An Open label Phase 2 Study to Evaluate the Safety and Efficacy of Lenvatinib with Pembrolizumab in Patients with Advanced Gastric Cancer

Investigator-initiated Study Protocol

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0. SYNOPSIS

Study Title	An Open label Phase 2 Study to Evaluate the Safety and Efficacy of Lenvatinib with Pembrolizumab in Patients with Advanced Gastric Cancer
Phase	Phase II
Objectives	To evaluate antitumor activity and safety of Lenvatinib with Pembrolizumab for AGC patients
Endpoint	**Primary endpoint：** Objective response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST) ver1.1 **Secondary endpoints:** ・Safety - The incidences and types of adverse events that occur during treatment will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. ・Efficacy - Objective response rate (ORR) according to immune-related (ir) RECIST - Progression-free survival (PFS) - Overall survival (OS) - Disease control rate (DCR) **Exploratory endpoints** **(performed as accompanying research in the present trial):** Tests of various biomarkers
Study population	**Inclusion criteria:** 1. Patients have histologically or cytologically confirmed advanced or recurrent gastric cancer. 2. Patients at least 20 years of age on the day of providing consent. 3. Patients have measurable disease as defined by RECIST 1.1 as determined by investigator. 4. Patients with a performance status of 0 or 1 on the Eastern Cooperative Oncology Group. 5. Patients with adequate organ function at the time of enrollment as defined below:

	・Neutrophil count ≥1200mm^3 ・Platelet count ≥7.5 × 10^4/mm^3 ・Hemoglobin (Hb) ≥ 8.0 g/dL, ・Total bilirubin ≤1.5 mg/dL ・AST (SGOT) and ALT (SGPT) ≤ 100 IU/L for subjects with liver metastases≤200 IU/L ・Creatinine ≤1.5-times the upper limit of normal ・International normalized ratio (INR) ≤ 1.5 ・Urinary protein : It satisfies one of the following (if any of the inspection criteria are satisfied, other examination may not be carried out) (i) urinary protein (test paper method) is 2+ or less (ii) Urine Protein Creatinine(UPC) ratio <3.5 (iii) 24-hour urine protein was measured, urinary protein ≦ 3500 mg 6. Patients who not received a blood transfusion within 7 days of registration. 7. Patients have recovered adverse events associated with chemotherapy, radiation and surgical operation as pretreatment to Grade 1 or lower with CTCAE v4.0 excluding stable symptoms (eg alopecia, peripheral sensory neuropathy, skin hyperpigmentation, dysgeusia etc.). 8. Female of childbearing potential who are negative in a pregnancy test within 14 days before enrollment. Both male and female patients should agree to use an adequate method of contraception (total abstinence, an intrauterine device or hormone releasing system, an contraceptive implant and an oral contraceptive) starting with the first dose of study therapy through 120 days after the last dose of study therapy. Duration will be determined when the subject is assigned to treatment. 9. Patients capable of taking oral medication 10. Patients who provided written informed consent to be subjects in this trial **Exclusion criteria:** 1. Patients who received prior anticancer treatment within 14 days (or 5 times the half-life time, whichever is shorter) or any investigational agent within 28 days prior to the first dose of study drugs.

	2. Patients who have undergone surgical treatment and radiotherapy with in 2 weeks before enrollment. 3. Patients with a history of prior treatment with Lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 4. Patients with hypertension that is difficult to control (systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with several hypotensive agents. 5. Patients with acute coronary syndrome (including myocardial infarction and unstable angina), and with a history of coronary angioplasty or stent placement performed within 6 months before enrollment. 6. Patients with symptomatic brain metastasis. 7. Patients with a history of New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months 8. Patients have an active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months 9. Patients have severe (hospitalization required) complications (intenstinal palsy, intestinal obstruction, pulmonary fibrosis, diabetes difficult to control, heart failure, myocardial infarction, unstable angina, renal failure, liver failure, mental disease, cerebrovascular disease etc). 10. Patients with a history of a gastrointestinal perforation and /or gastrointestinal fistula within 6 months before enrollment. 11. Patients with active hepatitis. 12. Patients with a history of human immunodeficiency virus (HIV). 13. Patients with active symptoms or signs of interstitial lung disease. 14. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease 15. Patients who require systemic corticosteroids (excluding temporary usage for tests, prophylactic administration for allergic reactions, or to alleviate swelling associated with radiotherapy) or immunosuppressants, or who have received such a therapy <14 days before enrollment. 16. Patients have a history of (non-infectious) pneumonitis that required steroids or have current pneumonitis

	17. Patients who are administered live vaccines <30 days before the initiation of treatment with the investigational drug. 18. Patients have serious non-healing wound, ulcer, or bone fracture. 19. Females who are pregnant or breastfeeding 20. Patients have no intention to comply with the protocol or cannot comply. 21. Patients were judged unsuitable as subject of this trial by investigator.
Duration of study participation	The investigational drug will be repeatedly administered until the criteria for discontinuation are met. In the event that the treatment is discontinued for reasons other than an exacerbation of the underlying disease via imaging (e.g., unacceptable side effects), tumor evaluation follow-up will continue until either an exacerbation of the underlying disease is observed via imaging or a new anticancer treatment is initiated, whichever happens first.
Number of patients Statistical analysis	First stage : 10 patients Second stage : 19 patients Total 29 patients
Administration method	Lenvatinib 20 mg /day orally Pembrolizumab 200 mg (every 3 weeks [Q3W], intravenous [IV]) One cyle will last 21 days
Safety evaluation	Evaluations will be performed using CTCAE version 4.0.
Efficacy evaluation	The antitumor effect will be evaluated in accordance with irRECIST and RECIST version 1.1 every 6 weeks. ・Image evaluation: computed tomography (CT) or magnetic resonance imaging (MRI) In all patients, PFS and survival will be evaluated.
Observations and tests	Physical examination, vital signs, PS, laboratory tests (hematology and biochemistry), urinalysis, laboratory findings, tumor markers, ECG, CT/MRI of chest, abdomen and pelvis, etc.
Trial Design	This trial is an open label phase II study to evaluate the safety and efficacy of Lenvatinib with Pembrolizumab in patients with ACG. The Simon's Optimal two-stage design will be used in this trial.
Statistical matters	Statistical procedures will be as follows: **Primary endpoint** The analysis set for the primary endpoint is the Full Analysis Set (FAS). The statistical criteria for main analysis will be based on the number of patients

	with the best overall response of Complete Response (CR) or Partial Response (PR) according to RECIST guideline version 1.1. In the first stage, if two or more objective response (CR or PR) was observed among 10 patients (no confirmation required), the study will proceed to the second stage. If objective response (CR or PR) was less than two, the study will not proceed to the second stage and we will consider discontinuation of this trial. on the basis of a precise method based on the binomial distribution In the second stage 19 patients will be enrolled. If there are ≥ 6 patients with objective response (CR or PR), the main objective of this trial will be achieved. An accurate confidence interval based on a binomial distribution is used for calculating the proportion of confidence intervals. **<u>Secondary endpoint</u>** The following analyses will be performed for ① FAS, ② ITT (Intention to Treat:ITT) and FAS, ③ SP (Safety Population). ① ORR by irRECIST, DCR Confidence intervals for ORR and DCR will be created using the exact test according to a binomial distribution. ② PFS, OS A survival function will be estimated using the Kaplan-Meier method. The median with the 95% CI and annual survival rate with the 95% CI will be estimated. ③ Incidence of adverse events As incidence of adverse events, in addition to tabulation of the frequency of adverse events, the incidence of Grade 3 or higher adverse events and the incidence of Grade 4 or higher adverse events will be calculated.
Planned period of the study	Planned enrollment period: October 2018 to Jun 2019 Planned observation period: 2 years from the date of enrollment of the last patient Entire study period (including a procedure for study completion): 3 year and 6 months from the date of enrollment of last patient When the administration of all subjects would be completed during the observation period, the observation period of the present trial will be also ended at the end of the observation period of the final administration subject.

Representative coordinating investigator	Kohei Shitara, National Cancer Center Hospital East
Planned study sites	National Cancer Center Hospital East

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Those requiring clinical judgements such as inclusion/exclusion criteria and criteria for treatment change: Coordinating investigators (Title page)

Enrollment procedure, electronic case report form (eCRF), etc.: Data Management Office, Clinical Research Support Unit, National Cancer Center Hospital East

(Attachment 1)

AE report, etc.: Clinical Research Support Unit, National Cancer Center Hospital East

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1. OBJECTIVES

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To evaluate antitumor activity and safety of Lenvatinib with Pembrolizumab for AGC patients

Primary endpoint

・Objective response rate (ORR)

by Response Evaluation Criteria In Solid Tumors (RECIST) ver1.1

Secondary endpoint

・Safety

- The incidences and types of adverse events that occur during treatment will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

・Efficacy

- Objective response rate (ORR) according to immune-related (ir) RECIST
- Progression-free survival (PFS)
- Overall survival (OS)
- Disease control rate (DCR)

Exploratory endpoints

Tests of various biomarkers

2. BACKGROUND and RATIONALE FOR THE THE SELECTION OF TE TREATMENT PLAN

2.1. Epidemiology of the Subjects

The number of deaths of gastric cancer in Japan is about 50,000 per year (about 13% of 360,000 deaths total) and is the second leading cause of death due to malignant neoplasms. However, the mortality rate (against 100,000 inhabitants) have tendency to decrease in male and female to 53.9, 33.2 (1980) and 50.5, 24.7 (2015), respectively[1]. On the otherhand, the morbidity rate (against 100,000 inhabitants) remained high, In 1980, male and female were 86.6 and 49.1 respectively, rising to 146.7 and 62.8 respectively in 2012, the first in male and the third in women most common cause of cancer-related death[2]. Gastric cancer is the fifth most common cancer worldwide and the third most common cause of cancer-related death (after lung and liver cancer), with an estimate of 723,073 deaths annually. Currently, patients with gastric cancer can be cured only when diagnosed with early stage disease in which a complete resection of the tumor can be therapy. Approximately 50% of patients with gastric cancer have advanced disease at the time of diagnosis.

2.2. The Standard of Care of Subjects

Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes, or irinotecan[4]. Based on the results of the ToGA study, the addition of trastuzumab to chemotherapy has become standard of care, where available, for first-line treatment of patients with HER2-neu-positive (HER2+) advanced or metastatic gastric adenocarcinoma[5]. As a second-line treatment, in two phase III trials, taxanes and irinotecan showed a significant survival extension compared with the best supportive care[6,7]. Ramucirumab, a vascular endothelial growth factor-2 (VEGFR-2) antibody, has been shown to increase OS when administered alone or in combination with paclitaxel in patients who have progressed following first-line therapy; and was recently approved in Japan for second-line therapy of gastric cancer[8]. Among patients with advanced metastatic gastric cancer who have received standard first-line therapies, the 5-year survival rate remains less than 5% and the median OS is less than 12 months, therefore, further development of effective treatment is urgent.

2.3. Molecular targeted drug of the Subjects

Trastuzumab and Ramucirumab mentioned above are approved in Japan for molecular targeted drug for gastric cancer. Clinical trials of EGFR inhibitors such as Panitumumab and

Cetuximab and anti-VEGF antibody drugs such as Bevacizumab were carried out, but all were negative. Other molecularly targeted drug under development are mainly drugs having angiogenesis inhibiting action. Apatinib is a novel small molecule tyrosine kinase inhibitor that selectively inhibits VEGFR2, and Phase III trials were conducted in China targeting second-line treatment. As a result, the median OS was significantly longer than 6.5 months in the Apatinib group and 4.7 months in the placebo group (HR = 0.709, p = 0.0149). The international joint Phase III trial (ANGEL test) is currently being conducted. Regorafenib is an oral multi-kinase inhibitor that targets factors related to angiogenesis (VEGFR1-3, TIE-2), tumor microenvironment (PDGFR, FGFR), tumor growth (RAF, RET, KIT) and is a drug whose efficacy has been confirmed in colon cancer and GIST. International joint Phase II trials were conducted for gastric cancer that became refractory to primary or secondary therapy. As a result, it was 2.6 months in the Regorafenib group and 0.9 months in the placebo group in PFS, the primary endpoint, and significantly prolonged in the Regorafenib group (HR = 0.40, p <0.0001). International joint Phase III trials are currently under way.

2.4.Immunotherapy for the Subjects

In recent years, “immunotherapy” has been attracting attention as the fourth treatment method for advanced or metastatic solid cancer. Immunotherapy is a treatment method used to remove the tumor via the human innate immune system. Various immunotherapies have been investigated, such as vaccine therapy using cancer antigen peptides and dendritic cells, and treatment using immune response-activating cytokines (e.g., interferon [IFN]-α, IFN-γ, and interleukin [IL]-2); however, the efficacy of such treatments has only been observed in some patients[9]. This is likely attributable to the tumor microenvironment inhibiting the antitumor immune response[9]. The tumor microenvironment is invaded with immune cells, including natural killer (NK) cells, dendritic cells, and T cells, which have a potent antitumor action and are responsible for the antitumor immune response that inhibits tumor growth.

Cancer cells have a wide variety of immunosuppressive mechanisms that are employed to evade the antitumor immune response[10]. Some notable examples include suppressive mechanisms whereby immune cells recognize cancer cells (decreased expression of cancer antigens and major histocompatibility complex-class I), expression of various immunosuppressive molecules (e.g., indoleamine-2, 3-dioxygenase, cytotoxic T lymphocyte-associated antigen-4 [CTLA-4], programmed cell death-ligand 1 [PD-L1], IL-10, and tumor growth factor-β), and the induction of immunosuppressive cells (e.g., myeloid-derived suppressor cells [MDSCs] and regulatory T cells)[10]. The antitumor immune response could potentially be activated by inhibiting these molecules that suppress the

antitumor immune response, as well as the function of immunosuppressive cells.

Treatments targeting immunosuppressive mechanisms that have resulted in remarkable clinical outcomes for several types of cancer include immune checkpoint inhibitors, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. Several agents are already approved by the US Food and Drug Administration as treatments for several types of cancer, including malignant melanoma and lung cancer. Additionally, in Japan, nivolumab (an anti-PD-1 antibody) has been approved for malignant melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma. Moreover, ipilimumab (an anti-CTLA-4 antibody) has been approved for malignant melanoma. On 22 September 2017, nivolumab was approved for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy. This approval was based on the phase III study ATTRACTION-2, in which nivolumab significantly reduced patients' risk of death by 37% (HR = 0.63; 95% CI = 0.51–0.78, $p < .0001$) when compared to placebo[11]. Similary, the FDA has approved Pembrolizumab for the treatment of patients with PD-L1–positive recurrent or advanced gastric cancer who have received 2 or more lines of chemotherapy, including fluoropyrimidine- and platinum-containing chemotherapy, and, if appropriate, HER2/neu-targeted therapy. The approval is based on findings from the phase II KEYNOTE-059 study. The overall response rate in all patients was 11.6% (95% CI, 8.2-20.0) and in PD-L1–positive patients was 15.5%. The phase III KEYNOTE-061 trial investigating pembrolizumab as a second-line treatment for patients with advanced gastric cancer did not meet its primary endpoint of overall survival (OS) (HR = 0.82, 95% CI = 0.66–1.03; $p = 0.042$) in patients whose tumors expressed PD-L1.

As mentioned above, the immunosuppressive mechanisms of cancer cells vary greatly. Therefore, the effect of immunotherapeutic agents is thus limited, and it is considered unlikely that all patients with solid cancer will benefit from of a single therapeutic agent. A trial is proposed to further activate the antitumor immune response and enhance drug efficacy by combining therapeutic agents that inhibit immunosuppression while simultaneously eliminating several immunosuppressive mechanisms. Clinical studies are actively underway to this end.

2.5. Rationales for the Selection of the Treatment Plan

2.5.1. Treatment regimen

As mentioned before, although immune checkpoint inhibitors exhibit a certain antitumor effect against solid cancers, the response rate to a single agent is only 10%–40% and the number of patients who respond to treatment remains limited. One reason for this is that the number of regulatory T cells, MDSCs, and tumor-associated macrophages (TAM) is

considered to increase as cancer progresses.

Angiogenic factors (vascular endothelial growth factor: VEGF) are considered to be involved in the production of regulatory T cells, MDSC, and TAM. It has therefore been reported that the suppression of VEGF or VEGF receptors (VEGFR) inhibits the production of these immunosuppressive cells and increases localized T-cell invasion of the tumor[12-16]. Similarly, stem cell factor (SCF)-mediated signaling of MDSCs was repressed by blocking the interaction with its receptor c-Kit. This inhibition resulted in decreased MDSC expansion and tumor angiogenesis[17]. In the studies conducted at our hospital, the analysis of biopsy tissue specimens before and after lenvatinib administration has revealed that the ratio of regulatory T cells decreases, which suggests that lenvatinib decreases the production of immunosuppressive cells (data not published)..

Lenvatinib showed a superior antitumor activity in immune-competent mice compared to in immune-deficient mice with immune modulating effects to decrease TAMs and MDSC. Lenvatinib also enhanced antitumor activity of PD-1 inhibitors treatment in two syngeneic models. In the phase Ib part of lenvatinib and pembrolizumab, patients with solid tumors that had progressed after treatment with approved therapies were administered either 24mg or 20mg of lenvatinib daily and 200mg of pembrolizumab intravenously every three weeks. DLTs were reported in two of three patients in lenvatinib 24mg / pembrolizumab 200mg group and no DLTs were reported in lenvatinib 20mg / pembrolizumab 200mg group of ten patients, and the MTD was confirmed as 20mg of lenvatinib / 200mg of pembrolizumab every three weeks. Out of the 13 patients, the objective response rate was 69.2%. Currently, several phase 2 or 3 trials are ongoing for renal cell cancer. However, to our knowledge, there is no study using lenvatinib in combination with anti-PD1 antibody for AGC patients. Therefore we planned this study.

2.6. Lenvatinib

Lenvatinib mesylate was developed at Eisai Tsukuba Research Laboratories to explore agents that inhibit RTKs activities associated with tumor angiogenesis. It is a multikinase inhibitor that exhibits potent inhibitory effects not only on VEGFR1 to VEGFR 3 at the level of inhibition constant Ki 1 nmol/L, but also on FGFR 1 to FGFR4 and KITs.

In nonclinical studies, lenvatinib showed inhibitory activities dose-dependently in VEGFR2-driven phosphorylation, tube formation and proliferation in human vascular endothelial cells (human umbilical vein endothelial cell – HUVEC) induced by VEGF. In vivo study where human cancer cells are transplanted in immune deficient mouse models, lenvatinib also demonstrated high anticancer effect in a wide variety of cancers. In addition, safety results in nonclinical studies showed lenvatinib was well tolerated within the

therapeutic range[18].

Three phase 1 studies were conducted in Japan, US, and Europe with different regimen to determine the safety, tolerability, and pharmacokinetics of lenvatinib. Treatment regimen for each study was: continuous once daily for E7080-E044-101 (Europe), continuous twice daily for E7080-A001-102 (US), and twice daily for 2 weeks with dosing intervals of 1 week for E7080-J081-103 (Japan). Based on the results from these studies, a continuous dose of 24 mg once daily has been selected to treat solid tumors for ongoing lenvatinib development. The tolerability in 24 mg once daily continuous dose in Japanese patients was confirmed in another study conducted in Japan (E7080-J081-105). There was no significant difference in tolerability and pharmacokinetics among patients in Japan, Europe, and US[19].

Lenvatinib is expected to be efficacious regardless of cancer type; clinical studies are being conducted for various solid malignancies including thyroid carcinoma, hepatocellular carcinoma, renal cell carcinoma, non-small-cell lung cancer, endometrial cancer, glioma, malignant melanoma, and ovarian cancer. Lenvatinib is approved in the US for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and approved in Japan with an indication for unresectable thyroid cancer.

As outlined below, data from Phase 2 clinical studies showed lenvatinib monotherapy has antitumor activity in multiple other tumors. In a 3 arm study of lenvatinib 24 mg once daily, everolimus 10 mg once daily, and the combination of lenvatinib 18 mg with everolimus 5 mg in patients with unresectable advanced or metastatic renal cell carcinoma (E7080-G000-205), lenvatinib monotherapy showed plonongation of PFS compared with everolimus monotherapy. Although a large scale study in gastric cancer has not been conducted, 3 out of 6 patients with advanced gastric cancer patients during phase 1 trials achieved durable stable disease.

2.7. 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).

Treatment studies using mouse models revealed that administration of an antibody, inhibiting interactions with PD-1/PD-L1, promoted the infiltration of tumor-specific CD8-positive T cells when administered alone or in combination with other treatments, and ultimately led to tumor rejection. It has been shown that anti-mouse PD-1 or PD-L1 antibody

alone has an antitumor effect in squamous cell carcinoma, pancreatic cancer, malignant melanomas and CRC models. The inhibition of the PD-1 pathway effectively promotes CD8-positive T cell infiltration into tumors and IFN-γ, granzyme B and perforin production. In a mechanism of action, *in vivo* local infiltration and activation of effector T cell function have been suggested to be involved. *In vivo* studies using syngeneic mouse models of tumors revealed that the inhibition of the PD-1 pathway by pembrolizumab alone and in combination with chemotherapy was effective. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications.

In the advanced adenocarcinoma of the gastric or gastroesophageal junction cohort in a Phase Ib study (KEYNOTE-012) of pembrolizumab in patients with PD-L1-positive solid tumors, pembrolizumab 10 mg/kg was administered every 2 weeks to 39 patients[20]. At 8.8 months of follow-up, the ORR was 22.2% and 6-month survival rate was 69%. In an additional analysis, the median duration of response was 40 weeks and very long. The median OS was 11.4 months and very good while 66.7% of patients had received 2 or more regimens. Treatment-related AEs occurred in 24 patients (61.5%). Grade 3/4 AEs occurred in 4 patients (decreased appetite, malaise, hypoxia, peripheral nerve disorder and pneumonitis). None of the treatment-related AEs led to treatment discontinuation.

In KEYNOTE-059 study cohort 2, the efficacy of pembrolizumab + 5-FU + cisplatin was investigated. Twenty-five patients were enrolled, ORR was 60% (95% CI, 38.7-78.9), median PFS was 6.6 months and median OS was 20.8 months. This study suggested that the combination of standard therapy and pembrolizumab encourage antitumor activity.

The ongoing phase III KEYNOTE-062 trial is evaluating pembrolizumab alone and in combination with chemotherapy in the frontline setting for PD-L1–positive advanced gastric cancer. In phase I study of the combination of pembrolizumab and ramucirumab for 28 patients, response rate was 14% and median PFS was 5.6 months.

The development of combination therapy of pembrolizumab and standard therapy or molecular targeted drug is underway in both front and secondary line.

2.8The combination of Lenvatinib and Pembrolizumab

2.8.1. Preclinical study

It is reported that VEGF/VEGFR signal exhibits proangiogenic properties but also has a key role in the induction of an immunosuppressive microenvironment[16]. Therefore, it is expected that lenvatinib which inhibit VEGFR can also have immune modulating activity.
The effect of combining lenvatinib with PD-1/L1 monoclonal antibodies (mAbs) has been

investigated in the CT26 murine colorectal cancer syngeneic model (PD-L1 mAb) as well as the LL/2 murine lung cancer syngeneic model (PD-1 mAb). Combination treatment with lenvatinib and PD 1/L1 mAb showed significant and superior antitumor effects compared with either compound alone. TAM cells express PD-L1 at a higher level than cancer cells in the CT26 syngeneic model, and lenvatinib significantly decreased the TAM population[21]. Because TAM cells produced interleukin 10 (IL-10) and transforming growth factor, beta 1 (TGFβ)[22], lenvatinib might increase antitumor immunity in the CT26 model and up-regulate the effect of the PD-1 signal inhibitors. Thus, immune-modulating effect of lenvatinib may result in potent combination effect with PD-1 signal inhibitors.

2.8.2. Clinical trial

E7080-A001-111 (Study 111) is an open-label Phase 1b/2 study in subjects with selected solid tumors (NSCLC, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma [excluding uveal melanoma]), which is conducted in US.

In Phase 1b, subjects were to enroll in 1-3 dose levels to determine and confirm the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib in combination with pembrolizumab. The dose of pembrolizumab did not change during the MTD phase, while lenvatinib started at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg. In the lenvatinib 24 mg cohort, 2 DLTs were observed in the first 3 subjects (2 renal cell carcinoma and 1 NSCLC): Grade 3 fatigue and Grade 3 arthralgia. The dose was de-escalated to 20 mg/day lenvatinib and 10 additional subjects (total of 6 renal cell carcinoma, 1 NSCLC, 1 Melanoma and 2 Endometrial) started the treatment. There were no DLTs in the lenvatinib 20 mg cohort, and the MTD and RP2D are confirmed at 20 mg lenvatinib once daily (QD) in combination with 200 mg Q3W of pembrolizumab.

In Phase II, subjects are assigned by tumor type to up to 6 cohorts to receive the MTD to assess the safety and efficacy of the combination in the selected tumor-types. This phase is ongoing.

2.9. Treatment regimen in the present trial

The protocol treatment of this trial is combination of lenvatinib and pembrolizumab. This study will begin with lenvatinib 20 mg/day orally and pembrolizumab 200 mg (every 3 weeks with each cycle of 21 days. The administration will be repeated until each subject falls under the criteria for discontinuation.

2.9.1. Rationale for setting Lenvatinib administration route, dose, and treatment

schedule

As described in Section 2.7.2, investigation in combination with Pembrolizumab was conducted in 111 trial. In this trial, once-daily Lenvatinib 20 mg confirmed as MTD and RP2D in 111 trial is considered to be appropriate as the starting dose.

2.9.2. Rationale for setting Pembrolizumab administration route, dose, and treatment schedule

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively

demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.
Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

2.10. Study Design

This trial is an open label phase II study to evaluate the safety and efficacy of lenvatinib with pembrolizumab in patients with ACG. The Simon's Optimal two-stage design will be used in this trial[23].

The analysis set for the primary endpoint is the Full Analysis Set (FAS).

1) First stage

In the first stage, ten patients will be enrolled in the FAS prescribed in Section 12.3. If two or more objective response (CR or PR) were observed among 10 patients (no confirmation required) in the first stage, the study will proceed to the second stage. If objective response (CR or PR) was less than two, the study will not proceed to the second stage and we will consider discontinuation of this trial.

2) Second stage

In the second stage 19 patients will be enrolled. If there are ≥ 6 patients with objective response (CR or PR), the main objective of this trial will be achieved.

2,10.1. Rationales for the Endpoint

Primary endpoint

・Objective response rate (ORR)

Secondary endpoint

- Objective response rate (ORR) according to immune-related (ir) RECIST
- Progression-free survival (PFS)
- Overall survival (OS)
- Disease control rate (DCR)
- Incidence of adverse events

Rationale for primary endopoint

In this trial, ORR was set as Primary endpoint. In the 111 test described above, ORR was 9 69.2%. It is suggested that lenvatinib may activate antitumor immunity also in gastric cancer and it is considered that there is a possibility that the combination of lenvatinib and pembrolizumab may be the object to obtain the tumor shrinking effect. If high ORR will be confirmed by this protocol treatment, it is considered that there is a sufficient possibility that life-prolonging effect will be confirmed when comparing with standard treatment in phase III following this trial, therefore, ORR will be set to Primary endpoint.

2.10.2. Clinical Hypothesis Planned Number of Enrollments

1) Clinical hypothesis

The clinical hypothesis is that the combination of lenvatinib and pertuzumab has a superior antitumor effect to that of pembrolizumab monotherapy.

2) Rationales for the determination of threshold and expectation of ORR

Based on the above clinical hypothesis, Simon's Optimal two-stage design is used with the threshold / expectation value. In the clinical study, the response rate of lenvatinib in gastric cancer was 0% (0/6)[19], the response rate to gastric cancer in the phase III trial of Apatinib, receptor type tyrosine kinase inhibitor including angiogenesis inhibitory effect, was 1.7%[24]. The response rate of receptor type tyrosine kinase inhibitor monotherapy to gastric cancer is estimated to be 1 to 2%. The response rate of anti-PD-1 antibody drug for gastric cancer in Phase III study was 11% in all patients, but this trial including PD-L1 negative patients, it could be lower than 11% depending on the proportion of negative patients. Therefore, the threshold level was set at 10%. Considering that it will show efficacy commensurate with the side effects of lenvatinib or pembrolizumab, we thought that at least 20% extra in ORR was necessary. Based on the above, the threshold ORR was set to 10% and the expected ORR was set to 30%.

3) Rationale for the determination of the sample size

The clinical hypotheses set up in this trial according to the above are as follows (OR of FAS

is p).

· Null hypothesis: p = 0.10 (threshold ORR)

· Alternative hypothesis: p = 0.30 (expected ORR)

Based on Simon's Optimal two-stage design calculation (one-side significance level 5%, power 80%), the number of patients is as follows.

In the first stage, ten patients will be evaluated, and if the number of patients of CR or PR according to RECIST 1.1 will be 2 or more, 19 patients as FAS will be added in the second stage. The result will be considered statistically significant when at least 6 of the total 29 patients as FAS have an object response.

2.10.3. Anticipated Enrollment of Patients, Enrollment Period and Follow-up Period

For a period of enrolling 29 patients in the FAS, 9 months were estimated. Since this is a study conducted at cancer hospitals, the abovementioned enrollment period is judged to be fully feasible to accumulate patients. The planned duration of follow-up will be 1 years from the date of enrollment of the last patient.

2.11. Summary of Expected Benefits and Disadvantages Associated with the Study Participation

In this study, if combination therapy with lenvatinib and pembrolizumab in patients with gastric cancer is judged to be effective, a prospective treatment regimen can be expected for a larger number of participarting subjects.

The anticipated disadvantages include any adverse events associated with lenvatinib and pembrolizumab. To minimize the risk and disadvantages of adverse events, the data center together with the Data and Safety Monitoring Committee will monitor any adverse events in the present trial to determine whether or not they are within the expected range. These bodies will also conduct a thorough examination in the event that serious or unexpected adverse events occur, and adopt an appropriate system to take any necessary actions.

2.12. Rationale for the Investigator-Initiated Study

Lenvatinib is a drug currently under development by Eisai, and pembrolizumab is a drug currently under development by MSD. Both drugs have been approved for the treatment of some types of cancer; however, these drugs have yet to be approved for the majority of cancers. Plans are currently underway internationally to move forward with various combination therapies, such as immune checkpoint inhibitors, cytocidal drugs, and molecular-targeting drugs. At present, the two drugs are unapproved drugs of different companies, and there are no plans in Japan or internationally for the company-led

development of combination therapy with lenvatinib and pembrolizumab. Furthermore, by analyzing biomarkers in accompanying research, we hope to pursue the significance of simultaneously inhibiting the VEGF, KIT, and PD1 pathways, as well as the possibility of further combined uses for the two drugs.

In the present trial, the safety of the use of lenvatinib in combination with pembrolizumab will be confirmed. When it is confirmed that a combined effect can be expected with these two drugs, this combination therapy will be regarded as a promising new treatment strategy for use in combination with immune checkpoint inhibitors.

3. Standards and definitions used in this study

3.1. Standards for disease staging

Staging will be classified in accordance with the “UICC-TNM 7th edition.”

3.2. Performance Status（ECOG classification）

(Refer to Appendix 1)

3.3. Evaluation criteria for adverse events

As for the term and grade of adverse events, “Common Terminology Criteria for Adverse Events (CTCAE) v4.0-JCOG) [CTCAE v4.03/MedDRA v12.0]” is to be used. In this study, adverse events are assessed in accordance with JCOG.

3.4. Evaluation criteria for response rate

The “New Guideline for Judging Therapeutic Effects on Solid Cancer (RECIST Guideline), revised version 1.1 JCOG version: Revised RECIST guideline (version 1.1)” is used for judging tumor-reducing effects (Refer to Appendix 3).

4. Eligibility criteria/exclusion criteria

Patients who satisfy the all the following eligibility criteria, and who do not fall any one of the exclusion criteria are to be judged as those eligible for registration.

4.1. Inclusion criteria

1. Patients have histologically or cytologically confirmed advanced or recurrent gastric cancer.
2. Patients at least 20 years of age on the day of providing consent.
3. Patients have measurable disease as defined by RECIST 1.1 as determined by investigator.
4. Patients with a performance status of 0 or 1 on the Eastern Cooperative Oncology Group.
5. Patients with adequate organ function at the time of enrollment as defined below:
   - Neutrophil count ≥1200mm^3
   - Platelet count ≥7.5 × 10^4/mm^3
   - Hemoglobin (Hb) ≥ 8.0 g/dL,
   - Total bilirubin ≤1.5 mg/dL
   - AST (SGOT) and ALT (SGPT) ≤ 100 IU/L
     for subjects with liver metastases≤200 IU/L
   - Creatinine ≤1.5-times the upper limit of normal
   - International normalized ratio (INR) ≤ 1.5
   - Urinary protein : It satisfies one of the following (if any of the inspection criteria are satisfied, other examination may not be carried out)
   (i) Urinary protein (test paper method) is 2+ or less
   (ii) Urine Protein Creatinine (UPC) ratio <3.5
   (iii) 24-hour urine protein was measured, urinary protein ≦ 3500 mg
6. Patients who not received a blood transfusion within 7 days of registration.
7. Patients have recovered adverse events associated with chemotherapy, radiation and surgical operation as pretreatment to Grade 1 or lower with CTCAE v4.0 excluding stable symptoms (eg alopecia, peripheral sensory neuropathy, skin hyperpigmentation, dysgeusia etc.).
8. Female of childbearing potential who are negative in a pregnancy test within 14 days before enrollment. Both male and female patients should agree to use an adequate method of contraception (total abstinence, an intrauterine device or hormone releasing

system, an contraceptive implant and an oral contraceptive) starting with the first dose of study therapy through 120 days after the last dose of study therapy. Duration will be determined when the subject is assigned to treatment.

9. Patients capable of taking oral medication
10. Patients who provided written informed consent to be subjects in this trial

4.2. Exclusion criteria

1. Patients who received prior anticancer treatment within 14 days (or 5 times the half-life time, whichever is shorter) or any investigational agent within 28 days prior to the first dose of study drugs.
2. Patients who have undergone surgical treatment and radiotherapy with in 2 weeks before enrollment.
3. Patients with a history of prior treatment with Lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
4. Patients with hypertension that is difficult to control (systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with several hypotensive agents.
5. Patients with acute coronary syndrome (including myocardial infarction and unstable angina), and with a history of coronary angioplasty or stent placement performed within 6 months before enrollment.
6. Patients with symptomatic brain metastasis.
7. Patients with a history of New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months
8. Patients have an active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months
9. Patients have severe (hospitalization required) complications (intenstinal palsy, intestinal obstruction, pulmonary fibrosis, diabetes difficult to control, heart failure, myocardial infarction, unstable angina, renal failure, liver failure, mental disease, cerebrovascular disease etc).
10. Patients with a history of a gastrointestinal perforation and /or gastrointestinal fistula within 6 months before enrollment.
11. Patients with active hepatitis.
12. Patients with a history of human immunodeficiency virus (HIV).

13. Patients with active symptoms or signs of interstitial lung disease.
14. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease
15. Patients who require systemic corticosteroids (excluding temporary usage for tests, prophylactic administration for allergic reactions, or to alleviate swelling associated with radiotherapy) or immunosuppressants, or who have received such a therapy <14 days before enrollment.
16. Patients have a history of (non-infectious) pneumonitis that required steroids or have current pneumonitis
17. Patients who are administered live vaccines <30 days before the initiation of treatment with the investigational drug.
18. Patients have serious non-healing wound, ulcer, or bone fracture.
19. Females who are pregnant or breastfeeding
20. Patients have no intention to comply with the protocol or cannot comply.
21. Patients were judged unsuitable as subject of this trial by investigator.

5. Registration/allocation

After confirming that target subjects satisfy all the eligibility criteria, and they are not corresponding to any one of the exclusion criteria, register them by the Web registration system.

5.1. Contact information for subject's registration and time in

The Web registration URL, etc. are to be notified separately with "EDC Input Manual".

(24-hour registration is possible; however, when access is impossible due to maintenance, etc., this is to be notified beforehand)

- **Inquiry on registration**

  Research Support Center at National Cancer Center

  TEL: +81-44-7133-1111 (Extension: 5106) E-mail:LenvaPembro_core@east.ncc.go.jp

  Weekday: from 10:00 to 17:00 (not in operation on festival day, Saturday and Sunday)

- **Inquiries on patients' registration**

  Representative coordinating investigator: Kohei Shitara

  Department Head,

  Department of Gastroenterology and Gastrointestinal Oncology,

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  6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577

  TEL: +81-4-7133-1111 (Extension: 91520) E-mail: kshitara@east.ncc.go.jp

  Coordinating investigator: Shota Fukuoka

  Exploratory Oncology Research & Clinical Trial Center, National Cancer Center

  Coordinating investigator: Akihito Kawazoe

  Department of Gastroenterology and Gastrointestinal Oncology,

  National Cancer Center Hospital East

  E-mail: LenvaPem_core@east.ncc.go.jp

5.2. Precautions for registration

1) Registration after start of the protocol treatment is not allowed without exception.

2) When confirmation of the contents of registration/eligibility confirmation sheet is inadequate, registration is not accepted until all the requirements are satisfied.

3) After confirmation of eligibility, a registration number is issued. Registration is completed upon issuance of the registration number.

4) When registered once, subject's registration is not cancelled (deletion from the database) except for cases of retraction of consent inclusive of rejection of the use of data for research. The initial registration information (registration number) is adopted in any cases of overlapped registration.

5) When erroneous registration/overlapped registration have been proved, this should be promptly informed.

6) When subjects are visiting other hospitals or departments continuously at the time of registration, inform the relevant investigator to the effect that the said subjects participate in this clinical trial.

6. TREATMENT PLAN AND CRITERIA FOR TREATMENT CHANGE

Treatment and treatment changes should be implemented as specified in this section unless otherwise threatening the patients' safety. When it is judged that compliance with the protocol may cause medical hazards, the principal investigator/subinvestigator (hereinafter referred to as the investigator) should change the treatment in accordance with the medical judgment.

6.1. Protocol Treatment

In the present trial, the protocol treatment will consist of the investigational drug, Lenvatinib, used in combination with Pembrolizumab. However, in the event that the termination criteria are satisfied for one of these drugs, the trial investigator can consider continuing the treatment protocol with either Lenvatinib or Pembrolizumab monotherapy upon deliberation with the trial coordinating committee. Each patients will undergo study treatment on an inpatient or outpatient basis.

The treatment protocol will commence within 14 days of enrollment, including the day of enrollment. Furthermore, in the event that administration of the investigational drug cannot be initiated within 14 days of enrollment (including the day of enrollment), the trial coordinating committee is to be contacted to examine how the patient should be handled.

The following terms are used in this protocol:

- Discontinuation: Investigational drug administration is not resumed.
- Treatment interruption: The protocol treatment is moved on to the next dosing schedule without administration of one or more doses of the investigational drug.
- Washout period: A period during which no investigational drug is give

6.1. 1 Study Treatment

1) Lenvatinib will be administered with water orally once a day (with or without food) in 21-day cycles at approximately the same time each day. On Day 1 of each cycle, in case concomitantly administered, it will be administered approximately within 1 hour after completion of pembrolizumab administration. Pembrolizumab will be administered as a dose of 200 mg as a 30-minute IV infusion, Q3W (25 minutes to 40 minutes are acceptable).
2) The initial dose of Lenvatinib will be 20 mg per day.
3) Continue administration until it will fall into "6.2.1. Discontinuation Criteria for the Protocol Treatment".

6.2. Discontinuation Criteria for the Protocol Treatment

6.2.1. Discontinuation Criteria for the Protocol Treatment

When the participating patients met any of the following criteria, the protocol treatment should be discontinued:

1) Progression of the primary disease (including evident progression based on diagnostic imaging and clinically clear progression)
2) Request for discontinuing the protocol treatment by the patient
3) Onset of protocol treatment-related Grade 4 non-hematotoxicity
(This is not applicable to transient abnormal laboratory values.)
4) Both lenvatinib and pembrolizumab are not administered for greater than 28 days.
5) Meeting the discontinuation criteria for the protocol treatment set forth in the Section “6.3. Criteria for Changes in the Protocol Treatment”
6) Recurrent Grade 2 pneumonitis
7) Pregnancy in the patients
8) Lost to follow-up
9) Death during the protocol treatment
10) Completed 35 treatments with Pembrolizumab
11) Treatment discontinuation after CR
Following at least eight cycles of pembrolizumab (approximately 6 months), when a subject is deemed to exhibit CR on the basis of diagnostic imaging, and receives at least two cycles of pembrolizumab after the initial determination of CR, termination of pembrolizumab can be considered upon consultation with the trial coordinating committee.
12) Other instances when the attending physician judges it necessary to terminate the trial (including when treatment with other anticancer drugs, surgery, or radiotherapy not stipulated in the protocol is needed for lesions that are subject to evaluation).

When, despite meeting the criteria for termination of the treatment protocol, there are clinical grounds that strongly suggest the efficacy of the treatment and there are reasons that justify the continuation of the protocol treatment, the decision shall be reconsidered with the trial coordinating committee on an individual basis according to the situation.

6.2.2. Data Collection and Follow-up of Patients after Discontinuation of the Protocol Treatment

When meeting the discontinuation criteria, the protocol treatment should be discontinued, its date, reason and clinical course should be recorded in the case report form (CRF), and

tests specified during the follow-up period should be performed. However, this is not applicable to the case where the investigator judges that the tests cannot be performed or are unnecessary in the light of ethics and the patients' safety and benefits.

6.3. Criteria for Dose Modifications for the Protocol Treatment

The treatment should be interrupted and resumed as instructed in this section. For patients who need to resume lenvatinib and pembrolizumab more than 28 days after the planned start day, the protocol treatment should be discontinued. However, even if lenvatinib or pembrolizumab therapy is discontinued, if another monotherapy can be resumed in accordance with this section, the protocol treatment may be resumed only monotherapy.

6.3.1. Criteria for Changes in Lenvatinib therapy

The safety profile of regorafenib has been established in the clinical trials. The dose adjustments for lenvatinib are according to the clinical trials conducted to date in table 6.3.1.

Table 6.3.1: Doses of Lenvatinib

Dose Level	Lenvatinib (mg,QD)
Initial dose	20 mg
Reduction 1	14 mg
Reduction 2	10 mg
Reduction 3	8 mg
Reduction 4	4 mg *

* Consult the coordinating committee for further dose reduction recommendations.

6.3.1.1 Dose modification of Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib and pembrolizumab combination therapy-related toxicity will be in accordance with the dose reduction instructions shown in the tables below for this study, respectively. Even if the following conditions are not met, it is possible to withdraw administration and reduce the dose at the discretion of the investigator. For management of hypertension, refer to the section 6.3.1.2. Once the dose has been reduced, it cannot be increased at a later date.

Table 6.3.1: Dose Modification of Lenvatinib

Lenvatinib Treatment-related Toxicity[a,]	**During Therapy**	**Adjusted Dose[d]**

Grade 1, Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[b] and Grade 3[c]		
First occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	No change or Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Grade 4[c]: Discontinue lenvatinib		

BMI = body mass index.

a: Excluding alopecia and asymptomatic laboratory abnormalities. Initiate optimal medical management for nausea, vomiting, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.

b: Applicable only to Grade 2 toxicities judged by subject and/or physician to be intolerable.

c: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3. Asymptomatic laboratory value abnormalities will not be included.

d: Refer to the table 6.3.1.

6.3.1.2 Dose modification for hypertension

When hypertension develops during lenvatinib treatment, dose modification will be made at the discretion of the principal investigator (or subinvestigator) with reference to “Table 6.3.1.2: Dose modification for hypertension.” Hypertensive subjects require careful observation and it is strongly recommended to administer suitable hypotensive treatment during lenvatinib treatment. The selection of hypotensive drug will be determined by the principal investigator (or subinvestigator) upon consideration of the treatment guidelines for

each institution participating in the trial.

Table 6.3.1.2 Dose modification for hypertension

NCI-CTCAE grade	Dose modification
Grade 2 Systolic blood pressure of 140–159 mmHg and/or diastolic blood pressure of 90–99 mmHg, or when the former is normal but diastolic blood pressure is increased > 20 mmHg and accompanied by symptoms.	Continue the dosing. If poorly controlled, consider a dose reduction. When accompanied by symptoms, withdraw treatment until the subject recovers from the symptoms, and diastolic blood pressure is restored to <90 mmHg. When resuming treatment, continue at the same dose level.
Grade 3 Elevated systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure of ≥100 mmHg, or pharmacotherapy of two or more types, and greater intensive therapy than before is needed.	Withdraw treatment until the diastolic blood pressure is decreased below 90 mmHg and if there are accompanying symptoms, until the subject recovers from the symptoms. When resuming treatment, consider decreasing the dose. When hypertension cannot be controlled with the addition of new hypotensive drugs or with more intensive therapy, decrease the dose by one level. When grade 3 hypertension recurs despite decreasing the dose and hypotensive treatment, decrease the dose further by one level.
Grade 4 Life-threatening (e.g., malignant hypertension, temporary or constant neuropathy, and hypertensive crises).	Terminate the administration of the investigational drug.

6.3.2. Criteria for Changes in Pembrolizumab therapy

6.3.2.1 Dose modification of Pembrolizumab

For AEs (whether serious or non-serious) related to pembrolizumab exposure, immunological factors may be involved. Such AEs may occur immediately after the start of investigational drug administration or several months after the last dose. For toxicity and

severe or life-threatening AEs related to pembrolizumab, pembrolizumab therapy should be interrupted or discontinued in accordance with Table 6.3.2.1.

Table 6.3.2.1. **Dose modification of Pembrolizumab**

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue	
Diarrhea / colitis	Grade 2 or 3	Withhold	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.
	Grade 4	Permanently discontinue	

			• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]	
Hyperthyroidism	Grade 2	Continue	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]	
Hypothyroidism	No provision		• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue	

Myocarditis	Grade 1 or 2	Withhold	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3 or 4	Permanently discontinue	
All Other immune-related AEs	intolerable/ persistent Grade 2	Withhold	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis	
	Grade 4 or recurrent Grade 3	Permanently discontinue	

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

6.3.2.2 Supportive therapies for AEs Suspected to Be Related to Pembrolizumab

Example supportive therapies for managing AEs, which may be immunological etiology suspected to be related to pembrolizumab, are presented below. For the details, see the guidance document on events of special interest. A reduction in the corticosteroid dose may

exacerbate symptoms; thus, attention should be paid that administration of corticosteroid as tapering the dose for a few cycles will be required. An additional supportive therapy may be needed so that an effort shall be made to eliminate other causes of disease such as metastatic lesions and bacterial or viral infections for each symptom.

Pneumonitis:

In case of Grade 2, systemic corticosteroid should be administered. If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks.

In case of Grade 3 to 4, treatment with intravenous corticosteroid should be immediately administered. As necessary, an anti-inflammatory agent should be additionally administered. If the duration of corticosteroid treatment is extended, an antibiotic should be additionally administered to prevent opportunistic infection.

Diarrhoea/Colitis:

Whether or not there is any sign or symptom of enterocolitis (e.g., whether or not being accompanied by diarrhoea, abdominal pain, bloody or mucous stools, or pyrexia) and sign or symptom of bowel perforation (signs of peritonitis or intestinal obstruction) should be checked.

All patients who developed diarrhoea/colitis should be instructed to take a sufficient amount of water. If it is difficult to take a sufficient amount of water, water containing electrolytes should be intravenously administered. In case of ≥ Grade 2 diarrhoea, consultation with a gastroenterologist and endoscopy are recommended for confirming or denying colitis.

In case of Grade 2 diarrhoea/colitis persisting for more than 3 days, oral corticosteroid should be administered.

In case of Grade 3 to 4 diarrhoea/colitis persisting for more than one week, intravenous corticosteroid followed by high-dose oral corticosteroid should be administered.

If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks.

Type 1 diabetes mellitus [if newly occurred, including diabetic ketoacidosis (DKA)], and ≥ Grade 3 hyperglycaemia with ketosis (ketonuria) or metabolic acidosis (DKA):

For type 1 diabetes mellitus, and Grade 3 to 4 hyperglycaemia with metabolic acidosis or ketonuria, insulin replacement therapy should be considered.

Serum glucose levels and metabolic laboratory values (urine ketone, glycohemoglobin and C-peptide) should be assessed.

Hypophysitis:

In case of Grade 2, corticosteroid should be administered. If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks. Since corticosteroid is administered as tapering the dose, appropriate hormone replacement therapy may be required.

In case of Grade 3 to 4, intravenous corticosteroid followed by oral corticosteroid should be administered. If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks. Since corticosteroid is administered as tapering the dose, appropriate hormone replacement therapy may be required.

Hyperthyroidism and hypothyroidism:

Thyroid dysfunction may occur at any time during dosing. Whether or not there is any change in thyroid function test values (Conduct at the start of the administration of the investigational drug, thereafter periodically and as necessary based on clinical evaluation.) and sign or symptom of thyroid dysfunction should be observed.

Grade 2 hyperthyroidism (and Grade 3 to 4 hypothyroidism):

For hyperthyroidism, non-selective β blockers (e.g., propranolol) are recommended as first-line drugs.

For hypothyroidism, thyroid-hormone replacement therapy with levothyroxine or liothyronine is recommended as standard therapy.

Grade 3 to 4 hyperthyroidism:

Intravenous corticosteroid followed by oral corticosteroid should be administered. If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks. Since corticosteroid is administered as tapering the dose, appropriate hormone replacement therapy may be required.

Liver:

In case of Grade 2, liver function tests should be performed frequently until values returned to baseline levels (Consider implementing the test every week.).

Intravenous or oral corticosteroid should be administered.

In case of Grade 3 to 4, intravenous corticosteroid should be administered over 24 to 48 hours.

If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks.

Renal failure or nephritis:

In case of Grade 2, corticosteroid should be administered.

In case of Grade 3 to 4, corticosteroid treatment should be given.

If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks.

Management of infusion reactions: Signs or symptoms of infusion reactions usually appear during or immediately after drug administration and often completely resolve within 24 hours postdose.

Actions to be taken if infusion reactions to pembrolizumab occurred are presented in Table 6.3.2.2

In the case where systemic corticosteroid treatment is judged to be necessary for immune-related Grade 2 or ≥ 3 toxicities other than those mentioned above upon discussion with the coordinating committee, the treatment should be administered. If the symptom recovered to Grade 1 or lower, the corticosteroid dose should be tapered over 4 or more weeks.

Table 6.3.2.2. Actions to be taken if infusion reactions to pembrolizumab occurred

NCI CTCAE Grade	Action	Pretreatment from the next dosing
Grade 1 Mild reaction; not requiring infusion interruption or treatment.	Vital signs should be more frequently monitored until the patient's symptom become stable at the discretion of the investigator.	None
Grade 2 Requiring infusion interruption, but immediately responding to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics, and intravenous infusion); requiring prophylactic treatment within 24 hours.	Pembrolizumab infusion should be interrupted, and the symptom should be monitored. An appropriate therapeutic action (e.g., administration of intravenous infusion, antihistamines, NSAIDs, acetaminophen and narcotic analgesics) should be taken. Vital signs should be more frequently monitored until the patient's symptom become stable at the discretion of the investigator. If the symptom resolved within one hour after treatment interruption, the treatment should be resumed at an infusion rate 50% slower than the original rate (e.g., from 100 mL/hr to 50 mL/hr). If the symptom does not resolve within one hour after treatment interruption, the treatment should be discontinued until	Pretreatment with the following drugs should be given 1.5 hours (± 30 minutes) before pembrolizumab infusion: Oral administration of diphenhydramine 50 mg (or equivalent antihistamine) Oral administration of acetaminophen 500 to 1000 mg (or equivalent antipyretic)

	the symptom resolves. Pretreatment should be given at the next dosing. Pembrolizumab therapy should be discontinued in patients who developed Grade 2 toxicity despite appropriate pretreatment (reintroduction prohibited).	
Grade 3 Prolongation (not quickly respond to symptomatic treatment or infusion interruption for a short period of time); recurring after improvement; and sequelae (e.g., renal disorder and lung infiltration) requiring hospitalization. Grade 4 Life-threatening; and requiring treatment with a hypertensive drug or artificial respiration	Pembrolizumab infusion should be interrupted. An appropriate therapeutic action (e.g., administration of intravenous infusion, antihistamines, NSAIDs, acetaminophen, narcotic analgesics, oxygen inhalation, hypertensive drugs, corticosteroids and epinephrine) should be taken. Vital signs should be more frequently monitored until the patient's symptom become stable at the discretion of the investigator. The patient should be admitted to the hospital as necessary. Pembrolizumab therapy should be discontinued (reintroduction prohibited).	Pembrolizumab should not be resumed.
During pembrolizumab infusion, an appropriate resuscitation device should be placed in the room so that the physician can promptly take an action.		

6.4. Special instructions for subjects

The attending physician and trial collaborators will instruct the subjects on the methods of lenvatinib and pembrolizmab administration and on observing the following matters. When administered on an outpatient basis, a thorough interview and investigation will be carried out regarding the state of lenvatinib administration (e.g., the collection of untaken lenvatinib [i.e., the investigational drug]), and the results will be recorded on a CRF.

6.5. Concomitant and Supportive Therapies

When subjects are undergoing post treatments, describe all the combination drugs and treatments that have been used during the period from start of administration until termination of the follow-up observation period (30 days after the final administration; in cases of undergoing of post treatments, until the day before the post treatments) in the CRFs. It is unnecessary to describe the agents that have been used for the purpose of various examinations/diagnoses in the CRFs, except for cases where the use of such agents is necessary for judging the causality of adverse events.

6.5.1. Recommended combination therapy/supportive therapy

The combination and supportive therapies listed below are recommended.

Nonadministration of the therapies will not be considered a deviation from the protocol.

1) Antiemetic agents/fluid replacement: For severe nausea and vomiting that impedes the continuation of oral therapy, the appropriate treatment will be administered using antiemetic agents or fluid replacement.

2) Antidiarrheal drugs.

3) Antifebrile agent, analgesics, and steroids will be administered for immune-related events.

6.5.2. Allowable combination therapy/supportive therapy

When zoledronic acid and denosumab are administered for bone metastasis before enrollment, such medications can be continued.

6.5.3. Unallowable combination therapy/supportive therapy

Except when required for the treatment of adverse events, safety, and ethical reasons, the concurrent use of the agents listed below shall not be permitted.

1) Other anticancer drugs

2) Other investigational drugs

3) Live vaccines administered <30 days before the initiation of treatment with the investigational drug and during the trial period. Examples of live vaccines are as follows (however, the list is not exhaustive): measles, mumps, rubella, chicken pox/herpes zoster, yellow fever, rabies*, BCG for tuberculosis, and typhoid vaccines*. Inoculation with inactive vaccines (e.g., seasonal influenza vaccines) is permitted; however, the intranasal administration of attenuated influenza vaccines (e.g., Flu-Mist®) is prohibited. (*In Japan, live vaccines are not approved).

4) Systemic glucocorticoids for purposes other than treating symptoms caused by notable events with a suspected immunological etiology. Upon deliberation with the trial coordinating committee, the use of corticosteroids may be permitted according to the physiological dose required to alleviate symptoms (e.g., to control symptoms of acute asthma).

Except when required for the treatment of adverse events, safety, and ethical reasons, the concurrent use of the drugs listed below is not permitted. However, use of these drugs to treat adverse events will not be considered a deviation from the protocol.

5) Other treatments that affect the evaluation of safety and efficacy (e.g., surgical treatment, radiotherapy, thermotherapy, immunotherapy, hormone therapy, and antibody therapy).

6.6. Subsequent Treatment

There will be no subsequent treatment for patients following the termination of the stipulated treatment protocol.

7. INFORMATION ON THE INVESTIGATIONAL DRUGS

7.1. Drug Information on Lenvatinib

Study drug	Lenvatinib
Dosage form	Capsule
Manufacturer	Eisai
Content	Capsule 4mg:This prodct contains 4.90 mg of lenvatinib mesilate in one capsule (4 mg as lenvatinib) Capsule 10mg:This prodct contains 12.25 mg of lenvatinib mesilate in one capsule (10 mg as lenvatinib)
Administration method	Oral
Expiration date	See the Procedures for Study Drug Management
Labelling	The outer box shows the content, storage method, and name, job title and address of the coordinating investigator, and indicates “For clinical study.” The job title of the coordinating investigator shown on the outer box should be that at the start of the study, and changes to the job tile, if any, should not be reflected on the label of the outer box.

Lenvatinib will be supplied by Eisai, the investigational drug supplier, free of charge. The manufacturing records and records of quality tests of the study drug will be also provided by the investigational drug supplier.

7.2. Drug Information on Pembrolizumab

Name of investigational drug:	Pembrolizumab
Dosage form:	Solution
Drug code:	MK-3475
Manufacturer:	MSD K.K.
Content:	100 mg/vial
Dosage:	Pembrolizumab should be diluted with normal saline or 5% glucose solution in a concentration range of 1 to 10 mg/mL, and 200 mg/body should be intravenously administered over 30 minutes.
Route of administration:	Intravenous infusion

Expiration date:	See the Procedures for Investigational Drug Management.
Labeling:	On the outer box, the investigational drug code, content, lot number, expiration date, quantity, storage method, and the names, job titles and addresses of the coordinating investigators, as well as the fact of being clinical study use only are mentioned. The job titles of the coordinating investigators to be indicated on the outer box should be those at the time of the start of the study and should not be changed even if they are changed during the study.
Storage method for the drug:	Store in a tight, light-resistant container at 2 to 8°C.

Pembrolizumab will be provided free of charge by, a supplier of the investigational drug, MSD K.K. The supplier of the investigational drug will also provide manufacturing and quality study records of the investigational drug, and pembrolizumab solution.

7.3. Management of Study Drugs

Lenvatinib will be supplied by Eisai to National Cancer Center Hospital East. Pembrolizuamb will be supplied by MSD to National Cancer Center Hospital East.
The Study Drug Manager of each study site will appropriately control the study drugs in accordance with the procedures for study drug management provided by the coordinating committee.

The investigator (subinvestigator) will prescribe the study drugs at doses specified in the protocol, and intravenously or orally administer to subjects. The study drugs must not be administered by other methods than those specified in the protocol.

7.4. Expected AEs

Expected AEs associated with lenvatinib and pembrolizumab are defined as follows: Events, of which the onset or onset trend such as the number of cases, frequency and onset conditions are not expected from the investigator’s brochure of the investigational drug using the latest investigator’s brochure as a reference, are defined as “unknown,” and those which are expected are defined as “known.” However, new events reported to the study sites can be handled as “known” even if they are not listed on the investigator’s brochure.

8. ENDOPOINTS, LABORATORY TESTS AND EVALUATION SCHEDULE

8.1. **Observations and tests**

Each endpoint in this study is presented below. All data required by the protocol should be recorded.

Table 8.1 Observations and tests

Treatment compliance	Doses of lenvatinib and pembrolizumab, date of fist dose, date of last dose or date of discontinuation (treatment interruption), presence/absence of dose change and its reason, and presence/absence of treatment interruption, its frequency and its reason
Patient background characteristics	Sex, age, past history, complications, histology (pap, tub1, tub2, por1, por2, sig, muc or other), HER2, EBV, PD-L1, presence or absence of the primary lesion, lesion site (primary site, target lesion, nontarget lesion) and presence or absence of previous treatment and its details
Physical examination	Body height and weight
Vital signs	Body temperature, pulse rate, systolic and diastolic blood pressure
General condition	PS(ECOG)
AEs	Presence/absence and severity of AEs will be evaluated in accordance with the CTCAE v 4.0.
Concomitant medications/therapies	Name of drug, route of administration, start date of treatment, end date of treatment and reason for concomitant use
Hematology	Red blood cell count, Hb, hematocrit, White blood cell count , neutrophil count, and platelet count
Biochemistry	AST(GOT), ALT(GPT), ALP, LDH, albumin, total bilirubin, BUN, creatinine, CK, electrolytes (Na，K，Cl，Ca), Amy, UA, blood glucose, CRP
Blood coagulation test	PT, INR, APTT
Thyroid function	Thyroid stimulating hormone, free triiodothyronine (fT3), and free thyroxine (fT4)
Tumor markers	CEA, CA19-9
Urinalysis	Urine protein, urinary sugar and urinary occult blood
Pregnancy test	If pregnancy is suspected by urinalysis, a serum test It will be performed in premenopausal women or women who had the last menstruation no more than one year
ECG	12-lead resting ECG
Infection	HIV antibody, HBs antigen, HBc antibody, HBs antibody ,HCV antibody, HBV-DNA

Tumor assessment	Chest and abdomen/pelvic contrast CT* or abdomen/pelvic contrast MRI*, as necessary, chest radiography, brain CT and brain MRI * For patients who are allergic or have hypersensitivity to contrast media to be used for CT and MRI, the tests may be performed without using the contrast media. When the treatment is discontinued because of reasons other than the progression of the primary disease based on imaging, the assessment should be made until progression is confirmed.
Investigation of outcome	Presence or absence of subsequent treatment, if subsequent treatment is given, a treatment method and start date Date of death or the last day of survival confirmed, and if died, the cause of death

8.2. Observation and schedule

The observation and testing schedule is presented in Table 8.2. When the principal investigator (or subinvestigator) deems it necessary to perform additional tests or observations, they will be performed in addition to the schedule presented in Table 8.2.

Table 8.2. Schedule

	At enrollment	During protocol treatment					Day of discontinuation[e)]	days after the last dose[f)]	After the follow-up period
		Cycle1			Cycle2 onwards				
Day Permissible range	-14～	1	8	15	1	15[d)]	0～＋7	-3～±7	
Visit	○	○	○	○	○	○	○	○	○
Informed Consent	○								
Treatment									
Lenvatinib Treatment		○	→	→	○	→			
Pembrolizumab treatment		○			○				
Patient background characteristics	○								

Body measurements	Height	○								
	Weight	○	○[c)]			○		○	○	
Vital signs ECOG PS		○	○	○	○	○	○	○	○	
Clinical findings (including AEs) Concomitant medications/concomitant therapie		○	○	→	→	→	→	→	→	
Laboratory tests										
Blood tests (blood count, biochemistry)		○	○[c)]	○	○	○	○	○	○	
Urine analysis		○	○[c)]	○	○	○	○	○	○	
Thyroid function		○	○[c)]			○				
Blood Coagulation test		○	○[c)]			○				
Pregnancy test[a)]		○								
Tumor markers		○	○[c)]			○		○		
12-lead ECG		○						○	○	
Infection test		○[b)]								
Tumor evalustion										
Chest/abdominal/pelvic CT (MRI) and other evaluations[g)]		○	Conducted at every 6 weeks after the start of treatment						△	
Follow-up										
Outcome investigation										○

○: Essential item, △:Performed as needed

a) Limited to women capable of childbearing. Refer to section 8.4.3

b) Tests conducted within 6 months of enrollment can be alternatively used.

c) Pre-enrollment tests (7 days before drug administration) can be used as tests conducted on day 1 (pretreatment).

d) From 3 cycle onwards, the implementation of day 15 is unnecessary unless the investigator condiers clinically necessary.

e) The day of termination is defined as the day when the principal investigator (or subinvestigator) decides to terminate the subject's administration of the investigational drug. When observations and tests cannot be conducted because of the subject's condition, they should be conducted as soon as possible.

f) Follow-up tests for safety are conducted 30 days after the last dose of the investigational drug. When observations and tests cannot be conducted because of the subject's condition, they should be conducted as soon as possible. When a new anticancer drug is initiated within 30 days of the last dose of the investigational drug, the follow-up tests for safety are to be conducted before initiating the new anticancer treatment. If the subject cannot come to hospital before the start of the new anticancer treatment, information will be collected by telephone regarding any new safety issues arising after tests upon completion of the last dose and before initiation of treatment with the new anticancer treatment.

Furthermore, when the follow-up tests of safety are conducted <2 weeks after the tests conducted at the time of the last dose of the investigational drug, the tests conducted at the time of the last dose of the investigational drug and the follow-up tests of safety can be conducted simultaneously.

g) Refer to section 8.6.

In screening, the results within 21 days before the trial registration are allowed to be used.

8.3. Examination findings

8.3.1. Patients Background

・Clinical diagnosis

Primary and metastatic lesion sites, etc.

・Clinical staging

Staging is determined in accordance with "UICC-TNM 7th Edition," and tumors will be classified according to the main histological type in each primary onset organ.

・The following details will be collected regarding the time of the initial histological diagnosis

(month and year), histological diagnosis, and the presence or absence of pretreatment.

・ Presence or absence of surgery, indicated site, surgical procedure, date of surgery and results (e.g., R0)

・ Presence or absence of adjuvant chemotherapy, treatment details, implementation period, and reason for termination

・Presence or absence of chemotherapy, treatment details, implementation period, and reason for termination

・Presence or absence of chemotherapy, site, implementation period, and radiation dose

・Presence or absence of other treatments, treatment details, and the implementation period

8.3.2. Height and weight measurements and vital signs

The subject's vital signs (i.e., blood pressure, heart rate, and body temperature) as well as body weight will be measured. Vital signs are to be measured at each examination with the subject in the same position each time.

8.3.3. ECOG Performance Status

The ECOG PS will be measured (refer to appendix 1).

8.3.4. Adverse events (subjective and objective symptoms)/combination therapy

During the period from the start of treatment until 30 days after completion of the treatment protocol, adverse events (subjective and objective symptoms) are to be monitored and recorded. Refer to section 11 on the reporting of adverse events for details regarding the handling of adverse events.

8.4. Laboratory tests

8.4.1. Blood tests/biochemical tests/blood coagulation tests/urine analysis/thyroid function tests

Blood tests/biochemical tests/blood coagulation tests/urine analysis/thyroid function tests

The items listed in Table 9 will be tested in accordance with the time indicated in the schedule presented in Table 10, and when deemed clinically necessary. If needed, the evaluation of clinically significant laboratory tests will be repeated until the test values return to baseline values, until clinically stable, or until a different treatment is initiated.

8.4.2. Tumor markers

The test items listed in Table 8.1 are to be measured in accordance with the time indicated

in the schedule presented in Table 8.2.

8.4.3. Pregnancy tests

In the case of a female subject capable of childbearing, confirmation that the subject is not pregnant will be obtained by urine test <14 days before enrollment in the trial. If pregnancy is suspected in the urine test, the pregnancy will be determined by a blood test. Female subjects deemed incapable of childbearing include those who have experienced menopause (the absence of menstrual periods for >1 year), and those who have undergone tube ligation or hysterectomy, the details of which are to be noted in the source document of the subject.

8.4.4. Infection tests

Anti-HIV antibodies, HBsAg, anti-HCV, HBs and HBc antibodies are to be measured before enrollment. Furthermore, in the event that results are available for tests conducted <12 months before enrollment, these results may be used instead.
HBV-DNA quantification is measured only when either HBs or HBc antibody is possible.

8.4.5. Twelve-lead ECG at rest

For the 12-lead ECG, data recording will be initiated after confirming that the subject is resting in the dorsal position. A physician suited to the ECG evaluation will evaluate the QT interval, as well as qualitative abnormalities in the ST segment form, the T-wave form, and the presence or absence of a U-wave.

8.5. Biomarkers

Biomarkers of tumor tissues of biopsies or past surgical specimens of patinets agreed with “elucidation of immune status and clinical significance in patients with solid tumor including gastrointestinal cancer (Research Project Number: 2015-048)” consider. Details are described in the plan of the accompanying research.

8.6. Tumor evaluation

For all patients, tumor evaluations will be conducted using the irRECIST and RECIST guidelines version 1.1. Tumor evaluations of the chest, abdomen, and pelvis (when deemed clinically necessary) will be conducted at each time point listed below until an exacerbation is confirmed. Thoracoabdominal and pelvic contrast-enhanced CT or MRI will be performed (if the subject is allergic to the contrast medium, plain scans are permitted).

- Less than 21 days before enrollment in this trial

Evaluations will be performed in weeks 6, 12, 18, and 24 after the beginning of treatment (followed by every 9 weeks until week 42, then every 12 weeks thereafter).

- When treatment is terminated for reasons other than an exacerbation of the underlying disease on imaging, an evaluation will be performed within 2 weeks of dosing completion. Furthermore, tumor evaluations are to be conducted in accordance with the schedule until an exacerbation of the underlying disease is confirmed, or until commencement of a new anticancer treatment.

The principal investigator and radiologist will conduct tumor evaluations in accordance with the irRECIST and RECIST guidelines version 1.1 (refer to appendices 2 and 3). The decision to continue the investigational drugs will be determined on the basis of these evaluations, including the effects on target and nontarget lesions and the appearance of new lesions. When disease progression is first observed on imaging in clinically stable patients according to irRECIST, participating medical institutions will conduct repeat scans 4 weeks after the initial identification of disease progression via an image evaluation to determine disease progression. Administration of the investigational drug can continue until the repeat scan is conducted (refer to Table 8.6). The criteria for clinical stability are listed below.

- Absence of clinical signs and symptoms indicating disease progression.
- No worsening of ECOG PS.
- No sudden disease progression observed
- Absence of tumor enlargement in the main anatomical site requiring new emergency medical intervention (e.g., spinal cord compression).

Furthermore, in the present trial, a maximum of 5 lesions can be included as target lesions, with a maximum of two lesions per organ.

Table 8.6: Imaging and investigational drug dosing after disease progression is first observed on imaging

	Clinically stable		Clinically unstable	
	Imaging	Investigational drug dosing	Imaging	Investigational drug dosing
Disease progression is first determined	To confirm disease progression, repeat the test after 4	Investigational drug dosing can be continued at the	If possible, repeat the test after 4 weeks to confirm	Interruption of dosing

by imaging	weeks	discretion of the attending physician until disease progression is confirmed by retesting at the participating medical institution	disease progression	
Disease progression is determined by repeat imaging	Additional imaging is not necessary	Terminate dosing of the investigational drug (exceptions can be permitted upon deliberation with the trial coordinating committee)	Additional imaging is not necessary	Not applicable
SD, PR, or SD is determined by repeat imaging	Continue the prescribed routine imaging every 6 weeks	Continue the investigational drug at the discretion of the attending physician	Continue the prescribed routine imaging every 6 weeks	When the subject's condition improves, or when the subject is clinically stable, dosing of the investigational drug can resume at the discretion of the attending physician

8.7. Follow-up

Outcome investigations will be performed after termination of the treatment protocol until the subject dies, or up to 2 year after the day that the last subject enrolled in the present trial. Even when direct follow-up is not possible (e.g., because of hospital transfer), the

hospital where the subject was transferred will be contacted to verify the outcomes as far as possible. The results of such contact are to be noted in the subject's source documents.

9. DATA COLLECTION

9.1. Handling and Retention of CRF Data

Data will be managed, and CRF data will be managed and retained by the Data Management Office, Clinical Research Support Unit, and National Cancer Center Hospital East. A data management plan will be prepared. In the plan, access restriction such as inputting in and browsing the database will be set, and records will be properly controlled and kept.

9.2. Identification of Source Documents

Source documents in this study will be as follows:

Medical records
Informed consent form
Investigational drug management table
Laboratory test data
Diagnostic imaging films, etc.

10. REPORTING OF ADVERSE EVENTS

10.1. Evaluation of AEs

10.1.1. Definition of AE

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease occurred in a patient administered the investigational drug, whether or not considered related to the investigational drug.

When ≥ Grade 1 subjective symptom or objective finding has been observed since before treatment initiation (at baseline evaluation), it will be handled as an AE only when the grade of the concerned AE worsened from the baseline value.

10.1.2. Method for Recording AEs

When grading an AE, the closest definition should be selected among the definitions of Grades 0 to 5.

When a sign (including an abnormal laboratory value) or symptom is included in a diagnosis, the diagnostic term based on the CTCAE should be entered in the CRF to the extent possible instead of individual signs or symptoms.

Abnormalities of laboratory values or vital sign alone should be reported as AEs only when the investigator determined that they fall into any of the following cases:

(1) Where a clinical sign or symptom is induced;
(2) Where it is judged to be clinically important;
(3) Where requiring treatment;
(4) Where requiring an additional test (excluding a retest only); or
(5) Where requiring treatment discontinuation or dose reduction for the investigational drug.

10.1.3. Items to Be Recorded for AEs

For AEs occurred, the following information should be reported in the CRF:

(1) AE term;
(2) Severity (CTCAE Grade 0 to 5 and serious/non-serious);
(3) Causal relationship with the each drug;
(4) Date of onset, date of outcome and outcome; and
(5) Presence or absence of therapeutic action.

10.1.4. Assessment of the Causal Relationship

The causal relationship with the each investigational drug should be assessed on the following two categories:

“Definite,” “probable,” “p

Possible” or “unassessable” → “The causal relationship cannot be ruled out.”

“Unlikely” or “not related” → “The causal relationship can be ruled out.”

Table 10.1.4 Classification of causal relationship

Classification	Definition
Definite (certain)	The causal relationship with the protocol treatment is plausible and cannot be explained based on the progression of the primary disease, complications, other drugs/treatments, etc.
Probable (likely)	The causal relationship with the protocol treatment is reasonable and is unlikely to be due to the progression of the primary disease, complications, other drugs/treatments, etc.
possible	The causal relationship with the protocol treatment is reasonable and can be explained based on the progression of the primary disease, complications, other drugs/treatments, etc.
unlikely	The causal relationship with the protocol treatment is improbable and can be explained based on the progression of the primary disease, complications, other drugs/treatments, etc.
not related (unrelated)	There is no causal relationship with the protocol treatment, and it can be clearly explained based on the progression of the primary disease, complications, other drugs/treatments, etc.
unassessable (conditional)	An AE on which data to be assessed are insufficient, for which more detailed data are necessary (conditional), or which is difficult to assess.

10.1.5. Follow-up of the Clinical Course at the Onset of AEs

When an AE occurred, the investigator should immediately take an appropriate therapeutic action.

A symptom (laboratory value) should be followed up until resolution or remission is confirmed even after the AE evaluation period is ended (see the Section 10.1.6). However, the follow-up of an AE may be terminated if falling into at least any one of the following cases:

* In the case of terminating the follow-up of an AE:

1) Where it is not an SAE, is assessed that the causal relationship can be ruled out, and occurred at least 30 days after the day of the last dose;

2) Where the principal investigator determined that the symptom is stable and is not of a medically significant concern;

3) Where subsequent treatment was implemented so that the causal relationship with the investigational drug is unassessable;

4) Where the clinical course cannot be followed up due to reasons such as transfer to another hospital;

5) Where the patient refused to be followed up; or

6) Where the patient died.

10.1.6. AE Evaluation Period

In this study, the AE evaluation period will be from the “the start day of the administration of the investigational drug” to “30 days after the day of the last dose of the investigational drug, or if subsequent treatment is initiated before that, before the start of the subsequent treatment, whichever comes earlier.” AEs occurring this period will be collected.

Even if it is 31 days after the last dose of the investigational drug, AEs assessed as related to the protocol treatment should be collected.

After PD is conformed, it is unnecessary to collet newly occurred AEs associated with the progression of the primary disease.

10.2. Reporting of Serious Adverse Events (SAEs)

10.2.1. Definition of SAE

Of the AEs specified in the Section “10.1 Evaluation of AEs” AEs falling into any of the following items are defined as “SAEs.”

(1) An event that results in death or is life-threatening;

(2) An event that results in persistent or significant disability/incapacity;

(3) An event that is a congenital anomaly/congenital defect; or

(4) An event that requires inpatient hospitalization or prolongation of existing hospitalization

However, excluding the following events:

- Hospitalization or death due to the primary disease after PD is confirmed;
- Hospitalization or prolongation of existing hospitalization for reducing a burden to a patient who visits the hospital from a remote place;
- Hospitalization or prolongation of existing hospitalization planned beforehand;
- Hospitalization or prolongation of existing hospitalization not related to AEs; or
- Hospitalization or prolongation of existing hospitalization for no more than 24 hours only for following up of the course.

(5) Medically important events are defined as those which possibly jeopardize the

patient or require a medical or surgical intervention to prevent the outcomes listed above.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, must be reported within 24 hours to the Sponsor and within 2 working days of but not longer than three 3 calendar days of receipt of the information to Merck Global Safety Providerz to meet certain local requirements. Therefore, these events are considered serious by Provider for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose

For the time period beginning when the consent form is signed until treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days of but not longer than three 3 calendar days of receipt of the information to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Provider product, must be reported within 24 hours to the Sponsor and within 2 working days of but not longer than three 3 calendar days of receipt of the information to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Provider product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +81-3-6272-0077

10.2.2. . Reporting Obligation of the Investigator and Reporting Procedures

1) Report to the head of the study site and the coordinating committee

① Initial report

When an SAE (see the Section “10.2”) occurred, the investigator should immediately take an appropriate action. The subinvestigators should promptly report it to the principal investigator.

The investigator should reported an SAE occurred in writing (e-mail* or fax) or orally (telephone) to the head of the study site and the coordinating committee within 24 hours after learning its onset. When the initial report is made without using the “SAE Report,” a report should be promptly made using the said form (e-mail or fax).

In addition, the details of the SAE should be reported in writing to the head of the study site and the coordinating committee within 2 business days after learning its onset.

* Reporting by e-mail is recommended.

② Additional report

The principal investigator should follow up the SAE (see the Section “10.2”). Additional information should be recorded in the “SAE Report” (additional report) and promptly sent to the head of the study site and the coordinating committee within 2 days after learning its onset.

Contact information of the coordinating committee: Clinical Study Coordinating Secretariat

E-mail: ctu_dc@east.ncc.go.jp

Tel: 04-7133-1111 (extension: 5200) Fax: 04-7134-6860

The investigator should provide further information upon request of the coordinating committee, the head of the study site, the institutional review board (IRB) and the investigational drug suppliers.

10.2.3. Reporting Obligation of the Coordinating Committee and Reporting Procedures

The coordinating committee should determine the seriousness, causal relationship, expectedness and the necessity for reporting to the regulatory authority (Pharmaceuticals and Medical Devices Agency (PMDA)) (pursuant to “Article 80-2, Paragraph 6 of the Pharmaceutical Affairs Law (PAL)” and “Article 273 of the Enforcement Regulations of the PAL”) for SAEs notified by initial and additional reports.

The details of reporting procedures should be as specified in the “Procedures for Handling

of Safety Information.”

1) Report to each principal investigator

The coordinating committee should promptly report the notified SAE with the details of the abovementioned determinations to each principal investigator. Each principal investigator should, as necessary, report them as soon as possible to the head of the study site in accordance with rules at each study site.

2) Report to the PMDA

When reporting to the PMDA is found necessary, the coordinating committee should handle the matter in accordance with Article 273 of the Enforcement Regulations of the PAL and relevant notifications.

3) Report to the efficacy and safety evaluation committee

When a review of an SAE by the efficacy and safety evaluation committee is judged to be necessary, the coordinating committee should report it in writing and seek its opinions on the appropriateness of the comments of the principal investigator and coordinating committee on the AE and handling (assessments of the seriousness, causal relationship and expectedness of the AE) of the AE.

4) Report to the investigational drug suppliers

The coordinating committee should promptly notify SAEs reported by the investigator to the investigational drug suppliers. In addition, the coordinating committee should, as necessary, provide information other than the “SAE Report” to the investigational drug suppliers upon their request.

10.2.4. Events of Clinical Interest

10.2.4.1. Definition of ECI

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

2. an overdose of Provider product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

10.2.4.2. Reporting of ECI

Selection non serious and serious adverse events are also kown as Events of Clinical Interest (ECI) and must be reported within 2 working days of but not longer than 3 calender days of receipt of imformation. But, if it shold be the serious adverse events, you don’t have any duty to report to the head of the institution.

For the time period beginning at treatment through 90 days following cessation of

treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Provider product, must be reported within 2 working days of but not longer than three 3 calendar days of receipt of the information.

10.2.5. Duties of the Efficacy and Safety Evaluation Committee

The efficacy and safety evaluation committee should examine the details of AE reports and advise, in writing, handling such as whether or not to continue the study and the necessity of protocol revisions to the coordinating committee. For their procedures, the separately stipulated “Procedures for the Efficacy and Safety Evaluation Committee” should be followed.

10.3. Collection of Safety Information

When safety information on the investigational drugs is received from the investigational drug suppliers, the coordinating committee should handle it in accordance with Article 273 of the Enforcement Regulations of the PAL and relevant notifications. The coordinating committee should report the safety information to each principal investigator. Each principal investigator should report it to the head of the study site as soon as possible in accordance with rules at each study site.

For the details of reporting procedures, the “Procedures for Handling of Safety Information” should be followed.

In addition, the necessity of revising the protocol and written information to patients as well as an explanation to the patients should be determined and implemented if needed.

10.4. Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy (subject or partner of a male subject) or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur from the time of treatment enrollment through 120 days following cessation of Pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious

events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Principal Investigator. Such events must be reported to Eisai coorpolation andwithin 2 working days of but not longer than three 3 calendar days of receipt of the information to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +81-3-6272-0077)

11. ASSESSMENT OF RESPONSE AND DEFINITIONS OF THE ENDPOINTS

11.1. Assessment of Respons

Assessments of tumor response should be made in accordance with the RECIST guideline Ver 1.1 (Appendices 2).

Chest and abdomen and pelvic contrast CT or MRI (Simple CT or MRI is acceptable if the patients are allergic to contrast media.) should be performed in accordance with Table 8.b to make the assessments based on image measurements.

11.2. Definitions of the Endpoints

11.2.1. Objective response rate:ORR

The ORR will be defined as the proportion of patients who achieved CR or PR for best overall response (confirmation required) according to irRECIST and RECIST v1.1.

11.2.2. Progression free survival：PFS

The period will be from the day of enrollment, as the starting date of the computation, to the day when progression is determined or the day of death of any cause, whichever comes earlier.

- “Progression” will be PD based on diagnostic imaging according to overall response by RECIST v1.1. The day of the imaging test will be defined as the day of progression. When the treatement are discontinued due to clinical PD and digagnositic imaging can not be performed, the day of clinical PD will be defined as the day of progression.
- Surviving patients, who are not assessed as progression will be censored on the last day when no progression is confirmed on imaging (last day of PFS confirmed) (If information on progression or progression-free is obtained from medical institutions to which the patients are transferred or referred, a statement on medical information provision documenting the rationales for a diagnosis should be received and retained. Notification only by telephone will not be acceptable.).
- For patients who died without being assessed as progression, whether to consider to be an “event on the day of death” or “censoring on the last day of PFS confirmed” should be decided at the time of data review performed prior to data fixation. In principle, they should be “an “event on the day of death” unless the period from the last day of PFS confirmed to the day of death is long.
- When another treatment is given as subsequent treatment in withdrawals due to AEs or refusal, they should be censored on the start day of the subsequent treatment.
- The development of secondary cancer (asynchronous double cancer) should not be handled as an event or censoring but as PFS until other events are observed.

11.2.3. Disease control rate：DCR

The DCR will be defined as the proportion of patients who achieved CR or PR, or SD

for best overall response according to RECIST v1.1.

11.2.4. Overall survival：OS

The period will be from the day of enrollment, as the starting date of the computation, to the day of death of any cause.

Surviving patients should be censored on the last day of PFS confirmed (Confirmation of survival by telephone inquiry will be acceptable. However, the fact of confirming survival should be documented in medical records.).

Patients who are lost to follow up should be censored on the last day when their survival is confirmed before being lost to follow up.

11.2.5. Incidence of AEs

All treated patients will be defined as a denominator, and the frequency of the worst grade according to the CTCAE v4.0-JCOG during all cycles will be calculated for each AE associated with the below mentioned protocol treatment.

12. STATISTICAL MATTERS

The Statistical Analysis Plan is summarized below. The details are presented in the separately prepared “Statistical Analysis Plan.

12.1. Handling of the Patients

The handling of the patients will be decided in accordance with the criteria for patient handling. The criteria for patient handling will be developed based on a data review.

12.2. Definitions of Analysis Populations

Each analysis population is defined as follows:

Abbreviation	Analysis population	Definition
All Enrolled Patients (ITT)	Intention to treat	Analysis target group based on the principle of Intention to treat. A population of enrolled patients excluding those with overlapping or incorrect enrollment
SP	Safety Population	A population of all enrolled patients who received at least one dose of the protocol treatment
FAS	Full Analysis Set	A population of all enrolled patients who met the entry criteria and received protocol treatment

12.3. Data Handling

Data handling (e.g., conditions for including in the analysis populations) will be decided by the coordinating committee upon discussion with the principal investigator. The details of data handling will be presented in the Statistical Analysis Plan.

12.3.1. Handling of Missing Data and Outliers

In principle, no imputation of missing data or analysis for outliers will be carried out. However, in the case where it is found that there are missing data and outliers, which may significantly affect analysis results, before data fixation, actions for such will be described in the Statistical Analysis Plan.

12.3.2. Actions for Additional Analyses

Analyses performed after the finalization of the Statistical Analysis Plan will be positioned as additional analyses. The results of the additional analyses should be reported in a manner that they are analyses not planned beforehand or by preparing a separate report of the additional analysis results.

12.4. Positioning of Analyses and Analysis Methods

In this study, no future decision-making criteria or development policy will be clearly specified. However, if the study statistically shows that “the primary endpoint ORR in accordance with the RECIST ver.1.1 is higher than the threshold of 10%,” and furthermore, improvement in the efficacy and safety in the secondary endpoints is confirmed, the study treatment will be judged to be promising treatment.

In this trial, we perform the following three analyzes.

1) Intermediate analysis: After the ORR has become evaluatable for FAS (10 cases) required for intermediate analysis to determine the ineffectiveness in the first stage, the analysis to be performed

2) Main analysis: After reaching FAS (29 cases) necessary for the main analysis, analysis to be performed on the ORR

3) Final analysis: analysis performed after the main analysis and after the observation period (12 months after the last case registration date)

12.5. Efficacy Analyses

12.5.1. Analysis of the Primary Endpoint

The analysis set for the primary endpoint is the Full Analysis Set (FAS). The statistical criteria for main analysis will be based on the number of patients with the best overall response of Complete Response (CR) or Partial Response (PR) according to RECIST guideline version 1.1. In the first stage, if two or more objective response (CR or PR) was observed among 10 patients (no confirmation required), the study will proceed to the second stage. If objective response (CR or PR) was less than two, the study will not proceed to the second stage and we will consider discontinuation of this trial. on the basis of a precise method based on the binomial distribution

In the second stage 19 patients will be enrolled. If there are ≥ 6 patients with objective response (CR or PR), the main objective of this trial will be achieved. An accurate confidence interval based on a binomial distribution is used for calculating the proportion of

confidence intervals.

If subgroup analyses are conducted, therapeutic efficacy between subgroups should be summarized using appropriate statistical procedures such as the Fisher's exact probability test and logistic regression model.

12.5.2. Analysis secondary endpoint

Analyses of the secondary efficacy endpoints are specified as follows:

(1) PFS

A survival function will be estimated using the Kaplan-Meier method. The median PFS with the 95% CI and monthly survival rate with the 95% CI will be estimated.

If subgroup analyses are implemented, therapeutic efficacy between subgroups should be summarized using appropriate survival analysis procedures such as the log-rank test and Cox proportional hazard model.

(2) OS

The same analysis as that for PFS will be carried out.

(3) ORR by irRECIST and DCR

Based on the definitions set forth in the Section 11.2, the DCR and ORR will be calculated. Exact 95% CIs based on the binomial distribution will be composed. If subgroup analyses are conducted, therapeutic efficacy between subgroups should be summarized using appropriate statistical procedures such as the Fisher's exact probability test and logistic regression model.

12.6. Safety Analyses

The safety analysis will be performed on the SP. The summary of frequency of each AE will be reported as the incidence of AEs. If necessary, 95% CIs using accurate methods based on the binomial distribution and spaghetti plots summarizing changes over time in laboratory values, etc. will be reported.

12.7. Planned Sample Size

[First stage] 10 patients as the FAS

[Second stage] A total 29 patienst as the FAS

12.8. Rationales for Determination

See the Section 2.10.2 Planned Number of Enrollment.

12.9. Interim Analysis

Position the first stage of Simon's Optimal two-stage design as an intermediate analysis. Based on the matters specified below, interim analysis will be carried out in principle.

12.9.1. Object and Timing of Intermediate Analysis

Intermediate analysis will be carried out to judge whether to proceed to the second stage to exam futility stopping when 10 patienst are confirmed to be included in the FAS.

12.9.2. Method of Intermediate Analysis

The statistical criteria for main analysis will be based on the number of patients with the best overall response of Complete Response (CR) or Partial Response (PR) according to RECIST guideline version 1.1. In the first stage, if two or more objective response (CR or PR) was observed among 10 patients (no confirmation required), the study will proceed to the second stage. If objective response (CR or PR) was less than two, the study will not proceed to the second stage and we will consider discontinuation of this trial.

However, whether or not two or more objective response (CR or PR) would be observed among 10 patients (no confirmation required) may be grasped at the time of study monitoring. In such a case, enrollment should not be terminated, and the study should be continued. If it cannot be grasped at the time of study monitoring, enrollment should be stopped at the time when 10 patients in the FAS are confirmed, and the follow-up should be continued until whether or not two or more objective response (CR or PR) would be observed among 10 patients can be confirmed. If at least 6 patients with CR/PR are identified in the first stage, it means that the threshold for the ORR in the final analysis has been achieved. In such a case, however, there may be problems such as no mature data on AEs, PFS, OS, etc., can be obtained. Thus, in principle, enrollment will be continued until “29 patients in the FAS” are achieved. When the study is to be terminated early based on efficacy, its appropriateness should be discussed with the coordinating committee.

12.10. Final Analysis

In the final analysis, all the endpoints will be analyzed. After completing the final analysis, a report of statistical analysis results should be prepared in accordance with the Statistical Analysis Plan.

12.11. Special Notes

12.11.1. Other Exploratory Analysis

1) Demographic and other baseline characteristics

They will be summarized using appropriate descriptive statistical procedures.

2) Tabulation of treatment compliance data

Details of a summary of treatment course and tabulations of, for example, reasons for discontinuation will be specified in the Statistical Analysis Plan.

3) Sub group analysis

The sub group analysis of efficacy will be performed exploratory regarding the following items.

These analyses will not be performed ensuring sufficient detection power, and not be adjusted multiplicity. The analysis results of sub group should be interpreted as exploratory results.

- Sex (male/ female)
- Age (＜65 years of age, ≧65 years of age)
- PS (0/1)
- Gastrectomy (No/Yes)
- Primary site (Junction / the other)
- Histology (Intestinal type/Diffuse type)
- Number of metastatic site (1/ 2 or more)
- Peritoneal dissemination (absence/ presence)
- Liver metastatis (absence/presence)
- Number of pretreatment regimens (1/2/3 or more)
- PD-L1 (positive/negative)
- EBV (positive/negative)
- MMR (Proficient/Deficient)

4) Form items covered in the clinical study report

The following items will be covered in the clinical study report.

< Efficacy evaluation (Target: All patients enrolled and FAS)>

- 11.2 Demographic data
- 11.4.1.1 Objective response rate（ORR）
- 11.4.1.2 Objective response rate（ORR） by irRECIST
- 11.4.1.3 Disease control rate（DCR）
- 11.4.1.4 Progression free survival（PFS）
- 11.4.1.5 Overall survival（OS）

< Safety evaluation (Target: SP)>

- 12.2.1 Incidence of DLT; incidence of adverse events (Number of onset and incidence by the worst grade)

・ 12.4.2 Summary statistics and change of laboratory values

＜Forms that are cited but not included in the main text of the clinical study report＞

・ 14.3.2 List of deaths, other serious adverse events, and significant adverse events

・ 14.3.4 List of laboratory values by patient

13. ETHICAL MATTERS

13.1. Policies, Laws and Regulations with Which the Study Complies

This clinical study will be conducted in compliance with the protocol, Declaration of Helsinki (http://www.med.or.jp/wma/), Article 80-2 of the PAL, “Ministerial Ordinance on Good Clinical Practice (GCP)” (Ordinance No. 28 of the Ministry of Health and Welfare dated March 27, 1997) and its revisions, and related notifications.

13.2. Informed Consent

13.2.1. Explanation to the Patients

The investigator should give the written information to patients approved by the IRB to the patients and orally explain the following information in detail:

1) That the study involves research
2) The purpose of the study
3) The name, title and contact address of the principal investigator or subinvestigators
4) The method of the study (including the experimental aspect of the study and inclusion/exclusion criteria for the patients)
5) Expected clinical benefits and foreseeable risks or inconveniences
6) The availability of alternative therapies and their important potential benefits and risks
7) The expected duration of the patient’s participation in the study.
8) That the patient’s participation in the study is voluntary and that the patient may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.
9) That the monitor(s), the auditor(s), and the regulatory authority(ies) will be granted direct access to the patient’s source documents without violating the confidentiality of the patient, and that, by signing the informed consent form, the patient is authorizing such access.
10) If the results of the study are published, the patient’s identity will remain confidential.
11) The person(s) to contact for further information regarding the study and the rights of patients, and whom to contact in the event of study-related injury.
12) The compensation and/or treatment available to the patient in the event of study-related injury
13) The approximate number of patients involved in the study
14) That the patient will be informed in a timely manner if information becomes available that may be relevant to the patient’s willingness to continue participation in the study
15) The foreseeable circumstances and/or reasons under which the patient’s participation in the study may be terminated.
16) The anticipated expenses, if any, to the patient for participating in the study.
17) The anticipated payment, if any, to the patient for participating in the study.
18) The patient’s responsibilities

19) Type of the IRB investigating and reviewing the appropriateness of the study, matters to be investigated and reviewed by each IRB, and other study-related matters concerning the IRB.

20) That the patient may check the written procedures for the IRB set forth in the preceding item and should request if he or she wants to do so. In addition, if the written procedures for the IRB, etc. are disclosed on a website, the fact that the address of the website is provided. If not disclosed, the fact that they are publicly available for review.

21) That data may be secondarily used.

13.2.2. Informed Consent

The investigator should request the patients to participate in the study after giving an explanation on the study and sufficient amount of time to think to the patients, and confirming that they have understood well about the contents of the study. If the patients personally consent to take part in the study, each of the investigator who gave the explanation, the study collaborator who provided a supplementary explanation, and the patient who received the explanations and consented should record the dates of the explanations or consent and sign the informed consent form approved by the IRB. The investigator should retain the signed informed consent form in the medical records and hand a copy of the signed informed consent form to the patient.

In the case where information, which may affect the patients' willingness to continue participating in the study, is obtained, the investigator should promptly notify it to the patients who are in the study, verify his or her willingness to continue his or her participation in the study, and record such a fact in a document. In addition, when the principal investigator judges that a revision of the written information to patients is necessary based on the information or because of other reasons, it should be promptly revised, and approval of the IRB should be obtained. After approval of the IRB, an explanation should be provided again using the revised written information to patients, and written informed consent should be obtained again.

13.3. Protection of Personal Information and Patient Identification

Personal information and information concerning privacy such as medical data should be recognized as those requiring strict protection and careful handling under the spirit of respecting individuals' personality, and full management measures should be taken to protect privacy. The Act on the Protection of Personal Information (Law No. 57 dated May 30, 2003; last revision, Law No. 49 dated June 5, 2009) should be followed.

13.3.1. Purposes of Using Personal Information, Items to Be Used and Methods of

Use

1) Information that can identify individuals

Subjects identification number, registration number

2) Supervision of de-identification and correspondence table

When providing personal information outside clinical trial medical institution is implemented, we provide it after making it anonymous. The subject identification number and the case number are used as "information capable of identifying an individual" as the minimum necessary information for identifying the subject. Under the responsibility of the investigator of each clinical trial medical institution, the correspondence table between the information such as the name of the patient and the case number is managed appropriately according to the policy of clinical trial medical institution.

That is, the medical institution, such as the name of the subject, which can independently identify individuals without a correspondence table does not inform the outside.

3) Handling methods

The personal information of the patients should be collected through reporting to the data center by the investigator or study collaborators. In addition, personal information should not be exchanged by e-mail.

13.3.2. Secondary Use of Data

Data obtained from this study may be secondarily used (e.g., metaanalysis) in a manner that they are not link to information identifying individuals only if the coordinating committee and investigational drug suppliers approved.

13.3.3. Safety Management Responsibility System

When using personal information, safety management measures should be taken in accordance with rules at each study site to minimize the risk of information leakage. The data center should properly manage personal information in accordance with the guidelines for personal information handled by the National Cancer Center.

13.3.4. Handling of Disclosure of the Patients' Information

The person who handles a request for the disclosure of privacy information possessed by the study by the patients if any, will be in principle, the investigator at the study site where the patient is enrolled.

13.4. Approval of the Institutional Review Board (IRB)

13.4.1. Approval at the Start of the Study

When implementing this study, the principal investigator shall submit the protocol and documents specified by the GCP Ordinance such as the written information to patients to the head of the study site and receive approval of the IRB. As soon as approval of the IRB is granted, the principal investigator should send a copy of the written approval of the IRB and written information to patients (study site version) to the Clinical Study Coordinating Secretariat, and retain the original of the written approval of the IRB.

The contents of the protocol shall not be modified by the individual study sites. The protocol in common among all the study sites shall be used. When the IRB requested to modify the main text of the protocol, the principal investigator should discuss with the coordinating committee to consider its handling.

13.4.2. Approval of the IRB for the Appropriateness of Continuing the Study

The appropriateness of continuing the study shall be reviewed by the IRB once a year. If the IRB approved the continuation of the study, the principal investigator should send a copy of the written approval of the IRB to the Clinical Study Coordinating Secretariat, and retain the original of the written approval of the IRB.

13.5. Changes in the Contents of the Protocol

When revising the protocol, written information to patients and other relevant documents, it should be made in accordance with procedures for preparation of each document.

13.5.1. Categories of Changes in the Contents of the Protocol

In this study, changes in the contents of the protocol should be handles as follows:

1) Revision

   A revesion refers to a change in the contents of the protocol. Approval of the IRB will be required.In addition, when the coordinating investigator determines that approval of the efficacy and safety evaluation committee is needed, a review should be obtained.

2) Notification letter

   Notification letter will be issued when deficiency is finded in the protocol and determined that it is required to disseminate to study related persons. The coordinating investigator determines whether approval of the IRB is required or

not.

3) Q&A

Q&A about the interpretation in the contents of the protocol will be issued to disseminate it to study related persons.

13.5.2. Approval of the IRB at the Time of Protocol Revision

When the protocol is revised during the study, the revised documents shall be approved by the IRB.

13.6. Management of Conflict of Interest (COI)

The conflict of interest (COI) for persons involved in this study such as the principal investigator, subinvestigators and coordinating investigators will be properly managed in accordance with the rules at the study sites. In addition, the COI for the companies has been managed in accordance with the companies' office regulations and compliance programs.

The investigational drug suppliers will not involve in any essential part of the study such as the operation of the study and the interpretation of results.

13.7. Compensation

In the event of injuries attributable to the study in the patients, the study site should provide compensation in accordance with the "Procedures for compensation for injuries" even if the study site is not legally responsible.

The details of compensation in this study will be the provision of medical care, and no medical expense, medical benefit or compensation money will be paid. In principle, compensation will not prevent the execution of the patients' right to seek damages.

14. MONITORING AND AUDITS

14.1. Monitoring

Monitoring will be performed in accordance with the monitoring procedures, and central monitoring and monitoring by visiting the sites will be conducted.

The central monitoring will verify that the clinical study is properly implemented and the reliability of data is adequately kept based on documents such as the CRF collected or through other means (e.g., telephone, e-mail, fax and post).

Monitoring by visiting the sites will check that the clinical study is properly implemented and the reliability of data is adequately kept through direct access to source documents.

After the monitoring is performed, a monitoring report should be prepared and submitted to the coordinating committee, sponsor-investigator and the head of the study site.

14.2. Protocol Deviations and Violation

The investigator should record all acts of protocol deviations regardless of reasons. Of acts of deviations, for incompliance with the protocol for avoiding immediate hazards to the patients or other medically inevitable reasons, the principal investigator should report it in writing to the head of the study site and submit a copy of the written report sent to the head of the study site to the coordinating committee in accordance with the procedures specified at each study site.

Deviations will be classified into any of the following items after review by the coordinating committee:

1) Major deviation

"Major deviations" are defined as deviations from the provisions of the protocol that are clinically inappropriate and meet two or more of the following items:

(1) Affecting the evaluations of the endpoints in the study;

(2) Intentional or systematic

(3) Hazardous or markedly high degree of deviation

2) Deviation

Deviations excluding the item 1)

14.3. Audit

Auditors will carry out audits in accordance with the "Audit procedures" and "Audit plan" and check that the clinical study is properly implemented and the reliability of data

is adequately kept through direct access to source documents.

14.4. Direct Access

The study site should collaborate in monitoring, audits and inspections by the IRB and regulatory authority and, as necessary, provide all study-related records such as source documents for direct access.

15. SPECIAL NOTES

15.1. Retention of Records

15.1.1. Sponsor-investigator

Records shall be retained from the day of marketing approval to the day 5 years after the day of approval (when learning that records are not attached to the application form, the day three years after the day of notification of such). For the details, the “Procedures for retention of records” should be followed.

15.1.2. Study Sites

The head of the study site and the founder of the IRB should retain essential documents, records and other relevant materials to be kept in accordance with the GCP Ordinance until the belowmentioned days whichever comes later. However, when it is necessary to archive the said documents for a longer period of time than this, the archiving period and method should be discussed with the coordinating committee. When retaining the records, the head of the study site should designate a record archiving manager:

(1) Day of marketing approval for the investigational drug (When development discontinuation or the fact of not attaching study results to the approval application is notified, the day three years after the day when development discontinuation is decided or the fact of not attaching the study results to the application is notified)

(2) Day three years after the discontinuation or termination of the study

15.2. Completion of the Study

When the study is completed, the principal investigator should inform in writing such a fact to the head of the study site and report a summary of study results in writing.

15.3. Discontinuation at the Study Site

When finding that major or continuous incompliance with the GCP Ordinance or protocol by the study site interferes with the proper conduct of the study, the sponsor-investigator may prematurely terminate the study at the study site. In such a case, the sponsor-investigator should report the fact of terminating the study at the study site to the head of the study site. Also, the sponsor-investigator should report the regulatory authority in writing that the study has been discontinued.

The investigator should promptly notify such a fact to the patients, provide appropriate medical care and take other necessary measures.

15.4. Interruption of the Study and Discontinuation of the Entire Study

15.4.1. Interruption of the Study

When the onset of AEs is found to be beyond the acceptable range while the study is ongoing or when the principal investigator and coordinating committee judge that the study has to be interrupted because serious ADRs or new information on the investigational drugs markedly damage the patients' safety, the principal investigator should promptly notify in writing such a fact and the details of the reason for interruption to the head of the study site. The coordinating committee should inform the regulatory authority in writing that the study has been interrupted.

15.4.2. Discontinuation of the Entire Study

When the principal investigator and coordinating committee judge that the entire study has to be discontinued because serious ADRs or new information on the investigational drugs markedly damage the patients' safety, the principal investigator should promptly notify in writing such a fact and the reason for discontinuation to the head of the study site. The principal investigator should inform the regulatory authority in writing that the study has been discontinued.

The investigator should promptly notify the patients, provide appropriate medical care and take other necessary measures.

15.5. Associated research

In the present trial, accompanying research will be conducted to analyze biomarkers. A separate protocol will be created for accompanying research and implemented as clinical research. The results of the accompanying research will not be included in the general report.

16. STUDY ORGANIZATION

This is a multicenter, investigator-initiated clinical study so that the coordinating committee will be organized.

16.1. Study Implementation Structure

See Sttachment 1.

16.2. Funding Source of the Study

The present trial is conducted with Eisai and MSD in part of the investigational fund and/or free of investigationa drugs free of charge. Furthermore, the Clinical Research Support Division, National Cancer Center Hospital East is responsible for data management, monitoring, auditing, and the office for the trial coordinating committee, and will carry out system maintenance through the support project to ensure clinical research safety for unapproved drugs (the ‘Project to develop core clinical research hospitals, National Cancer Center Hospital East”; chair: Atsushi Otsu, National Cancer Center Hospital East).

17. ATTRIBUTION OF STUDY RESULTS AND PUBLICATION OF STUDY RESULTS

Study results will belong to the National Cancer Center. The presentation or publication of study results at academic conferences or in papers will be decided by the coordinating committee upon discussion with the principal investigators and other relevant persons at the time of presentation or publication.

18. REFERENCES

1. http://www.mhlw.go.jp/toukei/list/81-1.html
2. http://ganjoho.ncc.go.jp/professional/statistics/
3. GLOBOCAN http://globocan.iarc.fr/
4. NCCN guideline
5. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (TOGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376:687-697
6. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer.* 2011 Oct;47(15):2306-14.
7. S. H. Park, D. H. Lim, K. Park, et al. A multicenter randomized phase III trial comparing second-line chemotherapy (SLC) plus best supportive care (BSC) with BSC alone for pretreated advanced gastric cancer (AGC). *J Clin Oncol* 29: 2011 (suppl; abstr 4004)
8. Wilke H, et al.Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial: *Lancet Oncol*., 2014; 15: 1224-35.
9. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nature medicine.* 2004;10:909-915.
10. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. *Current opinion in immunology.* 2014;27:16-25.
11. Yoon-Koo Kang, et al. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial.
12. Wada J, Suzuki H, Fuchino R, et al. The contribution of vascular endothelial growth factor to the induction of regulatory T-cells in malignant effusions. *Anticancer research.* 2009;29:881-888.
13. Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer research.* 2010;70:6171-6180.
14. Manzoni M, Rovati B, Ronzoni M, et al. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology.* 2010;79:187-196.
15. Osada T, Chong G, Tansik R, et al. The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients. *Cancer immunology, immunotherapy: CII.* 2008;57:1115-1124.
16. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med.* 2015.212(2):139-48.
17. Pan PY, Wang GX, Yin B, et al. Reversion of immune tolerance in advanced malignancy: modulation of myeloid-derived suppressor cell development by blockade of stem-cell factor function. *Blood.*2008.111(1):219-28.
18. Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell.* 2014
19. Nakamichi S, Nokihara H, Yamamoto N, et al. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. *Cancer Chemother Pharmacol.*2015.76(6):1153-61.
20. Muro K, Chung HC, Shankaran V, et al: Pembrolizumab for patients with PD-L1-postive advanced gastric cancer (KEYNOTE-012):a multicentere, open-label, phase 1b trial. *Lancet oncol.* 2016.17(6):717-26.
21. Kato Y, Matsui J. Effects of Lenvatinib on Tumor-Associated Macrophages Enhance

Antitumor Activity of PD-1 Signal Inhibitors. JCA. 2015.
22. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity*. 2014;41:49-61.
23. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials 1989: Vol. 10, No. 1, pp. 1–10.
24. Shukui Qin, et al. Phase III Study of Apatinib in Metastatic Gastric Cancer: A Randomized, Double-blind, Placebo-controlled Trial. *JCO*. 2014. supl;abstr 4003.

Appendix 1) Performance Status (Eastern Cooperative Oncology Group (ECOG) Classification)

PS	Contents
0	Fully active. Being 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, e.g., 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.

Appendix 2) New Response Evaluation Criteria in Solid Tumors (Revised RECIST guideline) version 1.1

The following sections are excerpts from the “New Response Evaluation Criteria in Solid Tumors (Revised RECIST guideline) version 1.1 - Japanese Translation by the Japan Clinical Oncology Group (JCOG) -: Revised RECIST guideline (version 1.1).”

2-1. Baseline Evaluation

In accordance with the test schedule, tumor lesions will be identified by chest and abdomen/pelvic contrast CT or abdominal/pelvic contrast MRI prior to enrollment. Each lesion will be categorized “measurable” or “non-measurable.”

A tumor diameter will be measured by cross-sectional CT or MRI. No measurement by a method to reconstruct three-dimensional sagittal or coronal images will be used.

2-2. Definitions of measurable lesions

A lesion falling into any of the following definitions is measurable (measurable lesion):

3) A lesion other than malignant lymph nodes (non-nodal lesions) meeting any of the following definitions:

(1) When CT or MRI with a slice thickness of ≤ 5 mm is used, the longest diameter of the lesion must be ≥ 10 mm.

(2) When CT or MRI with a slice thickness of > 5 mm is used, the longest diameter of the lesion must be at least twice the slice thickness.

(3) Osteolytic bone metastasis with soft tissue components meeting the Item (1) or (2)

(4) Absence of other measurable non-cystic lesions and the presence of a cystic lesion meeting the Item (1) or (2)

4) A lymph node must be ≥ 15 mm in short axis when assessed by CT with a slice thickness of ≤ 5 mm.

(A lymph node with ≥ 10 mm to < 15 mm in short axis is a non-target lesion, and a lymph node with < 10 mm in short axis is not a lesion.)

5) When chest X-ray is used, the longest diameter of the lesion must be ≥ 20 mm, and the lesion must be surrounded by the lung parenchyma (not adjacent to the mediastinum or thoracic wall)

6) For clinical lesions (e.g., superficial skin lesions), the longest diameter must be ≥ 10 mm as documented by color photography including a ruler

All lesions other than those listed above are non-measurable (non-measurable lesions).

Attention should be paid that non-measurable lesions include the following lesions irrespective of imaging technique or lesion size:

Bone lesions (excluding osteolytic lesions with measurable soft tissue components)
Cystic lesions (excluding measurable lesions defined in the above Item 1)-(4))
Lesions previously locally treated with radiation therapy
Leptomeningeal disease
Ascites, pleural or pericardial effusion
Lymphangitic involvement of skin or lung
Abdominal masses/abdominal organomegaly that is palpable but not measurable by imaging techniques

3-3. Selection and Baseline Documentation of Target Lesions

In this study, of measurable lesions identified at enrollment, 10 lesions at a maximum or 5 lesions at a maximum per organ will be selected in the order of the largest diameter (longest axis for non-nodal lesions; and short axis for malignant lymph nodes) and defined as target lesions. When selecting lesions, representative of all involved organs should be included to the extent possible, and reproducible repeated measurements should be taken into consideration (Even if the diameter is large, a lesion difficult to measure should be avoided.). For the selected target lesions, the sites in the order from the head to the caudal end of the body, test method, date of test, longest axis for non-nodal lesions, short axis for malignant lymph nodes, and the sum of diameters of all the target lesions (hereinafter referred to as the sum of diameters) will be recorded in the case report form (CRF).

3-4. Baseline Documentation of Non-target Lesions

All lesions other than those selected as target lesions should be identified as non-target lesions, irrespective of measurability. Their sites, test method and date of test will be recorded in the CRF. Multiple non-target lesions involving the same organ may be documented as a single lesion (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).

3-5. Assessment of Tumor Response

The target and non-target lesions will be assessed using the same test method as that used

at the time of enrollment. The diameters of the target lesions, and whether the non-target lesions disappeared or progressed will be recorded in the CRF.

3-6. Response Criteria for Target Lesions

Complete Response (CR)

Disappearance of all non-nodal target lesions. All nodal target lesions must have reduction in short axis to < 10 mm. If nodal target lesions are selected at baseline, even if the sum of diameters is not 0 mm, the target lesions may be assessed as CR.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD):

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not all Evaluated

No test can be performed for some reason, or lesions cannot be assessed as any of CR, PR, PD or SD.

Percent reduction in the sum of diameters = (Pre-treatment sum of diameters - sum of diameters at assessment) /(Pre-treatment sum of diameters) × 100%

Percent increase in the sum of diameters = (Sum of diameters at assessment – smallest sum of diameters) /(Smallest sum of diameters) × 100%

* All target lesions should have their actual measurements recorded whenever they are measurable (e.g., even when < 5 mm). However, if target lesions are reported as “too small to measure,” irrespective of CT slice thickness, the diameter will be recorded as 0 mm if the lesion has likely disappeared, or as 5 mm if the lesion is faintly seen but too small to measure.
* When the percent reduction meets the criteria for PR, and the percent increase meets the criteria for PD at the same time, PD should be determined.
* For lesions that split during treatment, the fragmented portions should be added together to calculate the sum of diameters.

* If multiple lesions have coalesced during treatment and they are no longer separable, the diameter of the coalesced lesion should be added to calculate the sum of diameters. If lesions coalesce, and a plane between them may be maintained, the diameter of each individual lesion should be added to calculate the sum of diameters.

3-7. Response Criteria for Non-target Lesions

Complete Response (CR):

Disappearance of all non-target lesions and all lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/non-PD

Persistence of one or more non-target lesion(s) (including persistence of non-target lymph nodes measuring ≥ 10 mm in short axis)

Progressive Disease (PD)

“Unequivocal progression” of existing non-target lesions (including recurrence).

When the patient also has measurable disease: In this setting, to achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the response of target lesions is SD or PR, an increase in the tumor burden of a non-target lesion much higher than a decrease in the tumor burden is considered to be “unequivocal progression.” If not, it is assessed as Non-CR/non-PD.

When the patient has only non-measurable disease: As an idea, “unequivocal progression” is an increase in a non-target lesion that is determined to clearly exceed the tumor burden representing a 20% increase in the diameter and an additional 73% increase in volume.

Not all Evaluated

No test can be performed for some reason or when lesions cannot be assessed as any of CR, Non-CR/non-PD or PD.

3-8. Presence or absence of new lesions

When a lesion, which was not present at baseline, is identified after the start of treatment, it should be considered to be the appearance of a “new lesion.”

The finding of a “new lesion” should be unequivocal: Not attributable to any difference from baseline in scanning technique, change in imaging modality or findings thought to represent something other than tumor. For example, necrosis of a liver metastatic lesion appeared as a new cystic lesion should not be handled as a new lesion. A lesion identified on a follow-

up examination in an anatomical location that was not required to be scanned at baseline (pre-enrollment evaluation) is handled as a new lesion.

If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently "disappeared" single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually "disappear" but are not visualized because they are beyond the resolving power of the imaging modality employed.

If a lesion may be new but equivocal, the lesion should not be recorded as a new lesion, but imaging examination should be repeated after a clinically appropriate interval. If a repeat imaging test confirms that it is a new lesion, then a new lesion should be declared using the date of the imaging test when it is confirmed to be a new lesion.

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD for overall response based on a new lesion (a positive FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image). No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT of MRI, and if the positive FDG-PET confirms a lesion not identified on CT or MRI at baseline, this is a new lesion.

3-9. Overall Response

Overall response will be assessed based on a combination of the response of target lesions, response of non-target lesions and the appearance of a new lesion in accordance with Table 9.a. below. If no non-target lesion is present at baseline, overall response will be assessed based on the target lesions and the appearance of a new lesion. If no target lesion is present at baseline, overall response will be assessed based on the non-target lesions and the appearance of a new lesion in accordance with Table 9.b.

Table 9a Overall response at each time point: Patients with target lesions

Target lesions	Non-target lesions	New lesions	Overall

			response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 9b Overall response at each time point: Patients with non-target lesions only

Non-target lesions	New lesions	Overall response
CR	No	PR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

3-10. Best Overall Response

Overall response will be considered “good” in the order of CR > PR > SD > PD > NE. Best overall response will be assessed based on the overall response during the entire study period in accordance with the criteria specified below. When corresponding to the definitions of multiple categories, a better category should be chosen in the order of CR > PR > SD > PD > NE.

Complete Response (CR):

The CR status for overall response is maintained in at least two consecutive tests performed at intervals of 4 weeks (28 days) or more. The day of confirming CR for overall response in the second test is considered to be the “day of confirming CR.”

Partial Response (PR):The PR or higher status for overall response (CR or PR) is maintained in at least two consecutive tests performed at intervals of 4 weeks (28 days) or more. The day of confirming the PR or higher status for overall response in the second test and PR is confirmed for best overall response is considered to be the “day of confirming PR.”

Stable Disease (SD):

No CR or PR is achieved for best overall response, but PD is not assessed for overall response before 6 weeks after the start of treatment, and SD or higher is assessed in at least one test for overall response.

Progressive Disease (PD):

No CR, PR or SD is assessed for best overall response and but is confirmed to be PD for overall response.

Not Evaluable (NE):

All overall responses were NE.

Table 9c Best overall response

First overall response	Second overall response	Third overall response	Best overall response
Either PR or CR	SD	PD	SD
Either PR or CR	SD	NE	SD
Either PR or CR	PD	-	PD
Either PR or CR	NE	NE	NE
Either PR or CR	NE	SD	SD
SD	PD	-	PD
SD	SD	PD	SD
SD	NE	PD	PD
NE	NE	PD	PD
NE	NE	NE	NE
NE	NE	PD	PD