Title: Regorafenib and Nivolumab Simultaneous Combination Therapy (REGONIVO)

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Regorafenib and Nivolumab Simultaneous Combination Therapy for Advanced and Metastatic Solid Tumors: Phase I Clinical Trial

Investigator-initiated trial protocol

Protocol Number: EPOC-1603

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1. Summary

Phase	Phase I
Subjects	Patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy
Objectives	**Primary objective** To examine the safety and tolerability of repeated dosing of regorafenib and nivolumab in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy, and to investigate the maximum tolerated dose (MTD) and recommended dose (RD) of the drug when used in combination therapy. Dose-escalation cohort The safety of regorafenib and nivolumab combination therapy will be evaluated in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy in order to determine the MTD and RD of regorafenib according to dose-limiting toxicity (DLT) when used in combination therapy. Expansion cohort An exploratory evaluation of the efficacy and safety of the combined treatment using the RD found in the dose-escalation cohort will be performed. **Secondary objective** ・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 4.03. ・Efficacy - Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST) version. 1.1, and immune-related (ir) RECIST - Progression-free survival (PFS) - Overall survival (OS) - Disease control rate (DCR) **Exploratory items (performed as accompanying research in the present trial):** Tests of various biomarkers
Trial design	The present trial is a phase I clinical trial intended to evaluate the safety of regorafenib

	and nivolumab combination therapy in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy.
Trial study population	Inclusion criteria 1. Patients who provided written informed consent to be subjects in this trial 2. Patients at least 20 years of age on the day of providing consent 3. Dose-escalation cohort: Patients with histologically or cytologically confirmed advanced or metastatic solid tumors. Expansion cohort: Patients with histologically or cytologically confirmed advanced or metastatic solid tumors (gastric, colorectal, or hepatocellular cancer). 4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 5. Patients capable of taking oral medication 6. Patients with evaluable or measurable lesions as per RECIST version 1.1 7. Patients with adequate organ function at the time of enrollment as defined below: [Acceptable 7 days examination before the same day of the registration date] ・Neutrophil count ≥1500mm^3 ・Platelet count ≥10.0 × 10^4/mm^3 ・Hemoglobin (Hb) ≥ 9 g/dL, ・aspartate transaminase (AST), alanine transaminase (ALT) ≤100 U/L (≤100 U/L in patients with Hepatocelular carcinoma, ≤250 U/L in patients with liver metastasis) ・Total bilirubin ≤1.5mg /dLtimes the upper limit of normal ・Creatinine ≤1.5mg /dL ・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) UPC (Urine Protein Creatinine) ratio <3.5 (iii) 24-hour urine protein was measured, urinary protein ≦ 3500 mg ・PT-INR: ≤ 1.5 (≦ 3.0 in case of anticoagulant administration) * It is Child A in the case of Expansion cohort's hepatocellular carcinoma 8. For women who are likely to become pregnant (including those without menstruation due to medical reasons such as chemical menopause) Note 1, we agreed to double contraceptive Note 2 for at least 5 months after the final administration of the investigational product from consent acquisition patient. Also, patients who agreed not to breast feeding for at least 5 months after the final investigational drug administration after acquiring consent.

	For men, patients agreeing to double contraceptive for at least 7 months after the final investigational drug administration from the time of starting investigational drug administration. Note 1): A woman who is likely to become pregnant is a woman who has experienced menarche and is not undergoing sterilization surgery (such as hysterectomy, bilateral salpingo ligation or bilateral oophorectomy), a woman without menopause Everything is included. The definition after menopause shall be amenorrhea continuously for 12 months or more even though there is no noteworthy reason. Women who are using oral contraceptives or mechanical contraceptive methods (such as intrauterine contraceptive devices or barrier methods) are considered to be pregnant. Note 2): With regard to contraception, it is necessary to use two of the vasectomy or condom of a male patient or male male, the uterine tube ligation of a female patient or the other woman, a contraceptive pessary, an intrauterine contraceptive device or an oral contraceptive I need to agree to heavy contraception. Exclusion criteria 1. Patients who have undergone systemic chemotherapy, radiotherapy, surgery, hormone therapy, or immunotherapy <2 weeks before enrollment. Immune checkpoint blockade as pretreatment is permitted. 2. Patients with a history of taking regorafenib. 3. 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 4. 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 5. Patients with a large amount of pleural effusion or ascites requiring drainage. 6. Patients with a ≥grade 3 active infection according to NCI-CTCAE version 4.03 7. Patients with symptomatic brain metastasis 8. Patients with partial or complete gastrointestinal obstruction 9. Patients with interstitial lung disease with symptoms or signs of activity 10. Patients who test positive for either anti-HIV-1 antibodies, anti-HIV-2 antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies* *Patients who test positive for either anti-HBs or anti-HBc antibodies, and those who have HBV-DNA measurements greater than the detection sensitivity will

	also be excluded. (However, patients with hepatocellular carcinoma in the expansion cohort will not be excluded even if they test positive for HBsAg and anti-HCV antibodies.) 11. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease 12. 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 in the present study 13. Patients with a history or findings of ≥grade III congestive heart failure according to the New York Heart Association functional classification 14. Patients with a seizure disorder who require pharmacotherapy 15. Patients who had grade 3 or higher bleeding during 4 weeks before enrollment. 16. Patients undergoing major surgery (thoracotomy or laparotomy, etc.), laparotomy biopsy, trauma within 28 days before registration. The same day of the week before 4 weeks can be registered (However, in case of an artificial anastomosis without intestinal resection, it shall be within 14 days before registration). 17. Non-healing wound, non-healing ulcer, or non-healing bone fracture. 18. Patients with a history of hypersensitivity to any of the study drugs, similar drugs, or excipients. 19. Pregnant women, lactating women or possibly pregnant women
Trial participation period	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.
Sample size	Dose-escalation cohort: A total of 3–6 patients per level, for a total of 9–18 patients Expansion cohort: Approximately 30 patients in total
Administration method	Dose-escalation cohort One course will last 28 days*, and tolerability will be verified for the following dosages. <u>Level 1</u> Regorafenib: Oral administration at a dose of <u>80 mg</u>/day for 21 consecutive days, with

	a 1-week washout period. Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg. When it is deemed that there are no safety issues associated with the above dosages, tolerability will be verified for the following level-2 dosages. Level 2 Regorafenib: Oral administration at a dose of 120 mg/day for 21 consecutive days, with a 1-week washout period. Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg. Level 3 Regorafenib: Oral administration at a dose of 160 mg/day for 21 consecutive days, with a 1-week washout period. Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg. When tolerability has been confirmed for the level-3 dosages, the above dosages will be the recommended dosages. The administered dose will increase using a 3 + 3 design in accordance with the DLT. Three or more patients will be enrolled at each level. In the event that DLT is not observed during the initial course in the first three patients, these patients will move onto the next level. In the event that DLT is observed in one of the first three patients, an additional three patients will be added to the level in question. When all three additional patients have completed the first course without presenting with any DLT, these patients will move onto the next level. If DLT is observed in one of the three additional patients, an additional three patients will be added to the level below to determine the MTD. Expansion cohort: The trial will be conducted using the estimated RD found in the dose-escalation cohort.
Safety evaluation:	Evaluations will be performed using CTCAE version 4.03.
Efficacy evaluation:	The antitumor effect will be evaluated in accordance with irRECIST and RECIST version 1.1. The tumor evaluation will be performed as follows: ・Image evaluation: computed tomography (CT) or magnetic resonance imaging (MRI) ・Image evaluation schedule: evaluations will be performed at baseline as well as at 6, 12, 18, and 24 weeks (thereafter every 9 weeks until week 42 and subsequently every 12 weeks after week 42).

	PFS and OS will be evaluated in all subjects.
TR	TR: A separate protocol will be prepared and implemented as ancillary research
Observation and test items	Physical measurements, vital signs, PS, laboratory tests (i.e., blood and biochemistry), urine analysis, clinical laboratory findings, tumor markers, as well as chest, abdominal and pelvic CT or MRI, etc.
Trial design	The present trial will comprise a dose-escalation cohort to simultaneously examine clinically RDs and tolerability of nivolumab and regorafenib combination therapy in patients with solid tumors, and an expansion cohort to examine the safety and efficacy of the clinically RDs in patients with multiple advanced solid tumors. In the dose-escalation cohort, three patients with solid tumors will be administered nivolumab at a dose of 3.0 mg/kg once every 2 weeks, and regorafenib at a dose of 80 mg (level 1), 120 mg (level 2) or 160 mg (level 3) for 21 consecutive days, with a 1-week washout period. As a general rule, one cycle will last 28 days (day 1–29). The DLT evaluation period will be 28 days. Furthermore, for each level, three additional subjects will be added depending on the occurrence of DLT. In the expansion cohort, approximately 30 patients with solid tumors will be administered the clinically RD of regorafenib found in the dose evaluation cohort.
Scheduled trial period	Planned enrollment period: January 2018 to October 2018 (10 months)Planned follow-up period: Two years from the last day of patient enrollment Overall trial period (including the procedures for trial completion): 2 years and 6 months after the last day of patient enrollment When the administration of all subjects would be completed during the observation period, the observation period of this study will be also terminated at the end of the observation period of the last administered patient.
Number of institutions	One institution (an additional one or two institutions are planned for the expansion cohort)
Cordinating investigator representative	Kouhei Shitara, National Cancer Center Hospital East
Planned trial institution	National Cancer Center Hospital East (an additional one or two institutions are planned for the expansion cohort)

Contact:

Queries regarding clinical decisions, such as eligibility criteria and criteria for treatment changes: Principal investigator (refer to front page)

Queries regarding enrollment procedures and eCRF, etc.: Clinical Trial Support Division, National

Cancer Center Hospital East

(Attachment 1)

Queries regarding the adverse event report, etc.: Clinical Trial Support Division, National Cancer Center Hospital East

(Attachment 1)

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1. Objectives

To examine the safety and tolerability of repeated dosing of regorafenib and nivolumab in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy, and to determine the MTD and RD of the drugs when used in combination therapy.

Dose-escalation cohort (an additional one to two institutions are planned for the expansion cohort)
The safety of regorafenib and nivolumab combination therapy will be evaluated in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy to determine the RD of regorafenib when used in combination therapy.

Expansion cohort
An exploratory evaluation of the efficacy and safety of the combined treatment will be performed on the basis of the RD found in the dose-escalation cohort.

Primary endpoint:
The safety of combination regorafenib and nivolumab combination therapy will be evaluated in patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy to determine the MTD and RD of regorafenib on the basis of the DLT when used in combination therapy.

Secondary endpoints:
・Safety
- According to the "Common Terminology Criteria for Adverse Events (CTCAE) v4.03-JCOG) [CTCAE v4.03 / MedDRA v12.0]" (hereinafter referred to as CTCA v4.03), the incidences and types of adverse events that occur during treatment will be evaluated.

・Efficacy
- ORR（Objective Response rate） according to "New guideline for judgment of therapeutic effect of solid cancer (RECIST guideline) - Revised version 1.1 - Japanese translation JCOG version ver. 1.0 (hereinafter referred to as RECIST version 1.1) and immune - related RECIST (hereinafter, irRECIST).
- PFS（Progression Free survival）
- OS（Overall survival：OS）
- DCR（Disease Control rate）

Exploratory items

Tests of various biomarkers

Furthermore, for this exploratory research, a separate protocol will be prepared and implemented as accompanying research. Moreover, the results will not be included in the clinical study report.

2. Background

2.1 Patient epidemiology

The term “cancer” indicates a disease in which abnormal cells (cancer cells) divide uncontrollably. Cancer cells arise when the genes of normal cells become damaged. In Japan, cancer has been the leading cause of death for over 30 years[1]. In a survey conducted in 2013, approximately 365,000 people died due to cancer that year, and it was reported that 26% of all men (1 in 4 individuals), and 16% of all women (1 in 6 individuals) died of cancer[2]. Furthermore, the mortality rate of cancer patients increases with age and it is reported that from 60 years of age onwards, the rate of cancer-related death increases for both men and women[1].

Cancer can arise in any part of the body. In general, cancer nomenclature is derived from the classification according to the organ and tissue of origin. Cancers arising from epithelial cells and nonepithelial cells (e.g., interstitial cells) are called solid cancers (e.g., lung cancer, gastric cancer, colorectal cancer, and osteosarcoma), whereas those arising from the hematopoietic system are called hematological cancers (e.g., leukemia). In Japan, cancers that carry a high mortality rate (>30,000 individuals per year) include lung cancer (approximately 73,000 individuals), gastric cancer (approximately 49,000 individuals), colorectal cancer (approximately 48,000 individuals), pancreatic cancer (approximately 31,000 individuals), and liver cancer (approximately 30,000 individuals), with solid cancers accounting for the majority of cancer-related deaths[3]. Solid cancers can invade and spread from the primary tumor to other organs and tissue in the body. Solid cancers exhibiting invasion or metastasis are called advanced or metastatic solid cancer. The prognosis of patients with solid cancer generally varies according to the cancer stage (e.g., tumor size, invasion depth, and presence or absence of metastasis). In highly advanced or metastatic solid cancer, the prognosis is poor.

2.2 Treatment of patients

The ultimate goal of cancer treatment is to prolong the survival of the patient. There are three main treatments for solid cancer, which include “surgery (surgical treatment)” and “radiotherapy” for localized treatment, and “pharmacotherapy (anticancer chemotherapy and hormone therapy)” for systemic treatment. Localized treatment is used when the lesion is limited to the primary onset site, and if no recurrence is observed, recovery can be expected. By contrast, systemic treatment is used when cancers (e.g., advanced or metastatic solid cancers) invade or metastasize to other organs and tissues. This is because with advanced or metastatic solid cancers, it is difficult to remove all the lesions using localized treatment. The effect of pharmacotherapy for advanced or metastatic solid cancers differs depending on the cancer type. Thus, the standard treatment (treatment system) differs according to the type of cancer according to the results of several clinical trials. However, some types of advanced and metastatic solid cancers are rarely reported in clinical trials and have no

established standard treatment. Furthermore, with the exception of some cancers (e.g., testicular and ovarian cancer), it is difficult to achieve a cure for most advanced or metastatic solid cancers despite standard treatment. As a result, patients with advanced or metastatic solid cancer who do not recover with pharmacotherapy have no treatment option other than palliative care, which ultimately leads to death. Multiple clinical trials are therefore currently underway to test the efficacy of new anticancer agents for prolonging the survival of patients with advanced or metastatic solid cancer.

2.3 Immunotherapy for patients

In recent years, "immunotherapy" has been attracting attention as the fourth treatment method for advanced or metastatic solid cancer[4]. 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[5]. This is likely attributable to the tumor microenvironment inhibiting the antitumor immune response[5]. 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[6]. 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)[6]. 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. For other solid cancers (e.g., gastric cancer[8] and hepatic cell carcinoma[9]), clinical developments are underway and efficacy has been reported. However, the immunosuppressive mechanisms of cancer cells vary

greatly. 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[10].

2.4 Rationale behind treatment plan setting

2.4.1 Trial 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 is considered to increase as cancer progresses. In fact, nivolumab likely increases the activity of tumor-cell-specific T cells present locally at the tumor site by binding to PD-1 on the surface of activated T cells and removing the immunosuppressive signal of PD-L1/PD-1; however, in clinical trials of malignant melanoma patients receiving combination vaccine therapy, the post-treatment level of peripheral blood regulatory T cells was found to be increased in patients with progressive disease (PD) compared with patients with complete response (CR), partial response (PR), or stable disease (SD)[11]. Furthermore, in a case study using gastric cancer specimens administered anti-PD1 antibodies, it was similarly suggested that the proportion of localized regulatory T cells tended to be higher in patients with a poor response to treatment (data not published). This suggests that inhibiting the function of immunosuppressive cells could improve the efficacy of immune checkpoint inhibitors.

Angiogenic factors (vascular endothelial growth factor: VEGF) are considered to be involved in the production of regulatory T cells, MDSC, and tumor-associated macrophages. 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[12-15]. Similarly, it has been reported that sunitinib and sorafenib, which are multikinase inhibitors that block signals downstream of VEGFR, suppress regulatory T cells and MDSCs[16-18], and activate antigen-presenting cells[19]. In the studies conducted at our hospital, the analysis of biopsy tissue specimens before and after regorafenib administration has revealed that the ratio of regulatory T cells decreases from 27.2% to 13.6%, which suggests that regorafenib decreases the production of immunosuppressive cells as mentioned before. On the other hand, it has also been reported that the administration of selective RAF and MEK inhibitors increases T-cell invasion of tumors[20, 21]. RAS/RAF pathway inhibitors are thus expected to enhance the effect of immune checkpoint inhibitors.

According to the findings described above, the combined effect of multi-kinase inhibitors that exert both an antiangiogenic effect and RAF-inhibitory action together with immune checkpoint inhibitors is promising.

In renal cell carcinoma, trials are underway regarding the combined effect of immune checkpoint and antiangiogenic agents. In particular, a phase I trial of nivolumab in combination with pazopanib/sunitinib is underway. In this trial, a high response rate has been observed in the sunitinib combination therapy group (52%) and the pazopanib combination therapy group (45%)[23].

We therefore believe that by combining nivolumab and regorafenib, we can expect a greater activation of the antitumor immune response and antitumor effect compared with the therapeutic effect of a single agent, and we have planned the present trial accordingly.

2.5 Nivolumab

Nivolumab, manufactured by Ono Pharmaceutical Co., Ltd., and Medarex (currently Bristol-Myers Squibb Co. [BMS Co.]), is an anti-PD-1 human monoclonal antibody (programmed cell death-1 [otherwise known as CD279]). It is under clinical development by Ono Pharmaceutical and BMS, and has been approved for manufacture and sale in Japan, the US, and Europe for the treatment of malignant melanoma. PD-1 (CD279) is a 55-kDa type-1 transmembrane protein that belongs to the CD28 family of T-cell costimulatory receptors, including CD28, CTLA-4, ICOS, and BTLA of the immunoglobulin superfamily. PD-1 is highly expressed on activated T cells and B cells. Furthermore, PD-1 expression is also found in memory T-cell subsets, but the level of expression varies. Two PD-1-specific ligands have been identified: PD-L1 (B7-H1 or CD274) and PD-L2 (B7-DC or CD273). In mice and humans, T-cell activation is found to be negatively regulated when PD-L1 and PD-L2 bind to PD-1.

Nivolumab is expected to exert an antitumor action by inhibiting the binding of PD-L1 and PD-L2 to PD-1, thereby blocking the PD-1 signal to inhibit T-cell activation, consequently resulting in T-cell activation within the tumor microenvironment. Under the commercial name of "Opdivo®", nivolumab was approved on July 4, 2014 as a therapeutic agent for curatively unresectable malignant melanoma. Furthermore, on December 22, 2014, nivolumab was approved in the US as a therapeutic agent for unresectable or metastatic malignant melanoma.

2.5.1 Summary of nonclinical trials of nivolumab

Nivolumab is a human monoclonal antibody against human PD-1. It is produced by recombinant DNA technologies using Chinese hamster ovary cells. For the bulk drug substance, nivolumab is an aqueous solution in the form of a clear to opalescent, colorless to pale yellow liquid that may contain some fine particles. The preparation is provided as an aqueous injection with 100 mg of nivolumab contained per vial, and is stored in a dark environment at 2°–8°C.

Nivolumab binds specifically to PD-1, and shows a high binding affinity to human and monkey PD-1, which is demonstrated by K_D values of 3.06 nmol/L and 3.92 nmol/L, respectively. *In vitro*, nivolumab inhibits the binding of PD-1 to PD-1 ligands (PD-L1 and PD-L2), and in a human mixed lymphocyte reactions, it has increased both T-cell proliferative capacity and IFN-γ production.

Nivolumab was shown to increase the amount of IFN-γ produced in response to antigen stimulation in a dose-dependent manner in an assay in which human peripheral mononuclear cells obtained from donors with a history of cytomegalovirus (CMV) infection were restimulated using CMV antigens. Furthermore, in monkeys inoculated with HBsAg, SKMel, and dinitrophenyl-Ficoll, nivolumab increased the specific antibody titers for the SKMel cell line. Several syngeneic tumor-bearing mouse models have shown that the anti-murine PD-1 antibody 4H2 delays tumor growth, which confirmed the antitumor effect of anti-PD-1 antibodies that inhibit PD-1 from binding to PD-1 ligands. It is therefore thought that nivolumab exerts an antitumor effect by blocking PD-1 from binding to PD-1 ligands and increasing antigen-specific T-cell activity, thereby enhancing the anticancer immune response.

When nivolumab was administered in a single intravenous dose to conscious monkeys, no effect on general symptoms, body temperature, heart rate, blood pressure, and electrocardiography was observed up to a dose of 50 mg/kg. Moreover, in a 13-week repeat-dose toxicity study using monkeys, no effect was seen in the central nervous system, cardiovascular system, or respiratory system in observations of general health and internal medical tests.

When monkeys received a single intravenous injection of 1, 10, or 50 mg/kg of nivolumab, the area under the curve (AUC) for serum concentrations of nivolumab generally exhibited a dose-dependent increase.

The steady-state volume of the distribution was comparable to that of plasma volume, which indicated that nivolumab is primarily distributed in the circulating blood. The serum concentrations of nivolumab in anti-nivolumab antibody-positive patients were lower than those in anti-nivolumab antibody-negative patients. In a reproductive and developmental toxicity study using pregnant monkeys, nivolumab was found in the serum of newborn animals, which suggested that nivolumab may be transferred to fetuses via the maternal placenta.

In the study of intravenous single-dose toxicity using monkeys, no death or toxicity changes were seen at a maximum dose of 10 mg/kg. In the study of intravenous repeat-dose toxicity using monkeys, no nivolumab-associated toxicity changes were observed at the maximum dose of 50 mg/kg given once a week for 4 weeks or when administered twice a week for 13 weeks. The no-observed adverse effect level was thus deemed to be 50 mg/kg/dose. Furthermore, these studies also found no changes suggestive of localized irritation at the site of injection or surrounding area for a nivolumab concentration of up to 10 mg/mL.

In an extended study of prenatal and postnatal development using pregnant monkeys, ≥10 mg/kg of nivolumab resulted in an increase in the mortality rates of embryos, fetuses, and newborns during the third trimester; however, no effect on the teratogenicity, neonatal growth, behavior, or immune function was observed.

In a cross-reactivity study using normal tissues from monkeys and humans, the results revealed a

positive reaction to the cell membrane of lymphocytes in monkeys and humans reported to express PD-1. Furthermore, as an unintentional response, a positive reaction was observed in the cytoplasm of pituitary endocrine cells in monkeys and humans; however, nivolumab is an antibody preparation and does not traverse the cell membrane. This means that nivolumab is not considered to act directly on the cytoplasm of pituitary endocrine cells. Moreover, in the 4-week and 13-week repeat-dose toxicity study using monkeys, no abnormalities were observed in pituitary hormones, pituitary organ weights, or in histopathological test findings.

In the presence of effector cells (using human peripheral blood mononuclear cells [PBMC], and human complement, nivolumab did not exhibit antibody-dependent-cellular cytotoxicity against activated human CD4+ T cells or complement-dependent cytotoxicity. Moreover, nivolumab did not affect the cytokine production in whole blood derived from humans.

Ipilimumab (a human anti-CTLA-4 monoclonal antibody) and BMS-986061 (an anti-LAG-3 monoclonal antibody) were also administered intravenously in combination with nivolumab to monkeys for 4 weeks. This resulted in inflammatory changes within the colon and central nervous system that were not observed with nivolumab monotherapy, suggesting that the combined use of nivolumab and agents that activate T cells could excessively increase T-cell immune responsiveness to regorafenib.

2.5.2 Summaries of clinical trial data and known or potential risks and benefits to subjects

Ono Pharmaceutical and BMS have conducted phase I, phase II, and phase III clinical trials in cancers, such as NSCLC, malignant melanoma, renal cell carcinoma, and esophageal cancer for examining the efficacy, safety and pharmacokinetics of nivolumab. Clinical trials are currently underway for nivolumab monotherapy as well as nivolumab in combination with chemotherapy, molecular-targeting agents, as well as other immunotherapies.

The pharmacokinetics of nivolumab when administered as a single dose were found to be linear and dose-dependent in the range of 0.3–10 mg/kg. The pharmacokinetics of nivolumab when administered repeatedly were also linear and exposure increased in a dose-dependent manner in the range of 0.1–10 mg/kg. Both the elimination and distribution of nivolumab appeared similar irrespective of the dose. Moreover, a population pharmacokinetics (PPK) analysis (interim data) revealed that in the range of 0.1–10 mg/kg, nivolumab clearance was independent of the cancer.

Approximately 12,300 subjects have received Nivolumab as a single dose of Nivolumab or in combination with other treatments. Frequent adverse events were fatigue, diarrhea, nausea, anemia, diarrhea, many of which were mild (Grade 1 to 2). Adverse events of altitude (Grade 3 to 4) that can not deny the causal relationship with investigational drugs are fatigue, anemia, m which is reported to rise in AST / ALT, and its frequency is relatively small in many studies. As described in Section 6.3.2, adverse events due to immunologic factors are also observed, with pneumonitis, colitis, hepatitis, pituitaryitis, nephritis and abnormal thyroid function as the main ones.

In nivolumab monotherapy, no major difference was found in the safety profile of each cancer type, and no dose-dependence was observed in the incidence, severity, or causality of adverse events. On the other hand, in patients with NSCLC, a numerically higher incidence of inflammatory lung disease was seen as an adverse event compared with that of patients with other types of cancer. This is attributable to the fact that in patients with NSCLC, it can be difficult to determine changes, as well as the presence or absence of a relationship with nivolumab, according to lung symptoms and radiographic findings.

Clinical trials currently underway involve examining the safety of nivolumab when used in combination with other agents, including ipilimumab, cytotoxic chemotherapy, angiogenesis inhibitors, and molecular-targeting agents. Among these trials, the most prioritized combination under development is nivolumab + ipilimumab for NSCLC, malignant melanoma, and renal cell carcinoma. Thus far, the combination of both agents has demonstrated a safety profile that is comparable to that shown by each agent when used alone; however, in some instances the incidence of adverse events is higher with combination therapy.

The efficacy and safety data found in various clinical trials that have been completed or are ongoing in Japan and elsewhere is noted in the latest investigator's brochure. Furthermore, it has been reported that some patients require long-term high-dose adrenocorticosteroid treatment or the administration of immunosuppressants to treat adverse events in which a causal relationship with nivolumab cannot be ruled out. In addition, although the incidence is rare, there have been some reported cases of patients who have developed opportunistic infections caused by treatment with immunosuppressants. In particular, one case involved a male patient with NSCLC receiving nivolumab combined with chemotherapy that developed corticosteroid-responsive pneumonitis. Immediately following the completion of treatment with corticosteroids, the recurrence of respiratory symptoms was observed. As the result of a subsequent lung biopsy, invasive aspergillosis was diagnosed and no inflammatory findings (pneumonia) were observed in the lungs. This patient died approximately 1 week after the diagnosis of invasive aspergillosis. In another case, a female patient with NSCLC developed corticosteroid-responsive pneumonitis after receiving nivolumab monotherapy for >24 weeks. Thereafter, the patient exhibited recurrence of respiratory symptoms, and as a result of a lung biopsy, aspergillus-related pneumonia was diagnosed without any findings of inflammation in the lungs (pneumonia). This patient recovered with antifungal treatment. The final case was of a male patient with renal cell carcinoma who, during treatment with nivolumab in combination with pazopanib, developed corticosteroid-responsive pneumonitis. The patient's condition improved while receiving treatment with high-dose corticosteroids for >2 months; however, the symptoms subsequently recurred. Examination of a specimen obtained by bronchoscopy led to a diagnosis of *Pneumocystis jirovecii* pneumonia. The patient made a complete recovery with antimicrobial therapy.

2.5.3 Japanese phase I trial of malignant melanoma

The safety and tolerability of nivolumab single-dose therapy and repeat-dose therapy administered intravenously in patients with malignant melanoma has been examined in a nonblinded, dose-escalation study. This study has been completed, and the data obtained as of July 26, 2013 has undergone an interim analysis for a total of 17 patients (three patients in the 1-mg/kg group, five patients in the 3.0-mg/kg group, six patients in the 10-mg/kg group, and three patients in the 20-mg/kg group). With regard to severe adverse events, the cutoff data was tabulated on July 26, 2013. With regard to safety, severe adverse events were observed in four out of 17 patients (23.5%). Severe adverse events that undeniably had a causal relationship with the investigational drug included dehydration in one patient in the 10-mg/kg group; however, this adverse event was alleviated with treatment. During the period of the study itself, there were no deaths because of nivolumab in any of the groups. In terms of efficacy, the antitumor effect was determined in accordance with the RECIST guidelines version 1.0, and a CR was observed in one out of 17 patients (5.9%), a PR in two patients (11.8%), and SD in three patients (17.6%). Of these responses, CR was observed in one patient with malignant melanoma in the 3.0-mg/kg group, whereas PR was observed in one patient with colorectal cancer in the 1-mg/kg group and one patient with thyroid cancer in the 10-mg/kg group.

The pharmacokinetics of an intravenous single dose of nivolumab were verified in a total of 17 patients administered nivolumab. AUC up to day 21 after nivolumab injection (AUC21 day) increased in a dose-dependent manner within the investigated dose range of 1–20 mg/kg. The peak serum concentration (Cmax) of nivolumab generally increased dose-dependently within the dose range of 1–10 mg/kg; however, in the 20-mg/kg group, a major difference was observed between the patients. In a comparison of the Cmax and AUC21 day of the CA20901 (phase I ascending dose trial of nivolumab in patients with treatment-refractory and recurrent malignancy [e.g., NSCLC, colorectal cancer, renal cell carcinoma, malignant melanoma, and metastatic castration-resistant prostate cancer]) and the ONO-4538-0 (a phase I repeat-dose-escalation trial following on from nonblinded, single-dose administration of nivolumab in Japanese patients with advanced and recurrent solid cancers) trials, the pharmacokinetics of nivolumab were found to be comparable, indicating no ethnic differences in the pharmacokinetics of nivolumab.

2.5.4 Japanese phase II trial of patients with malignant melanoma

The safety and efficacy of intravenous repeat-dose nivolumab therapy (2 mg/kg) at 3-week intervals in malignant melanoma patients with a history of treatment was examined in a multicenter collaborative nonblinded controlled study. After obtaining approval for the manufacture and sale of the nivolumab as an effective treatment for “curatively unresectable malignant melanoma” on July 4, 2014, the trial was changed to a post-marketing clinical trial (33-601). The data as of August 30,

2013 for all 35 patients was included in the interim analysis. In terms of safety, severe adverse events were observed in 17 out of the 35 patients (48.6%). Severe adverse events for which a causal relationship with the trial agent could not be ruled out were observed in five patients (14.3%), including liver damage in two patients (5.7%) as well as hypothyroidism, bacterial pneumonia, interstitial lung disease and psoriasis in one patient (2.9%) each. With regard to efficacy, the antitumor effect was determined in accordance with the RECIST guidelines version 1.0 in a total of the 35 patients administered nivolumab, and a response was observed in eight out of the 35 patients (ORR: 22.9%; 90% confidence interval [CI]: 13.4–36.2). The median PFS was 169.0 days (90% CI: 72.0–277.0), and the median OS was 473.0 days (90% CI: 276.0–).

2.5.5 Clinical efficacy in lung cancer patients

The CA209057 and CA209017 trials are randomized phase III trials comparing nivolumab and docetaxel in patients with unresectable and metastatic nonsquamous NSCLC [CA209057], and squamous NSCLC [CA209017] who have received pretreatment with two types of chemotherapy, including platinum-based agents. The two trials have ended and the results have been reported. The endpoints for efficacy associated with the tumor response were evaluated by a clinical trial physician according to the criteria in the RECIST guidelines version 1.1.

In patients with unresectable or metastatic nonsquamous NSCLC with a history of pretreatment (CA2090057), compared with docetaxel, nivolumab monotherapy resulted in a clinically and statistically significant improvement (hazard ratio [HR] = 0.73; 95.92% CI: 0.59–0.89; p = 0.0015 in a stratified log-rank test), and was associated with excellent OS[24]. In patients with unresectable or metastatic squamous NSCLC with a history of pretreatment (CA209017), compared with docetaxel, nivolumab monotherapy resulted in a clinically and statistically significant improvement (HR = 0.59; 96.85% CI: 0.43–0.81; p = 0.0002 in a stratified log-rank test), and was also associated with excellent OS[25].

2.5.6 The clinical efficacy in malignant melanoma patients

The CA209066 trial (phase III trial comparing nivolumab and decarbazine in patients with untreated B-RAF wild-type melanoma) has already ended, and the results have been reported. The endpoints for efficacy associated with the tumor response were evaluated by a clinical trial physician according to the criteria in the RECIST guidelines version 1.1.

In patients with untreated B-RAF wild-type advanced (unresectable or metastatic) malignant melanoma, compared with decarbazine, nivolumab resulted in superior OS and showed a clinically and statistically significant improvement (HR = 0.42; 99.79% CI: 0.25–0.73; p < 0.0001). As secondary and exploratory endpoints, the results for the PFS, ORR, duration of response and time to response further supported the persistent and sustained antitumor activity of nivolumab in the same population[26].

2.6 Regorafenib

Regorafenib is a new oral diphenylurea multikinase inhibitor of angiogenic, stromal, and oncogenic kinases with potent antitumor activity demonstrated in preclinical trials, and a long-term sustained antiangiogenic effect observed on dynamic contrast-enhanced MRI. In biochemical kinase phosphorylation assays (50% inhibitory concentration [IC50] of 4–311 nM) and cell-based kinase phosphorylation assays (IC50 of 3–200 nM), regorafenib exhibits a potent inhibition of angiogenic kinases VEGFR 1-3, TIE2, and PDGFRβ, as well as fibroblast growth factor receptor 1. Furthermore, regorafenib demonstrates a potent inhibition of mutant oncogenic kinases involved in gastrointestinal stromal tumors (GIST) and thyroid cancer, including KIT (IC50 c-KITK642E = 22 nM in cell-based assays) and RET (IC50 RETC634W to 10 nM in cell-based assays). Regorafenib also inhibits B-RAF located on RAS/RAF/MEK/ERK signal transduction pathways (IC50 of wild-type B-RAF = 28 nM and IC50 of B-RAFV600E = 19 nM in biochemical assays). Furthermore, regorafenib inhibits Raf-1 (IC50 = 2.5 nM) and p38 mitogen activated protein kinase (MAPK; IC50 = 24 nM). *In vivo*, tissue sections from human colon cancer and a xenograft model of breast cancer showed a reduction in the microvessel area, Ki-67 staining, and pERK 1/2 staining, suggesting that regorafenib has antiangiogenic and proliferation-inhibitory actions. In several xenograft models (e.g., breast cancer, colon cancer, renal cancer, NSCLC, malignant melanoma, pancreatic cancer, thyroid cancer, and ovarian cancer), regorafenib inhibited tumor proliferation in a dose-dependent manner and also had a tumor-reducing effect in a model of renal and breast cancer[27].

2.6.1 Regorafenib clinical outcomes

The clinical development of regorafenib began in July 2005. Several phase I, phase II, and phase III trials are underway to evaluate regorafenib for various types of advanced cancer. To date, clinical trials have been conducted in >1,100 patients treated with regorafenib for various types of cancer, including colorectal cancer (CRC), GIST, renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC). Moreover, all these phase I and phase II trials revealed antitumor action and long-term stability. In the CORRECT study, a randomized, double-blinded, placebo-controlled phase III international trial in patients with metastatic CRC exhibiting disease progression following standard treatment, regorafenib in combination with best supporting care (BSC) was compared with a placebo in combination with BSC, and the primary endpoint was satisfied (i.e., there was a statistically significant improvement in the OS)[28]. The GRID trial was a similar international collaborative study involving 199 patients (PS: 0 or 1, including 17 Japanese patients) with unresectable or metastatic GIST who exhibited disease progression following treatment with imatinib and sinitinib; as a result, a significant prolongation of PFS was observed[29]. Furthermore, 85% of the placebo group (56 out of 66 patients) crossed over to the regorafenib group following disease progression; however, regardless of this issue, the hazard ratio was 0.77, and the OS tended to be prolonged in the regorafenib group. The RESORCE trial evaluated the efficacy and safety of regorafenib in patients

with advanced liver cancer who have progressed on sorafenib treatment. Patients on regorafenib showed a 38% reduction in the risk of death and a 54% reduction in the risk of progression or death compared to placebo. PFS was 3.1 months with regorafenib and 1.5 months with placebo, while OS was 10.6 months for regorafenib and 7.8 months with placebo.

2.6.2 Summary of adverse events associated with regorafenib

Approximately 4000 safety analysis reports that received Regorafenib are listed in the study drug summary. Therapeutic-related adverse events with an incidence of over 20% were hand-foot syndrome (45.7%), fatigue (40.9%), loss of appetite (35.7%), diarrhea (34.7%), high blood pressure (34.5% %), Weight loss (27.9%), fever (21.4%). Adverse events of grade 3 and above with an incidence of over 5% were high blood pressure (15.6%), hand and foot syndrome (14.9%), fatigue (10.3%), diarrhea (5.9%), asthenia, (5.8% (5.7%). Severe adverse events that occurred during treatment with an incidence of> 1% were severe adverse events (8.1%), fever (2.4%), abdominal pain (2.2%), dyspnea (1.4%), pneumonia (1.3%), Diarrhea (1.2%), intestinal obstruction (1.1%).

Although many of the deaths occurring within 30 days of Regorafenib administration and within 30 days from discontinuation of treatment were disease progression, 65 cases of "adverse events not related to disease progression" or "toxicity related to investigational drugs" have been reported. Of 17 of them, it is judged that the association with regorafenib cannot be denied. Among them, rectal and vaginal bleeding (1 case), pulmonary bleeding (1 case), pulmonary embolism (1 case), pulmonary sepsis (1 case), femoral hematoma (1 case), cardiac arrest (4 cases) , A cardiopulmonary arrest (1 case), a heart failure (1 case), a cerebral vascular attack (1 case), a cerebral hemorrhage (1 case), a decrease in general health condition (1 case), sepsis (1 case), sudden death (1 case) It was acute liver failure (1 case).

2.7 Treatment regimen in the present trial

The treatment protocol in the present trial consists of nivolumab and regorafenib combination therapy. Nivolumab will be administered at a dose of 3.0 mg/kg given once every 2 weeks. Regorafenib will be administered orally as a single dose each day for 21 consecutive days with a 1-week washout period. One course will last 28 days, and will be repeated until the criteria for termination are satisfied.

2.7.1 Rationale for setting the nivolumab administration route, dose, and treatment schedule

In the phase I repeat-dose trial of nivolumab (CA209003) conducted overseas, patients with malignant melanoma were administered a 0.1–10 mg/kg dose intravenously, which was repeated at 2-week intervals. The trial included 306 patients primarily with NSCLC, malignant melanoma, or RCC for whom nivolumab was considered to exhibit a potent antitumor effect at a dose of ≥3 mg/kg.

Regarding safety, in phase I trials of nivolumab monotherapy conducted in Japan and internationally (respective trial numbers: ONO-4538-01 and CA209003), the tolerability of an intravenous repeat-dose therapy administered every 2 weeks was confirmed up to a dose of 20 mg/kg in Japan and 10 mg/kg internationally. According to these data concerning efficacy and safety, phase II and III trials have been conducted for nivolumab at a dose of 3 mg/kg (one dose administered every 2 weeks) in patients with NSCLC, malignant melanoma, and RCC.

Thus, many clinical trials have been conducted that involve the administration of nivolumab at a dose per body weight (mg/kg). The results of the PPK analysis have shown that the pharmacokinetics of nivolumab are linear with a dose-dependent increase in the exposure level (range: 0.1–10 mg/kg) and no difference in pharmacokinetics was observed according to the type of cancer.

The safety and tolerability of nivolumab up to a dose of 10 mg/kg has been confirmed, and the relationship between the exposure level and efficacy was relatively constant when administered at a dose of 3 mg/kg. To date, clinical trials for nivolumab monotherapy have shown that when administered for >60 min within a dose range of up to 10 mg/kg, the treatment can be administered safely and is event free over a long period. In a phase II trial in patients with advanced or metastatic RCC (CA209010), the dose was found to be associated with the incidence of localized reactions and hypersensitivity near the injection site (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg); however, all events were grade 1 or 2 and manageable. The administration of nivolumab at 3.0 mg/kg for 30 min corresponds to 30% of the dosage when administered at 10 mg/kg for 60 minutes. It is therefore thought that there is no concern regarding safety compared with when nivolumab is administered at 10 mg/kg for 60 min.

On the basis of the abovementioned findings, in the present trial, we chose to give nivolumab at an intravenous dose of 3.0 mg/kg repeated every 2 weeks, and set the administration time to at least 25-40 min.

2.7.2 Rationale for setting the regorafenib administration route, dose, and treatment schedule

On the basis of the phase I clinical trial outcomes obtained from the results of the regorafenib phase I trials, regorafenib was administered at a gradually escalating dose from 10 to 220 mg, with an intermittent schedule (continuous administration for 3 weeks with a 1-week washout period over a 4-week cycle). Signs of antitumor activity were observed in the subjects administered a dose of 60–220 mg. A reduction in the dose because of toxicity was required in eight out of 12 subjects who received a dose of 220 mg/day, whereas at the dose of 160 mg/day, only one out of 12 subjects required a dose reduction[31]. Therefore, according to the efficacy and toxicity data, the approved dose was 160 mg given once per day. However, the safety when used in combination with nivolumab was not confirmed. Consequently, in the present study, a dose-escalation cohort was included to determine the RD of regorafenib when used in combination with nivolumab.

2.8 Trial design

The present trial consists of a dose-escalation cohort to verify the tolerability of nivolumab and regorafenib when used in combination for patients with solid tumors, and to examine the clinical RD. The trial also consists of an expansion cohort to examine the safety and efficacy when the clinical RD is administered for several advanced solid tumors.

In the dose-escalation cohort, three patients with solid tumors will be administered 3.0 mg/kg of nivolumab once every 2 weeks and regorafenib daily for 21 days, with a 1-week washout period at dose of 80 mg (level 1), 120 mg (level 2), or 160 mg (level 3). As a general rule, one cycle will last 28 days (day 1–28); however, in the event of treatment prolongation, the cycle period will be extended. The DLT evaluation period will be 28 days. Furthermore, for each level, three additional subjects will be added depending on the state of DLT.

In the expansion cohort, the target subject sample will consist of approximately 30 patients who will be administered 3.0 mg/kg of nivolumab once every 2 weeks, and the clinical RD of regorafenib will be determined in the dose-escalation cohort.

In both parts of the study, treatment can be continued until the criteria for termination are satisfied; however, in the dose-escalation cohort, the subjects' consent must be obtained again for the continuation of treatment after completing the DLT evaluation period.

The trial will proceed as follows for all subjects. After providing written informed consent to participate in the trial, each subject will undergo preliminary examination in the preceding 2 weeks (day −14 to −1) before receiving the investigational drug. Subjects who are enrolled in the trial will be admitted to the hospital the day that the administration of the investigational drug begins (cycle 1, day 1), and they will receive the investigational drug at the appropriate dose for each level. After completing the prescribed observations and tests on cycle 1 day 4, the subjects are allowed to be discharged. Furthermore, the subjects will be administered the investigational drug and undergo the prescribed tests on cycle 1 day 8, cycle 1 day 15, cycle 1 day 22, cycle 2 day 1, and cycle 2 day 15, after which they will undergo the test once every 2 weeks until the criteria for termination are satisfied. After treatment is discontinued, the subjects will undergo follow-up tests on days 30 after the final day of treatment. Thereafter, the survival of each subject will be investigated every 90 days.

2.8.1 Setting of endpoints

Primary endpoints

In patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy, the safety and tolerability of a repeated dose of regorafenib and nivolumab will be evaluated, and the MTD and RD of the two drugs when used in combination will be examined.

Dose-escalation cohort

In patients with unresectable recurrent solid tumors who are refractory or intolerant to standard

chemotherapy, the safety of regorafenib and nivolumab combination therapy will be evaluated to determine the MTD and RD of regorafenib according to DLT when used in combination.

Expansion cohort

An exploratory evaluation of the efficacy and safety of the combination therapy will be performed on the basis of the RD found in the dose-escalation cohort.

Secondary endpoints

・Safety

- According to the NCI- CTCAE version 4.0, the incidence and type of adverse events that occur during treatment will be evaluated.

・Efficacy

- ORR according to RECIST ver. 1.1, and irRECIST
- PFS
- OS
- DCR

Exploratory items (performed as accompanying research in the present trial):

Tests of various biomarkers

2.8.2 Planned number of enrollments

Dose-escalation cohort: Three to six patients per level, for a total of 9–18 patients.

Expansion cohort: Approximately 30 patients in total.

If two or more cases of CR/PR or SD ≧ 4 months were observed in specific cancer types, we will consider adding around 10 patients with same cancer type in expansion cohort.

2.9 Summary of the anticipated advantages and disadvantages of participation in this trial

The present trial is a phase I trial designed to determine the optimal dose of regorafenib and nivolumab for concomitant use. Although it is difficult to predict the advantages that may be obtained, if the synergistic effect of the two drugs yields an antitumor effect, it will be beneficial to the participants.

The anticipated disadvantages include any adverse events associated with regorafenib and nivolumab. 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.

2.10 The significance of performing the present study as an investigator-led trial

Nivolumab is a drug currently under development by Ono Pharmaceutical, and regorafenib is a drug currently under development by Bayer Healthcare Pharmaceutical. 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 nivolumab and regorafenib. Furthermore, by analyzing biomarkers in accompanying research, we hope to pursue the significance of simultaneously inhibiting the VEGF, MEK/ERK, 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 regorafenib in combination with nivolumab 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 CRITERIA AND DEFINITIONS TO BE USED IN THE STUDY

3.1 Staging Criteria

Staging will be classified in accordance with the "TNM Classification of Malignant Tumours, 7th Edition by the Union for International Cancer Control (UICC-TNM 7th edition)." Classification will be made in accordance with the staging method for main histological types (squamous cell carcinoma in the esophagus and adenocarcinoma in other primary organs) in each primary organ (see Appendix 1).

3.2 Performance Status (Eastern Cooperative Oncology Group (ECOG) Classification)

(See Appendix 1.)

3.3 Assessment Criteria for AEs

For event terms and grades of AEs, the "Common Terminology Criteria for Adverse Events (CTCAE) v4.0 – Japanese Translation by the Japan Clinical Oncology Group (JCOG)" [equivalent to CTCAE v4.03/MedDRA v12.0] will be used. In this study, they will be as operated by the JCOG.

3.4 Assessment Criteria for Response Rate

For the assessment of tumor response, the "New Response Evaluation Criteria in Solid Tumors (RECIST guideline), Revised version 1.1 - Japanese translation by the JCOG-: Revised RECIST guideline (version 1.1)" and the irRECIST (immune-related response criteria), which is the RECIST version 1.1 with partial revisions, will be used (see Appendices 2 and 3).

4 INCLUSION AND EXCLUSION CRITERIA

4.1 Inclusion criteria

1. Patients who provided written informed consent to be subjects in this trial
2. Patients at least 20 years of age on the day of providing consent
3. Dose-escalation cohort: Patients with histologically or cytologically confirmed advanced or metastatic solid tumors.

Expansion cohort: Patients with histologically or cytologically confirmed advanced or metastatic solid tumors (gastric, colorectal, or hepatocellular cancer).

4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
5. Patients capable of taking oral medication
6. Patients with evaluable or measurable lesions as per RECIST version 1.1
7. Patients with adequate organ function at the time of enrollment as defined below: [Acceptable 7 days examination before the same day of the registration date]

・Neutrophil count ≥1500/mm^3

・Platelet count ≥10.0 × 10^4/mm^3 (transfusion >2 weeks before testing permitted)

・aspartate transaminase (AST), alanine transaminase (ALT) ≤100 U/L2.5-times the upper limit of normal (200U/L I patients with hepatocellular cancer ,or ≤250U/L in patients with liver metastasis)

・Total bilirubin ≤1.5-mg/dL

・Creatinine ≤1.5-times the upper limit of normal

・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) UPC (Urine Protein Creatinine) ratio <3.5
- (iii) 24-hour urine protein was measured, urinary protein ≦ 3500 mg
- PT-INR: ≤ 1.5 (≦ 3.0 in case of anticoagulant administration)

* It is Child A in the case of Expansion cohort's hepatocellular carcinoma

8. For women who are likely to become pregnant (including those without menstruation due to medical reasons such as chemical menopause) Note 1, we agreed to double contraceptive Note 2 for at least 5 months after the final administration of the investigational product from consent acquisition patient. Also, patients who agreed not to breast feeding for at least 5 months after the final investigational drug administration after acquiring consent.

For men, patients agreeing to double contraceptive for at least 7 months after the final investigational drug administration from the time of starting investigational drug administration.

Note 1): A woman who is likely to become pregnant is a woman who has experienced menarche and is not undergoing sterilization surgery (such as hysterectomy, bilateral salpingo ligation or bilateral oophorectomy), a woman without menopause Everything is included. The definition after menopause shall be amenorrhea continuously for 12 months or more even though there is no noteworthy reason. Women who are using oral contraceptives or mechanical contraceptive methods (such as intrauterine contraceptive devices or barrier methods) are considered to be pregnant.

Note 2): With regard to contraception, it is necessary to use two of the vasectomy or condom of a male patient or male, the uterine tube ligation of a female patient or the other woman, a contraceptive pessary, an intrauterine contraceptive device or an oral contraceptive I need to agree to heavy contraception.

4.2 Exclusion criteria

1. Patients who have undergone systemic chemotherapy, radiotherapy, surgery, hormone therapy, or immunotherapy <2 weeks before enrollment. Immune checkpoint blockade as pretreatment is permitted.
2. Patients with a history of taking regorafenib.
3. Patients with hypertension that is difficult to control (systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with several hypotensive agents
4. 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
5. Patients with a large amount of pleural effusion or ascites requiring drainage.
6. Patients with a ≥grade 3 active infection according to NCI-CTCAE version 4.03
7. Patients with symptomatic brain metastasis
8. Patients with partial or complete gastrointestinal obstruction
9. Patients with interstitial lung disease with symptoms or signs of activity
10. Patients who test positive for either anti-HIV-1 antibodies, anti-HIV-2 antibodies, anti-HTLV-1 antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies*
    *Patients who test positive for either anti-HBs or anti-HBc antibodies, and those who have HBV-DNA measurements greater than the detection sensitivity will also be excluded. (However, patients with hepatocellular carcinoma in the expansion cohort will not be excluded even if they test positive for HBsAg and anti-HCV antibodies.)
11. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease
12. 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 in the present study

13. Patients with a history or findings of ≥grade III congestive heart failure according to the New York Heart Association functional classification
14. Patients with a seizure disorder who require pharmacotherapy
15. Major surgical procedure or significant traumatic injury within 28 days before start of study medication.
16. Patients undergoing major surgery (thoracotomy or laparotomy, etc.), laparotomy biopsy, trauma within 28 days before registration. The same day of the week before 4 weeks can be registered

    (However, in case of an artificial anastomosis without intestinal resection, it shall be within 14 days before registration).
17. Non-healing wound, non-healing ulcer, or non-healing bone fracture
18. Patients with a history of hypersensitivity to any of the study drugs, similar drugs, or excipients.
19. Pregnant women, lactating women or possibly pregnant women.

5 Enrollment

5.1 Enrollment procedure

Verification that the target patients meet all the eligibility criteria and none of the exclusion criteria will be performed; then the Web enrollment system will be used to perform the enrollment.

■ Contact and reception hours for patient enrollment

Notification of the Web enrollment URL and other information will be given via the separate "EDC input manual."

(Enrollment can be made 24 h a day. However, in the event that the site is inaccessible [e.g., for maintenance], notification will be given in advance).

■ Contact for queries regarding enrollment:

Data Management Office, Clinical Trial Support Division, National Cancer Center Hospital East

TEL: 04-7133-1111 (Ext. 5106), E-mail: regonivo_core@east.ncc.go.jp

Weekdays: 10:00–17:00 (closed on national holidays, Saturday and Sunday)

■ Contact for queries regarding patient selection criteria:

Trial coordinating (principal) investigator: Dr. Kohei Shitara

Assistant Chief at the Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East

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

TEL: 04-7133-1111 (ext. 91520), E-mail: kshitara@east.ncc.go.jp

Coordinating investigator: Dr. Shota Fukuoka

Exploratory Oncology Research & Clinical Trial Center, National Cancer Center

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

5.2 Important notes regarding enrollment

1) Enrollments after the initiation of the treatment protocol will not be permitted without exception.
2) When the enrollment and eligibility checklist content is unsatisfactory, the enrollment will not be accepted until it is all the content is satisfied.
3) After confirmation of eligibility, a registration number will be issued. Enrollment will be completed once the registration number has been issued.
4) Except in the event of withdrawal of consent, including the refusal of the use of data in the trial, patients will not be removed from the trial (erased from the database) once they have been enrolled. In the event of a double registration, the information from the first enrollment (registration number) will be used.

5) When a misregistration or double registration is discovered, the data management office should be contacted as soon as possible.
6) At the time of enrollment, in the event of an ongoing medical examination at another hospital or department, the attending physician is to be contacted and notified that the patient concerned is participating in the present trial.

6 Dosing schedule and combination therapy

If the safety of the subject is not at risk, treatment and changes to treatment will be carried out in accordance with the content of this chapter. If a medical emergency is identified when the present protocol is followed, the treatment will be changed in accordance the medical judgment of the principal investigator (or subinvestigator) for the trial (hereinafter "principal investigator").

6.1 Protocol treatment

In the present trial, the protocol treatment will consist of the investigational drug, nivolumab, used in combination with regorafenib. 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 nivolumab or regorafenib monotherapy upon deliberation with the trial coordinating committee. 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 terminology is used in the present protocol:

- Termination: Administration of the investigational drug is not resumed.
- Washout: Omission of one or more doses of the investigational drug and moving onto the next dosing schedule.
    - Washout period: The duration of time that the investigational drug is not administered.

6.1.1 Dosing and administration method

In the dose-escalation cohort, the stipulated doses for each level are shown in Table 6.1.1a. At least 1 day will be left between the initial starting day of the trial protocol (cycle 1 day 1) for the first and second patient in each level. The expansion cohort will be given the clinically RD determined on the basis of the results of the dose-escalation cohort. The method of determining the clinical RD is described in section 7.1.2.

The dose administered to each individual subject will be calculated according to body weight at the time of enrollment. However, in the event of a change in body weight of >10% as measured on day 1 of each cycle compared with that at the time of enrollment, the dose will be calculated according to the new body weight. Thereafter, the same action will be taken, upon observation of a change of over 10% in body weight compared with the most recent body weight change. The administered dose (mg units) will be calculated and rounded to two decimal places.

Table 6.1.1a Doses of nivolumab and regorafenib

Level	Nivolumab dose	Regorafenib dose	Target number of subjects for the DLT evaluation
1	3.0 mg/kg	80 mg/day	3–6
2	3.0 mg/kg	120 mg/day	3–6
3	3.0 mg/kg	160 mg/day	3–6

Regorafenib will be administered with water once per day after eating (low-fat meal recommended) at a dose of 80 mg (level 1), 120 mg (level 2), or 160 mg (level 3). Regorafenib will be given orally for 21 consecutive days, followed by a washout period of 7 days. In the event of withdrawal because of adverse events, the period of withdrawal will be included in the 21-day oral therapy period, and will be followed by a washout period of seven days.

Nivolumab will be administered via intravenous infusion given once every 2 weeks at a dose of 3.0 mg/kg over a 30 min period after 1 h (up to 2 h permissible) has passed because the oral administration of regorafenib in the morning. The dosing period will be set to as close to 30 min as possible (25–40 min) by the medical institution administering the treatment.

For precautions regarding dosing, refer to “Patient instructions regarding the handling of the investigational drug.”

From cycle 2 onward, the treatment will commence after verifying that the dosing criteria listed in section 6.3 have been satisfied. The start day for nivolumab will be defined as day 1, including the washout period even in the event of conflict with the criteria defined in 6.3, and one cycle will last 28 days. If nivolumab is terminated and treatment is resumed as regorafenib monotherapy, the subsequent day of regorafenib resumption will be defined as day 1. In such an instance one cycle will also last 28 days.

Treatment will continue until the “criteria for treatment termination” are satisfied.

6.1.2 Recommended dose (RD) and transition to the expansion cohort

In the present trial, the starting dose of regorafenib will commence from level 1 (80 mg/day), and tolerability of combination therapy with nivolumab (3.0 mg/kg at 2-week intervals) will be verified. One cycle will last 28 days and DLT will be evaluated using a 3 + 3 design for the following doses to verify tolerability.

Level 1

Regorafenib: Oral administration at a dose of 80 mg given once per day for 21 consecutive days,

with a 1-week washout period.
Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg via an intravenous infusion.

When it is deemed that there is no problem with safety at the doses described above, tolerability will be verified at the level-2 dosages described below.

Level 2
Regorafenib: Oral administration at a dose of 120 mg/day for 21 consecutive days, with a 1-week washout period.
Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg.

When it is deemed that there is no problem with safety at the doses described above, tolerability will be verified at the level-3 dosages described below.

Level 3
Regorafenib: Oral administration at a dose of 160 mg/day for 21 consecutive days, with a 1-week washout period.
Nivolumab: Given once every 2 weeks at a dose of 3.0 mg/kg.

After starting the trial, three cases are registered at level 1, and temporary case registration is suspended until safety evaluation of the first course is completed in all cases. If there are cases in which evaluation of DLT cannot be performed properly, such as being canceled due to reasons other than safety during the course of the first course, the necessary number of cases is appropriately added to the administration level.
1) In cases where no DLT is observed in 3 cases, registration of the case is started at the next dose level, and the same procedure is repeated until MTD is reached with level 3 as the upper limit.
2) When DLT is observed in 2 cases or more in 3 cases, the administration level is judged as MTD.
3) If DLT is observed in 1 out of 3 cases, 3 further cases are additionally registered at the administration level (total 6 cases). When DLT is observed in 2 out of 6 cases, the administration level is judged as MTD. However, if there are two cases of DLT-expressing cases before the number of registered cases at the administration level reaches 6, the administration level is judged as MTD at that time point.
4) If it is judged that MTD is exceeded, 6 cases of DLT evaluation are already carried out at the level one level below and if the DLT is 1 case or less of 6 cases, the dose is taken as MTD and RD. At the relevant dose, if only 3 people are evaluating DLT, add 3 cases (total 6 cases). When the number of

DLT is 1 or less out of 6, the dose is defined as MTD and RD. If it is judged that Level 1 exceeds the MTD, review the dose or consider stopping the trial.
5) MTD should be the highest dose level of DLT expression less than 1 in 6 cases.

Expansion cohort: Implemented using the RD estimated in the dose-escalation cohort.

6.1.3 Definition of DLT

As a general rule, DLT includes the observation of any of the side effects listed below during the DLT evaluation period and will ultimately be determined upon deliberation between the sponsor and the principal investigator of the trial. Furthermore, the opinion of the Data and Safety Monitoring Committee can be sought as required (refer to attachment 1: trial protocol [supplement]).

• Hematotoxicity:

–Persistent grade 4 neutropenia lasting ≥7 days;

–When a neutrophil count of <1000/mm^3 and fever of ≥38.0°C is observed for >2 days;

–Grader 4 thrombopenia or thrombopenia associated with a hemorrhage requiring platelet transfusion.

- Grade 3 thrombocytopenia with bleeding.

• Non-hematotoxicity:

–≥Grade 3 non-hematotoxicities. However, any of the following non-hematotoxicities will be deemed DLT when it is judged by the principal investigator or subinvestigator that treatment cannot be continued even with supportive therapy.

- ✧ ≥Grade 3 diarrhea, nausea, vomiting, and loss of appetite for ≥5 consecutive days;
- ✧ ≥Grade 3 electrolyte imbalance for ≥7 consecutive days;
- ✧ ≥Grade 3 dermal toxicity for ≥7 consecutive days;
- ✧ ≥Grade 3 T-Bil, AST (GOT) and/or ALT (GPT) elevations: In subjects with liver metastasis or liver cancer, elevated AST (GOT) and/or ALT (GPT) of >10 times the upper limit of the institutional reference value;
- ✧ Grade 3 or more immune related adverse event that lasts more than 8 days even after steroid therapy is applied.

• General:

When 70% of the planned regorafenib dose cannot be administered, and/or when one dose of nivolumab cannot be administered because of toxicity during the DLT evaluation period

6.1.4 Target subjects for DLT evaluation

For each level, at least three subjects will be enrolled, and the presence or absence of DLT will be evaluated during the DLT evaluation period.

When it is determined that there is a subject who will not change levels, an additional subject will

be enrolled to evaluate the DLT determined in 6.1.3.

Furthermore, among the enrolled subjects, those who meet the following conditions will be excluded from DLT evaluation:

1) Subjects who are unable to receive regorafenib for ≥14 days in the first course for reasons other than toxicity.

2) Subjects for whom sufficient data cannot be obtained to determine the DLT evaluation because of missing mandatory tests, etc.

3) Cases in which adequate data for DLT evaluation judgment could not be obtained due to essential test defects

Furthermore, among the participants who withdraw from regorafenib and nivolumab during the first course for reasons other than adverse events or who withdraw from treatment for a long period because of toxicities other than DLT, the decision to subject such patients to a DLT evaluation will be determined upon deliberation between the trial coordinating committee and the participating institution.

6.1.5 Determining transition to the expansion cohort

After completion of the final DLT evaluation period of the subjects in the dose escalating cohort, the decision to move the subjects into the expansion cohort will be determined once it is decided, upon deliberation between the sponsor and the principal investigator, that there are no problems associated with moving on. Furthermore, the opinion of the Data and Safety Monitoring Committee can be sought as required (refer to attachment 1: trial protocol [supplement]).

6.2 Criteria for the commencement and termination of the treatment protocol

6.2.1 Criteria for terminating the treatment protocol

The treatment protocol will be terminated when the participating subjects meet any of the following criteria:

1) When an exacerbation of the underlying disease is observed (including marked exacerbation on diagnostic imaging, and clinically marked exacerbation).
2) When the subject requests to terminate the treatment protocol.
3) When treatment protocol-related grade 4 non-hematotoxicity is observed.

(However temporary abnormalities in test values shall not apply).

4) When nivolumab and regorafenib cannot be resumed for >28 days.
5) When the conditions for the termination of the treatment protocol apply as stipulated in "7.3 Criteria for changing the treatment protocol."
6) If the subject becomes pregnant.
7) When follow-up is not possible.
8) Death during the treatment protocol.
9) When 54 doses of nivolumab have been completed.
10) Termination following a CR.

    Following at least eight cycles of nivolumab (approximately 6 months), when a subject is deemed to exhibit CR on the basis of diagnostic imaging, and receives at least two cycles of nivolumab after the initial determination of CR, termination of nivolumab can be considered upon consultation with the trial coordinating committee. The decision to terminate or continue regorafenib administration after CR can be considered by the attending physician upon consultation with the trial coordinating committee, regardless of whether nivolumab is terminated or continued.
11) 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 after treatment termination and the follow-up of subjects

When the criteria for termination are satisfied, the treatment protocol will be terminated. The time, reason, and progress associated with termination will be recorded on a case report form (CRF), and the prescribed tests will be conducted during the following observation period. However, when the attending physician judges that various tests cannot be performed or are not required for ethical reasons or for the safety or benefit of the subject, such tests shall not apply.

6.3 Criteria for changing the treatment protocol

6.3.1 Criteria for changing the dose of regorafenib

The safety profile of regorafenib has been established in the clinical trials noted above. The dose adjustments for regorafenib are according to the clinical trials conducted to date. Dose modifications are to be applied in 40 mg (one tablet) steps. When treatment with regorafenib is terminated because of any reason, the continuation of nivolumab monotherapy as the treatment protocol is permitted. The maximum daily dose is 160 mg.

Table 6.3.1 Day dose of Regorafenib

Level	The dose of Regorafenib
0	40 mg/day(40 mg 1Tab)
1	80 mg/day(40 mg 2Tab)
2	120 mg/day(40 mg 3Tab)
3	160 mg/day(40 mg 4Tab)

6.3.1.1 Dose adjustments for skin reactions of the hands and feet

When skin reactions of the hands and feet occur during regorafenib treatment, dose adjustments will be made at the discretion of the principal investigator(or subinvestigator) with reference to “Table 3: Dose adjustments for skins reactions of the hands and feet.” Furthermore, in subjects who receive a dose reduction, when no ≥grade 2 rash or skin reaction of the hands and feet is observed at the decreased dose level throughout the subsequent cycle, the dose of the investigational drug can be increased to the starting dose at the discretion of the principal investigator (or subinvestigator).

Table 3: Dose adjustments for skins reactions of the hands and feet

Table Dose modifcation of hand-foot skin reaction

NCI CTC Grade		Dose adjustment
Grade 2	Painful erythema and swelling or discomfort of hands and feet that interfere with daily living	Support supportive therapy as necessary. Take asleep until toxicity relieves to Grade 0 to 1. When dosing is resumed, the same dose or dose is administered at a level reduced by 1 dose.
Grade 3	Wet scaling of limbs, work ulcers, blistering, severe pain, or severe discomfort	Wet scaling of limbs, work ulcers, blistering, severe pain, or severe

		discomfort.

6.3.1.2 Dose adjustment for hypertension

When hypertension develops during regorafenib treatment, dose adjustments will be made at the discretion of the principal investigator (or subinvestigator) with reference to "Table 4: Dose adjustments for hypertension." Hypertensive subjects require careful observation and it is strongly recommended to administer suitable hypotensive treatment during regorafenib 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.

Furthermore, in subjects who receive a dose reduction, when hypertension is controlled for at least one cycle, the dose of the investigational drug can be increased to the starting dose at the discretion of the principal investigator (or subinvestigator).

Table 4: Dose adjustment for hypertension

NCI-CTCAE grade	Dose adjustment
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.

6.3.1.3 Dose adjustment for elevated AST, ALT, and T-Bil levels

When an increase in AST, ALT, and/or T-Bil levels is observed during regorafenib treatment for which a causal relationship cannot be ruled out, the dose will be adjusted with reference to "Table 5: Dose adjustments for elevated AST, ALT, and T-Bil levels."

It is recommended to conduct liver function tests at least once a week until the liver function test results return to within the normal range or return to the grade at the time of enrollment.

Table 5: Dose adjustment for elevated AST, ALT, and T-Bil levels

NCI CTCAE Grade		Expression times	Dose adjustment
Grade 2	T-Bil exceeds 1.5 times the normal value upper limit and 3 times or less If AST or ALT exceeds 3 times the normal value upper limit and is 5 times or less	Regardless of the number	Continue administration and continue at least once a week for at least 4 weeks until T-Bil is less than 1.5 times the upper limit of normal value, AST or ALT is less than 3 times upper limit of normal value or recovered to Grade before administration, AST, ALT And T - Bil measurement should be carried out.
Grade 3	T-Bil exceeds 3 times the normal value upper limit and is 10 times or less If AST or ALT exceeds 5 times the normal value upper limit and is 20 times or less	First time	Regorafenib is withdrawn until T-Bil is less than 1.5 times the upper limit of normal value and AST or ALT is recovered to less than 3 times normal value upper limit or below registered Grade. When dosing is resumed, it is recommended to reduce the same amount or 1 level and measure AST, ALT and T-Bil once a week for a minimum of 4 weeks.
		Second time	Discontinue administration.
Grade 4	T-Bil exceeds the normal value upper limit by 10 times AST or ALT is over 20 times the normal value upper limit	Regardless of the number	Discontinue administration.

6.3.1.4 Resumption of regorafenib dosing

When regorafenib is administered, if you develop diarrhea, fatigue, loss of appetite, nausea, vomiting, and other adverse events judged by your doctor as Regorafenib (excluding asymptomatic test values) that cannot deny the causal relationship with Regorafenib, “Table 6.3.1.4 Dose Adjustment for Other Adverse Events ", the investigational physician judges and adjusts the dose.

Table 6.3.1.4 Dose Adjustment for Other Adverse Events

NCI CTCAE Grade	Possibility to continue administration	Dose adjustment
Grade 2	Continue administration	No change
Grade 3	Weigh out until recovering to Grade 2 or lower	Reduce one level
Grade 4	Discontinue administration	—

6.3.2 Criteria for changing the nivolumab dosage

Adverse events (irrespective of severity) associated with nivolumab exposure might be of immunological etiology. Such adverse events can occur immediately following the commencement of treatment with the investigational drug or several months after completion of treatment. For toxicities and severe or life-threatening adverse events with a causal relationship with nivolumab, the withdrawal and termination of nivolumab will be carried out in accordance with Table 6.3.2. For the guidelines regarding supportive therapy, including the use of corticosteroids, refer to section 6.3.2.1, and the investigator brochure (appendix 3 Management Algorithms).

In accordance with the instructions given in this section, administration is withdrawn and administration resumed. Subjects whose resumption of Nivolumab and Regorafenib need to be delayed for more than 28 days from the scheduled start date will cease protocol treatment. However, administration of Regorafenib was discontinued, but when Nivolumab resumption is possible according to 6.3.2, protocol treatment can be restarted with Nivolumab alone.

Table 6: Criteria for nivolumab withdrawal and termination

Toxicity	Grade requiring withdrawal	Timing of treatment resumption after withdrawal	Instance requiring nivolumab termination
Diarrhea/colitis	2–3	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to below 10 mg/day of prednisolone

			within 12 weeks.
	4	Nivolumab termination	Nivolumab termination
Elevated AST, ALT, and/or bilirubin	2	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose.
	3–4	Nivolumab termination (see exceptions below)[a]	Nivolumab termination.
Type I diabetes (T1DM: when newly developed) or hyperglycemia	T1DM or 3–4	When clinically and metabolically stable	Terminate nivolumab when the subject is not clinically and metabolically stable within 12 weeks of the last dose.
Hypophystitis	2–4	Toxicity is returned to below grade 1. When endocrine hormone replacement therapy has been initiated.	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to below 10 mg/day of prednisolone within 12 weeks.
Hyperthyroidism	3	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to <10 mg/day of prednisolone within 12 weeks.
	4	Nivolumab termination	Nivolumab termination
Hypothyroidism	Not stipulated	When thyroid hormone replacement therapy has been initiated	
Infusion reaction	2[b]	Toxicity is returned to below grade 1	Terminate nivolumab when toxicity develops despite appropriate pretreatment.
	3–4	Nivolumab termination	Nivolumab termination
Pneumonitis	2	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when

			corticosteroids cannot be decreased to <10 mg/day of prednisolone within 12 weeks.
	3–4	Nivolumab termination	Nivolumab termination
Renal impairment or nephritis	2	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to <10 mg/day of prednisolone within 12 weeks.
	3–4	Nivolumab termination	Nivolumab termination
All other toxicities with a causal relationship	Intolerance or persistent 2	The decision to withdraw and resume nivolumab can be made at the discretion of the attending physician	Terminate nivolumab when the toxicity persists after drug withdrawal and is not returned <grade 1 within 12 weeks from the last dose.
	3 or severe	Toxicity is returned to below grade 1	Terminate nivolumab when the subject does not recover from toxicity within 12 weeks of the last dose, or when corticosteroids cannot be decreased to <10 mg/day of prednisolone within 12 weeks.
	4	Nivolumab termination	Nivolumab termination

Note: In the event that severe or ≥grade 3 side effects recur or when life-threatening toxicity develops, administration of the investigational drug will be terminated.

a. In patients with liver metastasis and HCC, any treatment for grade 2 AST and/or and ALT elevation will be resumed, and nivolumab treatment will be terminated when AST and/or ALT levels continue to be 50% higher than at baseline for ≥1 week.

b. If the subject recovers from symptoms within 1 h of dose suspension, the dose will be resumed at an infusion rate of 50% of the initial rate (e.g., 50 mL/h from 100 mL/h). If the subject does not recover from symptoms within 1 h of dose suspension, the dose will be withdrawn until the symptoms recover and pretreatment will be administered at the time of the next dose. Refer to 6.3.2.1 for details.

6.3.2.1 Supportive therapy for adverse events suspected of being associated with nivolumab

A list is provided below of examples of supportive therapy to manage adverse events with possible immunological etiology suspected of being associated with nivolumab. For details, refer to the guidance document regarding such events. A dose reduction in steroids can exacerbate symptoms, and, therefore, due care should be paid to the fact that the steroid dose should be gradually decreased over a number of courses. Additional supportive therapy may be required, and, therefore, efforts should be made to exclude other causes of each symptom (e.g., metastatic lesions and bacterial and viral infections).

Pneumonitis:

- In the event of grade 2 pneumonitis, systemic corticosteroids will be administered. When symptoms are returned to below grade 1, the dose of steroids will gradually be decreased over ≥4 weeks.
- In the event of grade 3–4 pneumonitis, steroid therapy will be administered immediately via an intravenous infusion. In addition, anti-inflammatory drugs will be administered as required.
- When steroid therapy is prolonged, antibiotics will be additionally administered to prevent opportunistic infections.

Diarrhea/colitis:

- The presence or absence of signs and symptoms of enteritis (e.g., diarrhea, abdominal pain, blood or mucus in the stool, presence or absence of accompanying fever), as well as signs and symptoms of intestinal perforation (signs of peritonitis and/or intestinal obstruction) will be verified.
- All patients who develop diarrhea/colitis will be instructed to drink sufficient water. If it is difficult for patients to drink adequate water, an intravenous infusion of fluid containing electrolytes will be administered. In the event of ≥grade 2 diarrhea, to confirm or rule out colitis, consultation of a gastroenterologist and endoscopic examination will be recommended.
- In the event of persistent grade 2 diarrhea/colitis lasting ≥3 days, oral corticosteroids will be administered.
- In the event of persistent grade 3–4 diarrhea/colitis lasting ≥1 week, a steroid intravenous infusion, followed by high-dose oral steroids will be given.
- When symptoms are returned to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks.

≥Grade 3 hyperglycemia accompanied by type-1 diabetes (including diabetic ketoacidosis in the event of newly developed type-1 diabetes), ketosis (ketonuria), and/or metabolic acidosis:

- For grade 3–4 hyperglycemia accompanied by type-1 diabetes, metabolic acidosis, and/or ketonuria, insulin replacement therapy will be considered.

- The serum glucose level and metabolism test values (e.g., urinary ketones, glycohemoglobin, and C-peptides) will be evaluated.

Hypophystitis:

- For grade 2 hypophystitis, corticosteroids will be administered. When symptoms are returned to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks. Because the steroid dose is gradually decreased, appropriate hormone replacement therapy may be needed.
- For grade 3–4 hypophystitis, an intravenous infusion of corticosteroids, followed by oral corticosteroids will be given. When the symptoms return to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks. Because the steroid dose is decreased gradually, appropriate hormone replacement therapy may be required.

Hyperthyroidism and hypothyroidism:

Thyroid dysfunction can occur at any time during the dose administration. Changes in thyroid function test values (conducted at the start of investigational drug dosing, then as subsequently required according to routine and clinical evaluations), as well as the presence or absence of signs/symptoms of thyroid dysfunction should be monitored.

- Grade 2 hyperthyroidism (and grade 3–4 hypothyroidism):
  - In hyperthyroidism, nonselective beta-blockers (e.g., propranolol) are recommended as the first line of treatment.
  - In hypothyroidism, thyroid hormone replacement therapy (e.g., levothyroxine or liothyronine) are recommended as standard treatment.
- Grade 3–4 hyperthyroidism:

  Following the intravenous infusion of corticosteroids, oral corticosteroids will be administered. When symptoms return to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks. Because the steroid dose is decreased gradually, appropriate hormone replacement therapy may be required.

Liver impairment:

- For grade 2 liver impairment, liver function tests will be performed frequently until the baseline values are restored (performance of weekly tests will be considered).

  1) Corticosteroids will be administered via an intravenous infusion or orally.
- For grade 3–4 liver impairment, corticosteroid therapy will be administered for 24–48 h via an intravenous infusion.
- When symptoms are returned to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks.

Renal impairment and nephritis:

- For grade 2 impairment, corticosteroid therapy will be administered.

- For grade 3–4 impairment, corticosteroid therapy will be administered.
- When the symptoms return to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks.

Infusion reaction management: The signs and symptoms of an infusion reaction normally appear during administration of the drug or immediately after administration, and most patients completely recover within 24 h of administration.

Table 8 lists the countermeasures to take in the event that an infusion reaction associated with nivolumab occurs.

For grade 2 or grade 3-4 immunity-related toxicities (other than those listed above), systemic corticosteroid therapy will be administered as required upon deliberation with the trial coordinating committee. When symptoms are returned to below grade 1, the steroid dose will be gradually decreased over a period of ≥4 weeks.

Table 7: Countermeasures in the event of an infusion reaction associated with nivolumab

NCI-CTCAE grade	Countermeasures	Pretreatment upon the administration of the next and subsequent doses
Grade 1 Mild reaction; does not require infusion suspension or treatment.	Increase the frequency of monitoring of vital signs until the symptoms of the patient concerned are deemed stable by the attending physician.	None
Grade 2 Infusion suspension is needed; however, the subject responds instantly to symptomatic treatment (e.g., anti-histamines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intravenous transfusion); prophylactic treatment is required within 24 h.	Suspend nivolumab dosing and monitor symptoms. Administer appropriate treatment (e.g., intravenous transfusion, anti-histamines, NSAIDs, acetaminophen, and opioid analgesics). Increase the frequency of monitoring of vital signs until the symptoms of the patient concerned are deemed stable by the attending physician. If the subject recovers from symptoms within 1 h of dose suspension, dosing is resumed at an infusion rate of 50% of the	1.5 h (±30 min) before nivolumab dosing. administer pretreatment with the drugs below. Oral diphenhydramine at a dose of 50 mg (or similar antihistamine). Oral acetaminophen at a dose of 500–1000

	initial rate (e.g., 50 mL/h from 100 mL/h). If the subject does not recover from symptoms within 1 h of dosing suspension, the dose will be withdrawn until the symptoms recover, and pretreatment will be administered at the time of the next dose. In patients who develop ≥grade 2 toxicities despite appropriate pretreatment, nivolumab treatment will be terminated (no resumption of dosing permitted).	mg (or a similar antifebrile agent).
Grade 3 Prolongation (the subject does not respond quickly to symptomatic treatment and short-term infusion suspension); recurrence despite improving once; hospital admission is required for sequelae (e.g., renal impairment, pulmonary infiltration). Grade 4 Life-threatening; administration of hypertensive drugs and artificial respiration is needed.	Suspend nivolumab dosing and monitor symptoms. Administer appropriate treatment (e.g., intravenous transfusion, anti-histamines, NSAIDs, acetaminophen, opioid analgesics, oxygen inhalation, hypertensive drugs, corticosteroids, and epinephrine). Increase the frequency of monitoring of vital signs until the symptoms of the patient concerned are deemed stable by the attending physician. The patient is hospitalized as required. Nivolumab treatment is terminated (no resumption of dosing permitted).	Nivolumab dosing is not resumed.
During nivolumab dosing, appropriate resuscitation equipment is placed in the room so that the physician can respond quickly.		

6.4 Specific instructions for subjects

The attending physician and trial collaborators will instruct the subjects on the methods of regorafenib and nivolumab 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 regorafenib administration (e.g., the collection of untaken regorafenib [i.e., the investigational drug]), and the results will be recorded on a CRF.

6.5 Combination therapy and supportive treatment

All concomitant drugs and combination therapies used from the beginning of the treatment protocol until 30 days after the final dose (when aftertreatment is administered and up to the day before administration of aftertreatment) will be recorded on a CRF. Drugs used for various tests and diagnoses do not need to be recorded on the CRF, except when required to determine a causal relationship with adverse events or for another reason.

6.5.1 Recommended combination and supportive therapies

The combination and supportive therapies listed below are recommended. Nonadministration of the therapies will not be considered a deviation from the protocol.

1) G-CSF will be administered in accordance with the approved usage and dosage.
2) 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.
3) Antidiarrheal drugs.
4) Antifebrile agent, analgesics, and steroids will be administered for immune-related events.

6.5.2 Permitted combination and supportive therapies

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

6.5.3 Unpermitted combination and supportive therapies

During the study, strong CYP3A4 inhibitors (eg, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort) are not permitted (See appendix 3).

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 Aftertreatment

There will be no aftertreatment for subjects following the termination of the stipulated treatment protocol.

7 Investigational drug information

7.1 Nivolumab drug information

Investigational drug	Nivolumab
Formulation:	Injection solution
Manufacturer:	Ono Pharmaceutical Co., Ltd.
Content:	Nivolumab injection solution: 100 mg/10 mL (10 mg/mL)
Usage:	Nivolumab injection solution is injected undiluted (10mg/mL) or diluted with physiological saline or 5% glucose injection solution to the total injection volume of 160mL or less, and through the in-line filter with a pore size of 0.2 to 1.2μm. The whole amount is administered intravenously over 30 minutes (25-40minutes). However, for subjects weighing less than 40kg, the total injection volume should not exceed 4mL/kg. After intravenous administration, flush with a sufficient amount of physiological saline or 5% glucose solution. After preparation, if not used immediately, it is possible to save up to 24 h dosing liquid at refrigeration (2 ~ 8 ° C.), to store them at room temperature for up to 8 hours (up to 25 ° C.) and under room light It is possible. When storing at room temperature and in room light, use within 8 hours after preparation, including administration time. *When administering nivolumab from the CV port or PICC, it is recommended that the dosage of nivolumab be adjusted so that the final concentration after dilution is 1.9 mg / mL or more. * It is recommended that Nivolumab could be dipped in the CV port or PICC catheterization, and flushing be performed before administration of the drug through the CV port or PICC. * When administering nivolumab through the CV port or PICC, carefully observe the subject's condition during or after administration.
Administration route:	Intravenous infusion
Expiration date	Refer to the procedures regarding investigational drug management
Labeling	The outside of the box lists the content, lot number, expiration date, number of doses, and storage method along with the name, job title and address of the coordinating physician. The box will also note that the drug is for use in the trial.

	Furthermore, the job title of the coordinating physician noted on the box will be the title at the start of the trial. If the title changes during the trial, there will be no modification made to the labeling on the box.

Nivolumab will be provided free of charge by Ono Pharmaceutical who are the investigational drug sponsor. Records of the drug manufacturing and quality testing will also be provided by the sponsor.

7.2 Regorafenib drug information

Investigational drug	Regorafenib
Formulation:	Light red elliptical film coated tablet
Manufacturer:	Bayer Yakuhin, Ltd
Content:	Hard capsule containing 40 mg of regorafenib
Usage:	Given once daily for the first 21 days of each 28 day cycle.
Administration route:	Oral
Expiration date	Refer to the procedures regarding investigational drug management
Labeling	The outside of the box lists the investigational drug code name, content, lot number, expiration date, number of doses, and storage method along with the name, job title and address of the coordinating physician. The box will also note that the drug is for use in the trial. Furthermore, the job title of the coordinating physician noted on the box will be the title at the start of the trial, and if the title changes during the trial, there will be no modification made to the labeling on the box.
Storage method	Store at 2°C–8°C in an airtight container away from light.

Regorafenib will be provided free of charge by Bayer Yakuhin, Ltd who are the investigational drug sponsor. Records of the drug manufacturing and quality testing will also be provided by the sponsor.

7.3 Investigational drug management

After the investigational drugs (i.e., regorafenib and nivolumab) have been transported to the pharmacy at the National Cancer Center Hospital East from Bayer and Ono Pharmaceuticals, the drugs will be stored by the said pharmacy.

The investigational drug manager at each participating medical institution will receive, handle, manage, store, and dispense the investigational drugs in accordance with the procedures regarding investigational drug management provided by the principal investigator. The investigational drug manager will also return or dispose of nondispensed drugs and unused drugs that have been collected from subjects in an appropriate manner. Records of such procedures are to be created and maintained

on file.

Furthermore, the attending physician will prescribe the number of doses of the investigational drug considered valid according to this trial protocol, and collect any unused investigational drugs recovered from the subjects. The collected unused drugs will then be returned to the investigational drug manager.

Moreover, the investigational drugs are not to be administered by any method other than that stipulated in this trial protocol.

Throughout the study, all unused study medication will be accounted for. The information will be recorded in the drug dispensing log.

7.4 Anticipated adverse events

Regarding any anticipated adverse events caused by regorafenib and nivolumab, with reference to the latest investigator's brochure, adverse events for which the onset tendency (including the onset or the number of occurrences, incidence, and onset conditions) of the adverse event concerned cannot be foreseen according to the investigator's brochure of the investigational drug concerned shall be referred to as "unknown," whereas those that can be foreseen shall be "known."

8 Endpoints, laboratory tests, and evaluation schedule

8.1 Observations, tests, and endpoints

Table 8.1: Observations, tests, and endpoints

Item	Details
Dosing situation	The regorafenib and nivolumab dose, treatment start date, treatment completion date or treatment termination date (dose withholding date), presence or absence of dose changes and associated reasons, presence or absence of dose withholding, number of times doses are withheld and associated reasons.
Subject background	Medical record number or identification number (number with which the patient can be identified). Sex, age, main medical history/complications/drug allergies, type of cancer, histology (e.g., pap, tub1, tub2, por1, por2, sig, muc, or other), HER2 (negative, positive, or unknown), EBV (negative, positive, or unknown), presence or absence of RAS mutation (when known), MSI status (when known), lesion site (primary site, target lesion, or nontarget lesion) and history of prior treatment (chemotherapy, radiotherapy).
Physical measurements	Height and weight
Vital signs	Body temperature, heart rate, and systolic/diastolic blood pressure
General condition	PS (ECOG)
Adverse events	≥Grade 1 subjective and objective symptoms
Concomitant drugs/combination therapy	Drug name, administration route, administration start date, administration completion date, reason for combination therapy
Blood testing	White blood cell count, neutrophil count, red blood cell count, hemoglobin, hematocrit, and platelets
Biochemistry	AST (GOT), ALT (GPT), ALP, LDH, albumin, total bilirubin, direct bilirubin, BUN, creatinine, CK, lipase, electrolytes (Na, K, Cl, Ca, IP and Mg), UA, and blood glucose (fasting and intermittent)
Blood coagulation test	PT, INR, and APTT
Urine analysis	Urinary protein, urinary sugar, and occult blood in urine
Thyroid function	Thyroid stimulating hormone, free triiodothyronine (fT3), and free thyroxine (fT4)

Pregnancy test	When pregnancy is suspected on the basis of urine analysis, blood testing shall be performed. Tests shall be performed in premenopausal women and women who experienced their last menstruation <1 year ago.
Tumor markers	Stomach cancer/colorectal cancer: CEA, CA19-9, Hepatocellular carcinoma : PIVKA-II, and alfa-fetoprotein (AFP)
Electrocardiography	12-lead electrocardiography (ECG) at rest
Infection	HIV antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody and HBV-DNA assay
Tumor evaluation	Chest/pelvic contrast-enhanced CT*, or abdominal/pelvic contrast-enhanced MRI*, as well as chest X-ray, brain CT, and brain MRI as required *In subjects with allergies/hypersensitivities to the contrast medium used for CT and MRI, the tests can be performed without a contrast medium. When treatment is terminated for reasons other than an exacerbation of the underlying disease on imaging, evaluations shall be performed until an exacerbation is confirmed.
Outcome investigation	The presence or absence of aftertreatment shall be investigated, and in the event that aftertreatment is administered, the treatment method and the start date shall be recorded. The date of death, or last day of confirmed survival, and in the event of death, the cause of death shall be investigated. *Even if a subject cannot be directly followed up for reasons such as hospital transfer, survival is to be confirmed as far as possible by contacting the hospital where the subject was transferred, and the result of such contact is to be noted in the medical records.

8.2 Observation and test schedule

The observation and testing schedule is presented in Table 9. 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 9.

Table 8.2 Schedule

Cycle	Screening	Investigational drug administration period	Terminat	30 days	Follo

		period (−14 days to day 0)	Cycle 1				Cycle 2 onwards		ion date[d)]	after last dose[e)]	w-up perio d
Day Permissible range			1	8	15	22	1	15	Day 0 to +7	Day −3 to +7	
Visit			○	○	○	○	○	○	○	○	○
Treatment											
Regorafenib treatment			→	→	→		→	→			
Compliance			○				○				
Nivolumab treatment			○		○		○	○			
Background, etc.											
Consent acquisition		○									
Verification of inclusion criteria and exclusion criteria		○									
Subject background		○									
Body measurements	Height	○									
	Weight	○	○ c)				○		○	○	
vital signs/PS Weekly BP monitoring for the first 6 weeks		○	○	○	○	○	○	○	○	○	
Combination drugs/therapies with adverse events		○	○	→	→	→	→	→	→	→	
Laboratory tests											
Blood tests (blood count, biochemistry[g)])		○	○ c)	○	○	○	○	○	○	○	
Urine analysis		○	○ c)	○	○	○	○	○	○	○	

Thyroid function	○	○ c)				○		○		
Coagulation test	○	○ c)				○		○		
Pregnancy test[a)]	○									
Tumor markers	○	○ c)				○		○		
12-lead ECG	○	○ c)				○		○		
Infection test	○ b)									
Tumor evaluation										
Chest/abdominal/ pelvic CT (MRI) and other evaluations	○	Conducted at 6 (±1 week), 12 (±1 week), 18 (±1 week), and 24 weeks (±1 week) after the start of treatment, followed by every 9 weeks until week 42, then every 12 weeks thereafter.							△ f)	
Exploratory biomarker tests										
Tumor specimens, blood sampling	Refer to the TR protocol									
Follow-up										
Outcome investigation										○

a) Limited to women capable of childbearing. Refer to section 9.3.8

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).For lipase, the value measured 14 days before registration can be used.

d) 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.

e) Follow-up tests for safety are conducted 30 days after the last dose of the investigational drug. 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.

In addition, when observations and tests cannot be conducted because of the subject's condition, they should be conducted as soon as possible.

f) Refer to section 8.5.

g) Only subjects who received explanation from the doctor agree to perform before and after protocol treatment start 4-6 weeks, at the time of discontinuation. Refer to 8.6

8.3 Examination findings

8.3.1 Subject background

・Clinical diagnosis

Primary and metastatic lesion sites, etc.

・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.

・ surgery

・ chemotherapy(Number of enforcement regimens, pretreatment anti-PD1 / PD-L1 administration)

・radiation

・other treatments

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 height/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 (PS)

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

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.

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

The items listed in Table 8.1 will be tested in accordance with the time indicated in the schedule presented in Table 8.2, 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. And appropriate test items for adrenocorticotropic hormones (such as ACTH) will be added as needed.

8.4.2 Tumor markers

The 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 <7 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

HIV antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody and HBV-DNA assay 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 assay are measured only when either HBs antibody or HBc antibody are positive.

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 Tumor evaluation

For all subjects, 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, 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 10). 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 10 lesions can be included as target lesions, with a maximum of five lesions per organ.

Table 8.5: 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	To confirm disease	Investigational drug dosing can be	If possible, repeat the test	Interruption of dosing

determined by imaging	progression, repeat the test after 4 weeks	continued at the discretion of the attending physician until disease progression is confirmed by retesting at the participating medical institution	after 4 weeks to confirm 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

In the event of clear clinical progression according to symptom exacerbation as judged by the attending physician, treatment should be terminated even if there is no confirmed progression according to an image diagnosis. Symptoms indicating clinical progression must be recorded in the subject's medical records. Efforts shall be made to confirm progression objectively by imaging as much as possible, even after termination of treatment.

8.6 Biomarker Biopsy Blood sampling

Before and after the start of the investigational medicine, serum (or plasma), immunocompetent cells such as mononuclear cells, residual diseased tissue are obtained from peripheral blood and lesion tissue (biopsy specimen) around 4-6 weeks after start. For subjects who had a therapeutic effect, blood specimens and tissue specimens may be obtained after disease progression only when consent is obtained from subjects (for details see the accompanying research implementation plan).

8.7 Follow-up

Outcome investigations will be performed after termination of the treatment protocol until the subject dies, or up to 2 years 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 DATE 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, 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 Adverse event evaluation

10.1.1 Definition of adverse events

Adverse events include all undesirable or unintentional signs, symptoms, and conditions (including abnormal changes in laboratory test values) that arise in subjects administered the investigational drugs, regardless of the presence or absence of a causal relationship with the investigational drug concerned.

When ≥grade 1 subjective or objective symptoms are observed before the start of treatment (at the time of the baseline evaluation), only those for which the grade of the adverse event concerned deteriorates compared with the pretreatment level will be treated as adverse events.

10.1.2 Method of recording adverse events

When signs (including abnormal laboratory test values) and symptoms are included in the diagnosis, the name of the diagnosis according to the CTCAE will be recorded on the CRF as far as possible, rather than each individual sign and symptom.

Abnormalities in laboratory test values will be reported as adverse events only when the attending physician deems that any of the following conditions are satisfied:

1) When clinical signs or symptoms are induced
2) When deemed clinically important
3) When treatment is required
4) When additional tests are required (only repeat tests are exempt)
5) When termination or dose reduction of the investigational drug is required

10.1.3 Adverse event report items

For adverse events that develop, the following information will be reported on a CRF:

1) Name of adverse event
2) Severity (CTCAE grade 0–5 and serious/nonserious)
3) Causal relationship with the treatment protocol
4) Onset date, date of outcome confirmation, and outcome
5) Presence or absence of treatment

＊Investigator will assess if the AE is related to study procedure, regorafenib, or nivolumab, if possible

10.1.4 Determination of a causal relationship

A causal relationship with the treatment protocol is determined according to the following step:

- Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the

CRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Table 11: Classification of causal relationships

Classification		Definition
Definite (certain)	Definite	A causal relationship with the treatment protocol is plausible, and symptoms cannot be explained by an exacerbation of the underlying disease, complications, or other drugs/treatments
Probable (likely)	Probable, likely	A causal relationship with the treatment protocol is reasonable, and symptoms are unlikely attributable to the exacerbation of the underlying disease, complications, or other drugs/treatments
Possible	Possible	A causal relationship with the treatment protocol is reasonable, and symptoms can be explained even with an exacerbation of the underlying disease, complications, or other drugs/treatments
Unlikely	Unlikely	A causal relationship with the treatment protocol is improbable, and symptoms can be explained by exacerbation of the underlying disease, complications, or other drugs/treatments
Not related (unrelated)	Unrelated	There is no causal relationship with the treatment protocol, and symptoms can be clearly explained by an exacerbation of the underlying disease, complications, or other drugs/treatments
Unassessable (conditional)	Unassessable	There is insufficient data to determine a causal relationship, and more detailed data is required (conditional), or evaluation

		is difficult

10.1.5 Follow-up observation upon the onset of an adverse event

When adverse events develop, the attending physician will immediately take appropriate measures.

Follow-up observation will be performed even after completion of the adverse event evaluation period (refer to section 11.1.6) until recovery from or alleviation of the symptoms is confirmed (test values). However, when one or more of the following conditions apply, follow-up observation of adverse events can be concluded.

*Follow-up of adverse events shall be concluded when:

- It is deemed that the adverse event is not serious, a causal relationship can be ruled out, and at least 30 days have passed since the day of the last dose
- The principal investigator has judged that symptoms are stable and that there is no major medical problem
- Aftertreatment has been administered and a causal relationship with the investigational drug cannot be evaluated
- Follow-up observation is difficult because the subject has been transferred to another hospital or for another reason
- The subject refuses follow-up observation
- Death

10.1.6 Adverse event evaluation period

In the present trial, the adverse event evaluation period will last from “the treatment start date” until “30 days after the day of the final investigational drug doses, or before the start of aftertreatment if that occurs beforehand, whichever is earliest.” Data pertaining to any adverse events that occur during this period will be collected.

Data will also be collected regarding adverse events from 31 days after the day of the final investigational drug doses when it is deemed that there is a causal relationship with the treatment protocol.

After PD is confirmed, new adverse events that occur as a result of disease progression will not be included.

10.2 Reporting of serious adverse events

10.2.1 Definition of serious adverse events

Of the adverse events described in section “11.1 Adverse event evaluation,” those that meet any of the following will be defined as “serious adverse events.”

1) Adverse events that cause death or are life-threatening

2) Adverse events that cause permanent or marked impairment/dysfunction

3) Adverse events that cause congenital abnormalities/birth defects

4) Adverse events that require hospitalization or prolongation of the hospital stay

However, the following will be exempt:

－Hospitalization or death due to the underlying disease after PD is confirmed

－Hospitalization or prolongation of the hospital stay that was planned beforehand

－Hospitalization or prolongation of the hospital stay unrelated to adverse events

－Hospitalization or prolongation of the hospital stay of <24 h for follow-up observation only

5) Medically important events are defined as events that endanger the subject or events that require internal medicine or surgical treatment to prevent the abovementioned outcomes.

10.2.2 Mandatory reporting and reporting procedures for the principal investigator (or subinvestigator)

1) Reporting to the director of medical institution implementing the trial and the trial coordinating committee

① Initial report

In the event of a serious adverse event (refer to section "11.2.1 Serious adverse events"), the trial principal investigator (or subinvestigator) is to immediately take appropriate action. The subinvestigator will report promptly to the principal investigator.

The principal investigator (or subinvestigator) will report the occurrence of serious adverse events to the directors of the medical institutions implementing the trial and trial coordinating committee in writing (by e-mail or fax) or verbally (by telephone) within 24 h of discovery of the adverse event concerned. When the initial report is made without using the "Report form for serious adverse events," a written report is to be submitted in a promptly (by e-mail or fax).

Furthermore, the details of serious adverse events will be reported to the directors of the medical institutions implementing the trial and the trial coordinating committee within 5 working days of discovering the adverse event.

*Reporting by e-mail is recommended.

② Additional reports

The principal investigator (or subinvestigator) will follow-up serious adverse events (refer to section "11.1.5 Follow-up upon adverse event onset"). Additional information will be recorded on the "Report form for severe adverse events" (additional report), and sent to the directors of the medical institutions implementing the trial and the trial coordinating committee.

Trial coordinating committee contact details: Office of the trial coordinating

committee

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

TEL: 04-7133-1111 (Ext. 5200), FAX: 04-7134-6860

When the trial coordinating committee, directors of the medical institutions implementing the trial, institutional review board, or trial sponsor request further information, the principal investigator (or subinvestigator) will comply with additional reports.

10.2.3 Mandatory reporting and reporting procedures for the trial coordinating committee

With regard to serious adverse events reported in the initial and additional reports, the trial coordinating committee will judge the necessity of reporting (in accordance with "Article 80-2, paragraph 6 of the Pharmaceutical Affairs Law" and "Article 273 of the Pharmaceutical Affairs Law Enforcement Regulations") the severity, causal relationship, and predictability to the regulatory authority concerned (Pharmaceuticals and Medical Devices Agency: PMDA).

The detailed reporting procedure will be performed in accordance with the "Procedures regarding the handling of safety information."

1) Reporting to the principal investigator

According to the decision noted above, reported serious adverse events will be reported by the trial coordinating committee to each principal investigator without delay. Each principal investigator will report to the director of the medical institution concerned as quickly as possible in accordance with the regulations of each medical institution.

2) Reporting to the PMDA

When reporting to the PMDA is deemed necessary, the trial coordinating committee will comply in accordance with article 273 of the Pharmaceutical Affairs Law Enforcement Regulations and other related notifications.

3) Reporting to the Data and Safety Monitoring Committee

When the review of serious adverse events by the Data and Safety Monitoring Committee is deemed necessary, the trial coordinating committee will submit a written report requesting the opinion of the committee with regard to the assessment of the principal investigator and trial coordinating committee regarding the adverse event concerned, as well as the validity of the response to the adverse event concerned (judgments of the severity of the adverse event, causal relationship, and predictability).

4) Reporting to the investigational drug supplier/concomitant drug supplier

As a general rule, serious adverse events reported by the principal investigator(or subinvestigator) will be reported by the trial coordinating committee to the investigational drug

supplier (i.e., Ono Pharmaceutical) within 24 h.

10.2.4 Duties of the Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will examine the details of adverse event reports, and submit written advice to the trial coordinating committee with regard to countermeasures such as continuation of the trial and the need for protocol revision. Procedures will follow the prescribed "Procedures for the Data and Safety Monitoring Committee" attached separately.

10.3 Collection of safety information

When information regarding the investigational drugs is obtained from the investigational drug supplier, the trial coordinating committee will respond in accordance with article 273 of the Pharmaceutical Affairs Law Enforcement Regulations and other related notifications. The trial coordinating committee will report the safety information concerned to each principal investigator and each principal investigator will report to the director of their medical institution as promptly as possible in accordance with the regulations of each medical institution.

The detailed reporting procedures will follow the "Procedures for handling safety information."

In addition, the need for revision of the protocol and informed consent form, as well as the need to provide an explanation to subjects will be judged, and if deemed necessary, such needs will be addressed.

10.4 Pregnancy

During individual trial participation periods and during periods of contraception, when information regarding pregnancy is obtained from a subject, administration of the investigational drug will be terminated, and the information will be reported using the designated form without delay to the trial coordinating committee (as a general rule, within 24 h of obtaining the information). As a rule, the trial coordinating committee will submit the form obtained to the investigational drug suppler (Ono Pharmaceutical) within 24 h. The principal investigator (or subinvestigator) will conduct a follow-up survey regarding the pregnancy of the subject concerned, and report this in writing. The reporting procedures will follow the prescribed "Procedures for handling safety information" attached separately.

10.5 Overdosing

In the dose escalation cohort, overdosing is given when the dose exceeded the dose prescribed at each level shown in Table 6.1.1a, and Expansion cohort exceeds the RD determined based on the result of dose escalation cohort.

In the event of an overdose of the investigational drug, the principal investigator (or subinvestigator) will take the appropriate countermeasures, and report these using the designated

form without delay to the trial coordinating committee (as a general rule, within 24 h of obtaining the information). As a rule, the trial coordinating committee will submit the form obtained to the investigational drug suppler (Ono Pharmaceutical) within 24 h. The reporting procedures will follow the prescribed “Procedures for handling safety information” attached separately

11 Response evaluation and endpoints

11.1 Response evaluation

The tumor response evaluation will be conducted in accordance with the RECIST guideline version 1.1 and irRECIST (Appendices 2 and 3). Thoracoabdominal and pelvic contrast-enhanced CT or MRI will be performed (if the patient is allergic to the contrast medium, plain scans are permitted), and the tumor response will be according to image measurements. In the event of PD of the primary disease, refer to section “8.5 Tumor assessment.”

Furthermore, the period of 4 weeks (28 days) to determine the best overall response of CR or PR is not required in this study.

11.2 Definition of endpoints

11.2.1 Incidence of adverse events

Regarding AEs occurring during the protocol treatment, the incidence of each AE of the worst grade according to the CTCAE v4.03 throughout the entire cycles will be calculated.

11.2.2 Objective response rate (ORR)

ORR is defined as the proportion of patients whose best overall response, as per the RECIST guideline version 1.1 and irRECIST, is either CR or PR.

11.2.3 Progression-free survival (PFS)

PFS is defined as the time from the enrollment date to either the date when disease progression is determined or the date of death from any cause, whichever came earlier.

- "Progression" is defined as PD in the assessment of overall response by diagnostic imaging based on the RECIST guideline version 1.1, and the imaging examination date is set as the date of progression. For clinical PD, the date when clinical PD is documented is defined as the date of progression.
- Surviving patients who are not assessed as having progression will be censored on the last date on which an absence of clinical progression is confirmed (hereinafter referred to as the "last date of progression-free survival confirmed). (If information on progression or progression-free is obtained from a medical institution to which the patient was transferred or referred, a patient referral document indicating the basis for the diagnosis should be received and retained. Obtaining the information by telephone only is not permitted.)
- Patients who died without being assessed as progression are handled as having "an event occurring on the date of death" in principle, unless the period from the last confirmation date of progression-free survival to the date of death is long.

  Whether to handle the patient as being "censored on the last confirmation date of progression-free survival" should be determined in the case review meeting to be held as required, before the data are finalized.

- Patients with treatment discontinuation for reasons such as AEs and their refusal to continue participation, who are given another treatment as subsequent treatment, should be handled as being "censored on the start date of the subsequent treatment."
- The occurrence of a secondary malignancy (metachronous multiple cancers) will not be considered either an event or censoring, but will be considered PFS until another event is observed.

11.2.4 Disease control rate (DCR)

DCR is defined as the proportion of patients whose best overall response assessed based on the RECIST guideline version 1.1 and irRECIST is any of CR, PR, or SD.

11.2.5 Overall survival (OS)

OS is defined as the period from the date of enrollment to the date of death from any cause.

Surviving patients will be censored on the last confirmation date of survival (confirmation of survival by telephone is permitted; however, the fact that survival is confirmed should be recorded in the medical record, etc.).

Patients lost to follow-up will be censored on the last date on which their survival has been confirmed before being lost to follow-up.

12 Statistical Matters

This protocol stipulates the statistical analysis plan. If any change arises in the statistical analysis plan, it should be described in the clinical study report, including its background. A summary of the statistical analysis plan is described below.

12.1 Handling of patients

The handling of patients will be determined by the representative coordinating investigator after discussing with the data center.

12.2 All enrolled patients

"All enrolled patients" are defined as patients enrolled in this study in accordance with Section "5. Enrollment," excluding those who have been enrolled multiple times or mistakenly enrolled.

12.3 Definition of analysis populations

Each analysis population is defined below.

Abbreviation	Analysis population	Definition
None	DLT analysis set	See Section “6. Treatment Regimen and Treatment Modification Criteria.”
SP	Safety population	The population of patients who received the investigational product at least once among all enrolled patients.
FAS	Full analysis set	The population of patients that excludes those to whom the following applies from all enrolled patients: • Patients who should have been judged as clearly ineligible based on the information before enrollment (ineligible patients).

12.4 Data handling

The handling of data (e.g., inclusion or exclusion criteria for the analysis population) will be determined by the coordinating committee after discussing with the data center.

12.4.1 Handling of missing values and outliers

In principle, imputation of missing values and analyses dealing with outliers will not be performed. However, when the presence of missing values or outliers that may have a significant impact on analysis results is identified before data lock, the handling of such data will be determined at a case review meeting and the measures to be taken will be described in the case

review meeting minutes.

12.4.2 Dealing with additional analyses

All analyses planned in this study are specified in Section "12.5 Positioning of analyses and analysis methods." Analyses other than the final analysis are regarded as additional analyses. The results from additional analyses will be reported with a note clarifying that the analyses were not planned in advance, or will be reported in a separately prepared additional analysis report.

12.5 Positioning of analyses and analysis methods

As the purpose of this study is exploratory examination, future decision-making rules will not be specified. However, if this study allows the dose finding for the investigational products, demonstrates a certain level of safety, and confirms the efficacy and safety of the protocol treatment in other secondary endpoints, the future development of the protocol treatment of this study will be regarded as promising. In this study, the following one-time analysis (final analysis) will be performed. The advisability of the dose-level transition will be decided by the coordinating committee. However, since the decision on transition is made only based on the evaluation of the incidence of DLTs, analyses related to dose-level transition are positioned as part of monitoring.

12.6 Safety analysis

12.6.1 Analysis of the incidence of AEs

The occurrences of AEs in the SP will be summarized. Confidence intervals will not be constructed, and subgroup analysis will not be performed.

12.7 Analysis of secondary efficacy endpoints

The following analyses will be performed as required (only listings may be presented depending on the study results).

12.7.1 ORR, DCR

The confidence intervals of ORR and DCR will be constructed using an exact method based on a binominal distribution. When subgroup analysis is performed, proportions or odds ratios will be compared among subgroups using appropriate analytical procedures, such as Fisher's exact test and logistic regression.

12.7.2 PFS, OS

By estimating survival functions using the Kaplan-Meier method, median survival times and their confidence intervals will be constructed, as well as annual survival rates and their confidence intervals. The confidence intervals for median survival times will be estimated by the Brookmeyer and Crowley method. The confidence intervals for annual survival rates will be estimated using Greenwood's formula. When subgroup analysis is performed, treatment responses compared among

the subgroups will be summarized using appropriate analytical procedures, such as the log-rank test and Cox proportional hazards model.

The survival time will be calculated by defining 1 year as 365.25 days and 1 month as 365.25/12 days. The calculation formula is [("Event date" or "Censoring date") − "Study enrollment date" + "1 day"].

12.8 Target sample size

[Dose escalation cohort] 3 to 6 patients at each level; 12 to 18 patients in total

[Expansion cohort] About 30 patients in total

12.9 Rationale for the sample size

See Section "6. Treatment Regimen and Treatment Modification Criteria."

12.10 Interim analysis

No interim analysis will be performed in this study.

12.11 Final analysis

All endpoints will be analyzed in the final analysis. The final analysis will be performed according to the protocol and the analysis results will be reported in the clinical study report.

12.12 Special notes on analysis items

12.12.1 Items summarized and analyzed in the final analysis

In the final analysis, the following items will be analyzed.

<Items to be summarized>

- Demographic data
- Concomitant therapies
- Changes in laboratory values

To summarize a continuous variable, general descriptive statistics (mean, median, minimum, maximum, etc.) will be calculated.

<Items to be analyzed>

- Incidence of AEs
- Objective response rate (ORR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)

<Subgroup analysis to be performed>

Subgroup analyses will be performed in an exploratory manner for the following factors. In these

analyses, adequate statistical power is not guaranteed and adjustment for multiplicity is not performed. Therefore, the results of each subgroup analysis will be interpreted as exploratory results.

- Cancer type
- Presence or absence of anti-PD-1 antibody use in the prior treatment

Since data on the following factors will be collected in an additional study to this study, the following subgroup analysis results will not be included in the clinical study report of this study.

- PD-L1 (Negative / Positive)
- MMR (Proficient / Deficient)
- TMB (High / Low)

etc.

12.12.2 Analysis items included in the clinical study report

The following analysis items will be included in the clinical study report.

<Efficacy evaluation (Analysis population: all enrolled patients)>

- Demographic data
- Objective response rate (ORR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)

<Safety evaluation (Analysis population: SP)>

- Incidences of DLTs/AEs (number of patients with DLTs/AEs and the incidence, by the worst grade)
- Summary statistics of laboratory values and their changes

<Tables, figures and graphs referred to but not included in the text of the clinical study report>

- Listings of deaths, other serious and significant adverse events
- Laboratory value listing by patient

<Appendix>

- List of discontinued patients
- List of patients with serious protocol deviations
- List of patients excluded from FAS
- History of prior treatment
- List of concomitant medications and therapies
- Compliance
- List of efficacy response data by patient (tumor assessment, OS, PFS, subsequent treatment, and tumor markers)
- Adverse event listing 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

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.

13.2.3 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 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) Purposes of use

   In this study, the patients' personal information will be used for the purpose of properly implementing monitoring, etc.

2) Items to be used

   In consideration of the minimum necessity for identifying the patients and inquiries, items to be used will be as follows:

   Enrollment No., patient identification (ID) No.

   In other words, personal information other than the above items such as the patient's name will not be disclosed from the study sites to external parties. When study results are provided to parties other than the study sites, all information enabling to identify individuals will be anonymized and then provided.

3) Handling methods

   The personal information and medical data 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.

13.4.3 Changes in the Contents of the Protcol

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.

13.4.4 Categories of Changes in the Contents of the Protocol

In this study, changes in the contents of the protocol should be handles as amendments or revisions, and a supplementary explanation on the protocol should be handled as a memorandum or Q&A.

1) Amendment

   An amendment refers to a partial change in the protocol that may increase risk to patients enrolled in the study or substantially affect the primary endpoint of the study. Approval of the efficacy and safety evaluation committee and each study site will be required.

2) Revision

   A revision refers to a change in the protocol that may not increase risk to patients enrolled in the study nor substantially affect the primary endpoint of the study. Approval of each study site 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 requested.

3) Memorandum or Q&A

   A memorandum or Q&A refers to not a change in the contents of the protocol but a supplementary explanation on the protocol to be distributed from the coordinating committee to study related persons for the purposes of reducing variances in interpretation of the document and particularly calling for attention. No review by or approval of the efficacy and safety evaluation committee is required.

13.4.5 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.

13.5 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 (Sumitomo Dainippon Pharma Co., Ltd. and MSD K.K.) will not involve in any essential part of the study such as the operation of the study and the interpretation of results. However, contracts will be exchanged for the PK evaluation and the evaluation of the biomarkers (additional study) as joint studies.

13.6 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)

15 Special considerations

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 Accompanying 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.

1) Purpose

To analyze how administration of regorafenib and nivolumab in cancer patients affects immune cells, as well as the local effects on the tumor site and systemic effects.

2) Endpoints

i. Microsatellite instability

ii. HLA haplotype

iii. Analysis of the phenotype of immunologically competent cells

- T-cell fractionation (CD3/CD4/CD8/FoxP3/CD25/CD45RA, etc.)
- Effector T cells/memory T cells (CCR7/CD45RO/CD127, etc.)
- Exhausted T cells (CTLA-4/PD-1/Tim-3/LAG-3/TIGIT/GITR/ICOS, etc.)
- Effector regulatory T cells (CCR4, etc.)
- NK cells and NKT cells (CD16/CD161/CD56/CD117, etc.)

- Antigen-presenting cells, tumor-associated macrophages, and MDSCs (CD33/CD14/CD68/CD11b/CD11c, etc.)

iv. Serum protein analysis (cytokines, chemokines, and autoantibodies)

v. For the histopathological analyses (iii. above), the analysis will focus on immune checkpoint molecules such as PD-L1.

3) Handling of samples

In the present investigator-led trial, samples will be collected. The details regarding sample collection are noted in the accompanying research protocol.

4) Data analysis

Analysis of this accompanying research is described in the accompanying research protocol.

16 Research organization

The present trial is a multicenter collaborative investigator-led trial, supported by a trial coordinating committee.

16.1 Main research group of this trial

Refer to attachment 1

16.2 Funding of the present trial

The present trial is conducted in part using funds obtained from Bayer Healthcare and Ono Pharmaceuticals, with the investigational drugs supplied 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 Ownership of the trial outcomes and announcement of the trial results

The research results belong to the National Cancer Center. The presentation of the research results at conferences and in papers will be determined at the time of announcement by the trial coordinating committee upon deliberation with the principal investigators and other parties concerned.

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Center, Duarte, CA; Memorial Sloan Kettering Cancer Center, New York, NY; MD Anderson Cancer Center, University of Texas, Houston, TX; British Columbia Cancer Agency, Vancouver, BC, Canada; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; Bristol-Myers Squibb, Princeton, NJ; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC). *J Clin Oncol 32:5s*, *2014 (suppl; abstr 5010).* 2014.

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