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1. Aims

To evaluate the safety and efficacy of S-1 + cisplatin (CDDP) and S-1 + CDDP + trastuzumab combined therapy as preoperative chemotherapy for HER2-positive gastric cancer with bulky lymph node metastasis.

Primary endpoint: overall survival
Secondary endpoints: progression-free survival (PFS), rate of response to preoperative chemotherapy (RECIST v1.1), curative resection rate, rate of completion of treatment up to surgery, rate of completion of treatment up to postoperative adjuvant chemotherapy, rate of histological response, rate of incidence of adverse events (AEs), rate of incidence of serious adverse events (AEs)

2. Background and rationale for study protocol

2.1. Subjects

2.1.1. Epidemiology

In Japan, there are approximately 50,000 gastric cancer deaths per year (approximately 1/6 of the 300,000 cancer-related deaths overall). While it the second leading cause of death by malignant neoplasm, gastric cancer mortality has been declining in men and women from 53.9 and 33.2 (1980) to 53.3 and 26.3 (2011), respectively[1]. In contrast, the prevalence (per 100,000 population) of gastric cancer remains high for both men and women, with 86.6 and 49.1 in 1980, then increasing in 2008 to 135.1 and 59.3, respectively, making it the leading cancer for men and the 3rd leading cancer in women following breast cancer and colorectal cancer[2]. From a global viewpoint, the prevalence and mortality of gastric cancer in 2008 were estimated at 990,000 and 740,000 respectively, and while these figures are decreasing in advanced nations, it has the 4th highest prevalence among malignant neoplasms, and is the 2nd leading cause of cancer-related death following lung cancer[3].

2.1.2. Clinicopathology

The Japanese Classification of Gastric Carcinoma, 14th ed. [4], classifies adenocarcinomas, which constitutes the majority of gastric cancers, as the general type, and nonadenocarcinomas as special types. Clinicopathologically, general type adenocarcinomas are further subvidided into differentiated type and undifferentiated type. In general the differentiated type present as cancers with clear gland formation, an expansive growth pattern, in which the macroscopic formation often has a well-circumscribed border. Hematogenous hepatic metastasis often develops as the disease progresses, and the disease is relatively common in elderly individuals. On the other hand, undifferentiated type presents as a cancer with poor gland formation and diffuse invasion. Macroscopically the undifferentiated type often have an indistinct border, lymphogenous metastasis and peritoneal metastasis. There is a higher rate of young individiuals with undifferentiated type than differentiated type cancer.

According to histological type, it has been reported that prognosis is quite good for highly differentiated tubular adenocarcinoma (classified as differentiated cancer) and for signet ring cell carcinoma (classified as undifferentiated) with a 5-year survival rate of 80%, and in other histological types the 5-year survival is approximately 60%, indicating no major difference according to histological type[5]. Furthermore, while histological type is taken into consideration when determining the suitability of endoscopic treatment, in patients who are to undergo surgical resection there is no difference in standard treatment according to histological type.

2.1.3. Staging classification

Gastric cancer staging will be determined according to the T classification for invasion depth and N classification for the degree of lymph node metastasis. In the Japanese Classification of Gastric Carcinoma, 14th ed., invasion depth is classified into T1 (M: confined to the mucosa, or SM: submucosa), T2 (MP: muscularis propria), T3 (SS: subserosa), T4a (SE: serosal invasion), and T4b (SI: invasion into adjacent organs), whereas N classification is divided according to the presence or absence of lymph node metastasis within regional lymph nodes and the number of nodes affected. N classification included N0 (no regional lymph node metastasis), N1 (metastasis in 1-2 regional lymph nodes), N2 (metastasis in 3-6 regional lymph nodes), N3a (metastasis in 7-15 regional lymph nodes), and N3b (metastasis in 16 or more regional lymph nodes) [4].

Table 2.1.3. Japanese Classification of Gastric Carcinoma, 14th ed.

	N0	N1	N2	N3a/N3b	M1 (Any T, any N)
T1 (M/SM)	IA	IB	IIA	IIB	IV
T2 (MP)	IB	IIA	IIB	IIIA	
T3 (SS)	IIA	IIB	IIIA	IIIB	
T4a (SE)	IIB	IIIA	IIIB	IIIC	

T4b (SI)	IIIB	IIIB	IIIC	IIIC
M1 (Any T, any N)				

2.1.4. Prognosis and standard treatment according to staging

In the 2010 revised Gastric Cancer Treatment Guidelines (3rd ed. For doctors) [6], the treatment selection algorithm recommended in routine clinical practice is endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) is indicated for cT1a (M), cN0 differentiated, ulcer (-) cancers less than 2 cm in size. The expansion of EMR/ESD indications is currently being examined in the JCOG 0607 and JCOG 1009/ 1010 trials. In cT1a and cT1b, cN0 cancers not indicated for EMR/ESD, reduction of the extent of gastrectomy and lymph node dissection should be considered. In the event of cN+ and cT2-4a, standard gastrectomy (resection of 2/3 or more of the stomach with D2 dissection) will be performed. For lymph node dissection, the extent of dissection will be determined according to the type of gastrectomy indicated (D1/D1+/D2). Extended lymph node dissection exceeding D2 is classified as non-standard gastrectomy. For example, in the event of performing lymph node dissection of No.16 (abdominal paraaortic lymph nodes) 'D2+No.16' shall be noted. In the event of distal metastasis (M1), standard treatment is not determined, but may be treated with chemotherapy, radiotherapy, palliative surgery, and symptomatic treatment. In the event of cT4b, if M0, then extended surgery with combined resection will be performed.

According to the 2004 Japanese Gastric Cancer Treatment Guidelines (2nd edition for doctors) [7], the 5 year survival rate following standard gastrectomy for gastric cancer is 93.4% for stage IA cancers, 87.0% for stage IB, 68.3% for stage II, 50.1% for stage IIIA, 30.8% for stage IIIB, and 16.6% for stage IV (staging based on the Japanese Classification of Gastric Carcinoma, 13th ed.).

2.1.5. Tumor-related complications

In the preset trial, the following tumor-related complications are anticipated for H0, P0 gastric cancer with severe lymph node metastasis (refer to 2.1.8.2 for details) [8].

- Bleeding from the primary gastric lesion and associated anemia (20%)
- Disturbance of ingestion and oral intake of medications due to stenosis of the cardiac or pyloric part of the stomach (17.5%)
- Biliary tract obstruction due to lymph node metastasis in the porta hepatis, obstructive jaundice, and hepatic failure (<5%)

2.1.6. Forms of recurrence/ exacerbation

As a result of the ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer), which examined the significance of postoperative adjuvant chemotherapy with S-1 for stage II/III cancer, in the surgery alone group recurrence was observed in 41.7%, and sites of recurrence included peritoneal metastasis (18.9%), hematogenous metastasis (13.4%), lymph node metastasis (10.2%), and local recurrence (3.2%). In contrast, 30.6% of patients in the chemotherapy group exhibited recurrence at sites including peritoneal metastasis (14.6%), hematogenous metastasis (11.5%), lymph node metastasis (5.7%), and local recurrence (2.1%) [9]. Therefore, it is thought that regardless of the presence or absence of postoperative adjuvant therapy, in radically resected gastric cancer the main anticipated forms of recurrence include peritoneal metastasis, hematogenous metastasis, and lymph node metastasis. The incidence of recurrence continues to increase following surgery, peaking at 24 months postoperatively, however recurrence after 42 months following surgery is extremely rare[10].

2.1.7. Prognostic factors/ predictive factors

Maruyama et al. examined prognostic factors of gastric cancer by retrospective multivariate analysis and reported that distal metastasis, invasion depth, and lymph node metastasis were the most important factors that affected prognosis of gastric cancer[11]. Okashima et al. conducted a multivariate analysis and reported that gastric wall invasion depth, lymph node metastasis, age, and hepatic/peritoneal metastasis were important prognostic factors [12]. Furthermore, in a retrospective observational study of patients with local lymph node metastasis of 10 mm or greater (minor axis) conducted by the Shizuoka

Cancer Center, multivariate analysis revealed that gastric wall invasion depth and lymph node size were independent prognostic factors[13]. According to a questionnaire survey administered by the Gastric Cancer Group at the time of designing the JCOG 1002 trial, in 86 patients without hepatic metastasis or peritoneal metastasis, and who macroscopically and histopathologically were found to have metastasis in the paraaortic lymph nodes, the 3 year survival rate was 5%. Furthermore, following resection with level B curability (according to the Japanese Classification of Gastric Carcinoma, 13th ed.) for patients with bulky lymph node metastasis (detailed definition given in 2.1.8.2) at the National Cancer Canter Central Hospital, the 3 year survival rate was 24% and the 5 year survival rate was 13%. Based on the results above, the consensus has been reached that prognosis in patients with paraaortic lymph node metastasis and in patients with bulky lymph node metastasis (see 2.1.8.2 for details) is worse among patients with lymph node metastasis, and the JCOG Gastric Cancer Group has been independently developing treatments based on the definition of 'severe lymph node metastasis' also.

2.1.8. Rationale for subject group selection

1) Rationale for targeting HER2 positive gastric cancer

HER2 (human epidermal growth factor receptor type 2) is transmembrane epidermal growth factor receptor with tyrosine kinase activity. HER2 expression and presence or absence of amplification is determined by immunohistochemistry (IHC) and in situ hybridization (ISH) (HER2 testing hereafter).

In breast cancer, HER2 is overexpressed in 15-25%, and it is commonly accepted that over-expression of HER2 correlates with prognosis[14, 15]. In a phase III trial of metastatic breast cancer showing over-expression of HER2 (HER2-positive) conducted as an international collaborative trial[16], it was found that trastuzumab, a humanized monoclonal antibody that targets HER2, prolonged overall survival when used in combination with chemotherapy (anthracycline or paclitaxel (for patients who had previously received anthracycline therapy)) compared to systemic chemotherapy alone. Consequently, in April 2001 trastuzumab was approved in Japan as a therapeutic agent to treat HER2-positive metastatic breast cancer. HER2 overexpression in metastatic breast cancer is considered a strong predictor of the effect of trastuzumab. New agents are currently under development, including lapatinib, pertuzumab, and T-DM1 that similarly target HER2. Furthermore, the effectiveness of trastuzumab monotherapy had been acknowledged, and as a result the agent is used alone or in combination with chemotherapy as a pre- and post-operative adjuvant therapy (perioperative chemotherapy). Thus in breast cancer, the presence or absence of HER2 overexpression is a predictor of the therapeutic outcomes of chemotherapy for metastatic breast cancer as well as perioperative chemotherapy, and therefore treatments are currently under development for HER2-positive breast cancer as an independent disease group of breast cancer.

In gastric cancer on the other hand, with regards to the incidence of HER2 overexpression and the relationship between overexpression and prognosis, the results of the analysis of biomarkers in patients enrolled in the ACTS-GC trial was reported in the ASCO (American Society of Clinical Oncology) annual meeting in 2011. In gastric cancer the incidence of HER2 overexpression was 13%, and there was no relationship found between HER2 overexpression and prognosis[17]. On the other hand overseas reports have indicated that HER2 is a prognostic factor of gastric cancer. So far, no conclusions were drawn as to the impact of HER2 overexpression on survival for gastric cancer[18, 19].

Although HER2 has not altered treatments in the past, a phase III international collaborative trial examining HER2-positive unresectable advanced and recurrent gastric cancer has demonstrated that trastuzumab combined with chemotherapy (capecitabine (Xeloda®) + cisplatin (CDDP): XP) improves survival outcomes (ToGA trial)[20]. As a result of the ToGA trial, approval was obtained in Japan in March 2011 for the use of trastuzumab in the treatment of 'advanced/recurrent unresectable gastric cancer with confirmed HER2 overexpression'. As a result of the ToGA trial, trastuzumab was listed in the Gastric Cancer Treatment Guidelines Chemotherapy in combination with trastuzumab was considered a new standard treatment for HER2-positive unresectable advanced/recurrent gastric cancer, and the guidelines clearly recommended performing HER2 testing prior to chemotherapy in a preliminary report

in July 2011, [21]. As with breast cancer, treatments will be development in future for HER2-positive gastric cancer as an independent disease group of gastric cancer, and at present, in accordance with breast cancer, clinical trials have been completed or are underway of other anti-HER2 agents including lapatinib, pertuzumab, and T-DM1.

Therefore at the JCOG Gastric Cancer Study Group also we decided to develop treatments for HER2-positive gastric cancer as an independent disease group.

2) Rationale for targeting gastric cancer with severe lymph node metastasis

Preoperative chemotherapy is expected to be effective for advanced gastric cancer with poor prognosis because ① chemotherapy compliance is better when administered preoperatively, ②chemotherapy reduces lymph node metastasis and improves the rate of curative resection, and ③ chemotherapy can be administered from the early stage for micro metastases. On the other hand, there are limitations to preoperative diagnosis of staging, and care should be taken when selecting treatment subjects. Eefforts should be made to minimize the administration of preoperative chemotherapy that is originally unnecessary. Accordingly, preoperative chemotherapy treatments should be developed for patients with ① poor prognosis, and ② who very likely have pathologically advanced cancer.

In gastric cancer with extensive lymph node metastasis on preoperative diagnosis, prognosis is poor even when the lesion has been macroscopically completely resected, and the majority of such cases are thought to be pathologically advanced cancers.

In the present trial extensive lymph node metastasis is defined according to a) to c) below (see figure 2.1.8.a for details of a) and b)).

a) Paraaortic lymph node (No.16 a2/b1) metastasis: when lymph node metastasis 10 mm ≤ in length is observed in No. 16 a 2/ b1 by upper abdominal contrast enhanced CT (Fig. 2.1.8.a, dotted circles)

b) Bulky lymph node metastasis: When upper abdominal contrast enhanced CT shows lymph node metastasis in the lymph node adjacent to the celiac artery, common hepatic artery, splenic artery, near the proper hepatic artery, or anterior surface of the superior mesenteric vein (lymph node: No. 14v), and either ① or ② below are met (Fig. 2.1.8.a. Solid circles).

   ① Two or more adjacent or in continuity lymph nodes 15 mm ≤ in length.
   ② One lymph node 30 mm ≤ in length (a single node or agglomeration formed of various sized lymph nodes)

c) Regional lymph node metastasis 15 mm ≤ in minor axis: When upper abdominal contrast enhanced CT shows metastasis with minor axis of 15 mm ≤ in regional lymph nodes (No. 1-12, and No. 14v).

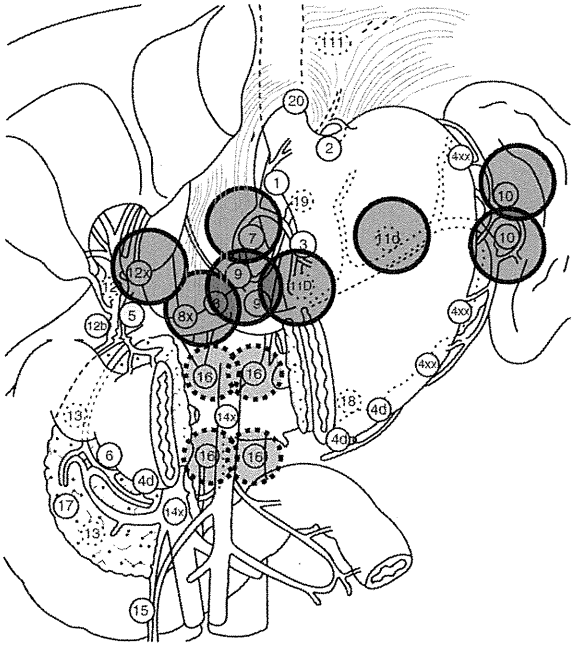

Fig. 2.1.8.a Lymph node metastasis

In patients with a) paraaortic lymph node metastasis (No.16a2/b1), and b) bulky lymph node metastasis the consensus has been reached by the JCOG Gastric Cancer Study Group that 'curative resection (resection without any residual cancer: R0 resection according to the Gastric Cancer Treatment Guidelines) is difficult without preoperative treatment, and that prognosis is extremely poor even when curative resection is achieved', and therefore the development of treatment has focused on preoperative chemotherapy. On the other hand, treatments for patents with c) regional lymph node metastasis (minor axis of 15 mm ≤) have been developed with such metastasis included under 'curative resectable advanced gastric cancer'. However a more recent report has indicated a correlation between the pathological lymph node size following curative resection of gastric cancer and prognosis[22], and an examination conducted by the Shizuoka Cancer Center of patients with advanced gastric cancer who underwent curative resection (including patients with paraaortic lymph node metastasis and bulky lymph node metastasis) revealed that the 5 year survival (48.4%) of patients (N=59) with swollen lymph nodes of 15 mm ≤ in size (minor axis) on preoperative MDCT (Multi Detector-row Computed Tomography) was poorer than the 5 year survival (68.1%) of patients with lymph node swelling of 10 – 14 mm[13]. Furthermore, when limited to cT2-4, lymph node metastasis was pathologically observed in 99% of patients with lymph node swelling of 15 mm ≤, and in 85% of patients there were 3 or more metastatic lymph nodes, all of whom were pStage IIa or greater.

Therefore, in patients with cT2-4, and in patients with lymph node swelling of 15 mm ≤ in the minor axis, prognosis is poor even in advanced gastric cancers able to undergo curative resection, and pathologically it is assumed that this population will highly likely have metastasis in 3 or more lymph nodes (N2 or above). Thus it is thought that c) regional lymph node metastasis of 15 mm ≤ in the minor axis, meets the aforementioned criteria for the development of preoperative chemotherapy including ① poor prognosis, and ② advanced cancer pathologically very highly likely, and thus we decided to develop treatment on the basis of a) paraaortic lymph node metastasis (No.16a2/b1), and b) bulky lymph node metastasis. However, c) regional lymph node metastasis of 15 mm ≤ in the minor axix, was considered allocation adjustment factor as patient profiles, treatment content and prognosis are assumed to differ in c) compared to a) and b), which have been conventionally targeted. Furthermore, a) paraaortic lymph node metastasis, b) bulky lymph node metastasis, and c) regional lymph node metastasis of 15 mm ≤ in the minor axis are not mutually exclusive. In the event of c) regional lymph

node metastasis of 15 mm ≤ in the minor axis in addition to a) paraaortic lymph node metastasis and/or b) bulky lymph node metastasis, it should be treated as a) paraaortic lymph node metastasis and/or b) bulky lymph node metastasis. That is, the shaded portion in the figure below will be treated as a) paraaortic lymph node metastasis and/or b) bulky lymph node metastasis.

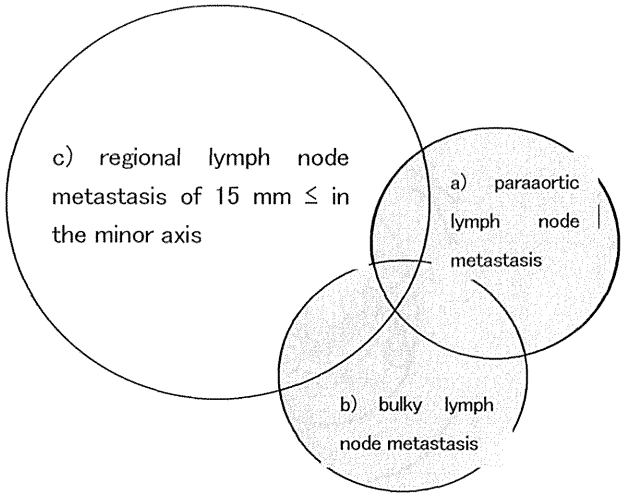

Fig. 2.1.8.b The relationship between paraaortic lymph node metastasis, bulky lymph node metastasis, and regional lymph node metastasis of 15 mm ≤ in the minor axis

Moreover, in the JCOG1012-A 'JCOG trial of advanced gastric cancer with severe lymph node metastasis (bulky N2 or clinically N3)', statistical analyses revealed that a HER2-positive rate of 27% in advanced gastric cancer with paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis. This incidence is higher than the generally reported incidence of HER2-positive gastric cancer (13%), and therefore it is inferred that there is a higher rate of HER2 positivity in patients with paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis[24].

3) Rationale for excluding type 4 and large type 3 gastric cancers

Gastric cancer is divided into 6 types from type 0 to type 5 according to gross morphology. Of these patients with type 4 and large type 3 gastric cancers are believed to have a different clinicopaghological characteristics to those with severe lymph node metastasis, which is examined in the present trial, on the basis that recurrence of type 4 and large type 3 cancers is commonly in the form of peritoneal recurrence. The JCOG 0501 'phase III trial of preoperative S-1 + CDDP combination therapy for large type 3 and type 4 gastric cancers able to undergo curative resection', is currently examining the superiority of preoperative S-1 in combination with CDDP compared to surgery plus postoperative S-1 adjuvant chemotherapy in terms of overall survival for large type 3 and type 4 gastric cancers (316 completed enrolments in July 2013, main analyses scheduled for 2016). Furthermore, the results of the subanalyses in the aforementioned ToGA trial (details of the trial results listed in 2.3.2.2) showed that the hazard ratio for diffuse type cancers in the chemotherapy group versus the chemotherapy + trastuzumab group was 1.07 (95% CI; 0.56-2.05), indicating that for type 4 and large type 3 cancers, in which diffuse type was the main histological type, it is believed that the added improvement from trastuzumab was limited. Therefore type 4 and large type 3 gastric cancers were not included in the present trial.

2.2. Standard treatment for subjects

2.2.1. Standard treatment in Japan

1) Standard treatment for patients positive for paraaortic lymph node (No.16a2/b1) metastasis and bulky lymph node metastasis

Conventionally, advanced gastric cancer such as with severe lymph node metastasis was

administered various treatments including surgery, surgery plus chemotherapy, or chemotherapy alone in accordance with the policies of each institution, and there was not established standard treatment. A previous study conducted by the JCOG Gastric Cancer Study Group revealed that in 86 patients with paraaortic lymph node metastasis the 5 year survival rate was 5%, while the 5 year survival rate following curative resection in patients with bulky lymph node metastasis was 24%, indicating poor prognosis overall.

In the 2010 revised Gastric Cancer Treatment Guidelines (3rd ed. For doctors), of advanced gastric cancers with severe lymph node metastasis, which are examined in the present trial, macroscopic metastasis in the paraaortic lymph nodes is categorized as M1 as per gastric cancers with distal metastasis, and therefore recommended treatments include chemotherapy, radiotherapy, palliative care, and symptomatic treatment. However the Gastric Cancer Treatment Guidelines broadly only provides broad treatment guidelines for each category, and therefore is no established recommended treatment for small subgroups present between categories including advanced gastric cancer with severe lymph node metastasis. The results of two phase II trials conducted to date by the JCOG Gastric Cancer Study Group examining paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis has led to the provisional establishment of preoperative chemotherapy combined with surgery (D2+No.16 lymph node dissection) as the standard treatment. However these results were both the results of phase II trials, and therefore have not been implemented as recommended treatments in the Gastric Cancer Treatment Guidelines. Consequently there is no established standard treatment for advanced gastric cancer with paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis. That is, according to the guidelines, the standard treatment is surgery combined with S-1 postoperative adjuvant chemotherapy, however many physicians treating gastric cancers find this inadequate.

2) Standard treatment for lymph node with minor axis of 15 mm ≤ on preoperative MDCT imaging

In the event of preoperative diagnosis of regional lymph node metastasis, the Gastric Cancer Treatment Guidelines recommends gastrectomy with D2 lymph node dissection. Furthermore, in patients diagnosed by pathological examination with pStage II or above (excluding T1N2-3 and T3 (SS) N0), adjuvant chemotherapy with S-1 for one year after surgery is recommended. As mentioned in 2.1.8.2), at the Shizuoka Cancer Center all patients with cT2-4 and lymph node minor axis of 15 mm ≤ on preoperative MDCT had pStage II or above cancer. Based on this finding also, the standard treatment in the present trial will be gastrectomy with D2 lymph node dissection plus adjuvant chemotherapy with S-1 for one year following surgery.

However, in the subanalysis results in the ACTS-GC trial, which provided the grounds for postoperative administration of S-1 for one year, the hazard ratio for metastasis in 3 or more lymph nodes (3-6 nodes: 0.740, 7 or more nodes: 0.820) was higher than that for metastasis in 2 or less lymph nodes (0 nodes: 0.317, 1-2 nodes: 0.454), and thus it was suggested that as the degree of lymph node metastasis increases, S-1 monotherapy for one year following surgery may be inadequate. A total of 85% of patients presenting lymph nodes with a minor axis 15 mm ≤ on preoperative MDCT, pathologically had metastasis in 3 or more lymph nodes, and it is thought that intense treatments should be developed by including preoperative chemotherapy.

3) Postoperative adjuvant chemotherapy

The results of the ACTS-GC examining the significance of adjuvant chemotherapy with S-1 following curative resection for stage II/III cancer were reported in 2007[25], and led to the establishment of postoperative chemotherapy as the standard treatment of stage II/III (excluding T1) gastric cancer patients who underwent curative resection. The chemotherapy involves S-1 (80 mg/m^2) administration within 6 weeks following surgery, followed by 4 weeks administration with 2 weeks rest for one year following surgery. Although 1 year administration of S-1, as in the ACTS-GC trial, has not been determined to be effective following preoperative chemotherapy plus surgery, the consensus has been reached by the JCOG Gastric Cancer Study Group that postoperative S-1 administration is required for

1 year in patients with advanced cancer who have received preoperative chemotherapy, and in the JCOG 1002 'a phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced gastric cancer with extensive lymph node metastasis' examining patients with paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis, 1 year of S-1 adjuvant chemotherapy following surgery is administered.

2.2.2. Standard treatment in Europe and the US

In Europe and the US, postoperative chemoradiation or pre- and postoperative chemotherapy is often administered for advanced gastric cancer with severe lymph node metastasis deemed resectable[26, 27]. Furthermore, patients with paraaortic lymph node metastasis are treated as unresectable advanced gastric cancers in many clinical trials[26, 27]. While the definition of bulky lymph node metastasis used by the Gastric Cancer Study Groups is not common in Europe and the US, it is thought that patients with bulky lymph node metastasis are often diagnosed as unresectable and are administered systemic chemotherapy.

2.3. Rationale for setting treatment protocol

Treatment regimens used in the present trial include 'preoperative S-1 + CDDP therapy + surgery + postoperative adjuvant chemotherapy' and 'preoperative S-1 + CDDP + trastuzumab therapy + surgery + postoperative chemotherapy'.

2.3.1. Agents

1) S-1 (tegafur, gimeracil, and oteracil potassium compound capsules, combination granules, and combination OD tablets)

S-1 is an anti-cancer agent consisting of tegafur (FT), gimeracil (CDHP), and oteracil potassium (Oxo) in a molar ratio of 1: 0.4: 1. Tegafur is a prodrug of 5-FU, gimeracil is a competitive inhibitor of the 5-FU degrading enzyme, dihydropyrimidine dehydrogenase (DPD), and oteracil potassium decreases gastrointestinal toxicities. In a late phase II trial of gastric cancer treated with S-1 at a dose of 80 mg/m^2/day - 120 mg/m^2/day given twice a day for 28 consecutive days with a 14 day rest period, the response rate was 46.5%, which is a higher response rate compared to existing agents approved for gastric cancer, and therefore S-1 was approved for the market[28].

In the JCOG 9912 'Randomized phase III study of 5-FU continuous infusion (5-FUci), CPT-11 plus CDDP (CP) versus S-1 alone (S-1) in advanced gastric cancer' comparing standard treatment with 5-FU continuous infusion against irinotecan (CPT-11) and S-1 monotherapy for curatively unresectable gastric cancer, the S-1 monotherapy group exhibited a MST of 11.4 months and 1 year survival of 47.9%, which was not inferior to the 5-FU continuous infusion group (MST: 10.8 months, 1 year survival: 44.0%), and thus at that point in time S-1 became the standard treatment for curatively unresectable gastric cancers[29]. The main toxicities include leukopenia (45.8%), neutropenia (44.0%), decreased hemoglobin (37.0%), thrombopenia (10.5%), loss of appetite (32.7%), nausea/ vomiting (26.8%), diarrhea (17.4%), stomatitis (15.7%), pigmentation (20.0%), and rash (10.9%).

2) Cisplatin (CDDP)

Cisplatin (CDDP) is an ionic complex containing the heavy metal platinum, and exhibits anti-tumor effect by cross-linking double stranded DNA. With monotherapy, the response rate for gastric cancer is approximately 17%, however it has been reported that it has a broader anti-tumor spectrum compared to 5-FU, and therefore as a central agent in combination therapy for various solid tumors, when combined with 5-FU class anti-tumor agents it clinically exhibits superior anti-tumor effect[30]. Main toxicities include nausea/vomiting, loss of appetite, hair loss, and general malaise. Cisplatin has been approved for the treatment of gastric cancer at a dose of 70 – 90 mg/m^2 administered once a day with at least 3 weeks rest period.

3) Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody that selectively binds to extracellular

region of HER2 receptors. It is a molecular targeting agent that primarily triggers antibody dependent cell mediated cytotoxicity (ADCC), and inhibits HER2-positive tumor cell proliferation pathways.

In HER2 positive breast cancer, it was shown to be effective as a chemotherapy for unresectable and recurrent breast cancer and as perioperative chemotherapy. Thus in Japan, the efficacy and effects of Trastuzumab have been recognized in 'breast cancer with confirmed HER2 overexpression', while administration methods and doses have been approved for 'A therapy (administration in 2 week intervals)' and for B therapy (administration in 3 week intervals). Furthermore, based on the results of the ToGA trial performed as an international collaborative trial, for HER2-positive gastric cancer, the efficacy and effects of trastuzumab have been recognized in 'curatively unresectable advanced/recurrent gastric cancer with confirmed HER2 overexpression', while administration methods and doses have been approved for 'B therapy (administration in 3 week intervals)'. In an overseas clinical trial of trastuzumab monotherapy for breast cancer it was reported that the principal toxicities were shivering (21.7%), fever (17.4%), diarrhea (15.2%), fatigue (13.0%), head ache (13.0%), chest pain (13.0%), and nausea (13.0%)[31].

【The use of trastuzumab in the present trial】

At present, under the law that ensures the effectiveness and safety of pharmaceuticals and medical devices (Pharmaceutical Affairs Law), trastuzumab (Herceptin ® infusion) is not approved as a preoperative chemotherapy for gastric cancer and is not covered by the national health insurance scheme. Therefore the present trial will be conducted under the Advanced Medical care B Program. Thus under the instructions of the Research and Development Division of the Health Policy Bureau at the Ministry of Health, Labour and Welfare, on the basis of a previously concluded agreement, trastuzumab will be offered free of charge from the manufacturer, Chugai Pharmaceuticals.

2.3.2. Preoperative chemotherapy

Preoperative chemotherapy has been trialed as a new treatment method for highly advanced gastric cancer, and based on the results thus far the treatment is considered promising for gastric cancer with estensive lymph node metastasis also. When selecting preoperative chemotherapy for gastric cancer with extensive lymph node metastasis the following 2 criteria should be met. First, the preoperative chemotherapy should be sufficient to reduce tumors in the regional lymph nodes and paraaortic lymph nodes. Second, following completion of 2-3 cycles of preoperative chemotherapy extended surgery including paraaortic lymph node dissection should be able to be performed safely in a relatively short period.

1) Evaluation of S-1 + CDDP therapy as preoperative chemotherapy

The non-inferiority of S-1 monotherapy to 5-FU continuous infusion for curatively unresectable gastric cancers was demonstrated by the JCOG 9912 trial[29]. In a subsequent post-marketing phase III trial (SPIRITS) comparing S-1 monotherapy (S-1 : 80 mg/m^2 [day 1-28] q6w) with S-1 + CDDP therapy (CDDP : 60 /mg/m^2 [day 8], S-1 : 80 mg/m^2 [day 1-21] q5w) (5 weeks per cycle), it was found that S-1 + CDDP therapy was superior to S-1 monotherapy, and at present S-1 + CDDP therapy is the standard treatment for curatively unresectable gastric cancer[32].

Koizumi et al. conducted a phase I/II trial investigating the effectiveness of S-1 + CDDP therapy for unresectable advanced gastric cancer, and found a high response rate (76%) with a low PD rate (< 5%) in lymph nodes[33]. Furthermore the JCOG 0210 'trial confirming the safety of preoperative S-1 + CDDP therapy for curatively unresectable large type 3 and type 4 gastric cancer' revealed a high rate of successful treatment at 72%. Therefore, in the JCOG Gastric Cancer Study Group, S-1 + CDDP therapy (CDDP : 60 /mg/m^2 [day 8], S-1 : 80 mg/m^2 [day 1-21] q4w) (4 weeks per cycle) has been adopted as a candidate regimen for preoperative chemotherapy.

The JCOG 0405 'A phase II study of systemic chemotherapy with TS-1 + CDDP followed by surgery in advanced gastric cancer with extensive lymph node metastasis' is a phase II trial of preoperative S-1 in combination with CDDP therapy plus surgical resection with D2+ N0.16 dissection. In the JCOG trial the rate of R0 resection was the primary endpoint, and there were 53 patients enrolled. Adverse events

in preoperative S-1 + CDDP therapy included grade 3/ 4 neutropenia (19.2%) and relatively mild diarrhea (1.9%), and there were no treatment-related deaths, thus the treatment could be administered safely. The response rate to S-1 +CDDP therapy was 64.7%, the R0 resection rate was 82.4% (95%C.I. 69.1-91.6%), which was above the initial threshold set for R0 resection rate (50%), and thus demonstrated the effectiveness of the treatment. Furthermore, in the final analysis conducted in 2012, the 5 year survival rate was 52.7%, which was much higher than the 5 year survival rate of 20% found in the JCOG 0001 trial with the same patient population, and therefore the JCOG Gastric Cancer Study Group provisionally defined S-1 + CDDP therapy as the standard preoperative chemotherapy regimen for gastric cancer with paraaortic lymph node (No.16a2/16b1) metastasis and/or bulky lymph node metastasis.

In the aim of improving therapeutic outcomes, the JCOG 1002 is an ongoing trial (enrollments completed in May 2013 (enrollment number 53), main analyses scheduled in 2014) that examines the safety and effectiveness of preoperative chemotherapy using triple agent S-1 + CDDP therapy and taxane-based docetaxel. Furthermore, the JCOG 1013 'Phase III study of cisplatinn plus S-1 (CS) compared with docetaxel and cisplatin plus S-1 (DCS) as first-line therapy for advanced gastric cancer' is currently underway to examine how adding docetaxel to S-1 + CDDP improves outcomes for HER2 negative (or unknown/untested HER2 status) unresectable advanced and recurrent gastric cancer. If the results of these trials demonstrate that adding docetaxel improves outcomes, then the superiority or inferiority of S-1 + CDDP + trastuzumab compared to docetaxel + S-1 + CDDP (DCS) may be clinically questioned, and it is possible that DCS combined with trastuzumab might become a treatment option for HER2 positive gastric cancer. However at this point in time it is known where DCS is positioned in the treatment of patients with extensive lymph node metastasis and/or unresectable advanced and recurrent gastric cancer, and therefore we were unable to consider it the most promising regimen for use in the present trial

In previous clinical trials of preoperative chemotherapy conducted by the JCOG Gastric Cancer Study Group, the HER2 expression status was not evaluated prior to enrolment, and therefore both HER2-positive and negative patients were included.

2) Evaluation of Trastuzumab

In the development of perioperative chemotherapy, promising agents for unresectable advanced and recurrent cancer often become candidate trial treatments, and based on the results of the ToGA trial, trastuzumab is considered a candidate agent for HER2 positive gastric cancer.

The ToGA trial was designed as a phase III international collaborative trial of first-line treatment of HER2-positive (IHC3+ or FISH+) unresectable advanced/recurrent gastric cancer and unresectable advanced esophagogastric junction cancer. The trial evaluated the addition of trastuzumab to the control group therapy (capecitabine (Cap®)+ CDDP) based on overall survival as the primary endpoint[20]. Patients were enrolled from 122 institutions in 24 countries including Japan, and the final analyses included 290 patients in the chemotherapy group, and 294 patients in the chemotherapy + trastuzumab group. Median overall survival was 11.1 months in the chemotherapy group, and 13.8 months in the chemotherapy + trastuzumab group, which demonstrated superiority of chemotherapy + trastuzumab to chemotherapy (hazard ratio 0.74, 95% CI: 0.60-0.91, p=0.0046). Moreover the response rate was higher in the chemotherapy + trastuzumab group (47%) than the chemotherapy group (35%). In addition, the results of post-hoc analysis demonstrated that on comparing IHC3+, or IHC2+ and FISH+ subjects, the median overall survival period was 11.8 months in the chemotherapy group compared to 16.0 months in the chemotherapy + trastuzumab group (hazard ratio 0.65, 95% CI: 051-0.83), and thus trastuzumab strongly improved outcomes. Based on the results of the ToGA trial, chemotherapy with trastuzumab has been established as a new standard treatment in the first-line treatment of HER2-positive unresectable advanced/recurrent gastric cancer and esophagogastric junction cancer. In Japan, the improved effect of trastuzumab for 'curatively unresectable advanced/ recurrent gastric cancer with confirmed HER2 overexpression' was acknowledged in March 2011.

Moreover, HER2 positivity was defined as IHC3+, or IHC2+ and ISH+ (details provided below in 3.9. Evaluation of HER2 test).

On the other hand, excluding grade 3/ 4 diarrhea (chemotherapy+ trastuzumab group: 9%, chemotherapy group: 4%), there was no difference in adverse events observed between the two groups, and the incidence of cardiovascular complications were comparable. In the ToGA trial the definition of 'infusion reaction' encompassed the onset of the following reactions within 24 hours, including hypersensitivity, puritus, rash, urticaria, shivering, head ache, joint pain, muscular pain, infusion-related reaction, fatigue, asthenia, lethargy, malaise, dizziness, nausea, vomiting, coughing, dyspnea, bronchial spasms, hypotension, hypertension, and tachycardia. On the basis of this definition, grade 3/ 4 'infusion reactions' were observed in 8% of the chemotherapy group, and 6% of the chemotherapy + trastuzumab group, with no difference between the two groups. There were no reported infusion-related reactions of grade 3 or above according to the CTCAE v.4.0 definition in the chemotherapy + trastuzumab group.

With regards to perioperative chemotherapy with trastuzumab, a Spanish research group reported their preliminary analysis results at the ASCO annual meeting in 2013 of their phase II trial of preoperative chemotherapy with trastuzumab for resectable, HER2-positive esophagogastric junction cancer and gastric cancer (NEOHX trial (36 enrollments, enrolments began in June 2010, and were completed in March 2012, with main analyses scheduled for March 2014, NCT01130337)[34]. The trial included patients with T1-2N+M0 and T3-4NxM0 resectable esophagogastric junction and gastric cancer, with HER2 positivity defined according to IHC3+ or IHC2+/FISH-positive. The treatment schedule involved the administration of 3 preoperative and 3 postoperative cycles of XELOX-T (Cap: 1,000 mg/ m^2 given twice per day for days 1-14; oxiliplatin: 130 mg/ m^2 on day 1; trastuzumab: 8 mg/kg (6 mg/kg for 2nd cycle and after) on day 1; q3w), followed by 12 cycles of trastuzumab monotherapy. A total of 36 enrollments were completed. Secondary endpoints including histological CR in 8% (3 patients), R0 resection rate of 78% (28 patients), and response rate of 39% (14 patients), and safety data were reported. Other overseas research groups plan to report the results of trials of perioperative chemotherapy using trastuzumab for resectable advanced gastric cancer, however at present in March 2014 3 trials have been confirmed, including the aforementioned NEOHX trial, the TOXAG trial conducted by a Turkish research group (40 planned enrollments, with enrollments starting in January 2013 and with main analyses scheduled for June 2016, NCT01748773), and the HerFLOT trial conducted by the German AIO Group (53 [planned enrollments, with enrollments starting in December 2011, and main analyses scheduled for February 2014, ICT01472029). These 3 trials are small scale phase II trials including gastric cancer and esophagogastric junction cancer. Because the perioperative chemotherapy treatment regimen, pre-and postoperative schedules, and surgical procedure differ to those in Japan, the effectiveness will be difficult to interpret even when the trial results are published, and unless there is a major safety problem reported, we believe that the present trial will not be affected.

Therefore, while there are currently no reports of clinical trials that demonstrate the perioperative effectiveness of trastuzumab for resectable HER2-positive gastric cancer, on the basis of the results of the ToGA trial a higher response rate can be expected by adding trastuzumab, and it is believed that combination regimen with trastuzumab can be administered safely as preoperative chemotherapy. Moreover in the ToGA trial trastuzumab is administered at a dose of 8 mg/kg for the first cycle, then at 6 mg/kg for subsequent cycles. This dosage is also listed in the trastuzumab package insert. Therefore in the present trial, trastuzumab will be administered at a dose of 8 mg/kg for the first cycle, then 6 mg/kg for subsequent cycles.

3) Evaluation of other anti-HER2 agents

Regarding other anti-HER2 agents for HER2-positive gastric cancer, lapatinib has been shown to be effective for breast cancer and the current results of trials examining effectiveness of lapatinib for unresectable advanced/recurrent HER2-positive gastric cancer (all included if FISH+) have been reported. The results of the TyTAN trial, a phase III trial comparing the trial treatment combining

paclitaxel and lapatinib as the second-line treatment following first-line treatment with fluoroprymidine and/or CDDP, with paclitaxel monotherapy as the standard treatment were reported at the 2013 ASCO-GI (ASCO Gastrointestinal Cancers Symposium). ITT analysis revealed that the OS (overall survival) and PFS (progression-free survival) in the paclitaxel monotherapy group compared to the paclitaxel + lapatinib group was 8.9 months/11.0 months (HR0.84, p=0.2088), and 4.4 months/ 5.4 months (HR0.85, p=0.2441), and for the primary endpoint of OS and PFS outcomes were not improved with combination therapy. However, when limited to IHC3+ patients, OS and PFS in the paclitaxel monotherapy group/ paclitaxel + lapatinib group were 7.6 months/ 14.0 months (HR0.59, p=0.0176), and 4.2 months/ 5.6 months (HR0.54, p=0.0101), indicating that when limited to patients with high HER2 expression combination therapy can be expected to be effective. Furthermore, at the ASCO annual meeting of the same year, in 2013, the results of the LOGiC trial, a phase III trial examining the effect of adding lapatinib to XELOX in the first-line treatment of unresectable, recurrent, HER2-positive gastric cancer (FISH+), were reported. On comparing the XELOX group and XELOX + lapatinib group, the OS and PFS were 10.5 months/ 12.2 months (HR0.91, p=0.3492) and 5.4 months /6.0 months respectively (HR0.82, p=0.0381), and for the primary endpoint OS, there was no improvement observed. The results demonstrate that in the subgroups with higher HER2 expression, i.e. IHC2+ and 3+, there was no difference in OS (HR:0.86) and therefore it is considered difficult to continue the development of lapatinib for gastric cancer.

Trials of pertuzumab and T-DM1, confirmed effective treatments for HER2-positive breast cancer, are ongoing for use in the treatment of unresectable advanced/recurrent HER2-positive gastric cancer, and other agents have been scheduled for development for use in the treatment of HER2-positive gastric cancer. However, the results of such trials are yet to be reported, and at present, except for than trastuzumab, the effectiveness of anti-HER2 agents for HER2-positive gastric cancer has not been demonstrated.

4) S-1+CDDP treatment schedule

Overseas, fluoroprymidine + CDDP combination regimen is used as the standard treatment for unresectable advanced gastric cancer, and has been often developed in combination with newly developed agents. Such regimens are mostly administered in 3-week cycles, however in an American phase III trial (FLAGS trial) comparing S-1 + CDDP therapy (CDDP : 75 /mg/m^2 [day 1]、S-1 : 50 mg/m^2 [day 1-21] q4w) and 5-FU + CDDP combination therapy, the administration schedule uses a 4-week cycle[35]. In contrast to fluoroprymidine + CDDP combination regimen used overseas, the dose intensity of S-1 + CDDP combination therapy used in Japan (5-week cycle) is low (table 2.3.2).

Table 2.3.2. Treatment schedule for fluoroprymidine + CDDP therapy

	Fluoropyrimidine	CDDP	CDDP Dose interval	CDDP dose intensity ($mg/m^2/w$)	Comments
SPIRITS[33]	S-1 80 mg/m^2 day 1-21	60 mg/m^2 day 8	5 w	12	
JCOG0210[39]	S-1 80 mg/ m^2 day 1-21	60 mg/ m^2 day 8	4 w	15	
SOS[40]	S-1 80 mg/ m^2 day 1-14	60 mg/ m^2 day 1	3 w	20	
FLAGS[35]	S-1 50 mg/ m^2 day 1-21	75 mg/ m^2 day 1	4 w	18.8	
	5-FUci 1000 mg/ m^2 day 1-5	100 mg/ m^2 day 1	4 w	25	
V325[41]	5-FUci 750 mg/ m^2 day 1-5	75 mg/ m^2 day 1	3 w	25	In combination with docetaxel
	5-FUci 1000 mg/ m^2 day 1-5	100 mg/ m^2 day 1	3 w	33.3	
ML17032[42]	5-FUci 800 mg/ m^2 day 1-5	80 mg/ m^2 day 1	3 w	26.7	
	Cap 1000 mg/ m^2 day 1-14	80 mg/ m^2 day 1	3 w	26.7	
REAL2[43]	5-FUci 200 mg/ m^2 day 1-21	60 mg/ m^2 day 1	3 w	20	In combination with epirubicin
	Cap 625 mg/ m^2 day 1-14	60 mg/ m^2 day 1	3 w	20	In combination with epirubicin

Cap : Capecitabine

In recent years, a phase II trial has been conducted in Japan and Korea examining S-1 + CDDP therapy with an increased dose intensity of CDDP (CDDP : 60 mg/m^2 [day 1]、S-1 : 80 mg/m^2 [day 1-14] q3w) (3-week cycle) from the treatment schedule for lung cancer and gastric cancer, and for both effectiveness and toxicity profiles the results were not much different to those with 5-week cycle[36, 37]. In Korea, the results of this phase II trial have been accepted and the 3-week cycle has been included as a treatment option for unresectable advanced gastric cancer, Moreover the Asan Medical Center reported the results of an observational study of the safety and effectiveness of S-1 + CDDP therapy administered with the same schedule to 159 patients with unresectable advanced gastric cancer. In their report, the effectiveness was shown to be not inferior to the SPIRITS trial with a response rate of 42.4%, median PFS of 5.8 months and MST of 11.3 months[38]. During the initial 3 cycles the dose was reduced in 9 patients (11.9%), the start of treatment was delayed in 35 patients (22%), there was a median of 6 cycles given, and the relative dose intensity was 87.9%, which were comparable results to the SPIRITS trial. Furthermore, to examine the optimal schedule for S-1 + CDDP combination therapy, the WJOG (West Japan Oncology Group) in collaboration with Korea conducted a phase III international collaborative trial (S-1 Optimal Schedule Study : SOS study) comparing S-1 + CDDP combination therapy given in 5-week cycles and 3-week cycles, and the results of which were reported at the ASCO Annual Meeting 2013[40]. On comparing 309 patients allocated to the 5-week cycle (SP5) group and 306 patients in the 3-week cycle (SP3) group, the SP5/SP3 response rate, median PFS, and MST were 50%/60% (p=0.065), 4.9 months/5.5 months (p=0.042、HR0.82 [95% CI: 0.68-0.99]), and 13.9 months/14.4 months (p=0.907、HR0.99 [95% CI: 0.81-1.21]). Furthermore, the incidence of major adverse events of grade 3 or above included neutropenia (9%/39%), febrile neutropenia (1%/2%), anemia (9%/19%), thrombopenia (7%/10%), loss of appetite (5%/7%), nausea (2%/5%), and fatigue (6%/8%). Compared to the SP5 group, the SP3 group tended to exhibit stronger toxicities, however the response rate and PFS tended to be higher, which therefore suggests that a schedule with a shorter administration period will be more like to achieve the maximum cytoreductive effect in preoperative chemotherapy.

Therefore although there is currently no established optimal S-1 + CDDP treatment schedule for unresectable advanced gastric cancer throughout the world, a 3-week cycle is considered promising. Similarly, in the JCOG 0210, JCOG 0405, and JCOG 0501 the 4-week cycle treatment schedule in preoperative S-1 + CDDP therapy has not been established.

Accordingly, in the present trial, we focused on the results of the SOS trial and decided to implement the S-1 + CDDP therapy using the 3-week cycle, which is expected to have cytoreductive effect.

5) Rationale for selecting S-1 + CDDP therapy (3 weeks per cycle) as the regimen in combination with trastuzumab

The only clinical evidence of combination regimens for HER2-positive, unresectable, advanced/recurrent gastric cancer is the use of 5-FU + CDDP therapy and capecitabine + CDDP therapy used in the ToGA trial. However, in Japan, the approval of trastuzumab only mentions 'usage in combination with anti-malignant tumor agents', and therefore it may be used in combination with other anti-malignant tumor agents and not just 5-FU, capecitabine (Cap) and CDDP used in the ToGA trial. Although there is no phase III trial that directly compares Cap + CDDP and S-1 + CDDP, in a previous phase III trial the PFS in Cap + CDDP therapy was shown to be non-inferior to 5-FU + CDDP therapy[42], and in the phase III trial (FLAGS) conducted to examine the superiority of S-1 + CDDP to 5-FU + CDDP superiority was not demonstrated, however the effects were comparable and therefore the effectiveness of Cap + CDDP and S-1 + CDDP are considered equal[35].

The safety of S-1 in combination with trastuzumab has been confirmed for HER2-positive breast cancer[44]. Furthermore, the OGSG (Osaka Gastrointestinal Cancer Chemotherapy Study Group) conducted a phase II trial (HERBIS-1 trial) (n=66) with a regimen of trastuzumab in addition to 3-week cycles of S-1 + CDDP for gastric cancer, and reported the data pertaining to the safety and efficacy at the 2012 ASCO-GI[45]. Reported major adverse events of grade 3 or above included neutropenia in 31.2%, anemia in 9.4%, loss of appetite in 20.8%, leukopenia in 7.5%, diarrhea in 7.5%, hypoalbuminemia in 7.5%, elevated serum creatinine levels in 5.7%, and vomiting in 5.7%, which were acceptable results. Furthermore, as the primary endpoint the response rate was 67.9% (95% CI, 53.7-80.1%), and although a simple comparison cannot be made because it was a phase II trial and the inclusion criteria differed, the results were better than the 47% response rate of the trastuzumab combination therapy group in the ToGA trial, and the 57% response rate of the S-1 + CDDP therapy group in the SPIRITS trial. Furthermore, S-1 adjuvant chemotherapy is the standard treatment following curative resection of gastric cancer, and therefore replacing fluoroprymidine with pre- and post-operative S-1 has the advantage in that toxicity profiles obtained with preoperative treatment may be put to use in postoperative treatment.

Therefore, S-1 +CDDP therapy in combination with trastuzumab is considered the most suitable preoperative chemotherapy regimen.

Furthermore as mentioned in 2.3.2.4), there is no established treatment schedule for preoperative S-1 + CDDP therapy. At present there is no data from prospective studies of the safety and efficacy of a regimen including 4- or 5-week cycles of S-1 + CDDP therapy combined with trastuzumab. However given the safety and efficacy found with the regimen of 3-week cycles of S-1 + CDDP in combination with trastuzumab used in the HERBIS-1 trial, the regimen was deemed acceptable. Furthermore, considering that trastuzumab is administered every 3 in terms of convenience it is recommended to use 3-week cycles of S-1 –CDDP therapy.

2.3.3. Surgery

Gastric cancer will rarely completely disappear (histological complete response) with preoperative chemotherapy, and therefore in the event of preoperatively observed paraaortic lymph node (No.16a2/b1) metastasis we decided to perform lymph node dissection (D2+No.16 dissection) with D2 and No.16 dissection in addition to resection of the primary lesion following preoperative chemotherapy. Furthermore, in patients with bulky lymph node metastasis diagnosed prior to chemotherapy, paraaortic lymph node metastasis is histologically often observed, and therefore in the JCOG 1002, D2+No.16 lymph node dissection is performed and will be performed in the present trial also. In the event that No.16a2/b1 and/or bulky lymph node have not developed prior to preoperative chemotherapy, D2 dissection will be performed in addition to resection of the primary lesion, and No.16 dissection will not be performed.

In the JCOG 0001 irinotecan + CDDP therapy was administered to treat patients with paraaortic lymph node metastasis and/or bulky lymph node dissection, and treatment-related deaths thought to be

caused by the long duration of surgery and excessive invasion due to thoracotomy, occurred in patients with esophageal invasion. Consequently, as a general rule, highly invasive surgery such as thoracotomy and pancreaticoduodenectomy will not be performed. Furthermore, the safety and efficacy of laparoscopic surgery has not been established in the treatment of patients with advanced gastric cancer and severe lymph node metastasis in the present trial, and therefore all procedures will be performed by laparotomy, and laparoscopic surgery is not permitted.

2.3.4. Postoperative adjuvant chemotherapy

As mentioned in 2.2.1.3), on the basis of the results of the ACTS-GC trial[25], postoperative administration of S-1 for one year is considered the standard treatment for patients included in the present trial. In the event that R0 resection is achieved, postoperative adjuvant chemotherapy with S-1 therapy will be initiated within 6 weeks of surgery at a dose of 80-120 mg/body, then if possible, continued for one year after surgery in a cycle of 4-week administration and 2-week rest.

At present, there is no data available indicating the safety of adjuvant chemotherapy with trastuzumab following gastrectomy. Furthermore, in the present trial, under the Advanced Medical care B Program, trastuzumab will be provided free of charge from the manufacturer, Chugai Pharmaceuticals, however because the postoperative supply of trastuzumab will be difficult, in the present trial trastuzumab will not be used as postoperative adjuvant chemotherapy.

2.3.5. Summary of the risks/benefits of standard treatment and trial treatment

According to the Guidelines the standard treatment of resectable advanced gastric cancer is gastrectomy with D2 lymph node dissection and one-year of S-1 therapy. Based on the results of the JCOG 0405 trial, a high response rate and increased survival can be expected with the use of S-1 + CDDP therapy as preoperative chemotherapy for advanced gastric cancer with extensive lymph node metastasis. However, in the event that preoperative chemotherapy is ineffective, the tumor may grow during preoperative chemotherapy and become unresectable, which can be a risk of preoperative chemotherapy. Furthermore if adverse events during preoperative chemotherapy cause the suspension or termination of treatment, the tumor might grow during the waiting period for surgery, which is also a risk.

The addition of trastuzumab to S-1 + CDDP therapy as preoperative chemotherapy is expected to increase the response rate and prolong survival. However, adding trastuzumab will likely increase the incidence of grade 3/ 4 diarrhea and infusion-related reactions. When these adverse events are prolonged, treatment may need to be suspended or terminated, which are also risks.

2.3.6. Post-treatment care

In the present trial, after completion of the protocol treatment patients will be followed up without treatment until recurrence is observed. There is no stipulated standard treatment in the event that curative resection is not possible despite preoperative chemotherapy with either S-1 + CDDP therapy or S-1 + CDDP + trastuzumab therapy, and in the event of recurrence developing during or following postoperative adjuvant chemotherapy with S-1. Furthermore, when recurrence develops despite preoperative administration of trastuzumab, the significance of administering trastuzumab in combination with systemic chemotherapy is unknown. In the event of disease progression during trastuzumab therapy, the continuation of trastuzumab or anti-HER2 agents such as lapatinib, pertuzumab (not approved for gastric cancer), and T-DM1 (not approved for gastric cancer) is considered effective for metastatic breast cancer, however there is no evidence that this is the case in gastric cancer. Thus there is no established standard chemotherapy in the event of discontinuation of protocol treatment, or recurrence, and there is no stipulated after treatment care in the present trial.

2.4. Trial design

The provisional standard treatment for patients with paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis is preoperative S-1 + CDDP therapy + surgery + postoperative S-1 therapy, whereas the standard treatment for patients with lymph node metastasis of 15 mm or more in

size (minor axis) is gastrectomy + postoperative S-1 therapy. However according to the observational study conducted by the Shizuoka Cancer Center, in the population with lymph nodes 15 mm or more in size (minor axis) 85% are pN2, of which approximately 50% have metastasis in 7 or more nodes. Accordingly, it is believed that patients with lymph node metastasis of 15 mm in size (minor axis) will require more intense treatment with added preoperative chemotherapy, and in the present trial also, we decided to make preoperative S-1 + CDDP therapy + surgery + postoperative S-1 therapy the provisional standard treatment for such patients. The validity of the provisional treatment will be ensured by establishing the decision rules outlined below (listed in 12.1). The present trial is an exploratory randomized phase II screening design that compares the (provisional) standard treatment and protocol treatment.

2.4.1. Planned phase III trial design

The present trial will demonstrate the efficacy of preoperative S-1 + CDDP + surgery + postoperative S-1 in the treatment of patients with paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis, as well as patients with lymph node metastasis of 15 mm in size (minor axis) (excluding patients with paraaortic lymph node (No.16a2/b1) metastasis, and/or bulky lymph node metastasis). Furthermore, if the improved effect of additional trastuzumab is demonstrated through exploratory analysis, then a phase III trial will be conducted of preoperative S-1 + CDDP + trastuzumab as the trial treatment to investigate the effect of adding preoperative trastuzumab therapy to the standard treatment (preoperative S-1 + CDDP therapy) for HER2-positive gastric cancer with extensive lymph node metastasis.

Data from the Shizuoka Cancer Center revealed that in patients with regional lymph node metastasis of 15 mm or more in size (minor axis) and invasion depth of cT2 or greater, the 3-year survival rate was 60.5%. Perioperative chemotherapy is expected to improve this rate by 10%, and thus in patients with lymph node metastasis of 15 mm in size (minor axis) if the 3 year survival with S-1 + CDDP therapy exceeds the point estimate of 70%, then the efficacy of preoperative S-1 + CDDP therapy will be demonstrated, and its establishment as the provisional standard treatment will be deemed valid. However in the event that preoperative S-1 + CDDP therapy is not found to be effective for patients with regional lymph node metastasis of 15 mm in size (minor axis) (excluding paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis) (point estimate : 70%), the standard treatment will be re-examined within the group when conducting the subsequent phase III trial, even if the present study revealed that additional preoperative therapy with trastuzumab is found to improve outcomes.

The subsequent phase III trial will likely proceed as described below.

First, in the event that the efficacy of additional trastuzumab is shown in the present trial, then the JCOG plans to conduct a phase III trial under the Advanced Medical care B Program or as a clinical trial (industry/ physician sponsored). However, the means of procuring medications (supplied by the manufacturer or purchased with research funds) for such a trial has not yet been established. Furthermore the efficacy of trastuzumab as perioperative chemotherapy for HER2-positive gastric/esophagogastric junction cancer is currently being evaluated in clinical trials in Spain, Turkey, and Germany. Based on the results of these trials, if pharmaceutical approval (including the widespread use of specific applications and dosages based on certain evidence) is obtained for the use of trastuzumab to treat HER2-positive resectable advanced gastric cancer in any country in the US or Europe (the USA, UK, Germany, France, Canada, and Australia), then it will be submitted through the Japanese Gastric Cancer Association for examination by a review group on off-label trial agents and non-approved agents that are highly needed in medical care.

2.4.2. Rationale for establishing endpoints

The purpose of the present multicenter collaborative trial is to examine the effect of adding trastuzumab to preoperative S-1 + CDDP therapy + surgery for patients with HER2-positive advanced gastric cancer. In a controlled trial of preoperative chemotherapy for gastric cancer, histological

response rate and curative resection rate were considered candidate surrogate endpoints for overall survival, however at present there is no clear evidence to support this, and in the present trial overall survival was used as the primary endpoint. Moreover, response rate (RECIST v1.1) was established as the secondary endpoint. Other secondary endpoints used include progression free survival, histological response, curative resection rate, preoperative treatment completion rate, treatment completion rate until postoperative adjuvant chemotherapy, incidence of adverse events, and incidence of severe adverse events. The rate of treatment-related deaths is the most important secondary endpoint for safety.

2.4.3. Rationale for setting clinical hypothesis and number of enrollments

The present trial is a randomized phase II screening design that examines the safety and efficacy of the trial treatment (preoperative S-1 + CDDP + trastuzumab therapy + surgery) in the treatment of HER2-positive gastric cancer with extensive lymph node metastasis. The 3 year survival is estimated at 70% for the S-1 + CDDP group, and is expected to be increased by 10% in the S-1 + CDDP + trastuzumab group. When α=0.20 (one-sided) and statistical power is 75%, 63 patients will be required in each group. Thus the planned number of enrollments was set at 65 patients in one group, and 130 patients for the 2 groups to account for the potential inability to follow-up several patients.

2.4.4. Potential patient enrollment

The JCOG 1002 trial, which included patients with paraaortic lymph node (No.16a2/b1) metastasis and/or bulky lymph node metastasis, was conducted with an anticipated enrollment of 50 patients in 2.5 years (20 enrollments/year), however 52 patients had been enrolled after one year and 11 months. In the observational study conducted by Shizuoka Cancer Center, the eligibility criteria included regional lymph node metastasis of 15 mm or more in size (minor axis), and approximately 10 times more patients were included in the study. Assuming a HER2-positive rate of 25%, the annual number of enrollments is expected to be 60 patients (25×10×0.25=63), and enrollments of 130 patients/3 years is considered quite feasible.

2.4.5. Rationale for setting allocation adjustment factors

1) Institutions

It is commonly known that enrolled patient background, treatment, efficacy assessment, and safety assessment varies between institutions, and therefore any adjustments in institutions will be standardized by the JCOG.

2) Paraaortic lymph node (No.16a2/b1) metastasis and/or Bulky lymph node metastasis (with vs. without)

As mentioned in section 2.2.2.1), the Gastric Cancer Study Group has established S-1 + CDDP preoperative chemotherapy + surgery as the provisional standard treatment for paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis. In the treatment of such patients, the JCOG 1002 trial (enrollments completed in May 2013) is currently examining the efficacy of preoperative chemotherapy with S-1 + CDDP + docetaxel in combination with surgery and postoperative adjuvant chemotherapy with S-1. On the other hand, for patients with cT2 invasion and regional lymph node metastasis of 15 mm in size (minor axis) (excluding paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis), the standard treatment is surgery + postoperative adjuvant chemotherapy with S-1 (based on the histopathological results of the resected specimen), and the standard treatment differs according to the presence or absence of paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis.

Furthermore, gastrectomy with D2 lymph node dissection is performed for patients with cT2 invasion and regional lymph node metastasis of 15 mm in size (minor axis) (excluding paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis), however gastrectomy with D2+No.16 lymph node dissection is performed for patients with paraaortic lymph node (No.16a2/b1) metastasis and/ or bulky lymph node metastasis, and therefore the therapeutic outcomes of treatment and