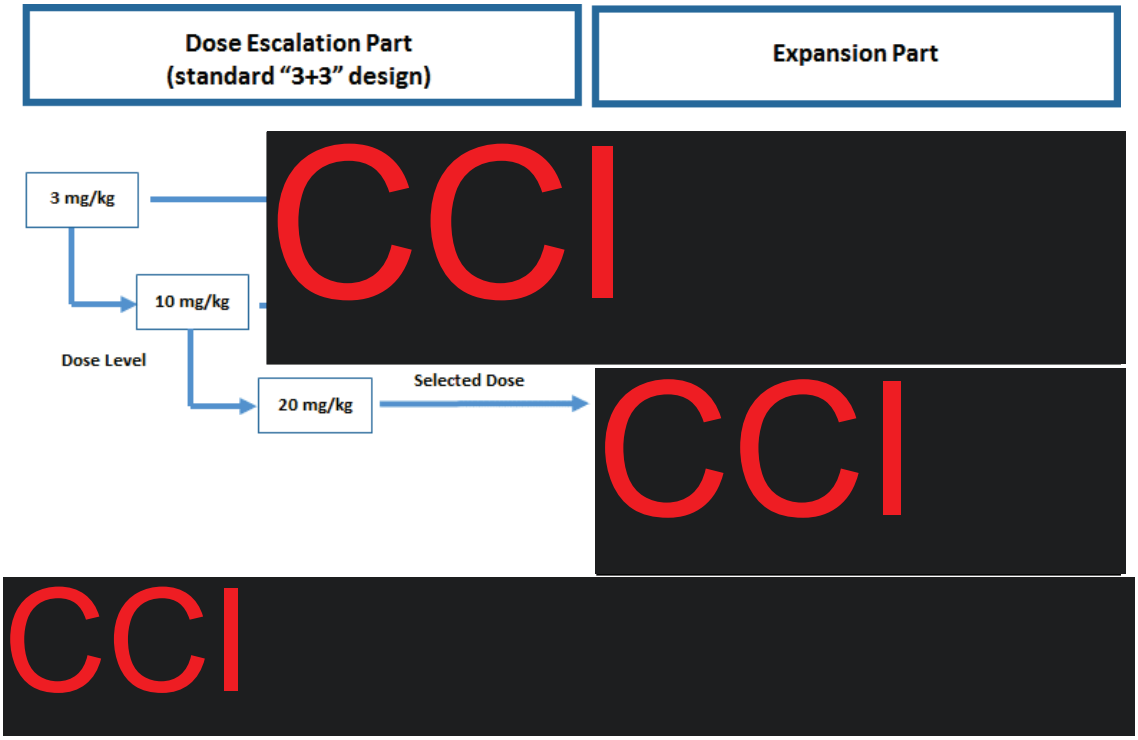
For subjects in the BTC cohort only, symptom severity will be assessed using 4 patient-reported outcomes questionnaires:

- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the EORTC QLQ-BIL21 (cholangiocarcinoma and gallbladder cancer module)
- Select items from the EORTC QLQ-HCC18 (hepatocellular carcinoma module)

Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

Figure 1 Schematic of Study Design



CCI ; BTC=biliary tract cancer.

Document No. CCI
Object No. CCI

Figure 2 Dose Escalation Schematic

5.1.2 Trial Medication Administration and Schedule

Subjects will receive intravenous infusion of MSB0011359C over 1 hour (- 10 minutes/+20 minutes, ie, over 50 to 80 minutes) once every 2 weeks. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous 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. If Grade 2 infusion reactions are seen during the first two infusions, then 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 Section 6.1 and Section 6.6.

5.1.3 MSB0011359C Dose Escalation

5.1.3.1 Starting Dose

CCI [redacted]

5.1.3.2 Dose Escalation

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.3.3 Dose-Limiting Toxicity

CCI [redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

CCI

[redacted]

5.1.4 Expansion Cohorts

CCI

After confirmation of tolerability at 20 mg/kg in the dose escalation part, the MSB0011359C dose for further investigation is 1200 mg in the expansion cohorts of subjects with CCI BTC after confirmation by the SMC.

Document No. CCI
Object No. CCI

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 part: CCI [redacted]

Expansion part: Up to CCI subjects (CCI, up to 100, CCI subjects in the CCI, BTC CCI cohorts, respectively).

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:

- Up to 28-day Screening period (decision will be made in this period for subjects' trial inclusion if all eligibility criteria are met).

CCI [redacted]

- 12-month treatment duration period until confirmed PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5).
- End-of-Treatment visit 28 days (± 5 days) after the last dose of MSB0011359C administration.
- Safety follow-up period 10 weeks (± 2 weeks) after the last administration of MSB0011359C.
- Long-term follow-up period: Subjects without PD at the End-of-Treatment visit will be followed up for disease progression (computed tomography [CT]/magnetic resonance imaging [MRI] scans every 12 weeks) until PD.

CCI [redacted]

Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months after confirmation, 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. 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 a CR, PR, or SD 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. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. 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 Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1 (see Table 2).

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

5.1.7 Dose Modification and ADRs Requiring Treatment Discontinuation

5.1.7.1 Dose Modification

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 Section 5.1.7.2 and Section 6.5.4 and subsections. There are no dose reductions.

5.1.7.2 Adverse Drug Reactions Requiring Treatment Discontinuation

Certain ADRs, defined in this trial as any 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 5 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 within 7 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation <u>except</u> 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.
- 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 trial 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.
- 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. CCI [redacted]
- Increases in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 that resolves to ≤ 2 by cycle 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 dematological irAEs, treatment should be delayed and treatment started according to Table 5, 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 5, 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 5.

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 is manageable and/or not clinically relevant, the ADR should be discussed with the medical monitor. Based on the discussion, it is possible that 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,

another discussion should occur with Medical Monitor to consider 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 may lead to permanently discontinuation.
- Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the guidelines provided in Section 6.5.4.1 and Section 6.5.4.2, respectively.
- Anemia should be handled according to the guidelines provided in Section 6.5.4.4.
- If immune-related ADRs, see Table 5.

5.1.8 Analysis Cut-Off Dates

CCI [redacted]

The primary data cut-off for the analysis of each expansion cohort separately will be 6 months after the last subject in that cohort started treatment.

The final data cut-off is 1 year after the last subject has received the last dose of MSB0011359C.

5.2 Discussion of Trial Design

This is a Phase I, open-label, dose escalation trial with an expansion part in cohorts of subjects with CCI [redacted], BTC CCI [redacted]. An open-label, unblinded design is appropriate for a dose escalation trial with expansion cohorts in advanced cancer subjects since subjects have exhausted treatment options.

CCI [redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

The dose to be used in the expansion part of the trial will be determined based on the data from the dose escalation part. The parameters considered for selection of the dose to be used in expansion part will include safety profile, PK, pharmacodynamics, and antitumor efficacy. 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. There will be 4 cohorts of subjects with CCI, BTC CCI in the expansion part. In order to obtain a trend of biological/clinical activity, to assess target engagement based on tumor tissue 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.

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

5.3.1.2 Inclusion Criteria for Expansion Cohorts

1. Able and willing to give written informed consent and has signed the appropriate written ICF, prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥ 20 years.

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3. Subjects must have one of the following:

- **BTC, second line:** Histologically or cytologically confirmed biliary tract cancer. Must have failed or are intolerant to one line of systemic treatment. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible.

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CCI [redacted]

5. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1.
6. ECOG PS of 0 to 1 at trial entry.
7. Life expectancy ≥ 12 weeks as judged by the Investigator.
8. For subjects with CCI [redacted] BTC, adequate hematological function defined by WBC count ≥ 3 × 10^9/L with ANC ≥ 1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, and Hgb ≥ 9 g/dL (in absence of blood transfusion).
9. For subjects with CCI [redacted] BTC, adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN.
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.
12. Woman of childbearing potential must have a negative serum pregnancy test at screening visit and a negative serum or urine pregnancy test at Day 1 before dosing, if applicable.

5.3.2 Exclusion Criteria

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

1. Concurrent treatment with non-permitted drugs (see Section 6.5.2).
2. Prior therapy with any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody (consult Medical Monitor if necessary), or anti-4-1BB antibody is not allowed, inclusive of intrahepatic, localized administration of such agents.

Document No. CCI [redacted]
Object No. CCI [redacted]

3. Prior therapy with any antibody/drug targeting TGFβ/TGFβ receptor.

4. Anticancer treatment within 21 days before the start of trial treatment, eg, cytoreductive therapy, radiotherapy involving more than 30% of the bone marrow (with the exception of palliative bone directed radiotherapy), immune therapy, or cytokine therapy.

5. Anticancer treatment with antibody within 28 days before the start of trial treatment.

6. Major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy).

7. 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.

8. Previous malignant disease other than the target malignancy to be investigated in this trial with the exception of cervical carcinoma in situ and superficial or non-invasive bladder cancer (treated with curative intent) within the last 5 years or basal cell or squamous cell carcinoma in situ within the last 3 years.

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

10. 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 where no therapeutic intervention is needed should be discussed with the Sponsor.

11. 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).

12. Significant acute or chronic infections including, among others:
    - Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
    - CCI [redacted], HBV infection (HBV surface antigen positive or HBV core antibody positive with reflex to positive HBV DNA) or HCV infection (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)

Document No. CCI [redacted]
Object No. CCI [redacted]

13. 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 ≤ 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.

14. Interstitial lung disease or its history.

15. Known history of hypersensitivity reactions to MSB0011359C or its products, or known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), any history of anaphylaxis, or recent, within 5 months, history of uncontrolled asthma.

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

17. Pregnancy or currently in lactation. Subject is not eligible even if lactation is suspended.

18. Known alcohol or drug abuse.

19. 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.

20. Clinically relevant diseases (eg, 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.

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

22. Legal incapacity or limited legal capacity.

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

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: 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 any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs 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/noncompliance 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.

CCI [redacted]

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 in the event of any of the following:

- 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 has failed to attend scheduled trial assessments, the Investigator must determine and record 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 (End-of-Treatment visit) should be performed (see Section 7.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate End-of-Treatment 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. CCI [redacted]

5.6 Premature Discontinuation 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(s), eg, due to:
  - Evidence of inefficacy of the IMP(s),
  - 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, eg, 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(s).
- Withdrawal of the IMP(s) from the market for safety reasons (applicable to trials with marketed products only).

The Health Authorities and Independent Ethics Committee (IEC)/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 the Health Authorities.

5.7 Definition of End of Trial

If the trial is not terminated for any reason given in Section 5.6, the end of the trial is defined as 1 year after the last subject receives the last dose of MSB0011359C.

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.

There is no placebo or active control arm in this trial.

6.1 Description of 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 the 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. 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 intravenous infusion of MSB0011359C over 1 hour (- 10 minutes/+20 minutes, ie, over 50 to 80 minutes) once every 2 weeks as detailed in the Schedules of Assessments (see Table 1 and Table 2). Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4.1. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous 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. If Grade 2 infusion reactions are seen during the first two infusions, then 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.

CCI [redacted]

CCI [redacted]

A flat dose of 1200 mg MSB0011359C will be used for all subjects in the expansion cohort CCI [redacted] after confirming the tolerability of MSB0011359C at 20 mg/kg. 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 a CR, PR or SD should continue treatment through the end of 12 months at the discretion of the Investigator and in consultation with the Medical Monitor. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor.

For subjects who achieve a CR, PR, or SD 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. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments for the expansion part of the trial (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. Enrollment in the dose escalation and expansion parts will utilize an interactive web response system.

6.4 Non-investigational Medicinal Products to be Used

In order to mitigate potential infusion-related reactions premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous 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. If Grade 2 infusion reactions are seen during the first two infusions, then 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 (intravenous antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Infusion of MSB0011359C will be stopped in case of Grade ≥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, CCI [redacted] 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 nonsteroidal anti-inflammatory drug (NSAID), eg, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of MSB0011359C intravenous 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 bone directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST 1.1 (Eisenhauer 2009) and not based on the necessity for palliative bone-directed radiotherapy.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had chemotherapy, radiotherapy involving more than 30% of the bone marrow (other than palliative bone directed radiotherapy as described in Section 6.5.1) within 21 days before the start of trial treatment, and anticancer treatment with antibody, 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, immunosuppressive drugs (eg, 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 (ie, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are 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 (eg, inactivated influenza vaccines).

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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, antiemetics, 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 (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Subjects should not abuse alcohol or other drugs during the trial.

6.5.4 Special Precautions

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In the expansion part of the trial, there is no in-house observation and no waiting period between subjects.

As a routine precaution, subjects enrolled in this trial (ie, 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 ≥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. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like ANAs.

6.5.4.1 Infusion-related Reactions

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

B. Management (see Table 4)

Table 4 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 (eg, 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 (eg, 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 4 (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 (eg, 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.

Document No. CCI
Object No. CCI

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

B. Management
1. Epinephrine injection and intravenous 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, an NSAID, eg, 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 CCI [redacted]

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 5.

Table 5 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	Continue MSB0011359C therapy	Close monitoring for worsening symptoms Educate subject to report worsening immediately

Document No. CCI [redacted]
Object No. CCI [redacted]

Colitis: asymptomatic	Symptomatic treatment (eg, loperamide)	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 (eg, antihistamines, topical steroids) Continue MSB0011359C therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Delay 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)

Document No. CCI [redacted]
Object No. CCI [redacted]

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 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 (eg, 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
Grade 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 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 returns to Grade 2: Taper steroids over at least 1 month 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 (e.g. 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 avelumab 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]	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

	Methylprednisolone 1 to 2 mg/kg/day.	

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 free 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 (eg, 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	

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=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

6.5.4.4 Anemia

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

- Subjects must enter the trial 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)
- RBC morphology will be assessed in the case of anemia onset caused by hemolysis, or other unknown causes
- Instructions for trial treatment discontinuation or modification in case of anemia will be provided, briefly described here:

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- 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, activated partial thromboplastin time, 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 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, anti-drug antibodies (ADAs).

6.5.4.5 Rash with Hyperkeratosis/Keratoacanthoma/Squamous Cell Carcinoma of the Skin

Monitoring will include skin assessments as defined in the Schedules of Assessments (Table 1 and Table 2), with biopsy of suspicious lesions. Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed. Hyperkeratotic rash/keratoacanthoma/squamous cell carcinoma will be considered as AESI requiring expedited reporting from the Investigator to the Sponsor.

6.5.4.6 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.

6.5.4.7 Dose Interruptions for Adverse Events No Related to Study Drug

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

If the AE reduces to a lower tolerable grade, the study treatment may 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), the event should be discussed with the Medical Monitor to consider either a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment.

If upon resuming study treatment, the subject experiences the same AE again, this should be discussed again 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 / 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 (2°C to 8°C) that are monitored with temperature control devices.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP Guidelines.

6.7 Preparation, Handling and Storage

MSB0011359C drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with MSB0011359C.

MSB0011359C drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. MSB0011359C must not be frozen. Rough shaking of the reconstituted solution must be avoided.

For application in clinical trials, the freeze-dried MSB0011359C drug product must be reconstituted with 4.5 mL of Water for Injection and diluted with 0.9% saline solution (sodium chloride injection), while the liquid formulation must be diluted with 0.9% saline solution. The chemical and physical in-use stability for the infusion solution of MSB0011359C in 0.9% saline solution has been demonstrated for a total of 72 hours at room temperature; however, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. No other drugs should be added to the infusion containers containing MSB0011359C.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

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

The contents of the MSB0011359C vials are sterile and non-pyrogenic, 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 Head of the trial site is responsible for ensuring accountability for the IMP, including reconciliation of drugs and maintenance of drug records. The head of the trial site can delegate the control of and accountability for trial drug to the investigational product storage manager**.**

- Upon receipt of the IMP, the head of the trial site or the investigational product storage manager will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation provided by the Sponsor and returning it to the Sponsor. A copy will retained by the head of the trial site.

- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor's Medical Monitor 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 by the Sponsor and prepared at the site.
- The use of each dose by each subject.
- The return to the Sponsor or alternative disposition of unused trial drug.
- Dates, quantities, batch numbers, expiry dates, formulation (for IMP prepared at the site), and the subjects' trial numbers.
  - The Investigator should maintain records that adequately document the following:
  - The subjects received the doses specified by the clinical trial protocol/amendment(s); and
  - The head of the trial site should maintain records that adequately document that all IMP provided by the Sponsor were fully reconciled.

The unused IMP must not be discarded or used for any purpose other than the present trial. Any IMP that has been dispensed to a subject must not be re-dispensed 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 head of the trial 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.

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive IMP (MSB0011359C intravenous 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 Method of 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 appropriate reporting form (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 part of the trial is provided in Table 1 and for the expansion part in Table 2. Sample collection for PK, biomarkers, tumor tissues, and changes in gene expression are provided in Table 3.

Prior to performing any study 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 21-day washout/recovery period for prior anticancer treatment (eg, cytoreductive therapy, radiotherapy involving more than 30% of the bone marrow [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin) and 28 days for prior anticancer treatment with antibody, 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, recording vital signs, including body weight and height (height only at Screening), 12-lead electrocardiogram (ECG), dermatological assessment, 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, CCI , and full urinalysis. Adrenocorticotropic hormone (ACTH), ANA, 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, HCV and HIV testing will be performed for all Screening subjects as these conditions are trial entry exclusion criteria. Females who are postmenopausal (age-related amenorrhea ≥12 consecutive months and if needed increased FSH > 40 mIU/mL [in the postmenopausal range]), 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. CCI

- The tumor evaluation (type/staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory) as well as tumor markers or any other established methods (see Section 7.2.5 for details). Brain CT/MRI scan (either, with contrast preferred) is required if not performed within the previous 6 weeks. Bone scans should be performed as clinically indicated.

Collection of tumor tissues or archived surgical specimen will also be done during this period, if applicable CCI . Subjects in the expansion cohorts are required to provide tumor tissue samples, see Section 5.3.1 and Section 7.6.1.3 for details.

Baseline samples for ADAs (the term for ADA on the CRF is human antihuman antibodies [HAHA]), biomarkers, blood samples for optional PGt/PGx, and for mRNA analysis (gene expression evaluation) should be collected.

For subjects in the CCI BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, CCI) will be administered and completed by the subjects at Screening to collect baseline data about their symptom severity.

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 CR, PR or SD should continue treatment through the end of 12 months after confirmation, 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. 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 CR, PR, or SD 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. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. 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 samples must be drawn and results 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 Schedule of Assessments for the expansion part of the trial (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 trial procedures (except on Day 2 and the Day 43-50 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 Part Treatment Period

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[redacted]

Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia MS200647-0008

[redacted] 98/177

Document No. CCI
Object No. CCI

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7.1.2.2 Expansion Part 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 CCI BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, CCI) 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.
- 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.
- Any new concomitant procedures will be documented in each study visit. In the event cytology was collected (eg, diagnostic and/or therapeutic paracentesis, thoracentesis, etc) will require completing and forwarding a Cytology Form as outlined in the Imaging Site Operations Manual. For any biopsies or other procedures resulting in tissue acquisition, official pathology reports must be filed and available for review if requested.
- Physical examination will be performed prior to trial treatment on Day 1 (Week 1). After Day 1, a directed physical examination indicated by subject's symptoms will be performed according to Table 2.
- At each visit, 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 assessment.
- SpO_2 will be measured.
- Vital signs, including body weight, will be assessed prior to trial treatment according to Table 2.
- 12-lead ECG will be assessed prior to and as soon as possible after infusion according to Table 2.
- The laboratory hematology and hemostaseology tests will be assessed 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.

Document No. CCI
Object No. CCI

- 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 as detailed in Table 2.
- A serum β-HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed prior to each administration of the study drug every 4 weeks (if applicable). If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
- 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.
- Tumor biopsies at Week 7 (Days 43 to 50, see 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).
- Soluble factors will be drawn as detailed in Table 3 and as described in Section 7.6.1.2.
- Samples for TGFβ determination will be drawn as detailed in Table 3.

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- Blood samples for gene expression evaluation will be collected according to Table 3 (prior to study drug administration where applicable).

7.1.3 End-of-Treatment

7.1.3.1 Discontinuation Visit

Any subject who experiences an AE that mandates discontinuation of trial treatment should have a discontinuation visit within 7 days after the decision to discontinue trial treatment (see Table 1 and Table 2). For all these subjects, the discontinuation visit consists of:

- Documentation of AEs and concomitant medications.
- Physical examination including vital signs and body weight.
- Dermatological assessment.
- SpO_2 will be measured.
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis.
- ECOG PS will be assessed.

Document No. CCI [redacted]
Object No. CCI [redacted]

7.1.3.2 End-of-Treatment Visit

The End-of-Treatment 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. The End-of-Treatment 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 CCI BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, CCI) will be completed prior to any study-related procedures as indicated in Table 2.
- AEs, concomitant medications.
- Vital signs and body weight.
- Physical examinations.
- Dermatological assessment.
- SpO_2 will be measured.
- 12-lead ECG will be assessed.
- The laboratory hematology, hemostaseology, full serum chemistry, CCI and full urinalysis.
- ECOG PS will be assessed.
- Urine β-HCG pregnancy test (in females of childbearing potential).
- Tumor evaluation (only to be performed, if no disease progression was documented previously).
- Free T4 and TSH.
- PK sample.
  - ADA sample (see Section 7.7.1). The term for ADA on the CRF is human antihuman antibodies (HAHA)
  - Soluble factors will be drawn as described in Section 7.6.1.2 and Table 3.
  - Samples for TGFβ determination as described in Table 3.
  - Blood samples for gene expression evaluation for subjects with PD.
  - Samples for viral load testing (HBV, HCV) CCI
  - If the therapy is discontinued due to regrowth of the tumor, then a repeat biopsy at the end of treatment is advisable (optional). A PK sample should be collected as close as possible to the time of the biopsy (ie, same day).

7.1.4 Post-Treatment Follow-up

7.1.4.1 Safety Follow-up Visit

All subjects will have a subsequent visit scheduled 10 weeks (±2 weeks) after the last administration of MSB0011359C. The visit will include the following full assessment of safety parameters (refer to Table 1, Table 2, and Table 3):

- For subjects in the CCI BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, CCI) will be completed prior to any study-related procedures as indicated in Table 2.
- AEs that are deemed attributable to trial drug by the Investigator and concomitant medications (including further anticancer therapy) will be documented.
- Vital signs and body weight will be measured.
- Physical examination will be performed.
- Dermatological assessment.
- SpO_2 will be measured.
- ECOG PS will be assessed.
- 12-lead ECG will be assessed.
- Laboratory testing consisting of the following will be assessed:
  - Hematology, hemostaseology, full serum chemistry, and full urinalysis
  - Free T4, and TSH levels.
    - PK sample will be collected.
    - ADA sample. The term for ADA on the CRF is human antihuman antibodies (HAHA)

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- A urine β-HCG pregnancy test (in women of child bearing potential) will be conducted.

7.1.4.2 Long-term Follow-up/Trial Termination

All SAEs ongoing at the End-of-Treatment 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 End-of-Treatment visit and ongoing at the Safety Follow-up visit have to be followed up in the same manner.

Subjects without PD at the End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 12 weeks) until PD.

After the End-of-Treatment visit, subjects will be followed quarterly (±14 days) 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 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 60 mL/day and 300 mL in an 8-week period for safety laboratory testing, pregnancy testing, PK analyses, exploratory biomarker investigation, 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 recoded:

- 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.
- 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.

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.

A complete physical examination will be performed. Oxygen saturation will be measured. 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 period.

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) 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 nontarget lesions [redacted] 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 under institution's guidance 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, RR duration and corrected QT intervals, and possible arrhythmias.

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 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; CCI [redacted] 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, PD 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 End-of-Treatment 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, nontarget, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation) CCI [redacted]

- 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 nontarget lesions according to RECIST 1.1 and CCI [redacted]

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. 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. Following PD on RECIST 1.1, modified "immune-related response criteria" (irRC; see below and Nishino 2013) should be used as guidance for further clinical care.

Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months after confirmation, 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. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Table 1 and Table 2).

7.3.1 Modified Immune-related Response Criteria (irRC), Derived from RECIST 1.1

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. For this trial, the concepts of the irRC (Nishino 2013) are combined with RECIST 1.1 to come up with the modified irRC, which uses unidimensional measurements.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1, the modified irRC criteria

a) require confirmation of both progression and response by imaging at 4 to 6 weeks (preferably 6 weeks) after initial imaging, and

b) do not necessarily score the appearance of new lesions as PD if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at Baseline, during the trial, and at the End-of-Treatment visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified irRC are defined as follows:

- New measurable lesions: Incorporated into tumor burden.
- New non-measurable lesions: Do not define progression but precludes immune-related complete response (irCR).

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm or less.

Overall immune-related partial response (irPR): Sum of the longest diameters of target and new measurable lesions decreases ≥30%.

Overall immune-related stable disease (irSD): Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD; compared to nadir).

Overall immune-related progressive disease (irPD): Sum of the longest diameters of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Documentation of irPD (based on modified irRC) does not mandate discontinuation of the trial treatment, even after irPD is confirmed with CT scan 6 weeks after the initial observation of irPD. Please refer to Section 5.5.1 (Withdrawal from the Trial Treatment) to determine when it is appropriate to discontinue treatment with the study drug.

Overall responses derived from changes in index, non-index, and new lesions are shown in Table 6.

Table 6 Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)	Non-Index Lesions	New, Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR[a]
Decrease 100%	Stable	Any	irPR[a]
Decrease 100%	Unequivocal progression	Any	irPR[a]
Decrease ≥30%	Absent/Stable	Any	irPR[a]
Decrease ≥30%	Unequivocal progression	Any	irPR[a]
Decrease <30% increase <20%	Absent/Stable	Any	irSD
Decrease <30% to increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

irCR= immune-related complete response; irPD= immune-related progressive disease; irPR= immune-related partial response; irSD= immune-related stable disease.

[a] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at at least 4 weeks apart (normally it should be done 6 weeks apart).

CCI [redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

CCI

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[redacted]

[redacted]

[redacted]

Document No. CCI
Object No. CCI

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analyzing 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 related to AE*

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.

*Note: Death (Grade 5 as defined by NCI-CTCAE version 4.0) is mainly regarded as an outcome, to be documented as described below.

If death occurs, the primary cause of death or the 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 (eg, 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 suspected to be 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: Suspected to be 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 (eg, 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 (eg, 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 Event

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

- Results in death.
- Is life-threatening (NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

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 in this definition. 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 the IMP is also considered an SAE, and all such cases should be reported in an expedited manner 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 (eg, 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 (eg, 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 study are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs or reported as SAEs, if they meet criteria for seriousness.

7.4.1.1.4 Pre-defined AEs of Special Interest (AESI) for Safety Monitoring

Any AE that is suspicious to be a potential irAE (see Section 6.5.4.3), including ophthalmologic findings, has to be reported in an expeditious manner and will be considered an AESI.

Infusion-related reactions/hypersensitivity, regardless of grade, must be reported as AESIs.

In addition, rash with hyperkeratosis/keratoacanthoma/squamous cell cancer of the skin are regarded as AESIs. Please note that squamous cell cancer of the skin should be considered as medically important condition and thus as a serious AESI, which has to be reported in an expedited manner as a SAE.

Anemia suspected by the Investigator to be drug related should also be reported as an AESI.

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. CCI [redacted]

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 End-of-Treatment visit, defined as 28 days (±5 days) after last trial drug administration. After the End-of-Treatment visit, only AEs that are deemed attributable to trial drug by the Investigator should be documented until the 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 (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, 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/reporter must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor may have on the AE within the same timelines as initial reports. This is necessary to ensure a prompt assessment of the event by the Sponsor or designee and, where applicable, to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Medical Monitor. In exceptional cases where a particularly critical event occurs, 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*** 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.

CCI [redacted]

[redacted]

7.4.1.5 Safety Reporting to Health Authorities, 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 report SAEs in accordance with applicable site-specific requirements to the IRB that approved the trial.

In accordance with the ICH GCP guidelines and the Japanese ministerial ordinance on GCP, the Sponsor or designee will immediately inform all the trial investigators and the Heads of the trial sites of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IRB's approval/favorable opinion to continue the trial." In particular and in line with respective applicable regulations, the Sponsor/designee will immediately inform all the trial investigators and the Heads of the trial sites of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). In addition, according to applicable regulations, the Sponsor/designee will inform the trial investigators and the Heads of the trial sites of all SAEs which were reported to the health authorities. In accordance with the Japanese regulatory requirements concerning safety reporting, the Investigator should place copies of the safety reports in the Investigator Site File. The Head of the trial site should also maintain copies of safety reports appropriately. 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 IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IRB of any safety reports provided by the Sponsor or designee and for 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 Guidances.

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 End-of-Treatment visit. After the End-of-Treatment visit, only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.

All SAEs ongoing at the End-of-Treatment 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 End-of-Treatment 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 (eg, 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 in female partners of male subjects. The Investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process 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 study.

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

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. CCI [redacted] Blood samples for the tests listed in Table 8 will be taken from non-fasted subjects during the Screening period, at the End-of-Treatment visit, and during the treatment period 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.

CCI [redacted] ACTH, ANA, RF, free 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, an FSH level will also be performed at Screening, see Section 7.1.1.

Table 8 Required Laboratory Panel Tests

Full Chemistry	Hematology
CCI [redacted]	[redacted]
Albumin	ANC
Alkaline phosphatase*	Hematocrit
ALT*	Hemoglobin
Amylase	Platelet count
AST*	RBC count
GGT	WBC count and differential count
BUN/total urea*	RBC morphology**
Calcium*	Reticulocytes
Chloride*	MCH
Cholesterol	Mean corpuscular volume
Creatine kinase	MCHC
Creatinine*	
CRP	**Hemostaseology**
Glucose*	aPTT
LDH	Prothrombin time/INR
Lipase	
Phosphorus/phosphates*	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)
Magnesium*	
Potassium*	Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End-of-Treatment visits and a basic urinalysis prior to each administration of the IMP.
Sodium*	
Total bilirubin/indirect bilirubin*	
Total protein	Totality of binding ADAs
Uric acid	
Triglycerides	**ACTH, ANA, RF, TSH, and free T4**
Hormone	
FSH (if applicable)	

ACTH=adrenocorticotropic hormone; ADA-anti-drug antibody; CCI [redacted]; ALT=alanine aminotransferase; ANA=antinuclear antibody; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle stimulating hormone; GGT=gamma-glutamyltransferase; IMP=Investigational Medicinal Product; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RBC=red blood cell; RF=rheumatoid factor; TSH=thyroid stimulating hormone; T4=thyroxine; WBC=white blood cell.

* Core serum chemistries. ** This test will be conducted in cases that a patient has anemia due to hemolysis or anemia of unknown etiology.

Document No. CCI [redacted]
Object No. CCI [redacted]

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. In addition, RBC morphology will be assessed in case of anemia onset caused by hemolysis, or other unknown causes.

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 and SpO_2 measured 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 at Screening and at trial visits as indicated in the Schedules of Assessments (Table 1 and Table 2) until Week 13 (Visit 10).

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 period. A urine or serum β-HCG test will be performed once a month during the treatment period as indicated in the Schedules of Assessments (Table 1 and Table 2), at the End-of-Treatment 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 ≥ 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 Part

CCI [redacted]

7.5.2 Expansion Part

Pharmacokinetics parameters will include C_{max} and C_{min}. 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 (2.5 mL per sample) will be collected for PK assessments. Post-infusion samples should be drawn from a site other than the infusion site (ie, 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 300 mL and during the first 85 days will not exceed the total of 350 mL.

Further details will be summarized in the Laboratory Manual.

7.6 Biomarkers and Pharmacogenetics/Genomics

To better understand the immune-associated biological activities induced by MSB0011359C in cancer subjects in relation to drug exposure, a number of relevant biomarkers including pharmacogenomics markers will be studied. Therefore, in addition to determining the MTD, the study will serve to:

1. Evaluate the drug effect on TGFβ concentrations in plasma CCI [redacted];
2. Investigate the overall MoA of the drug by monitoring the activation status of the immune system (eg, cytokines profile) in order to establish the optimal biological dose;
3. Investigate safety markers (see Section 7.7.2);
4. Explore antitumor-specific immune responses induced by the exposure to MSB0011359C; and

5. Evaluate potential predictive/prognostic biomarker candidates related to the drug and/or the cancer (eg, level of PD-L1 tumor expression, profile of tumor infiltrating lymphocytes).

Details of time points and sampling are provided in the Schedule of Assessments (Table 3). Time points and markers proposed in the expansion part may change based on biological activities to be observed in the escalation part and /or indications.

In order to complete all the assessments on tumor materials, blood (whole blood, plasma and serum samples), the Sponsor or the designated CRO will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. Please refer to the Laboratory Manual for detailed information.

All proposed biomarker analyses are exploratory and dependent on the quality and availability of sufficient materials. Collection and storage of samples will be detailed in the Laboratory Manual. The panel of biomarkers might be adjusted based on results from ongoing research related to anti-PD-1/PD-L1 therapies and/or safety, therefore, each subject will also be asked whether any remaining tumor tissue and blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug and/or disease-related aspects. A subject's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the subject's participation in the current trial.

7.6.1 Biomarker Investigation in Dose Escalation and Expansion Cohorts

7.6.1.1 Target-related Biomarkers

Blood will be collected to analyze TGFβ concentrations according to the Schedule of Assessments (Table 3). Details of the blood collection will be provided in the Laboratory Manual.

7.6.1.2 Immunomonitoring

Antitumor specific immune responses and cellular composition in the tumor environment will be explored in the tumor samples.

Soluble factors (eg, cytokines profile) will be assessed on blood samples collected according to the Schedule of Assessments (Table 3).

7.6.1.3 Predictive/Prognostic Biomarkers

It is important to identify biomarkers that help to predict and/or evaluate the efficacy of the therapy, in order to achieve the optimal benefit from targeted therapies. No thoroughly validated biomarkers are available to date for anti-PD-1/PD-L1 and anti-TGFβ therapies; therefore, this

study plans to evaluate biomarkers from tumor tissues and blood samples that might be predictive of therapy outcome for all indications. Of note, availability of tumor tissue will be a prerequisite for all subjects to be enrolled in the expansion part.

The following requirements apply to the tissue samples collected during the study, unless specified otherwise:

Tissue collection: Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suited. Fine needle aspiration biopsies are not suited. The most recent biopsy or surgical specimen is required.

Tissue processing: The cancer tissues should be fixed in 10% neutral buffered formalin, paraffin-embedded and routinely processed for histological evaluation. Formalin substitutes are not suited as fixative.

Tissue storage: Fresh tumor tissue obtained from subjects in any cohort should be stored as described in the Laboratory Manual.

Provision of samples: 1. Priority: tumor containing formalin fixed, paraffin embedded tissue block; 2. Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided which are freshly cut, 4 µm thick and mounted on positively charged microscope slides. SuperFrost Plus glass slides are recommended. Preferably, 25 slides should be provided; if not possible, a minimum of 10 slides is required to conduct only a subset of the planned analyses. Tumor tissues suitable for biomarker analysis are required. Suitable means that the central laboratory can confirm that the tissue is evaluable (enough viable tumor cells are present). If any of these requests are not met, the Sponsor should be contacted.

Sample shipment: The tumor blocks and freshly prepared slides should be sent with next shipment to the central lab at room temperature.

Sample storage: At the central laboratory, the formalin fixed, paraffin embedded tissue blocks shall be stored at room temperature and the tumor slides shall be frozen in sealed containers at -80°C.

A panel of putative markers including molecular, soluble and cellular markers will be analyzed at baseline from archived tumor tissue (or fresh tumor biopsy, if available), and/or serum/plasma samples to investigate a possible correlation between clinical efficacy and analyzed markers.

The following assessment will be considered:

- Level of PD-L1 expression in tumor tissues by immunohistochemistry staining. Of note, further techniques to evaluate the expression of PD-L1 and/or marker candidates impacting the targeting or contributing to improve its expression may be also investigated if needed.
- Level of TGFβ signaling in tumor by various assays.

- Frequency and localization of tumor-infiltrated leukocytes (eg, CD8, CD4 T-cells, Treg, NK cells, macrophage [M1/2 profile]) by immunohistochemistry.
- Further exploratory markers related to the MoA of the drug such as intratumoral cytokine profile, and auto-antigen proteomic arrays may be explored.
- Further cellular and/or molecular markers specific to the cancer may be also investigated according to the indication.

7.6.2 Pharmacogenetics

Blood samples (two 3 mL samples to be obtained during the screening period or prior to first dose) will be collected to enable germline DNA testing. The genetic analysis will be restricted to analyses intended to provide further understanding of the genetics of:

- The MoA of the study drug. (For example, genes related to the immune system and cancer-associated genes.)
- The treated cancer type or neoplasms in general.
- AEs possibly associated with the study drug, any other concomitant treatment, or the disease

The genetic sample may be analyzed in the context of this study or beyond this individual study in the context of the development of MSB0011359C.

The sample will be stored in Merck Serono's/EMD Serono's biobank after de-identification using a single code. The Sponsor of the trial will be permitted to link the sample to the individual clinical and laboratory outcomes of the investigational treatment in order to enable scientific analyses.

The sample will not be utilized to obtain information about individual genetic risks not related to neoplasms or drug effects. Genetic data obtained during the analysis of the sample will not be reported back to the individual or any third person, including her/his healthcare providers. Storage and analyses of samples will be handled according to the specifications as described in the ICF. The subject can request the destruction of the sample at any time.

7.7 Other Assessments

7.7.1 Anti-drug antibody 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 Schedule of Assessments (Table 3). Whole blood (3.5 mL per sample) will be collected for ADA analysis at each sampling point.

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

Further details will be summarized in the Laboratory Manual.

7.7.2 Safety Biomarkers

As an inhibitor of T-cell check-point, irAEs may potentially occur under treatment with MSB0011359C; therefore, it is planned to analyze safety biomarkers (Section 7.6).

7.7.3 Health-related Quality of Life

For subjects in the CCI BTC expansion cohorts, symptom severity will be assessed using a generic question to assess severity of symptoms (PGIS) and using instruments for the assessment of cancer-specific symptoms (Table 2). Each of the instruments and the selected items for administration are described below.

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?). The PGIS will be administered in the CCI BTC expansion cohorts.

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). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much). 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, as follows:

CCI

- BTC: Fatigue (3 items)

CCI

Document No. CCI
Object No. CCI

- **EORTC QLQ-BIL21**: The EORTC QLQ-BIL21 is a 21-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to cholangiocarcinoma and gallbladder cancer (Friend 2011). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).
- BTC: Stomach/back pain (3 items), early satiety (1 item), and itching (1 item)

EORTC QLQ-HCC18: The EORTC QLQ-HCC18 is an 18-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to HCC (Blazeby 2004). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much). While not specifically designed for BTC, the EORTC QLQ-HCC18 includes two items that are a key symptom associated with BTC:

- BTC: Fevers (2 items)

8 Statistics

8.1 Sample Size

8.1.1 Dose Escalation

CCI [redacted]

8.1.2 Expansion Cohorts

The ORR will be determined as the proportion of patients with confirmed BOR of PR or CR.

Thirty subjects will be enrolled in each cohort. The goal of these cohorts is an exploration of initial clinical activity and viewed as hypothesis-generating, and not intended as a test of a hypothesis. The sample size in these cohorts is a practical number in order to obtain preliminary estimates of efficacy. The confirmed ORR according to RECIST 1.1 as adjudicated by the IRC will be determined as the proportion of subjects with confirmed BOR of PR or CR. A 95% exact (Clopper-Pearson) confidence interval (CI) will be calculated for the ORR. Table 9 provides precision of estimated response rates based on a total sample size of 30 subjects under different assumptions on the true response rate in the overall population. CCI [redacted] After confirming the safety of 20 mg/kg in the dose escalation part, the 1200 mg flat dose will be used in the dose expansion part CCI [redacted].

After determination of the MTD in the dose escalation part, an MSB0011359C dose for further investigation will be selected and enrollment in the expansion cohorts of subjects with CCI [redacted] BTC will start.

For expansion cohorts of subjects with CCI [redacted] BTC, the primary secondary efficacy endpoint is the BOR, as adjudicated by the IRC and will be evaluated by confirmed ORR according to RECIST 1.1 based on IRC assessment.

Table 9 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)

Up to CCI [redacted] subjects are planned in the expansion cohorts (CCI [redacted] up to 100, CCI [redacted] in the CCI [redacted], BTC CCI [redacted] cohorts, respectively).

The total sample size at the end of the trial (based on the dose escalation part and the expansion part) is expected to be up to approximately CCI [redacted] subjects.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

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

CCI

8.3.2 Secondary Endpoints

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

CCI

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

- BOR according to RECIST 1.1 as adjudicated by the IRC
- BOR according to RECIST 1.1 per investigator assessments
- Duration of response according to RECIST 1.1 as adjudicated by the IRC
- Disease control rate according to RECIST 1.1 as adjudicated by the IRC
- PFS time according to RECIST 1.1 as adjudicated by the IRC
- OS time.

8.3.3 Exploratory Endpoints

Exploratory endpoints for the dose escalation part of the trial are:

CCI

Exploratory endpoints for the expansion part of the trial are:

- irBOR according to modified irRC as adjudicated by the IRC and per investigator assessments
- irPFS according to modified irRC as adjudicated by the IRC and per investigator assessments

- Changes in blood, tumor, and tumor environment biomarkers
- Potential predictive markers
- Exploratory endpoints for the CCI BTC expansion cohorts also include:

  - Changes in symptom severity for subjects with BTC as assessed by the PGIS item and selected items from the EORTC QLQ-C30, cholangiocarcinoma and gallbladder cancer module (EORTC QLQ-BIL21), and hepatocellular carcinoma module (EORTC QLQ-HCC18).

8.3.4 Safety Endpoints

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

- Laboratory parameters
- Vital signs
- ECG parameters.

8.4 Analysis Sets

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

[redacted]

- **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.
- **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 1 post-treatment serum sample.
- **Biomarker analysis set for genetic markers in tumor tissue:** All subjects who received at least 1 dose of trial treatment and have provided at tumor sample prior to any MSB0011359C treatment and at least 1 post-treatment tumor sample.
- **Biomarker analysis set for PGx:** All subjects who have provided a sample (tumor or whole blood) prior to any MSB0011359C treatment.

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 trial 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. All data will be presented in a descriptive manner. Each cohort will be analyzed separately and no multiplicity adjustment across cohorts will be performed. All other analyses are considered as exploratory, even if statistical tests are used.

Descriptive statistics will be used to summarize the trial results, ie, 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 CIs. Unless otherwise specified, the calculation of proportions will be based on the sample size of the population 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.

CCI 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.

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

CCI

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Efficacy Parameters

Clinical efficacy parameters will be analyzed descriptively in the full analysis set.

Does escalation

CCI

Document No. CCI
Object No. CCI

CCI [redacted]

Dose expansion

For the dose expansion part of the trial, the primary secondary efficacy endpoint is confirmed BOR according to RECIST 1.1 as adjudicated by the IRC (Section 2.2.2) for the CCI [redacted] BTC cohorts.

For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) will be required for the final analysis for both escalation and expansion parts. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The ORR and associated 95% CIs will be tabulated for each cohort.

The following secondary endpoints will also be reported:

- Duration of response according to RECIST 1.1 as adjudicated by the IRC will be defined as the time from first confirmed response until the first documented disease progression that is subsequently confirmed. It will be analyzed using Kaplan-Meier method. Subjects without an event at the analysis cut-off date will be censored on the date of the last tumor assessment.
  - Disease control rate, defined as the proportion of subjects with BOR of CR, PR, or SD with minimum duration of 12 weeks according to RECIST 1.1 as adjudicated by the IRC, will be tabulated within each expansion cohort.
  - PFS time according to RECIST 1.1 as adjudicated by the IRC
    - The PFS time is defined as the time (months) from first administration of trial drug to the first observation of radiological PD (as assessed by the IRC) or occurrence of death due to any cause. PFS will be presented in listings and analyzed using the Kaplan-Meier method in CCI [redacted] BTC cohorts separately if the cohort enrolls the full planned number of subjects. The detailed censoring rules will be provided in the SAP.
    - OS, defined as the time between the first dose date and death. If a patient has not died, the patient will be censored at the time of last contact (last known alive date). OS will be presented in listings and analyzed using the Kaplan-Meier method in CCI [redacted] BTC cohorts separately if the cohort enrolls the full planned number of subjects.
- OS time.

8.5.3.2 Pharmacokinetics Profile

Serum concentrations of MSB0011359C will be determined by a validated method at the times listed in the Schedule of Assessments (refer to Table 3).

The following PK parameters will be estimated and reported:

CCI

- C_{max} : Maximum serum concentration observed postdose (for the expansion phase, 2 postdose samples in 3 cycles).
- C_{min} : Minimum serum concentration observed postdose.

CCI

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:

- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (April 2008. EMEA/CHMP/BMWP/14327/2006).
- Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (24 May 2012. EMA/CHMP/BMWP/86289/2010).
- Food and Drug Administration (December 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.

8.5.3.4 Biomarkers

Summary statistics for biomarkers will be provided for all preplanned time points, separately for each dose level or cohort. Changes to baseline levels will also be presented as applicable. Profiles over time will be displayed on a per subject basis. Details of the statistical analysis of biomarkers will be presented in the SAP, separately for the dose escalation and expansion parts of the trial.

8.5.4 Analysis of Exploratory Endpoints

The following will be reported as the exploratory analyses:

Dose escalation:

Dose expansion:

- irBOR according to modified irRC as adjudicated by the IRC and per investigator assessments will be evaluated by irORR, which is defined as having an irBOR assessment of irCR/irPR. The irORR and associated 95% CI will be tabulated for each cohort.
- irPFS according to modified irRC as adjudicated by the IRC and per investigator assessments will be presented in listings and analyzed using the Kaplan-Meier method in CCI BTC cohorts separately if the cohort enrolls the full planned number of subjects. The detailed censoring rules will be provided in the SAP.

- Changes in blood, tumor, and tumor environment biomarkers tabulated by dose-level or cohort, using descriptive statistics.
- Potential predictive markers tabulated by dose-level or cohort, using descriptive statistics.
- Exploratory endpoints for the CCI BTC expansion cohorts also include:

- Changes in symptom severity for subjects with BTC as assessed by the PGIS item and selected items from the EORTC QLQ-C30, cholangiocarcinoma and gallbladder cancer module (EORTC QLQ-BIL21), and hepatocellular carcinoma module (EORTC QLQ-HCC18).

8.5.5 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/2 weeks), 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, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology and serum chemistry).

8.5.5.1 Adverse Events

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

The incidence TEAEs 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 TEAEs 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. AEs occurring after the last trial drug administration will always be classified as TEAE if it is considered trial drug-related by the Investigator. All premature terminations will be summarized by primary reason for treatment withdrawal.

8.5.5.2 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.

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

Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination will therefore not be provided.

Vital signs (including body temperature, respiratory rate, heart rate, and blood pressure), and 12-lead ECG recorded according to the Schedules of Assessments (refer to Table 1 and Table 2) will be descriptively presented.

Further details on the safety analyses will be provided in the SAP.

8.6 Interim 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.

CCI [redacted]

[redacted]

BTC Cohort

One interim analysis is planned for this cohort 12 weeks after the 20th subject in the cohort started treatment. The endpoint in this interim analysis is BOR (confirmation is not required). No multiplicity adjusted is applied to the interim analysis.

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 his/her site. Throughout this clinical trial protocol, Investigator refers to both the principal investigator and any subinvestigators. He/she will ensure that the trial is performed in accordance with the clinical trial protocol, the ethical principles that have their origin in the Declaration of Helsinki, and with the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law; and "Ministerial Ordinance on Standards for the Implementation of Clinical Studies on Pharmaceutical Product (GCP). In particular, the Investigator must ensure that only subjects who have given their informed consent are included in the trial.

In 1998, the United States' FDA introduced a regulation (21 CFR, Part 54) entitled "Financial Disclosure by Clinical Investigators". For studies conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP(s) (named "covered studies" by the FDA), the Investigator and all sub-Investigators 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 a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). With the cooperation of the Sponsor, and in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator or designee will prepare the ICF and other written information to be used in obtaining informed consent from the trial subjects. The Sponsor should provide the Investigator or designee with documents/information necessary for preparing the aforementioned written information and cooperate with the Investigator to prepare it. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject of all pertinent aspects of the trial orally as well as in writing. The language used in the aforementioned oral and written information about the trial must be fully and readily understandable to lay persons.

Before consent may be obtained, the Investigator should provide the prospective subject (the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative) with ample time and opportunity to inquire about details of the

clinical trial and to decide whether or not to participate in the trial. In such cases, the Investigator or the trial collaborator giving supplementary explanation should answer all questions about the trial to the satisfaction of the prospective subject (or of the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative).

Depending on 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 personally dated by the subject and the Investigator.

CCI [redacted]

The signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived by the Investigator 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 the subject's consent, the Investigator will revise the subject information sheet and any other written information 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 his/her written consent for continued participation in the trial.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion by the interactive web response system. 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 regulatory 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 PGx 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 enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

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, s/he will answer any questions. Any subsequent action (eg, unblinding) will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, Merck Serono/EMD Serono or designee will provide the appropriate means to contact a Sponsor physician. This includes the provision of a 24- hour contact number at a call centre, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this trial 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 trial site, and/or the subject. The Sponsor will provide insurance to fulfill the responsibility.

Insurance coverage shall be provided for each country participating in the trial. Insurance conditions shall meet good local standards, as applicable.

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, through the Head of the trial site, 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 in the Trial Master File at the CRO.

The Sponsor will initiate the trial at a site after obtaining written approval from the Head of the trial site based on 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, its membership list, and names of members who were present and voted at the meeting. Written favorable opinion/approval should clearly identify the trial, the clinical trial protocol version and the Subject Information and ICF version that were reviewed at the meeting. Where possible, copies of the meeting minutes should also be obtained.

Plans for any substantial amendments to the clinical trial will also be submitted to the concerned IEC/IRB before they are implemented (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 (eg, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the country involved in the trial.

10 Trial Management

10.1 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: (adapt to trial as necessary)

- Subject's full name
- Date of birth
- Sex
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification (MS200647-0008)
- Date of subject's inclusion into the trial (ie, 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 the 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

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or in accordance with the requirements of Japan GCP or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus 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.

The Head of the trial site must retain all records, including documents and data, which relate to the clinical trial in accordance with GCP. The Head of the trial site must retain the records 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 trial site should ensure that no destruction of medical records is performed without the written approval of the Sponsor. The principal investigator must retain records, including documents and data, which relate to the clinical trial in accordance with the instructions from the Head of the trial site.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to access all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the IMP, IMP accountability records, and the subjects' original medical records/files.

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.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IRB through the Head of the trial site for approval or favorable opinion. In such cases, the amendment will be implemented only after written approval from the Head of the trial site based on favorable opinion/approval from the relevant IRB 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 IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see 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 Coordinating Investigator.

10.6.2 Publication

The first publication may 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 pre-submission 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.

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12 Appendices

Appendix 1 Eastern Cooperative Oncology Group Performance Status

ECOG PS	
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, eg, 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*])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[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] 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

[4] 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

*not approved in Japan

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Addition to Table 5

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. 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 avelumab 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 (e.g. 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

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Document No. CCI [redacted]
Object No. CCI [redacted]

Appendix 4 Signature Pages and Responsible Persons for the Trial

Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

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 with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	18 April 2017/Version 5.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

Signature	Date of Signature
Name, academic degree	PPD
Function	PPD
Institution	Merck Serono Co., Ltd, R&D Japan, North East Asia Hub
Address	Arco Tower 4F 8-1 Shimomeguro 1-chome Meguro-ku, Tokyo 153-8926, Japan
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Document No. CCI
Object No. CCI

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

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 with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	18 April 2017/Version 5.0

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Signature Date of Signature

Name, academic degree	PPD
Function	PPD
Institution	PPD
Address	PPD
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

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Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

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 with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	18 April 2017/Version 5.0
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, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected 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.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

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Document No. CCI [redacted]
Object No. CCI [redacted]

M7824 (MSB0011359C) MSB0011359C in Metastatic or Locally Advanced Solid Tumors in Asia
MS200647-0008

Address:

Telephone number:

Fax number:

E-mail address:

Further Sponsor Responsible Persons

Sponsor Responsible Persons not Named on the Cover Page

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Name, academic degree	PPD
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Fax number	PPD
E-mail address	PPD

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Object No. CCI [redacted]