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

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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

CIRCUIT trial

Statistical Analysis Plan

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1. Definition of Statistical Analysis Plan

The purpose of this Statistical Analysis Plan is to specify the rationale and details of the analysis methods to be used in the clinical trial, entitled "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". This Statistical Analysis Plan was prepared in accordance with the Study Protocol of this clinical trial.

2. General matters

2.1 Software used

SAS for Windows ver. 9.4 or R software (version 4.0.3.).

2.2 Significance levels and confidence coefficients

Unless otherwise noted, confidence intervals are two-tailed with a confidence coefficient of 95%.

2.3 Numerical display of results

As a rule, the results of the analysis should be displayed in the formats shown below. Rounding of the displayed value is done by round off.

Minimum value maximum value	Significant digits of data
Average value, quantile	Significant digits of data + 1 digit
standard deviation	Significant digits of data + 2 digits
%	1 decimal place
P-value	3 decimal places; however, if the value is 0.001 or less, it is expressed as "< 0001".

3. Case handling and analysis population

3.1 Case handling

The principal investigator decides on the handling of cases before the data are fixed, following a review of eligibility and non-compliance with the Study Protocol at the case review meeting.

1) All enrolled cases: the population of enrolled patients excluding duplicate enrollments and incorrect enrollments.
2) All eligible cases: the population excluding ineligible cases (posterior ineligibility, ineligibility at enrollment, offending enrollment) from all enrolled cases.
3) Largest analyzed population (FAS): all eligible patients for whom treatment was administered.
4) Safety analysis population: all enrolled cases, those for whom treatment was administered.

3.2 Analysis population

Efficacy is examined in the FAS and safety is examined in the safety analysis population.

4. Examination of test reliability

1) **Purpose**

Describe the occurrence of major registration violations, discontinuations, drop-outs, etc. in all enrolled cases, and specify the population to be analyzed.

2) **Analysis population**

All enrolled cases.

3) **Analysis items**

(1) Number of cases belonging to the analyzed population.

(2) Early discontinued or not.

(3) Any deviations from the Study Protocol.

4) **Method of analysis**

(1) Number of cases in the enrolled, eligible, and largest analyzed cohort are tabulated.

(2) Cases of early discontinuation are tabulated according to reason and institution.

(3) Cases of deviation from the Study Protocol are tabulated according to reason and institution.

(4) A list of cases of treatment failure, early discontinuation, and deviations from the Study Protocol is prepared.

5. Comparability considerations

5.1 Demographic items and baselines

1) **Purpose**

To get an overview of the analyzed population in terms of patient background and baseline.

2) **Analysis population**

FAS and safety analysis population.

3) **Analysis items**

Gender, age, presence or absence of allergies, presence or absence of medical history, presence or absence of complications, history of treatment for cancer, general condition (ECOG PS), cancer lesions, organs with cancer, rheumatoid factor (RA), antinuclear antibodies (ANA), SP-D, KL-6, thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4), tumor markers (CEA, CA19-9).

4) **Method of analysis**

For continuous quantities, summary statistics (mean, standard deviation, minimum, first quartile, median, third quartile, maximum) are calculated. For categorical data, frequencies and proportions are calculated.

5.2 Treatment status

1) **Purpose**

Assessing treatment status.

2) **Analysis population**

FAS.

3) **Analysis items**

(1) Number of subjects who do not complete radiotherapy or discontinue radiotherapy by Day 14 and the reasons for those discontinuations.

(2) During protocol treatment (from the start of radiotherapy to the sixth dose of nivolumab), distribution of the number of doses of nivolumab, distribution of the number of days between doses, and reasons for discontinuation of nivolumab.

4) **Analysis methods**

(1) Calculate the completion rate of radiotherapy and determine the frequency of uncompleted treatment by reason of incompletion.

(2) Calculate the distribution of nivolumab dosing frequency and the proportion of protocol treatment completed. Calculate the basic statistics of the number of days between doses.

(3) Prepare a list of the above treatments.

6. Efficacy considerations

6.1 Investigation of primary endpoint

1) **Purpose**

To explore the efficacy of protocol treatment for unresectable advanced or recurrent gastric cancer, determine the disease control rate of the best overall response, which is SD or better, confirmed by Day 180.

2) **Analysis items**

Disease control rate of non-irradiated target lesions.

3) **Analysis methods**

(1) Construct a waterfall plot for disease control.

(2) Summarize the responses of non-irradiated target lesions in a contingency table, and calculate the cumulative disease control rate and the Clopper & Pearson two-side 90% confidence interval.

6.2 Investigation of secondary endpoints

6.2.1 Median survival time

1) **Purpose**

To explore the efficacy of protocol treatment for unresectable advanced or recurrent gastric cancer, determine the median survival time using overall survival defined as the period from the start date of radiotherapy until the date of death from any cause.

2) **Analysis items**

Survival time from the start date of study treatment to death from any cause.

3) **Analysis methods**

(1) Estimate and draw the survival function using the Kaplan-Meier method with log-rank test.

(2) Estimate of the median survival time is calculated using the Kaplan-Meier method, along with a two-sided 95% confidence interval using the Brookmeyer-Crowley method.

(3) Estimate of the probability survival rate is calculated using the Kaplan-Meier method, along with a two-sided 95% confidence interval using the Greenwood's formula.

6.2.2 Local control rate

1) **Purpose**

To explore the efficacy of protocol treatment for unresectable advanced or recurrent gastric cancer, determine the local control rate of the best overall response, which is SD or better, confirmed by Day 180.

2) **Analysis items**

Local control rate (disease control rate of irradiated target lesions).

3) **Analysis methods**

(1) Construct a waterfall plot for the local control rate.

(2) Summarize the responses of irradiated target lesions in a contingency table, and calculate the cumulative disease control rate and the Clopper & Pearson two-side 90% confidence interval.

6.3 Interim analysis

Not conducted in this study.

6.4 Adjustment analysis by patient background and baseline

Not conducted in this study.

6.5 Sensitivity analysis (handling of omissions or missing values)

Not conducted in this study.

6.6 Examination of homogeneity between institutions

Not conducted in this study.

6.7 Subgroup and supplementary analyses

The disease control rate and local control rate are analyzed in the same manner as in the main analysis by irradiation site and administration status, etc.

Survival is analyzed in the same manner as the main analysis by completion of study treatment and by irradiation site, etc.

7. Safety considerations

7.1 Investigation of adverse events

1) **Purpose**

Examine the occurrence of adverse events to examine the safety of the protocol treatment.

2) **Analysis items**

Name of adverse event, date of onset, worst grade, severity, outcome, and association with protocol treatment.

3) **Analysis methods**

The frequency of adverse events occurring from the start date of radiotherapy to the end of study is tabulated by adverse event name and worst grade (toxicity) according to CTCAE ver.4.0, and the Clopper & Pearson two-sided 95% confidence interval is calculated. Calculate the frequency and rate of adverse events, the frequency and rate of adverse events by severity, and the frequency and rate of grade 3 or higher adverse events.

A serious adverse event is defined as having occurred if at least one of the following adverse events is observed, and the frequency and proportion of serious adverse events is calculated.

① Death during protocol treatment or within 30 days of last protocol treatment.

② Death with undeniable causal relationship to protocol treatment after 31 days of last protocol treatment.

③ Grade 4 infection with neutropenia.

④ Grade 4 non-hematological toxicity (excluding adverse events in the blood/bone marrow).

Prepare a list of adverse event cases.

7.2 Investigation of clinical laboratory values

1) **Purpose**

Examine the clinical laboratory values to examine the safety of protocol treatment.

5) **Analysis population**

FAS.

2） **Analysis items**

Vital signs (temperature, pulse, blood pressure).

Subjective and objective findings (PS, fever, nausea, vomiting, diarrhea, decreased appetite).

Hematological examination (white blood cell count, neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio, red blood cell count, hemoglobin concentration, MCV, MCH, MCHC, Ht, platelets).

Blood biochemical tests (total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, BUN, creatinine, LDH, uric acid, CPK, P, Ca, Na, K, Cl, CRP, blood sugar, rheumatoid factor (RF), anti-nuclear antibodies (ANA), SP-D, KL-6, thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4), CEA, CA19-9).

3） **Analysis methods**

Prepare transition graphs (per individual and group) of the measured values. Calculate the basic statistics (median and quartiles, or frequency and rate) of the measured values.

Prepare lists of vital signs, subjective and objective findings, hematological examination, and blood biochemistry tests.

8. List of patient data

8.1 List of cases excluded from safety analysis (untreated cases)

1） **Purpose**

Prepare a list of untreated cases.

2） **Analysis object**

Untreated cases

3） **Analysis items**

Case number, institution name, age, gender, reason for not treated.

8.2 List of cases excluded from efficacy analysis

1） **Purpose**

Prepare a list of cases excluded from FAS.

2） **Analysis object**

Cases excluded from FAS.

3） **Analysis items**

Case number, institution name, age, gender, reason for exclusion from analysis.

8.3 List of early discontinuation cases

1） **Purpose**

Prepare a list of early discontinuation cases.

4） **Analysis object**

Safety analysis population.

2） **Analysis items**

Case number, institution name, age, gender, date of discontinuation, reason for discontinuation.

8.4 List of cases of deviation from the Study Protocol

1） **Purpose**

Prepare a list of cases of deviation from the Study Protocol.

2） **Analysis object**

Cases of deviation from the Study Protocol.

3） **Analysis items**

Case number, institution name, age, gender, reason and extent of the deviation.

8.5 Lists regarding demographic data/baselines

1） **Purpose**

Prepare a list of enrolled cases.

2） **Analysis object**

All enrolled cases.

3） **Analysis items**

Case number, institution name, age, gender, allergies, smoking cessation history, alcohol consumption history, medical history, complications, history of cancer chemotherapy, PS, RA, ANA, SP-D, KL-6, TSH, free T3, free T4, CEA, CA19-9.

8.6 List of treatment status

1） **Purpose**

Prepare a list of treatment status for cases subjected to safety analysis.

2） **Analysis object**

Safety analysis population.

3） **Analysis items**

Case number, age, gender, radiotherapy start date, radiotherapy end date, nivolumab administration date, concomitant medications.

8.7 List of effective response data

1） **Purpose**

Prepare a list of effective response data for cases subject to efficacy analysis.

2） **Analysis object**

FAS.

3） **Analysis items**

Case number, age, gender, radiotherapy start date, date of death or last verified survival, alive or dead status, regimen, irradiation site, best overall response on disease control, best overall response on local control, and changes in lesions over time (examination date, tumor diameter).

8.8 List of adverse events per patient

1） **Purpose**

Prepare a list of adverse events in cases in which adverse events are observed among the cases subjected to safety analysis.

2） **Analysis object**

Safety analysis population.

3） **Analysis items**

Case number, age, gender, name of adverse event (serious adverse events are marked with *), date of occurrence (day), worst grade, severity, outcome, date of outcome (day), relevance.

8.9 List of individual laboratory values and other information for each patient

1） **Purpose**

Prepare a list of laboratory values for cases in which vital signs, subjective and objective findings, and laboratory tests were performed.

2） **Analysis object**

Safety analysis population.

3） **Analysis items**

Vital signs (temperature, pulse, blood pressure).

Subjective and objective findings (PS, fever, nausea, vomiting, diarrhea, decreased appetite).

Hematological examination (white blood cell count, neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio, red blood cell count, hemoglobin concentration, MCV, MCH, MCHC, Ht, platelets).

Blood biochemistry tests (total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, γ-GTP, BUN, creatinine, LDH, uric acid, CPK, P, Ca, Na, K, Cl, CRP, blood glucose, rheumatoid factor (RF), antinuclear antibody (ANA), SP-D, KL-6, thyroid stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4), CEA, CA19-9.