Identifiers: NCT03453164 Unique Protocol ID: RK29040

Brief Title: Checkpoint Inhibitor and Radiotherapy for Recurrent Gastric Cancer (CIRCUIT)

Date: 13 Nov, 2017

Informed Consent Form

Clinical Trial

Explanation for

Phase I/II Clinical Trial of Nivolumab (Anti-PD-1 Antibody) in Combination with Local Radiation Therapy for Unresectable Advanced or Recurrent Gastric Cancer Refractory to Standard Therapy

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This study is a "clinical trial" planned and conducted by the principal investigator. Clinical trial is research in which patients participate and cooperate to investigate in detail how well a new treatment or diagnostic method works against a disease (efficacy) and what types of side effects or complications occur and at what rate (safety).
We explain this study in an easy-to-understand manner. Please make your own decision whether or not to participate in this study after fully understanding the contents. If you have any questions, please do not hesitate to ask.

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1. Purpose and significance

Multi-drug anticancer therapy combining several anticancer agents is currently recommended in Japan for the treatment of unresectable advanced or recurrent gastric cancer. Recent advances in chemotherapy have allowed a relatively high rate of tumor shrinkage, but the prognosis is still poor. The immune checkpoint inhibitor of nivolumab (anti-PD-1 antibody)[1] was shown to be effective in the treatment of unresectable advanced or recurrent gastric cancer that is refractory or intolerant to standard treatment. In September 2017, nivolumab was approved as a third-line chemotherapy for patients who have failed to standard primary/secondary chemotherapy.[2] However, the response rate of 11.2% was not as high as expected, and there is an urgent need to develop new treatments and combination therapies.

Radiotherapy has long been widely used as a symptomatic treatment for patients with unresectable advanced or recurrent gastric cancer, including cancer pain associated with bone metastases, etc. In recently, it has been reported that cancer antigen-specific immunity (reacting only to cancer cells) is activated after radiotherapy. Furthermore, case reports and clinical trials have reported synergistic effects when radiotherapy is combined with immunotherapy with immune checkpoint inhibitors such as anti-PD-1 antibody and anti-CTLA-4 antibody, etc. However, there are no reports of this combination therapy for patients with advanced or recurrent gastric cancer. Therefore, we plan to conduct the study to investigate the efficacy and safety of the combination of radiotherapy and nivolumab.

If this study proves that the combination therapy using radiotherapy and nivolumab is more effective and safer than conventional treatments, it may be new treatment for many patients with the same disease as yours.

[1] Nivolumab is an antibody that binds specifically to PD-1, a protein on the surface of lymphocytes responsible for immunity. By binding to PD-1, nivolumab prevents PD-1 from binding to PD-L1 on the

surface of cancer cells. Thus, nivolumab prevents lymphocytes from decreasing their function, which is thought to allow them to attack cancer cells and reduce the size of the tumor.

[2] The first anticancer drug treatment is called 'primary chemotherapy', and when this treatment becomes ineffective and the patient moves on to the next type of chemotherapy, it is called 'secondary chemotherapy'.

2. Methods and duration

1) Description of procedures

Enrolled patients receive radiotherapy for five consecutive days, followed by nivolumab (an anti-PD-1 antibody) intravenously once every two weeks for a total of six doses of 3 mg/kg (body weight) or 240 mg per dose (dosage and administration of nivolumab follow the recommended treatment for unresectable advanced or recurrent gastric cancer).

2) Observation and inspection schedules

This study period is divided into a pre-observation period, a treatment (radiotherapy + nivolumab) period, and a post-observation period. Please see the table below for the medical examinations and tests you will undergo during each period. For the clinical examination, a blood sample of 10–50 ml is collected. If the attending doctor decides that it is necessary, the number of tests may be increased, or other tests may be required.

If you are currently attending another hospital, please inform us of that the name of hospital, the disease for which you are receiving treatment, and what medication you are using. Please also let us know if you are taking any medications that you buy and use from pharmacies or other sources. Informing us of such medications is important to ensure the safety of the study. Please also note that if you are attending another hospital, we may inform that hospital that you are taking part in the study.

① Pre-observation period

After you have agreed to participate in this study, and before treatment begins, attending doctor

investigate your health status and previous illnesses and treatments to ensure that you meet the conditions for participation. In addition, attending doctor examine you and take standard measurements (e.g., height, weight, blood pressure, pulse) and general condition, as well as perform imaging tests such as chest-abdominal-pelvic enhanced CT, blood tests, urine tests, electrocardiogram (12-lead ECG), and others. Please do not eat or drink anything for eight hours prior to each examination.

② Treatment (Radiotherapy + Nivolumab) duration

If you can participate this study, your health and other conditions is re-examined before each treatment. If no problems are found, radiotherapy is given first. Then, nivolumab treatment start within two weeks of the end of radiotherapy and is given every two weeks, for a total of six doses. You also be asked to visit the hospital at regular intervals to monitor the efficacy and safety of the treatment; during these visits, attending doctor check your condition and perform examinations. If the scheduled visit date is not convenient, you can consult attending doctor and come back within 14 days of the scheduled treatment date. On the day of the clinical examination, please do not eat or drink anything for eight hours prior to each examination.

③ Post-observation period

Approximately 1 month and 3 months after your last nivolumab treatment (120 and 180 days after the start of radiotherapy, respectively), a health status check is performed. Depending on the results of each examination, you may be required to undergo additional tests. Please do not eat or drink anything for at least eight hours before you come to the hospital until you have had the examination.

④ At the time of cessation of treatment

All medical examinations and tests should be done within 14 days after the decision to stop treatment has been made. There is no need to do them if you are unable to come to the hospital, e.g., because you are admitted to another hospital. In such cases, please inform us that you cannot

come to the hospital.

Schedule

Period	Registration	At the end of radiotherapy	Nivolumab administration						Day 120	Day 180	At the time of cessation of treatment
			1st	2nd	3rd	4th	5th	6th			
Patient background	○										
General findings	○	○	○	○	○	○	○	○		○	○
General condition	○	○	○	○	○	○	○	○		○	○
Subjective and objective findings	○	○	○	○	○	○	○	○		○	○
Imaging	○				○			○	○	○	○
ECG	○										
Blood count	○		○	○	○	○	○	○		○	○
Coagulation	○										
Blood biochemistry	○		○	○	○	○	○	○		○	○
Urinalysis	○										
Infection	○										
Pregnancy test (if necessary)	○										
Immunological [1]parameters ①[1]	○										
Immunological parameters ②[2]	○		○		○		○			○	○

[1] **Histology** (analysis of tumor microenvironment by Immunohistochemical staining)

* No new burden, because the tumor tissue samples from the previous diagnosis are used.

[2] **Peripheral blood testing** (peripheral blood lymphocyte subset analysis, plasma cytokine assays,

regulatory T cell function analysis, and antigen-specific T cell function analysis, etc.).

3) Expected duration of participation in this study and number of expected participants

This study take place between March 2018 and January 2021.

Your participation in this study last for approximately six months (of which approximately 13 weeks is spent receiving treatment).

A total of 40 patients are expected to participate.

3. About the patients who will be included in this study

The conditions under which you can or cannot participate in this study are listed below. However, please note that even after you have given your consent, you may not be able to participate depending on the results of the tests.

Inclusion criteria

1) Patients with unresectable advanced or recurrent gastric cancer that was intolerance or had progression after standard treatment (primary or secondary chemotherapy).
2) Those aged 20 years and over.

Exclusion criteria

1) Patients with no tumor lesions that can be irradiated.
2) Patients with metachronous or simultaneous overlapping cancers.
3) Patients with a history of severe hypersensitivity reactions to other antibody products.
4) Patients taking immunosuppressive drugs or corticosteroids (prednisone or prednisolone equivalent 15 mg or more/day).
5) Patients with autoimmune diseases or a history of recurrent autoimmune diseases. However,

patients with type I diabetes mellitus, hypothyroidism that can be controlled by hormone replacement therapy and skin diseases that do not require systemic management are eligible to participate.

6) Patients with complications or history of interstitial pneumonia or pulmonary fibrosis.

There are many other criteria for participation in this study, which is determined by the attending doctor after a detailed examination and consultation. In some cases, even if you meet all of the above criteria, you may not be able to participate in this study. In addition, even if the study has already started, we may stop the study if it becomes clear that you do not meet the criteria for participation, or if the attending doctor decides that it would be better for you not to continue with this study.

4. Anticipated benefits and disadvantages/burdens of participation

Anticipated benefits

There is a possibility that the disease may improve more than when radiotherapy and nivolumab treatment are administered separately. The information obtained from this study may also be useful for patients suffering from the same disease.

Disadvantages/burdens

The side effects that may occur with the treatment administered in this study may be more severe than those that occur with radiotherapy and nivolumab, respectively. However, these potential side effects are unknown at this time. Serious side effects of nivolumab treatment that have been reported at this time are summarized below.

Types of serious side effects	Frequency of appearance (%)
Interstitial pneumonia	3.0

Myasthenia gravis, myocarditis, myositis, rhabdomyolysis	Frequency unknown, frequency unknown, 0.1, frequency unknown
Colitis, severe diarrhea	1.3, 1.0
Type 1 diabetes mellitus	0.4
Immune thrombocytopenic maculopathy	Frequency unknown
Liver dysfunction, hepatitis, sclerosing cholangitis	0.7, 0.3, frequency unknown
Thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis)	7.1, 3.1, 1.2
Neuropathies (peripheral neuropathy, polyneuropathy, autoimmune neuropathy)	1.2, 0.1, frequency unknown
Renal impairment (renal failure, tubulointerstitial nephritis)	0.5, 0.1
Adrenal disorders (adrenal insufficiency)	1.0
Encephalitis	Frequency unknown
Severe skin disorders (toxic epidermal necrolysis, cutaneous mucous membrane eye syndrome, erythema multiforme)	Frequency unknown, frequency unknown, 0.2
Venous thromboembolism (deep vein thrombosis, pulmonary thrombosis)	0.1, 0.1
Infusion reaction	2.5

Additional side effects can be found in the nivolumab package insert.

The side effects of radiotherapy depend on the irradiated area. The attending doctor of radiotherapy provide an explanation tailored to the irradiated site.

In this study, the attending doctor carefully administer treatment, and if any side effects occur, the attending doctor treat them promptly and appropriately.

5. Other treatment options if you do not participate in this study

If you do not wish to participate in this study, we discuss and decide which of the other treatment options may be best for you. Other treatment options include:

1) Nivolumab alone
2) Radiotherapy alone

3) Other anticancer drugs (fourth-line treatment or later)

If you prefer any other treatment, please do not hesitate to talk to us.

6. Freedom to participate in this study and freedom to withdraw the consent

Your participation in this study is your own choice. Please read this document carefully and make your own decision whether or not to participate in this study after careful consideration, including consultation with your family. If you have any questions, please do not hesitate to ask. If you agree to participate, please sign (or write your name and seal) the consent document.

You can withdraw from the participation of this study at any time, even during the course of the study, so please do not hesitate to inform your attending doctor.

If you decline to participate in this study or withdraw from participation during the course of the study, you will not be disadvantaged in any way with regard to your subsequent treatment. We provide you with the treatment that we determine to be best for you at that point in time.

In addition, if new information (e.g., changes of the study protocol or the occurrence of serious adverse events in other subjects for which a direct causal link to this study cannot be ruled out and which cannot be foreseen) becomes available after the initiation of the study, you may be asked again about participating in this study.

7. Protection of personal data and handling of the study results

1) If you participate in this study, in order to confirm that the study is being conducted properly, people involved in this study (e.g., staff of Fukushima Medical University Hospital and Kanagawa Cancer Center, monitoring personnel, audit personnel, committee officials responsible for clinical research review, and officials of the Ministry of Health, Labor and Welfare) will have access to your medical records and research records. Even in such cases, these persons are obliged to maintain confidentiality (not to divulge the contents of the records to outside parties), and your

personal information is strictly protected and never revealed to any third party.

2) Upon your request, materials related to the Study Protocol may be disclosed to the extent that it does not affect the protection of the personal information of other subjects or the originality of this study.

3) When the results of this study are presented at conferences or in scientific journals, they will be anonymized so that individuals cannot be identified before publication.

By signature (or name and seal) on the consent document, you agree that the above 1), 2), 3) and the attending doctor obtain your personal information related to this study, which deemed necessary by the attending doctor. In addition, the samples and data (test data, etc.) provided by you in this study will be used only for this study and will not be used for any other purpose (see also items 8 and 11 below).

8. Methods of storage and disposal of samples and information

During your participation in this study, your personal data, including your health condition and treatment details and samples such as blood, will be stored strictly at Fukushima Medical University Hospital as anonymized data (coded data) that do not contain your personal information. The samples will be stored for five years from the date of completion of this study or five years from the date of publication of the results (whichever is later). The data will be stored for five years from the date of completion of this study or five years from the date of publication of the results (whichever is later). They are then processed appropriately, such as by shredding, and discarded.

9. Treatment and compensation in the event of health problems related to this study

If you have any symptoms during or after this study, please do not hesitate to contact us. We will treat you appropriately in the same manner as a regular medical treatment. Your health insurance will be

used to cover your medical expenses, and you will pay a part of the cost of your medical care.

In addition, there is no special compensation, such as medical expenses, medical benefits, or compensation payments, for any health problems that occur in this study. Please make sure that you fully understand this point before making a decision to participate in this study.

10. Treatment after completion of this study

After the Study Protocol is completed, treatment will continue under normal insurance coverage.

11. The possibility of using the data and samples for future research

Data and samples collected for this study may be used for other researches. This is a case where something is not yet planned or anticipated now but will require very significant investigation in the future. If we plan to use your data in the future beyond the scope of the purposes and items explained to you when you participated in this study, we will separately proceed with the prescribed screening procedures at Fukushima Medical University as new research. We will also publicize this information on our website, etc., and ensure that you have the opportunity to express your refusal to participate in new research.

12. Conflicts of interest (interests with companies, etc.)

When a research group receives funding from pharmaceutical companies or other sources other than public funds, questions can arise as to whether the study is being conducted for the benefit of the company and/or whether the results of the study will not be fairly published (i.e., there can be concerns that only results that are favorable to the company will be published). This is called a conflict of interest (a conflict between the interests of the patients and of the research group or pharmaceutical company). In order to ensure the transparency of economic interest relationships to ensure the fairness and reliability of the study, economic interest relationships in this study are managed in accordance with

the Conflict of Interest Management Standards and Conflict of Interest Management Plan approved by the Certificated Clinical Research Review Committee.

This study is funded by an academia-initiated contract research agreement from Ono Pharmaceutical Industries, Ltd. and Bristol-Myers Squibb K.K., which manufacture the drug being used in this study, nivolumab. The principal investigator of this study, Prof. Kono, has received a speaker fee from Ono Pharmaceutical Industries, Ltd. The funders of Ono Pharmaceutical Industries, Ltd. and Bristol-Myers Squibb K.K. are only involved in providing information on the study drug, and are not involved in the planning of this study, and progress, data collection, analysis, interpretation of results, reporting, etc. after the start of this study. Conflicts of interest between the principal investigator and Ono Pharmaceutical Industries, Ltd. and Bristol-Myers Squibb K.K. are appropriately managed.

In addition, some analyses of immunological parameters will be carried out by scientific research funds (national research funds) obtained by researchers from Fukushima Medical University Hospital and other sources.

13. Participant's cost sharing

The treatment provided in this study is covered by your health insurance and your.co-payment. There is no honorarium.

14. Methods of disclosing information

An overview of this study is registered with the University Hospital Medical Information Network Research Centre Clinical Trials Registry System (UMIN-CTR, https://www.umin.ac.jp/ctr/index-j.htm) and the US clinical trials registry system (ClinicalTrials.gov, https://clinicaltrials.gov) before starting the study. The content of registration will be updated according to changes in the Study Protocol and the progress of the study. When this study is completed, the results will be registered and may also be published at conferences and in scientific journals.

15. The review of the suitability of this study to be carried out

After the Certificated Clinical Research Review Committee thoroughly examined not only the medical aspects but also the human rights, safety, and welfare of the patients, and concluded that there are no problems with the implementation of this study, and following approval by the head of each institution, this study is conducted. In addition, a summary of the Study Protocol is submitted to the Minister of Health, Labor and Welfare. The review committee for this study is as follows.

Name of the Certificated Clinical Research Review Committee: The Certificated Clinical Research Review Committee of Fukushima Medical University School of Medicine

Authorization number: CRB2180002

Location: 1 Hikarigaoka, Fukushima-City, Fukushima, Japan

16. Name of the research organizations, principal investigator, and chief investigators

Principal Investigator: Koji Kono, Chief Professor, Gastrointestinal Tract Surgery, Fukushima Medical University Hospital

Chief Investigators: Koji Kono, Chief Professor, Gastrointestinal Tract Surgery, Fukushima Medical University Hospital

Takashi Oshima, Chief of Gastro-esophageal Division, Gastrointestinal Surgery, Kanagawa Cancer Center

17. Matters to be observed

If you agree to participate in this study, please observe the following:

1) Follow the precautions set in this study until the study is completed.

2) Contact us immediately if your condition is unusual or you have any unusual symptoms.

3) During the study period, there are certain medications that cannot be used because they may affect the evaluation of the study treatment. If you decide to use a new medication, please inform your

attending doctor before using the medication. Even if you purchase the medication at a pharmacy, etc., do not take it at your own discretion, but consult your attending doctor in advance.

4) If you consult or will consult another department in our hospital or another hospital, please notify your attending doctor of your consultation. To ensure your safety and to evaluate the potential influence on this study, we may, with your approval, inform your doctor that you are participating in this study and inquire about your treatment (e.g., medications used, etc.).

5) Contact your attending doctor if you are unable to come to the hospital on the appointed date for any reason.

6) Do not disclose any information related to this study to any third party.

7) Consult your attending doctor if you have any other concerns.

18. Consultation service

If you have any questions about this study, please contact us at the following address.

Weekdays: 9:00 a.m. to 5:00 p.m. (We can not respond on National Holidays, Saturdays, Sundays, and during the year-end and New Year's holidays).

Contact

Kosaku Mimura

Gastrointestinal Tract Surgery, Fukushima Medical University Hospital, 1 Hikarigaoka, Fukushima-city, Fukushima 969-1295, Japan TEL: 024-547-1220

Yoshiyuki Suzuki

Radiation therapy, Fukushima Medical University Hospital, 1 Hikarigaoka, Fukushima-city, Fukushima 969-1295, Japan TEL: 024-547-1590

The following consultation service is available for complaints, consultations, or inquiries regarding the research conducted at Fukushima Medical University Hospital, including this study.

Please use this service if you have any questions that you would like to discuss with someone other than the attending doctors in this study.

Contact

Consultation Service for Clinical Research Participants

Fukushima Medical University Hospital, 1 Hikarigaoka, Fukushima-city, Fukushima 969-1295, Japan

TEL:090-1938-7374 (Reception hours: 9:00–17:00)　E-mail: c-kiban@fmu.ac.jp

Please note that we may not be able to provide a response from the standpoint of protecting the personal information of other subjects or the intellectual property rights of the researcher.

Consent Form

To Principal investigator Koji Kono

I agree to be a subject for the following research project.
I add that I have given my consent based on the written explanation and that I understand the following conditions.

Title of clinical trial:
Phase I/II Clinical Trial of Nivolumab (Anti-PD-1 Antibody) in Combination with Local Radiation Therapy for Unresectable Advanced or Recurrent Gastric Cancer Refractory to Standard Therapy

Chief investigator

Name: _____

Belonging to: _____

Official title: _____

Conditions of consent

1. I can withdraw this consent at any time for my own reasons.
2. I will not suffer any disadvantage in treatment etc. as a result of the withdrawal of my consent.
3. On my request, I can obtain information regarding the results of this study on me at any time.
4. The principal investigator and those involved in this study do their best to treat my illness or maintain my health in relation to this study.
5. During the course of study protocol, the principal investigator and those involved in this study take appropriate measures to manage any unexpected incidents that occur to me in relation to this study.
6. The confidentiality of any personal information regarding me obtained by anyone involved in this study in relation to this study will be strictly protected.

[Patient's signature]

Date of consent: _____

Name (Signature): _____

[Signature of the attending doctor who explained the consent form]

Date of explanation: _____

Belonging to: _____

Name (Signature): _____

Consent Withdrawal Form

To Principal investigator Koji Kono

I withdraw my consent to participate as a subject in the following research project.

Title of clinical trial:
Phase I/II Clinical Trial of Nivolumab (Anti-PD-1 Antibody) in Combination with Local Radiation Therapy for Unresectable Advanced or Recurrent Gastric Cancer Refractory to Standard Therapy

Chief investigator

Name: _____

Belonging to: _____

Official title: _____

With regard to this withdrawal of consent:

□ The information can be used until the withdrawal of consent form is submitted.

□ I withdraw my consent to the use of all information.

[Patient's signature]

Date of withdrawal of consent: _____

Name (Signature): _____