・Scheduled hospitalization/ prolongation of hospitalization
・Hospitalization/prolongation of hospitalization to perform tests of adverse events
・Hospitalization/prolongation of hospitalization for follow-up of patients who recovered or showed an improvement after an adverse event
・Hospitalization/prolongation of hospitalization to ease the burden on patients who live far to receive a medical examination.
・Other, hospitalization/prolongation of hospitalization that is not medically required

4) Adverse events deemed other serious medical events

Adverse events that do not fall under any of the following are exempt from expedited reporting.

① Any adverse events (including death) that occur more than 31 days after the final day of protocol-based treatment, and that do not have a causal relationship with treatment (either unlikely or not related) ※ ('31 days' indicates 31 days counted from the day after the last day of protocol-based treatment, which is counted as day 0)

※Because it is thought that a relationship with the present research is unlikely.

② Myelodysplastic syndrome (MDS), secondary cancer※

※ Data will be collected in the follow-up survey, and the incidence will be reported in the monitoring report.

③ Adverse events equivalent of grade 4/3/2/1 listed in the table below

※ In the field of cancer, the incidence of secondary cancer is adequately anticipated, and thus can be safely treated upon onset.

SOC (CTCAE ver4.0)	AE term
Blood and lymphatic disorders	Anemia, hypocellular marrow, febrile neutropenia
Gastrointestinal disorders	Constipation, diarrhea, vomiting
Systemic disorders and administration site conditions	Fever
Laboratory testing	Elevated levels of ALT, AST, and ALP, CD4 lymphopenia, high levels of cholesterol, elevated GGT, increased lipase, lymphopenia, neutropenia, thrombopenia, increased serum amylase, and leukopenia
Metabolic and nutritional disorders	Loss of appetite, hyperuricemia, hypoalbuminemia, hyponatremia, hypokalemia

10.2. Mandatory reporting and report procedures of the institution's principal investigator

10.2.1. Expedited reporting

In the event of an adverse event that requires expedited reporting, the attending physician should immediately notify the institution's principal investigator. If the institution's primary investigator is unavailable, then the institution coordinator or attending physician must assume the duties of the institution's principal investigator.

1) Adverse events that fall under 10.1.1. 1) and 2)

Primary report:

The institution's principal investigator must record the prescribed items on the 'JCOG adverse event report' within 72 hours of discovering the adverse event and report to the research secretariat (e-mail permitted).

The primary report is only required within the JCOG, and does not need to be submitted to director of the relevant Regional Bureau (branch) of Health and Welfare, and to the director of the Health Bureau of the Ministry of Health, Labour and Welfare.

Secondary report:

The institution's principal investigator must complete the 'severe adverse event (SAE) report' with detailed information of the adverse event, and if necessary attach a copy of test data, image data, and the biopsy results report, then submit to the research secretariat office within 15 days of discovering the adverse event (email permitted).

The secondary report corresponds to the safety report of 'patient death or patients at risk of death' (report deadline: 7 days) in the advanced medical care notification.

2) Adverse events that fall under 10.1.1. 3) and 4)

The institution's principal investigator must complete the 'severe adverse event (SAE) report', and if necessary attach a copy of test data, image data, and the biopsy results report, then submit to the research secretariat office within 10 days of discovering the adverse event (email permitted).

This report corresponds to the safety report of 'cases set forth below' in the advanced medical care notification (report deadline: 15 days).

10.2.2. Reporting to the medical institution director

In the event of adverse events that requiring expedited reporting, the institution's principal investigator is to report it as a 'severe adverse event related to the clinical trial' to the director of the medical institution in accordance with the regulations of the medical institution concerned. Furthermore, when reporting the adverse event, they must notify the Data and Safety Monitoring Committee via the research chairman/research coordinator of the planned examinations.

10.3. Duties of the research chair and research secretariat

10.3.1. Guidelines for the urgent notification to the medical institutions and termination of enrollment

On receiving reports from the institution's principal investigator, the research secretariat will report to and consult with the research chair and the group representative to determine the urgency, importance, and degree of influence of the report content, and when necessary, they will take measures to temporarily suspend enrollment (contact the JCOG Data Center and all participating institutions) and immediately communicate the findings to the participating facilities. The Data Center or medical institution may be contacted by telephone in an emergency; however written communication (fax, mail, email, or in person) should follow as soon as possible.

10.3.2. Reporting to the director of the relevant Regional Bureau (branch) of Health and Welfare, and to the director of the Health Bureau of the Ministry of Health

If the research secretariat determines that an adverse event reported by a medical institution via expedited or reporting falls under 'section 10.1. Adverse events with mandatory reporting', after consulting with the research chair and the group representative, a written report must be submitted to the director of the relevant Regional Bureau (branch) of Health and Welfare, and to the director of the Health Bureau of the Ministry of Health via the coordinating medical institution (15.1.1.-2).

10.3.3. Reporting to the Data and Safety Monitoring Committee

If the research secretariat determines that an adverse event reported by a medical institution via expedited reporting falls under 'section 10.1. Adverse events with mandatory reporting', after consulting with the research chair and the group representative, a written report must be submitted to the Data and Safety Monitoring Committee within 15 days of discovering the adverse event. At the same time, they are asked to examine the research secretariat's/research chair's opinion of the adverse event concerned and the appropriateness of the responses to the adverse event.

At this time, the 'severe adverse event (SAE) report' sent from the facility should include a written opinion noting the results of the investigations and measures taken (including determination of trial continuation/termination) by the research secretariat and research chair. Moreover, for 10.1.1. 1) Death, and 2) grade 4 adverse events, reporting should include details on whether the incidence was within the expected range, irrespective of the individual patient's progress.

10.3.4. Notification to institutional researchers

In the event of the research secretariat/research chair having reported to the Data and Safety Monitoring Committee, they must communicate the content of the investigations and advice of the Data and Safety Monitoring Committee (email is permitted) to the principal investigators of all institutions participating in the trial.

In the event of not having reported to the Data and Safety Monitoring Committee, the research secretariat/research chair must communicate their decision in writing (email is permitted) to the principal investigator of the institution that submitted the report.

10.3.5. Examination of adverse events in routine monitoring

In the event of routine monitoring, the research chair/research secretariat should carefully examine the adverse event report in the monitoring report created by the Data Center, and verify that there are no omissions in the report from the institution. In addition, they must verify that all reported adverse events have been listed in the routine monitoring report. Any report omissions will be specified in the space for group examination reporting on the routine monitoring report.

10.4. Measures taken by the principal investigator of participating institutions (including the institution concerned)

The principal investigators of the institutions participating in the present trial will take measures as instructed by the research secretariat/research chair, Moreover in the event of an adverse event requiring expedited reporting, the institution's principal investigator will report the event as a 'clinical trial related serious adverse event' to the director of the medical facility concerned in accordance with the

regulations of that particular medical facility.

10.5. Examinations by the Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will examine/verify the report content according to the procedures described in the 'guidelines for clinical safety data management', and those approved by the JCOG operations committee, after which they will communicate in writing the measures to be implemented, including whether the enrollment should be continued or if the protocol should be revised, to the research chair, research secretariat, group representative, group coordinator, director of the JCOG Data Center, director of the JCOG operations office, and the JCOG chair.

11. Definition of therapeutic outcomes and endpoint

11.1. Response evaluation

Cytoreductive response evaluation will be performed with the following procedure in accordance with the 'latest revised response evaluation criteria in solid cancers (RECIST guidelines) version 1.1-Japanese JCOG edition Revised RECIST guideline (version 1.1)' [47]. The original RECIST v 1.0 states that 'these guidelines are not to be used to determine treatment continuation', and in the RECIST v 1.1, the same statement is as follows:

> 'Many oncologists in their daily clinical practice follow their patient's malignant disease by means of imaging and make their decision about continued therapy on the basis of both objective and symptomatic criteria. However the revised RECIST guidelines is not intended for use in the decision making of whether to continue treatment for each individual patient, except if determined appropriate by the treating oncologist'.

Accordingly, the 'overall response', determined using the response evaluation based on the RECIST guidelines, should be 'used to determine whether or not the results are promising and worth continuing the development research for medications and regimens'. That is, the decision to continue treatment for each individual patient is not made on the basis of an overall response of CR/PR/SD/PD, but should be a 'clinical decision' encompassing image findings, as well as symptomatic and physical findings, and various test values.

Therefore, even when Progressive Disease (PD) is determined as the overall response based on image findings, it may be clinically valid to continue the protocol-based treatment. In such instances the decision to continue protocol-based treatment should be based on clinical judgment and not response evaluation, however the day that an overall response of PD is determined may be employed as a progression-free survival event day. There are 3 reasons for this, i) the decision of whether or not to continue the protocol-based treatment can differ for each group, (ii) RECIST is criteria intended to standardize the response rate as well as progression-free survival, and (iii) if the standard definition for overall response used by American cooperative groups is PD, then for whatever reason it may be considered an event of progression-free survival.

On the other hand, if the attending physician determines that a patient exhibits 'clinical exacerbation' on the basis of clinical and general judgment, irrespective of image diagnosis, even when the patient does not correspond to 'PD' in the response evaluation criteria based on image findings, then the protocol-based treatment should be terminated in accordance with section '6.2.2. Criteria for the termination of protocol-based treatment'. If 'clinical exacerbation' is determined, even without determination of 'PD' response, the day that 'clinical exacerbation' determined will be the day of progression-free survival. After determination of 'clinical exacerbation' imaging may not proceed as scheduled, and therefore if the progression-free survival event is not determined upon 'clinical exacerbation' there is ultimately a high risk of overestimating progression-free survival. Furthermore, processing the 'end' of progression-free survival upon 'clinical exacerbation exclude close patients at high risk of exacerbation and death, and therefore is not statistically correct (informative censoring).

Moreover, in the criteria for PD of non-target lesions in the original RECIST v 1.1, it is stated that 'unequivocal progression' is 'marked exacerbation of a non-target lesion, an overall increase in tumor volume, to the extent that elicits the termination of treatment', and therefore the evaluation of PD in non-target lesions partially includes "the decision to continue treatment in each individual patient", which is a statement that causes confusion. Caution should be paid with the term "unequivocal progression" in that it is an evaluation criteria limited to 'PD of non-target lesions'.

In the JCOG, the relationship between 'PD', 'clinical exacerbation', 'exacerbation', and progression-free survival events is as shown in the figure below.

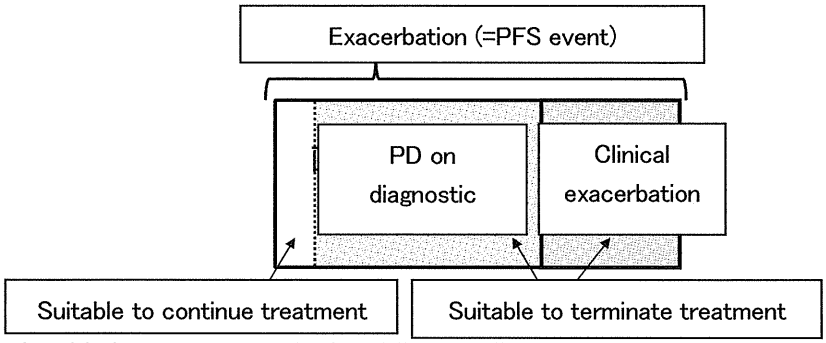


Fig. 11.1. The relationship between exacerbation, PD according to diagnostic imaging and clinical exacerbation

11.1.1. Baseline values

In accordance with section '8.1 Evaluations prior to enrollment', chest contrast-enhanced CT (slice thickness < 5 mm), upper abdominal/pelvic contrast-enhanced CT (slice thickness < 5 mm), and upper gastrointestinal endoscopy (required items) are performed to identify the neoplastic lesions prior to enrollment. Any lesions found via these tests are classified into 'measurable lesions' and 'non-measurable lesions'.

Tumor size is measured by CT in the transverse plane, and measurements will not be taken using a three-dimensional model in the sagittal and coronal planes. Baseline values will be determined using the most recent image tests performed less than 28 days prior to enrollment. Following enrollment, if image tests are reexamined prior to the start of treatment the most recently reexamined images will be used.

11.1.2. Definition of measurable lesions

The following lesions will be considered measurable lesion.

Lesions of 15 mm or greater (minor axis) in the lymph nodes as measured by CT with slice thickness < 5 mm.

(Lymph node lesions > 10 mm and < 15 mm in the minor axis will be considered non-target lesions, and lymph nodes < 10 mm in the minor axis will not be considered lesions)

All lesions other than those above will be considered non-measurable lesion.

11.1.3. Target lesion selection and baseline recording

Of measurable lesions identified at the time of enrollment, up to 5 lesions in descending order of minor axis length will be selected and considered target lesions. Selection will be made while taking the reproducible repeated measurement into consideration (excluding lesions that are difficult to measure despite having a large short axis). For the selected target lesions, the following will be recorded in order of the most cranial to caudal on the 'pretreatment report 3', including site (code), test method, test day, minor axis of target lesion, and the sum of the minor axis of all target lesions.

11.1.4. Baseline recording of non-target lesions

Lesions that cannot be selected as target lesions will be recorded as non-target lesions irrespective of whether the lesion is measurable or not. The lesion site (code) test method, test day will be recorded on the 'pretreatment report 3'. Multiple non-target lesion found in the same organ can be recorded as 1 lesion (e.g. multiple swollen lymph nodes in the pelvis, and multiple hepatic metastases).

11.1.5. Evaluation of cytoreduction

During the period from the day of completion of the 1st cycle of S-1 therapy until the day of the start of the 2nd cycle, and from the day of completion of the 3rd cycle of S-1 therapy until days 7 to 14 (counting the last day of treatment as day 0), target lesions and non-target lesions will undergo the same evaluations as those conducted at the time of enrollment in accordance with section '8.2. Tests and evaluations during the treatment period'. The minor axis of the target lesions, and disappearance and presence or absence of exacerbation of the non-target lesions will be recorded on the 'cytoreduction report'.

11.1.6. **Response criteria of target lesions**

・CR: Complete Response

When the minor axis of all target lesions is less than 10 mm. Even when the axis sum is not 0 mm, the target lesion response will be CR.

・PR: Partial Response

A decrease of 30% or more in the axis sum compared to the baseline axis sum.

・PD: Progressive Disease

An increase of 20% or more in the target lesion axis sum and an increase of 5 mm or more in absolute value of the axis sum compared to the smallest axis sum during the course (in the event that the baseline is the smallest value during the course it will be referenced as the smallest axis sum), and

・SD: Stable Disease

No tumor reduction corresponding to PR, and no tumor enlargement corresponding to PD.

・NE: Not all Evaluated

When the lesion cannot be examined for whatever reason, or CR, PR, PD, and SD cannot be determined.

$$\text{Axis sum reduction rate} = \frac{\text{Pretreatment axis sum} - \text{axis sum at the time of evaluation}}{\text{Pretreatment axis sum}} \times 100\%$$

$$\text{Axis sum increase rate} = \frac{\text{Axis sum at the time of evaluation} - \text{smallest axis sum}}{\text{Smallest axis sum}} \times 100\%$$

※ The measured value for the axis of the target lesion will be recorded so long as it can be measured (e.g. even when < 5 mm), however if it is determined that the target lesion axis is 'too small to measure', irrespective of the CT slice thickness, when it is determined that there is no residual tumor the axis will be recorded as 0 mm, and if it is determined that there is some residual tumor, the axis will be recorded as 5 mm.

※ When the reduction rate meets the criteria for PR, while at the same time the increase rate meets the criteria for PD, then PD will be recorded.

※ During treatment, if one lesion separates, the minor axis of each will be added to the axis sum.

※ During treatment, if multiple lesions fuse and the boundaries can no longer be distinguished, the minor axis of the fused lesion will be added to the axis sum. If lesions come in contact with each other but it is possible to distinguish the lesion boundaries, then the minor axis of each lesion will be added to the axis sum.

11.1.7. **Evaluation criteria of non-target lesions**

・CR: Complete Response

When the minor axis of all non-target lymph node lesions is less than 10 mm, and tumor markers (CA 19-9, CEA) are all less than the upper threshold of the reference range.

・Non-CR/non-PD

Non-CD/ non-PD will be determined when residual tumor is determined for one or more non-target lesions (including residual tumor of lymph node non-target lesions with minor axis > 10 mm), or when the minor axis of all lymph node non-target lesions is less than 10 mm but tumor markers are not measured.

・PD : Progressive Disease

'Clear exacerbation' of an existing non-target lesion (including recurrence).

In the event of measurable lesions: the determination of 'clear exacerbation' based on a change in the non-target lesion, despite a target lesion response of SD or PR, requires observation of marked exacerbation of the non-target lesion as an increase in overall tumor volume to the extent that it deserved the termination of treatment. When the target lesion response is SD or PR, an increase in volume of the non-target lesion that considerably exceeds the reduction in tumor volume will be considered 'clear exacerbation', otherwise it will be considered non-CR/ non-PD.

In the event of non-measurable lesions: as a general rule, an increase in non-target lesion will be considered 'clear exacerbation' when it is determined that the axis has increased more than 20% and the tumor volume corresponds to an increase of 73%

・NE: Not all Evaluated

When the lesion cannot be examined for whatever reason, and CR, non-CR/ non-PD or PD cannot be determined.

11.1.8. The appearance of new lesions

When a lesion that did not exist at baseline is observed after the start of treatment, it will be considered to be the appearance of a 'new lesion'.

However, for a 'new lesion' to be confirmed, there must be no change on imaging due to a difference in imaging technique with that of tests at the time of baseline evaluation or change in image modality, and there must be no change in the patient's condition on imaging except for the tumor. For example, a cystic lesion occurring within a lesion due to necrosis of a metastatic lesion in the liver will not be considered a new lesion. A lesion that is newly observed on examination of a site that did not have to be examined at baseline (pre-enrollment evaluation) will be considered a new lesion.

Measurements are to be continued when a lesion disappears, then subsequently reappears. However, the response of a lesion at the time that it reappears will differ from the status of other lesions. When a lesion reappears after the determination of an overall response of CR, the response determined at the time of reappearance will be PD. On the other hand, when the overall response is PR or SD, if a lesion reappears after having disappeared, then the minor axis of the lesion concerned will be added to the axis sum of the residual tumor to calculate the response. That is, in most cases the residual tumor status will be assessed as PD when the axis sum of all lesions meet the criteria of PD, and not simply upon the reappearance of one lesion that seemed to have 'disappeared'. This is because the majority of the lesion had not actually 'disappeared' but simply could not be depicted due to the limited resolution of the image modality used.

Any new lesion that is suspected but cannot be confirmed will not be considered a new lesion, and the imaging will be re-examined after a clinically sufficient period. When a new lesion is confirmed by re-examined imaging, the day when the images, in which the new lesion was confirmed, were taken will be declared as the point in time when the new lesion appeared.

11.1.9. Overall Response

The overall response is determined upon completion of the 3rd cycle based on the target lesion response, non-target lesion response and presence or absence of appearance of new lesions combined as shown in table 11.1.9.a below. Overall response will not be evaluated upon completion of the 1st cycle, upon completion of the 2nd cycle, or upon completion of the 4th cycle if a 4th cycle is administered. When there are no target lesions at baseline then the overall response is determined by the non-target lesion response and by the appearance of new lesions in accordance with table 1.1.9.b.

Table 11.1.9.a) Overall response at each point in time: In the event of target lesions (irrespective of the presence or absence of non-target lesions)

Target lesion	Non-target lesion	New lesion	Overall response

CR	CR	without	CR
CR	Non-CR/non-PD	without	PR
CR	No evaluation	without	PR
PR	Non-PD or NE	without	PR
SD	Non-PD or NE	without	SD
NE	Non-PD	without	NE
PD (clear exacerbation)	Any	with or without	PD
Any	PD	with or without	PD
Any	Any	with	PD

Table 11.1.9.b Overall response at each point in time: In the event of non-target lesions

Non-target lesion	New lesion	Overall response
CR	without	CR
Non-CR/non-PD	without	Non-CR/non-PD
NE	without	NE
PD (clear exacerbation)	with or without	PD
Irrelevant	with	PD

11.1.10. Histological response

In all patients who undergo resection, the histological response will be evaluated in accordance with the Japanese Classification of Gastric Carcinoma, 14th ed., as shown below.

Grade 0 (no effect): no evidence of therapeutic effect in cancer tissue/ cancer cells

Grade 1 (slight effect):

Grade 1a (very slight effect): When 'viable' cancer cells occupy 2/3 of the tumorous area

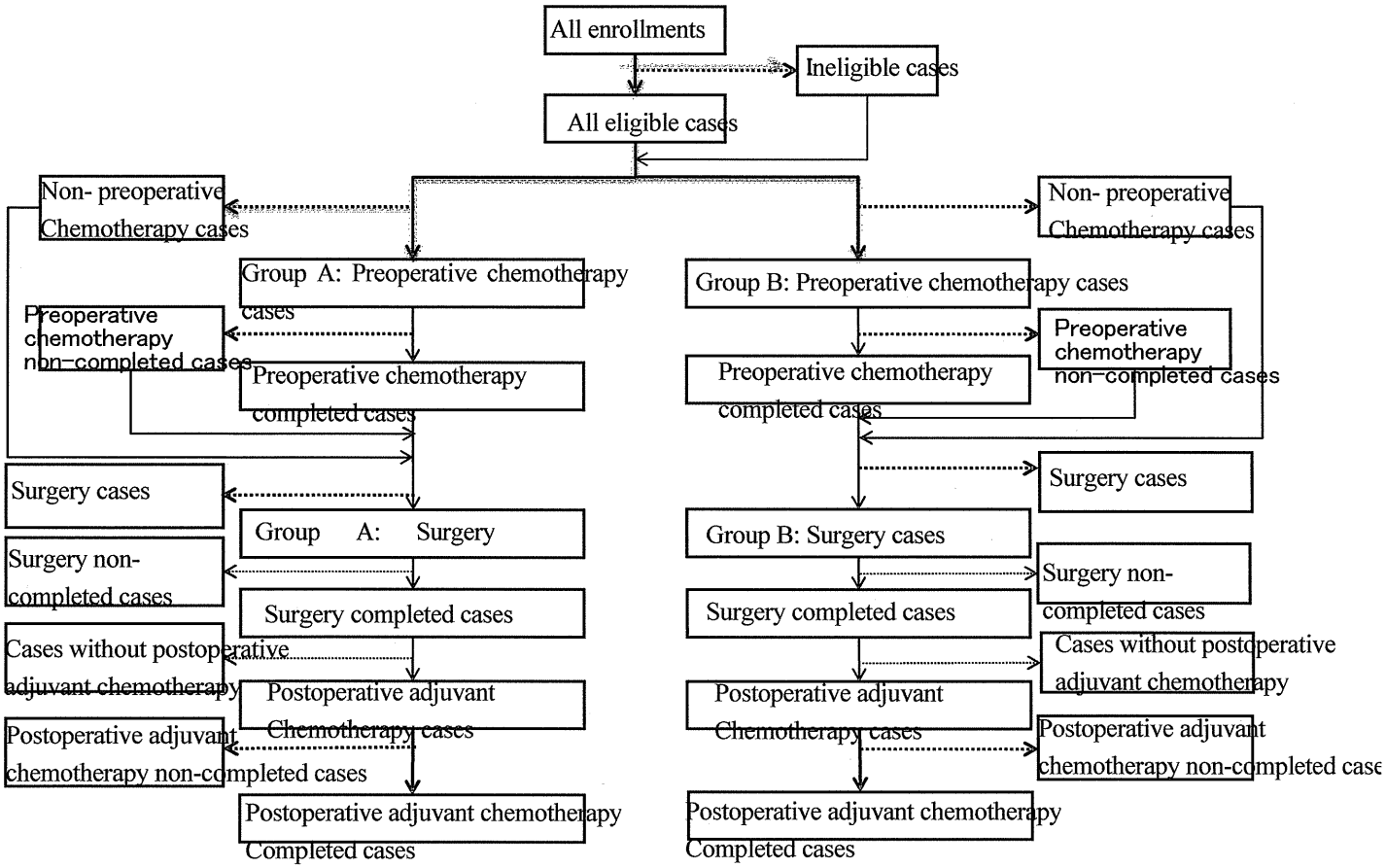
Grade 1b (slight effect): When 'viable' cancer cells remain in more than 1/3 but less than 2/3 of the tumorous area.

Grade 2 (considerable effect): When 'viable' cancer cells remain in less than 1/3 of the tumorous area, and the cancer cells tend to have disintegrated nuclei.

Grade 3 (complete response): When no 'viable' cancer cells remain, and when there are only cancer cells that tend to be disintegrated, or when only traces of cancer can be seen (when grade 3 is evaluated with a typical section, it is recommended to examine on additional sectioning)

11.2. Definition of analysis group

Analysis groups used in routine monitoring, interim analysis, and final analysis will be defined as follows. Furthermore, the flow chart below shows the analysis groups.



11.2.1. All enrollments

Of patients enrolled according to section '5.1. Enrolment procedures', the group excluding double or erroneous enrolments will be called 'all enrollments'.

11.2.2. All eligible cases

From all enrollments, the group excluding those deemed 'ineligible cases (ineligible after enrollment, ineligible at the time of enrollment, and enrollment violations)' by group examination will be called 'all eligible cases'.

'Ineligible cases' will be included in 'all eligible cases' at the discretion of the attending physician, institution coordinator and the institutions principal investigator only.

11.2.3. All treatment cases

Of all enrollments, those who undergo part of or all of protocol treatment will be called 'all treatment cases'.

The Data Center, with the approval of the research secretariat, may decide whether 'non-treated cases' that do not undergo any protocol treatment will be excluded from safety analyses. Furthermore, the research secretariat will determine whether or not ineligible patients will be included in analyses upon examination of the ineligibility and consultation with the JCOG Data Center.

11.2.4. Preoperative chemotherapy cases

Of all enrollments, those who undergo part of or all of preoperative chemotherapy will be called 'preoperative chemotherapy cases'.

11.2.5. **Preoperative chemotherapy completed cases**

All patients who undergo preoperative chemotherapy will be included in the 'preoperative chemotherapy completed' group, except those who do not satisfy section 6.2.1.1) 'Definition of completion of preoperative chemotherapy' (cases that do not complete preoperative chemotherapy).

11.2.6. **Surgery cases**

Of patients who have completed preoperative chemotherapy, patients who did not receive preoperative chemotherapy, and patients who did not complete preoperative chemotherapy, the group including patients who underwent surgery will be called 'surgery cases'. However the decision to include patients who undergo exploratory laparotomy or palliative resection will be determined upon consultation with the research secretariat and the JCOG Data Center.

11.2.7. **Surgery completed cases**

Of patients who undergo surgery, the group of patients who underwent R0 resection will be called the 'surgery completed cases'.

11.2.8. **Postoperative adjuvant chemotherapy cases**

Of patients who complete surgery, the group of patients who receive postoperative adjuvant chemotherapy will be defined as postoperative adjuvant chemotherapy cases'. Patients who undergo R1 or R2 resection and who receive the same treatment regimen as postoperative adjuvant chemotherapy as 'after treatment care' will not be included in 'postoperative adjuvant chemotherapy cases'.

11.2.9. **Postoperative adjuvant chemotherapy completed cases**

All patients who receive postoperative adjuvant chemotherapy will be included in the 'postoperative adjuvant chemotherapy completed' group, except those who do not satisfy section 6.2.1.3) 'Definition of completion of postoperative adjuvant chemotherapy'.

11.3. Definitions of endpoints

Endpoint	Event (whichever is earliest)	Day of closure
Overall survival (OS)	All deaths	Final confirmed date of survival
Progression-free survival (PFS)	All deaths, exacerbation/recurrence	The last day when the absence of exacerbation was clinically confirmed.

11.3.1. **Overall survival**

With the day of enrollment as the initial day, the period until death of the patient due to any cause.

- The case will be deemed closed on the final confirmed date of survival in surviving cases (survival may be confirmed by telephone. However confirmation of survival must be recorded on the medical chart).
- In cases for which follow-up is impossible, the case will be deemed closed on the final day of survival confirmed prior to follow-up became impossible.

11.3.2. **PFS (Progression-free survival)**

With the day of enrollment as the initial day, the period until the day when exacerbation is diagnosed, the day when recurrence of the appearance of a new lesion is observed, or the day of death due to any cause, whichever comes first.

(1) **Event and event day**

- Death due to any cause
- Exacerbation. 'Exacerbation (progression)' includes exacerbation of the primary lesion that cannot be confirmed by image diagnosis (clinical exacerbation), and PD (progressive disease) based on image diagnosis in section '11.1.9. Overall response'. When exacerbation is determined based on image diagnosis, the date that said imaging was performed will be the date of exacerbation, and in the event of clinical exacerbation, the date of clinical diagnosis will

be the date of exacerbation.

- When the tumor diameter becomes extremely small, and PD should be determined according to the response criteria but it is clinically determined that there is no 'clear exacerbation', then PD according to the response criteria will be given priority and exacerbation will be declared (in this situation, clinical diagnosis will be given priority when deciding on whether or not to continue the protocol-based treatment).
- If it is clinically determined that there is clear exacerbation without PD according to the response criteria, the clinical diagnosis will be given priority and exacerbation will be declared.
- When exacerbation is determined by image diagnosis, the event will not be declared on the test date of 'imaging with suspicious results' but on the subsequent 'test date' of imaging in which 'clear diagnosis' was obtained. When exacerbation is clinically determined without image diagnosis, the event will be declared on the date exacerbation is found.
- In patients who discontinue chemotherapy for reasons of toxicity or patient refusal, and other treatments are given as post-treatment care, the event and closure will be treated the same. In other words, the case will not be closed upon treatment termination or the start of post-treatment care.
- If clinical exacerbation and tumor growth is observed after the start of preoperative chemotherapy, and tumorectomy is not performed, exacerbation will be declared on the date that tumor growth or clinical exacerbation is diagnosed (exacerbation for which salvage surgery cannot be performed will be declared as an event).
- If clinical exacerbation and tumor growth is observed after the start of preoperative chemotherapy, and despite attempting tumorectomy, R0/1 resection is deemed impossible, exacerbation will be declared on the day of surgery.
- If there is no tumor growth or clinical exacerbation observed on imaging after the start of preoperative chemotherapy, and despite attempting tumorectomy R0/1 resection is deemed impossible, or if non-curative factors are found after resection of the primary lesion and prior to abdominal closure, then exacerbation will be declared on the date of surgery.
- If tumor growth and clinical exacerbation is observed after the start of preoperative chemotherapy, and on performing R0/R1 resection there is no 'exacerbation', then exacerbation will be declared on the date that 'recurrence' (when there is no residual tumor after surgery) or 'exacerbation' (when there is residual tumor after surgery is found on imaging or on clinical findings following surgery.
- If definite diagnosis of recurrence or new lesions is found by biopsy pathology, an event will be declared on the date of clinical diagnosis when clinical recurrence or new lesions are identified, or on the biopsy date when recurrence is diagnosed by biopsy pathology without clinical diagnosis of recurrence.

Table 11.3.2 The relationship between preoperative chemotherapy response, residual tumor and events

Preoperative chemotherapy response	Residual tumor	Event date
CR、PR、SD、NE	R0	The date of postoperative exacerbation and recurrence
	R1	
	R2	The date of surgery
PD	R0	The date of postoperative exacerbation and recurrence
	R1	
	R2	The date of surgery
	Surgery not performed	The date of preoperative chemotherapy exacerbation

(2) **Closure and closure date**

- In surviving patients without exacerbation, the trial will be closed on the last date of clinically confirmed absence of exacerbation (last day of confirmed progression-free survival).
- Confirmation of the absence of progression by imaging and laboratory tests is not mandatory, and the clinical confirmation of the absence of progression by outpatient examination is sufficient. Communication by telephone alone is not permitted. When a medical institution of a transferred or referred patient obtains information regarding the presence or absence of progression, the patient referral document noting the grounds for diagnosis should be received and kept on file. In this instance also, communication by telephone alone is not permitted.

(3) **Cases without events or closure**

- The onset of secondary cancer (asynchronous multiple cancers) will be considered progression-free survival and an event or closure will not be declared until some other event is observed

11.3.3. **Preoperative chemotherapy Response proportion (Response rate)**

Of all enrollments, the proportion of patients for which the overall survival in section 11.1.9 is either CR or PR will be declared as the response rate.

11.3.4. **Radical resection proportion**

The radical resection proportion shall be calculated with all enrollments as the denominator, the number of patients for whom the degree of histological residual tumor is deemed R0 as the nominator.As a general rule, radical resection proportion will also be calculated with the number of patients in whom the non-curative factor is CY1 only as the numerator.

11.3.5. **The rate of treatment completion before surgery**

The rate of treatment completion shall be calculated with all enrollments as the denominator, and the number of patients who complete preoperative chemotherapy (see section 6.2.1) and for whom the degree of histological residual tumor is R0 as the nominator. However, patients who do not undergo lymph node dissection as per the guidelines will be excluded from the numerator.

11.3.6. **The rate of treatment completion before postoperative adjuvant chemotherapy**

The rate of treatment completion shall be calculated with all enrollments as the denominator, and the number of patients who complete the protocol-based treatment (see section 6.2.1) as the numerator. As in section '11.3.5. The rate of treatment completion before surgery', patients who do not undergo lymph node dissection as per the guidelines will be excluded from the numerator.

11.3.7. **Histological response rate**

The rate of histological response shall be calculated with all enrollments as the denominator, and the number of patients who underwent surgery and for whom the 'histological response' (section 11.1.10) is grade 1b, 2, or 3.

11.3.8. **The incidence of adverse events (adverse reactions)**

1) The incidence of adverse events during preoperative chemotherapy

The incidence of the worst grade of the following adverse events (toxicities) during all cycles shall be calculated according to the CTCAE v4.0-JCOG, with the number of patients who received preoperative chemotherapy as the denominator.

- Laboratory testing: leukocytopenia, neutropenia, anemia (hemoglobin), thrombopenia, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated alkaline phosphatase, elevated gamma-glutamyl transferase, elevated blood bilirubin, elevated creatinine, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypercalcemia, and hypocalcemia.
- Systemic disorders and administration site conditions: fatigue and fever

- General/ systemic disorders and administration site conditions: infusion0related reaction (group B only)
- Cardiac disorders: heart failure
- Ear and labyrinthine disorders: hearing impairment and tinnitus
- Gastrointestinal disorders: Constipation, diarrhea, nausea, oral mucositis, and vomiting
- Nervous system disorders: peripheral motor neuropathy, and peripheral sensory neuropathy
- Skin and subcutaneous tissue disorder: alopecia, skin hyperpigmentation, palmar/ plantar erythrodysathesia syndrome, maculopapular rash.
- Metabolic and nutritional disorders: loss of appetite, hyperglycemia
- Ophthalmopathy: lacrimation
- Blood and lymphatic disorders: febrile neutropenia
- Infection: upper respiratory infection, pulmonary infection, urinary tract infection, and other infections.
- Other grade 3 or higher adverse events (non-hematological toxicities※)

As a general rule, adverse events will be noted on the treatment progress report only when non-hematological toxicities※ of grade 3 or above are observed, and therefore the incidence of adverse events (toxicities) other than those listed above will not be tabulated except when a specific adverse event is repeatedly observed,

※ Non-hematological toxicities indicates adverse events other than those listed below in the CTCAE v4.0-JCOG: anemia, hypocellular bone marrow, lymphopenia, neutropenia, leukopenia, thrombopenia, and CD4 lymphopenia.

2) The onset of intraoperative complications

With all surgery cases as the denominator, the incidence of the worst grade according to the CTCAE v4.0-JCOG will be found for the following adverse events.

Intraoperative complications: from incision until completion of surgery (abdominal closure)

- Acute coronary syndrome, thromboembolism, intraoperative damage to the hepatobiliary system (pancreas, common bile duct, portal vein, intraoperative arterial injury, intraoperative venous injury, intraoperative gastrointestinal disorders (esophagus, duodenum, jejunum, ileum, colon), and intraoperative splenic injury

As a general rule, complications will be noted on the treatment progress report only when non-hematological toxicities※ of grade 3 or above and unexpected non-hematological toxicities※ of grade 2 or above are observed, and therefore the incidence of adverse events (toxicities) other than those listed above will not be tabulated except when a specific adverse event is repeatedly observed,

※ Non-hematological toxicities indicates adverse events other than those listed below in the CTCAE v4.0-JCOG: anemia, hypocellular bone marrow, lymphopenia, neutropenia, leukopenia, thrombopenia, and CD4 lymphopenia.

3) The incidence of postoperative complications

With all surgery cases as the denominator, the incidence of the worst grade according to the CTCAE v4.0-JCOG and Clavien-Dindo classification will be found for the following adverse events.

i) Early stage postoperative complications: from completion of surgery until the initial discharge after surgery.

CTCAE v4.0 -JCOG /Clavien-Dindo classification

- Pancreatic fistula/ pancreatic fistula

- Postoperative hemorrhage/ postoperative hemorrhage
- Abdominal infection/ peritoneal abscess
- Gastrointestinal anastomotic leak/ gastrointestinal suture failure
- Injury, poisoning and other procedural complications- other (anastomotic stenosis)/ Gastrointestinal anastomotic stenosis
- Cholecystitis / cholecystitis
- Gastrointestinal disorder-other (dumping syndrome) / dumping syndrome
- Gastrointestinal disorder-other (delayed gastric emptying)/ Delayed gastric emptying
- Gastroesophageal reflux disease / gastroesophageal reflux disease
- Small intestinal obstruction / Occlusive ileus
- Ileus/ Paralytic ileus
- Thromboembolic event / Thrombosis and embolism
- Lung infection / postoperative pneumonia
- Pleural effusion/ postoperative pleural effusion
- Gastrointestinal disorders- other (milky ascites) / Milky ascites
- Wound infection / postoperative wound infection
- Wound dehiscence/ wound dehiscence

ii) **Late stage postoperative complications: from the initial discharged after surgery until 5 years after surgery**

CTCAE v4.0-JCOG /Clavien-Dindo classification

- Abdominal infection/ peritoneal abscess
- Injury, poisoning and other procedural complications- other (anastomotic stenosis)/ Gastrointestinal anastomotic stenosis
- Cholecystitis / cholecystitis
- Gastrointestinal disorder-other (dumping syndrome) / dumping syndrome
- Gastroesophageal reflux disease / gastroesophageal reflux disease
- Small intestinal obstruction / Occlusive ileus
- Ileus/ Paralytic ileus
- Lung infection / postoperative pneumonia
- Wound infection / postoperative wound infection
- Wound dehiscence/ wound dehiscence

As a general rule, complications will be noted on the treatment progress report only when complications (non-hematological toxicities※) of grade 3 or above are observed, and therefore the incidence of adverse events (toxicities) other than those listed above will not be tabulated except when a specific adverse event is repeatedly observed,

※ Non-hematological toxicities indicates adverse events other than those listed below in the CTCAE v4.0-JCOG: anemia, hypocellular bone marrow, lymphopenia, neutropenia, leukopenia, thrombopenia, and CD4 lymphopenia.

Incidence of adverse events in postoperative adjuvant chemotherapy

The frequency (by group) of the worst Grade of the following adverse events (poisoning) during all courses will be found according to the CTCAE v4.0, with the number of cases in which postoperative adjuvant chemotherapy was conducted as the denominator. Patients registered in JCOG1104 for whom postoperative adjuvant chemotherapy was deemed necessary and who were assigned to Group A are to be included.

-General disorders and administration site conditions: fever, fatigue
-Gastrointestinal disorders: abdominal pain, diarrhea, nausea, vomiting, oral mucositis
-Cutaneous and subcutaneous tissue damage: alopecia, skin hyperpigmentation, palmar plantar

erythrodysathesia syndrome, maculopapular rash
-Metabolic and nutritional disorder: loss of appetite
-Blood and lymphatic disorder: febrile neutropenia
-Laboratory testing: leukocytopenia, neutropenia, anemia (hemoglobin), thrombopenia, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated blood bilirubin, elevated creatinine
-Metabolic and nutritional disorder: hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia
-Other Grade 3 or higher adverse events (*non-hematotoxicity)

Adverse events other than the above will be noted in the CRF only when non-hematotoxicity of Grade 3 or greater is observed, and thus as a rule, not tabulated in the incidence except for instances when multiple specific adverse events are observed.
*Non-hematotoxicity indicates adverse events other than those listed below in the CTCAE v4.0: anemia, hypocellular marrow, lymphopenia, neutropenia, leukopenia, thrombocytopenia, bone marrow failure and CD4 lymphopenia

11.3.9. Incidence of severe adverse events (adverse responses)

1) The incidence of grade 4 non-hematological toxicities

The incidence of grade 4 non-hematological toxicities shall be calculated as a ratio of all treated cases as the denominator and the number of patients with one or more grade 4 non-hematological toxicities※ as the numerator defined as among adverse events reported in the free comment field of the CRF that show a causal relationship with the protocol-based treatment (either definite, probable, or possible).

※ "Non-hematological toxicities" indicates adverse events other than those listed below in the CTCAE v4.0-JCOG: "anemia," "hypocellular bone marrow," "lymphopenia," "neutropenia," "leukopenia," "thrombopenia," and "CD4 lymphopenia."

2) The incidence of early stage death

The incidence of early stage death shall be calculated with all treated cases as the denominator, and the number of all deaths that occur during the protocol-based treatment, or within 30 days after the last day of protocol-based treatment as the numerator. The causal relationship with protocol-based treatment is irrelevant to the cause of death.

3) The incidence of treatment-related death (TRD incidence)

The incidence of treatment-related death shall be calculated with all treatment cases as the denominator, and the number of deaths among all deaths that are deemed to have a causal relationship with the protocol-based treatment (definite, probable, or possible) as the numerator.

12. Statistical items

12.1. Main analysis and evaluation criteria

The purpose of the main analysis in the present trial is to identify whether the trial treatment group, group B (preoperative S-1 + CDDP + trastuzumab) exhibits increased overall survival, the primary endpoint, compared to the standard treatment group, group A (preoperative S-1 + CDDP therapy).

To test the null hypothesis that overall survival is equal for the two groups, a stratified log-rank test including all enrolled cases shall be conducted using allocation adjustment factors other than institution ([with vs. without] paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis). However, in the event that it is expected that the stratified log-rank test cannot be conducted adequately using one factor due to a small number of events/participants in each stratification, then the processing of allocation adjustment factors shall be determined in the analysis plan created without data pertaining to group comparison prior to confirmatory analysis with group comparison. Furthermore, sensitivity analysis shall be conducted including all eligible cases.

In the event that the trial treatment group is inferior to the standard treatment group, whether or not it is statistically significant is of no interest (the conclusion that "the trial treatment, i.e. preoperative S-1 + CDDP + trastuzumab therapy is not a promising treatment," will not change whether there is a significant difference or not), and therefore we shall conduct one-sided tests. The present trial is an exploratory phase II trial, and thus the level of significance for all tests shall be 20% for one side. For main analysis, a two-sided confidence interval of 60% shall be calculated, which corresponds to one-sided level of significance.

As described in section "2.4. Study design," unlike paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis, for patients with cT2 or deeper invasion, and regional lymph node metastasis with minor axis of 15 mm≤ (excluding paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis), gastrectomy with D2 lymph node dissection + S-1 oral administration for one year after surgery is considered the standard treatment. Therefore, preoperative S-1 + CDDP therapy, which is administered to the standard treatment group in the present trial, is provisionally considered the standard treatment. Accordingly, in the event that the following two conditions are satisfied, it shall be concluded that preoperative S-1 + CDDP + trastuzumab therapy, the trial treatment, is more effective in all groups included in the present trial.

① The 3 year survival in the standard treatment group (preoperative S-1 + CDDP therapy) exceeds the point estimate of 70% in patients with regional lymph node metastasis cT2 or deeper, and ≥ 15 mm minor axis (excluding paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis).

② The trial treatment group is statistically significantly higher than the standard treatment group

In the event that conditions ① and ② are satisfied, it shall be concluded that preoperative S-1 + CDDP therapy, the trial treatment, is a promising treatment method. In the event that condition ① only is satisfied, it shall be concluded that provisional standard treatment with preoperative S-1 + CDDP therapy, will be the standard treatment in all targeted groups of the present trials in future. In the event that condition ② only is satisfied, it shall be concluded that preoperative S-1 + CDDP + trastuzumab therapy, the trial therapy, is a promising treatment method; however, target groups and standard treatment of the next phase III trial shall be reexamined within groups. In the event that neither condition ① nor ② are satisfied, preoperative S-1 + CDDP therapy shall continue to be the standard treatment for patients with No.16a2/b1 metastasis and/or bulky lymph node metastasis, while gastrectomy with D2

lymph node dissection + one year of postoperative S-1 oral administration shall continue to be the standard treatment for patients with regional lymph node metastasis of cT2 or deeper, and ≥ 15 mm minor axis (excluding No.16a2/b1 metastasis, and/or bulky lymph node metastasis).

The cumulative survival curve, median survival time, and annual survival rate were estimated using the Kaplan-Meier method, and the 95% confidence interval for the medial survival time shall be calculated using the Brookmeyer and Crowley, while the confidence interval for the annual survival rate shall be calculated using the Greenwood formula. As estimated values for therapeutic effect, a stratified Cox proportional hazard model with the same factors as those used in the main analysis shall be used to obtain the hazard ratio for therapeutic effect between the groups and the associated 95% confidence interval. As necessary, in addition to allocation adjustment factors, Cox regression adjusted for background factors in which biases are observed shall be, performed.

The results of the main analysis shall be summarized by the Data Center as a "main analysis report," which will be submitted to the study secretariat, principal investigator chairperson, group representative, group secretariat, data and safety monitoring committee, and JCOG representative. The research chairperson/research secretariat shall summarize the content in the main analysis report, and produce a "general report" from a clinical perspective mainly summarizing the overall conclusions of the trial, problem areas, interpretation and discussion of the results, and future course. After obtaining the approval of the group representative and JCOG Data Center director, the general report shall be submitted to the Data and Safety Monitoring committee and JCOG chairperson.

12.2. Planned number of enrollment/enrollment period/follow-up period

On the basis of background shown in section "2.4.3. Rationale for setting the clinical hypothesis and the number of enrollment," in the event that a superiority trial is designed to detect whether the rate for group B will exceed that figure by 10% assuming that 3 year survival of group A is 70%, the target number of patients necessary for analyses, using the Schoenfeld & Richter method[48] with three-year enrollment, three-year follow-up, α = 20% (one-sided), and detectability at 75%, will be calculated to be 63 cases for one group and 126 cases needed for both groups (required number of events: 43). Moreover, when the three-year survival rate for the standard treatment group deviates from the anticipated rate, the required number of eligible patients (required number of events) would be as shown in table 12.2.1 below.

Table 12.2.1. Three-year survival of both groups and the target number of patients necessary for analyses corresponding to detectability

	Detectability		
Three-year survival	70%	75%	80%
65.0% vs 76.4%	88 (35)	108 (43)	134 (53)
70.0% vs 80.0%	102 (35)	126 (43)	154 (53)
75.0% vs 83.5%	122 (35)	150 (43)	184 (53)

※ The number of required events shown in parentheses

Thus taking into account the potential inability to follow-up several patients, the following was established.

Planned number of enrollment: 65 patients in each group, giving a total of 130 patients for both groups.

Enrollment period: 3 years, follow-up period: 5 years following completion of enrollment (main analysis shall be performed 3 years after completion of enrollment, and final analysis after 5 years)

However, extension of the enrollment period within 6 months does not require protocol revision.

In the event that prognosis determined by routine monitoring is found to be better than expected or there is a large deviation from the prior estimation, redesign of the sample size shall be considered. In doing so, the clinically significant difference shall also be re-examined, and redesigning of analysis shall

be performed under the blind test prior to implementation in the analyses.

12.3. Interim analysis and early trial termination

12.3.1. Purpose and period of interim analysis

Even in the event that interim results of the present trial suggest that efficacy is more favorable than expected, this trial is not a confirmatory study, in other words, since this is a randomized phased II screening trial to determine the feasibility of proceeding onto a phase III trial on the basis of an α (20%) greater than normal, and in addition sufficient data regarding safety needs to be accumulated for the subsequent phase III trial, early termination for efficacy shall not take effect on the basis of interim analysis.

In contrast, in the event that it is found during enrollment period that efficacy is clearly inferior to anticipated, enrollment must be terminated, and therefore interim analysis shall be performed once during enrollment to determine whether or not to terminate for futility. The trial shall be terminated due to futility in the event that it is determined that the efficacy of the trial treatment is considerably poor, and the trial results shall be presented at academic meetings and published in an article as soon as possible.

The first interim analysis shall be performed using data from the initial routine monitoring conducted as an inquiry subsequent to the time when half of the planned number of enrollment (65 patients) have been obtained.

As a general rule, enrollment shall not be suspended during interim analysis. Furthermore, in the event that the trial progresses as planned, if the first interim analysis is conducted 1.5 years after the start of enrollment, it is expected that there will be 4 events at the time of conducting the interim analysis under the premise described in section 12.2.

In the present trial, in the event that the prognosis of the standard treatment group is as expected, although at the time of the scheduled interim analysis fewer events may be observed than expected, and since it is conceivable that it may not turn our as expected in advance, the interim analysis shall be performed whether or not to terminate the trial for futility. However, in the event that information time is 25% or less (when there are 130 enrollments planned, and there are 10 events or fewer observed), and it is expected that the number of accumulated enrollments is 90% or more of the planned number of enrollment (117 or more enrollments in the event that there are 130 enrollments planned) at the time when the Data and Safety Monitoring Committee examines the results of the interim analysis, it will be determined that there is insufficient data to assess the advantages and disadvantages of termination due to inefficacy, and therefore the interim analysis shall not be performed.

12.3.2. Method for interim analysis

Interim analyses shall be conducted by the Data Center. The advantages and disadvantages of termination due to efficacy will not be assessed in the interim analyses of the present trial, and therefore multiplicity adjustments of the test to preserve the 20% α error for the trial overall will not be necessary, and thus shall not be performed. In the present trial, in the event that the survival curve is lower for the trial treatment group than the standard treatment group, the advantages and disadvantages of trial termination (inefficacy-based termination) shall be examined overall. However, to use the decision resulting from such examination as a reference, detectability of conditions and Bayesian predictive probability shall be calculated.

12.3.3. Examination and reporting of the results of the interim analysis

The results of interim analysis will be submitted to the Data and Safety Monitoring Committee by the Data Center as an interim analysis report, who will investigate whether to continue the trial and whether to publish the results. The Data and Safety Monitoring Committee will investigate whether to continue the trial in meetings, and recommend whether to continue the trial and whether to publish the results to the research representative based on the results of this examination.

However, the relevant group members shall not participate in the examination by the Data and Safety

Monitoring Committee. Furthermore, the research chairperson, research secretariat and researchers at participating facilities cannot know the results of interim analysis for this trial until completion of the trial as long as a recommendation on discontinuation of the trial has not been made by the Data and Safety Monitoring Committee based on the results of interim analysis

If a recommendation to discontinue or change of part or all of the trial is made by the Data and Safety Monitoring Committee based on the investigation into the interim analysis report, the research chairperson will examine the details related to that recommendation and determine whether to discontinue or change part of the trial.

In the event of discontinuation or change to part of the trial, the research chairperson will submit to the Data and Safety Monitoring Committee a request in writing to revise the protocol or a request for permission to discontinue the trial. The research chairperson may discontinue or change part of the trial with the permission of the Data and Safety Monitoring Committee.

The research chairperson may disagree with the recommendation of the Data and Safety Monitoring Committee. However, the instructions of the JCOG representative will be followed if an agreement cannot be reached in discussion with the Data and Safety Monitoring Committee.

If the trial is discontinued, the subsequent follow-up period will be five years from final enrollment.

12.4. Analysis of secondary endpoints

Secondary endpoints shall be analyzed in order to conduct investigation for which the main analysis for this trial is complemented. Multiplicity adjustment shall not be made in the analysis of secondary endpoints due to their exploratory nature. While groups will be compared as necessary, it should be noted that in the event that the results of comparison between groups do not indicate significant difference, it does not necessarily mean there is no difference between the groups.

12.4.1. Analysis of secondary endpoints for safety

Among secondary endpoints, safety endpoints include the incidence of adverse events, and the incidence of severe adverse events, which as a general rule shall be included in routine monitoring items ("14.1 Routine monitoring").

The incidences of adverse events and severe adverse events are expected not to be much higher in the trial treatment group than the standard treatment group.

The incidence of adverse events shall be calculated as the incidence of each adverse event, as well as those incidence of grade 3 and above. In addition, for the adverse events other than the laboratory testing values, incidence of grade 2 and above shall also be calculated. The incidence of severe adverse events including grade 4 non-hematological toxicities, early stage death, and treatment-related death shall be reported in detail with the registration number on the routine monitoring report. Moreover, the incidence of grade 4 non-hematological toxicities, early stage death, and treatment-related death shall be calculated at the time of the interim analyses, main analysis, and final analysis.

The interval estimate for incidence shall be calculated using the exact confidence interval based on binomial distribution. These endpoints will not be assessed on the basis of any statistical testing; however, groups shall be compared using the Fisher's exact test as needed.

12.4.2. Analysis of secondary endpoints for efficacy

Among secondary endpoints, efficacy endpoints include progression-free survival, response rate to preoperative chemotherapy, rate of curative resection, rate of treatment completion prior to surgery, rate of treatment completion prior to postoperative adjuvant chemotherapy, and histological response. These shall only be analyzed in the interim analyses, main analysis, and final analysis. However, it appears that these endpoints cannot be interpreted at the time of interim analyses, and therefore data shall be tabulated to confirm whether or not the data has been appropriately obtained, and the results shall not be presented in the interim analysis report.

Progression-free survival, preoperative chemotherapy response rate, curative resection rate, and histological response are all indicators of whether or not trastuzumab will improve surgical curability, and therefore they are expected to be higher in the trial treatment group than in the standard treatment