60 years of age>	2

The maximum total score is 26 points. A score of 21 or more indicates low risk, and a score of 20 or below indicates high risk.

※2 The present trial included patients aged 20 years and older, and therefore 'does not apply to individuals aged 16 years or younger' was deleted from the original guidelines for the treatment of febrile neutropenia [published by the Japanese Society of Medical Oncology].

3) Precautions for the day of CDDP treatment

On the day of CDDP treatment aminoglycoside antibiotics, vancomycin, and nonsteroidal anti-inflammatory drugs should not be administered, or if given in combination should be given with extreme care.

Prior to CDDP treatment, adequate daily urinary output (more than 2-3L) should be ensured through the combined use of sufficient transfusion and diuretics for at least 24 hours. To prevent renal dysfunction.

4) Nausea and vomiting

For nausea and vomiting, antiemetics should be actively administered in accordance with the guidelines for proper use of antiemetic agents[46].

5) Stomatitis, pharyngitis, and spontaneous pain/ swallowing pain associated with dysphagia and esophagitis

Analgesics, topical anesthetics, gargling agents including hachiazure, and mucosa protective agents such as alloid G oral solution will be used as required to manage symptoms. If pain is severe, opiates can be used.

6) Diarrhea

In the event that diarrhea of grade 2 or above develops, antidiarrheal loperamide shall be initiated at a dose of 4 mg, and it is recommended that the agent be administered every 2 hours until the diarrhea stops.

7) Inoculation of the influenza and pneumococcus vaccines

There is no clear evidence in relation to the effectiveness of preventive vaccination given before the start of and during chemotherapy, or prior to surgery and the timing of vaccination. However, it has been found that infection can become severe in immunocompromized patients, and therefore following the guidelines of the Infectious Disease Society of America, in the "Japanese guidelines for the treatment of febrile neutropenia (FN)" published by the Japanese Society of Medical Oncology (JSMO guidelines) as well, a grade A recommendation for the influenza vaccine and grade B recommendation for the vaccine against pneumococcus are stated. Thus in the event that it is determined that the vaccination will be beneficial and safety will be ensured, vaccination shall be considered in reference to the JSMO guidelines after taking into account the protocol-based treatment and the timing of vaccination.

6.4.3. Acceptable combination and supportive therapies

The following combination and supportive therapies can be administered as required.

1) Erythrocyte transfusion may be conducted as necessary to correct anemia due to chronic bleeding from lesions.
2) Treatment for complications such as hypertension.
3) Symptomatic treatment for pain.
4) Premedication to prevent infusion-related reaction to trastuzumab.

6.4.4. Unacceptable combination and supportive therapies

During the protocol-based treatment, none of the following treatments shall not be administered.

1) Administration of anti-cancer agents other than those included in the regimens of the protocol-based treatment.

2) Radiation therapy
3) Immunotherapy

6.4.5. Precautions for concurrent agents that require special attention when co-administered

Refer to the most recent drug information sheet. The following agents require particular special attention.

① Warfarin

The effects of warfarin may be increased when used in combination with S-1. When used in combination with S-1, special attention shall be paid to the incidence of hemorrhagic symptoms such as subcutaneous bleeding and nasal bleeding, while monitoring PT-INR. The warfarin dosage should be adjusted so that PT-INR is 1.5-2.0. If any abnormalities are observed, warfarin shall be discontinued or the dosage will be reduced.

② Allopurinol

Allopurinol is an inhibitor of orotate phosphoribosyltransferase (OPRT), an anabolic enzyme of 5-FU, and may reduce the effect of S-1. Therefore the risks and benefits should be taken into consideration when used in combination.

③ Flucytosine and fluoropyrimidine antifungal agents
④ Phenytoin
⑤ Sorivudine
⑥ Folic acid preparations

6.5. Post-treatment

Following completion of protocol-based treatment, the patient shall be observed without treatment until recurrence is found.

The patient is free to pursue any post-treatment care in the event that the protocol-based treatment is terminated.

No treatment for recurrence is stipulated after completion of the protocol-based treatment.

In the event that the main analysis and interim analysis results lead to the conclusion that outcomes are good in any of the treatment groups, patients enrolled in the trial shall be explained the trial results as required, and after taking into consideration the course of treatment of each individual patient, the treatment method considered the best shall be provided.

In the event that: R0 resection is deemed impossible, the protocol-based treatment is terminated without performing surgery, and clinical significance is acknowledged such as bleeding control and release of stenosis, palliative surgery may be performed as post-treatment.

After "termination of protocol-based treatment" has been determined, "the same surgery as the protocol-based treatment" or "the same treatment regimen as the preoperative chemotherapy and the postoperative adjuvant chemotherapy" shall not be permitted as "post-treatment." However, in the event that the "continuation of protocol-based treatment" is deemed clinically valid although the criteria for the termination of protocol-based treatment apply, then as a general rule, (except in the event that there is no margin for time), the decision is not made by the attending physician, but the study secretariat shall be consulted through the principal investigator at the institution or the institution coordinator. After a consensus is reached between the study secretariat and the principal investigator/institution coordinator, a decision will be made as to whether to "shift treatment to post-treatment from cessation of protocol-based treatment" or "continue protocol-based treatment in deviation." The circumstances of the decision making and details of consultation with the study secretariat shall be described in detail in the comment fields of the case report form and therapy completion report form for the patient in question. Furthermore, in the event that "continuation of protocol-based treatment in deviation" often occurs, then the criteria for termination of protocol-based treatment may be clinically inappropriate. Therefore, in such a case, the study secretariat shall consider revision of the criteria for termination of protocol-based treatment using group meetings and group mailing lists.

7. Anticipated adverse events

7.1. Anticipated adverse reactions to medications

For anticipated adverse reactions to each drug, refer to the most recent drug information sheet in the appendix.

7.2. Anticipated adverse reactions to combination chemotherapy and multimodal treatment

In the present trial, the following adverse reactions are anticipated.

7.2.1. Anticipated adverse reactions to preoperative chemotherapy

For adverse reactions of each medication, refer to "7.1. Anticipated adverse reactions to each medication." All items listed in the "warning" and "precautions" on the drug information sheet may be anticipated adverse reactions.

Table 7.2.1.a lists adverse events of the trial treatment group (S-1 + CDDP therapy given every 3 weeks) in the SOS trial (phase III trial) which was conducted in patients with unresectable or recurrent gastric cancer irrespective of HER2 status (positive or negative). Furthermore, table 7.2.1.b lists adverse events observed in the HERBIS-1 trial (phase II trial) conducted including HER2-positive patients with unresectable or recurrent gastric cancer.

Table 7.2.1.a. Adverse reactions to S-1+CDDP therapy (SOS trial, n =306, CTCAE v3.0)

	≧Grade 3(%)
Neutropenia	39
Anemia	19
Thrombopenia	10
Infection with G3-4 neutropenia (infection of unknown origin)	2
Loss of appetite	7
Nausea	5
Vomiting	3
Diarrhea	2
Fatigue	8
Neuropathy (sensory/motor)	1
Skin reaction of the hands and feet	0.3
AST/ALT	2
Creatinine	0

Table 7.2.1.b. Adverse reactions to combination therapy with S-1+CDDP+trastuzumab (HERBIS-1 trial, n =53, CTCAE v4.0)

	All grades(%)	≧Grade 3(%)
Leukopenia	64.2	7.5
Neutropenia	50.9	30.2
Febrile neutropenia	3.8	3.8
Anemia	58.5	9.4
Thrombopenia	37.7	0.0
Elevated creatinine	32.1	5.7
Elevated total bilirubin	11.3	0.0
Elevated AST	11.3	0.0
Elevated ALT	24.5	0.0
Hypoalbuminemia	39.6	7.5
Loss of appetite	73.6	20.8
Nausea	52,8	1.9
Vomiting	18.9	5.7
Stomatitis	26.4	1.9
Diarrhea	35.8	7.5
Constipation	17.0	0.0
Fatigue	58.5	3.8
Rash	17.0	0.0

	All grades(%)	≧Grade 3(%)
Nasal bleeding	7.5	0.0
Edema	9.4	0.0
Dysgeusia	17.0	0.0
Hypertension	3.8	0.0
Infusion-related reaction	3.8	0.0

7.2.2. Anticipated adverse reactions to surgery and surgical complications

The CTCAE v4.0-JCOG and Clavien-Dindo classification shall be used for evaluations in the present trial. The underlined sections below may be severe adverse reactions.

1) Complications of general anesthesia

Fever[*1], allergic reaction, tracheal obstruction, oliguria, increased CPK[*1], acidosis[*1], hyperkalemia[*1], muscular pain[*1], delirium, hoarseness, laryngeal edema, laryngeal spasm, hematoma[*2], and catheter-related infection[*3].

*1 Items for which malignant hyperthermia is anticipated as a complication of general anesthesia

*2 Items for which epidural hematoma, or spinal subdural hematoma is anticipated as complications of epidural and spinal anesthesia.

*3 Items for which epidural abscess, or spinal subdural abscess is anticipated as complications of epidural and spinal anesthesia

2) Anticipated adverse reactions during surger

Intraoperative bleeding, thromboembolism, myocardial infarction, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular arrhythmia, cerebral ischemia, fever, hypothermia, esophageal hemorrhage, gastric hemorrhage, duodenal hemorrhage, hepatobiliary injury, spleen injury, endocrine system impairment, gastrointestinal disorders, arterial injury, venous injury, nervous system injury, other injuries/toxicities and procedural complications (peritoneum, and lymph ducts), peripheral neuropathy, and allergic reactions.

3) Anticipated adverse events early after surgery (until first hospital discharge)

① Anticipated adverse events cause by postoperative hemorrhage
Esophageal hemorrhage, gastric hemorrhage, duodenal hemorrhage, hypotension, hyperkalemia, dehydration, and hemoglobin

② Anticipated adverse events caused by postoperative pancreatitis/pancreatic fistula
Pancreatitis, pancreatic fistula*, peritoneal abscess*, disseminated intravascular coagulation. Pancreatic hemorrhage, intraperitoneal hemorrhage

③ Anticipated adverse events caused by general anesthesia
Allergic reaction, and voice abnormality

④ General anticipated adverse events early after surgery
Fatigue, fever, chills, excess sweating, hypothermia, lethargy, nausea, vomiting, loss of appetite, diarrhea, stomach pains, colitis, cholecystitis, biliary infection, salivary gland infection, inflammatory phlebitis, catheter-related infection, bladder infection, kidney infection, urinary tract infection, ileus, jejunal obstruction, ileal obstruction, large bowel obstruction, small bowel obstruction, suture failure*, gastric anastomotic leakage, gastrointestinal anastomotic leakage (leakage in the region of esophageal anastomosis, esophageal stenosis, gastric stenosis, duodenal stenosis, jejunal stenosis, ileal stenosis, colonic stenosis, other gastrointestinal disorder (dumping syndrome), biliary fistula, gastric fistula, duodenal fistula, jejunal fistula, ileal fistula, colonic fistula, pancreatic fistula, esophageal necrosis, gastric necrosis, ileal ulcer, jejunal ulcer, colonic ulcer, esophageal perforation, gastric perforation, duodenal perforation, jejunal perforation, ileal perforation, colonic perforation, pleural infection (empyema), abdominal infection, wound infection, wound complications, ascites, lymphorrhea (chylous ascites*), pleural effusion, other nervous system disorders (phrenic nerve injury), urinary retention*, pulmonary infection,

atelectasis, pneumothorax, hypoxemia, hiccups, increased aspartate aminotransferase, increased alanine aminotransferase, increased serum amylase, increased alkaline phosphatase, increased creatinine, hypernatremia, hyponatremia, hyperglycemia, hypoalbuminemia, delirium, thromboembolism, myocardial infarction, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular arrhythmia, cerebral ischemia, other gastrointestinal disorders (delayed gastric emptying), wound dehiscence, infection-related enterocolitis, abdominal infection, septicemia, depression, spleen infection, liver infection, other injuries/poisoning and procedural complications (hepatic infarction, liver abscess, splenic infarction, and splenic abscess)

4) Anticipated complications late after surgery (after the first hospital discharge)

① Anticipated complications with the surgical wound
Skin induration, wound dehiscence, wound complications, and wound infection.

② Anticipated complications in gastrectomy
Dysgeusia, constipation, diarrhea, abdominal pain, weight loss, anemia, esophagitis, esophageal stenosis, small intestinal stenosis, and colonic stenosis.

③ General anticipated complications late after surgery
Pulmonary infection, other gastrointestinal disorders (dumping syndrome), jejunal obstruction, ileal obstruction, colonic obstruction, esophageal stenosis, gastric stenosis, duodenal stenosis, jejunal stenosis, ileal stenosis, colonic stenosis, ileus, swelling of the limbs, swelling of the trunk, cholecystitis, gall bladder infection, biliary infection, anemia, osteoporosis, infection-related enterocolitis, abdominal infection, septicemia, loss of appetite, depression, splenic infection, liver infection, other injuries/poisoning and procedural complications (hepatic infarction, liver abscess, splenic infarction, splenic abscess).

Table 7.2.2 lists the incidence of complications in the JCOG 9501, 0001, 0002-DI, 0210 trials. The JCOG 9501 trial compared D2 and D3 dissection in T2b-T4 gastric cancer, the JCOG 0001 trial examined surgery performed after preoperative adjuvant chemotherapy with CPT-11 + DCCP to treat gastric cancer with bulky N2/N3, the JCOG 0002-DI trial examined surgery performed after preoperative adjuvant chemotherapy with S-1 to treat type 4 gastric cancer, and the JCOG 0210 trial examined surgery performed after preoperative adjuvant chemotherapy with S01 + CDDP to treat large type 3 and type 4 gastric cancer.

Table 7.2.2. The incidence of postoperative complications in the JCOG 9501, 0001, 0002-DI, 0210

	JCOG9501 (T2b-T4)	JCOG0001 (N3/bulky N2)	JCOG0002-DI (type 4)	JCOG0210 (large type 3/ type 4)
Suture failure	2% (11/523)	2% (1/46)	0% (0/24)	0% (0/48)
Pancreatic fistula	6% (30/523)	13% (6/46)	4% (1/24)	8% (4/48)
Peritoneal abscess	6% (29/523)	4% (2/46)	4% (1/24)	6% (3/48)
Pneumonia	3% (16/523)	4% (2/46)	0% (0/24)	4% (2/48)
Postoperative wound infection	1% (5/523)	4% (2/46)	4% (1/24)	6% (3/48)
Anastomotic stenosis	2% (11/523)	2% (1/46)	0% (0/24)	0% (0/48)
Other	11% (60/523)	13% (6/46)	25% (6/24)	10% (5/48)
Pulmonary infarction	0.4% (2/523)	0% (0/46)	0% (0/24)	0% (0/48)

7.2.3. Anticipated adverse reactions to chemotherapy

Table 7.2.3 lists data pertaining to adverse events observed in the ACTS-GC trial (randomized trial

comparing postoperative adjuvant chemotherapy with S-1 versus surgery alone), which targeted patients with stage II/III gastric cancer who had undergone D2 lymphadectomy.

Table 7.2.3. Adverse events in the ACTS-GC trial (NCI-CTC ver2.0)

	S-1 (n = 517)		Surgery alone (n = 526)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Hematotoxicities				
Leukocytes	1.2	0	0.4	0
Hemoglobin	1.2	0	0.6	0.2
PLatelets	0.2	0	0.4	0
Non-hematotoxicities				
AST	1.7	0	3.2	0.2
ALT	1.2	0	3.0	0.2
Total bilirubin	1.4	0.2	1.0	0.2
Creatinine	0	0	0.2	0.2
Gastritis	0.2	0	0	0
Loss of appetite	5.8	0.2	1.5	0.6
Nausea	3.7	-	1.1	-
Vomiting	1.2	0	1.3	0.6
Diarrhea	3.1	0	0.2	0
Rash	1.0	0	0.4	0.2
Fatigue	0.6	0	0.6	0

7.2.4. Anticipated adverse reactions to deterioration of the underlying disease

Adverse events anticipated in form of exacerbation of the underlying disease shall be described using the terminology in the CTCAE v4.0. Note that such adverse events are 'anticipated' only when an applicable form of exacerbation is observed.

1) Anticipated adverse events caused by the primary lesion or lesions from peritoneal dissemination
Loss of appetite, constipation, bloating, indigestion, nausea, gastric obstruction, gastric stenosis, gastric perforation, gastric hemorrhage, duodenal obstruction, duodenal stenosis, duodenal perforation, duodenal hemorrhage, jejunal obstruction, jejunal stenosis, jejunal perforation, jejunal hemorrhage, ileal obstruction, ileal stenosis, ileal perforation, ileal hemorrhage, colonic obstruction, colonic stenosis, colonic perforation, colonic hemorrhage, vomiting, hyponatremia, genitourinary obstruction (bladder and ureter), and kidney failure.

2) Anticipated adverse events caused by exacerbation of liver metastasis
Increased aspartate aminotransferase, increased alanine aminotransferase, increased serum bilirubin, increased alkaline phosphatase, GGT, and liver dysfunction

3) Anticipated adverse events caused by exacerbation of pulmonary metastasis
Atelectasis, respiratory failure, hypoxia, bronchial obstruction, pulmonary infection, and bronchial infection

4) Anticipated adverse events caused by exacerbation of pancreatic invasion
Pancreatitis, and increased serum amylase.

5) Anticipated adverse events caused by exacerbation of other metastatic lesions
Sharp pain, and hypercalcemia.

6) Anticipated adverse events associated with the worsening of the patient's general condition
Fatigue, weight loss, anemia, thrombopenia, hypotension, edema (face, limbs, trunk, and genitals), hypoalbuminemia, increased aspartate aminotransferase, increased alanine aminotransferase, acidosis, increased creatinine, hyperglycemia, hypoglycemia, hypernatremia, hyponatremia, hyperkalemia, hypocalelmia, disseminated intravascular coagulation, pleural effusion, respiratory failure, hypoxia, bladder infection, acute renal failure, urinary retention, ascites, and constipation.

7.3. Evaluation of adverse events/ adverse reactions

To evaluate adverse events/reactions, the JCOG Japanese translated version of the 'Common

Terminology Criteria for Adverse Events v4.02 (MedDRA 12.0/MedDRA-J 12.1 equivalent) should be consulted.

Adverse events should be graded according to the definitions of grade 0-4, whichever is closest.

Moreover, when specific treatments are listed for a particular grade, the adverse event should be graded according to those clinical requirements. For example, if pleural effusion increases the patient may refuse oxygen inhalation or thoracic cavity drainage despite being a candidate for those treatments. In such instances, grading should be based on the medical judgment of what should be done rather than what was actually done.

In the event of a treatment related death, the adverse event that caused the original NCI-CTAE is grade 5, however in the present trial, 'grade 4' and not 'grade 5' will be recorded on the CRF. Considerations on the causal relationship observed between the adverse event and the TRD should be noted in the section 'condition at the time of death' on the treatment discontinuation report and the follow-up survey. Thereafter an urgent report will be dispatched (classification of grade 5 will be determined via post-hoc investigation, including the urgent report).

For adverse events defined in '8.2. Test and evaluation items during the treatment period', the grade and the day that the grade first appeared should be noted on the appropriate CRF. For any other adverse events, only those greater than grade 3 should be noted in the free comment section on the progress report form, with the adverse event, grade, and day of grade appearance.

The grade recorded on the CRF should also be recorded on the medical chart for verification in the event of a site-visit audit.

8. Evaluation items, laboratory testing and evaluation schedule

8.1. Evaluation items prior to enrollment

8.1.1. Tests performed prior to enrollment (irrespective of the time so long as it is performed prior to enrollment)

HBs antigen, HBs antibody*, HBc antibody*, HCV antibody

* When HBs antibodies, and/or HBc antibodies are positive, HBV-DNA shall also be measured prior to the start of treatment (see 6.4.1).

8.1.2. Tests conducted within 56 days prior to enrollment

1) Height and weight
2) Tumor markers: CEA, CA19-9
3) Histopathological examination of the endoscopic biopsy from the primary lesion (tests conducted at a different hospital are allowed).
4) HER2 test (IHC score (0/1+/2+/3+), FISH (positive/negative), HER2/17cen（CEP17) ratio*)
   * Measured only if IHC score is 2+.
5) Chest X-P (frontal view): lung window
6) Resting 12-lead electrocardiogram
7) Respiratory function test: FEV1.0%, %VC

8.1.3. Tests conducted within 28 days prior to enrollment

1) Chest contrast-enhanced CT (slice thickness ≤ 5 mm)※1
2) Upper abdominal/ pelvic contrast-enhanced CT (slice thickness ≤ 5 mm)※1
3) Upper gastrointestinal endoscopy
4) Laparoscopy or bypass surgery with intraperitoneal examination
5) Echocardiography

   * 1 In the event of an allergy to the contrast medium, renal dysfunction, or asthma, plain CT is allowed.

8.1.4. Tests conducted within 14 days prior to enrollment

1) Physical status: PS (ECOG)
2) Peripheral blood count: leukocytes, neutrophils (ANC: band cells + segmented cells), hemoglobin, and platelets.
3) Blood biochemistry: albumin, total bilirubin, AST, ALT, creatinine, sodium, potassium, and fasting blood sugar (FBS).
4) Ccr: 24 hour Ccr (not corrected for BSA) and estimated Ccr value calculated using the Cockcroft-Gault equation. However, if the estimated value is less than 60 mL/min, the 24 hour Ccr (not corrected for BSA) shall be measured using urine.

8.2. Evaluation items and tests during the treatment period

The minimum frequency for safety endpoint evaluations are listed below. It shall not be forbidden to perform these tests more frequently at the discretion of the attending physician. However, conducting more frequent evaluations of efficacy endpoints may often cause a bias in the evaluation of efficacy, and therefore except for in the case of suspected exacerbation, evaluations shall be performed at the stipulated frequency.

8.2.1. Evaluation of safety endpoints during preoperative chemotherapy (CTCAE v4.0-JCOG)

1) Safety endpoints evaluated once a week in the 1st cycle

Tests will be performed prior to the start of the 1st cycle (the previous day or actual day). For the 1st cycle, tests shall be required on day 8 and day 15.

i) Peripheral blood count: leukocytes, neutrophils (ANC: band cells + segmented cells), hemoglobin,

and platelets.

ii) Blood biochemistry: total bilirubin, AST, ALT, creatinine, sodium, potassium, calcium, ALP, and γGTP.

iii) Subjective and objective symptoms (CTCAEv4.0-JCOG)

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

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

2) Safety endpoints evaluated in the 2nd and subsequent cycles

Tests shall be performed prior to the start of each cycle (the previous day or actual day) in the 2nd and subsequent cycles. Additional tests shall be performed during the cycles as required.

i) Peripheral blood count: leukocytes, neutrophils (ANC: band cells + segmented cells), hemoglobin, and platelets.

ii) Blood biochemistry: total bilirubin, AST, ALT, creatinine, sodium, potassium, ALP, and γGTP.

iii) Subjective and objective symptoms (CTCAEv4.0-JCOG)

- Systemic disorder and administration site conditions: fatigue, fever
- General/systemic disorders and administration site conditions: infusion-related reactions
- Cardiac disorders: heart failure
- Gastrointestinal disorders: constipation, diarrhea, nausea, oral mucositis, and vomiting
- Nervous system disorders: peripheral motor neuropathy and peripheral sensory neuropathy
- Skin and subcutaneous tissue disorder: alopecia, skin hyperpigmentation, palmar/plantar erythrodysesthesia syndrome, and maculopapular rash.
- Metabolic and nutritional disorders: loss of appetite
- Ophthalmopathy: lacrimation
- Blood and lymphatic disorders: febrile neutropenia
- Infection: upper respiratory infection, pulmonary infection, urinary tract infection, and other infections.
- Other grade 3 or higher non-hematological toxicities

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

3) Safety endpoints evaluated after completion of 3 cycles and prior to surgery

The following tests shall be performed by days 7 and 14 after the last day of S-1 treatment (the final day of treatment shall be counted as day 0) of the 3rd cycle

i) Echocardiography, electrocardiography (group B only)

8.2.2. Efficacy endpoints evaluated during preoperative chemotherapy

The following tests shall be performed during the period from the day of completion of the 1st cycle of S-1 therapy until the start of the next cycle, and by days 7 and 14 after the day of completion of the 3rd cycle of S-1 therapy (given that the final day of treatment is counted as day 0).

In the event that a 4th cycle is administered, the following tests shall be performed by days 7 and 14 after the day of completion of the 4th cycle of S-1 therapy (given that the final day of treatment is counted as day 0).

In the event that preoperative chemotherapy is terminated in the 1st or 2nd cycle, the outcomes shall be assessed in accordance with 8.2.2.2).

Overall outcomes shall be evaluated only after completion of 3 cycles in accordance with "11.1. Determination of outcomes."

The same CT slice thickness used for evaluations prior to enrollment shall be used when evaluating efficacy.

1) Tests performed between the day of completion of the 1st cycle of S-1 and the day of the start of the 2nd cycle
   - i) Upper abdominal and pelvic contrast-enhanced CT*
   - ii) Tumor markers: CEA, CA19-9
   - iii) Plain chest X-P
2) Tests performed by days 7 and 14 after the day of completion of the 3rd cycle of S-1 (given that the final day of treatment is counted as day 0)
   - i) Upper abdominal and pelvic contrast-enhanced CT*
   - ii) Tumor markers: CEA, CA19-9
   - iii) Plain chest X-P
3) (If a 4th cycle is given) Tests performed by days 7 and 14 after the day of completion of the 4th cycle of S-1 (given that the final day of treatment is counted as day 0)
   - i) Upper abdominal and pelvic contrast-enhanced CT*
   - ii) Tumor markers: CEA, CA19-9
   - iii) Plain chest X-P

   * In the event of an allergy to the contrast medium, renal dysfunction, or asthma, plain CT shall be allowed.

8.2.3. Safety endpoints evaluated prior to surgery

Tests performed within 14 days prior to surgery.

- i) Peripheral blood count: leukocytes, neutrophils (ANC: band cells + segmented cells), hemoglobin, and platelets.
- ii) Blood biochemistry: albumin, total bilirubin, AST, ALT, BUN, creatinine, sodium, and potassium.
- iii) Subjective and objective symptoms: fatigue, diarrhea, pneumonitis.

8.2.4. Surgical evaluation items

1) Day of surgery, surgical time, amount of blood loss (from opening to closure), and presence or absence of homologous transfusion (from the time laparotomy until the following morning).
2) Surgical procedure, organs concurrently resected, presence or absence of thoracotomy, degree of lymph node dissection, and reconstruction method.
3) Macroscopic type and tumor diameter
4) Primary site of tumor and site of tumor
5) Surgical findings: invasion depth, lymph node metastasis, hepatic metastasis, peritoneal dissemination, peritoneal cytology, distal metastasis, proximal resection stump, distal resection stump, degree of post-surgical residual cancer, and surgical stage.
6) Presence or absence of dissection of each lymph node
7) Intraoperative complications of grade 3 or above (CTCAE v4.0-JCOG): from abdominal incision to

closure. The decision made by the attending physician regarding the causal relationship with treatment shall also be reported.

- Acute coronary syndrome, thromboembolism, intraoperative damage to the hepatobiliary system (pancreas, common bile duct, portal vein), intraoperative arterial injury, intraoperative venous injury, intraoperative gastrointestinal disorders (esophagus, duodenum, jejunum, ileum, colon), and intraoperative splenic injury.
- Intraoperative complications of grade 3 or above aside from those listed above.

8.2.5. Evaluation items for the postoperative period of hospitalization

1) Day of postoperative initial discharge of patient
2) AMY level in drainage fluid on the third postoperative day (only for cases with indwelling drains) , presence or absence of postoperative hemorrhage
3) Presence or absence of repeat surgery
4) Histopathological findings
   Histological type, invasion depth, lymph node metastasis, hepatic metastasis, peritoneal dissemination, distant metastasis, peritoneal lavage cytology, lymphatic invasion, vascular invasion, proximal stump, distal stump, degree of residual tumor, pathological stage, presence or absence of metastasis in each lymph node, and histological therapeutic effect.
5) Early stage postoperative complications: from completion of the procedure until postoperative initial discharge of the patient. The decision made by the attending physical regarding the causal relationship of surgery with treatment shall also be reported. Grading shall be performed by both CTCAE v4.0-JCOG and the Clavien-Dindo classification (see table 8.2.5).

Table8.2.5. Early-stage postoperative complications – JCOG classification of postoperative complications (Clavien-Dindo classification) v2.0

Evaluation item	**CTCAE v4.0–JCOG**	**Clavien-Dindo classification**
Pancreatic fistula	Pancreatic fistula	Pancreatic fistula
Postoperative hemorrhage	Postoperative hemorrhage	Postoperative hemorrhage
Peritoneal abscess	Abdominal infection	Peritoneal abscess
Gastrointestinal suture failure	Gastrointestinal anastomotic leak*1	Gastrointestinal suture failure
Gastrointestinal anastomotic stenosis	Injury, poisoning, and procedural complications-other (anastomotic stenosis)	Gastrointestinal anastomotic stenosis
Cholecystitis	Cholecystitis	Cholecystitis
Dumping syndrome	Gastrointestinal disorder-other (dumping syndrome)	Dumping syndrome
Delayed gastric emptying	Gastrointestinal disorder-other (delayed gastric emptying)	Delayed gastric emptying
Reflux esophagitis	Gastroesophageal reflux disease	Reflux esophagitis
Occlusive ileus	Small intestinal obstruction	Occlusive ileus
Paralytic ileus	Ileus	Paralytic ileus
Thrombosis/embolism	Thromboembolism	Thrombosis/embolism
Postoperative pneumonia	Lung infection	Postoperative pneumonia
Postoperative pleural effusion	Pleural effusion	Postoperative pleural effusion
Chylous ascites	Gastrointestinal disorders- other (chylous ascites)	Chylous ascites
Postoperative wound infection	Wound infection	Postoperative wound infection
Wound dehiscence	Wound dehiscence	Wound dehiscence
	Other non-hematotixicities of grade 3 or above*2	

*1 In the present trial, anastomotic leakage shall be graded as a "gastrointestinal anastomotic leak" regardless of the site.

*2 Non-hematotoxicities refers to adverse events listed in the CTCAE v4.0, except for the following:
"anemia," "hypocellular marrow," "lymphopenia," "neutropenia," "leukopenia," "thrombopenia," and "CD4 lymphopenia."

8.2.6. Evaluation items examined prior to the start of postoperative adjuvant chemotherapy (only in patients who received postoperative adjuvant chemotherapy)

1) Weight
2) PS (ECOG)
3) Peripheral blood count: leukocytes, neutrophils, hemoglobin, and platelets
4) Blood biochemistry: albumin, total bilirubin, AST, ALT, creatinine, sodium, and potassium
5) Creatinine clearance (estimated values or measured values)

8.2.7. Safety endpoints evaluated during postoperative adjuvant chemotherapy (only in patients who received postoperative adjuvant chemotherapy)

During postoperative adjuvant chemotherapy, the items listed below shall be evaluated within 7 days prior to the start of each cycle. Items 2)- 4) below shall be measured once every 2 weeks until completion of the 1st cycle, once every 3 weeks from the 2nd cycle until completion of the protocol-based treatment. However, in the event that two or more cycles are continued as 4 week administration and 2 week rest without falling under the criteria for skips or dosage reduction (dosage can be reduced), and without changing the treatment schedule to a 2 week administration and 1 week rest period, then in subsequent cycles the evaluations may be conducted once or more every 6 weeks.

1) Physical status: PS (ECOG)
2) Peripheral blood count: leukocytes, neutrophils, hemoglobin, and platelets
3) Blood biochemistry: albumin, total bilirubin, AST, ALT, creatinine, sodium, and potassium
4) Subjective and objective symptoms (CTCAE v4.0-JCOG): If grade 1 or above, the decision made by the attending physician regarding the causal relationship with treatment shall also be reported.
   - Systemic disorder and administration site conditions: fever and fatigue
   - Gastrointestinal disorders: abdominal pain, diarrhea, nausea, vomiting, and oral mucositis
   - Skin and subcutaneous tissue disorder: alopecia, skin hyperpigmentation, palmar/plantar erythrodysesthesia syndrome, and maculopapular rash
   - Metabolic and nutritional disorders: loss of appetite
   - Ophthalmopathy: lacrimation
   - Blood and lymphatic disorders: febrile neutropenia
   - Other grade 3 or higher adverse events (non-hematological toxicities*)
     * Non-hematological toxicities indicate adverse events other than those listed below in the CTCAE v4.0-JCOG: "anemia," "hypocellular bone marrow," "lymphopenia," "neutropenia," "leukopenia," "thrombopenia," and "CD4 lymphopenia."

8.3. Tests and evaluation items after completion of treatment

After completion of the protocol-based treatment, or termination of the protocol-based treatment (in accordance with 6.2.3.), the following tests shall be performed regularly to evaluate the presence or absence of recurrence.

Furthermore, the items listed below include some tests conducted during the protocol-based treatment, such as tests performed immediately after surgery and those during postoperative adjuvant chemotherapy.

* In the event that recurrence occurs, patient's physical status (PS) at the time of recurrence shall be recorded.

8.3.1. Evaluation of safety endpoints after completion of surgery and after completion of the

protocol-based treatment

Performed every 6 months to 5 years after the initial postoperative discharge

1) Late stage postoperative complications: The causal relationship with treatment as determined by the attending physician will be reported. Grading will be performed according to the CTCAE v4.0-JCOG and Clavien-Dindo classification systems (refer to table 8.3.1.).

Table 8.3.1. Late stage postoperative complications – JCOG classification of postoperative complications (Clavien-Dindo classification) v2.00

Evaluation item	**CTCAE v4.0–JCOG**	**Clavien-Dindo 分類**
Peritoneal abscess	Abdominal infection	Peritoneal abscess
Gastrointestinal anastomotic stenosis	Injury, poisoning and procedural complications-other (anastomotic stenosis)	Gastrointestinal anastomotic stenosis
Cholecystitis	Cholecystitis	Cholecystitis
Dumping syndrome	Gastrointestinal disorder-other (dumping syndrome)	Dumping syndrome
Reflux esophagitis	Gastroesophageal reflux disease	Reflux esophagitis
Occlusive ileus	Small intestinal obstruction	Occlusive ileus
Paralytic ileus	Ileus	Paralytic ileus
Postoperative pneumonia	Lung infection	Postoperative pneumonia
Postoperative wound infection	Wound infection	Postoperative wound infection
Abdominal wall hernia	Wound dehiscence	Abdominal wall hernia
	Other non-hematotixicities of grade 3 or above[*1]	

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

Once every 3 months for 3 years following surgery and once every 6 months for the subsequent 2 years.

1) Physical status: weight and PS (ECOG)
2) Peripheral blood count: leukocytes, neutrophils (ANC: band cells + segmented cells), hemoglobin, and platelets
3) Blood biochemistry: albumin, total bilirubin, AST, ALT, creatinine, sodium, and potassium

8.3.2. Evaluation of efficacy after completion of surgery and after completion of the protocol-based treatment

To evaluate the presence or absence of recurrence the tests listed below shall be conducted regularly for 5 years after enrollment counted from the actual day of enrollment.

After 5 years and more have passed since the enrollment, physical findings shall be evaluated once a year for the presence or absence of recurrence. If recurrence is suspected, it shall be evaluated by blood tests and imaging.

Once every 3 months for 3 years following surgery, and once every 6 months for the subsequent 2 years.

1) Tumor markers: CEA, CA19-9

Once every 6 months for 3 years following surgery, and once a year for the subsequent 2 years.

1) Upper abdominal and pelvic contrast-enhanced CT (if contrast-enhanced CT cannot be performed due to an allergy to the contrast medium, plain CT is allowed)

Note: The same CT slice thickness used for evaluations prior to enrolment shall be used when evaluating efficacy.

Performed every year from the day of surgery until 5 years after surgery

1) Plain chest X-P
2) Upper gastrointestinal endoscopy: only in the event of distal gastrectomy

8.4. Study calendar

Group A

	Prior to enrollment	During preoperative chemotherapy													Prior to surgery	Early stage after surgery	During postoperative adjuvant chemotherapy		Follow-up period	
Cycle		1			2			3				4					1	2-8	<5 years	>5 years
Week		1	2	3	4	5	6	7	8	9	10	11	12	13						
Physical status																				
Physical findings	○	●	●	●	●	△	△	●	△	△		●	△	△			▲	▼	①	
Height, weight	○[56]																○		①	
PS	○[14]															○			①	
Laboratory testing																				
Peripheral blood count	○[14]	●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼	①	◇
Biochemistry	○[14]	●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼		◇
CEA, CA19-9	○[56]			○							○				○[4]				①	◇
HBs antigen, HBs antibodies, HBc antibodies, HCV antibodies	○[iii]																			
Radiographic examination																				
Upper abdominal/pelvic contrast-enhanced CT	○[28]			○							○				○[4]				②	
Contrast-enhanced chest CT	○[28]																			◇
Chest X-P	○[56]			○							○				○[4]					
Upper gastrointestinal endoscopy	○[56]																			
HER2 measurement	○[56]																			
Respiratory function test	○[56]																			
Echocardiography	○[28]																			
12-lead electrocardiography	○[56]																			
Toxicity evaluation																				
Subjective symptom check		●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼	①	
Objective symptom check		●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼		
CRF submission																				
Pretreatment report form		□																		
Preoperative chemotherapy course report				□			□			□				□						
Preoperative chemotherapy completion report form															□					
Therapeutic outcomes report															□					

form																			
Preoperative report form															□				
Surgical findings report form															□				
Postoperative findings report form															□				
Pathological findings report form															□				
Postoperative chemotherapy course report																□	□		
Postoperative chemotherapy completion report																	□		
Follow-up survey form *																		□twice/year	

$\circ^{pre-}$: conducted before enrollment, $\circ^{56}$: conducted within 56 days prior to enrollment, $\circ^{28}$: conducted within 28 days prior to enrollment, $\circ^{14}$: conducted within 14 days prior to enrollment, $\circ^{4}$conducted only upon administration of a 4th cycle, ○ : conducted, △ : conducted as required, ● : conducted once or more a week, ▲ : conducted once or more every 2 weeks, ▼ : conducted once or more every 3 weeks (however, can be conducted once or more every 6 weeks if 2 or more consecutive cycles have been administered for 4 weeks with 2 week rest, ◇ : conducted as required upon suspicion of recurrence, □ : submission

[1]: once every 3 months for 3 years following surgery, and once every 6 months for the subsequent 2 years, [2]: once every 6 months for 3 years following surgery, and once a year for the subsequent 2 years, [3]: once a year, [4]: once a year only in the event of distal gastrectomy

* The follow-up survey shall be sent within 5 years after completion of enrollment, therefore these forms shall be submitted for each patient in accordance with the deadline even more than 5 years after enrollment.

Group B

	Prior to enrollment	During preoperative chemotherapy													Prior to surgery	Early stage after surgery	During postoperative adjuvant chemotherapy		Follow-up period	
Cycle		1			2			3				4					1	2-8	< 5 years	> 5 years
Week		1	2	3	4	5	6	7	8	9	10	11	12	13						
Physical status																				
Physical findings	○	●	●	●	●	△	△	●	△	△		●	△	△			▲	▼	①	
Height, weight	○[56]																○		①	
PS	○[14]															○			①	
Laboratory testing																				
Peripheral blood count	○[14]	●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼	①	◇
Biochemistry	○[14]	●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼		◇
CEA, CA19-9	○[56]			○							○				○[4]				①	◇
HBs antigen, HBs antibodies, HBc antibodies, HCV antibodies	○[iii]																			
Radiographic examination																				
Upper abdominal/pelvic contrast-enhanced CT	○[28]			○							○				○[4]				②	
Contrast-enhanced chest CT	○[28]																			◇
Chest X-P	○[56]			○							○				○[4]					
Upper gastrointestinal endoscopy	○[56]																			
HER2 measurement	○[56]																			
Respiratory function test	○[56]																			
Echocardiography	○[28]										○									
12-lead electrocardiography	○[56]										○									
Toxicity evaluation																				
Subjective symptom check		●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼	①	
Objective symptom check		●	●	●	●	△	△	●	△	△		●	△	△	○	○	▲	▼		
CRF submission																				
Pretreatment report form		□																		
Preoperative chemotherapy course report				□			□			□				□						
Preoperative chemotherapy completion report form															□					
Therapeutic outcomes report															□					

form																			
Preoperative report form															□				
Surgical findings report form															□				
Postoperative findings report form															□				
Pathological findings report form															□				
Postoperative chemotherapy course data																□	□		
Postoperative chemotherapy completion report																	□		
Follow-up survey form *																		□ twice/year	

$\circ^{pre-}$: conducted before enrollment, $\circ^{56}$: conducted within 56 days prior to enrollment, $\circ^{28}$: conducted within 28 days prior to enrollment, $\circ^{14}$: conducted within 14 days prior to enrollment, $\circ^{4}$conducted only upon administration of a 4th cycle, ○ : conducted, △ : conducted as required, ● : conducted once or more a week, ▲ : conducted once or more every 2 weeks, ▼ : conducted once or more every 3 weeks (however, can be conducted once or more every 6 weeks if 2 or more consecutive cycles have been administered for 4 weeks with 2 week rest, ◇ : conducted as required upon suspicion of recurrence, □ : submission

[1]: once every 3 months for 3 years following surgery, and once every 6 months for the subsequent 2 years, [2]: once every 6 months for 3 years following surgery, and once a year for the subsequent 2 years, [3]: once a year, [4]: once a year only in the event of distal gastrectomy

* The follow-up survey shall be sent within 5 years after completion of enrollment, therefore these forms shall be submitted for each patient in accordance with the deadline even more than 5 years after enrollment.

9. Data collection

9.1. Case Report Form (CRF)

9.1.1. Types of CRF and submission deadlines

Case Report Form (CRF) and deadlines used in the present trial are as follows.

1) Pretreatment report (blue) — Submit within 2 weeks of enrollment
2) Preoperative chemotherapy progress report (yellow) —Submit within 2 weeks after termination/ completion of protocol-based treatment
3) Tumor shrinkage report (green) — Submit within 2 weeks of determination of therapeutic outcomes
4) Preoperative chemotherapy completion report (red) — Submit within 2 weeks of completion/ termination of preoperative chemotherapy
5) Preoperative report (green) —Submit within 2 weeks of surgery
6) Surgical findings report (green) —Submit within 2 weeks of surgery
7) Postoperative findings report (green) —Submit within 2 weeks of surgery
8) Pathological findings report (green) — Submit within 2 weeks after determination of pathological diagnosis
9) Postoperative adjuvant chemotherapy course report (yellow) —Submit within 2 weeks after termination/ completion of protocol-based treatment (only for patients who receive postoperative adjuvant chemotherapy)
10) Overall treatment completion report (red) —Submit within 2 weeks after termination/

completion of protocol-based treatment

11) Follow-up survey (white) survey form — Submit by the deadline noted on the follow-up

- CRFs from "pretreatment report" to the "overall treatment completion report" (1-10 above) shall be mailed from the Data Center preprinted with the patient's basic information (registration number, facility name, etc.) after enrollment. If the forms are not received after 1 week of enrollment or if the CRFs are lost or destroyed, a request shall be made to ask the Data Center to reissue of the CRFs.
- The "follow-up survey" (11 above) shall be mailed from the Data Center during the monitoring period, or follow-up survey conducted in conjunction with the interim/final analyses by the Data Center.

9.1.2. CRF archiving

- When paper CRF forms are used, a copy or electronic scan is to be made of all filled out CRFs, and kept by the institution
  The CRF copy will be referred to when filling out other CRFs, or referred to when responding to inquiries from the Data Center, and therefore shall be kept until issuance of the final analysis report.
- In the event of using EDC (Electronic Data Capturing), the content of the CRF can be verified on the EDC screen at the institution, and therefore the institution does not need to output the paper CRF to keep it.

9.1.3. CRF submission

- All CRFs shall be mailed to the Data Center or delivered in person. **CRFs cannot be submitted by FAX.**
- To avoid potential disclosure of patient identity, when contacting the Data Center for CRF submission, etc., the patient registration number shall be used, but **not the facility's medical chart number.**

9.1.4. CRF corrections

After the trial has started, if the CRF is incomplete, i.e., missing required data or incorrect category classification, etc. are found, it may be corrected by mutual agreement of the Data Center Director and the study secretariat, so long as it is determined that the correction does not exceed the range of collected data stipulated in section "8. Evaluation items, laboratory tests and evaluation schedule," and the correction will cause no further medical or financial burden to the patient. For CRF corrections that do not require protocol revision, the JCOG shall not revise the protocol. Submission of a report on CRF corrections or revision application to the director of the medical facility shall follow the regulations of the institution.

10. Adverse event reporting (compatible with the Advanced Medical care B Program)

In accordance with the guidelines set forth in this chapter based on the "JCOG guidelines for clinical safety data management," and the partially revised "guidelines established by the Minister of Health, Labour and Welfare regarding precautions for the implementation of advanced medical care in accordance with institution standards, and the handling of reports in relation to advanced medical care" (Health Bureau notification No. 1129-25, Pharmaceuticals and Food Safety Bureau notification No. 1129-1, Health Insurance Bureau notification No.1129-2, November 29, 2013) (advanced medical care notification hereafter), any "adverse events with mandatory reporting" shall be reported by the principal investigator of the institution to the study secretariat/principal investigater of the present study. In the event that the study secretariat/principal investigater of the present study determines that the adverse event reported by the principal investigator of the institution falls under "10.1 Adverse events that require reporting," the event shall be reported to the director of the relevant Regional Bureau (branch) of Health and Welfare, and to the director of the Health Bureau of the Ministry of Health, Labour and Welfare[*1]. The details of the report will be reported to the Minister of Health, Labour and Welfare by the director of the relevant Regional Bureau (branch) of Health and Welfare.

The latest report forms can be obtained via the JCOG home page (http://www.jcog.jp/), and therefore the latest version of the "severe adverse events (SAE) report" shall be used when reporting.

Furthermore, reports on adverse events shall be appropriately made to the Ministry of Health, Labour and Welfare in accordance with the Pharmaceutical and Medical Devices Law, which ensures the quality, efficacy and safety of pharmaceuticals and medical devices (addressed to the Pharmaceutical and Medical Devices Agency, First Safety Information Division, FAX : 0120-395-390 、 E-mail : anzensei-hokoku@pmda.go.jp, forms at http://www.info.pmda.go.jp/info/houkoku.html), and reports on severe adverse events based on the ethical guidelines on clinical research (public notice 415; the Ministry of Health, Labour and Welfare, 2008, http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html) shall be made to the director of each institution, reports regarding unexpected severe adverse events are to be submitted by the director of the medical institution to the Ministry of Health Labour and Welfare, and reports on adverse event shall be made by institutions to manufacturers and distributors. The principal investigator of each facility shall responsively report in accordance with the regulations of each medical facility.

10.1. Adverse events with mandatory reporting

10.1.1. Adverse events that require expedited reporting

An adverse event falling under any of the criteria below requires expedited reporting.

For 1) and 2) below, expedited reporting is required of 'patient death or patients who are at risk of death' in 'sections 3-8 of the advanced medical care performance report -(3) safety report' in the advanced medical care notification, while in 3) and 4), expedited reporting is required of 'patients who require long-term hospitalization or different hospitalization for the treatment of side effects' that are "unexpected in the implementation of the protocol", 'patients who exhibit or are at risk of developing dysfunction to the extent of impairing activities of daily life', and 'patients who might be exposed to risks'.

1) Death

2) Grade 4 adverse events

3)) Unexpected Grade 3/2/1 adverse events, and adverse events that require prolongation of hospitalization or hospitalization for more than 24 hours for treatment

※ 'Hospitalization and prolongation of hospitalization' refers to the hospitalization of 24 hours or more/prolongation of hospitalization that is medically required for the treatment of adverse events, and the following instances are exempt from reporting.