Non-Interventional Study Protocol
B1771015 and B1771016

TORISEL 25mg Injection Special Investigation All patient surveillance

TORISEL 25 mg Injection Special Investigation Long-term use surveillance

Statistical Analysis Plan

Version: 3.0

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[redacted]

TABLE OF CONTENTS

1. AMENDMENTS FROM PREVIOUS VERSIONS

Version	Date	Author(s)	Summary of Changes/Comments
1.0	14/SEP/2012	PPD	Initial version
2.0	09/MAR/2016	PPD	• Section 2.1.2: The study design of long-term use survey was added. (Omission) • Section 2.2.2: The objective of long-term use survey was added. (Omission) • Section 3: With analyses for periodic safety update reports positioned as interim analyses, the description was modified. • Section 5.1: Patients in whom a resurvey cannot be performed were deleted from patients to be excluded from the safety analysis set. • Section 5.1: Patients with experience of treatment with TORISEL were deleted from patients to be excluded from the safety analysis set. (Clerical error) • Section 5.2: Patients who did not use the specified dosage regimen were deleted from patients to be excluded from the efficacy analysis set. (Clerical error) • Section 5.2: Patients with experience of treatment with TORISEL were added to patients to be excluded from the efficacy analysis set. (Clerical error) • Section 6.1: The duration of treatment was added. • Section 8.1.1: The details of summary statistics were added. • Section 8.1.3: The details of confidence interval and test method were added. • Section 8.1.4: The analysis of time data (time to the onset of event) was added. • Section 8.2: It was specified to tabulate and analyze

Version	Date	Author(s)	Summary of Changes/Comments
			data from the all patient surveillance and data from the long-term use survey together. • Section 8.2.4: "8.2.4 Analysis of patient demographics" was divided to "8.2.4 Overview of patients" and "8.2.5 Patient demographics and treatment history." (Description adjustment) • Section 8.2.5: The categories of each item were specified in "patient demographics." • Section 8.2.5: The categories of each item were specified in "status of exposure to this drug." • Section 8.2.6: The categories of each item were specified in "further tabulation of adverse reactions." • Section 8.2.6: Major investigation items to be tabulated and analyzed were specified in "cumulative incidence of adverse reactions." • Section 8.2.6: Major investigation items to be tabulated and analyzed were specified in "cumulative incidence of CTCAE Grade ≥ 3 adverse reactions." • Section 8.2.6: Demographic items specified in "incidence of adverse reactions by patient demographic" were moved to Section10.1.1 "Patient demographics to be used to evaluate safety and efficacy" and categories were specified. In addition, major investigations items to be tabulated and analyzed were specified. • Section 8.2.6: Major investigations items to be tabulated and analyzed were specified in "incidence of CTCAE Grade ≥3 adverse reactions by patient demographic." • Section 8.2.6: Major investigations items to be tabulated and analyzed were specified in "incidence of CTCAE Grade ≥ 3 adverse reactions by patient

Version	Date	Author(s)	Summary of Changes/Comments
			demographic." • Section 8.2.6: "Incidence of adverse reactions by medical history, prior treatment history, and concomitant therapy" was added. • Section 8.2.6: The description "patients with special background" was changed to "subgroups." • Section 8.2.6: Tabulation by presence/absence of treatment, the outcome of patients with CTCAE Grade 1 events, and the time course of CTCAE Grade were added to "further tabulation of interstitial lung disease." • Section 8.2.6: "Further tabulation of diabetes mellitus/hyperglycemia" was added. • Section 8.2.6: "Further tabulation of hypercholesterolemia/hyperlipidemia" was added. • Section 8.2.6: "Further tabulation of infection" was added. • Section 8.2.6: "Further tabulation of mucositis-related adverse events" was added. • Section 8.2.6: "Further tabulation of skin disorder" was added. • Section 8.2.6: Tabulation of the duration of treatment was added to CCI [redacted] analyses. • Section 8.2.7: Clinical benefit rate was added to the tabulation of response rate. In addition, the categories of each item were specified. • Section 8.2.7: Demographic items specified in "response rate by patient demographic" were moved to Section 10.1.1 "Patient demographics to be used to evaluate safety and efficacy." • Section 8.2.7: "CCI [redacted] tabulation analyses" was

Version	Date	Author(s)	Summary of Changes/Comments
			added. • Section 10 CCI tabulation analyses" in the previous version was deleted, and the CCI tabulation analysis plan was moved to Section 8.2.6 and Section 8.2.7. • Other modifications of clerical errors and description adjustments were made.
3.0	15/SEP/2016	PPD	• Section 6.2: Progression-free survival (PFS) was added. • Section 8.1.4: The calculation of 95% confidence interval was added. • Section 8.2.7: An analysis in the safety analysis set was added to calculate the response rate and clinical benefit rate in the case where patients who were "unassessable" in the efficacy evaluation (patients excluded from the efficacy evaluation) are considered as patients who did not respond to treatment or did not achieve clinical benefit. • Section 8.2.7: The tabulation analysis of progression-free survival was added.

2. INTRODUCTION

This statistical analysis plan describes the analysis plan for the special investigation (all patient surveillance and long-term use surveillance) of TORISEL 25 mg Injection. In this plan, sentences cited from the protocol are shown in italics.

2.1. Study Design

2.1.1. All Patient Surveillance

This study is a non-interventional study in a cohort of 600 patients who received TORISEL 25 mg Injection for unresectable or metastatic renal cell carcinoma for 24 weeks.

<Subjects>

All patients who received this drug will be included in the all patient surveillance that will be conducted for a certain period.

Target number of cases: 600 cases

Target number of cases observed: 300 cases treated for 12 weeks or longer (300 cases with Booklet 03 case report form)

(Cases who discontinued the drug before 12 weeks will also be included.)

[Rationale]

The incidence of all the adverse events included in the major investigation items of this study was 1.0% or higher in the drug group of the foreign phase 3 clinical study (304-WW Study). Assuming that the true incidence of an adverse event (particularly an adverse event included in the major investigation items) is 1.0%, 300 cases are required to observe at least 1 case with the event at a probability of at least 95%. The incidence of interstitial lung disease was 17.1% (14/82) in the multinational (Asian) phase 2 clinical study (2217-AP Study). Assuming that the true incidence of interstitial lung disease is 17.1%, at least 40 cases with the disease can be observed at a probability of at least 95%.

Further, clinical study results showed that interstitial lung disease occurred on Week 4 after the start of the drug or later, and that, in rare cases, some adverse events had an increased incidence or delayed onset as the administration period was prolonged. Considering these results, it was decided to set a target that this study would include 300 cases treated with this drug for 12 weeks or longer.

Clinical study results showed that this drug could be continued for 12 weeks or longer in about 60% of the whole treated cases, with a discontinuance/drop-out rate at 12 weeks of about 40%. Considering that this study will be conducted under actual use condition, it is assumed that the discontinuance/drop-out rate at 12 weeks in this study will be increased by 10% to 50%. That is, it is assumed that this drug will be continued for 12 weeks or longer (the Booklet 03 case report form will be collected) in 50% of the cases included in this study.

Therefore, this surveillance was planned to register 600 cases to collect 300 cases treated with this drug for 12 weeks or longer. In addition, because cases which discontinue the drug before 12 weeks will be included in the study, the case report form will be collected from them to evaluate safety and effectiveness.

2.1.2. Long-term Use Surveillance

This study is a non-interventional study in a cohort of patients who were registered in the all patient surveillance and received this drug for unresectable or metastatic renal cell carcinoma for more than 24 weeks.

Among the patients registered and treated in the all patient surveillance, those to be continuously treated with this drug for more than 24 weeks will be included in this study. That is, the target number of cases to be registered in the all patient surveillance is 600 (rationale stated in the protocol of the all patient surveillance) and those to be continuously treated for more than 24 weeks will be registered again in this study. Therefore, no definite target number of cases is set for this study. However, the expected number of cases to be registered in this study is shown below and considered as the target number of cases to be registered.

Expected number of cases: about 120 cases

[Rationale]

The expected number of cases to be registered in this study is described. In the clinical trials, (304-WW and 2217-AP Studies), about 35% of the subjects could be continuously treated for 24 weeks or longer, with a discontinuance/drop-out rate at 24 weeks being about 65%. Considering that the all patient surveillance will be conducted under actual use condition, and that it is necessary to re-register from all patient surveillance to this study, it is assumed that the discontinuance/drop-out rate at 24 weeks in the all patient surveillance will be further increased by 15% to 80%. That is, it is assumed that 20% of the cases included in the all patient surveillance will be registered in this study after the completion of the all patient surveillance. It is therefore expected that about 120 cases will be registered in this study when 600 cases will be registered in the all patient surveillance. However, the actual number of cases registered may be different from the expected number because it depends on the conditions and results of the all patient surveillance.

2.2. Study Objectives

2.2.1. All Patient Surveillance

The objective of this study is to assess the following subject matters in patients treated with TORISEL 25mg Injection (hereinafter called this drug) in post-marketing actual use conditions, thereby providing proper-use information.

1. *To confirm the effectiveness and safety of this drug under actual use conditions.*
2. *To examine the onset state of adverse events and potentially influencing factors (particularly, major investigation items).*
3. *To examine the onset state and potential onset risk factors of interstitial lung disease.*

2.2.2. Long-term Use Surveillance

The objective of this study is to assess the safety of the long-term use of TORISEL 25 mg Injection (hereinafter called this drug) particularly for the onset of interstitial lung disease from Weeks 25 to 96 after the start of administration.

3. INTERIM AND FINAL ANALYSES

Interim analyses for periodic safety update reports will be periodically performed in this study. Among statistical analyses specified in this plan, only those necessary for periodic safety update reports will be performed at interim analyses. In addition, the final analysis for application for reexamination will be performed. All analyses specified in this plan will be performed at the final analysis.

4. HYPOTHESIS AND DECISION RULES

Because this study is not a confirmatory study, tests are CCI [redacted]. Unless otherwise specified, tests are 2-sided and the significance level is 5%. Two-sided confidence interval will be used in interval estimation, and the confidence coefficient is 95%.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set basically consists of patients who received at least 1 dose of this drug.

However, patients who violate safety criteria among separately specified patient inclusion criteria will be excluded.

Contract deficiency, contract violation, registration violation, no visit after the date of initial dose, no administration, safety evaluation “unassessable”

5.2. Efficacy Analysis Set

The efficacy analysis set basically consists of evaluable patients (patients considered to have undergone an appropriate evaluation).

However, patients who violate efficacy criteria among separately specified patient inclusion criteria will be excluded.

Not meeting conditions for target patients, experience of treatment with this drug, efficacy evaluation “unassessable” (not meeting conditions for assessment).

5.3. Other Analysis Sets

Not applicable.

5.4. Subgroups

Not applicable.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

1. *Onset state of adverse events/adverse reactions (particularly the major investigation items).*
2. *Onset state of adverse reactions and potential influencing factors (particularly the major investigation items).*
3. *Safety in patients with special background (pediatric patients, elderly patients, pregnant women, patients with renal or hepatic dysfunction).*
4. *Safety in patients with hepatic dysfunction (including the comparative examination with results from the foreign phase 1 clinical study).*
5. *Onset state of interstitial lung disease (including asymptomatic cases with imaging findings of the disease).*

6. *Potential risk factors of interstitial lung disease.*

7. *Characteristics of interstitial lung disease (imaging findings, onset timing, duration, and breakdown by severity).*

8. *List of clinical course of interstitial lung disease (contents of treatment, response to treatment, and outcome) and clinical course after the drug is restarted (presence/absence of recurrence/exacerbation, etc.).*

9. *Onset state of various related events suspected of causing interstitial lung disease (pneumonitis/lung infiltration and pulmonary fibrosis, etc.).*

10. Duration of treatment (Defined as the period from the date of initiation of treatment with this drug to the date of completion of treatment with this drug in this study. Patients for whom the completion of treatment is not reported in this study will be censored at the date of last dose.).

6.2. Efficacy Endpoints

1. Response rate (percentage of complete response [CR] + partial response [PR])

2. Clinical benefit rate (percentage of CR + PR + stable disease [SD] for at least 24 weeks)

3. Progression-free survival (PFS): Time from the date of initiation of treatment with this drug in this study to the date progressive disease (PD) or all-causality death is first confirmed during the treatment period (including 28 days after the completion of treatment with this drug) and the period up to the date of final evaluation of tumor response. PD or death occurring during the treatment period (including 28 days after the completion of treatment with this drug) or the period up to the date of final evaluation of tumor response, whichever period is the earlier, will be handled as a PFS event, and patients without a PFS event will be censored at the date of final evaluation of tumor response. Patients with no record on tumor response at all will be censored at the date of initiation of treatment with this drug.

7. HANDLING OF MISSING DATA

Not applicable.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, maximum, and minimum) will be calculated.

8.1.2. Analysis of Categorical Data

The frequency of each category and its percentage will be calculated.

8.1.3. Analysis of Binary Data

Frequency and its percentage will be calculated. If the confidence interval for percentage is calculated, the 2-sided 95% confidence interval (exact method) will be calculated.

If a test is performed, Fisher's exact test will be performed for the relationship with nominal scale data and Cochran-Armitage test (exact method) for the relationship with ordered scale data.

8.1.4. Analysis of Time Data (time to the onset of event)

Ninety-five percent confidence intervals for median, first quartile, and third quartile by the Kaplan-Meier method will be calculated. In addition, Kaplan-Meier plots will be prepared.

8.2. Statistical Analyses

Unless otherwise specified, data from the all patient surveillance and data from the long-term use surveillance will be tabulated and analyzed together.

8.2.1. Appendix Form 3 (list of the summary of included patients)

Appendix Form 3 (list of the summary of included patients) will be prepared for registered patients.

8.2.2. Appendix Form 2 (list of the onset state of adverse reactions and infections)

Appendix Form 2 (list of the onset state of adverse reactions and infections) will be prepared for patients included in the safety analysis.

8.2.3. Appendix Form 10 (list of the onset state of serious adverse events)

Appendix Form 10 (list of the onset state of serious adverse events) will be prepared for patients included in the safety analysis.

8.2.4. Summary of Patients

- **Number of study sites and number of patients by type of establisher.**

The number and percentage of study sites and the number and percentage of patients will be tabulated by type of establisher in patients for whom the case report form was collected.

In addition, the mean, minimum, and maximum of the number of patients per site will be tabulated.

> University hospitals, national hospitals established by the Ministry of Health, Labour and Welfare, prefectural and municipal hospitals, public organizations, and hospitals and clinics other than the above 4 types established by corporations and individuals

- **Composition of patients.**

The number of registered patients, patients for whom the case report form was collected, patients included in the safety analysis, and patients included in the efficacy analysis, and the number of patients excluded from registration, patients for whom the case report form was not collected, patients excluded from the safety analysis, and patients excluded from the efficacy analysis, and the number of patients by reason will be tabulated in registered patients.

- **Status of discontinuation and dropout.**

The number of patients will be tabulated by whether the study was discontinued and reason for discontinuation by volume of case report form in the safety analysis set.
Similarly, the number of patients will be tabulated by whether the study was discontinued and reason for discontinuation by duration of treatment.

- **List of excluded patients and reasons for exclusion.**

The list of patients excluded from the safety analysis, patients excluded from the efficacy analysis, and reasons for exclusion will be prepared.

8.2.5. Patient Demographics and Treatment History

- **Patient demographics**

The frequency tabulation of the following patient demographics and baseline characteristics will be performed in the safety analysis set and efficacy analysis set. Basic statistics will be tabulated for continuous scales.

For items using reference laboratory test values, results using corporate reference values will be tabulated separately from results using institutional reference values as necessary.

[Demographic and other baseline characteristics]:

- Sex [male, female];
- Age (continuous data);
- Age [<15 years, ≥15 to <65 years, ≥65 years];
- Age [<45 years, ≥45 to <55 years, ≥55 to <65 years, ≥65 to <75 years, ≥75 to <85 years, ≥85 years];
- Age [<15 years, ≥15 years];
- Age [<65 years, ≥65 years];
- Body surface area (m^2) [<1.2, ≥1.2 to <1.4, ≥1.4 to <1.6, ≥1.6 to <1.8, ≥1.8];
- Height (continuous data);
- Weight (continuous data);
- Body mass index (BMI) (continuous data);
- BMI [low weight (< 18.5), ordinary weight (≥18.5 to <25.0), Obese Class I (≥25.0 to <30.0), Obese Class II (≥30.0 to <35.0), Obese Class III (≥35.0 to <40.0), Obese Class IV (≥40.0)];
- Inpatient/outpatient status [inpatient, outpatient];
- Past medical history [absent, present];

- Past history of lung disease [absent, present];
- Past history of interstitial lung disease [absent, present];
- Past history of hepatitis B, tuberculosis, and herpes zoster [absent, present];
- Past history of diabetes mellitus [absent, present];
- Complications [absent, present];
- Comorbid lung disease [absent, present];
- Comorbid interstitial lung disease [absent, present];
- Comorbid hepatitis B, tuberculosis, and herpes zoster [absent, present];
- Comorbid diabetes mellitus [absent, present];
- Hepatic dysfunction [absent, present];
- Severity of hepatic dysfunction [mild, moderate, severe];
- Renal dysfunction [absent, present];
- Severity of renal dysfunction [mild, moderate, severe];
- ECOG Performance Status [0，1，2，3，4];
- Karnofsky Performance Status [10-20，30-40，50-60，70-80，90-100];
- Risk classification (Memorial Sloan Kettering Cancer Center [MSKCC] Risk) [good (0 of 5 items), intermediate (1 to 2 of 5 items), poor (3 to 5 of 5 items)];
- Risk classification (Modified Risk) [low risk (0 to 2 of 6 items), high risk (3 to 6 of 6 items)];
- Risk classification, time from the diagnosis of renal cell carcinoma to the initial systemic chemotherapy <1 year [yes, no];
- Risk classification, Karnofsky Performance Status ≤70 [yes, no];
- Risk classification, hemoglobin < institutional lower reference limit [yes, no];

- Risk classification, adjusted calcium >10 mg/dL [yes, no];
- Risk classification, LDH >1.5-fold of institutional upper reference limit [yes, no];
- Risk classification, number of metastatic foci ≥2 [yes, no].

[Characteristics of target disease and prior treatment history]:

- Target disease [unresectable or metastatic renal cell carcinoma, others];
- Presence or absence of metastasis (at the initiation of treatment) [absent, present];
- Number of metastatic foci (at the initiation of treatment) [0, 1, ≥2];
- Site of metastasis (at the initiation of treatment) [lung, liver, bone, brain, others];
- Histopathologic diagnosis [clear cell, non-clear cell, not performed];
- Histopathologic diagnosis (description) [clear cell, granule cell, chromophobe cell, spindle cell, cyst-associated renal cell, cyst-derived renal cell, cystic renal cell, papillary renal cell, others];
- Disease stage (at the diagnosis of target disease) [STAGE 0, STAGE 1, STAGE 2, STAGE 3, STAGE 4];
- Duration of illness [≥0 to ≤12 months, ≥13 to ≤24 months, ≥25 to ≤48 months, ≥49 months];
- Prior treatment history (history of surgery: primary focus) [absent, present];
- Prior treatment history (history of surgery: nephrectomy) (partial or total resection of primary focus) [absent, present];
- Prior treatment history (history of surgery: metastatic focus) [absent, present];
- Prior treatment history (history of radiation therapy) [absent, present];
- Prior treatment history (history of non-drug therapy) [absent, present];
- Prior treatment history (drug therapy) [absent, present];

- Prior treatment history (description of drug therapy) [IFN-α, IL-2, Sutent, Nexavar, Afinitor, others].

[Criteria for the proper use of this drug]:

- Whether criteria for proper use are met [yes, no];
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 2 [yes, no];
- Neutrophil count ≥1.5 x 10^9/L (1500/mm^3) [yes, no];
- Hemoglobin ≥8 g/dL [yes, no];
- Platelet count ≥100 x 10^9/L (10 x 10^4/mm^3) [yes, no];
- Serum creatinine ≤1.5-fold of institutional upper reference limit [yes, no];
- BUN ≤1.5-fold of institutional upper reference limit [yes, no];
- Total bilirubin ≤1.5-fold of institutional upper reference limit [yes, no];
- AST/ALT ≤3-fold of institutional upper reference limit (≤5-fold of institutional upper reference limit if liver metastasis is observed) [yes, no];
- Chest CT normal [yes, no];
- Chest X-ray normal [yes, no];
- Measurement of markers for interstitial lung disease such as KL-6, normal [yes, no];
- Pulmonary function test (PFT) normal [yes, no];
- Measurement of oxygen saturation normal [yes, no];
- Total cholesterol ≤350 mg/dL (9.9 mmol/L) [yes, no];
- Triglyceride ≤400 mg/dL (4.56 mmol/L) [yes, no];
- Hemoglobin A1C < 10% [yes, no];

- Fasting blood glucose ≤1.5-fold of institutional upper reference limit [yes, no].

[Concomitant therapies and other background information]:

- Concomitant therapy (drug therapy) [absent, present];
- Concomitant therapy (non-drug therapy) [absent, present];
- History of smoking [absent, present];
- Family history of diabetes mellitus [absent, present];
- History of pulmonary surgery [absent, present];
- History of steroid use [absent, present];
- History of occupational and environmental exposure to asbestos, pneumoconiosis-producing dusts, etc. [absent, present];
- History of administration of highly concentrated oxygen for treatment of respiratory disease [absent, present];
- Drug allergies [absent, present];
- Allergies other than drug allergies [absent, present].

Corporate reference value

Test parameter	**Unit**	**Lower limit**		**Upper limit**	
		Male	**Female**	**Male**	**Female**
Hemoglobin	g/dL	13.5	11.3	17.6	15.2
White blood cell count	/μL	3900	3500	9800	9100
White blood cell differential/neutrophil	%	27	28	87	90
Platelet count	$\times 10^4/\mu L$	13.1	13	36.2	36.9
AST	IU/L	7		38	

Test parameter	Unit	Lower limit		Upper limit	
		Male	Female	Male	Female
ALT	IU/L	4		44	
Total bilirubin	mg/dL	0.2		1	
Total cholesterol	mg/dL	130		219	
Triglyceride	mg/dL	30		150	
Fasting blood glucose	Mg/dL	60		110	
HbA1C	%	4.3		5.8	
BUN	mg/dL	8		20	
Serum creatinine	mg/dL	0.8	0.6	1.2	0.9
K	mEq/L	3.7		4.8	
P	mg/dL	2.5		4.5	
	mmol/L	0.8		1.4	
CRP	mg/dL			0.3	
SpO2	%	95		100	
KL-6	U/mL			500	
SP-D	ng/mL			<110	
SP-A	ng/mL	15		34.2	
LDH	IU/L	106		220	
Serum albumin	g/dL	3.8		5.5	
Serum calcium	mg/dL	8.5		10.2	
	mEq/L	4.2		5.1	
	mmol/L	2.1		2.5	
ALP	IU/L	106		345	

- **Past medical history**

The number and percentage of patients will be tabulated by past medical history in the safety analysis set.

- **Complications**

The number and percentage of patients will be tabulated by complication in the safety analysis set.

- **Concomitant medications**

The number and percentage of patients will be tabulated by concomitant medication in the safety analysis set.

- **Non-drug therapies**

The number and percentage of patients will be tabulated by non-drug therapy in the safety analysis set.

- **Prior medications**

The number and percentage of patients will be tabulated by prior medication in the safety analysis set.

- **Other reasons for use**

The list of other reasons for use of this drug will be prepared in the safety analysis set.

- **Status of exposure to this drug**

The frequency distribution of the following status of exposure to this drug will be tabulated in the safety analysis set and efficacy analysis set. Basic statistics will be tabulated for continuous scales.

[Status of exposure to this drug]:

- Dose at initiation [>0 to ≤5 mg, >5 to ≤10 mg, >10 to ≤15 mg, >15 to ≤20 mg, >20 to ≤25 mg, >25 mg];

- Duration of treatment (weeks) [>0 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, >96 weeks];
- Total dose (mg) [>0 to ≤200 mg, >200 to ≤400 mg, >400 to ≤600 mg, >600 to ≤1200 mg, >1200 to ≤1800 mg, >1800 to ≤2400 mg, >2400 mg];
- Dose intensity (mg/week) [>0 to ≤10 mg, >10 to ≤15 mg, >15 to ≤20 mg, >20 to ≤25 mg, >25 to ≤30 mg, >30 mg];
- Relative dose intensity [>0.0 to ≤0.4, >0.4 to ≤0.6, >0.6 to ≤0.8, >0.8 to ≤1.0, >1.0 to ≤1.2, >1.2];
- Presence or absence of temporary discontinuation of treatment [absent, present];
- Reason for temporary discontinuation of treatment [adverse event, others];
- Presence or absence of dose reduction [absent, present];
- Reason for dose reduction [adverse event, others].

- **Duration of observation**

The frequency distribution of the duration of observation will be tabulated in the safety analysis set and efficacy analysis set. In addition, basic statistics will be tabulated.

- **Status of implementation of chest CT**

The frequency distribution of the status of implementation of chest CT will be tabulated in the safety analysis set.

The same tabulation will be performed in patients in whom measurement was performed in all timing categories.

8.2.6. Safety Analysis

- **Incidences of adverse reactions and adverse events**

The number of patients with adverse reactions, serious adverse reactions, adverse events, serious adverse events, and Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 adverse reactions and the incidences of these events will be calculated by system organ class (SOC) and preferred term (PT).

In addition, the number of patients with adverse reactions and the incidence of adverse reactions by inclusion/exclusion from the safety analysis set will be tabulated by SOC and PT in patients for whom the case report form was collected.

- **Further tabulation of adverse reactions**

The number of patients with adverse reactions and the incidence of adverse reactions will be tabulated by SOC and PT by category shown below.

- Seriousness [serious, non-serious];
- Known/unknown [known, unknown];
- Outcome [resolved/recovered, recovering, recovered with sequelae, not recovered];
- Timing of initial onset [>0 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, >96 weeks];
- Intervention [absent, present];
- Administration of this drug [no change in dose, temporary discontinuation, dose reduction, dose increase, discontinuation];
- Duration of treatment [>0 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, >96 weeks];
- Total dose [>0 to ≤200 mg, >200 to ≤400 mg, >400 to ≤600 mg, >600 to ≤1200 mg, >1200 to ≤1800 mg, >1800 to ≤2400 mg, >2400 mg];
- CTCAE Grade[Grade 1,Grade 2,Grade 3,Grade 4,Grade 5].

- **Further tabulation of serious adverse reactions**

The number of patients with serious adverse reactions and the incidence of serious adverse reactions will be tabulated by SOC and PT by category shown below. “•Further tabulation of serious adverse reactions” will be followed for categories.

- Known/unknown;
- Outcome;

- Timing of initial onset;
- Intervention;
- Administration of this drug;
- Duration of treatment;
- Total dose;
- CTCAE Grade.

- **Further tabulation of CTCAE Grade ≥3 adverse reactions**

The number of patients with CTCAE Grade ≥3 adverse reactions and the incidence of CTCAE Grade ≥3 adverse reactions will be tabulated by SOC and PT by category shown below. •Further tabulation of serious adverse reactions" will be followed for categories.

- Seriousness;
- Known/unknown;
- Outcome;
- Timing of initial onset;
- Intervention;
- Administration of this drug;
- Duration of treatment;
- Total dose.

- **Further tabulation of adverse events**

The number of patients with adverse events and the incidence of adverse events will be tabulated by SOC and PT by category shown below. "• Further tabulation of serious adverse reactions" will be followed for categories.

- CTCAE Grade.

- **Further tabulation of unknown adverse reactions**

The number of patients with unknown adverse reactions and the incidence of unknown adverse reactions will be tabulated by SOC and PT by category shown below. "•Further tabulation of serious adverse reactions" will be followed for categories.

  - Outcome.

- **Cumulative incidence of adverse reactions**

The cumulative incidence of adverse reactions will be graphically presented with the time to onset on the horizontal axis.

The cumulative incidence will be graphically presented in the same manner for interstitial lung disease, diabetes mellitus/hyperglycemia, hypercholesterolemia/hyperlipidemia, infection, mucositis-related adverse events, and skin disorder among major investigation items.

- **Cumulative incidence of CTCAE Grade ≥3 adverse reactions**

The cumulative incidence of CTCAE Grade ≥3 adverse reactions will be graphically presented with the time to onset on the horizontal axis.

The cumulative incidence will be graphically presented in the same manner for interstitial lung disease, diabetes mellitus/hyperglycemia, hypercholesterolemia/hyperlipidemia, infection, mucositis-related adverse events, and skin disorder among major investigation items.

- **Incidence of adverse reactions by patient demographic**

The number of patients with adverse reactions and the incidence of adverse reactions will be tabulated by item listed in "Section 10.1.1. Patient demographics to be used to evaluate safety and efficacy."

Fisher's exact test will be performed for nominal scale data and Cochran-Armitage test (exact method) for ordered scale data.

Tabulation will be performed in the same manner for interstitial lung disease, diabetes mellitus/hyperglycemia, hypercholesterolemia/hyperlipidemia, infection, mucositis-related adverse events, and skin disorder among major investigation items.

For items using reference laboratory test values, results using corporate reference values will be tabulated in addition to results using institutional reference values.

- **Incidence of CTCAE Grade ≥3 adverse reactions by patient demographic**

The number of patients with CTCAE Grade ≥3 adverse reactions and the incidence of CTCAE Grade ≥3 adverse reactions will be tabulated by item listed in "Section 10.1.1. Patient demographics to be used to evaluate safety and efficacy."

Tabulation will be performed in the same manner for interstitial lung disease, diabetes mellitus/hyperglycemia, hypercholesterolemia/hyperlipidemia, infection, mucositis-related adverse events, and skin disorder among major investigation items.

For items using reference values, results using corporate reference values will be tabulated in addition to results using institutional reference values.

- **Incidence of adverse reactions by medical history, prior treatment history, and concomitant therapy**

The number of patients with adverse reactions and the incidence of adverse reactions will be tabulated by category shown below.

The number of patients and incidence will be tabulated in the same manner for interstitial lung disease among major investigation items.

  - Past medical history;
  - Complications;
  - Prior medications.

- **Incidence of CTCAE Grade ≥3 adverse reactions by medical history, prior treatment history, and concomitant therapy**

The number of patients with CTCAE Grade ≥3 adverse reactions and the incidence of CTCAE Grade ≥3 adverse reactions will be tabulated by category shown below.

  - Past medical history;
  - Complications;

- Concomitant medications;
- Non-drug therapies;
- Prior medications.

- **Subgroups**

Safety in the following subgroups will be analyzed.

1. Children (<15 years), adults (≥15 years).
2. Elderly (≥65 years), non-elderly (<65 years).
3. Presence or absence of pregnancy.
4. Presence or absence of hepatic dysfunction.
5. Presence or absence of renal dysfunction.
6. By indication.
7. By whether criteria for proper use are met.
8. History of hepatitis B, tuberculosis, and herpes zoster.
9. Severity of hepatic dysfunction.
10. Sex.
11. Complications.

The number of patients with adverse reactions, serious adverse reactions, and CTCAE Grade ≥3 adverse reactions and the incidence of these adverse reactions will be calculated by SOC and PT.

For items using reference values, results using corporate reference values will be tabulated in addition to results using institutional reference values.

- **Major investigation items**

The number of patients with adverse reactions falling under major investigation items and the incidence of these adverse reactions will be calculated by SOC and PT. The number of patients with adverse events and the incidence of adverse events will be tabulated in the same manner.

The same tabulation will be performed for each of the following items.

1. Interstitial lung disease.
2. A wide range of related events suspected of interstitial lung disease.
3. Dyspnea.
4. Diabetes mellitus/hyperglycemia.
5. Hypersensitivity reaction.
6. Diarrhea.
7. Hypophosphatemia.
8. Hypokalemia.
9. hypercholesterolemia/hyperlipidemia.
10. Infection.
11. Intracerebral hemorrhage.
12. Abnormality in wound healing.
13. Mucositis-related adverse events.
14. Skin disorder.
15. Acute renal failure.
16. Gastrointestinal perforation.

- **Further tabulation of interstitial lung disease**

The number of patients with adverse reactions and adverse events of interstitial lung disease and the incidences of these adverse reactions and adverse events will be tabulated by presence or absence of past or present history of lung disease and presence or absence of abnormal imaging findings at the initiation of treatment by category shown below.

- Seriousness;
- Clinical symptoms;
- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks);
- Imaging findings suspected of interstitial lung disease.

The worst CTCAE Grade and treatment effect will be tabulated by presence or absence of treatment of interstitial lung disease.

The outcome in patients in whom interstitial lung disease was CTCAE Grade 1 at onset will be tabulated by status (continued/discontinued) of treatment.

The list of the course of interstitial lung disease and the list of the time course of CTCAE Grade will be prepared.

Graphs of time from the initiation of treatment to initial onset (weeks), outcome, and administration of this drug will be prepared by CTCAE Grade at onset. Graphs will be prepared in the same manner by maximum CTCAE Grade.

- **Further tabulation of diabetes mellitus/hyperglycemia**

The number of patients with adverse reactions of diabetes mellitus/hyperglycemia and the incidence of these adverse reactions will be tabulated by category shown below.

- Seriousness;
- Clinical symptoms;

- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks);

Graphs of time from the initiation of treatment to initial onset (weeks) and outcome will be prepared by CTCAE Grade at onset.

- **Further tabulation of hypercholesterolemia/hyperlipidemia**

The number of patients with adverse reactions of hypercholesterolemia/hyperlipidemia and the incidence of these adverse reactions will be tabulated by category shown below.

- Seriousness;
- Clinical symptoms;
- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks).

Graphs of time from the initiation of treatment to initial onset (weeks) and outcome will be prepared by CTCAE Grade at onset.

- **Further tabulation of infection**

The number of patients with adverse reactions of infection and the incidence of these adverse reactions will be tabulated by category shown below.

- Seriousness;
- Clinical symptoms;
- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks).

Graphs of time from the initiation of treatment to initial onset (weeks) and outcome will be prepared by CTCAE Grade at onset.

- **Further tabulation of mucositis-related adverse events**

The number of patients with mucositis-related adverse reactions and the incidence of these adverse reactions will be tabulated by category shown below.

- Seriousness;
- Clinical symptoms;
- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks).

Graphs of time from the initiation of treatment to initial onset (weeks) and outcome will be prepared by CTCAE Grade at onset.

- **Further tabulation of skin disorder**

The number of patients with adverse reactions of skin disorder and the incidence of these adverse reactions will be tabulated by category shown below.

- Seriousness;
- Clinical symptoms;
- Severity (CTCAE Grade);
- Time from the initiation of treatment to initial onset (weeks);
- Cumulative duration (weeks).

Graphs of time from the initiation of treatment to initial onset (weeks) and outcome will be prepared by CTCAE Grade at onset.

[redacted]

[redacted]

8.2.7. Efficacy Analysis

- **Response rate and clinical benefit rate**

The number and percentage of patients by best overall response, the response rate and its 95% confidence interval, and the clinical benefit rate and its 95% confidence interval will be tabulated in the safety analysis set and efficacy analysis set.

The response rate is defined as the percentage of patients whose best overall response is CR or PR.

The clinical benefit rate is defined as the percentage of patients whose best overall response is CR, PR, or SD.

The best overall response is defined as the best response among recorded overall response.

Table 1 of "New Guideline for the Assessment of Treatment Effect on Solid Cancer (Response Evaluation Criteria in Solid Tumors [RECIST] Guideline)–Japan Clinical Oncology Group [JCOG] version in Japanese" will be used for overall response, but overall response based on combinations of tumor response not corresponding to the table because of unknown data and no entry of data was uniquely defined. Therefore, the

tabulation analysis is not in complete compliance with the guideline and uses the guideline for reference.

Table 1. Overall Response Based on Combinations of Tumor Response in Target and Non-target Lesions Including the Presence or Absence of New Lesions

Target lesion	Non-target lesion	New lesion	Overall response
HCR	CR	Absent	CR
CR	IR/SD	Absent	PR
PR	Other than PD	Absent	PR
SD	Other than PD	Absent	SD
PD	Any response	Any response	PD
Any response	PD	Any response	PD
Any response	Any response	Present	PD

The following tumor response will be converted as shown by the arrow.

Non-target lesion: Absent → CR, not entered → IR/SD.

New lesion: Not entered → absent.

Overall response not corresponding to any combination in Table 1 after the above conversion will be considered as "unassessable."

In addition, tabulation will be performed in the same manner by category shown below.

For items using reference laboratory test values, results using corporate reference values will be tabulated separately from results using institutional reference values as necessary.

- Site of metastasis [none, lung, liver, bone, lung + 1 organ, lung + 2 organs, lung + ≥3 organs, ≥2 organs other than lung, others];
- Whether criteria for proper use are met [yes, no];

- Prior treatment history [IFN-α, IL-2, Sutent, Nexavar, Afinitor, others];
- Baseline LDH (1.5-fold of institutional upper reference limit) [high value (>1.5-fold), normal (≤1.5-fold)];
- Baseline LDH (1.0-fold of institutional upper reference limit) [high value (>1.0-fold), normal (≤1.0-fold)].

In addition, the above tabulation will be performed using the best overall response as a study not requiring determination of CR and PD.

- **Response rate and clinical benefit rate by patient demographic**

The response rate and clinical benefit rate will be calculated by item listed in "Section 10.1.1. Patient demographics to be used to evaluate safety and efficacy." For the response rate and clinical benefit rate, tests specified in Section 8.1.3 will be performed between categories of each demographic factor.

For items using reference laboratory test values, results using corporate reference values will be tabulated in addition to results using institutional reference values.

[redacted]

9. LISTINGS

- List of patients.
- List of patients with adverse events.
- List of patients with adverse reactions.
- List of patients with serious adverse events.
- List of patients with serious adverse reactions.
- List of patients with adverse events (CTCAE Grade ≥3).
- List of patients with adverse reactions (CTCAE Grade ≥3).
- List of deaths (for which the causal relationship was not ruled out).
- List of deaths (for which the causal relationship was ruled out).
- List of patients with adverse reactions among children.
- List of patients with adverse reactions among the elderly.
- List of patients with adverse reactions among pregnant and parturient women.
- List of patients with adverse reactions among patients with off-label use.
- List of patients with adverse reactions among patients not meeting criteria for proper use.
- List of patients with adverse reactions among patients with hepatic dysfunction.
- List of patients with adverse reactions among patients with renal dysfunction.
- List of patients with adverse reactions among patients with a history of hepatitis B, tuberculosis, and herpes zoster [major investigation].
- List of patients with adverse reactions among patients with hepatic dysfunction (mild).

- List of patients with adverse reactions among patients with hepatic dysfunction (moderate).
- List of patients with adverse reactions among patients with hepatic dysfunction (severe).
- List of patients with adverse reactions among patients with hepatic dysfunction (hepatic transplant).
- List of patients with interstitial lung disease [major investigation].
- List of patients with a wide range of related events suspected of interstitial lung disease [major investigation].
- List of patients with dyspnea [major investigation].
- List of patients with diabetes mellitus/hyperglycemia [major investigation].
- List of patients with hypersensitivity reaction [major investigation].
- List of patients with diarrhea [major investigation].
- List of patients with hypophosphatemia [major investigation].
- List of patients with hypokalemia [major investigation].
- List of patients with hypercholesterolemia/hyperlipidemia [major investigation].
- List of patients with infection [major investigation].
- List of patients with intracerebral hemorrhage [major investigation].
- List of patients with abnormality in wound healing [major investigation].
- List of patients with mucositis-related adverse events [major investigation].
- List of patients with skin disorder [major investigation].
- List of patients with acute renal failure [major investigation].
- List of patients with gastrointestinal perforation [major investigation].

- List of tumor response.
- List of whether criteria for proper use are met.
- List of whether criteria for proper use are met (corporate reference values are used as reference laboratory test values).
- List of chest CT.

10. APPENDICES

10.1.1. Patient Demographics To Be Used To Evaluate Safety And Efficacy

Nominal scale

Item	Category	Remarks
Sex	Male, Female	
Age 1	<15 years, ≥15 to < 65 years, ≥65 years	
Age 2	<45 years, ≥45 to <55 years, ≥ 55 to <65 years, ≥65 to <75 years, ≥75 to <85 years, ≥85 years	
Age 3	<15 years, ≥15 years	
Age 4	<65 years, ≥65 years	
Body surface area (m^2)	<1.2, ≥1.2 to <1.4, ≥1.4 to <1.6 ≥1.6 to <1.8, ≥1.8	
BMI	Low weight (<18.5), Ordinary weight (≥18.5 to <25.0), Obese Class I (≥25.0 to <30.0), Obese Class II (≥30.0 to <35.0), Obese Class III (≥35.0 to < 40.0), Obese Class IV (≥40.0)	
Inpatient/outpatient status	Inpatient, Outpatient	
Past medical history	Absent, Present	
Past medical history (lung disease)	Absent, Present	
Past medical history (interstitial lung disease)	Absent, Present	
Past medical history (hepatitis B, tuberculosis, and herpes zoster)	Absent, Present	
Past medical history (diabetes mellitus)	Absent, Present	
Complications	Absent, Present	
Complication (lung disease)	Absent, Present	
Complication (interstitial lung disease)	Absent, Present	
Complication (hepatitis B, tuberculosis, and herpes zoster)	Absent, Present	

Nominal scale

Item	Category	Remarks
Complication (diabetes mellitus)	Absent, Present	
Hepatic dysfunction	Absent, Present	
Severity of hepatic dysfunction	Mild, Moderate, Severe	
Renal dysfunction	Absent, Present	
Severity of renal dysfunction	Mild, Moderate, Severe	
ECOG Performance Status	0, 1, 2 ,3 4	
Karnofsky Performance Status	10-20, 30-40, 50-60, 70-80, 90-100	
Risk classification (MSKCC Risk)	Good (0 of 5 items), Intermediate (1 to 2 of 5 items), Poor (3 to 5 of 5 items)	
Risk classification (Modified Risk)	Low risk (0 to 2 of 6 items), High risk (3 to 6 of 6 items)	
Risk classification: Time from the diagnosis of renal cell carcinoma to the initial systemic chemotherapy <1 year	Yes, No	
Risk classification: Karnofsky Performance Status ≤70	Yes, No	
Risk classification: Hemoglobin < institutional lower reference limit	Yes, No	
Risk classification: Adjusted calcium >10 mg/dL	Yes, No	
Risk classification: LDH >1.5-fold of institutional upper reference limit	Yes, No	

Nominal scale

Item	Category	Remarks
Risk classification: Number of metastatic foci ≥2	Yes, No	
Target disease	Unresectable or metastatic renal cell carcinoma, Others	
Presence or absence of metastasis (at the initiation of treatment)	Absent, Present	
Number of metastatic foci (at the initiation of treatment)	0, 1, ≥2	
Site of metastasis (at the initiation of treatment)	Lung, Liver, Bone, Brain, Others	No test
Histopathologic diagnosis	Clear cell, Non-clear cell, Not performed	
Histopathologic diagnosis (description)	Clear cell, Granule cell, Chromophobe cell, Spindle cell, Cyst-associated renal cell, Cyst-derived renal cell, Cystic renal cell, Papillary renal cell, Others	No test
Disease stage (at the diagnosis of target disease)	STAGE0,STAGE1,STAGE2,STAGE3,STAGE4	
Duration of illness	≥0 to ≤12 months, ≥13 to ≤24 months, ≥25 to ≤48 months, ≥49 months	
Prior treatment history (history of surgery: primary focus)	Absent, Present	
Prior treatment history (history of surgery: nephrectomy) (partial or total resection of primary focus)	Absent, Present	
Prior treatment history (history of surgery: metastatic focus)	Absent, Present	

Nominal scale

Item	Category	Remarks
Prior treatment history (history of radiation therapy)	Absent, Present	
Prior treatment history (history of non-drug therapy)	Absent, Present	
Prior treatment history (drug therapy)	Absent, Present	
Prior treatment history (description of drug therapy)	IFN-α, IL-2, Sutent, Nexavar, Afinitor, Others	No test
Whether criteria for proper use are met	Yes, No	
ECOG PS 0～2	Yes, No	
Neutrophil count ≥1.5 x 10^9/L (1500/mm^3)	Yes, No	
Hemoglobin ≥8 g/dL	Yes, No	
Platelet count ≥ 100 x 10^9/L (10 x 10^4/mm^3)	Yes, No	
Serum creatinine ≤1.5-fold of institutional upper reference limit	Yes, No	
BUN ≤1.5-fold of institutional upper reference limit	Yes, No	
Total bilirubin ≤1.5-fold of institutional upper reference limit	Yes, No	

Nominal scale

Item	Category	Remarks
AST/ALT ≤3-fold of institutional upper reference limit (≤5-fold of institutional upper reference limit if liver metastasis is observed)	Yes, No	
Chest CT normal	Yes, No	
Chest X-ray normal	Yes, No	
Measurement of markers for interstitial lung disease, such as KL-6, normal	Yes, No	
Pulmonary function test (PFT) normal	Yes, No	
Measurement of oxygen saturation normal	Yes, No	
Total cholesterol ≤350 mg/dL (9.9 mmol/L)	Yes, No	
Triglyceride ≤400 mg/dL (4.56 mmol/L)	Yes, No	
Hemoglobin A1C <10%	Yes, No	
Fasting blood glucose ≤1.5-fold of institutional upper reference limit	Yes, No	
Concomitant therapy (drug therapy)	Absent, Present	
Concomitant therapy (non-drug therapy)	Absent, Present	
History of smoking	Absent, Present	
Family history of diabetes mellitus	Absent, Present	
History of pulmonary surgery	Absent, Present	

Nominal scale

Item	Category	Remarks
History of steroid use	Absent, Present	
History of occupational and environmental exposure to asbestos, pneumoconiosis-producing dusts, etc.	Absent, Present	
History of administration of highly concentrated oxygen for treatment of respiratory disease	Absent, Present	
Drug allergies	Absent, Present	
Allergies other than drug allergies	Absent, Present	
Dose at initiation	25 mg, others	
Duration of treatment (weeks)	>0 to ≤8 weeks, >8 to ≤16 weeks, >16 to ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, >96 weeks	No test
Total dose (mg)	>0 to ≤200 mg, >200 to ≤400 mg, >400 to ≤600 mg, >600 to ≤1200 mg, >1200 to ≤1800 mg, >1800 to ≤2400 mg, >2400 mg	No test
Dose intensity (mg/week)	>0 to ≤10 mg, >10 to ≤15 mg, >15 to ≤20 mg, >20 to ≤25 mg, >25 to ≤30 mg, >30 mg	No test
Relative dose intensity	>0.0 to ≤0.4, >0.4 to ≤0.6, >0.6 to ≤0.8, >0.8 to ≤1.0, >1.0 to ≤1.2, >1.2	No test

Ordered scale

Item	Category	Remarks
Age 1	<15 years, ≥15 to <65 years, ≥65 years	
Age 2	<45 years, ≥45 to <55 years, ≥55 to <65 years, ≥65 to <75 years, ≥75 to <85 years, ≥85 years	
Body surface area (m^2)	<1.2, ≥1.2 to <1.4, ≥1.4 to <1.6 ≥1.6 to <1.8, ≥1.8	

Ordered scale

Item	Category	Remarks
BMI	Low weight (<18.5), Ordinary weight (≥18.5 to <25.0), Obese Class I (≥25.0 to <30.0), Obese Class II (≥30.0 to <35.0), Obese Class III (≥35.0 to < 40.0), Obese Class IV (≥40.0)	
Severity of hepatic dysfunction	Mild, Moderate, Severe	
Severity of renal dysfunction	Mild, Moderate, Severe	
ECOG Performance Status	0, 1, 2, 3, 4	
Karnofsky Performance Status	10-20, 30-40, 50-60, 70-80, 90-100	
Risk classification (MSKCC Risk)	Good (0 of 5 items), Intermediate (1 to 2 of 5 items), Poor (3 to 5 of 5 items)	
Number of metastatic foci (at the initiation of treatment)	0, 1, ≥2	
Disease stage (at the diagnosis of target disease)	STAGE0, STAGE1, STAGE2, STAGE3, STAGE4	
Duration of illness	≥0 to ≤12 months, ≥13 to ≤24 months, ≥25 to ≤48 months, ≥49 months	