incidence of postoperative complications might differ. Moreover, prognosis might differ between the two groups. Accordingly the presence or absence of paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis was defined as an allocation adjustment factor.

#### 2.4.6. Central pathology review

In the present study there will be no central pathology review performed.

#### 2.4.7. Central review of effects

In the present study there will be no central review of effects.

### 2.5. Summary of anticipated advantages and disadvantages associated with participation in the trial

#### 2.5.1. Anticipated benefits

In the present study, patients allocated to group B will fall under the Advanced Medical Care B Program, and therefore the agent (trastuzumab), which is not covered by the national health insurance scheme and is not approved under the Pharmaceuticals and Medical Devices Law, will be provided free of charge, which may be called a benefit. However, the superiority of the treatment in group B compared to group A will be determined by the results of the phase III trial planned to follow the present trial, and therefore at this point in time, it is unclear whether the free provision of trastuzumab will actually be a benefit. Furthermore, other than the cost of trastuzumab, medical expenses including hospital admission fees, costs of surgery, and treatment for adverse events in preoperative chemotherapy will be incurred by the patient and the national health insurance scheme. Thus there will be no particular financial benefit gained in participating in the present trial.

#### 2.5.2. Anticipated risks and disadvantages

Surgery and postoperative adjuvant chemotherapy conducted in Group A will be performed as routine medical care covered by the national health insurance scheme, and thus compared to everyday routine medical care there will be no particular risk or disadvantage incurred. While group B will be administered Herceptin, the associated toxicities are extremely mild and not severe, and thus there will be no particular risk or disadvantage compared to everyday routine medical care.

Furthermore, in patients who do not respond to preoperative chemotherapy, surgery will be delayed and the cancer may progress, which can reduce the possibility of cure. To minimize the risk of these adverse events and disadvantages, the '4. Patient selection criteria', '6.3. Criteria for Change of Treatment', and '6.4. Combination therapy and supportive therapy' will be thoroughly examined by the Group. In the present trial, assuming that the point-estimate for treatment-related deaths does not exceed 5% in either group, at the point in time when the number of treatment-related deaths reached 4 cases in either group, temporary discontinuation of enrollments will be investigated because it will be clear that the final point-estimate will exceed 5%.

Furthermore, in JCOG clinical trials, routine monitoring every 2 years after the start of the trial is mandatory. The monitoring will be performed by the Data Center and the Data and Safety Monitoring Committee to determine whether any adverse events are within the expected range, and a system is in place so that the onset of any severe or unexpected adverse events will be thoroughly examined and discussed in accordance with the rules stipulated in the JCOG 'Guidelines for Clinical Safety Data Management', and measures will be taken as required.

### 2.6. Significance of the present trial

On the basis of the results of the ToGA trial, a regimen including trastuzumab will be the first treatment choice for HER2-positive unresectable advanced gastric cancer. However, the efficacy and safety of perioperative chemotherapy with trastuzumab for HER2-positive gastric cancer thought to be resectable has not yet been examined.

If exploratory analyses in the present trial demonstrate the safety and efficacy of S-1 + CDDP + trastuzumab as preoperative chemotherapy, then it will strongly impact the development of perioperative chemotherapy for HER2-positive chemotherapy, and provide the grounds for the future

development of different treatments according to HER2 status for curatively resectable gastric cancers. Furthermore, in the event the phase III trial following the present trial demonstrates the efficacy of S-1 + CDDP + trastuzumab, and if a public knowledge-based application is deemed valid after examination by a review group on unapproved and off-label agents, then trastuzumab (Herceptin ® infusion) might be approved under the Pharmaceuticals and Medical Device Law as preoperative chemotherapy for gastric cancer. In the event that S-1 + CDDP + trastuzumab is not shown to be safe and effective as preoperative chemotherapy, then preoperative trastuzumab will not be recommended for HER2-positive gastric cancer. Further developments of treatments including postoperative therapies and the use of other anti-HER2 agents are needed, and will influence treatment development strategies in perioperative chemotherapy for HER2-positive gastric cancer.

## 2.7. Accompanying research (including translational research)

The following translational research is planned as accompanying research of the present trial.

### 2.7.1. Accompanying research of biomarkers in relation to prognostic factors of HER2-positive gastric cancer and predictive factors of trastuzumab outcomes

No specific prognostic factors have been found that are specific to HER2-positive gastric cancer, irrespective of resectable or unresectable cancer. Furthermore there have been no factors found that predict the outcomes of trastuzumab for HER2-positive gastric cancer. Therefore an exploratory analysis of prognostic and predictive will be performed by examining the relationship between the results of protein and gene expression analyses using biopsy specimens and blood samples (whole blood) obtained prior to preoperative chemotherapy, with the efficacy data including cytoreduction effect and survival period obtained in the present study.

If prognostic factors of HER2-positive gastric cancer can be clarified, then they will help physicians and patients with their decision-making in selecting treatment. Furthermore, if the effects of trastuzumab can be predicted using pretreatment specimens then it will enable to avoid the unnecessary administration of trastuzumab.

### 2.7.2. Accompanying research of biomarkers in relation to trastuzumab-resistance in HER2-positive gastric cancer

It is assumed that residual gastric cancer tissue following preoperative chemotherapy contains many chemotherapy-resistant cancer. The mechanism of chemotherapy resistance can be investigated by performing protein and gene expression analyses using biopsy specimens obtained prior to preoperative chemotherapy and surgical specimens obtained following preoperative chemotherapy, then profiling gene and protein expression and subsequently comparing both. Furthermore, a comparison of profiles in the trastuzumab administered group and the non-trastuzumab group will enable the mechanism of trastuzumab-resistance to be examined. If the trastuzumab resistance mechanism can be clarified, then such a mechanism can be targeted in the development of treatments using other agents.

These analyses will be performed separately in the '2.8. biobank' below. The details of the accompanying research will be noted in the translational research protocol, and approval will be obtained for examination by the JCOG protocol review committee and the ethics review board of participating institutions.

## 2.8. JCOG Biobank project

The present trial will be included in the JCOG biobank project.

In the JCOG biobank project, samples will be collected and stored from patients enrolled in clinical trial conducted by the JCOG, regardless of any prior plans for sample analyses. The purpose of the project is to provide appropriate clinical information obtained through the present trial, and samples for subsequent sample analyses.

Of patients who consent to participation in the present trial, the JCOG biobank project will include individuals who consent to providing samples for the biobank and who consent to their usage in future

sample analyses and research (consent to banking hereafter).

The samples collected will include whole blood and pathological tissues preserved in routine medical care. Plasma and DNA isolated and extracted from serum samples will be stored by the JCOG biobank, and supplied for future sample analyses and research. Furthermore, preserved pathological tissue from routine medical care including surgery, biopsy and laboratory testing will also be collected, however at this point in time the specific processing method is undecided, such as in determining whether the preserved tissue can be supplied without difficulty for the medical care of the patient concerned, the type of pathological tissue, sample preparation method and tissue amount, as well as the time and methods of collection. Accordingly, consent for utilization of the preserved pathological tissue following treatment will be obtained at the time of consent for banking, however actual collection will begin upon establishment of the details after revision of the JCOG biobank project protocol outlined hereafter.

The detailed procedure regarding sample collection, storage, and the method in which samples will be supplied for translational research conducted in future is established in the 'JCOG biobank project protocol' for all JCOG trials. Participation in the JCOG biobank project requires examination and approval by the ethics review board of participating institutions.

Furthermore, when conducting translational research using samples stored in the JCOG biobank, a 'translational research protocol' will be newly created, and subsequently require examination and approval by the ethic review board of institutions involved in the translational research and by the JCOG protocol review committee.

# 3. Criteria and definitions in the present trial

## 3.1. Anatomical items

### 3.1.1. Primary lesion siteof gastric cancer

The greater curvature and lesser curvature of the stomach is divided into 3 equal section, with each corresponding point connected to divide the stomach into 3 areas, i.e. the U (upper), M (middle), and L (lower) areas. E (esophageal) and D (duodenal) invasion will also be mentioned. In the event that the lesion extends over two adjacent areas, the main area will be noted first followed by the area where the invasion has spread to.

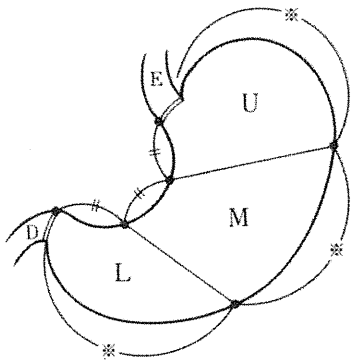



Fig. 3.1.1. Three portions of the stomach

## 3.2. Macroscopic classification

Basic classification

Type 0: superficial type
Type 1: mass type
Type 2: Ulcerative type
Type 3: Infiltrative ulcerative
Type 4: Diffuse infiltrative type
Type 5: Unclassable (difficult to classify in types 0-4 above)

Subclassification of type 0 (superficial type)

Type I: protruding
Type II: superficial type

IIa : superficial elevated type

IIb : superficial flat type

IIc : superficial depressed type

Type III : excavated type

## 3.3. Histological classification

The shaded types are included in the present trial.

Common type

Papillary adenocarcinoma (pap)
Tubular adenocarcinoma (tub)
Well differentiated type (tub1)
Moderately differentiated type (tub2)

Poorly differentiated adenocarcinoma (por)
Solid type (por1)
Non-solid type (por2)
Signet-ring cell carcinoma (sig)
Mucinous adenocarcinoma (muc)

Special type
Carcinoid tumor
Endocrine carcinoma
Carcinoma with lymphoid stroma
Hepatoid adenocarcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Undifferentiated carcinoma
Miscellaneous carcinomas

## 3.4. Staging criteria

### 3.4.1. Data recording method

Finding categories include T (invasion depth), N (lymph node), H (hepatic metastasis), P (peritoneal metastasis) and M (distal metastasis), which shall all be indicated in capital letters. The extent of each of these findings is to be shown in numerals after the finding category and if unclear place an 'X'. Two types of findings at the time of diagnosis, i.e. clinical classification, pathological classification are to be indicated by the small letters c and p before the finding category. Any data without a prefix indicates clinical classification.

### 3.4.2. Gastric wall invasion depth

The depth of gastric wall invasionby the tumor is defined as follows.

T1 : Cancer invasion confined to the mucosa (M) or submucosa (SM)
T1a-M : Cancer invasion confined to the mucosa
T1b-SM : Cancer invasion confined to the submucosal layer
T2-MP : Cancer invasion exceeds the submucosal tissue but is confined to the muscularis propria (MP)
T3-SS : Cancer invasion exceeds the submucosal tissue, but is confined to the subserosa (SS)
T4 : Cancer invasion is contiguous to or exposed beyond the serosa, or has spread to adjacent organs
T4a-SE : Cancer invasion is contiguous to or exposed beyond the serosa surface (SE)
T4b-SI : Cancer invasion has spread directly to adjacent organs (SI)
TX : The depth of cancer invasion is unknown

Regardless of the presence or absence of lymph node metastasis, T1 is called 'early stage gastric cancer', and T2-4 is called 'advancedcgastric cancer'

### 3.4.3. Lymph node metastasis

The number, name, and limit of the lymph nodes involved in the stomach are defined below and in Fig. 3.4.3.

#### 1) Lymph node number and name

No. 1 Right paracardil lymph node
No. 2 Left paracardial lymph node
No. 3a Lesser curvature lymph node (along the left gastric artery)
No. 3b Lesser curvature lymph node (along the right gastric artery)
No. 4sa Left greater curvature lymph nodes (along the short gastric artery)
No. 4sb Left greater curvature lymph nodes (along the left gastroepiploic artery)
No. 4d Right greater curvature lymph nodes (along the right gastroepiploic artery)
No. 5 Suprapyloric lymph nodes

No. 6 Infrapyloric lymph nodes
No. 7 Lymph nodes along the trunk of the left gastric artery
No. 8a Anterosuperior lymph nodes along the common hepatic artery
No. 8p Posterior lymph nodes along the common hepatic artery
No. 9 Celiac artery lymph nodes
No. 10 Splenic hilar lymph nodes
No. 11p Proximal splenic artery lymph nodes
No. 11d Distal splenic artery lymph nodes
No. 12a Hepatoduodenal ligament lymph nodes (along the hepatic artery)
No. 12b Hepatoduodenal ligament lymph nodes (along the bile duct)
No. 12p Hepatoduodenal ligament lymph nodes (along the portal vein)
No. 13 Lymph nodes on the posterior surface of the pancreatic head
No. 14v Lymph nodes along the superior mesenteric vein
No. 14a Lymph nodes along the superior mesenteric artery
No. 15 Lymph nodes along the middle colic vessels
No. 16a1 Abdominal para-aortic lymph nodes, a1
No. 16a2 Abdominal para-aortic lymph nodes a2
No. 16b1 Abdominal para-aortic lymph nodes b1
No. 16b2 Abdominal para-aortic lymph nodes b2
No. 19 Infradiaphragmatic lymph nodes
No. 20 Lymph nodes in the esophageal hiatus
No.110 Paraesophageal lymph nodes in the ower thorax
No.111 Supradiaphragmatic lymph nodes

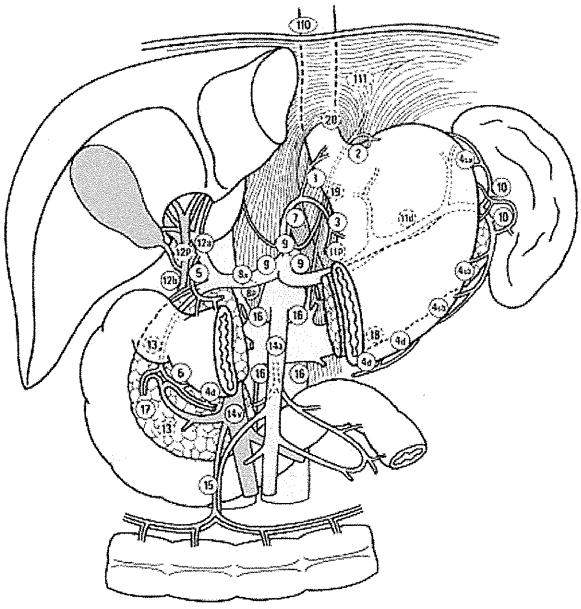


Fig 3.4.3.a. Lymph node number

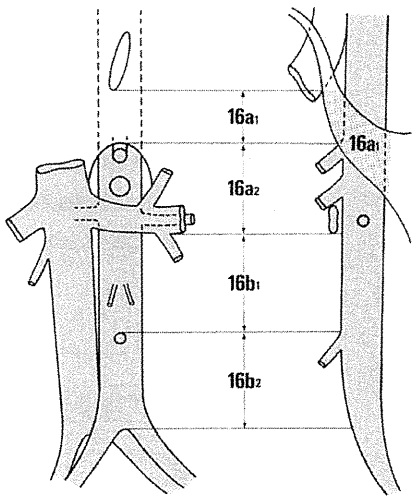



Fig 3.4.3.b. Paraaortic lymph node

**2) Regional lymph node**

lymph nodes No. 1-12 and No. 14v are defined as regional lymph nodes of the stomach. All lymph node metastasis other than in these regional lymph nodes of the stomach will be defined as M1. However in the event of esophageal invasive cancer, lymph nodes No. 19, 20, 110, and 111 will be considered regional lymph nodes.

**3) Lymph node metastasis**

N0 : No regional lymph node metastasis observed
N1 : Metastasis in 1-2 regional lymph nodes
N2 : Metastasis to 3-6 regional lymph nodes

N3 : Metastasis to 7 or more regional lymph nodes
N3a : Metastasis in 7-15 regional lymph nodes
N3b : Metastasis in 16 or more regional lymph nodes
NX : The presence or absence of regional lymph node metastasis is unknown

### 3.4.4. Other metastasis

#### 1) Distal metastasis

M0 : No metastasis outside of regional lymph nodes
M1 : Metastasis observed outside of regional lymph nodes
MX : The presence or absence of metastasis outside of the regional lymph nnodes is unknown

In the event of M1 the site must be recorded. The sites are listed below.
Peritoneum (PER) , liver (HEP) , lymph nodes (LYM) , skin (SKI) , lungs (PUL) , bone marrow (MAR), bone (OSS) , pleura (PLE) , brain (BRA) , meninx (MEN) , adrenal (ADR) , and other (OTH) .

#### 2) Peritoneal metastasis

P0 : No peritoneal metastasis observed
P1 : Peritoneal metastasis observed
PX : The presence of absence of peritoneal metastasis is unknown

#### 3) Peritoneal cytology

CY0 : Peritoneal cytology negative for carcinoma cells
CY1 : Peritoneal cytology positive for carcinoma cells
CYX : Peritoneal cytology not performed

#### 4) Hepatic metastasis

H0 : No hepatic metastasis observed
H1 : Hepatic metastasis observed
HX : The presence or absenceof hepatic metastasis is unknown

### 3.4.5. Stage

Table 3.4.5. Staging

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1a-M、T1b-SM | IA | IB | IIA | IIB |
| T2-MP | IB | IIA | IIB | IIIA |
| T3-SS | IIA | IIB | IIIA | IIIB |
| T4a-SE | IIB | IIIA | IIIB | IIIC |
| T4b-SI | IIIB | IIIB | IIIC | IIIC |
| H1,P1,CY1,M1 (regardless of T) | IV | IV | IV | IV |

## 3.5. Evaluation after resection (Japanese Classification of Gastric Carcinoma, 14th ed.)

### 3.5.1. Surgicak specimen resection margin

#### 1) Proximal margin (PM)

PMX : Cancer invasion of the proximal margin is unknown
PM0 : No cancer invasionobserved in the proximal margin
PM1 : Cancer invasion observed in the proximal margin

**2) Distal margin (DM)**

DMX : Cancer invasion of the distal margin is inknown
DM0 : No cancer invasion observed in the distal margin
DM1 : Cancer invasion observed in the distal margin

**3) Residual tumor**

Residual tumor after surgery is indicated by R (residual tumor). R0 is curative resection, and R1, and R2 are non-curative resections.

R0 : No residual tumor
R1 : Microscopic residual tumor (positive resection margin or positive peritoneal cytology)
R2 : Macroscopic residual tumor
RX : Presence of residual tumor cannot be assessed

### 3.6. Definition of lymphadectomy (Japanes Gastric Cancer Treaytment Guidelines, revised 3rd ed.)

The systematic extent of lymphadectomy is deterimed according to the type of gastrectomy.

1) Total gastrectomy
   - D0 : Less than D1 dissection
   - D1 : No. 1～7
   - D1+ : D1 + No.8a、9、11p
   - D2 : D1 + No.8a、9、10、11p、11d、12a
   - D2+ : Extended dissection exceeding D2

   However in esophageal invasive cancer, No.110 will be additionally removed in D1, and nodes N0. 19, 20, 110, and 111 will be removed in D2.

2) Distal gastrectomy
   - D0 : Less than D1 dissection
   - D1 : No. 1、3、4sb、4d、5、6、7
   - D1+ : D1 + No.8a、9
   - D2 : D1 + No.8a、9、11p、12a
   - D2+ : Extended dissection exceeding D2

3) Pyloorus preserving gastrectomy
   - D0 : Less than D1 dissection
   - D1 : No. 1、3、4sb、4d、6、7
   - D1+ : D1 + No.8a、9

4) Proximal gastrectomy
   - D0 : Less than D1 dissection
   - D1 : No. 1、2、3a、4sa、4sb、7
   - D1+ : D1 + No.8a、9、11p

### 3.7. Paraaortic lymph nodes

'Paraaortic lymph node (No.16a2/b1) metastasis' will be diagnosed on the basis of lymph nodes with a maximum diameter (major axis) of 10 mm or greater in the No. 16a2/b1 on upper abdominal contrast enhanced CT. CT measurements taken in the transverse section will be used for all lymph node measurements. There will be no anteroposterior measurements taken using 3-D reconstruction.

### 3.8. Bulky lymph nodes

Bulky lymph node metastasis will be diagnosed when abdominal CT reveals that either of the conditions outlined below are met by lymph nodes adjacent to the celiac artery, common hepatic artery, splenic artery, proper hepatic artery or anterior surface of the superior mesenteric vein (lymph node: No.14v). All measurements of lymph nodes will be performed by transverse section CT. Anteroposterior measurements with not be taken using a 3-D reconstruction.

①The presence of two or more adjacent or contiguous lymph nodes 1.5 cm or longer

②Lymph nodes longer than 3 cm (composed of a single lymph node or agglomeration formed by various sized lymph nodes)

Important note) In the event that it is difficult to identify the lymph node station on imaging, findings shall be recorded as described below.

i) When it is difficult to distinguish between lymph nodes No.1, 3, and 7, then the node adjacent to the main branch of celiac trunk, the origin of the left gastric artery, will be eligible, and No.7 will be recorded.

ii) In the event that No.8a and No.8p are difficult to distinguish, then No.8a will be recorded.

iii) Lymph nodes at the origin of the superior mesentery artery (SMA) will be eligible as No. 16a2 in accordance with the Gastric Cancer Treatment Guidelines.
Lymph nodes along the SMA completely independent of the aorta will not be eligible as

No.14a in accordance with the Guidelines.

iv) When it is difficult to distinguish lymph nodes No. 6 and No, 14v, then the node adjacent to the anterior surface of the SMA will be eligible, and recorded as No.14v.

### 3.9. HER2 (human epidermal growth factor receptor type 2) test evaluation

1) Evaluation method

HER2 testing in gastric cancer cells is conducted by 2 methods, including the IHC technique (immunohistochemistry) to test for the presence or absence of protein overexpression, and the ISH technique (in situ hybridization) to examine gene amplification. ISH is performed using either the FISH method (fluorescence in situ hybridization), or the DISH method (dual color in situ hybridization).

2) Testing criteria for HER2-positivity

HER2-positivity is defined as 'IHC evaluation of 3+', or 'IHC evaluation of 2+ and positive ISH results (FISH or DISH) (HER2 gene amplification of 2 or more)'. HER2-positive status will not be identified based on ISH-positivity alone.

3) IHC scoring guideline (biopsy)

IHC scores will be determined based on the criteria listed in the guidelines on HER2 testing in gastric cancer created by the pathology committee for the use of trastuzumab in gastric cancer.

| Score | Finding |
|---|---|
| 0 | No positive staining, or no tumor cells with positive staining of the cell membrane |
| 1+ | One or more tumor cell clusters (aggregations) with faint/barely perceptible membranous reactivity, irrespective of the percentage of tumor cells stained. |
| 2+ | One or more tumor cell clusters (aggregations) with weak to moderate complete, basolateral, or lateral membranous reactivity, irrespective of the percentage of tumor cells stained. |
| 3+ | One or more tumor cell clusters (aggregations) with strong complete, basolateral, or lateral membranous reactivity, irrespective of the percentage of tumor cells stained. |

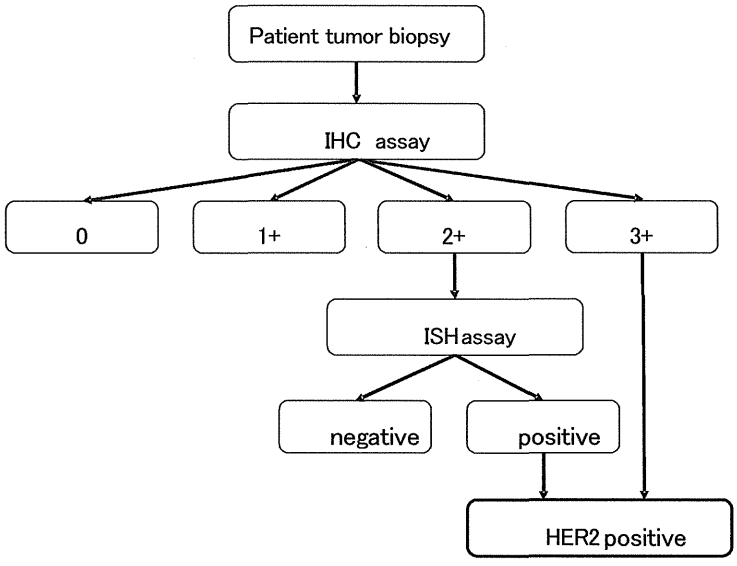
* : A cluster is defined as 5 or more tumor cells.

4) ISH assay scoring guideline

FISH and DISH scores will be determined using the following HER2 test scores.

| Finding | ISH result |
|---|---|
| Negative | HER2/17cen (CEP17) ratio < 2.0 |
| Positive | HER2/17cen (CEP17) ratio ≥ 2.0 |

Fig. 3.9. HER2 assessment flowchart



## 4. Patient selection criteria

Patients who satisfy all the following eligibility criteria, and who did not meet any of the exclusion criteria are eligible for enrollment.

### 4.1. Eligibility criteria (inclusion criteria)

1) Cytodiagnosis of endoscopic biopsy specimen from the primary gastric lesion of gastric cancer (any histological type).
2) HER2-positive (IHC3+, or, IHC2+ and ISH+).
3) One or more of the following lesions confirmed by contrast-enhanced upper abdominal CT performed less than 28 days prior to enrollment (Plain CT permitted if contrast enhanced CT cannot be performed) (irrespective of invasion depth for ① and ②, or cT2-4 invasion in ③).
   ① Paraaortic lymph node (No.16a2/16b1) metastasis (any T) (refer to 3.7)
   ② Bulky lymph node metastasis (any T) (refer to 3.8)
   ③ Regional lymph node of 15 mm in minor axis (cT2-4)
4) Absence of distal metastasis other than in the paraaortic lymph node No. 16a2/16b1, as confirmed by chest CT, contrast-enhanced upper abdominal CT, and contrast-enhanced CT of the pelvis performed less than 28 days prior to enrollment (Plain CT permitted if contrast enhanced CT cannot be performed).
5) Absence of macroscopic type 4 or large type 3 lesion (tumor diameter of 8 cm or greater on macroscopic diagnosis by upper gastrointestinal endoscopy).
6) No esophageal invasion, or esophageal invasion less than 3 cm.
7) No residual gastric cancer.
8) No history of chemotherapy, radiation therapy, or endocrine therapy to treat other types of cancer.
9) No history of surgery for gastric cancer. However, gastric bypass surgery, and endoscopic mucosal resection are eligible.
10) Absence of hepatic and peritoneal metastasis, with negative peritoneal lavage cytology on laparotomic findings at the time of laparoscopy and or bypass surgery performed less than 28 days prior to enrollment.
11) Aged between 20 and 75 years of age on the day of enrollment.
12) Performance status (PS) of 0 or 1 according to the ECOG scale (PS will be recorded on the medical chart).
13) Left ventricular ejection fraction (LVEF) greater than 50% on echocardiography performed less than 28 days prior to enrollment.
14) The most recent test values obtained less than 14 days prior to enrollment satisfy all of the following conditions (tests performed on the same day 2 weeks prior to the day of enrollment are permitted).
   ① Neutrophil count ≧1,500/$mm^3$
   ② Hemoglobin ≧8.0 g/dL (blood transfusion should not be performed during the 14 days prior to blood collection for enrollment)
   ③ Platelet count ≧$10\times10^4$ / $mm^3$
   ④ Total bilirubin ≦2.0 mg/dL
   ⑤ AST (GOT) ≦100 IU/L
   ⑥ ALT (GPT) ≦100 IU/L

⑦ Serum creatinine ≦1.3 mg/dL

⑧ Creatinine clearance *≧60 mL/min

The creatinine clearance is estimated at 60 mL/min/body or greater calculated using the Cockcroft-Gault equation. In the event that the estimation is less than 60 mL/min/body, but the actual measured value is greater than 60 mL/min/body, then the patient will be eligible.
For males: Ccr= { (140-age) × weight (kg) } / {72× serum creatinine level (mg/dL) }
For females: Ccr=0.85× { (140-age) × weight (kg) } / {72× serum creatinine level (mg/dL) }

15) Written consent obtained from the patient for participation in the trial.

**4.2. Exclusion criteria**

1) Active double cancer (synchronous double/multiple cancers and metachronous double/multiple cancer with a disease-free interval of less than 5 years. However carcinoma in situ (intraepithelial carcinoma) cured by local therapy and lesions equivalent to intramucosal carcinoma will not be included in active double/multiple cancers).
2) Infection that requires systemic treatment.
3) Fever of 38°C or higher at the time of enrollment.
4) Women who are pregnant, possibly pregnant, breast feeding, or within 28 days postpartum.
5) Patients for whom participation in this trial was deemed difficult because of complications of mental illness or psychiatric symptoms.
6) Receiving therapy with continuous systemic steroid or other autoimmune suppressors (oral or intravenous).
7) HBs antigen positivity.
8) Continuous use of flucytosine, or warfarin potassium required.
9) Chest CT diagnosis of concurrent interstitial pneumonia, pulmonary fibrosis, and/or severe pulmonary emphysema.
10) History of myocardial infarction or unstable angina within 6 months of enrollment.
11) Poorly controlled hypertension.
12) Ongoing treatment of continuous insulin use, or poorly controlled diabetes.

# 5. Enrollment/ allocation

## 5.1. Enrollment procedure

Once it has been confirmed that the target patient satisfies all the inclusion criteria and does not fall under any of the exclusion criteria, the patient can be enrolled using the JCOG Web Entry System. An individual account and password will be required for Web enrollments on the JCOG Web system. Contact the JCOG Data Center for any queries.

Patient enrollments JCOG Web Entry System
URL : https://secure.jcog.jp/dc/ (Web enrollment is possible 24 hours a day)

For queries regarding patient enrollments and JCOG Web Entry System
JCOG Data Center
TEL : 03-3542-3373
Week days from 9 am to 5 pm (closed on public holidays, Saturday, Sunday and during the New Year's break)
E-mail : JCOGdata@ml.jcog.jp

For queries regarding the patient selection criteria
Masanori Tokunaga : Division of Gastric Surgery, Shizuoka Cancer Center
TEL : 055-989-5222
FAX : 055-989-5783
E-mail : m.tokunaga@scchr.jp

5.1.1. Important notes regarding enrolment

① Without exception, enrollments will not be permitted after the start of the protocol treatment.
② Patients are to be enrolled via the URL listed in 5.1 'patient enrollment'.
③ Eligibility can be confirmed on the enrollment site, and therefore there is no need to send the enrollment eligibility confirmation firm by fax or post to the Data Center.
④ If the input data is incomplete, the enrollment will not be accepted until it is completed.
⑤ After confirmation of eligibility on the enrolment screen, enrolment will be completed upon issue of a registration number.
⑥ After completion of enrollment, the Data Center will send an 'enrollment confirmation notification' along with a CRF to the institutional coordinator to be kept on file.
⑦ Excluding the withdrawal of consent which includes refusal of the use of data in this trial,, patients who have been enrolled will not be removed from the trial (erased from the database). In the event of double registration, enrollment data (registration number and allocated group) from the first enrollment will be used.
⑧ In the event that misregistration or double enrollment is discovered, the Data Center should be contacted as soon as possible.
⑨ Body surface area and agent dose is to be calculated by the facility, and at the time of enrollment the body surface area and agent dose displayed on the Web entry system should be double checked by the attending physician. The facility should calculate and verify body surface area and agent dose. If the body surface calculation formula used by the hospital data system differs from the calculation formula used by the JCOG (Dubois formula: body surface area ($m^2$) = body weight (kg) $^{0.425}$ x height (cm) $^{0.725}$ x 71.84 ÷ 10,000), it may result in a difference in dosage according to the hospital system or the calculation formula used by the JCOG, in which case the research supervisor will choose which dosage will be used.

## 5.2. Random allocation and adjustment factors for allocation

Treatment groups will be randomly assigned by the Data Center upon registration.

A minimization method will be used with adjustment factors for ① institution, ② paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis (with vs. without), so that large biases do not emerge in these factors during random allocation. Researchers at the participating institutions will not be informed of the details of the methods used for random allocation.

# 6. Treatment planning and criteria for change of treatment

Treatment and changes in treatment will proceed as outlined in this section while doing the utmost to preserve the safety of patients.

Treatment may be changed as per the medical judgment of the attending physician when he/she determines that there is medical risk in following the protocol. This results in "deviation of protocol." Cases will be treated as "clinically appropriate deviation" when this deviation is deemed medically appropriate (refer to '14.1.4 Deviation from and violation of protocol'). Deviations conducted in an attempt to increase efficacy and not for safety will not be treated as "clinically appropriate deviation."

## 6.1. Protocol-based treatment

The protocol-based treatment will be initiated within 10 days of enrollment.

If for any reason the treatment is initiated after 11 days, the reason for doing so should be noted on the treatment progress case report form. If it is judged that treatment cannot be initiated, then the details should be noted in the 'termination of treatment report' as 'cessation of protocol-based treatment'.

Following enrollment, if the patient's laboratory values deteriorate before the treatment is initiated, and the patient no longer satisfied the eligibility criteria, the decision as to whether to start or terminate the protocol-based treatment will be made at the discretion of the attending physician.

'6.3. Criteria for change of treatment' does not apply on initiation of the first treatment cycle.

**Agents used in the present trial**

- Cisplatin
- S-1 : Tegafur, gimeracil, and oteracil potassium compound capsule, combination granules, combination OD tablets
- Trastuzumab

Furthermore, the use of generic drugs is not permitted for S-1.

The use of generic drugs for cisplatin is permitted.

The protocol treatment in the present trial is outlined below.

**Group A: preoperative chemotherapy (S-1+CDDP therapy) + surgery + postoperative adjuvant chemotherapy (S-1)**

**group B: preoperative chemotherapy (S-1+CDDP+trastuzumab therapy) + surgery + postoperative adjuvant chemotherapy (S-1)**

**(S-1)**

**Trastuzumab procurement**

Trastuzumab (Herceptin ® infusion) is not approved as a preoperative chemotherapy for gastric cancer under the Pharmaceutical and Medical Device Law, and is not covered by the national health insurance scheme. Therefore in the present trial, under the Advanced Medical care B Program, trastuzumab will be supplied free of charge by Chugai Pharmaceuticals. The method/ process of trastuzumab procurement is stipulated in the 'present trial protocol for trial agent management'.

**1) Preoperative chemotherapy**

- Following enrollment, each group will be administered 3 cycles of preoperative chemotherapy with S-1 + CDDP. CDDP therapy will be administered on an inpatient basis.
- In Group A and group B, S-1 and CDDP will be counted as cycles. In group B, trastuzumab will be counted as 'doses'. Blood sampling and imaging will be performed per S-1 + CDDP cycle.
- When patients fall under the criteria for the discontinuation of preoperative chemotherapy in 6.2.2., preoperative chemotherapy including trastuzumab will be discontinued.
- In group B, trastuzumab will be administered for a maximum of 4 doses every 3 weeks (or a maximum of 5 doses when one cycle is given in addition to S-1 + CDDP). If the S-1 + CDDP therapy is suspended, trastuzumab therapy will be continued independently every 3 weeks when the criteria for trastuzumab treatment is satisfied.

- If patients in group B fall under 6.3.3.2) criteria for the cessation of trastuzumab therapy, then treatment with trastuzumab only will be discontinued, and preoperative chemotherapy will not be discontinued (S-1 + CDDP therapy will continue so long as patients do not fall under 6.2.2., criteria for the cessation of preoperative chemotherapy).
- On completion of the first cycle, imaging will be performed in accordance with '8.2.2. Evaluation of efficacy endpoints during preoperative chemotherapy'. The treatment will proceed to the 2nd cycle unless clear exacerbation is observed.
- In the event that chemotherapy is discontinued in the 1st or 2nd cycle, treatment outcomes will be determined according to 8.2.2.2). If R0 resection is deemed possible, then after confirming that '6.3.4. Eligibility for surgery' is satisfied, surgery will be performed according to '6.1.2. Surgery'.
- On completion of the 3rd cycle, imaging will be performed in accordance with '8.2.2. Evaluation of efficacy endpoints during preoperative chemotherapy'. The decision to conduct surgery after, or without, an additional cycle of preoperative chemotherapy, will be determined based on the following criteria.

Table 6.1.1) Criteria for additional 4 cycles

| Image diagnosis of efficacy following 3 cycles (refer to 8.2.2) | | Measures to be taken |
|---|---|---|
| R0 resection deemed possible (irrespective of tumor exacerbation or shrinkage) | → | Confirm that '6.3.4. Eligibility for surgery' is satisfied, and perform surgery as per '6.1.2 Surgery'. |
| R0 resection deemed not possible, even with observation of slight reduction in lymph node metastasis. | → | Administer an additional cycle of preoperative chemotherapy. Thereafter confirm that '6.3.4. Eligibility for surgery' is satisfied, and perform surgery as per '6.1.2 Surgery'. |
| R0 resection deemed not possible, and no reduction in lymph node metastasis observed. | → | Terminate protocol-based treatment. |

- In the event that an additional cycle of preoperative chemotherapy is to be administered, Group A shall be given an additional cycle of S-1 + CDDP. Group B shall be given an additional cycle of S-1 + CDDP, and addidional dose of trastuzumab on day 1 of the 4th cycle of S-1 + CDDP.
- When the 4th cycle of preoperative chemotherapy is administered, imaging shall be performed on completion of the 4 cycles in accordance with 'Evaluation of efficacy endpoints during preoperative chemotherapy'. If R0 resection is deemed possible, then surgery shall be performed as per '6.1.2. Surgery' after confirmation that '6.3.4. Eligibility for surgery' is satisfied.
- No more than 5 cycles of preoperative chemotherapy is to be given.

**2) Surgery**

Following preoperative chemotherapy, surgery shall be performed as described in '6.1.2. surgery' after confirmation that the '6.3.4. Eligibility for surgery' is satisfied.

**3) Postoperative adjuvant chemotherapy**

When surgery results in histological residual tumor of R0, postoperative adjuvant chemotherapy with S-1 shall be administered for one year. However, in the event that clear exacerbation is found on imaging after each cycle of preoperative chemotherapy, with Grade 0 histological outcome, the protocol treatment shall be terminated on finding the results (day of surgery) of the histological outcomes, and the patient will be free to pursue after-treatment.

### 6.1.1. Preoperative chemotherapy

The following chemotherapies will be administered.

Group A: S-1+CDDPtherapy

B group: S-1+CDDP+trastuzumab therapy

**1) S-1+CDDP therapy (Group A and B combined)**

The regimens below will be administered as 3-week cycles for 3 repeated cycles. As mentioned in 6.1.1) Preoperative chemotherapy, depending on the evaluation results for efficacy on completion of 3 cycles, a 4th cycle will be administered.

| Agent | Dosage | Route | Administration day |
|---|---|---|---|
| S-1 | 80-120 mg/body | p.o. | day 1～14 |
| CDDP | 60 mg/m$^2$ | Div | day 1 |

S-1 shall be administered from the morning of day 1 until the evening of day 14, or from the evening of day 1 until the morning of day 15.

The initial dose level for the 1st cycle of CDDP and S-1 will be determined on the basis of pre-enrollment creatinine clearance value.

Creatinine clearance will be estimated using the Cockcroft-Gault equation*. In the event that actual measured values at the time of enrollment are used, measurements taken at the time of enrolment shall be used when determining dose level also.

* The Cockcroft-Gault equation is shown below

For males: Ccr= { (140-age) × weight (kg) } / {72× serum creatinine level (mg/dL) }

For females: Ccr=0.85× { (140-age) × weight (kg) } / {72× serum creatinine level (mg/dL) }

Initial dosage level for CDDP

| Pre-enrollment CCr | Dosage level | Dosage/ route | Administration day |
|---|---|---|---|
| CCr≧80 mL/min | Level 0 | 60 mg/m$^2$ div | day 1 |
| 60 mL/min≦CCr＜80 mL/min | Level -1 | 50 mg/m$^2$ div | day 1 |

Initial dosage level for S-1

| Pre-enrollment CCr | Dosage level | Dosage/route | | | Administration day |
|---|---|---|---|---|---|
| | Body surface area | BSA＜ 1.25m$^2$ | 1.25m$^2$≦ BSA＜ 1.5m$^2$ | BSA≧1.5m$^2$ | |
| CCr≧80 mL/min | Level 0 | 80 | 100 | 120 | day 1-14 |
| 60 mL/min≦CCr＜80 mL/min | Level-1 | 65 | 80 | 100 | day 1-14 |

**S-1 administration daily dose**

| Dosage | After breakfast | After dinner |
|---|---|---|
| 120 mg/day | 20 mg x 3 cap | 20 mg x 3 cap |
| 100 mg/day | 25 mg x 2 cap | 25 mg x 2 cap |
| 80 mg/day | 20 mg x 2 cap | 20 mg x 2 cap |
| 65 mg/day | 25 mg x 1 cap | 20 mg x 2 cap |
| 50 mg/day | 25 mg x 1 cap | 25 mg x 1 cap |

- The CDDP dosage calculated from BSA will be rounded off to the nearest 1 mg/ body. As an example of CDDP dosage, a patient who is 171 cm tall, weighing 68 kg with a BSA of 1.795 m$^2$, will give 1.795 x 60 = 107.7, which after rounding off 7.7 would give a result of 100 mg/ body. The specified dosage is dissolved in 500 mL of physiological saline, stored away from light, then administered as an intravenous drip infusion over a 2 hour period. To reduce renal toxicity, the preparation should be administered to ensure urinary output of 100 mL/h or more for at least 24 hours.
- Cessation of S-1 due to forgetfulness or self-judgment of the patient, and that does not fall under the criteria for skipping/ dosage reduction (6.3.2.2) will not be considered as suspend and the treatment shall be completed in 14 days.
- BSA and agent dosage is to be calculated by the institution, and the BSA and agent dosage provided by the Data Center at the time of enrollment should be used for double check. The institute should calculate and verify BSA and agent dosage.
- With regards to changes in body weight after the start of treatment, if the weight is within ±5 kg compared to body weight at the time of enrollment then there will be no adjustment in dosage made, however if the weight change exceeds ±5 kg, then the BSA and dosage should be recalculated. Furthermore if after recalculating, the patient shows a weight change of more than ±5 kg compared to the re-calculated weight, the BSA and dosage should be re-calculated again.
- Concurrent apprepitant, 5-HT3 inhibitor, and long-acting corticosteroids as an antiemetic shall be administered as required in accordance with the guidelines for proper use of antiemetic agents[46].

**2) Trastuzumab (group B only)**

Administered every 3 weeks, up to a maximum of 4 doses (in the event of 4 cycles of S-1 + CDDP, up to 5 doses of trastuzumab can be administered).

| Agent | Dosage | Administration route | Administration day |
|---|---|---|---|
| Trastuzumab | 8 mg/kg (1$^{st}$ cycle)<br>6 mg/kg (2$^{nd}$ and subsequent cycles) | Div | Administered every 3 weeks after day 1 of the 1st cycle of S-1+CDDP |

- If the criteria for trastuzumab treatment is satisfied, trastuzumab therapy will be continued independently every 3 weeks even if S-1 + CDDP is suspended.
- The trastuzumab dosage calculated from BSA will be rounded off to the nearest 1 mg/ body. As an example of trastuzumab dosage, a patient weighing 68 kg will give 68 x 8 = 544, and 68 x 6 = 408, which after rounding off would give a dosage of 540 mg for the 1$^{st}$ cycle and 400 mg for the 2$^{nd}$

cycle.

- BSA and agent dosage is to be calculated by the institution, and the BSA and agent dosage provided by the Data Center at the time of enrollment should be used for double check by the attending physician. The institute should calculate and verify BSA and agent dosage.
- With regards to changes in body weight after the start of treatment, if the weight is within ±5 kg compared to body weight at the time of enrollment then there will be no adjustment in dosage made, however if the weight change exceeds ±5 kg, then the BSA and dosage should be recalculated.
- Trastuzumab will be administered as an intravenous infusion at a dose of 8 mg/ kg on day 1 of the 1st dose, then 6 mg/kg every 3 weeks for the 2nd and subsequent doses. The intravenous infusion will be given over a period of 90 min or more in the 1st dose, then the administration period can be reduced to 30 min for the 2nd and subsequent doses.
- If 30 days have passed (including day 30) since the previous administration day, which is counted as day 1, the trastuzumab will be administered at a dosage of 8 mg /kg.
- Trastuzumab will be administered up to day 8 (including day 8) of the last cycle of S-1 + CDDP therapy (refer to Fig. 6.1.1.a).
- E.g. If the scheduled administration day of the 4th dose falls after day 9 of the 3rd cycle of S-1 + CDDP then the 4th dose will not be administered, and trastuzumab therapy will be completed after the 3rd dose. (E.g. Trastuzumab treatment will be completed after 3 doses in the event of ① to ③ in Fig. 6.1.1.a, and after 4 doses in the event of ④ to ⑥).

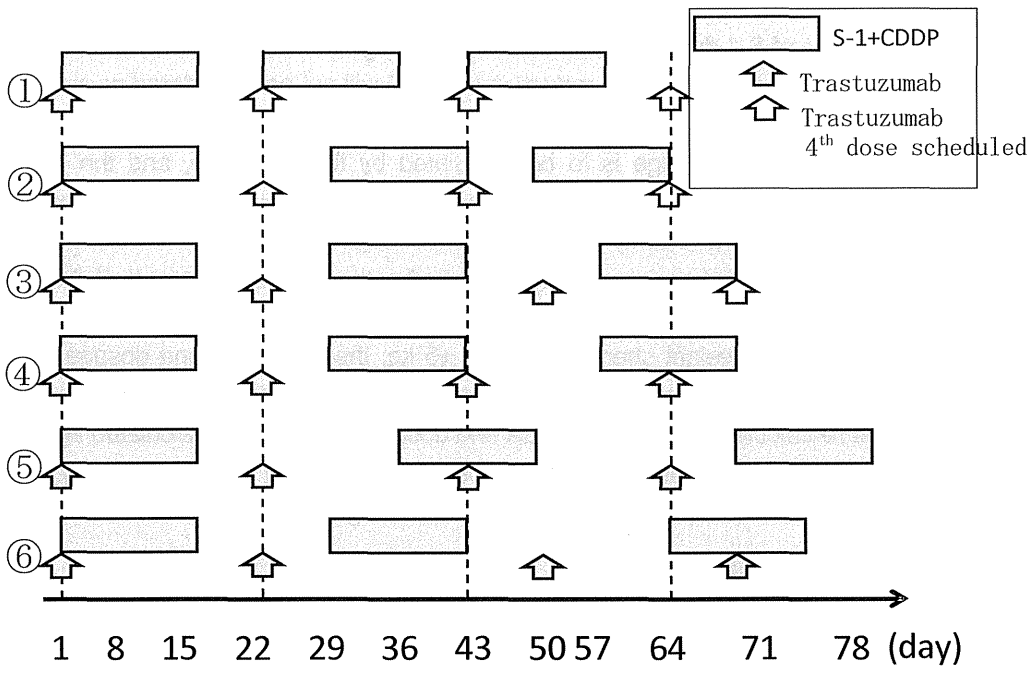



Fig. 6.1.1.a) The relationship between S-1+CDDP therapy and trastuzumab (e.g. up to 3rd cycle)

- Concurrent apprepitant, 5-HT3 inhibitor, and long-acting corticosteroids as an antiemetic shall be administered as required in accordance with the guidelines for proper use of antiemetic agents[46].

**3) In the event of an additional cycle of S-1+CDDP to give 4 cycles**

- On completion of the 3rd cycle, imaging will be performed in accordance with '8.2.2. Evaluation of efficacy endpoints during preoperative chemotherapy'. The decision to conduct surgery after, or without, an additional cycle of preoperative chemotherapy, will be determined based on table 6.1.1). In the event that an additional cycle of preoperative chemotherapy is given, group A will be given an

additional cycle of S-1 + CDDP.

- Group B will be given an additional dose of trastuzumab on the first day (day 1) of the 4th cycle of S-1 + CDDP.

  (When 2, 3, and 4 doses of trastuzumab have been given before the 3rd cycle of S-1 + CDDP, they will be considered the 3rd, 4th, and 5th doses respectively).
- The 4th cycle of S-1+CDDP (± trastuzumab), will be given on day 29, given that the first day of the 3rd cycle is day 1.
- Additional trastuzumab will be given at a dose of 6 mg/kg if before day 29 with the last dose of trastuzumab counted as day 1, or at a dose of 8 mg/kg if after day 30 (including day 30).
- If trastuzumab cannot be given on day 1 at the start of the 4th cycle of S-1 + CDDP, then it shall be given before day 8 (including day 8). If trastuzumab cannot be given before day 8, then it shall be omitted.

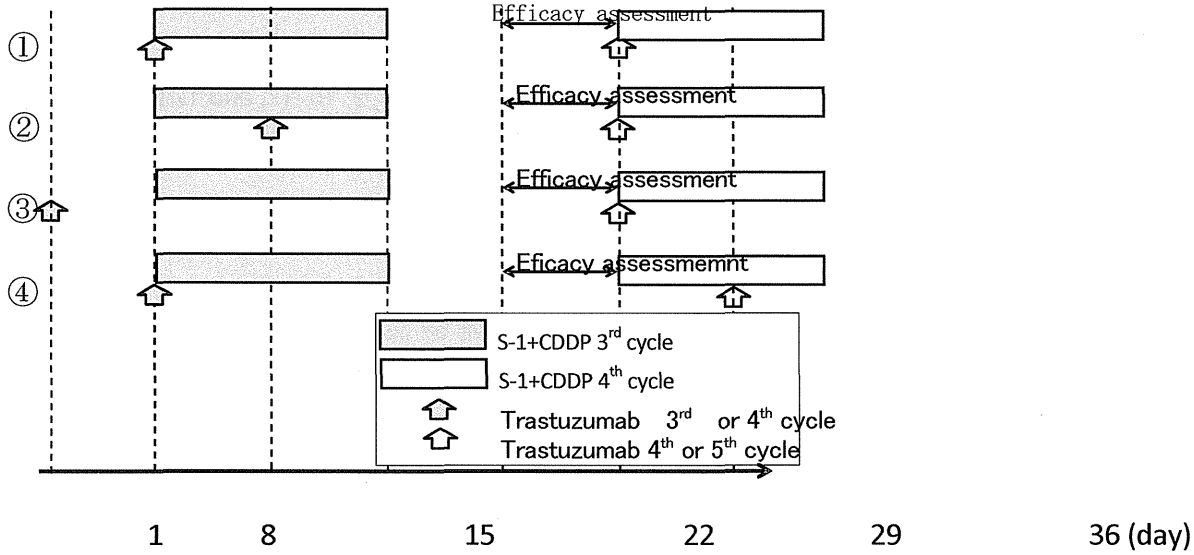



Fig. 6.1.1.b) The relationship between S-1+CDDP therapy and trastuzumab (4th cycle)

Fig. 6.1.1.b) In the event of ① and ②, additional trastuzumab will be given at a dose of 6 mg/kg.

Fig. 6.1.1.b) In the event of ③ and ④, additional trastuzumab will be given at a dose of 8 mg/kg.

### 6.1.2. Surgery

On completion of the final cycle, efficacy will be assessed by imaging (see 8.2.2) and, preoperative assessment (see 8.2.3) will be conducted to confirm that all the eligibility criteria for surgery (see 6.3.4) are met. If R0 resection is deemed possible by image evaluation, surgery will be performed within 56 from the last day of S-1 administration in the final cycle days (less than 56 days given that the final day of administration is day 0) (within 28 days is recommended). If surgery cannot be performed by this time, then the protocol treatment will be terminated.

The surgical procedures in the present trial include open total gastrectomy and distal gastrectomy as defined below.

① Laparotomy: Performed by open surgery. Laparoscopic and laparoscopy assisted surgery is not