1 TITLE PAGE

Clinical Study Protocol

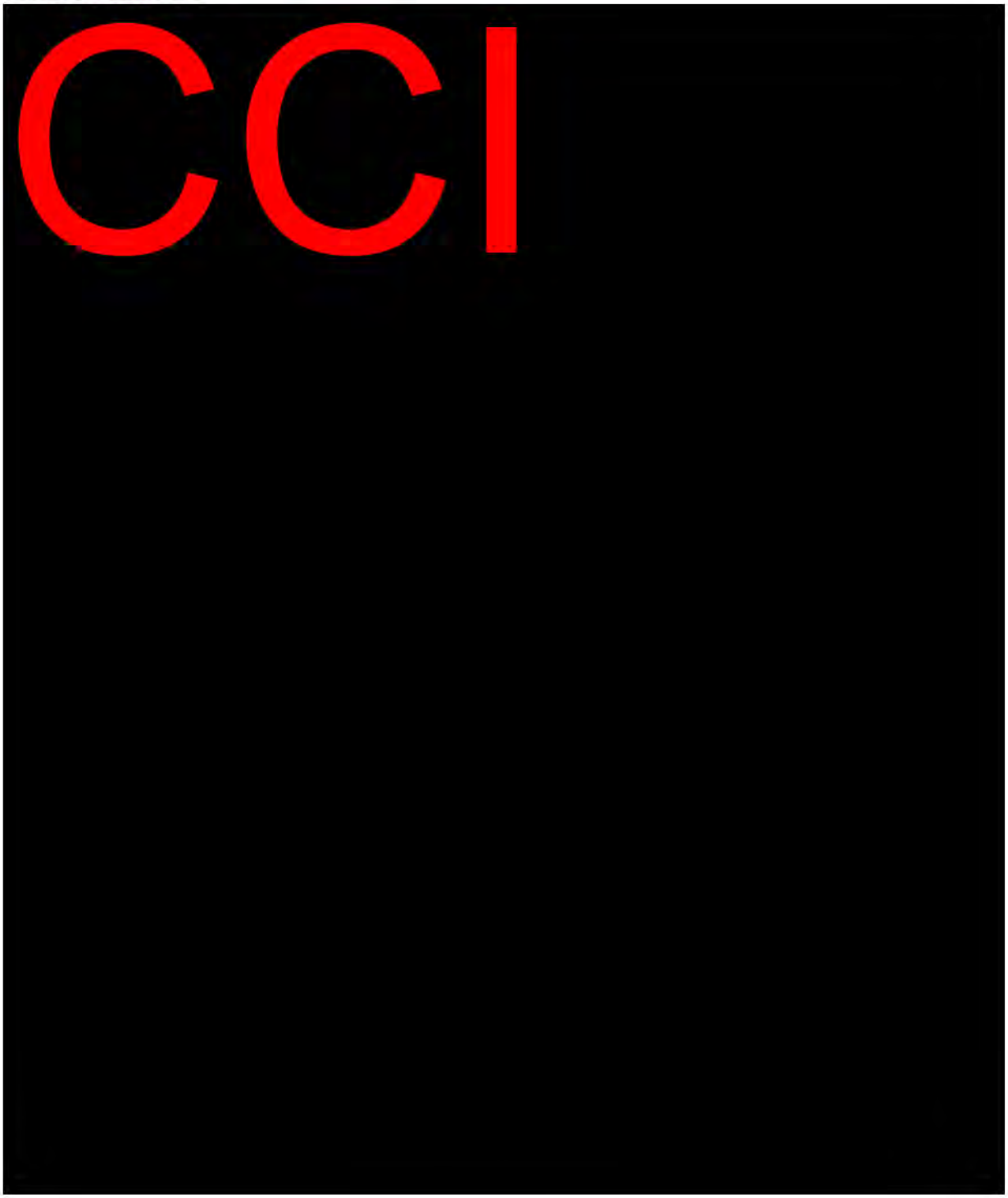
Study Protocol Number:	E7386-G000-201
Study Protocol Title:	An Open-Label, Multicenter, Phase 1b/2 Study of E7386 in Combination With Pembrolizumab in Previously Treated Subjects With Selected Solid Tumors
Sponsor:	Eisai Inc. 200 Metro Boulevard Nutley, NJ 07110 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Sponsor's Investigational Product Name:	E7386
Indication:	Melanoma, hepatocellular carcinoma, and colorectal cancer
Phase:	Phase 1b/2
Approval Date(s):	CCI [redacted] 25 Jan 2023 [redacted] Amendment 04
IND Number:	136799
EudraCT Number:	2021-001568-10
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study

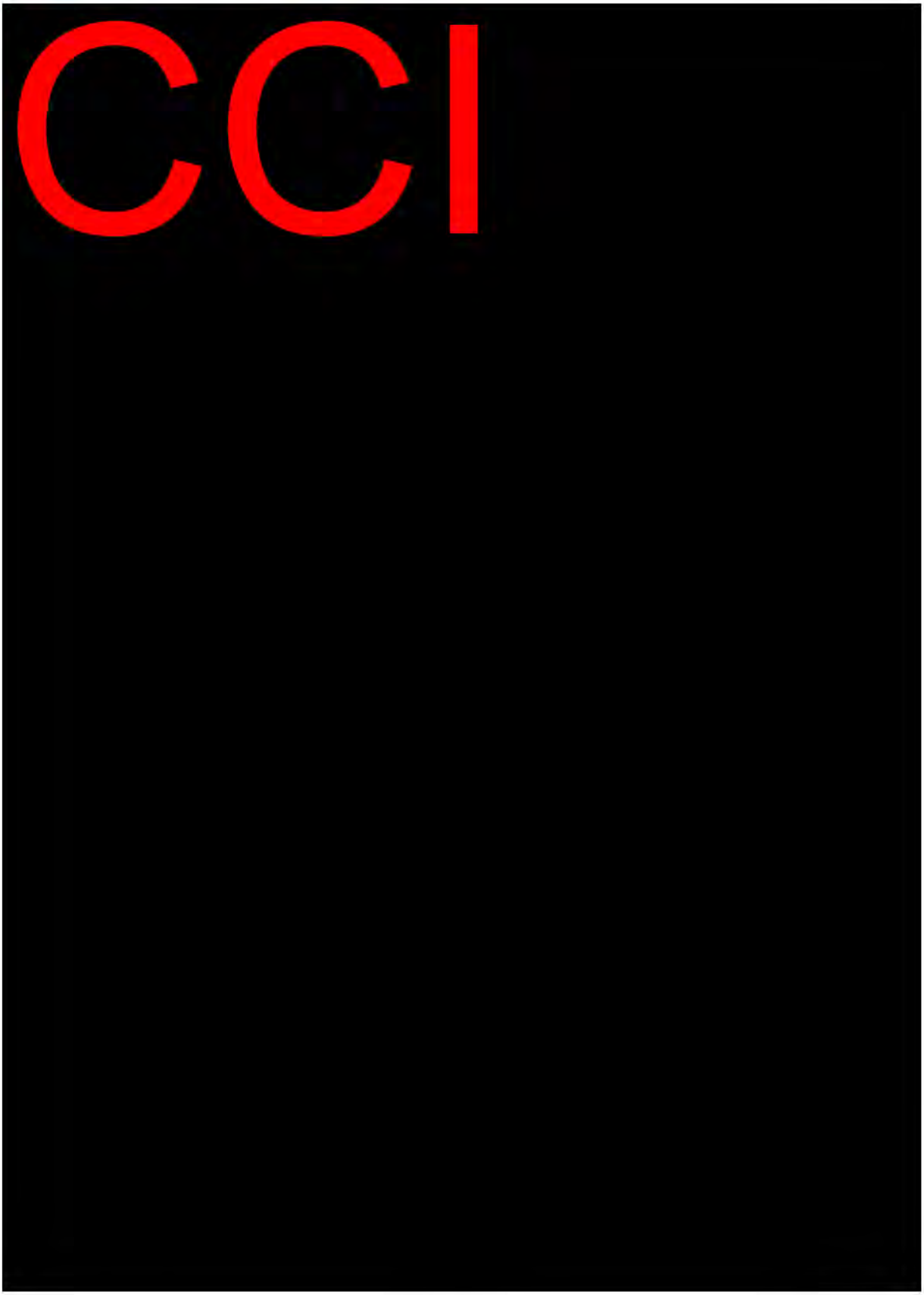
	documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Protocol Amendment 04

Date: 25 Jan 2023

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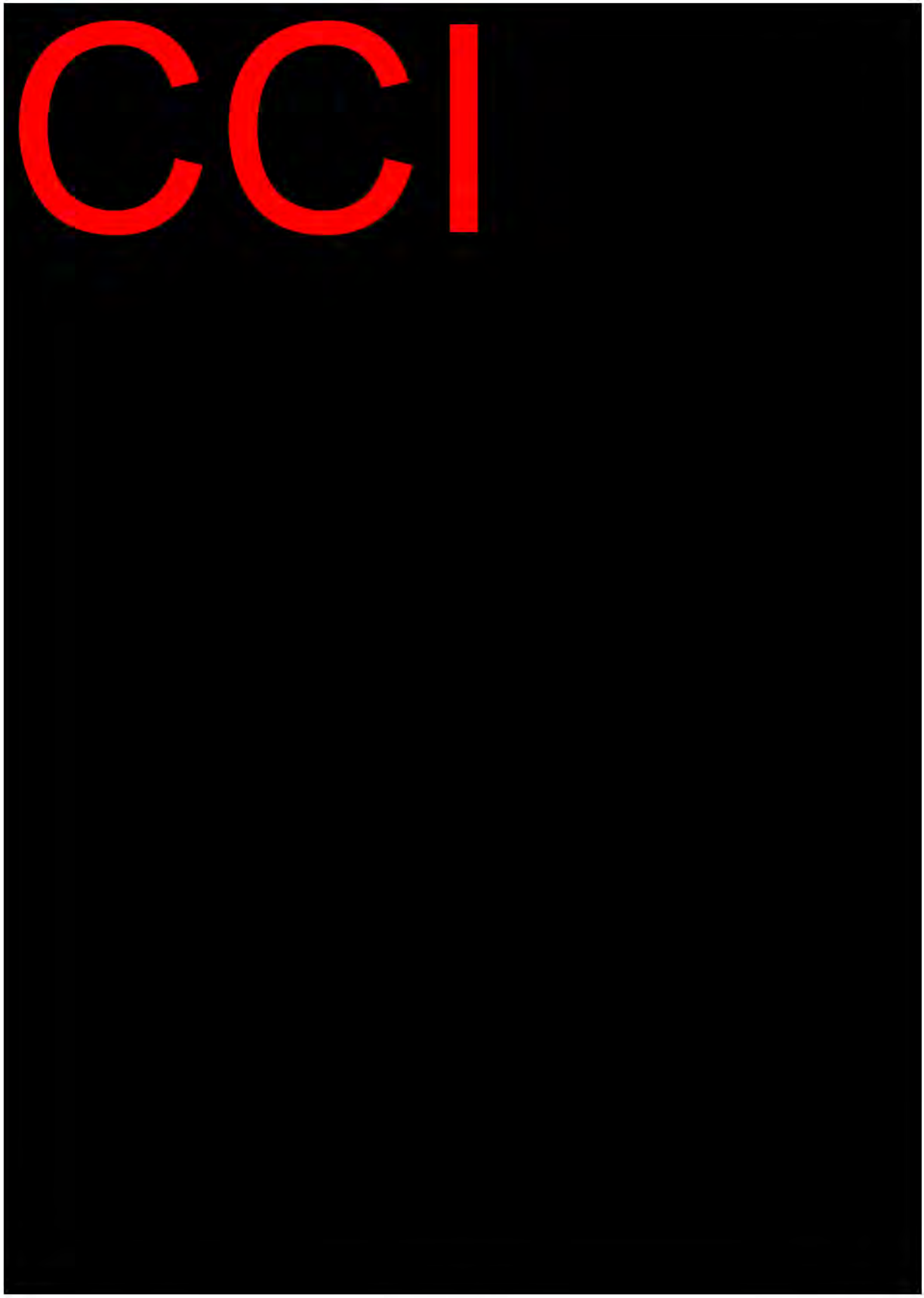
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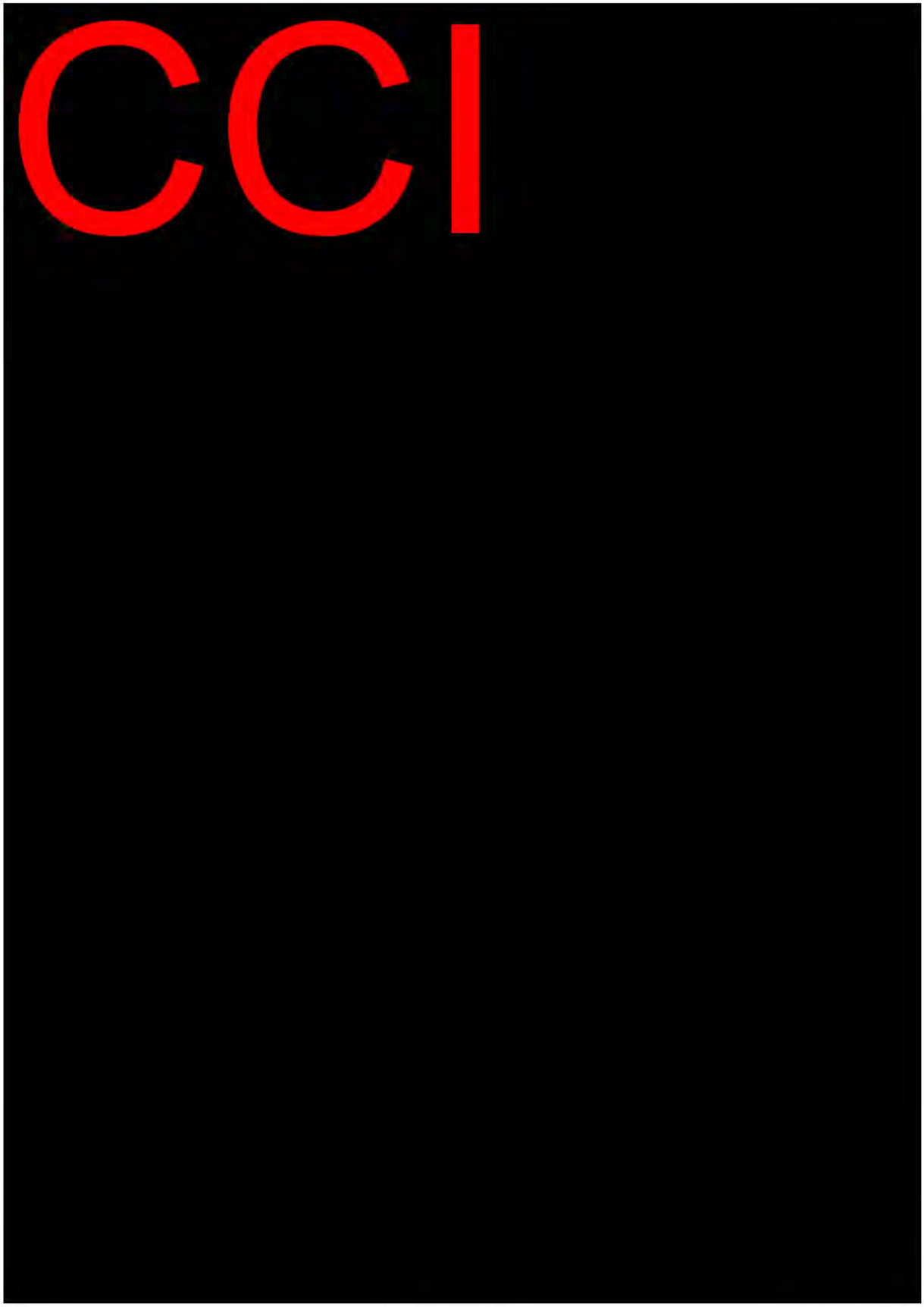
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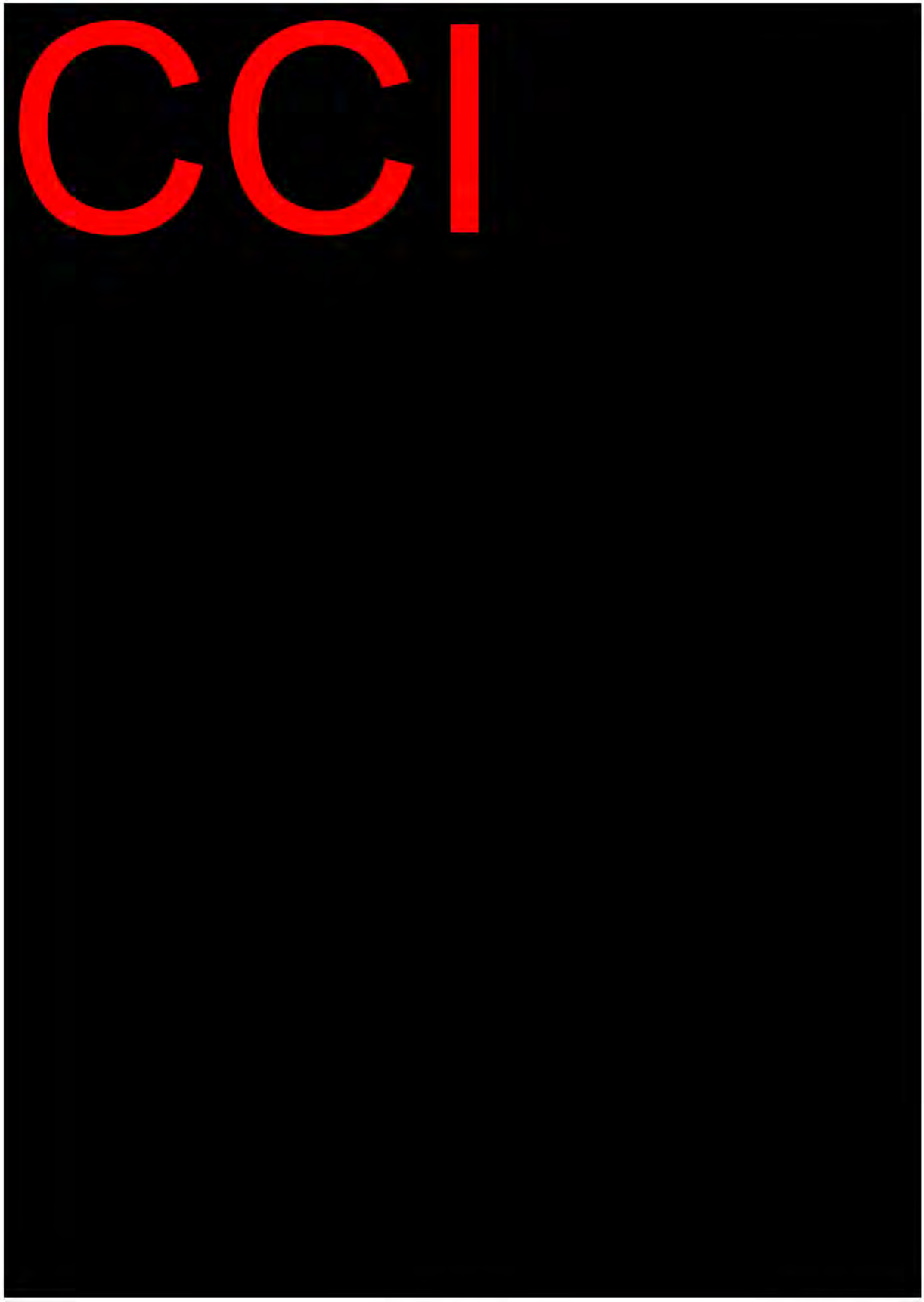
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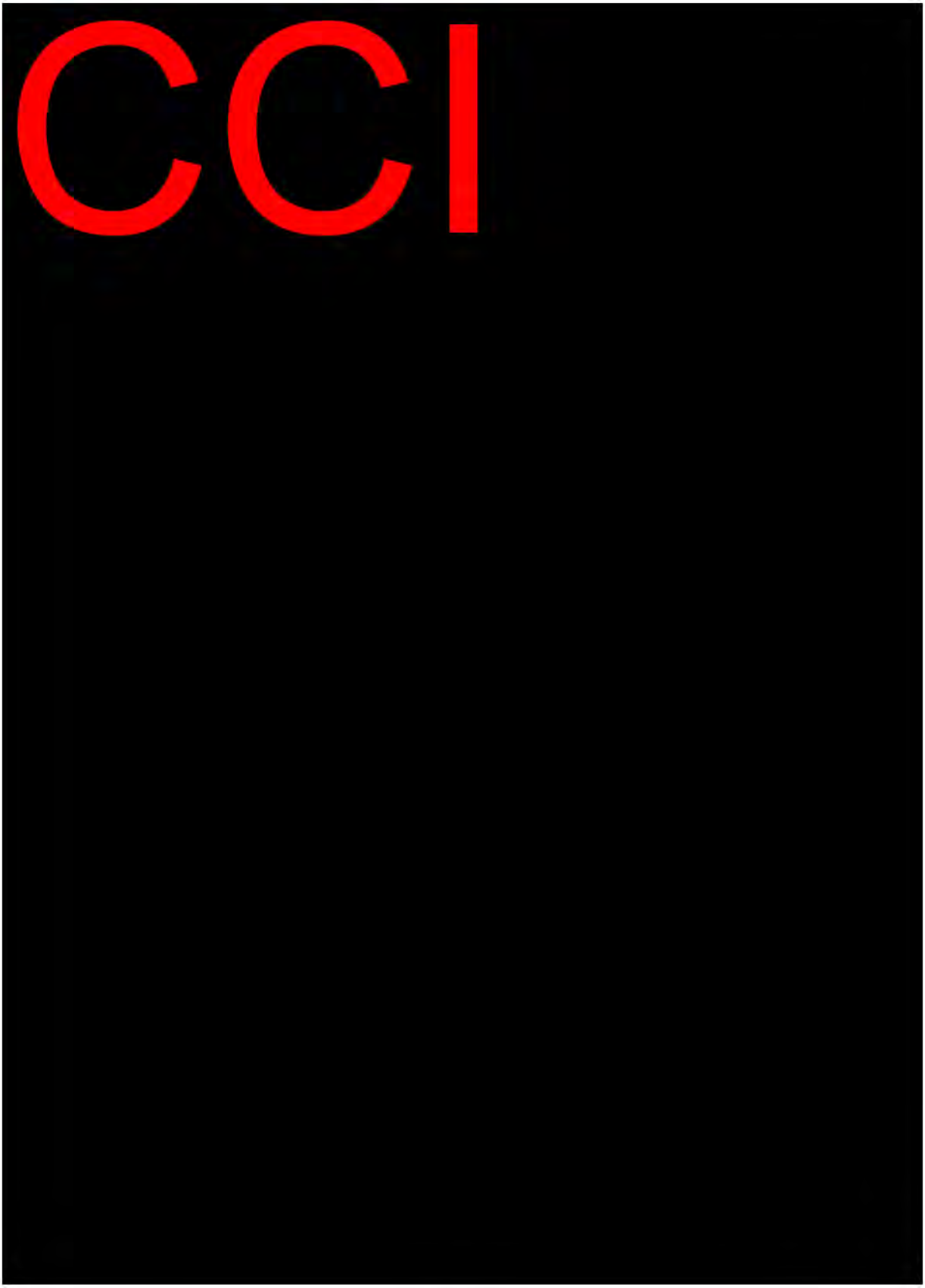
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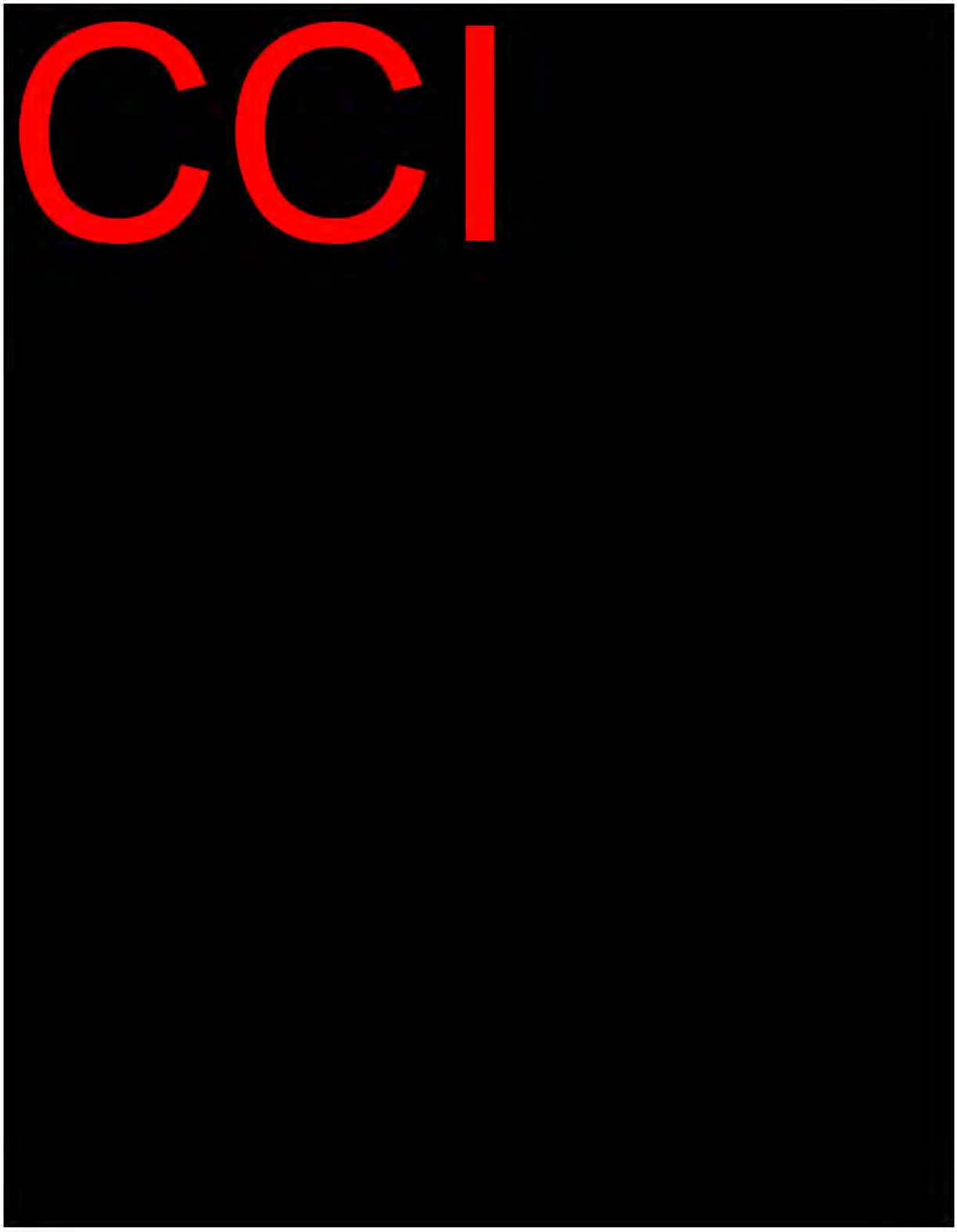
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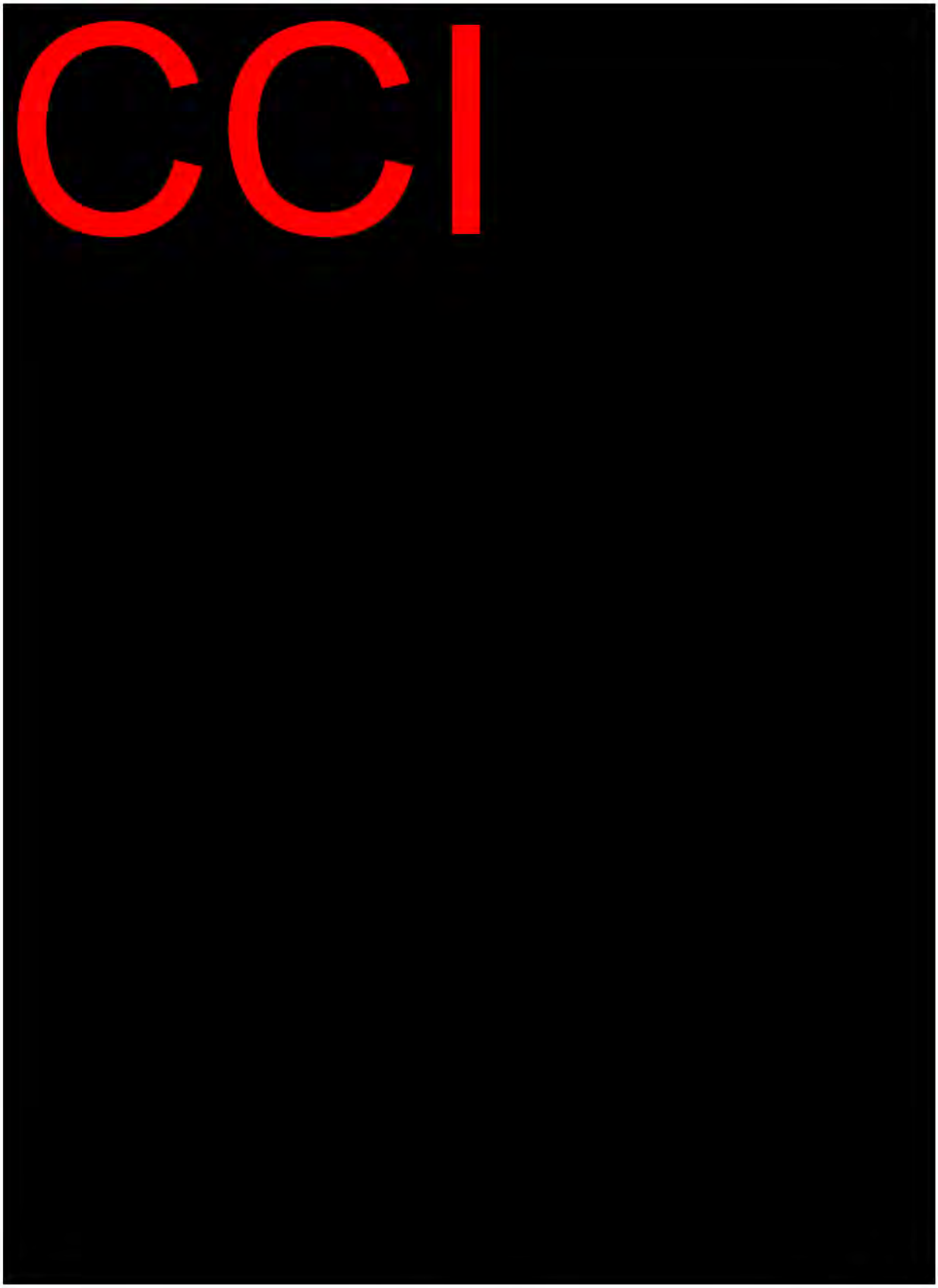
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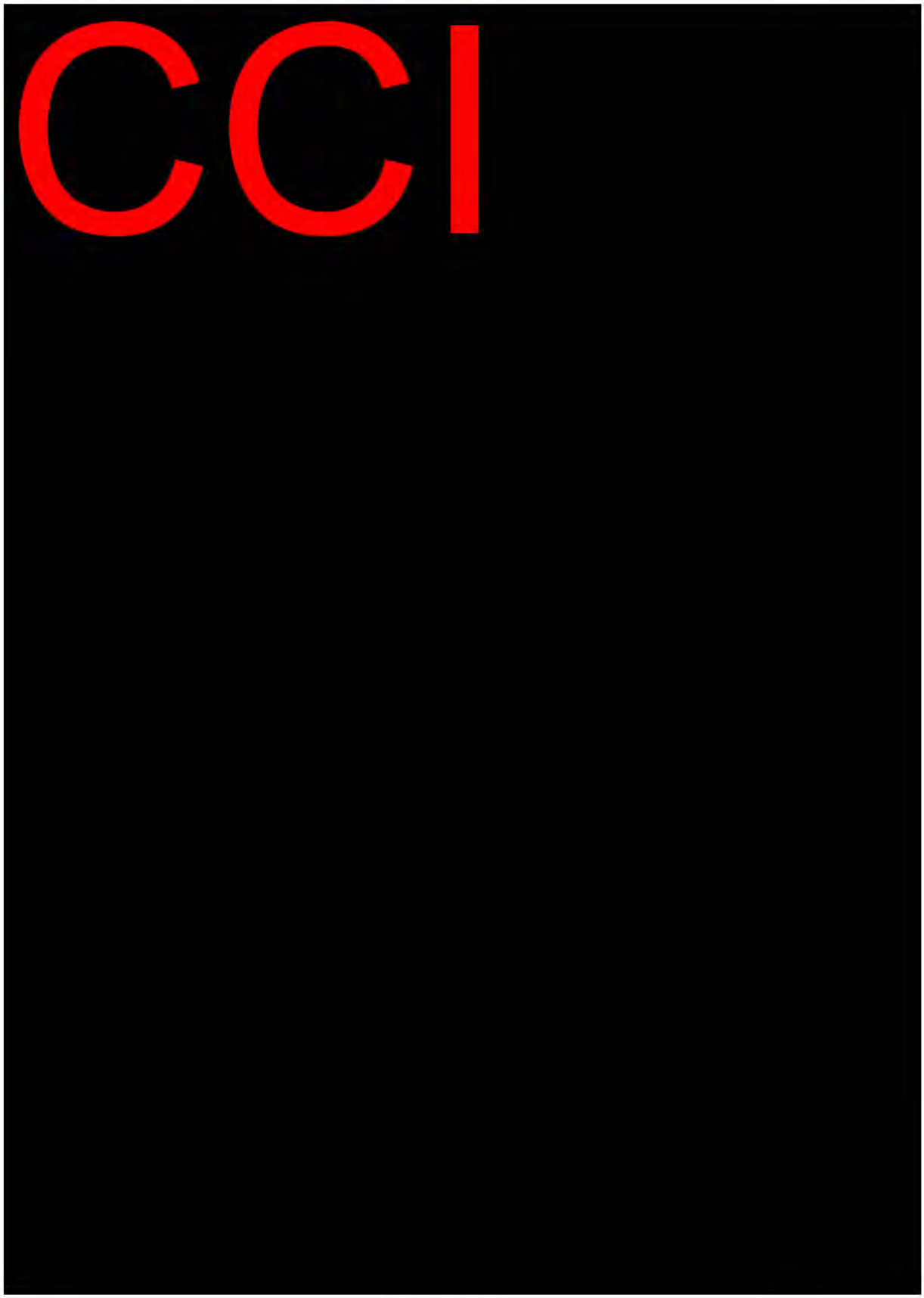
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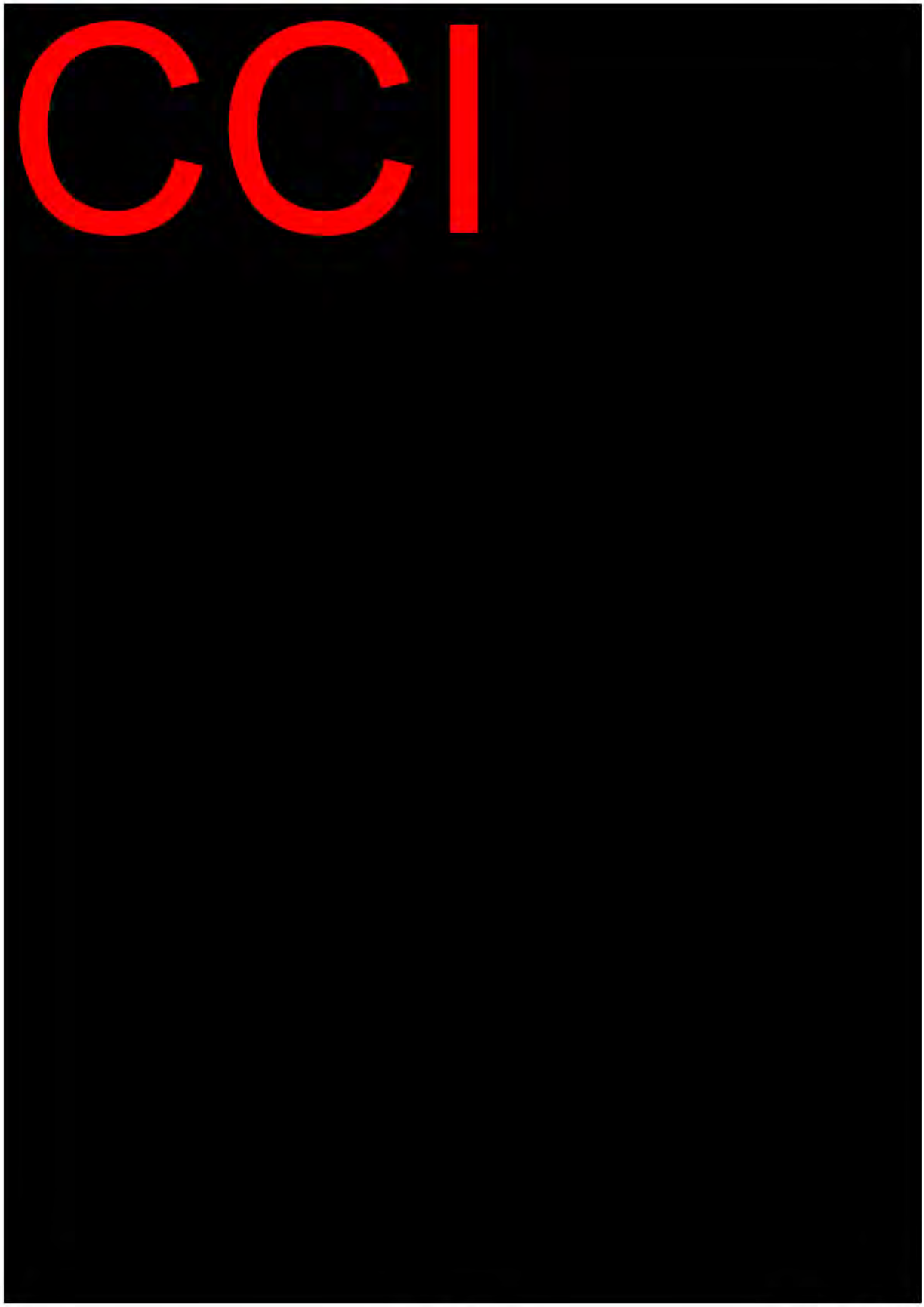
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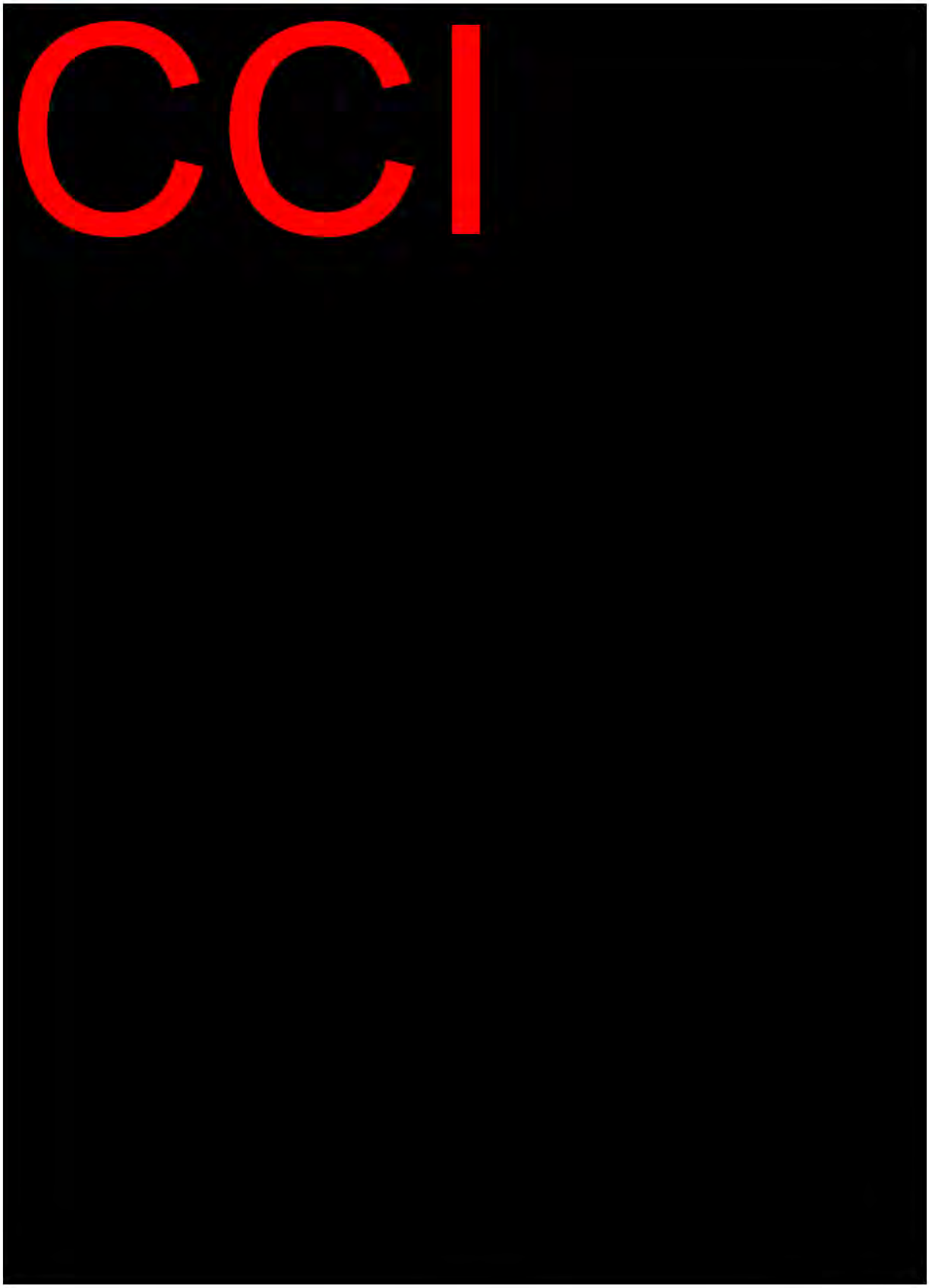
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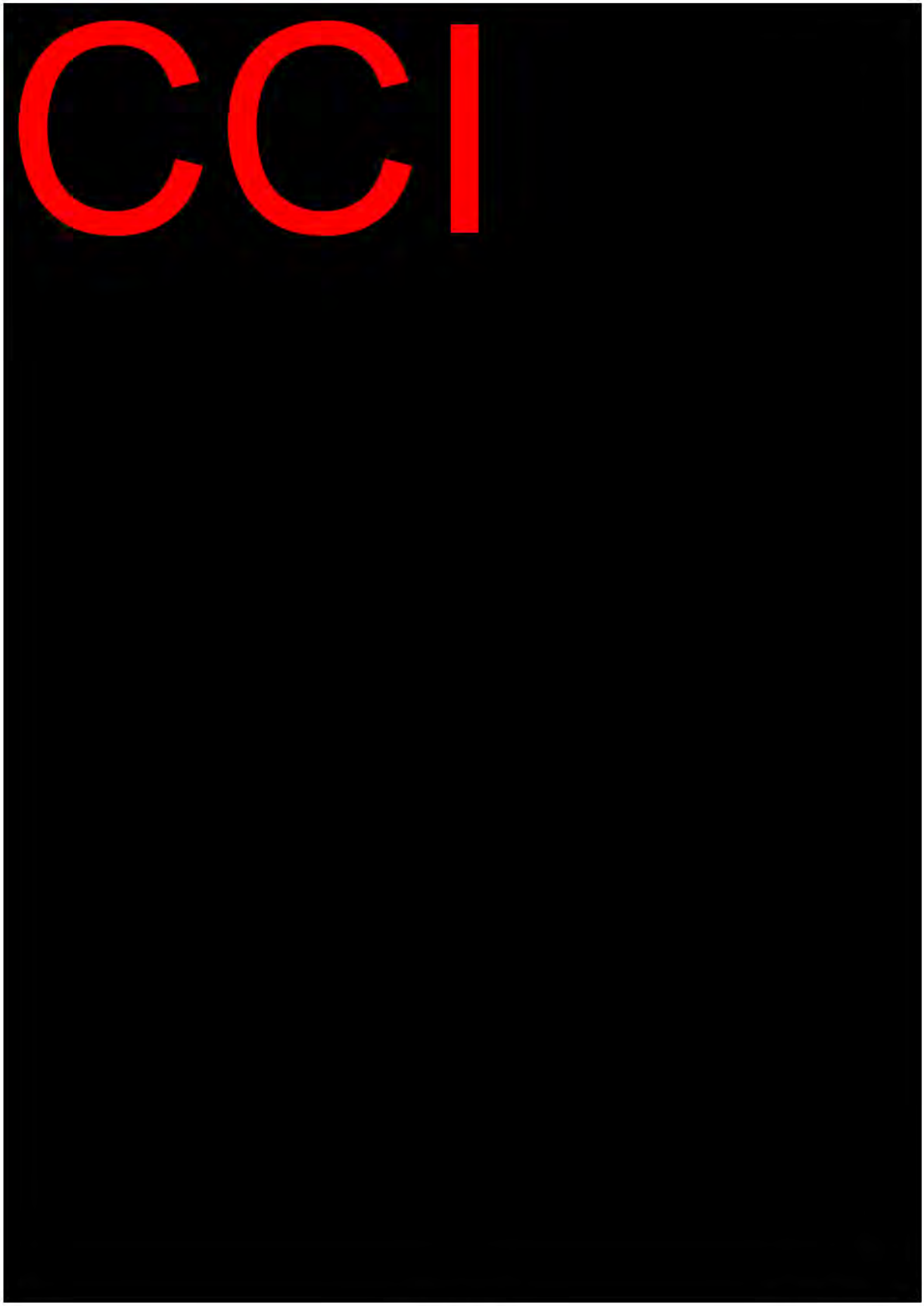
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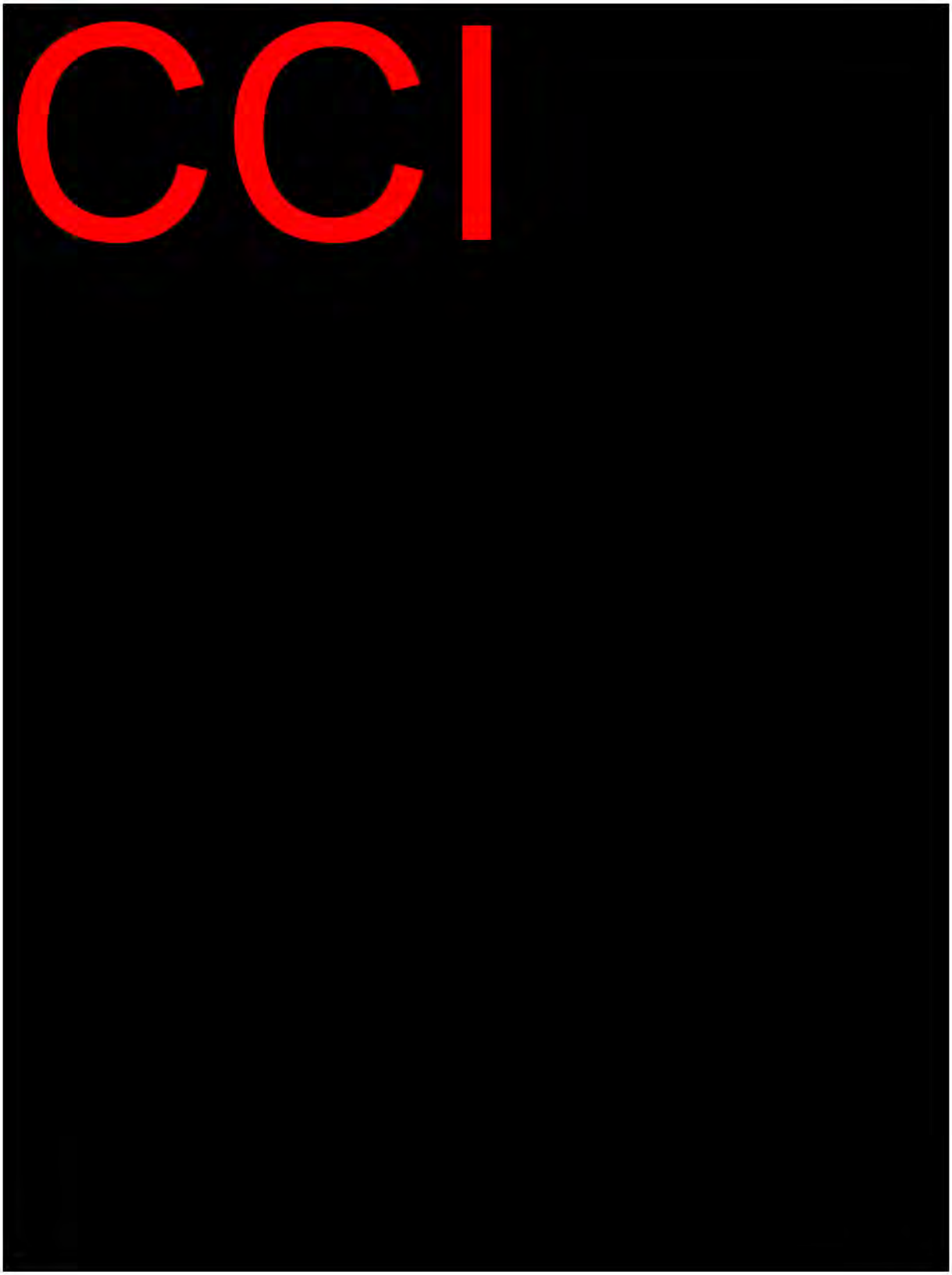
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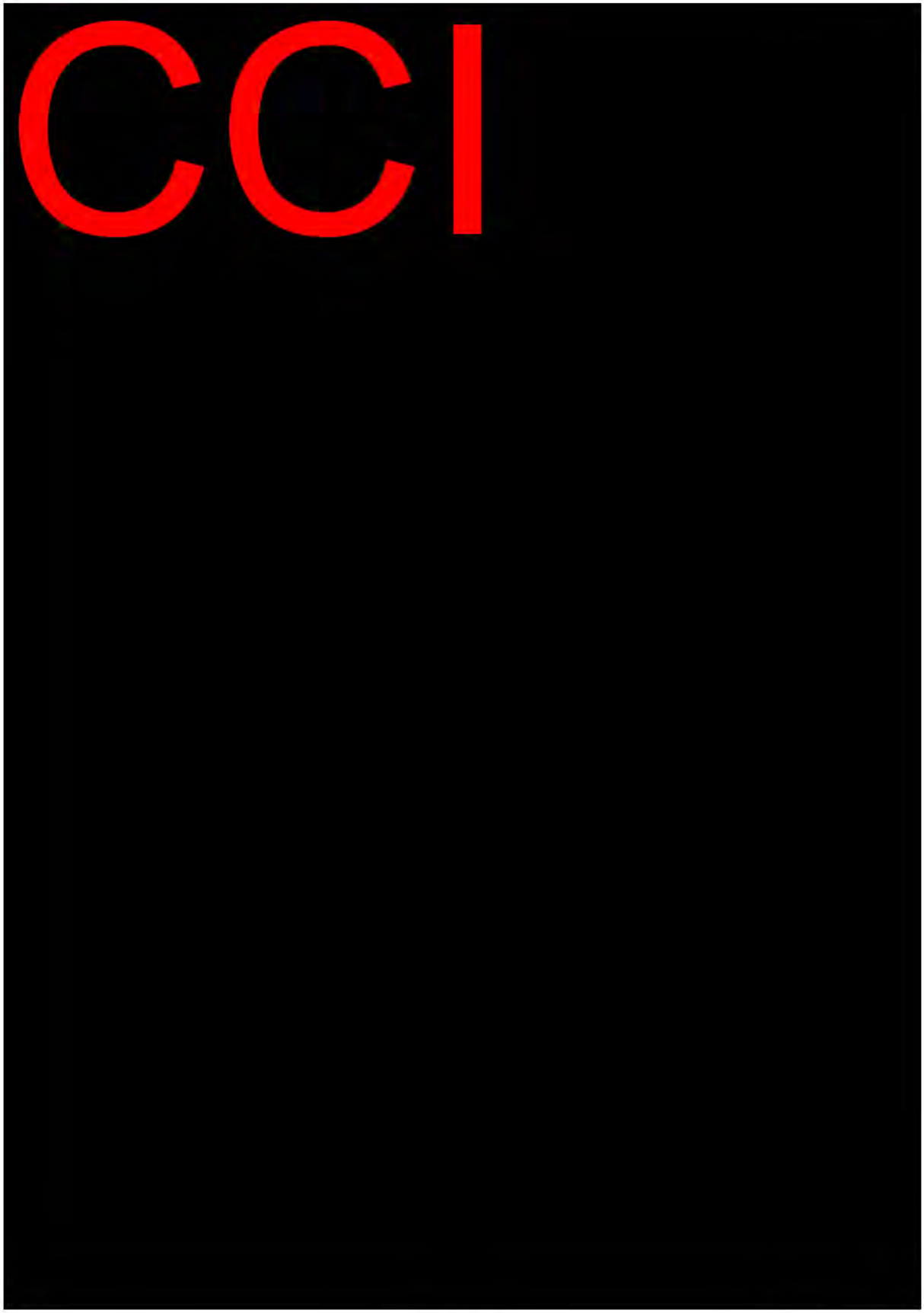
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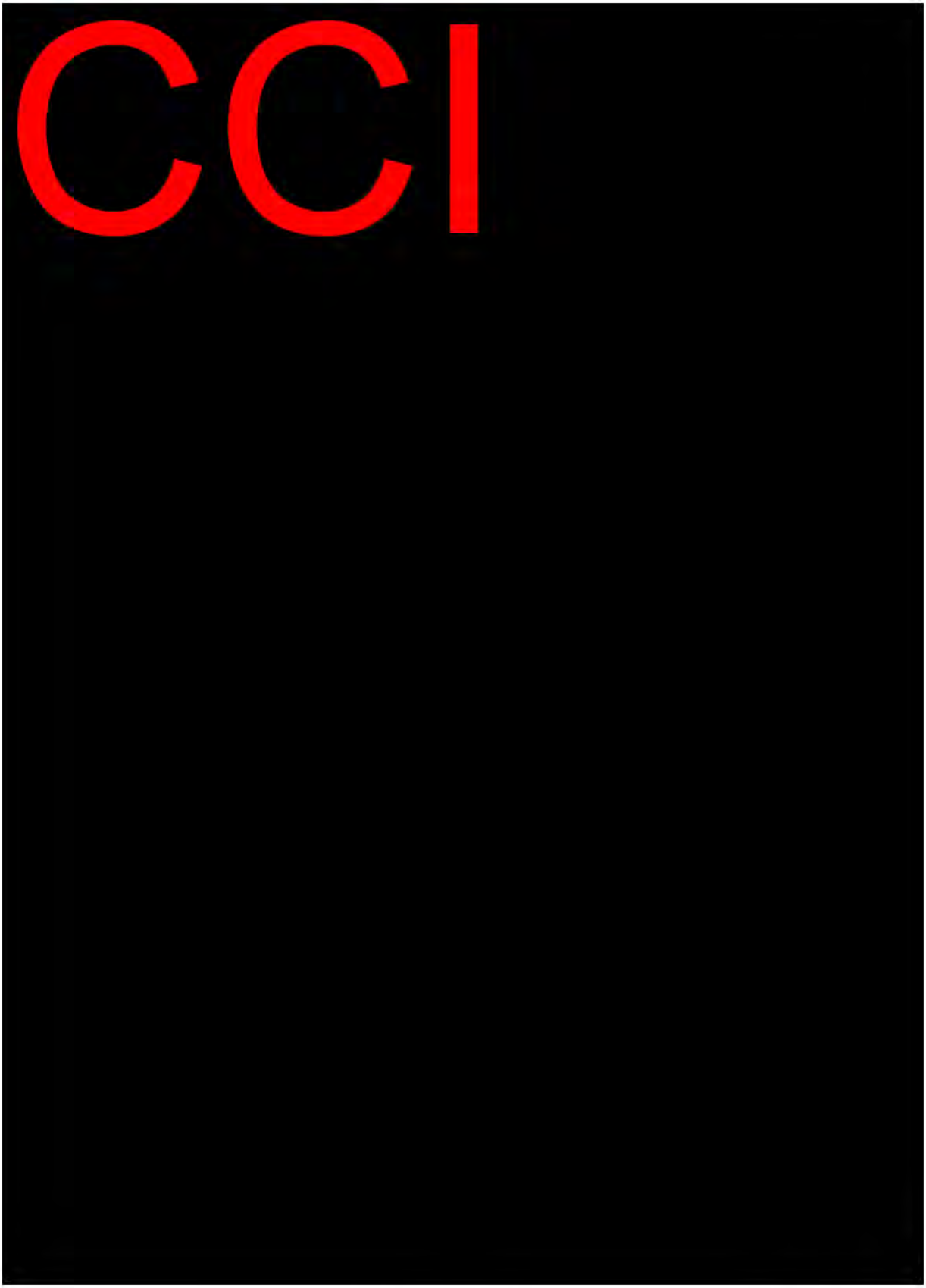
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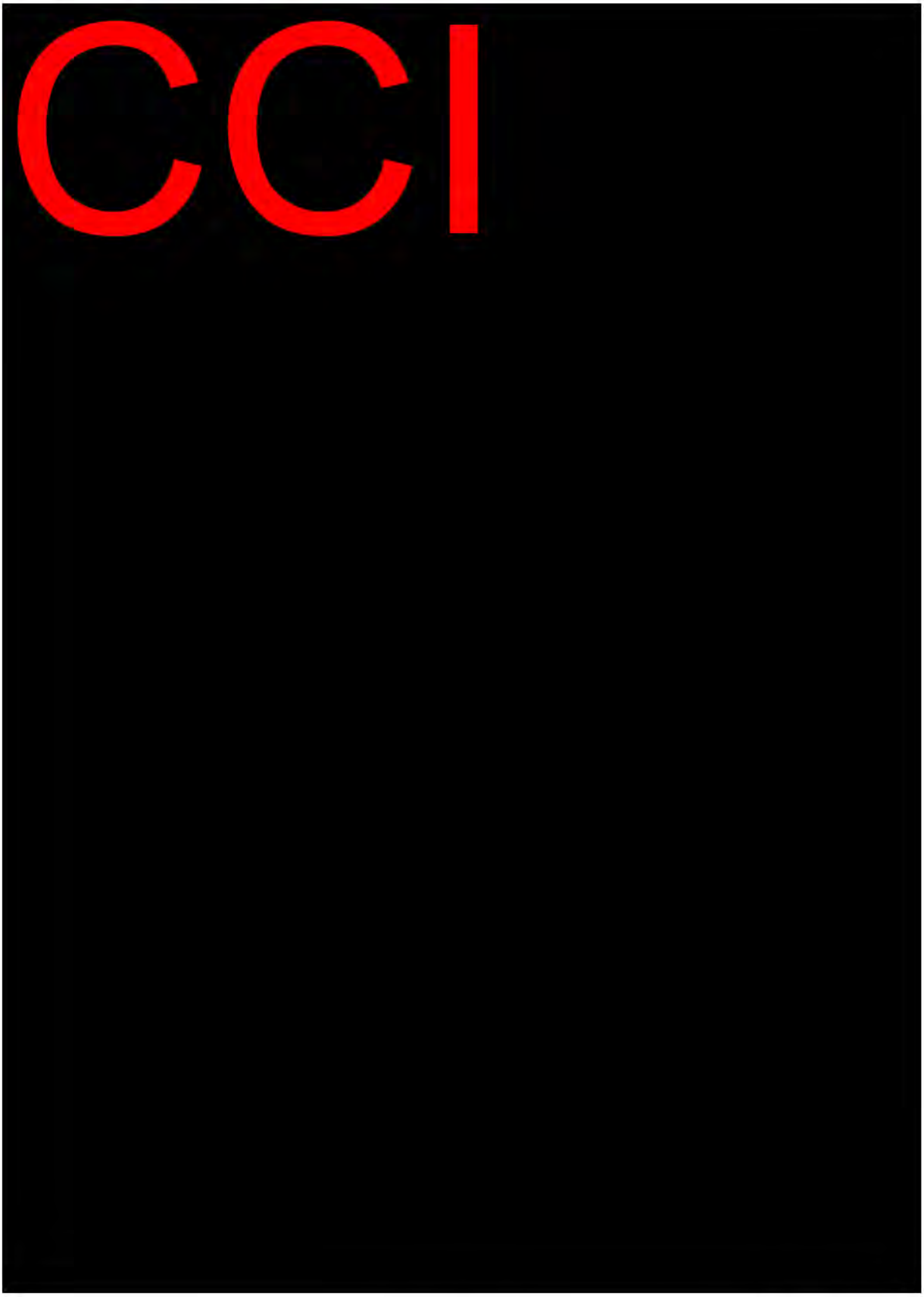
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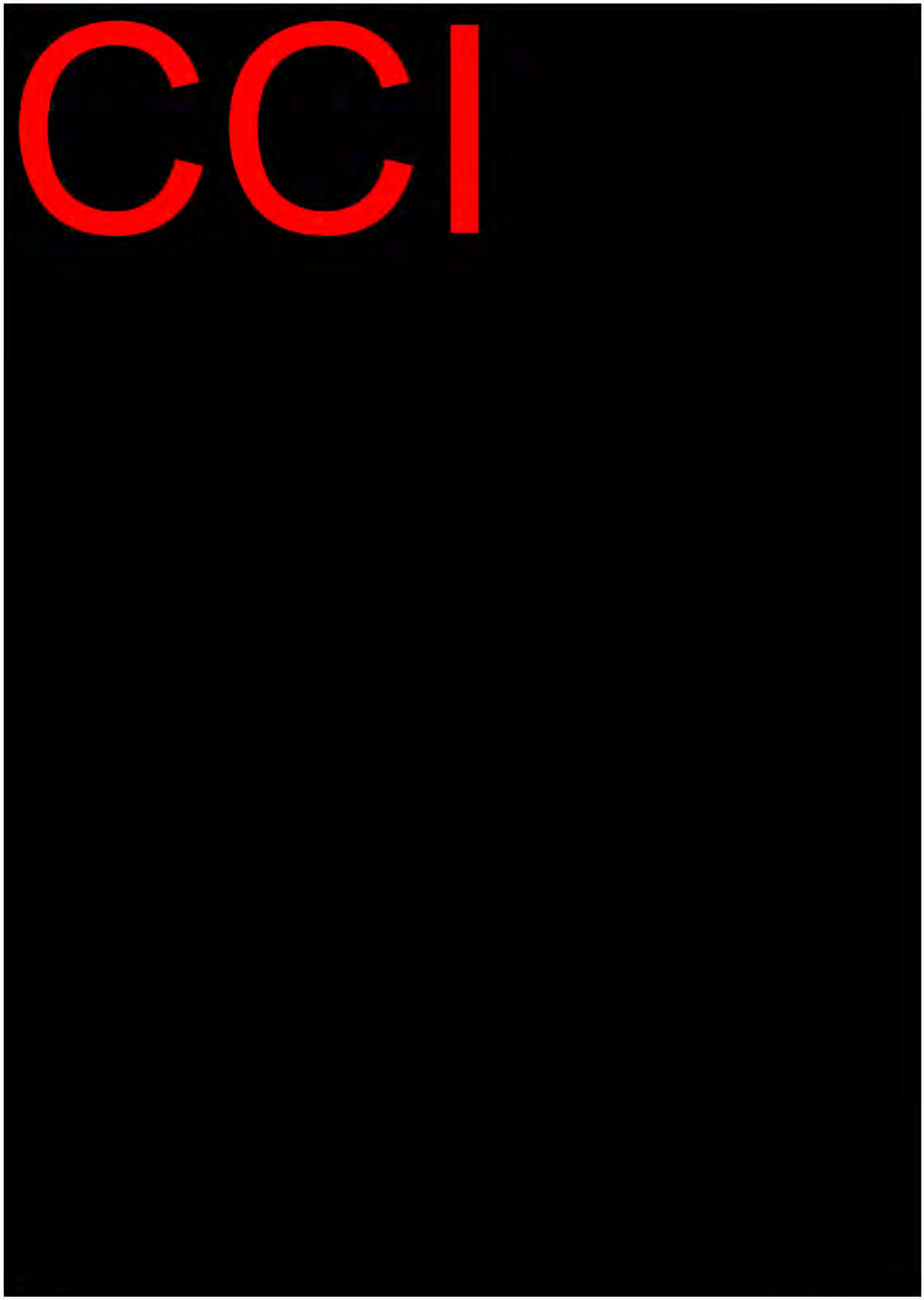
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2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7386; MK-3475; E7080

Name of Active Ingredient:

(6*S*,9a*S*)-*N*-Benzyl-8-({6-[3-(4-ethylpiperazin-1-yl)azetidin-1-yl]pyridin-2-yl}methyl)-6-(2-fluoro-4-hydroxybenzyl)-4,7-dioxo-2-(prop-2-en-1-yl)hexahydro-2*H*-pyrazino[2,1-*c*][1,2,4]triazine-1(6*H*)-carboxamide; pembrolizumab; lenvatinib

Study Protocol Title:

An Open-Label, Multicenter, Phase 1b/2 Study of E7386 in Combination With Pembrolizumab in Previously Treated Subjects With Selected Solid Tumors

Sites:

Multinational with approximately 40 investigational sites in North America, Europe, and Asia-Pacific (APAC) regions.

Study Period and Phase of Development

Total study period: Approximately 50 months; Phase 1b/2 parts

Objectives

Primary Objectives

Phase 1b part:

- To assess the safety and tolerability of E7386 in combination with pembrolizumab in subjects with previously treated selected solid tumors
- To determine the recommended Phase 2 dose (RP2D) of E7386 in combination with pembrolizumab

Phase 2 part:

- To assess the objective response rate (ORR) of E7386 in combination with pembrolizumab (melanoma, colorectal cancer [CRC], hepatocellular carcinoma [HCC]) or of E7386 in combination with pembrolizumab plus lenvatinib (HCC) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary Objectives

Phase 1b part only:

- To assess tumor response according to RECIST 1.1

Phase 1b and Phase 2 parts:

- To assess duration of response (DOR) according to RECIST 1.1 per tumor cohort
- To assess the disease control rate (DCR: the proportion of subjects with complete response [CR], partial response [PR], or stable disease [SD] after ≥5 weeks from the first dose) according to RECIST 1.1 per tumor cohort
- To assess the clinical benefit rate (CBR: the proportion of subjects with CR, PR, or durable SD [duration of SD ≥23 weeks]) according to RECIST 1.1 per tumor cohort
- To assess the safety and tolerability of E7386 in combination with pembrolizumab and E7386 in combination with pembrolizumab plus lenvatinib
- To evaluate the pharmacokinetic (PK) profile of E7386 when co-administered either with pembrolizumab or with the combination of pembrolizumab plus lenvatinib

- To evaluate the PK profile of lenvatinib when co-administered with E7386 plus pembrolizumab
- To determine the optimal dose level of E7386 in combination with pembrolizumab plus lenvatinib

Exploratory Objectives

CCI [redacted]

Study Design

This is an open-label, multicenter, Phase 1b/2 study that will evaluate the safety and efficacy of E7386 in combination with pembrolizumab, and E7386 in combination with pembrolizumab plus lenvatinib.

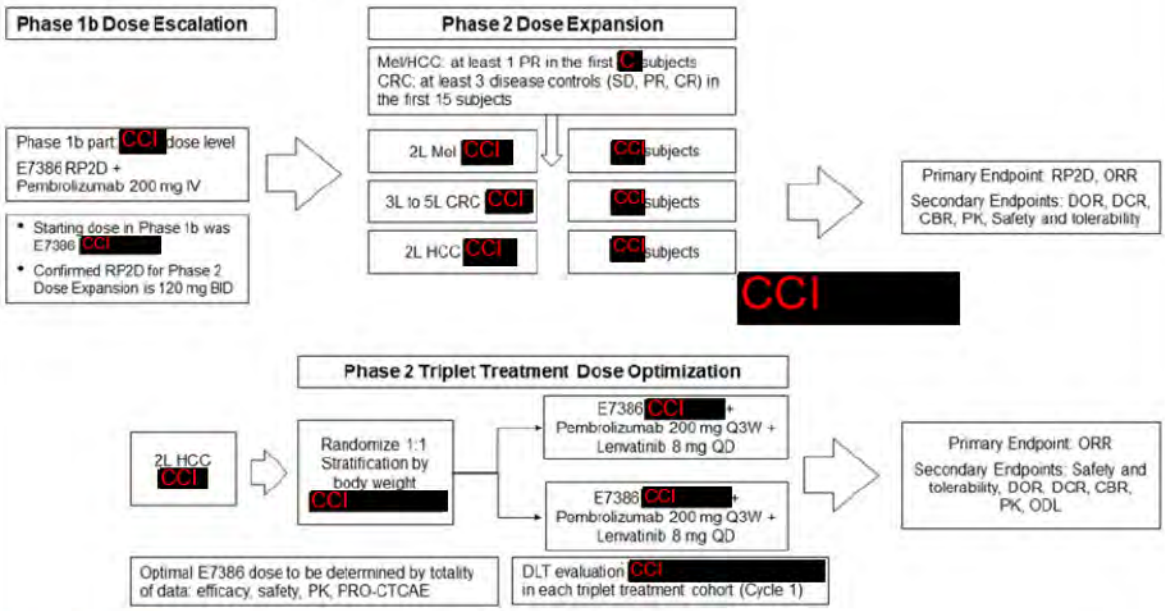
The study is divided into 3 parts (Phase 1b part, Phase 2 part, and Extension part).

E7386 in combination with pembrolizumab: Eligible subjects will be enrolled into 1 of 3 tumor cohorts: melanoma, CRC, and HCC. Phase 1b part will determine the RP2D based on safety and tolerability in up to 18 evaluable subjects overall. At least 1 subject with HCC will be enrolled at each dose level in Phase 1b part. The Phase 2 part will be conducted in 2 stages. CCI [redacted]

E7386 in combination with pembrolizumab plus lenvatinib: Based on emerging nonclinical data demonstrating promising antitumor activity of the triplet combination (E7386 in combination with pembrolizumab plus lenvatinib) in HCC, triplet treatment cohorts are included in the currently ongoing Phase 2 part of the study. Given the known safety profile of lenvatinib plus pembrolizumab in HCC, as well as the tolerability confirmation of E7386 in combination with pembrolizumab or lenvatinib (Study E7386-J081-102 [Study 102]), no separate Phase 1b for triplet treatment cohort was considered necessary.

The efficacy, safety and tolerability (including evaluation of dose-limiting toxicities [DLTs]), and optimal dose of E7386 (CCI [redacted] versus CCI [redacted] twice daily [BID]) in combination with pembrolizumab (200 mg once every 3 weeks [Q3W]) plus lenvatinib (single 8 mg starting dose once daily [QD]) will be evaluated in approximately CCI [redacted] subjects in second-line (2L) HCC who will be randomized (1:1) into 2 triplet treatment cohorts.

Since there will be doublet (E7386 plus pembrolizumab) and triplet treatment cohorts (E7386 in combination with pembrolizumab plus lenvatinib) open for 2L HCC subjects, to minimize the risk of enrollment bias, enrollment will be prioritized to the triplet cohorts. Subjects may be enrolled into the Phase 2 doublet cohort if the triplet treatment cohorts do not open at the site or the subject is ineligible for the triplet cohort.

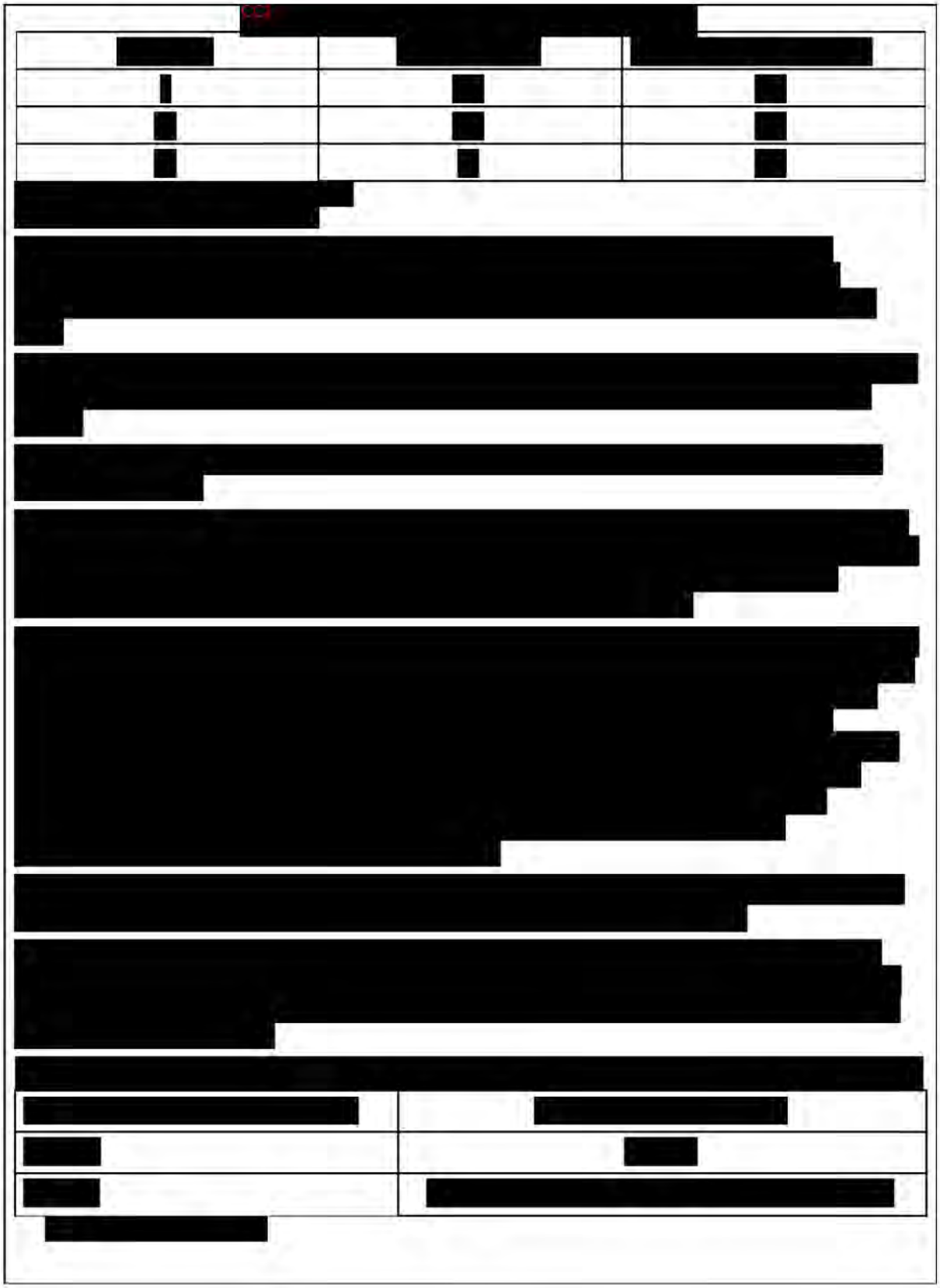


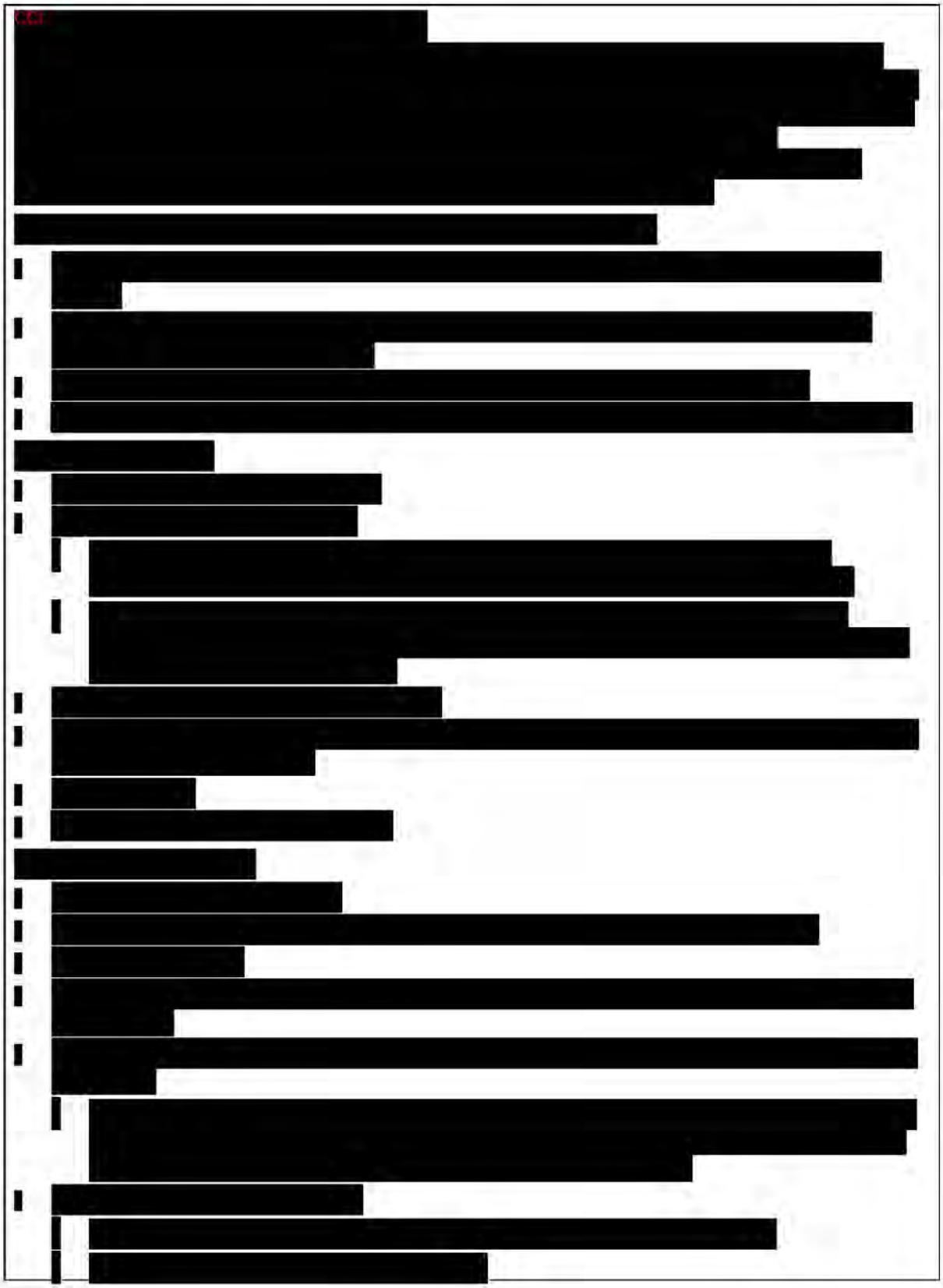
Study Schema

Phase 1b Part – Dose Escalation

This part will assess the safety and tolerability of E7386 in combination with pembrolizumab in previously treated subjects with selected solid tumors. Subjects in Phase 1b part will have one of the following tumors: melanoma, CRC, or HCC. At least 1 subject with HCC will be enrolled at each dose level in Phase 1b part.

E7386 will be administered on Days CCI at a dose of CCI BID orally; pembrolizumab will be administered at a dose of 200 mg intravenously (IV) Q3W. Six evaluable subjects per dose level will be enrolled in Phase 1b part. The dose of pembrolizumab will not change during the study. If the initial dose of E7386 (Dose Level 0) is considered tolerable, the dose of E7386 may be escalated to the next higher dose level of CCI (Dose Level 1). If the initial dose level is not considered tolerable, the dose of E7386 may be reduced to the next lower dose level of CCI (Dose Level –1).





If following de-escalation from Dose Level 0 (to Dose Level –1), 2 or more DLTs are observed of 6 subjects, the Sponsor will decide on further de-escalation of the dose or study may be stopped based on emerging results.

Subjects who discontinue study drug prior to completing Cycle 1 for any reasons other than DLT will be replaced. Once they complete Cycle 1, each subject still receiving study drug will continue the Treatment Phase. A decision regarding DLT will be made by the investigators in collaboration with the Sponsor.

The Sponsor will maintain a Dose Escalation Plan, which specifies the operational and communication procedures followed during the conduct of the Phase 1b part.

The Sponsor will assess all the DLTs and safety data, including any induced late long-term toxicities such as any unexpected immune-related AEs and determine the RP2D. Once the RP2D is determined, all sites will be informed and enrollment into Phase 2 Part will begin.

As per Protocol Amendment 03, there were no DLTs in the Phase 1b portion of the study, and the RP2D was determined at Dose Level 1 (E7386 CCI and pembrolizumab 200 mg Q3W).

Phase 2 Part – Dose Expansion (E7386 Plus Pembrolizumab Cohorts)

After the RP2D is confirmed, and depending on the safety and efficacy observed, 3 cohorts of subjects (Cohort A melanoma; Cohort B CRC; Cohort C HCC) will be enrolled to assess safety, tolerability and efficacy using the combination dose determined in Phase 1b part. Approximately 90 eligible subjects (30 subjects per selected tumor) who meet all the inclusion criteria and none of the exclusion criteria will be stratified by tumor cohort and enrolled to receive E7386 in combination with pembrolizumab. For melanoma and HCC, subjects must have received 1 prior therapy that included an anti-programmed cell death protein-1 (PD-1)/PD-1 ligand 1 (PD-L1) monoclonal antibody (mAb).

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Further details regarding criteria of the interim data reviews are described in the Interim Analyses section.

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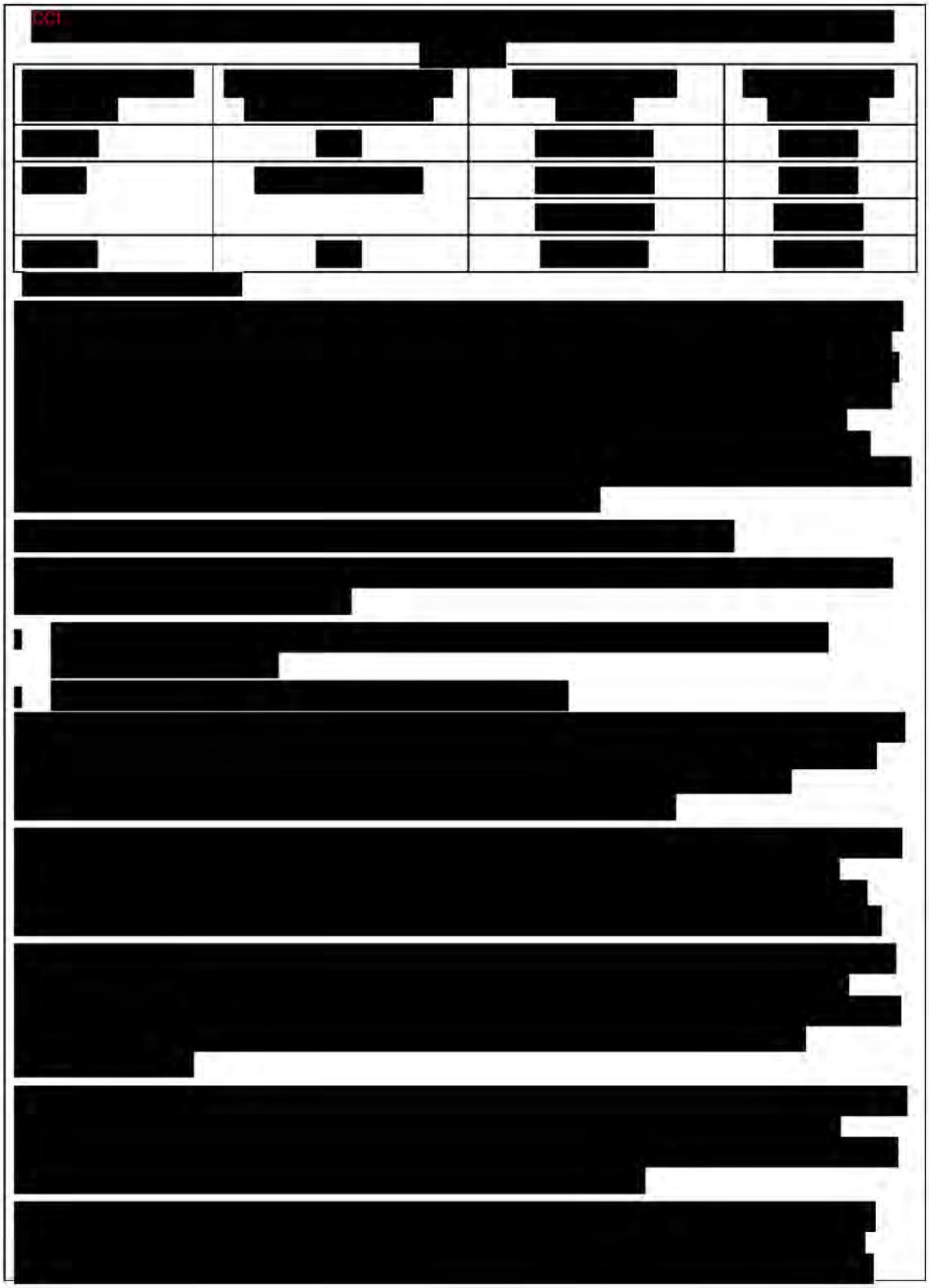

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Extension Part

All subjects who are still on study drug or in follow-up at the time of data cutoff for the primary analysis of Phase 2 part will be eligible to enter the Extension part on the same treatment if still on treatment as in the Phase 1b part or Phase 2 part.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows are outlined in the Schedule of Procedures/Assessments for Extension Part. Assessment procedures will be assessed similarly to Phase 1 b and Phase 2 parts.

Study Periods

This study will be conducted in 3 Phases: Pretreatment, Treatment, and Follow-Up.

The **Pretreatment Phase** will last no longer than 28 days and includes a Screening Period, to obtain informed consent and establish protocol eligibility, and a Baseline Period, to confirm protocol eligibility prior to treatment.

CCI [redacted]

Subjects will continue to receive study drug until confirmed disease progression, development of unacceptable toxicity, subject request, withdrawal of consent or study termination by the Sponsor. The EOT Visit will occur within 30 days following the last dose of the study drug. Note that all adverse events (AE) must be recorded for 30 days after the last dose of treatment. In addition, all serious AEs (SAE) up to 90 days after the last dose of study drug will be recorded, or up to 30 days following cessation of study drug if the subject initiates new anticancer therapy, whichever is earlier.

The **Follow-Up Phase** will start after the EOT Visit. Following the completion of the EOT Visit, subjects will transition to the Follow-Up Phase. Follow-up will continue as long as the study subject is alive unless the subject withdraws consent or until the Sponsor terminates the study. Subjects will be followed every 12 weeks (±1 week) for survival and subsequent anticancer treatments. The Sponsor may decide to terminate survival follow-up at any time or when all subjects discontinue all study drugs.

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A subject is considered to have completed the study if he or she has completed all phases of the study including the last assessment or the last scheduled procedure shown in the Schedule of Procedures/Assessments. The end of study will be the last subject/last visit, including discontinuation from study for any reason.

Number of Subjects

Phase 1b part will enroll 6 DLT-evaluable subjects with previously treated selected solid tumors per dose level. **Phase 2 part** will enroll approximately 150 eligible subjects: 30 subjects per selected tumor (melanoma, CRC, HCC) to be treated with E7386 in combination with pembrolizumab and CCI [redacted]

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

2. Male or female, age ≥18 years (or any age ≥18 years as determined by country legislation) at the time of informed consent.
3. Life expectancy of ≥12 weeks.
4. Have a histologically or cytologically-documented, advanced (metastatic and/or unresectable) selected solid tumor for which prior standard systemic therapy has failed. Selected tumor types: melanoma (excluding uveal melanoma), CRC, HCC.
5. For **Melanoma Cohort only (Phase 2 part),** subject must have:
   a. Unresectable Stage III or Stage IV melanoma, per American Joint Committee on Cancer staging system version 8, not amenable to local therapy.
   b. At least one measurable lesion by computer tomography (CT) or magnetic resonance imagery (MRI) based on RECIST 1.1 (cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as nontarget lesions).
      - Lesions in a previously irradiated area should not be considered measurable unless there has been documented growth of the lesions since the completion of radiotherapy.
   c. Progressed on or after prior treatment with one anti-PD-1/PD-L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. PD-1 progression is defined as:
      - Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb (eg, pembrolizumab, nivolumab, nivolumab plus ipilimumab) and
      - Has demonstrated disease progression after PD-1/PD-L1 as defined by RECIST v1.1. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/PD-L1 mAb (refractory disease). The initial evidence of disease progression is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression.
      - This determination is made by the investigator. Once progressive disease is confirmed, the initial date of disease progression documentation will be considered the date of disease progression.
   d. Received only 1 or, if BRAF mutation positive, 2 lines of therapy in the locally advanced or metastatic setting prior to study enrollment. Note: Adjuvant anti-PD-1/PD-L1 mAb/ BRAF inhibitor treatment will be counted as prior line of treatment if relapse occurred during active treatment or within 12 weeks of treatment discontinuation.
   e. No restriction with regards to PD-L1 and BRAF status
   f. In case melanoma is known to be BRAF mutation positive, subjects must have progressed on one prior BRAF inhibitor.
6. For **CRC Cohort only (Phase 2 part)**, subjects must have received at least two prior systemic therapies from the following, in adjuvant and/or metastatic setting, if approved and locally available (not exceeding 4 lines of therapies in the metastatic setting, progressed on at least 1 prior regimen in the metastatic setting or could not tolerate standard treatment):

   Note: Adjuvant chemotherapy counts as prior systemic treatment in the metastatic setting if there is documented disease progression within 6 months of treatment completion.

   Note: If a subject is determined to be intolerant to prior standard treatment, the subject must have received at least of 2 cycles of that therapy.

   a. Fluoropyrimidine, irinotecan and oxaliplatin

      Note: Capecitabine is acceptable as equivalent to fluoropyrimidine in prior treatment.

Note: Subjects who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) or fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), may be eligible after discussion with the Sponsor.

b. Chemotherapy with or without an anti-vascular endothelial growth factor (VEGF) mAb (eg, bevacizumab)

c. Chemotherapy with anti-endothelial growth factor recptor (EGFR) mAb (cetuximab or panitumumab) for subjects with RAS (KRAS/NRAS) wild type (WT) CRC

Note: RAS (KRAS/NRAS) WT subjects with right or left CRC lesions who may have not been treated with anti-EGFR mAb based on local guidelines are eligible

d. *BRAF* inhibitor (in combination with cetuximab ± binimetinib) for BRAF V600E mutated tumors.

7. Subjects with **HCC (Phase 2 part)** must have:
   a. A diagnosis of HCC that is histologically or cytologically confirmed (excluding fibrolamellar, sarcomatoid or mixed colangio-HCC tumors) or clinically confirmed according to American Association for the Study of Liver Disease criteria in cirrhotic subjects. Subjects without cirrhosis require histological confirmation of diagnosis.
   b. Stage B (not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment) or stage C based on Barcelona Clinic Liver Cancer staging System and Child-Pugh class A only.
   c. Subjects must have received only one prior line of systemic therapy in the locally advanced or metastatic setting, and must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Note: Subjects must have received at least 2 doses of the anti- PD-1/PD-L1 mAb.
8. For subjects with **HCC**:
   a. In case of hepatitis B surface antigen (HBsAg) (+) subjects: Antiviral therapy for hepatitis B virus (HBV) must be given for at least 3 months prior to the first dose of study drug, and HBV viral load must be less than 100 IU/mL prior to the first dose of study drug
      - Subjects who are HBsAg (+) and on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy while on study drug.
      - Subjects without HBV prophylaxis who are anti-hepatitis B core antibody (HBcAb) (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA do not require prophylaxis.
      - Subjects with HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA should continue the prophylaxis.
      - All the subjects above need monitoring with HBV DNA every 3 weeks while on study drug.
   b. Therapy for hepatitis C virus (HCV) must be completed at least 4 weeks prior to first dose of study drug in case of hepatitis C subjects who are on active HCV treatment. Hepatitis C subjects who are untreated or uncured may also be enrolled
9. Triplet treatment cohorts only: Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening/Baseline and no change in antihypertensive medications within 1 week before starting treatment in this study.
10. ECOG PS of 0 to 1.

11. Subject must have disease progression on current or since the last anticancer treatment.
12. At least one measurable lesion by CT or MRI based on RECIST 1.1 confirmed by the investigator:
    a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using CT/MRI.
    b. Lesions that have had external beam radiotherapy or loco-regional therapies such as radiofrequency ablation, or transarterial chemoembolization (TACE)/ transarterial embolization (TAE) must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.
13. Agree to consent for archival tumor tissue or a newly obtained biopsy tissue must be acquired prior to the first dose of study drug for biomarker analysis. Formalin-fixed paraffin embedded tissue block is preferred to slide. Newly obtained biopsy samples are preferred to archival tissue. In the case archival tissue cannot be provided, subjects with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the Sponsor. **For subjects with melanoma**, in addition to pretreatment biopsy, C2D1 biopsy samples will be collected from the pre-designated non-target lesion, if they have recovered adequately from the biopsy taken prior to starting therapy). Note: if subject has only measurable lesion and no accessible non measurable disease, the subject can be enrolled without a biopsy upon consultation and agreement by the Sponsor).

    Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut (details pertaining to the tumor tissue submission can be found in the Laboratory Manual).
14. Adequate renal function [redacted]
15. Adequate bone marrow function [redacted]
16. Adequate liver function [redacted]
17. All AEs due to previous anticancer therapy must have returned to Grade 0–1 except for alopecia and Grade 2 peripheral neuropathy.
18. Subjects must agree to take Vitamin D continuous supplementation as per local institutional guideline/investigator's clinical discretion if their 25-hydroxyvitamin D levels are less than 10 ng/mL.
19. Adequate serum mineral level:
    a. Calcium (albumin-corrected) within normal range
    b. Potassium within normal reference range

c. Magnesium ≥1.2 mg/dL or 0.5 mmol/L.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. History of other active malignancy (except for original disease, or definitively treated basal or squamous cell skin carcinoma, carcinoma in-situ of the bladder or cervix) within the past 24 months prior to the first dose of study drug.
2. Major surgery within 21 days prior to starting study drug or minor surgery (ie, simple excision) within 1 week (subject must also have recovered from any surgery-related toxicities to less than CTCAE Grade 2). Note for triplet treatment cohorts: Adequate wound healing after major surgery must be assessed clinically.
3. CCI [redacted]
4. Any of the cardiac conditions as follows:
   a. New York Heart Association (NYHA) congestive heart failure Class II or above
   b. CCI [redacted]
   c. Prolongation of corrected QT Fridericia (QTcF) interval to >450 msec
   d. Left ventricular ejection fraction (LVEF) below the institutional normal range, as determined by multigated acquisition (MUGA) or echocardiogram (ECHO)
5. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to study drug administration. The subject can receive diuretic drugs as needed per the treating physician, outside of the above-mentioned conditions. Consult with the Sponsor if the subject has more than trivial/trace fluid accumulation.
6. Prior treatment with E7386, or has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, [CTLA-4], OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related (ir)AE.
7. Subjects who have received treatments below before first study drug administration:
   a. Any prior anticancer treatment or investigational drug: within 4 weeks or 5 times the half-life, whichever is shorter
   b. Any investigational device: within 4 weeks
   c. Radiotherapy: within 2 weeks of start of study drug. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
   d. Have received a live or live-attenuated vaccine within 30 days prior to the first dose of study drug. Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

e. Has not recovered adequately from the toxicity and/or complications from the intervention if subject received major surgery prior to starting study drug.

f. CCI [redacted]

g. Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen within 4 weeks.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
9. Subjects with CNS metastases are not eligible unless they are previously treated, are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), and are clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
10. Diagnosed meningeal carcinomatosis
11. Has severe hypersensitivity (Grade ≥3) to study drugs and/or any of its excipients including previous clinically-significant hypersensitivity reaction to treatment with another mAb.
12. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
14. Active infection requiring systemic treatment.
15. Active viral hepatitis (B or C) as demonstrated by positive serology for subjects with **melanoma and CRC**.

    For subjects with HCC:

    - Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry
16. Known to be human immunodeficiency virus (HIV) positive. (Note: the Sponsor has evaluated whether to include subject with HIV. Given that this is the first combination study of E7386 with pembrolizumab and that the main mechanism of action of E7386 is immunomodulation of the tumor microenvironment along with the fact that several anti-retroviral therapies have drug-drug interaction with cytochrome P450 3A (CYP3A) substrates, the Sponsor has decided not to include these subjects at the current time. However, further considerations will be made moving forward based on new emerging data).
17. Evidence of current COVID-19 infection or ongoing unrecovered sequelae of COVID-19 infection.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
19. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.

20. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
21. Scheduled for major surgery during the study.
22. Any of the bone disease/conditions as follows:
    a. Osteoporosis with T-score of <–2.5 at the left or right total hip, left or right femoral neck or lumbar spine (L1-L4) as determined by dual energy x-ray absorptiometry (DXA) scan.
    b. Metabolic bone disease, such as hyperparathyroidism, Paget's disease or osteomalacia
    c. Symptomatic hypercalcemia requiring bisphosphonate therapy.
    d. History of any fracture within 6 months prior to starting study drug.
    e. History of symptomatic vertebral fragility fracture or any fragility fracture of the hip, pelvis, wrist or other location (defined as any fracture without a history of trauma or because of a fall from standing height or less).
    f. Moderate (25% to 40% decrease in the height of any vertebrae) or severe (>40% decrease in the height of any vertebrae) morphometric vertebral fracture at baseline.
    g. Any condition requiring orthopedic intervention.
    h. Bone metastases not being treated with a bisphosphonate or denosumab. Subject may be included if treatment with bisphosphonate or denosumab have been started at least 14 days prior to Cycle 1. Subjects with previous solitary bone lesions controlled with radiotherapy are eligible.
23. Has had an allogenic tissue/solid organ transplant (large organ transplants, stem-cell transplant requiring chronic immunosuppressant therapy necessary to prevent graft rejection).
24. Received blood/platelet transfusion or G-CSF within 4 weeks before study entry.
25. CCI [redacted]
26. CCI [redacted]

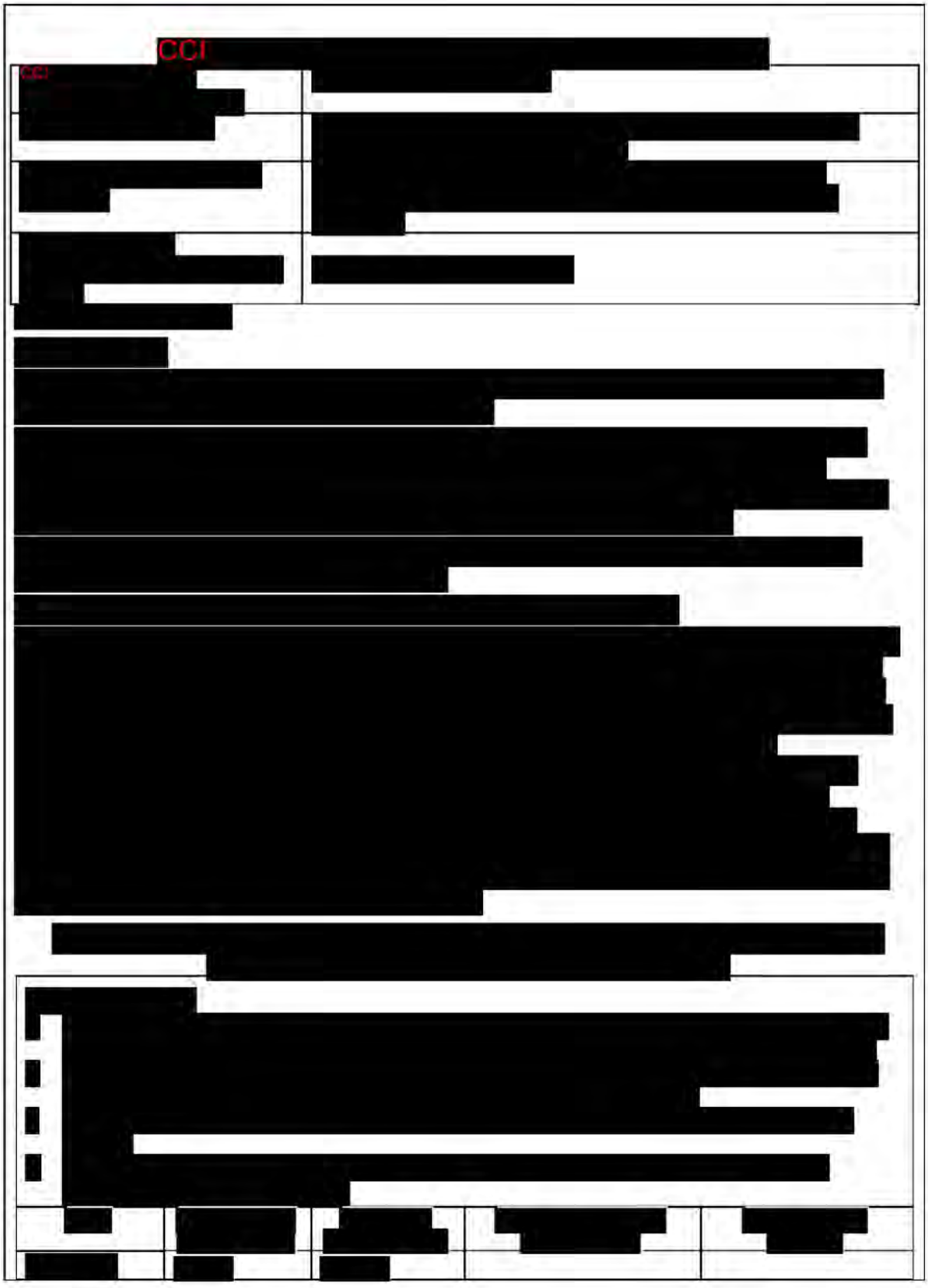
CCI [redacted]

27. Males who have not had a successful vasectomy (confirmed azoospermia) if their female partners meet the exclusion criteria above (ie, the female partners are of childbearing potential and are not willing to use a highly effective contraceptive method throughout the study period and for 5 times the half-life of the study drug plus 120 days after study drug discontinuation). No sperm donation is allowed during the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation.
28. For subjects with **melanoma only**, subjects with ocular melanoma are excluded. Note: Subjects with mucosal melanoma will not exceed 20% of the enrolled subjects in melanoma cohort in Phase 2.
29. For subjects with **CRC only**, subject is excluded if:
    a. has a tumor that is microsatellite instability high (MSI H)/DNA mismatch repair-deficient (dMMR) positive
    b. has received prior treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
30. For subjects with **HCC only**, subjects are excluded if:
    a. clear invasion to bile duct
    b. has had esophageal or gastric variceal bleeding within the last 6 months. Subjects in triplet treatment cohorts will be screened for esophageal or gastric varices unless such screening has been performed in the past 3 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study intervention; esophageal or gastric varices that require interventional treatment within 28 days prior to first dose of study drug are excluded
    c. history of hepatic encephalopathy within 6 months prior to starting study drug unresponsive to therapy within 3 days. Participants on rifaximin or lactulose during screening to control their hepatic encephalopathy are not allowed
31. For subjects in the **triplet treatment cohorts only**:
    a. Proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 hours will be ineligible
    b. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring (eg, warfarin or similar agents). Treatment with low molecular weight heparin and factor X inhibitors is permitted
    c. Clinically significant hemoptysis from any source or tumor bleeding within 3 weeks prior to the first dose of study drug
    d. Preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula

Study Drugs

Test drugs: E7386; pembrolizumab; lenvatinib (HCC triplet treatment cohorts [redacted]

[redacted]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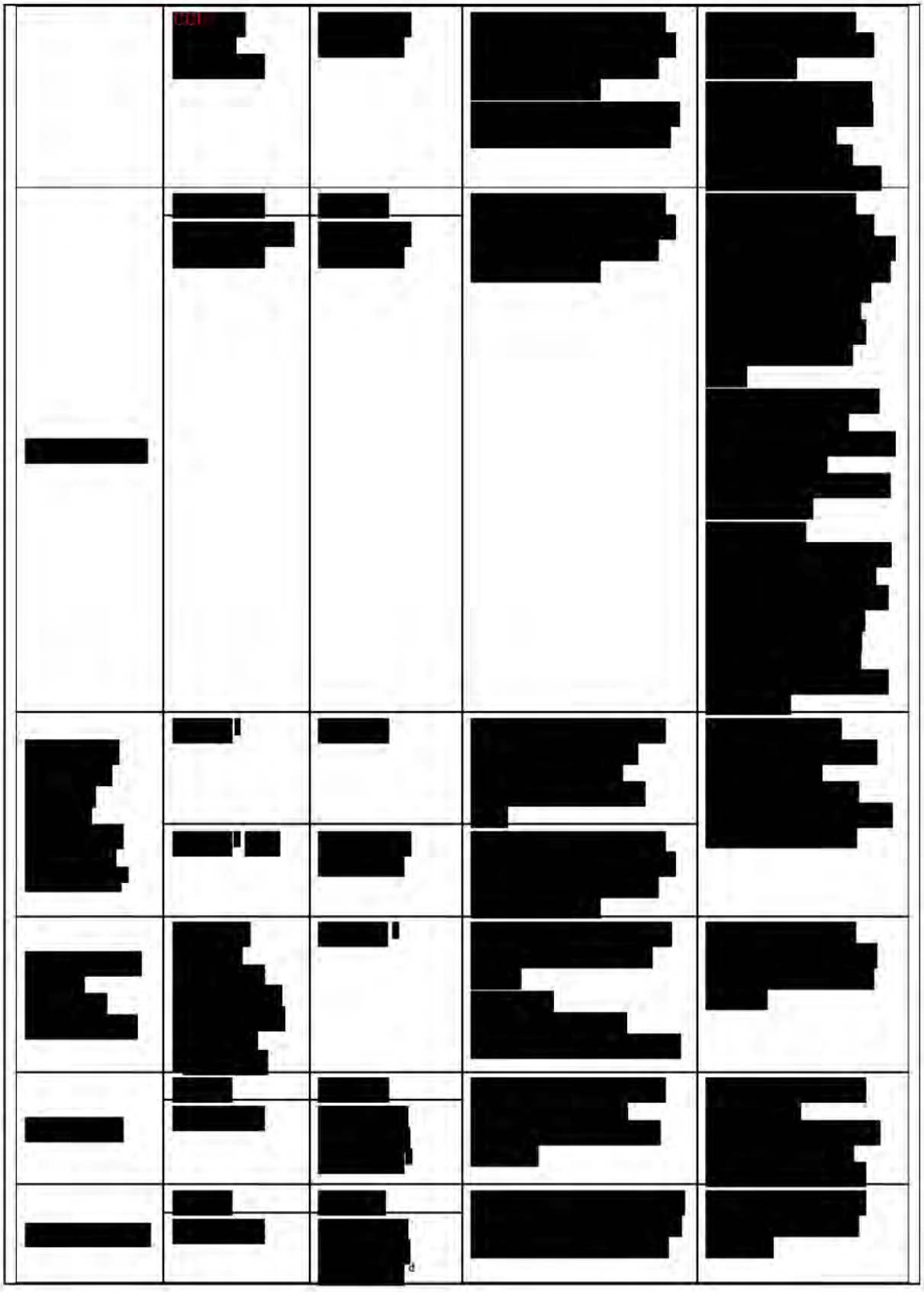

CCI [redacted]

Lenvatinib

CCI [redacted] The starting dose of lenvatinib will be 8 mg (2 x 4 mg capsules) QD, in immediate succession to E7386 and approximately at the same time everyday, with or without food continuously in CCI [redacted].

For subjects with HCC who receive CCI [redacted] after treatment with E7386 plus pembrolizumab, the starting dose of lenvatinib will be either 8 mg (2 x 4 mg capsules) for subjects with BW CCI [redacted], or 12 mg (3 x 4 mg capsules) for subjects with BW CCI [redacted] QD approximately at the same time everyday with or without food continuously in CCI [redacted].

Dose modifications for lenvatinib will be in accordance with the dose modification guidelines described in the table below.

An interruption of study intervention for more than 21 days will require Sponsor approval before treatment can be resumed. CCI [redacted]

Management of Lenvatinib Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment[c]
Grade 1 or Tolerable Grade 2	Continue treatment	No change
Intolerable Grade 2[c,d] or Grade 3[e,f]		
1st occurrence	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
2nd occurrence (same toxicity or new one)	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
3rd occurrence (same toxicity or new one)	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
4th occurrence (same toxicity or new one)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]	Discontinue lenvatinib[h]	

BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.
Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.
a: An interruption of study treatment for more than 21 days will require Sponsor's approval before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, hypothyroidism, or diarrhea prior to any lenvatinib interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e: For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.
f: For Grade 3 thromboembolic events, permanently discontinue lenvatinib. Refer to section below on management of thromboembolic events.
g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
h: If lenvatinib is discontinued due to an adverse event, the investigator can continue with E7386 and pembrolizumab in the triplet treatment cohorts.

[redacted]

Duration of Treatment

Subjects will remain on study drug until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice or termination of the study program.

Prohibited Concomitant Therapies and Drugs:

[redacted]

Assessments

Efficacy Assessments

Tumor assessments will be performed by investigators based on RECIST 1.1. Tumor assessments will be performed by CT/MRI every 6 weeks (±1 week counting from C1D1) until Week 24, then every 9 weeks (±1 week), at the EOT visit, and if clinically indicated. Investigator-determined response assessments will be performed at each assessment time point. Copies of all tumor assessment scans will be sent to an Imaging Core Lab (ICL) designated by the Sponsor for archival and potential blinded independent central review (BICR) assessment. After the primary analysis, the Sponsor may discontinue requiring copies of tumor assessment scans to be sent to the ICL.

Tumor assessments will be carried out following the guidelines provided by the ICL. Historical CT or MRI scans performed within 28 days before C1D1, but before the signing of informed consent, may be used as screening scans, provided they meet minimum standards as separately defined by the ICL.

Tumor assessments (CT chest, and CT or MRI abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Screening Period and then every 6 weeks (±1 week, starting from the date of C1D1) until Week 24 and every 9 weeks thereafter, or sooner, if clinically indicated. The same imaging modality and image-acquisition protocol should be used consistently across all time points. For subjects with HCC, an additional triphasic liver CT or MRI will be performed at all time points.

CCI [redacted]

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) will be performed at screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 6 weeks).

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

Subjects who discontinue study drug without disease progression in the Treatment Phase will continue to undergo tumor assessments every 6 weeks until Week 2 CCI [redacted]

Radiological images performed during the study may be used for future imaging biomarker discovery. The decision to perform exploratory image analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies. These findings may be used for identification and validation of early markers of treatment response and for potential diagnostic development.

CCI [redacted]

CCI

Pharmacokinetic Assessments

CCI

Phase 2 part: Blood samples for PK analysis of E7386 (doublet and triplet treatment cohorts) and lenvatinib (triplet treatment cohorts) will be collected as below:

CCI

CCI

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood Biomarkers:

CCI

CCI [redacted]

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE grades (for both increasing and decreasing severity) and serious AEs (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs, ECG, echocardiograms or MUGA and CCI [redacted] In addition, physical examinations will be performed, and ECOG PS will be assessed. AEs will be graded according to the NCI CTCAE version 5.0.

Evaluation of DLTs in the Phase 1b and Phase 2 (triplet treatment cohorts) parts of the study will be performed as described in the study protocol.

Bioanalytical Methods

Plasma concentrations of E7386 and lenvatinib will be measured by ~~a~~ validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods

Study Endpoints

For the tumor response related endpoints, the tumor assessments by BICR (if conducted) may be used in the primary analysis for the cohorts in Phase 2 part. Otherwise, tumor assessments by the investigator will be used for the analysis.

Primary Endpoints:

- Phase 1b part: Safety related endpoints including DLT
- Phase 2 part: ORR is defined as the proportion of subjects who have best overall response (BOR) of confirmed CR or PR per RECIST 1.1

Secondary Endpoints:

- BOR per RECIST 1.1 (for Phase 1b part)
- DOR is defined as the time from the first documentation of CR or PR to the first documentation of disease progression or death due to any cause, whichever occurs first, in subjects with confirmed CR or PR per RECIST 1.1
- Disease control rate (DCR) is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or SD: after ≥5 weeks from the first dose per RECIST 1.1
- Clinical benefit rate (CBR) is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or durable SD (duration of SD ≥23 weeks) per RECIST 1.1
- Safety and tolerability (eg, treatment-emergent adverse events, treatment-related adverse events) for E7386 in combination with pembrolizumab and safety and tolerability including DLTs for E7386 in combination with pembrolizumab plus lenvatinib
- PK profile of E7386 when co-administered with pembrolizumab or with pembrolizumab plus lenvatinib
- PK profile of lenvatinib in combination with E7386 and pembrolizumab

Exploratory Endpoints:

- CCI [redacted]

Analysis Sets

CCI [redacted]

CCI [redacted]

Efficacy Analyses

All efficacy analyses (except for DOR) will be performed within each cohort/tumor type on the Efficacy Analysis Set. The analysis for DOR will be performed in the subjects who show a confirmed CR or PR within each cohort/tumor type on the Efficacy Analysis Set.

Best overall response (BOR) is CR, partial response (PR), SD, progression of disease (PD), or not evaluable (NE)/Unknown, where SD has to be achieved at ≥5 weeks after the first dose. The BOR of CR and PR requires confirmation by a subsequent assessment of response at least 28 days later. However, for the consideration of cohort expansion in the interim data review, response confirmation will not be required.

Best overall response will be summarized and ORR, DCR, and CBR will be provided with 95% CI based on the method of Clopper and Pearson.

Objective response rate is the proportion of subjects who have best overall response of CR or PR.

Waterfall plots for maximum tumor shrinkage (ie, post baseline nadir) in sum of diameters of target lesions will also be provided.

Duration of response, PFS, and OS will be estimated and plotted over time using the Kaplan-Meier method. Median and quartiles will be provided with 95% confidence intervals (CI). Censoring rules will be detailed in the statistical analysis plan (SAP).

Data cutoff of the primary analysis in the Phase 2 part for each tumor cohort may be performed based on the Efficacy Analysis Set when all subjects in that cohort have completed a tumor assessment CCI [redacted] and/or have adequate follow-up to be evaluated the DOR, or discontinued early due to any cause.

Pharmacokinetic Analyses

The PK analysis will be performed on the Pharmacokinetic Analysis Set using plasma concentrations of E7386 in combination with pembrolizumab or in combination with pembrolizumab plus lenvatinib. Plasma concentrations of E7386 and lenvatinib (triplet treatment cohorts) will be tabulated and summarized by dose level, day, and time. The primary PK parameters of E7386 will be calculated using noncompartmental analysis for the Phase 1b part. Plasma concentration data for E7386 and lenvatinib in the Phase 2 part will be used to conduct population PK analysis and/or graphical presentation by integrating plasma concentration data from the Phase 1b part and/or other studies. PK/PD relationships (ie, exposure-efficacy, exposure-safety, and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach, for effects of study treatment. Efficacy endpoints will include primary endpoint of ORR (based on RECIST 1.1) and other efficacy-related metrics including but not limited to DOR. Safety endpoints will be most frequent AEs and dose reductions of E7386. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and, if possible, will be followed by model-based analyses for E7386. For population PK and PK/PD analyses, the details will be described in

a separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Details of the PD and other biomarker analyses will be provided in a separate analysis plan.

Tolerability and Safety Analyses

All tolerability analyses will be performed by dose level (if applicable) on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated.

The Safety Analysis Set will be used for all other safety analyses. Safety analyses will be assessed within each cohort/tumor type. The number and percentage of subjects with all AEs and SAEs observed after first dosing (ie, treatment-emergent adverse events) will be listed and summarized by system organ class (SOC), preferred term (PT), and CTCAE grade. Summary statistics will be presented for laboratory test values, vital signs, T-score[redacted], LVEF and 12-lead ECG parameters. If needed, the changes from Baseline will also be summarized.

Other Analyses

Patient-Reported Outcomes Analysis (Triplet Treatment Cohorts)

The impact of treatment will also be evaluated by subjects for a selection of AEs utilizing the PRO-CTCAE. Symptomatic AEs that are expected in the treatment group for the triplet treatment are based on previous clinical studies for each of the three treatments including the following: hoarseness (dysphonia), pain and swelling at the injection site, decreased appetite, nausea, vomiting, constipation, diarrhea, hand-foot syndrome, general pain, fatigue, and rash.

Interim Analyses

[redacted]

- CCI [redacted]

Sample Size Rationale

CCI [redacted]

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LIST OF IN-TEXT TABLES

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
1L	first-line
2L	second-line
AE	adverse event
AEI	adverse events of interest
AJCC	American Joint Committee on Cancer
ADA	anti-drug antibody
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBc	anti-hepatitis B core antibody
Anti-HBs	anti-hepatitis B surface antibody
APC	adenomatous polyposis coli
AST	aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
CCI	[redacted]
BICR	blinded independent central review
CCI	[redacted]
BID	twice daily
BMD	bone mineral density
BW	body weight
CA	Competent Authority
CBP	CREB-binding protein
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CREB	cAMP response element binding protein
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CT	computed tomography

Abbreviation	Term
CTLA-4	cytotoxic T-lymphocyte associated protein-4
CYP3A	cytochrome P450 3A
DLT	dose-limiting toxicity
dMMR	DNA mismatch repair-deficient
DOR	duration of response
CCI	[redacted]
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FGF	fibroblast growth factor
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
CCI	[redacted]
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
CCI	[redacted]
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
ICL	Imaging Core Laboratory
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IB	investigator's brochure

Abbreviation	Term
IgG4	immunoglobulin G4
LVEF	left ventricular ejection fraction
MedDRA	medical dictionary for regulatory activities
mAb	monoclonal Ab
MMTV	mouse mammary tumor virus
MRI	magnetic resonance imaging
MSS	microsatellite stable
MSI H	microsatellite instability high
MUGA	multiple gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	PD ligand 1
PD-L2	PD ligand 2
PFS	progression-free survival
CCI	[redacted]
PD	pharmacodynamic(s)
PG	pharmacogenomic(s)
PK	pharmacokinetic(s)
PR	partial response
PRO	Patient-Reported Outcomes
CCI	[redacted]
PS	performance status
PT	preferred term
Q3W	every 3 weeks
QTcF	corrected Fridericia QT interval
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation	Term
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class or standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse event
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VEGF	Vascular endothelial growth factor
WHO DD	World Health Organization Drug Directory
WT	wild type

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (GCP), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate (CRAs), change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or Sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the Sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the time of data cut-off for the final analysis or the date of the last study visit or last study assessment for the last subject in the study, whichever occurs later. The Sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator or designee, as appropriate, should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse event (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or the subject's legally authorized representative), the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement or electronic version, if allowed per country-specific regulations, written in nontechnical language. The subject (or the subject's legally authorized representative) should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject (or the subject's legally authorized representative), and after the subject (or the subject's legally authorized representative) has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

In the case of a subject lacking capacity to consent in the investigator's opinion, subject's assent plus written informed consent of a legally authorized representative should be obtained, if required in accordance with local laws, regulations, and customs. In countries where local laws/regulations and customs do not permit subjects lacking capacity to consent to participate in this study (eg, Germany and Spain), the subjects will not be enrolled. Capacity to consent and definition of legally authorized representative should be determined in accordance with applicable local laws and regulations. The investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study, and when a subject's family member expresses concern about the subject's study participation. The method and frequency of reassessment of capacity is at the investigator's discretion (taking into account any relevant local laws and regulations). During the study, should a subject decline to the point of lacking capacity in the investigator's opinion, the investigator should obtain the assent of the subject and consent of a legally authorized representative in accordance with local laws/regulations and customs for the subject to continue in the study. In countries where local laws/regulations do not permit subjects lacking capacity to consent to continue in this study (eg, Germany), then subjects who have declined to the point of lacking capacity to consent during the study will be discontinued.

An electronic consent (eConsent) process may be used, if allowed per country regulations, agreed by Sponsor and approved by IRB/EC.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

The subject (or the subject's legally authorized representative) should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

With regard to the pharmacogenomic (PG) assessments described in Section 9.5.1.3.2, an informed consent for collection of samples during the study for PG analysis will be prepared separately. Subjects may still participate in the study if they do not give informed consent for PG analysis.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the Sponsorship of Eisai (the Sponsor) at approximately 40 investigational sites in North America, Europe, and Asia-Pacific (APAC) regions.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of the contract research organizations (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Compound Overview

7.1.1 Background of E7386

E7386 is a potential first in class Wnt/β-catenin signaling pathway modulator. E7386 inhibits protein-protein interaction between a transcriptional co-activator, cAMP response element binding protein (CREB)-binding protein (CBP) and β-catenin, resulting in the modulation of Wnt/β-catenin signaling pathway-dependent gene expression. E7386 can inhibit not only ligand-dependent activation but also adenomatous polyposis coli (APC) or β-catenin mutation-dependent activation of Wnt/β-catenin signaling because of the downstream action of E7386 on APC and β-catenin in the Wnt/β-catenin signaling cascade. Therefore, E7386 is considered to be potentially active in tumors with aberrant Wnt/β-catenin signaling activation. In addition, E7386 also has the potential to eliminate drug-resistant cancer stem cells and tumor-initiating cells via forced differentiation, and to sensitize or re-sensitize resistant tumors to conventional therapy as a monotherapy, and in combination with chemotherapy and other agents (Kahn, 2014). In vivo, oral administration of E7386 significantly inhibited intestinal polyp formation in $Apc^{Min/+}$ mice (an engineered mouse model where aberrant activation of the Wnt/β-catenin pathway generates spontaneous polyposis in intestine). This demonstrates that E7386 modulated the Wnt/β-catenin pathway in vivo. E7386 also demonstrated antitumor activity against mouse mammary tumors developed in mouse mammary tumor virus (MMTV)-Wnt1 transgenic mice. These in vivo nonclinical results suggest that E7386 may provide a novel anticancer therapy against malignancies with aberrant activation of Wnt/β-catenin pathway (Yamada, et al., 2021).

7.1.2 Background of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable nonclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma (HCC); malignant melanoma; and renal cell carcinoma. Tumor-

infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley, et al., 2005; Hunder, et al., 2008).

The programmed cell death protein 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Encoded by the gene Pdcd1, PD-1 is an immunoglobulin superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) (Greenwald, et al., 2005; Okazaki, et al., 2001).

The structure of murine PD-1 has been resolved (Zhang, et al., 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki, et al., 2001; Chemnitz, et al., 2004; Sheppard, et al., 2004; and Riley, 2009). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry, et al., 2005; Francisco, 2010). As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma, HCC, and colorectal cancer (CRC).

7.1.3 Background of Lenvatinib

Lenvatinib is a potent multiple-receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1 [FLT1], VEGFR2 [KDR], VEGFR3 [FLT4]) in addition to other pro-angiogenic and oncogenic pathway-related receptor tyrosine kinases (RTKs), including fibroblast growth factor (FGF) receptors FGFR1 to 4, platelet-derived growth factor (PDGF) receptor α receptor-α (PDGFRα), stem cell factor receptor (KIT), and ret proto-oncogene (RET).

In the CT26 syngeneic model, lenvatinib significantly decreased the TAM population and increased the percentage of activated CD8+ T cells (Kimura, et al., 2018; Kato, et al., 2019; Adachi, et al., 2022). Thus, in addition to the direct anti-angiogenic effects of lenvatinib, the immune-modulating effect of lenvatinib may also result in potent combination effect with PD-1 signal inhibitors in multiple syngeneic tumor models. The effect of combining lenvatinib with PD-1/L1 (programmed death, ligand 1) monoclonal antibodies (mAbs) has been investigated and was more effective than either compound alone.

Lenvatinib alone or in combination with pembrolizumab is approved for several indications in many regions (refer to the Investigator's Brochure [IB] for specific details). Lenvatinib monotherapy is approved as first-line (1L) treatment in HCC in many parts of the world. In addition, lenvatinib is currently being investigated in combination with E7386 in the ongoing Study E7386-J081-102 (Study 102).

E7386 has been shown to enhance the antitumor activity of lenvatinib and/or suppress lenvatinib resistance in nonclinical studies (Ozawa, et al., 2017; Yamada, et al., 2018).

7.1.4 Melanoma, Colorectal Cancer, and Hepatocellular Carcinoma

The immune checkpoint inhibitors (ICIs), such as antibodies (Ab) that block (CTLA-4), the programmed cell death protein 1 (PD-1), PD ligand 1 (PD-L1), and PD-L2 is widely approved in many types of cancers as the standard of care (SOC). Although significant improvement has been made in patients' outcomes, the efficacy of these drugs is still limited and primary or acquired resistance to ICIs remain an issue, especially in 3 different cancer indications: melanoma and HCC after failing ICI therapy and primary resistance in microsatellite stable (MSS) CRC. Taken together, these limitations underline the need to develop better therapies or combination strategies that can address this key unmet medical need in subjects with metastatic melanoma, HCC, and MSS CRC.

In 2020, 324,635 new diagnoses of melanoma and 57,043 deaths for this disease were estimated globally (Sung, et al., 2021). The management of metastatic melanoma has changed dramatically since the introduction of targeted therapy and immunotherapy. In particular, Abs targeting PD-1, such as pembrolizumab and nivolumab alone or nivolumab in combination with a CTLA-4 inhibitor (ipilimumab) have been shown to improve objective response and progression free survival (PFS) (Wolchok, et al., 2017; Robert, et al., 2019). Tumor regression after therapeutic PD-1 blockade requires pre-existing $CD8^+$ T-cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance (Tumeh, et al., 2014). There is no standard of care after failing these therapies. The response rates in patients with advanced melanoma who experienced disease progression on immunotherapy and who had been treated with available therapy such as chemotherapy, CTLA-4 inhibitor, and combination of CTLA-4 inhibitor with PD-1 blockade are approximately 10% to 21% (Larkin, et al., 2018; Zimmer, et al., 2017).

Therefore, there remains an unmet medical need for patients after immunotherapy failure. In addition, primary or acquired resistance to anti-PD-1 therapy remains an issue. In particular, one mechanism of innate resistance to PD-1/PD-L1 inhibitors is the activation of the Wnt/β-catenin signaling pathway, which results in T-cell exclusion (Spranger, et al., 2015). Therefore, modulation of this intrinsic Wnt/β-catenin signaling in melanoma may offer an opportunity to overcome resistance to anti-PD-L1 Ab therapy.

For CRC, over 1.9 million new CRC cases and 935,000 deaths were estimated to occur globally in 2020 (Sung, et al., 2021). The standard of care in the metastatic setting includes cytotoxic agents such as folinic acid and 5-fluorouracil combined with either oxaliplatin (FOLFOX) or with irinotecan (FOLFIRI), biological targeted agents in combination with

chemotherapy agents and multikinase inhibitors such as regorafenib. Although regorafenib and trifluridine/tipiracil (TAS-102) are approved in patients with previously treated metastatic CRC based on survival benefit data, the objective response rates (ORR) in these patients are ≤2% for both agents (Grothey, et al., 2013; Mayer, et al., 2015). Immune checkpoint inhibitors are effective in patients with the hypermutated subtype of CRC, specifically those with microsatellite instability high (MSI H)/DNA mismatch repair-deficient (dMMR) CRC or those with hereditary mutations (Andre, et al., 2020; Diaz, et al., 2015; Grothey, 2020; Le, 2015). However, only a small proportion of patients with CRC have MSI-H tumors. Patients with MSS CRC do not benefit from single agent ICI therapy (Hermel and Sigal, 2019). In particular, >90% of CRC exhibit mutations in the APC gene and in other Wnt signaling components that result in hyperactivation of the Wnt pathway, and these mutations are the earliest known genetic alterations, indicating that they represent the initiating event in the path to CRC (Bugter, et al., 2021; The Cancer Genome Atlas Network, 2012; Silva, et al., 2014). Therefore, effective treatment in patients with MSS CRC still remains an unmet medical need. PRI-724, a second-generation CREB/β-catenin antagonist, inhibits the interaction between CBP and β-catenin (Takemaru and Moon, 2000). In an effort to increase the anti-tumor efficacy of PD-1/PD-L1 Ab, combination of PRI724 and PD-L1 Ab has been tested in a mouse model of colon cancer liver metastasis. This approach has shown regression of tumor growth compared to monotherapy alone. This study shows a new potential therapeutic strategy for treating this disease (Osawa, et al., 2019).

For liver cancer, approximately 906,000 new cases and 830,000 deaths were estimated to occur globally in 2020 (Sung, et al., 2021). Hepatocellular carcinoma is the most common primary liver malignancy worldwide and leading cause of death and represents 75%-85% of primary liver cancer (Sung, et al., 2021). Beside several targeted tyrosine kinase inhibitors including lenvatinib, treatment options include ICIs which have shown antitumor activity. Combination of atezolizumab and bevacizumab has shown a survival benefit relative to sorafenib in the first line setting and is widely used (Finn, et al., 2020). In this study, 28% of patients tested positive for treatment-emergent anti-drug antibody (ADA) and had a lower systemic atezolizumab exposure as compared to patients who were ADA-negative (Atezolizumab [TECENTRIQ®] Package Insert). Although several vascular endothelial growth factor (VEGF) inhibitors are available as second-line treatment options, such as regorafenib and cabozantinib, the ORR <10% for these treatments and many of these treatments are limited to use after sorafenib (Bruix, et al., 2017; Abou-Alfa, et al., 2018). Therefore, there is no standard of care and there is an unmet medical need for effective treatment after ICI-based regimens. Recently, next generation sequencing studies have shown that the presence of an activated Wnt/β-catenin signaling was associated with innate resistance to ICIs (Harding, et al., 2019). Based on recent nonclinical data described below, the Wnt/β-catenin signaling pathway is also a key pathway in lenvatinib resistance development. Therefore, the Wnt/β-catenin signaling pathway is key in ICIs and lenvatinib resistance and targeting this signal may overcome resistance to these agents.

7.2 Nonclinical evidence

In nonclinical studies, E7386 induced infiltration of $CD8^+$ cells into tumor tissues in immunohistochemistry experiments. Furthermore, E7386 showed synergistic antitumor

activity against MMTV-Wnt1 tumor in combination with an anti- mouse PD-1 Ab in nonclinical tumor isograft experiments (Yamada, et al., 2021).

Regarding pembrolizumab, therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific $CD8^+$ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano, et al.,2005; Blank, et al., 2004; Weber, 2010; Strome, et al., 2003; Spranger, et al., 2014; Curran, et al., 2010; Pilon, et al., 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome, et al., 2003; Curran, et al., 2010; Pilon, et al., 2010; Nomi, et al., 2007; Zhang, et al., 2004). In such studies, tumor infiltration by $CD8^+$ T cells and increased interferon-γ (IFN-γ), granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran, et al., 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB/approved labeling).

In nonclinical studies, lenvatinib inhibits both VEGF- and FGF-driven angiogenesis in vitro and in vivo. Lenvatinib demonstrated antitumor activity against a wide variety of xenograft athymic mouse models in which cancer cells (such as differentiated thyroid cancer, renal cell cancer, HCC) are transplanted. Lenvatinib also showed antitumor activity in a murine HCC isograft model in athymic mice. Lenvatinib monotherapy significantly decreased microvessel density in tumors in an isograft model of 4T1 murine breast cancer cells. In tumors treated with lenvatinib, the ratio of tumor vessels covered with pericytes, which are known to be resistant against VEGF inhibitors, were increased. The combination of E7386 with lenvatinib showed enhanced antitumor activity and resulted in a significant decrease in the microvessel density and greater reduction in the rate of tumor vessels covered with pericytes compared with E7386 and lenvatinib individual treatments in HCC xenograft tumor models. These data suggest E7386 suppresses lenvatinib-resistant vascularization and enhances anti-angiogenesis activity by lenvatinib (Ozawa, et al., 2017; Yamada, et al., 2018).

More recently, triplet treatment of E7386 with anti-mouse PD-1 antibody plus lenvatinib in syngeneic mouse HCC and RCC models showed increased antitumor activity of triplet treatment compared with either anti-PD-1 plus lenvatinib or E7386 plus lenvatinib combination (data on file).

7.3 Clinical Experience

7.3.1 E7386

Two Phase 1 studies (Study E7386-G000-101 [Study 101] and Study E7386-J081-103 [Study 103]) are ongoing to evaluate the safety and tolerability of E7386 monotherapy, and to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) in subjects with specific types of advanced solid tumors.

Study 101 is a first-in-human (FIH) study. CCI [redacted]

Study 103 aims to evaluate the safety and tolerability of E7386 in subjects with advanced solid tumors including CRC. CCI [redacted]

The most common toxicities associated with E7386 in both monotherapy studies were Grade 1 or 2 nausea and vomiting, but these toxicities are well manageable up to the120 mg BID dose level with 5 HT_3 antagonists. There was no significant difference in safety and PK profiles between Study 101 and Study 103.

Study E7386-J081-102 (Study 102) is a Phase 1b Study of E7386 in combination with other anticancer drugs in subjects with solid tumors and HCC in Japan. The purpose of the study is to evaluate the safety and tolerability of E7386, and to determine the RP2D of E7386 (tablet formulation) in combination with other anticancer drugs. This study is ongoing; preliminary data showed antitumor activity of E7386 plus lenvatinib in subjects with unresectable HCC including those who had received prior lenvatinib. CCI [redacted]

Refer to the current E7386 IB for further details.

7.4 Study Rationale

The rationale for the proposed study is to test whether E7386 can unlock the pembrolizumab-resistant tumor immune microenvironment. Therefore, E7386 may sensitize tumors unresponsive to anti-PD-1/PD-L1 Ab by increasing tumor-infiltrating T cells through the modulation of the Wnt/β-catenin signaling pathway. Nonclinical data is supportive of this synergistic effect of combination therapy with alteration of the tumor immune microenvironment in the MMTV-Wnt1 mouse tumor model (Yamada, et al., 2021). In addition, given the fact that E7386 is a small molecule and pembrolizumab is a monoclonal Ab, there are no expected overlapping clearance, metabolic pathways, or any known overlapping toxicities between E7386 and pembrolizumab.

In addition, the Wnt/β-catenin signaling pathway is a key player in lenvatinib resistance, and E7386 plus lenvatinib suppressed lenvatinib-resistant pericyte-covered vessels, which is a known mechanism of resistance to VEGF inhibitors, suggesting E7386 sensitizes tumors to lenvatinib through modulation of the tumor microenvironment (Ozawa, et al., 2017; Yamada, et al., 2018). It is hypothesized that the proposed triplet treatment (E7386 in combination with pembrolizumab plus lenvatinib) may further improve efficacy through the "add-on approach" and overcome immuno-oncology (IO) resistance as well as resistant mechanisms against anti-angiogenic therapies.

In line with its mechanism of action, available in-house and emerging external nonclinical and clinical data for the same class of compounds, E7386 is planned to be developed both as a monotherapy agent and in combination with other anticancer agents including pembrolizumab and lenvatinib.

7.5 Risk/Benefit Assessment

The proposed combination of E7386 with pembrolizumab addresses a key unmet medical need. The hypothesis of testing whether E7386 could unlock the pembrolizumab-resistant tumor microenvironment is worth exploring given the strong scientific rationale and requires to be tested in a clinical setting. Based on the proposed rationale, this study is primarily focusing on subjects with cancer who had no response or had disease progression on prior anti-PD-1 /PD-L1 Ab treatment including second-line (2L) melanoma and 2L HCC after prior treatment with one anti-PD-1/PD-L1 Ab, and 3L MSS CRC.

More than 50 subjects have been treated with E7386 in the ongoing Phase 1 studies (Study 101 and Study 103). In these studies, the most common treatment-emergent adverse events (TEAEs) that have been reported as treatment related have been nausea and vomiting. Nonclinical findings of E7386 were toxicities in the bone marrow, lymphoid organs, gastrointestinal, epithelial tissues in dogs and rats. In addition, bone toxicity in rats was observed and is considered to be an on-target effect since Wnt signaling has been shown to regulate osteoblast and osteoclast proliferation and differentiation (Krishnan, 2006; Kobayashi, 2016). Therefore, the potential effects of E7386 on bone needs to be monitored carefully. Preliminary safety data available from the dose escalation part for this combination (see Section 9.1.2) showed there were no DLTs in the Phase 1b portion of the study. Since limited data are available for E7386 in combination with pembrolizumab, close safety monitoring assessment will be conducted in this clinical study. Overall, given the possible synergy of these 2 agents without apparent overlapping toxicity profiles, the benefit/risk profile for the proposed study is considered to be positive. Taken together, current available data provides a scientific rationale to test the combination of E7386 with pembrolizumab in subjects with cancer.

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8 STUDY OBJECTIVES

8.1 Primary Objectives

Phase 1b part:

- To assess the safety and tolerability of E7386 in combination with pembrolizumab in subjects with previously treated selected solid tumors
- To determine the RP2D of E7386 in combination with pembrolizumab

Phase 2 part:

- To assess the ORR of E7386 in combination with pembrolizumab (melanoma, colorectal cancer [CRC], hepatocellular carcinoma [HCC]) or of E7386 in combination with pembrolizumab plus lenvatinib (HCC) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

8.2 Secondary Objectives

Phase 1b part only:

- To assess tumor response according to RECIST 1.1

Phase 1b and Phase 2 parts:

- To assess duration of response (DOR) according to RECIST 1.1 per tumor cohort
- To assess the disease control rate (DCR: the proportion of subjects with complete response [CR], partial response [PR], or stable disease [SD] after ≥5 weeks from the first dose) according to RECIST 1.1 per tumor cohort
- To assess the clinical benefit rate (CBR: the proportion of subjects with CR, PR, or durable SD [duration of SD ≥23 weeks]) according to RECIST 1.1 per tumor cohort

- To assess the safety and tolerability of E7386 in combination with pembrolizumab and E7386 in combination with pembrolizumab plus lenvatinib
- To evaluate the pharmacokinetic (PK) profile of E7386 when co-administered either with pembrolizumab or with the combination of pembrolizumab plus lenvatinib
- To evaluate the PK profile of lenvatinib when co-administered with E7386 plus pembrolizumab
- To determine the optimal dose level of E7386 in combination with pembrolizumab plus lenvatinib

8.3 Exploratory Objectives

CCI [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, multicenter, Phase 1b/2 study that will evaluate the safety and efficacy of E7386 in combination with pembrolizumab or E7386 in combination with pembrolizumab plus lenvatinib. CCI [redacted] Safety, tumor response, PK, and PD assessments (all cohorts), as well as determination of the optimal dose level and the effect of triplet treatment on PRO (triplet treatment cohorts) will be performed on every subject; details are described in the Schedule of Procedures/Assessments.

The study is divided into 3 parts (Phase 1b part, Phase 2 part, and Extension part), and each part will be conducted in 3 phases: Pretreatment Phase (including Screening Period and Baseline Period), Treatment Phase, and Follow-Up Phase (after the End of Treatment [EOT]).

Eligible subjects will be enrolled into 1 of 3 tumor cohorts: melanoma, CRC, and HCC. The Phase 1b part will determine the RP2D based on safety and tolerability in up to 18 evaluable subjects overall. At least 1 subject with HCC will be enrolled at each dose level in Phase 1b part.

Phase 2 part will be conducted in 2 stages for the cohorts administered E7386 plus pembrolizumab. CCI

An overview of the study design is presented in Figure 1.

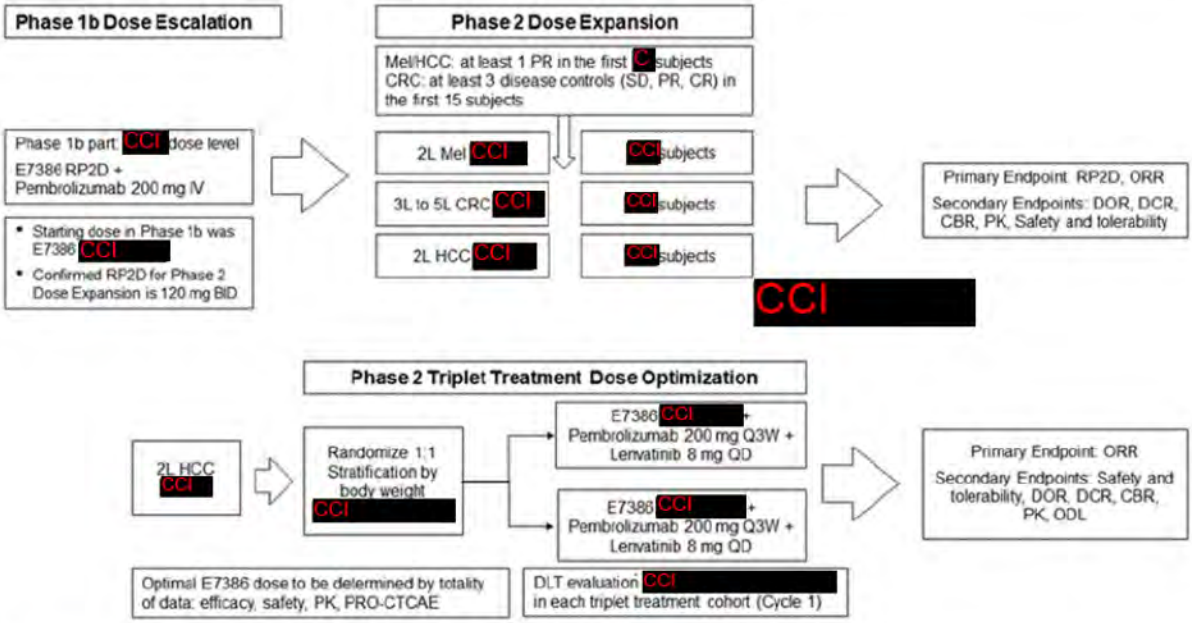


Figure 1 Study Schema

9.1.1 Phase 1b Part

This part will assess the safety and tolerability of E7386 in combination with pembrolizumab in previously treated subjects with selected solid tumors. Subjects in Phase 1b part will have one of the following tumors: melanoma, CRC, or HCC. At least 1 subject with HCC will be enrolled at each dose level in Phase 1b part.

E7386 will be administered on Days CCI at a dose of CCI orally; pembrolizumab will be administered at a dose of 200 mg intravenously Q3W. Six evaluable subjects per dose level will be enrolled in Phase 1b part. The dose of pembrolizumab will not change during the study. If the initial dose of E7386 (Dose Level 0) is considered tolerable, the dose of E7386 may be escalated to the next higher dose level of CCI (Dose Level 1). If the initial dose level is not considered tolerable, the dose of E7386 may be reduced to the next lower dose level of CCI (Dose Level –1; Table 1).

Table 1 Study Drug Dose Levels for Phase 1b Part

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]
*Dose Level 0 refers to the starting dose.

[redacted]

Table 2 Criteria for Addition of Subjects for Evaluation and Reducing to a Lower Dose Level

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

9.1.2 Phase 2 Part

As per protocol Amendment 03, there were no DLTs in the Phase 1b portion of the study, and the RP2D was determined at Dose Level 1 CCI [redacted] After the RP2D is confirmed, and depending on the safety and efficacy observed, 3 cohorts of subjects (Cohort A melanoma; Cohort B CRC; Cohort C HCC) will be enrolled to assess safety, tolerability and efficacy using the combination dose determined in Phase 1b part. Approximately 90 eligible subjects (30 subjects per selected tumor) who meet all the inclusion criteria and none of the exclusion criteria will be stratified by tumor cohort and enrolled to receive E7386 in combination with pembrolizumab. For melanoma and HCC, subjects must have received 1 prior therapy that included an anti-PD-1/PD-1 ligand 1 (PD-L1) monoclonal antibody.

CCI [redacted]

[redacted]

Further details regarding criteria of the interim data reviews are described in the Interim Analyses section (Section 9.7.3 for the Phase 2 doublet treatment cohorts).

[redacted]

[redacted]

[redacted]

CCI

[redacted]

9.1.3 Extension Part

All subjects who are still on study drug or in follow-up at the time of data cutoff for the primary analysis of Phase 2 part will be eligible to enter the Extension part on the same treatment if still on treatment as in the Phase 1b part or Phase 2 part.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows are outlined in the Schedule of Procedures/Assessments for extension part (Table 16). Assessment procedures will be assessed similarly to Phase 1b and Phase 2 Parts.

9.1.4 Study Phases

This study will be conducted in 3 Phases: Pretreatment, Treatment, and Follow-Up.

9.1.4.1 Pretreatment Phase

The Pretreatment Phase will last no longer than 28 days and includes a Screening Period, to obtain informed consent and establish protocol eligibility, and a Baseline Period, to confirm protocol eligibility prior to treatment.

Screening will occur between Day –28 and Day –3. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. The Baseline Period will occur between Day –3 and C1D1 (prior the first dose of study drug administration).

Subjects must have a histologically-confirmed diagnosis of melanoma, HCC or CRC.

Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.4.2 Treatment Phase

CCI

[redacted]

CCI [redacted]

9.1.4.3 Follow-Up Phase

The Follow-Up Phase will start after the EOT Visit. Follow-up will continue as long as the study subject is alive unless the subject withdraws consent or until the Sponsor terminates the study. Subjects will be followed every 12 weeks (±1 week) for survival and subsequent anticancer treatments. The Sponsor may decide to terminate survival follow-up at any time or when all subjects discontinue study drug.

If a subject becomes unavailable for follow-up (eg, misses scheduled assessment, telephone contact), the investigator or designee will make every attempt to contact the subject to determine his or her status. All attempts at contact will be recorded in the subject's medical notes. Subjects will only be deemed lost to follow-up:

- After a minimum of 3 attempted contacts (eg, telephone, letter) with the subject, the subject's family, or the primary care (family) physician, at least 4 weeks apart. The last attempt at contact must occur no earlier than 3 months after the subject's last successful contact
- If the last attempt at contact is unsuccessful, the site should write a letter with certified proof of posting or regional equivalent method to the subject, subject's family, or the primary care (family) physician to request information on the subject's status

CCI [redacted]

[redacted]

9.1.5 End of Study

A subject is considered to have completed the study if he or she has completed all phases of the study including the last assessment or the last scheduled procedure shown in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17).

The end of study will be the last subject/last visit, including discontinuation from study for any reason.

9.2 Discussion of Study Design

This is an open-label, multicenter, Phase 1b/2 study of E7386 in combination with pembrolizumab in previously treated subjects with selected solid tumors or E7386 in combination with pembrolizumab plus lenvatinib in previously treated subjects with HCC. The study is divided into 3 parts (Phase 1b part, Phase 2 part and Extension part). Eligible subjects will be enrolled into 1 of 3 tumor cohorts: melanoma, CRC, and HCC.

The Phase 1b part of this study will determine the RP2D of E7386 in combination with pembrolizumab in subjects with selected tumor types, based primarily on an evaluation of the safety and tolerability profile. Assessment at each dose level will be based initially on the safety and tolerability shown in 6 subjects. Any decision to escalate or to de-escalate the dose of E7386 will be based on the numbers of subjects reporting DLT; this is an established method to identify a well-tolerated RP2D based on the safety and tolerability profile of the study drug in a limited number of subjects. Available data from other ongoing studies of E7386 will also be considered before escalating the dose of E7386, to minimize the risk to study subjects.

The Phase 2 part of this study will evaluate the anti-tumor activity, safety, tolerability and PK profile of E7386 at the RP2D of E7386 in combination with pembrolizumab, and will also explore PD markers of E7386 activity. CCI

[redacted]

All subjects who are still on study drug or in follow-up at the time of data cutoff for the primary analysis of Phase 2 part will be eligible to enter the Extension part on the same treatment, if still on treatment as in the Phase 1b part or Phase 2 part.

9.3 Selection of Study Population

In Phase 1b part, up to 18 evaluable subjects with advanced (metastatic and/or unresectable) melanoma, CRC or HCC will be enrolled at sites in the US, Japan, and Europe/UK. In Phase 2 part, up to approximately 90 subjects will be enrolled at multinational sites. Subjects will be enrolled into 1 of 3 tumor cohorts (melanoma, CRC, HCC), with up to approximately 30 subjects in each cohort. Subjects with melanoma or HCC must have received one prior line of therapy in the locally advanced or metastatic setting.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.
2. Male or female, age ≥18 years (or any age ≥18 years as determined by country legislation) at the time of informed consent.
3. Life expectancy of ≥12 weeks.
4. Have a histologically or cytologically-documented, advanced (metastatic and/or unresectable) selected solid tumor for which prior standard systemic therapy has failed. Selected tumor types: melanoma (excluding uveal melanoma), CRC, HCC.

5. For **Melanoma Cohort only (Phase 2 part)**, subject must have:
   a. Unresectable Stage III or Stage IV melanoma, per American Joint Committee on Cancer (AJCC) staging system version 8, not amenable to local therapy.
   b. At least one measurable lesion by computer tomography (CT) or magnetic imaging resonance (MRI) based on RECIST 1.1 (cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as nontarget lesions).
      – Lesions in a previously irradiated area should not be considered measurable unless there has been documented growth of the lesions since the completion of radiotherapy.
   c. Progressed on or after prior treatment with one anti-PD-1/PD-L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. PD-1 progression is defined as:
      – Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb (eg, pembrolizumab, nivolumab, nivolumab plus ipilimumab) and
      – Has demonstrated disease progression after PD-1/PD-L1 as defined by RECIST v1.1. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/PD-L1 mAb (refractory disease). The initial evidence of disease progression is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression.
      – This determination is made by the investigator. Once progressive disease is confirmed, the initial date of disease progression documentation will be considered the date of disease progression.
   d. Received only 1 or, if BRAF mutation positive, 2 lines of therapy in the locally advanced or metastatic setting prior to study enrollment. Note: Adjuvant anti-PD-1/PD-L1 mAb/ BRAF inhibitor treatment will be counted as prior line of treatment if relapse occurred during active treatment or within 12 weeks of treatment discontinuation.
   e. No restriction with regards to PD-L1 and BRAF status
   f. In case melanoma is known to be BRAF mutation positive, subjects must have progressed on one prior BRAF inhibitor
6. **For CRC Cohort only (Phase 2 part)**, subjects must have received at least two prior systemic therapies from the following, in adjuvant and/or metastatic setting, if approved and locally available (not exceeding 4 lines of therapies in the metastatic setting, progressed on at least 1 prior regimen in the metastatic setting or could not tolerate standard treatment):

   Note: Adjuvant chemotherapy counts as prior systemic treatment in the metastatic setting if there is documented disease progression within 6 months of treatment completion.

Note: If a subject is determined to be intolerant to prior standard treatment, the subject must have received at least of 2 cycles of that therapy.

a. Fluoropyrimidine, irinotecan and oxaliplatin
Note: Capecitabine is acceptable as equivalent to fluoropyrimidine in prior treatment.

Note: Subjects who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) or fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), may be eligible after discussion with the Sponsor.

b. Chemotherapy with or without an anti-VEGF mAb (eg, bevacizumab)

c. Chemotherapy with anti-EGFR mAb (cetuximab or panitumumab) for subjects with RAS (KRAS/NRAS) wild type (WT) CRC

Note: RAS (KRAS/NRAS) WT subjects with right or left CRC lesions who may have not been treated with anti-EGFR mAb based on local guidelines are eligible

d. *BRAF* inhibitor (in combination with cetuximab ± binimetinib) for BRAF V600E mutated tumors.

7. **Subjects with HCC (Phase 2 part)** must have:

a. A diagnosis of HCC that is histologically or cytologically confirmed (excluding fibrolamellar, sarcomatoid or mixed cholangio-HCC tumors) or clinically confirmed according to American Association for the Study of Liver Disease criteria in cirrhotic subjects. Subjects without cirrhosis require histological confirmation of diagnosis.

b. Stage B (not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment) or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging System and Child-Pugh class A only.

c. Subjects must have received only one prior line of systemic therapy in the locally advanced or metastatic setting, and must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Note: Subjects must have received at least 2 doses of the anti- PD-1/PD-L1 mAb.

8. **For subjects with HCC**:

a. In case of hepatitis B surface antigen (HBsAg) (+) subjects: Antiviral therapy for hepatitis B virus (HBV) must be given for at least 3 months prior to the first dose of study drug, and HBV viral load must be less than 100 IU/mL prior to the first dose of study drug.

- Subjects who are HBsAg (+) and on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy while on study drug.
- Subjects without HBV prophylaxis who are anti-hepatitis B core antibody (HBcAb) (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA do not require prophylaxis.
- Subjects with HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA should continue the prophylaxis.

- All the subjects above need monitoring with HBV DNA every 3 weeks while on study drug.

b. Therapy for hepatitis C virus (HCV) must be completed at least 4 weeks prior to first dose of study drug in case of hepatitis C subjects who are on active HCV treatment. Hepatitis C subjects who are untreated or uncured may also be enrolled.

9. **Triplet treatment cohorts only**: Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening/Baseline and no change in antihypertensive medications within 1 week before starting treatment in this study.
10. ECOG PS of 0 to 1.
11. Subject must have disease progression on current or since the last anticancer treatment.
12. At least one measurable lesion by CT or MRI based on RECIST 1.1 confirmed by the investigator:
    a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using CT/MRI.
    b. Lesions that have had external beam radiotherapy or loco-regional therapies such as radiofrequency ablation, or transarterial chemoembolization (TACE)/transarterial embolization (TAE) must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.
13. Agree to consent for archival tumor tissue or a newly obtained biopsy tissue must be acquired prior to the first dose of study drug for biomarker analysis. Formalin-fixed paraffin embedded tissue block is preferred to slide. Newly obtained biopsy samples are preferred to archival tissue. In the case archival tissue cannot be provided, subjects with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the Sponsor. **For subjects with melanoma**, in addition to pretreatment biopsy, C2D1 biopsy will be collected from the pre-designated non-target lesion, if they have recovered adequately from the biopsy taken prior to starting therapy).

    Note: If subject has only measurable lesion and no accessible non measurable disease, the subject can be enrolled without a biopsy upon consultation and agreement by the Sponsor).

    Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut (details pertaining to the tumor tissue submission can be found in the Laboratory Manual).
14. Adequate renal function CCI [redacted]
15. Adequate bone marrow function [redacted]

- [redacted] CCI [redacted]

16. Adequate liver function
    - [redacted]
    - [redacted]
    - [redacted]
17. All AEs due to previous anticancer therapy must have returned to Grade 0–1 except for alopecia and Grade 2 peripheral neuropathy.
18. Subjects must agree to take Vitamin D continuous supplementation as per local institutional guideline/ investigator's clinical discretion if their 25-hydroxyvitamin D levels are less than 10 ng/mL.
19. Adequate serum mineral level:
    a. Calcium (albumin-corrected) within normal range
    b. Potassium within normal reference range
    c. Magnesium ≥1.2 mg/dL or 0.5 mmol/L.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. History of other active malignancy (except for original disease, or definitively treated basal or squamous cell skin carcinoma, carcinoma in-situ of the bladder or cervix) within the past 24 months prior to the first dose of study drug.
2. Major surgery within 21 days prior to starting study drug or minor surgery (ie, simple excision) within 1 week (subject must also have recovered from any surgery-related toxicities to less than CTCAE Grade 2). Note for **triplet treatment cohorts**: Adequate wound healing after major surgery must be assessed clinically.
3. CCI [redacted]
4. Any of the cardiac conditions as follows:
    a. New York Heart Association (NYHA) congestive heart failure Class II or above
    b. CCI [redacted]

CCI [redacted]

c. Prolongation of corrected QT Fridericia (QTcF) interval to >450 msec

d. Left ventricular ejection fraction (LVEF) below the institutional normal range, as determined by multi-gated acquisition (MUGA) or echocardiogram (ECHO)

5. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to study drug administration. The subject can receive diuretic drugs as needed per the treating physician, outside of the above-mentioned conditions. Consult with the Sponsor if the subject has more than trivial/trace fluid accumulation.

6. Prior treatment with E7386, or has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, cytotoxic T-lymphocyte associated protein-4 (CTLA)-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related (ir)AE.

7. Subjects who have received treatments below before first study drug administration:

   a. Any prior anticancer treatment or investigational drug: within 4 weeks or 5 times the half-life, whichever is shorter

   b. Any investigational device: within 4 weeks.

   c. Radiotherapy: within 2 weeks of start of study drug. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.

   d. Have received a live or live-attenuated vaccine within 30 days prior to the first dose of study drug. Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

   e. Has not recovered adequately from the toxicity and/or complications from the intervention if subject received major surgery prior to starting study drug.

   f. CCI [redacted]

   g. Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen within 4 weeks.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. Subjects with CNS metastases are not eligible unless they are previously treated, are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), and clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
10. Diagnosed meningeal carcinomatosis
11. Has severe hypersensitivity (Grade ≥3) to study drugs and/or any of its excipients including previous clinically-significant hypersensitivity reaction to treatment with another mAB.
12. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
14. Active infection requiring systemic treatment.
15. Active viral hepatitis (B or C) as demonstrated by positive serology for subjects with **melanoma and CRC**.

    For subjects with **HCC**:

    - Has dual active HBV infection (HBsAg [+] and /or detectable HBV DNA) and HCV infection (anti-HCV Ab [+] and detectable HCV RNA) at study entry.
16. Known to be human immunodeficiency virus (HIV) positive. (Note: the Sponsor has evaluated whether to include subject with HIV. Given that this is the first combination study of E7386 with pembrolizumab and that the main mechanism of action of E7386 is immunomodulation of the tumor microenvironment along with the fact that several anti-retroviral therapies have drug-drug interaction with cytochrome P450 3A4 (CYP3A) substrates, the Sponsor has decided not to include these subjects at the current time. However, further considerations will be made moving forward based on new emerging data).
17. Evidence of current COVID-19 infection or ongoing unrecovered sequelae of COVID-19 infection.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
19. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.

20. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
21. Scheduled for major surgery during the study.
22. Any of the bone disease/conditions as follows:
    - [redacted]
    - b. Metabolic bone disease, such as hyperparathyroidism, Paget's disease or osteomalacia.
    - c. Symptomatic hypercalcemia requiring bisphosphonate therapy.
    - d. History of any fracture within 6 months prior to starting study drug.
    - e. History of symptomatic vertebral fragility fracture or any fragility fracture of the hip, pelvis, wrist or other location (defined as any fracture without a history of trauma or because of a fall from standing height or less).
    - f. Moderate (25% to 40% decrease in the height of any vertebrae) or severe (>40% decrease in the height of any vertebrae) morphometric vertebral fracture at baseline.
    - g. Any condition requiring orthopedic intervention.
    - h. Bone metastases not being treated with a bisphosphonate or denosumab. Subject may be included if treatment with bisphosphonate or denosumab have been started at least 14 days prior to Cycle 1. Subjects with previous solitary bone lesions controlled with radiotherapy are eligible.
23. Has had an allogenic tissue/solid organ transplant (large organ transplants, stem-cell transplant requiring chronic immunosuppressant therapy necessary to prevent graft rejection).
24. Received blood/platelet transfusion or G-CSF within 4 weeks before study entry.
25. [redacted]
26. [redacted]

[redacted]

27. Males who have not had a successful vasectomy (confirmed azoospermia) if their female partners meet the exclusion criteria above (ie, the female partners are of childbearing potential and are not willing to use a highly effective contraceptive method throughout the study period and for 5 times the half-life of the study drug plus 120 days after study drug discontinuation). No sperm donation is allowed during the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation.
28. For subjects with **melanoma only**, subjects with ocular melanoma are excluded. Note: Subjects with mucosal melanoma will not exceed 20% of the enrolled subjects in melanoma cohort in Phase 2.
29. For subjects with **CRC only**, subject is excluded if:
    a. has a tumor that is MSI H/dMMR positive
    b. has received prior treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
30. For subjects with **HCC only**, subject is excluded if:
    a. clear invasion to bile duct
    b. has had esophageal or gastric variceal bleeding within the last 6 months. Subjects in triplet treatment cohorts will be screened for esophageal or gastric varices unless such screening has been performed in the past 3 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study intervention; esophageal or gastric varices that require interventional treatment within 28 days prior to first dose of study drug are excluded.

c. history of hepatic encephalopathy within 6 months prior starting study drug unresponsive to therapy within 3 days. Subjects on rifaximin or lactulose during screening to control their hepatic encephalopathy are not allowed

31. For subjects in the **triplet treatment cohorts only**:

a. Proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 hours will be ineligible

b. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring (eg, warfarin or similar agents). Treatment with low molecular weight heparin and factor X inhibitors is permitted

c. Clinically significant hemoptysis from any source or tumor bleeding within 3 weeks prior to the first dose of study drug

d. Preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Subjects will continue to receive study drug until any of the following occur(s):

- Radiological Disease Progression
- Clinical Disease Progression
- Treatment discontinued due to adverse event
- Subject choice to discontinue treatment
- Lost to follow-up
- Withdrawal of consent from the study
- Study Terminated by Sponsor
- Other

The investigator may discontinue treating a subject with study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented.

After completion of specified EOT Visit, the subject will enter the Follow-Up Phase and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study drug but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

Subjects who have discontinued study drug without progression should have disease assessments every 6 weeks until Week 2 CCI [redacted]

During the Follow-Up Phase, all subjects will be followed for survival until death, except where a subject withdraws consent or until the subject is lost to follow-up. Follow-up will be terminated at the time of the last subject's discontinuation or 12 months after the last subject's enrollment, whichever is later, or if the Sponsor chooses to end survival follow-up after completion of the primary study analysis of Phase 2 part.

All subjects who are still on study drug or in follow-up at the time of data cutoff for the primary analysis of Phase 2 part will be eligible to enter the Extension part. During the Extension part, all subjects will be followed for the disease assessment and/or survival until death, except where a subject withdraws consent or until the subject is lost to follow-up. Follow-up will be terminated at the time of the last subject's discontinuation or 12 months after the last subject's enrollment whichever is later, or if the Sponsor chooses to end survival follow-up.

A subject who discontinues study drug should be followed for subsequent protocol-specified visits and procedures. If a subject discontinues study drug(s) but remains in the study, the set of end-of-treatment procedures will be administered, and follow-up information will be collected. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected. If a subject discontinues study drug and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatments

9.4.1 Treatments Administered

CCI [redacted]

In the triplet treatment cohorts, the initial dose of E7386 will be CCI (Cohort 1) or CCI

The interventions to be used in this study are outlined below in Table 5.

Table 5 Treatments Administered

Drug Name	Strength	Dose Form	Dose, Frequency, Route	Duration
CCI				
CCI				

9.4.1.1 Criteria for Dose Modification

Dose reduction and interruptions for subjects who experience combination therapy-related toxicity will be managed as described in Tables 6 to 13. Investigators will decide the probability of the event being related to one or more drugs as to whether dose modification of one or more drugs is required.

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with 1 drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. Nausea and vomiting have been the most common treatment-related toxicities associated with E7386 thus far. However, certain AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

Since lenvatinib is administered daily and continuously due to a relatively short half-life (~28 hours), E7386 is administered BID and continuously also due to a relatively short half-life (~5 hours), and pembrolizumab is administered Q3W due to a long half-life, lenvatinib and E7386 can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

- If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib and/or E7386 interruption is needed
- If an AE is identified at the beginning of a treatment cycle, lenvatinib and/or E7386 can be interrupted and dosing of pembrolizumab should be held

If the subject recovers from an AE in response to lenvatinib or E7386 interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib or E7386. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting *all* drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, T1DM) and other supportive care should be taken promptly.

In case of any uncertainty regarding the event or causality, the investigators should use clinical judgement and consider prompt communication with an agreement by the Sponsor.

Attribution of Toxicity

When study drugs are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, or to E7386 alone, or to pembrolizumab alone for AEs listed in Table 9, interventions must be held according to the criteria in Table 9.

Holding Study Interventions

When study drugs are administered in combination, if the AE is considered immune-related other than Table 9 and not part of known reference safety information of pembrolizumab then all study drugs should be held according to recommended dose modifications.

In case of any uncertainty regarding the event or causality, the investigators should use clinical judgement and consider prompt communication with an agreement by the Sponsor.

Restarting Study Interventions

Subjects may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 9.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from all study drugs.

If the toxicities do resolve and conditions are aligned with what is defined in Table 9 the combination of E7386 with pembrolizumab or pembrolizumab plus lenvatinib may be restarted at the discretion of the investigator.

For doublet treatment cohorts, in cases where the toxicity is attributed to the combination or to E7386 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with an agreement by the Sponsor. For triplet treatment cohorts, if the toxicity is attributed to one or more drug(s), re-initiation of one or more drug(s) in the combination may be considered after communication with an agreement by the Sponsor.

CCI [redacted]

Table 6 Criteria for Dose Interruption, Dose Reduction and Discontinuation of Treatment with E7386

Table 7 Dose Reduction Recommendation for E7386 Treatment-Related Toxicity

CCI

[redacted]

[redacted]

9.4.1.1.2 Dose Modification and Toxicity Management Guidance for Pembrolizumab

Dose Modification and Toxicity Management of Immune-Related Adverse Events Associated With Pembrolizumab

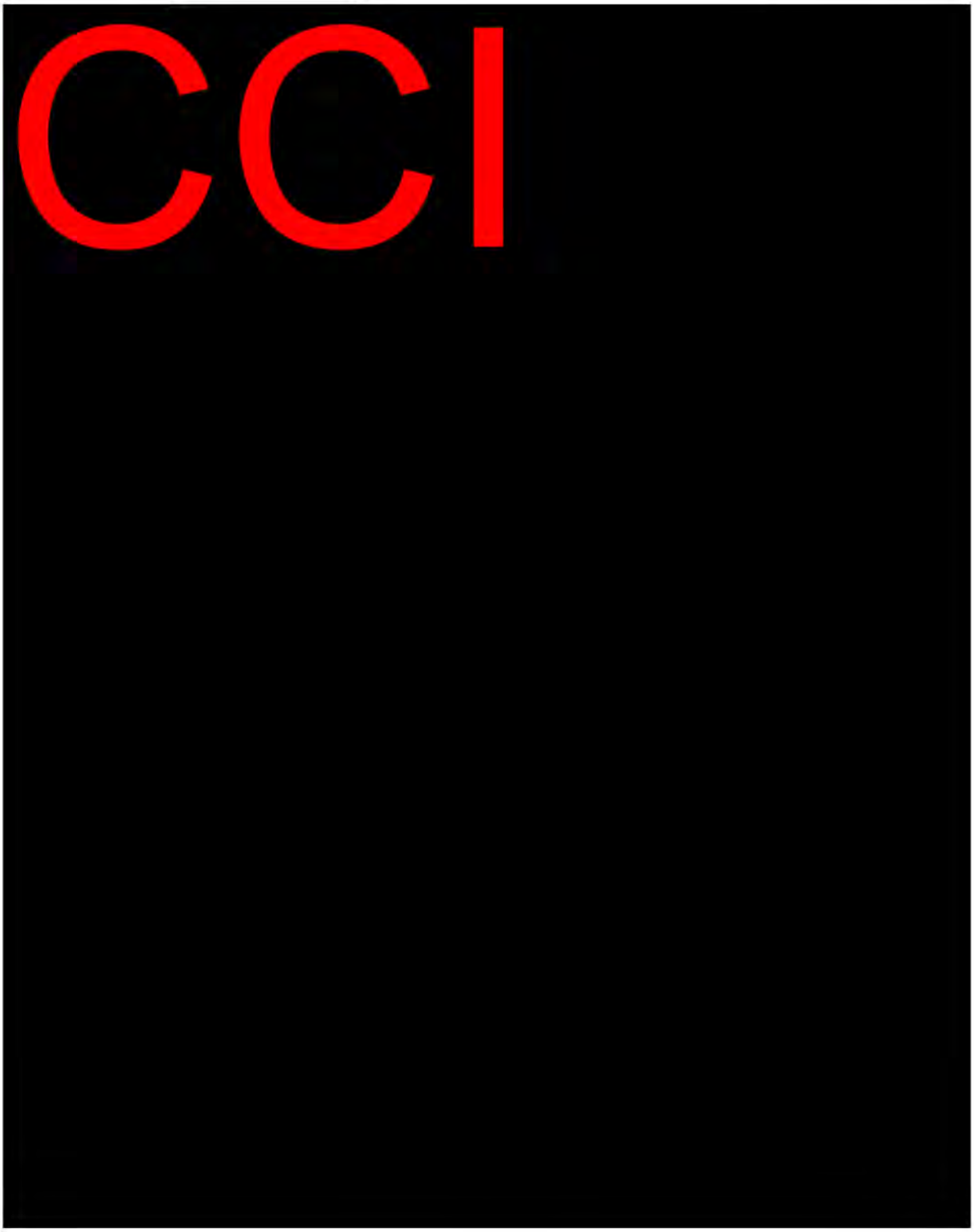
Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy, may be included as part of evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification

and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 9.

Table 9 CCI

CCI

Table 9 [redacted]



[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

Table 10 CCI

CCI

CCI

CCI

Table 11 CCI

CCI

Table 11 CCI

Table 11 CCI

9.4.1.1.3 Dose Modification and Toxicity Management for Lenvatinib

Lenvatinib dose reductions and interruptions for subjects who experience lenvatinib/pembrolizumab or lenvatinib/E7386 combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 12. Adverse events will be graded using NCI CTCAE, v5.0. Investigators will decide the probability of the event being related to 1 or more drugs as to whether dose modification is required. Refer to the subsections below for management of hypertension, proteinuria, diarrhea, hepatotoxicity, thromboembolic events, posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS), hypocalcemia, hemorrhage, gastrointestinal perforation or fistula formation, QT prolongation, and osteonecrosis of the jaw, as appropriate, before consulting the dose modification tables.

Triplet Treatment Cohorts

CCI [redacted]

An interruption of study intervention for more than 21 days will require Sponsor's approval before treatment can be resumed. Any dose reduction below 2 mg must be discussed with the Sponsor.

CCI [redacted]

[redacted]

[redacted]

Table 12 Management of Lenvatinib Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2	Continue treatment	No change
Intolerable Grade 2[c,d] or Grade 3[e,f]		
1st occurrence	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
2nd occurrence (same toxicity or new one)	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
3rd occurrence (same toxicity or new one)	Interrupt lenvatinib until resolved to Grade 0–1, or tolerable Grade 2	One-level reduction
4th occurrence (same toxicity or new one)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]	Discontinue lenvatinib[h]	

BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.
Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.
a: An interruption of study treatment for more than 21 days will require Sponsor's approval before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, hypothyroidism, or diarrhea prior to any lenvatinib interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e: For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.
f: For Grade 3 thromboembolic events, permanently discontinue lenvatinib. Refer to section below on management of thromboembolic events.
g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
h: If lenvatinib is discontinued due to an adverse event, the investigator can continue with E7386 and pembrolizumab in the triplet treatment cohorts.

Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have blood pressure (BP) of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17). Hypertension will be graded using CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension (eg, BP ≥160/100 mm Hg) with significant risk factors for severe complications, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities. Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Subjects who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary may be provided to the subject to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

1. Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours
   - Additional dose reduction should be discussed with the Sponsor

The following guidelines should be followed for the management of Grade 4 hypertension (life threatening consequences):

1. Institute appropriate medical management.
2. Discontinue study drug.

Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the Schedule of Procedure/Assessments. Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot UPCR test) is required in the following situations:
   - The first (initial) occurrence of CCI proteinuria on urine dipstick (or urinalysis) while the subject is receiving lenvatinib
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level

- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is CCI [redacted]

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the subject has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 12.

Monitoring

Urine dipstick or urinalysis testing for subjects with proteinuria CCI [redacted] should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.

Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.

In the event of nephrotic syndrome, lenvatinib must be discontinued.

Management of Diarrhea

An anti-diarrheal agent should be recommended to the subject at the start of study treatment, and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 12 should be followed.

Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Procedure/Assessments and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 12 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5.0) occurs, lenvatinib must be discontinued.

Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a

thromboembolic event is confirmed, instructions contained in Table 12 should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences a Grade 3 or a life threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, instructions in Table 12 should be followed.

Management of Hypocalcemia

Serum calcium should be monitored per the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

Management of Hemorrhage

Instructions in Table 12 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any subjects who develop gastrointestinal perforation of any grade or Grade 4 fistula.

Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or to baseline value. Monitor potassium, calcium and magnesium, and replenish as appropriate.

Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise subjects regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in subjects at higher risk. For subjects requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of osteonecrosis of the jaw (ONJ). Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution.

9.4.2 Identity of Investigational Products

E7386 is supplied as tablets in strengths of [CCI] and [CCI]. E7386 will be administered orally [CCI] continuously in [CCI]. The tablets should be taken with water every 12 hours at the same times of the day without regard to food intake. E7386 will be administered approximately 30- 60 minutes post administration of pembrolizumab on Day 1 of the cycle.

Note: if the subject vomits after E7386 administration, this will be regarded as completion of administration, and E7386 should not be re-administered.

Pembrolizumab will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab.

Lenvatinib is supplied as capsules in strengths of 1 mg and 4 mg. Lenvatinib will be administered orally QD continuously in [CCI]. Lenvatinib capsules may be taken with or without food.

9.4.2.1 Chemical Name of E7386

Test drug code: E7386

Generic name: Not applicable

Chemical name: (6S,9aS)-N-Benzyl-8-({6-[3-(4-ethylpiperazin-1-yl)azetidin-1-yl]pyridin-2-yl}methyl)-6-(2-fluoro-4-hydroxybenzyl)-4,7-dioxo-2-(prop-2-en-1-yl)hexahydro-2H-pyrazino[2,1-c][1,2,4]triazine-1(6H)-carboxamide

Molecular formula: $C_{39}H_{48}FN_9O_4$

Molecular weight: 725.87 (free form)

9.4.2.2 Information on Pembrolizumab

Pembrolizumab is a humanized mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Refer to the Pembrolizumab IB

9.4.2.3 Information on Lenvatinib

Lenvatinib is a potent multiple RTK inhibitor (RTKI) that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptor (FGFR) 1 to 4, PDGF receptor alpha (PDGFRα), KIT, and RET.

Refer to the Lenvatinib IB.

9.4.2.4 Comparator Drug

Not applicable.

9.4.2.5 Labeling for Study Drug

E7386, pembrolizumab, and lenvatinib will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.6 Storage Conditions

Study drugs will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the pharmacist or its designee) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

For the Phase 1b and Phase 2 doublet treatment cohorts, the study is open-label, and single-arm studies. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive E7386 in combination with pembrolizumab. There is no randomization in these cohorts. For the Phase 2 triplet treatment cohorts, the study is randomized and open-label. Randomization will be performed centrally by an interactive voice and web response system. All subjects with HCC will be randomized in 1:1 ratio to receive E7386 [redacted] or [redacted] in combination with pembrolizumab plus lenvatinib and stratified by weight [redacted]. Enrollment in subjects with 2L HCC will be prioritized for triplet treatment cohorts. If subjects do not meet eligibility criteria for triplet treatment cohorts or the triplet treatment cohorts are not opened at the site, then subjects may be enrolled on the doublet cohorts.

9.4.4 Selection of Doses in the Study

9.4.4.1 Justification for Dose for the Combination of E7386 With Pembrolizumab

9.4.4.1.1 E7386

The initial CCI [redacted] tablet E7386 dose was selected as the recommended dose for combination with pembrolizumab because it was tolerated in terms of DLT with no major safety concerns in the monotherapy Study 101 and Study 103 (Section 7.3). Furthermore, no major regional differences in the safety profile and PK data were observed between subjects in the UK and in Japan. CCI [redacted]

9.4.4.2 Justification for Dose for the Combination of E7386 With Pembrolizumab Plus Lenvatinib

9.4.4.2.1 E7386

CCI [redacted]

CCI [redacted]

9.4.4.2.2 PEMBROLIZUMAB

CCI [redacted]

9.4.4.2.3 LENVATINIB

CCI [redacted]

9.4.5 Selection and Timing of Dose for Each Subject

CCI [redacted]

CCI [redacted]

[redacted]

9.4.6 Blinding

This study will not be blinded at any Phase or part.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) or therapy administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with E7386 may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) E7386.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. G-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell counts.

9.4.7.1 Drug-Drug Interactions

CCI [redacted]

9.4.7.2 Prohibited Concomitant Therapies and Drugs

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

9.4.7.3 Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Sections 9.4.1.1.1, 9.4.1.1.2, and 9.4.1.1.3.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Sections 9.4.1.1.1, 9.4.1.1.2, and 9.4.1.1.3 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during the study and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the Sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the Sponsor and investigator

- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form Food and Drug Administration (FDA) 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license (required in the US) or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to GCP guidelines, as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the Sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:
(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the Sponsor. Any comparable forms that the site wishes to use must be approved by the Sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the Sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects,

are to be returned to the Sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the Sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the Sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the Sponsor's personnel, study drugs that are to be returned to the Sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by Sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the Sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening and Baseline Assessments

Screening and baseline assessments will be performed as designated in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17). The results of all screening assessment and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit.

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at the Screening Visit. Demography information includes age, sex, race/ethnicity. Baseline characteristics will include ECOG PS (Appendix 2), NYHA cardiac disease classification (Appendix 5), tumor staging such as TNM (Appendix 8). For subjects with HCC, BCLC staging (Appendix 6), macroscopic invasion, extrahepatic spread, and Child Pugh score (Appendix 4) will also be included.

9.5.1.1.2 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history considered by the investigators to affect the efficacy, safety, and PK evaluations and all current and clinically significant medical conditions confirmed at the Screening and Baseline Visit must be recorded on the case report form (CRF).

9.5.1.1.3 PRIOR CANCER HISTORY

During Screening, the following characteristics will include the detailed medical history of subjects with carcinoma including, but is not limited to:

- Pathology
- Date of initial diagnosis and method of diagnosis [histology/cytology]
- TNM staging classification by AJCC staging system version 8
- Specify whether disease is locally advanced or metastatic, and if metastatic, to which organs
- Any surgical procedures
- Radiotherapy
- Prior anticancer therapy
- Prior treatments administered (including dates and modality)
- Known gene alteration and mutation status
- Archival tumor tissue sample must be acquired prior to first dose. If archival tumor tissue sample is not available, please consult Sponsor

Subjects with melanoma only:

- BRAF mutation status

Subjects with CRC only:

- Primary site of disease
- History of Lynch syndrome
- KRAS mutation status
- BRAF mutation status
- MSI/MMR mutation status

Subjects with HCC only:

- Cause of HCC (hepatitis B, hepatitis C, alcohol, non-alcoholic steatohepatitis (NASH), other, unknown)
- Macrovascular invasion including portal vein invasion
- Extra hepatic spread
- BCLC staging
- AFP (alpha-fetoprotein)

9.5.1.2 Efficacy Assessments

Tumor assessments will be performed by investigators based on RECIST 1.1. Tumor assessment will be performed by CT/MRI every 6 weeks (±1 week counting from C1D1) until Week 24, then every 9 weeks (±1 week), at the EOT visit, and if clinically indicated. Investigator-determined response assessments will be performed at each assessment time point. Copies of all tumor assessment scans will be sent to an Imaging Core Lab (ICL) designated by the Sponsor for archival and potential blinded independent central review (BICR) assessment. After the primary analysis, the Sponsor may discontinue requiring copies of tumor assessment scans to be sent to the ICL.

Tumor assessments will be carried out following the guidelines provided by the ICL. Historical CT or MRI scans performed within 28 days before C1D1, but before the signing of informed consent, may be used as screening scans, provided they meet minimum standards as separately defined by the ICL.

Tumor assessments (CT chest, and CT or MRI abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Screening Period and then every 6 weeks (±1 week, starting from the date of C1D1) until Week 24 and every 9 weeks thereafter, or sooner, if clinically indicated. The same imaging modality and image-acquisition protocol should be used consistently across all time points. For subjects with HCC, an additional triphasic liver CT or MRI will be performed at all time points.

CCI [redacted]

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) will be performed at screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 6 weeks).

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

Subjects who discontinue study drug without disease progression in the Treatment Phase will continue to undergo tumor assessments every 6 weeks until Week 2 CCI [redacted]

Radiological images performed during the study may be used for future imaging biomarker discovery. The decision to perform exploratory image analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies. These findings may be used for identification and validation of early markers of treatment response and for potential diagnostic development.

CCI [redacted]

CCI [redacted]

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Phase 1b part: Blood samples for PK analysis of E7386 will be collected as below:

CCI [redacted]

Note: All predose samples should be taken within 2 hours prior to administration of E7386. Postdose samplings on C1D8 will be omitted if E7386 administration is skipped on C1D8.

Plasma concentrations of E7386 and lenvatinib will be measured by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

Subject enrollment in the PK assessment portion of the protocol will be limited to sites with appropriately trained staff and adequate equipment for procuring and processing the specimens. Blood samples will be collected as specified in Table 15. See *PK and/or laboratory manual* for a description of collection, handling, and shipping procedures for PK samples.

The exact date and time at which PK samples were collected will be recorded. The time and date of the 2 most recent doses preceding the samples obtained will also be recorded on the eCRF. Blood will also be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

Leftover PK samples may be used for exploratory biomarker analyses.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Blood Biomarkers

CCI

[redacted]

Tumor Tissue Biomarkers

CCI

[redacted]

CCI [redacted]

Pharmacogenetic/Pharmacogenomic

CCI [redacted]

9.5.1.4 Safety Assessments

CCI [redacted]

9.5.1.4.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drugs are E7386 and pembrolizumab.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should generally be captured under efficacy assessments and not as an AE (see Section 9.5.1.4.2).
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose. Refer to Section 9.5.4.1 for the time period after the EOT for SAE collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study drug.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) (Cancer Therapy Evaluation Program, 2017). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Drug

Items to be considered when assessing the relationship of an AE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Disease-related Events and/or Disease-related Outcomes not Qualifying as AEs or SAEs

Disease progression should not be recorded as an AE or SAE term. Fatal events, even if due to disease progression, should always be recorded as an SAE and should be reported in accordance with Section 9.5.4.1. Also, disease progression SAEs, that are considered as "Related" to study drug by the investigator must also be reported in accordance with Section 9.5.4.1.

The Sponsor will monitor aggregated efficacy and safety data to ensure the safety of the subjects in the study. Any event that upon receipt of further information is not progression of the disease under study should be captured as an AE and, if the event meets serious criteria, should be reported in accordance with Section 9.5.4.1.

9.5.1.4.3 Serious Adverse Events and Events Associated with Special Situations

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

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

CCI [redacted] AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

- For hospitalization involving events or outcomes related to the disease under study, see Section 9.5.1.4.2

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.4 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events of bone toxicity (including fragility fractures of cortical bone of long bones), should always be considered AEs and reported on the Adverse Event CRF and if the event meets the SAE criteria above, the event must also be reported on an SAE form as per protocol Section 9.5.4.

9.5.1.4.5 LABORATORY MEASUREMENTS

Table 14 Clinical Laboratory Tests

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.6 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17) by a validated method. Blood pressure and pulse will be measured after the subject has been supine for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.4.7 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17).

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. In addition, ascites and encephalopathy will be assessed for Child Pugh assessment for the subjects with HCC (Appendix 4). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Starting from C3D1 and onwards, only CXD1 visit will be performed onsite. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.4.8 Electrocardiograms

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

QTc intervals will be evaluated via 12- Single, 12-Lead ECG. Subjects must be in recumbent position for a period of 5 min prior to ECG. 12-Lead ECGs will be collected at Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of Cycle: 2, 3, and 6. After that, Day 1 of every 3 Cycles such as Cycle 9, Cycle 12, up to Cycle 18, and then every 6 months

and at the EOT Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed. QT interval will be measured from Lead II and will be corrected for QTc using Fredericia's (QTcF) correction factors. The primary QTc parameter would be QTcF. Secondary parameters (heart rate, PR interval and QRS) and T wave morphology will be evaluated. For the purpose of QT assessment, exposure response analysis will be performed on the relationship between E7386 plasma level and ΔQTcF.

CCI [redacted]

9.5.1.4.10 Other Safety Assessments

Left Ventricular Ejection Fraction Assessments

A MUGA scan (using technetium-^{99}m-pertechnetate) or an echocardiogram to assess LVEF will be performed at screening, during EOT (window of ±1 week), and if clinically indicated.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

Also, height will be measured at Screening, C2D1 and Day 1 of every 3 cycles and if clinically indicated.

Eastern Cooperative Oncology Group Performance Status

All subjects will be assessed for ECOG PS (see Appendix 2) at Screening, Baseline, and at the time points listed in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17).

9.5.1.5 Other Assessments

CCI [redacted]

Patient-Reported Outcomes (Phase 2 –Triplet Treatment Cohorts)

The impact of treatment on PROs will be assessed utilizing the PRO-CTCAE questionnaire which will be administered electronically. Informed by early phase studies and the known safety profile for E7386, pembrolizumab, and lenvatinib, the following events will be monitored: hoarseness, decreased appetite, nausea, vomiting, diarrhea, constipation, hand-foot syndrome, general pain, fatigue, rash, and pain and swelling at the injection site (Appendix 9). Data will be collected at Baseline and at every site visit until the EOT visit.

The PRO-CTCAE was developed by the National Cancer Institute to evaluate symptomatic toxicities in clinical studies reported by patients and is intended to be utilized as a companion to the CTCAE. The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic toxicities; however, for the purposes of this investigation only the symptoms outlined above will be assessed. This measurement system specifically measures the frequency, severity, interference, and presence/ absence of symptomatic toxicities which are not collected by the CTCAE. This measurement proposes to enhance the precision of

symptomatic toxicity events in clinical studies and allow for subjects to contribute to the reporting of drug-related toxicity events in clinical studies (Basch, et al., 2014).

Survival Status

Subjects will be followed for survival until death, except where a subject withdraws consent or until the subject is lost to follow-up as described in the Schedule of Procedures/Assessments (Table 15, Table 16, and Table 17).

9.5.2 Schedule of Procedures/Assessments

Table 15 presents the Schedule of Procedures/Assessments for Phase 1b and 2b parts of the E7386-G000-201 study.

Table 16 presents the Schedule of Procedures/Assessments for the Extension part of the study.

Table 1 CCI [redacted]

Table 15 Schedule of Procedures/Assessments in E7386-G000-201 Study: Phase 1b and Phase 2 Parts

Table 15 Schedule of Procedures/Assessments in E7386-G000-201 Study: Phase 1b and Phase 2 Parts

Table 15 Schedule of Procedures/Assessments in E7386-G000-201 Study: Phase 1b and Phase 2 Parts

Table 15 Schedule of Procedures/Assessments in E7386-G000-201 Study: Phase 1b and Phase 2 Parts

Table 16 Schedule of Procedures/Assessments in E7386-G000-201 Study: Extension Part

Table 16 Schedule of Procedures/Assessments in E7386-G000-201 Study: Extension Part

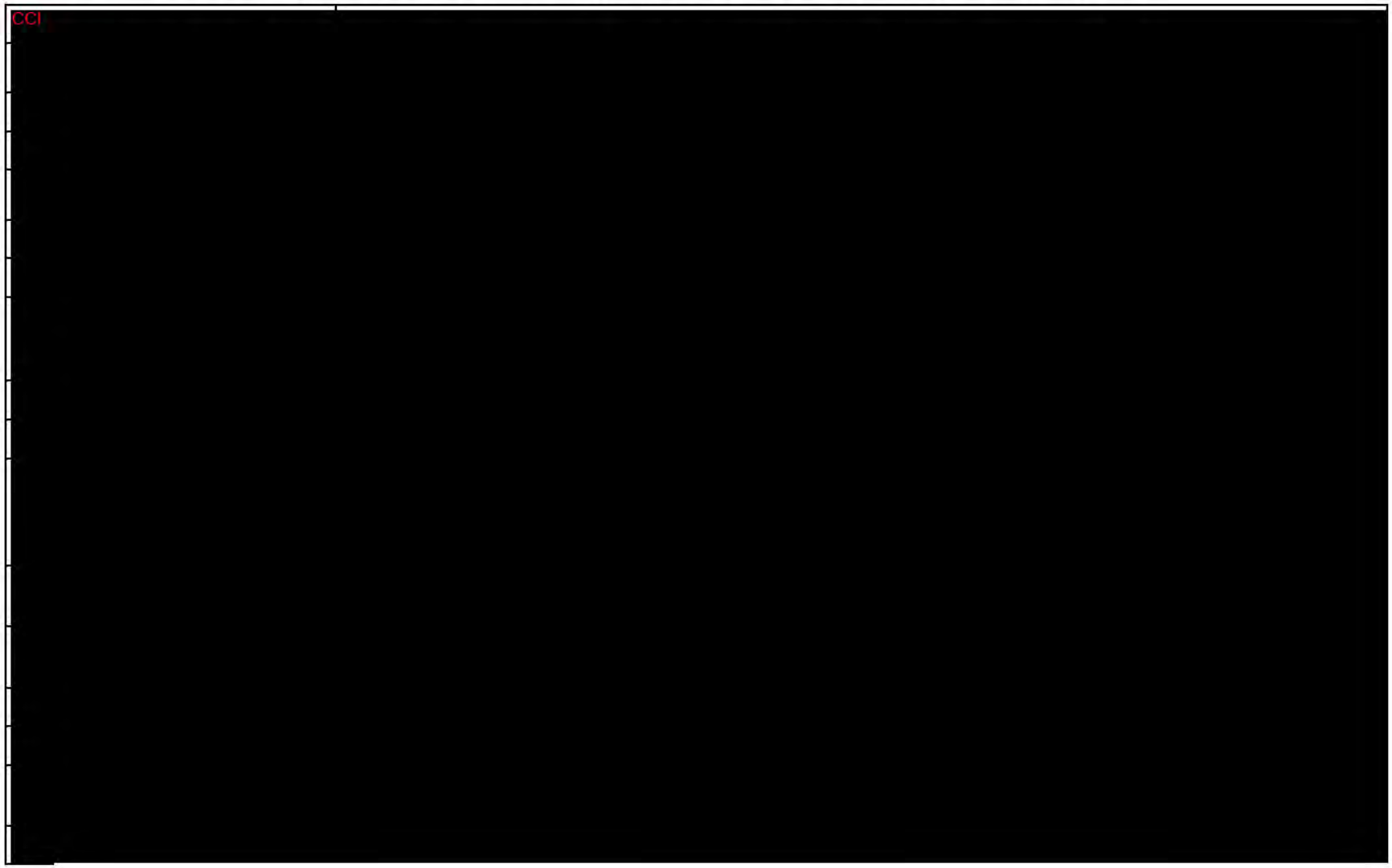
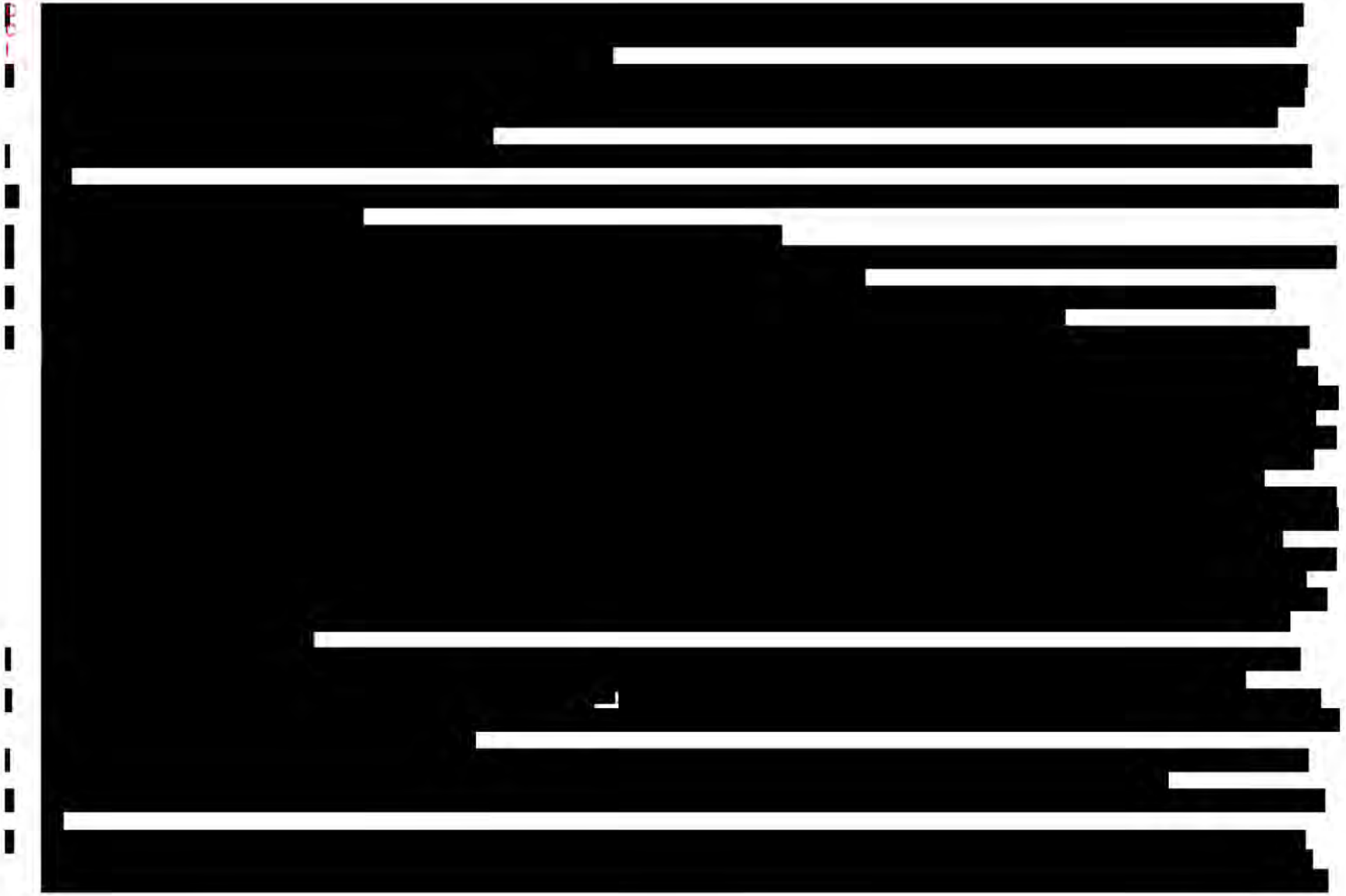


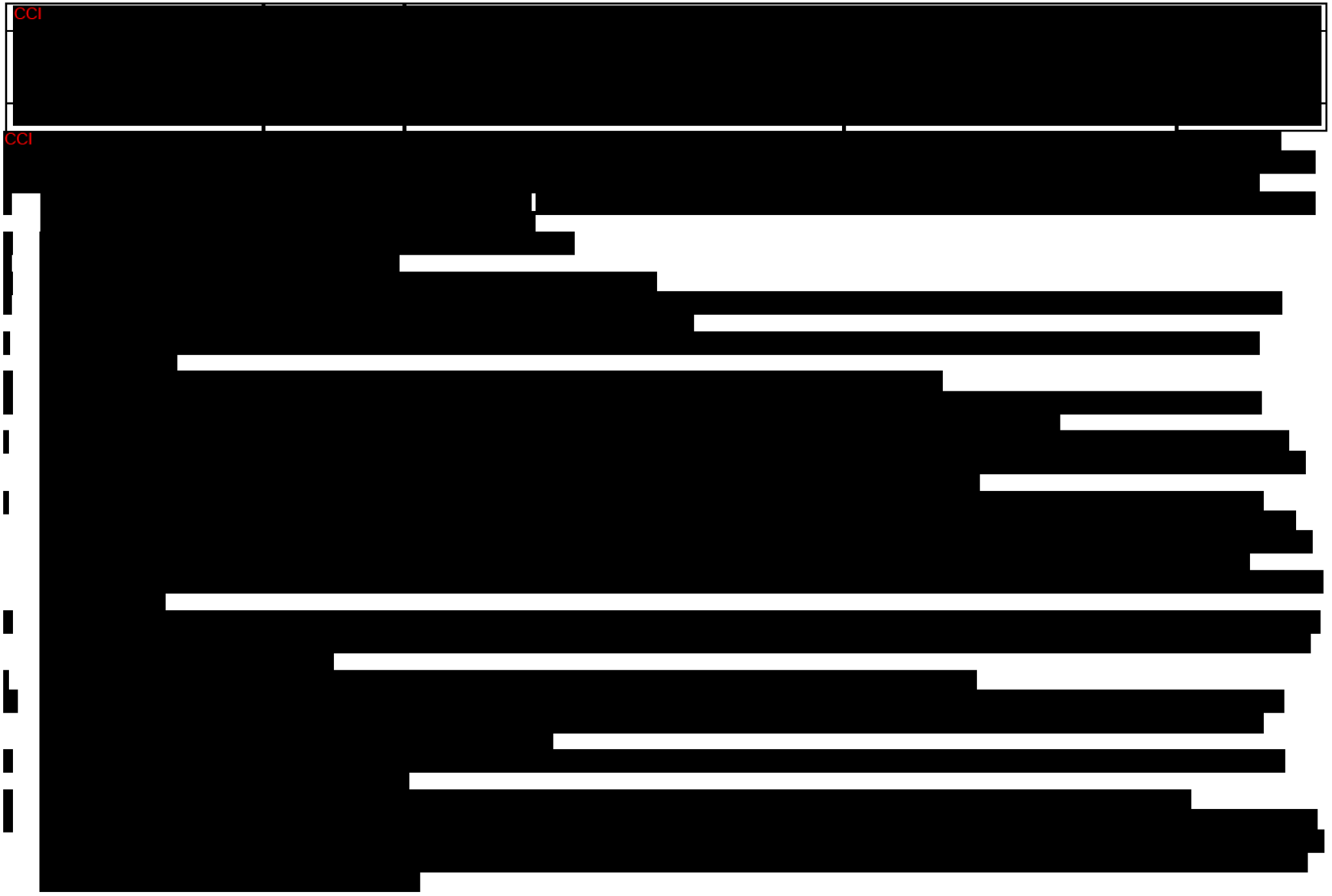
Table 16 Schedule of Procedures/Assessments in E7386-G000-201 Study: Extension Part



CCI

Table 17 CCI

CCI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9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of melanoma, HCC, and CRC.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study drug, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected for 90 days after the subject's last dose, or up to 30 days following cessation of study drug if the subject initiates new anticancer therapy, whichever is earlier. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study drug or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor to be filed in the Sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

CCI [redacted]

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study drug.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

CCI [redacted] Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. It is unknown whether pembrolizumab is excreted in human milk.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional/Unintentional Overdose, even if asymptomatic, are always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

Note: For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5.4.3.2 CCI [redacted]

CCI [redacted]

CCI [redacted]

9.5.4.3.3 Reporting of Study-Specific Events

Study-specific events of bone toxicities (including fragility fractures of cortical bone of long bones) should always be considered as adverse events and be entered on the Adverse Event CRF and if serious, reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1).

9.5.4.4 Expedited Reporting

The Sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 15).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, [redacted] study terminated by Sponsor or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason during Phase 2 will not be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 or Investigator and Site Information Form must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

Statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released. An earlier database lock may also be performed for the purpose of writing a clinical study report. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

For the tumor response related endpoints, the tumor assessments by BICR (if conducted) may be used in the primary analysis for the cohorts in Phase 2 part. Otherwise, tumor assessments by the investigator will be used for the analysis.

9.7.1.1.1 PRIMARY ENDPOINTS

- Phase 1b part: Safety related endpoints including DLTs
- Phase 2 part: ORR is defined as the proportion of subjects who have best overall response (BOR) of confirmed CR or PR per RECIST 1.1

9.7.1.1.2 SECONDARY ENDPOINTS

- BOR per RECIST 1.1 (for Phase 1b part)
- DOR is defined as the time from the first documentation of CR or PR to the first documentation of disease progression or death due to any cause (whichever occurs first), in subjects with confirmed CR or PR per RECIST 1.1
- DCR is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or SD: after ≥5 weeks from the first dose) per RECIST 1.1
- CBR is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or durable SD (duration of SD ≥23 weeks) per RECIST 1.1
- Safety and tolerability (eg, treatment-emergent adverse events, treatment-related adverse events) for E7386 in combination with pembrolizumab and safety and tolerability including DLTs for E7386 in combination with pembrolizumab plus lenvatinib

- PK profile of E7386 when co-administered either with pembrolizumab (doublet treatment cohorts) or with pembrolizumab plus lenvatinib (triplet treatment cohorts)
- PK profile of lenvatinib in combination with E7386 and pembrolizumab (triplet treatment cohorts)

9.7.1.1.3 EXPLORATORY ENDPOINTS

[redacted]

9.7.1.2 Definitions of Analysis Sets

[redacted]

9.7.1.3 Subject Disposition

The number (percentage) of subjects who were screened for the study (ie, those who signed informed consent), continued in the study after screening, failed screening, and the primary reason for screen failures will be presented.

The number (percentage) of subjects who were treated, continued, or discontinued study drug at data cutoff date, along with the primary reason for discontinuation from the study drug will be presented. The number (percentage) of subjects who discontinued treatment but were on survival follow-up at data cutoff date will also be provided.

The number (percentage) of subjects who were on study or off study (ie, discontinued from the study) at data cutoff date and the primary reason for discontinuation from study will be presented.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Efficacy Analysis Set will be summarized for each dose level/tumor cohort, and for phase/overall (as needed) using descriptive statistics. Continuous demographic and baseline variables include age, weight, and height; categorical variables include sex, age group, race, ethnicity, region/country, ECOG PS and NYHA cardiac disease classification.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Efficacy Analysis Set by Anatomical Therapeutic Chemical class (ie, Anatomical class, Pharmacological class), and WHO DD preferred term (PT). Prior medications will be defined as medications that started before the first dose of study drug regardless if they were either stopped before the first dose of study drug or continued during the study. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. The summary will be presented for each dose level/tumor cohort, and for phase/overall (as needed). A medication that cannot be determined as prior/concomitant/post treatment due to missing/incomplete dates will be regarded as a concomitant medication. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

All efficacy analyses (except for DOR) will be performed within each cohort/tumor type on the Efficacy Analysis Set. The analysis for DOR will be performed in the subjects who show a confirmed CR or PR within each cohort/tumor type on the Efficacy Analysis Set.

BOR is CR, PR, SD, PD, or not evaluable (NE)/Unknown, where SD has to be achieved at ≥5 weeks after the first dose. The BOR of CR and PR requires confirmation by a subsequent assessment of response at least 28 days later. However, for the consideration of cohort expansion in the interim data review, response confirmation will not be required.

Data cutoff of the primary analysis in the Phase 2 part for each tumor cohort may be performed based on the Efficacy Analysis Set when all subjects in that cohort have

completed a tumor assessment CCI and/or have adequate follow-up to be evaluated the DOR, or discontinued early due to any cause.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Phase 1b part:

There is no primary efficacy analysis, since the primary objective of Phase 1b part is to assess the safety and tolerability and determine the RP2D of E7386 in combination with pembrolizumab. Thus, the efficacy analyses for Phase 1b part are described in the subsequent sections according to the study endpoints.

Phase 2 part:

ORR will be provided with 95% CI based on the method of Clopper and Pearson. A summary of BOR will also be presented.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

BOR for Phase 1b part will be summarized in the same manner as described above.

Waterfall plots for maximum tumor shrinkage (ie, postbaseline nadir) in sum of diameters of target lesions will be provided.

DOR will be estimated and plotted over time using Kaplan-Meier method. Median and quartiles will be provided with 95% CIs.

DCR and CBR will be calculated with 95% CIs using the Clopper and Pearson method.

Censoring rules for DOR will be detailed in the SAP.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

CCI

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK analysis will be performed on the Pharmacokinetic Analysis Set using plasma concentrations of E7386 in combination with pembrolizumab or in combination with pembrolizumab plus lenvatinib. Plasma concentrations of E7386 and lenvatinib (triplet

treatment cohorts) will be tabulated and summarized by dose level, day, and time. The primary PK parameters of E7386 will be calculated using noncompartmental analysis for the Phase 1b part. Plasma concentration data for E7386 and lenvatinib in the Phase 2 part will be used to conduct population PK analysis and/or graphical presentation by integrating plasma concentration data from the Phase 1b part and/or other studies. PK/PD relationships (ie, exposure-efficacy, exposure-safety, and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach, for effects of study treatment. Efficacy endpoints will include primary endpoint of ORR (based on RECIST 1.1) and other efficacy-related metrics including but not limited to DOR. Safety endpoint will be most frequent AEs and dose reductions of E7386. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and, if possible, will be followed by model-based analyses for E7386. For population PK and PK/PD analyses, the details will be described in a separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

9.7.1.7.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Details of the PD and other biomarker analyses will be provided in a separate analysis plan.

9.7.1.8 Safety Analyses

All tolerability analyses will be performed by dose level (if applicable) on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated.

The Safety Analysis Set will be used for all other safety analyses. Safety analyses will be assessed within each cohort/tumor type, and for phase/overall (as needed) on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, quartiles, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, vital signs, T-score[CCI], LVEF and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 Extent of Exposure

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions and/or treatment interruption will be summarized for the Safety Analysis Set.

9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is defined as an AE that emerges during treatment (on or after the first dose of study drug up to 30 days after the subject's last dose), having been absent at pretreatment (Baseline) or:

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state when the AE is continuous

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by system organ class (SOC) and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade according to the CTCAE v5.0.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.5, the actual value and the change from baseline to each postbaseline visit and to the EOT (defined as the last on-treatment value including assessment) will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.5 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to EOT will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to CTCAE v5.0 and shifts from baseline CTCAE grades to worst postbaseline grades will be assessed. The number (percentage) of subjects with postbaseline values worsened from baseline (with at least 1 CTCAE grade increase) will be presented. Likewise, subjects with postbaseline values of CTCAE grades 3 or 4 worsened from baseline will also be summarized.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

The number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF, CCI [redacted], and T-score changes from baseline will be calculated and summarized.

Shift table for ECOG PS will present change from baseline classification to worst postbaseline classification.

Summary statistics of the scores for the PRO-CTCAE questionnaire according to the scoring manual and the frequency, severity, interference, and presence/absence of symptomatic toxicities will be summarized for each triplet treatment cohort at each time point. A separate pre-specified analysis following the National Cancer Institute (NCI) PRO-CTCAE Guidelines will be performed and detailed in a separate SAP and PRO-CTCAE report.

9.7.2 Determination of Sample Size

CCI [redacted]

CCI

[redacted]

9.7.3 Interim Analysis

CCI

[redacted]

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the CSR.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the Sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the Sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The Sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email etc. between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs [redacted]
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Clinical Outcome Assessment (eCOA)

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the Sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Study drug compliance (eg, the reason for any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in the case of lost to follow-up due to the subject choice)
- Sampling date and time for the drug concentration
- Sampling date for the clinical laboratory test

- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 for US sites), Investigator and Site Information Form (for non-US sites), ICFs, and IRB/IEC correspondence. The site should plan to retain study documents, unless otherwise instructed by the Sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the Sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the Sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor's CRA (or designated contractor) or, when approval is given by the Sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the Sponsor/CRO and the institution/investigator. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the Sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the Sponsor/CRO.

11.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the Sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The Sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 CCI

[redacted]

Appendix 2 Eastern Cooperative Oncology Group Performance Status

Scale	ECOG Performance Status
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 more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

ECOG = Eastern Cooperative Group.
Adapted from Oken MM, Creech RM, Tormey DC, Horton J, Davis TE, McFadden T, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group, et al. Am J Clin Oncol. 1982;5(6):649-55.

Appendix 3 Response Evaluation Criteria in Solid Tumors 1.1

Tumor response assessments in this clinical study will use Response Evaluation Criteria in Solid Tumours (RECIST 1.1) based on the 2009 article by Eisenhauer, et al. entitled, New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1).

The sole modification to RECIST 1.1 to be implemented in this study is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. As required by RECIST 1.1, the protocol states that the minimum duration of SD is 7 weeks following the date of first dose of study drug.

The Eisenhauer article, available online at: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eu J Cancer. 2009;45(2):228-47. Retrieved at http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

Appendix 4 Child-Pugh Classification

Parameter	Score[a]		
	1	2	3
Ascites	Absent	Mild (Respond to treatment)	Moderate (Refractory)
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.30	>2.30
Encephalopathy[b]	0	1–2	3–4

INR = international normalized ratio.
a: Child-Pugh A: 5 or 6 points; Child-Pugh B: 7–9 points; Child-Pugh C: >9 points.
b: Encephalopathy grades defined as follows:
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable, coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

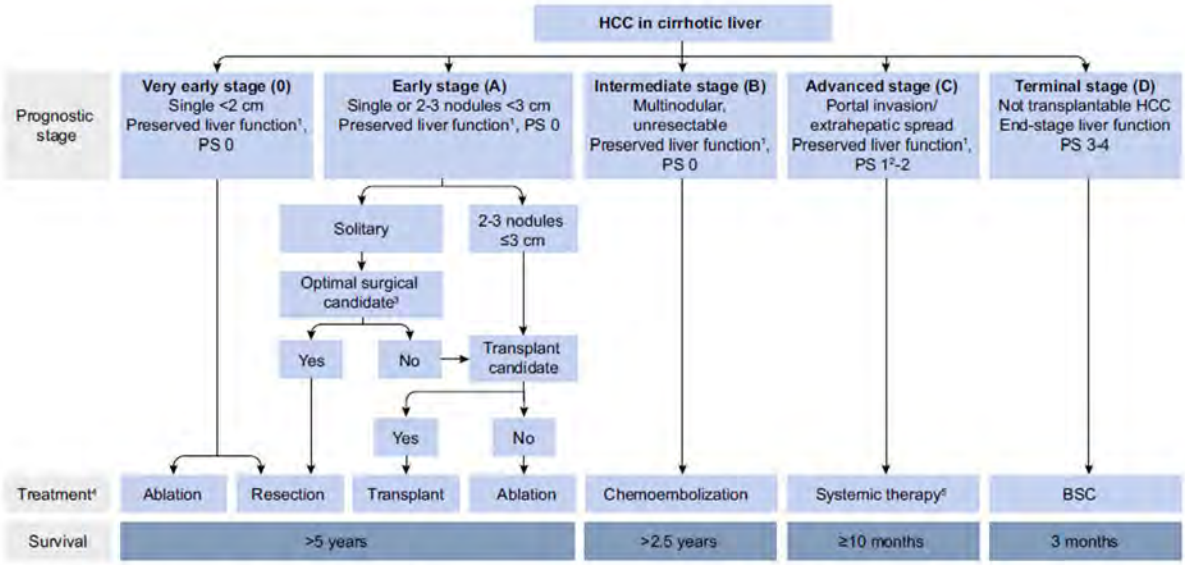
Appendix 5 New York Heart Association Cardiac Disease Classification

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

Class	NYHA Status
Class I:	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.
Adapted from The Criteria Committee of the NYHA. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. New York: Little Brown; 1994. p.253-6.

Appendix 6 Barcelona Clinic Liver Cancer Staging System



European Association for The Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Apr;56(4):908-43. Erratum to: ''EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma'' [J Hepatol 2012;56:908-43]. J Hepatol. 2012. In press. http://www.easl.eu/_clinical-practice-guideline/issue-7-April-2012-management-of-hepatocellular-carcinoma

Appendix 7 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Objective

Subjects enrolled in this clinical study will have biologic samples collected for PD, PG, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a subject would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded.

Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The Sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Medical institutions
- Clinical research organizations retained by the Sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians.

If at any time, PD, PG, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

Appendix 8 Tumor, Node, and Metastasis Staging of Hepatocellular Carcinoma, Colorectal Cancer and Melanoma

The TNM (tumor-node-metastasis) classification for staging of **hepatocellular carcinoma** per the AJCC is provided below:

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	>2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

The TNM (tumor-node-metastasis) classification for staging of **colorectal cancer** per the American Joint Committee on Cancer (AJCC) is provided below:

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor direct invades or adheres to adjacent organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa mesentery or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
Distant metastasis (M)	
M0	No distant metastasis by imaging, etc. ; no evidence of tumor in distant sites or organs (this category is not assigned by pathologists)
M1	Distant metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis

Anatomic stage/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
IIIA	T1	N2a	M0

Stage	T	N	M
IIIB	T3-T4a	N1/N1c	M0
IIIB	T2-T3	N2a	M0
IIIB	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
IIIC	T3-T4a	N2b	M0
IIIC	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

The TNM (tumor-node-metastasis) classification for staging of **melanoma** per the AJCC is provided below:

Primary tumor (T)		
Category	**Thickness**	**Ulceration status**
TX: primary tumor cannot be assessed		Not Applicable
T0: No evidence of primary tumor		Not Applicable
Tis (melanoma in situ)		Not Applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	≤0.8 mm	Without ulceration
T1b	≤0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration
Regional lymph nodes (N)		
Category	**Number of tumor-involved**	**Presence of in-transit, satellite, and/or microsatellites metastases**
NX	Regional lymph nodes cannot be assessed Exception: pathological N category is not required for T1 melanomas, use cN, if regional lymph nodes not assessed for subject with T1 melanoma	No
N0	No regional lymph node metastasis	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	

N1a	One clinically occult	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
Distant metastasis (M)		
Category	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

CNS – central nervous system

Anatomic stage/prognostic groups

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b or T2a	N0	M0
IIA	T2b or T3a	N0	M0
IIB	T3b or T4a	N0	M0
IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

Source: AJCC Cancer staging Manual Eighth Edition, Editors: Amin, MB, Edge, S, Greene F, Byrd DR, Brookland RK, Washington, MK. Springer: 2017.

Appendix 9 Attributes Measured by Adverse Events Collected by the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events

Symptom/Toxicity	Attributes
Hoarseness	S
Decreased Appetite	S, I
Nausea	F, S
Vomiting	F, S
Constipations	S
Diarrhea	F
Hand-Foot Syndrome	S
General Pain	F, S, I
Fatigue	S, I
Rash	P
Pain and Swelling at Injection Site	P

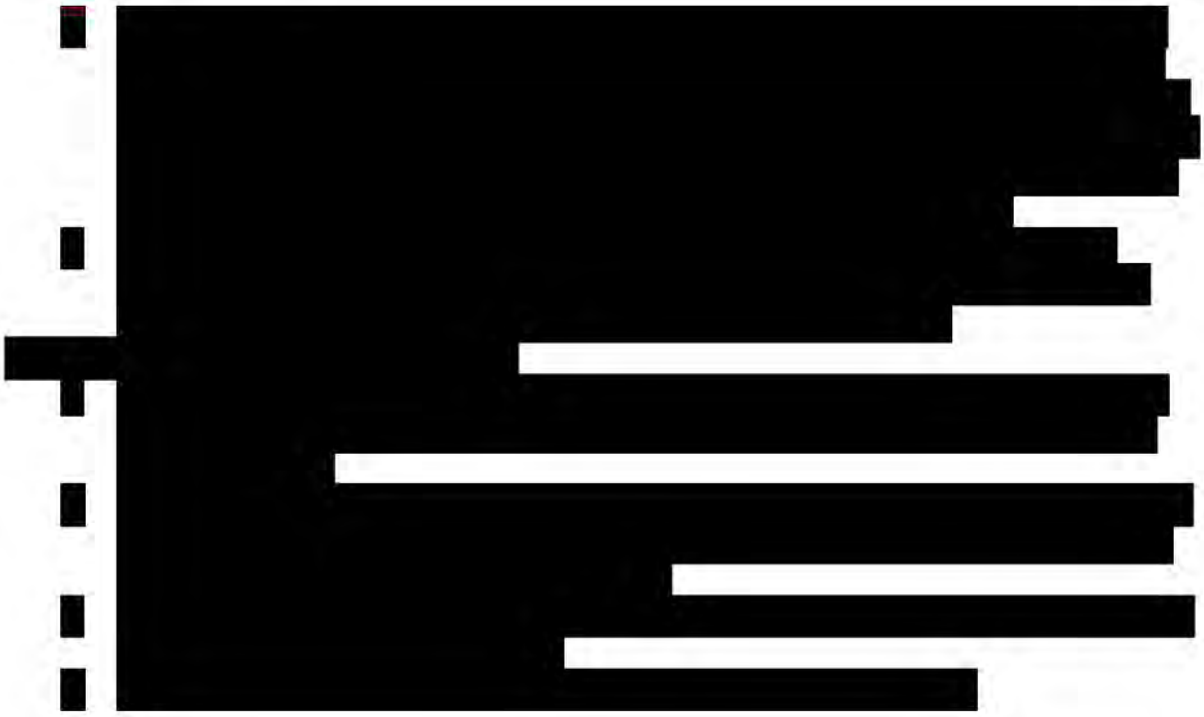
For each attribute there is a separate question for each symptom/toxicity evaluated.
F = frequency; I = interference; P = presence/absence; S = severity.

CCI

[redacted]

CCI

[redacted]



PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7386-G000-201
Study Protocol Title:	An Open-Label, Multicenter, Phase 1b/2 Study of E7386 in Combination With Pembrolizumab in Previously Treated Subjects With Selected Solid Tumors
Investigational Product Name:	E7386
IND Number:	136799
EudraCT Number:	2021-001568-10

SIGNATURES

Authors:

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 27-Jan-2023 | 11:04:15 EST
6A2D46D13AAE497A9708ED0EEC123FDB

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Date

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Signing Reason: I approve this document
Signing Time: 27-Jan-2023 | 14:30:52 GMT
PPD 7B9F356142F5386A13
PPD
Eisai, Inc

Date

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I am the author of this document
Signing Time: 27-Jan-2023 | 09:30:08 EST
PPD F4576A86292F20A5EDA46
Biostatistician
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Eisai, Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7386-G000-201
Study Protocol Title:	An Open-Label, Multicenter, Phase 1b/2 Study of E7386 in Combination With Pembrolizumab in Previously Treated Subjects With Selected Solid Tumors
Investigational Product Name:	E7386
IND Number:	136799
EudraCT Number:	2021-001568-10

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Site Number	Signature	Date

As regionally required.

<Title of signatory for Japan/Asia clinical research>	Signature	Date