An open-label randomized multi-center phase III study of TAS-118 plus Oxaliplatin versus S-1 plus Cisplatin as first-line therapy in patients with advanced gastric cancer

PROTOCOL

SPONSOR : Taiho Pharmaceutical Co., Ltd.

PROTOCOL No.: [redacted]
VERSION: P05
DATE: 07 Nov 2019

CONFIDENTIAL

TABLE OF CONTENTS

TABLE OF CONTENTS **3**
ABBREVIATIONS **8**
PROTOCOL SYNOPSIS **10**
1. Study Administrative Structure **15**
1.1 Title of Protocol, Protocol Number and Date of Preparation 15
1.2 Sponsor 15
1.3 Contract Research Organization 15
2. Background Information **16**
2.1 Background of disease 16
2.2 Current standard treatment 16
2.3 Introduction of novel anti-cancer therapy 17
2.3.1 TAS-118 17
2.3.2 Clinical Studies .....
2.3.2.1 [redacted] .....
2.3.2.2 .....
2.3.2.3 .....
2.3.2.4 .....
2.4 Rationale for considering the new therapy as promising 23
3. GCP Compliance and Ethical Conduct of the Study **24**
3.1 GCP Compliance 24
3.2 Protection of Subjects' Privacy 24
3.3 Institutional Review Board/Independent Ethics Committee Approval 24
4. Study Objectives **25**
4.1 Primary objective 25
4.2 Secondary objective 25
5. Study Design **25**
5.1 Endpoints 25
5.1.1 Primary 25
5.1.2 Secondary 25
5.2 Study Type 25
5.2.1 Study Type by Objectives 25
5.2.2 Study Type by Design 25
5.3 Description of Study Design 25
5.4 Patient Numbering and Randomization 26
5.5 Blinding 26
6. Study Procedures **27**
6.1 Explanation of Study Schedule to Individual Subjects 27
6.1.1 Definition of Study Period 27
7. Study Drug **28**
7.1 Study Drug 28
7.1.1 TAS-118 28
7.1.2 S-1 29
7.2 Oxaliplatin (L-OHP) 30
7.3 Cisplatin (CDDP) 30

7.4 Packaging and Labeling of Study Drug 30
7.5 Delivery, Storage, Control, Retrieve of Study Drug 30
8. Criteria for Inclusion and Exclusion of Patients....31
8.1 Inclusion Criteria....31
8.2 Exclusion Criteria....32
8.3 Informed Consent....33
8.3.1 Procedure for obtaining informed consent....33
9. Subject Registration 34
10. Administration 35
10.1 Dose, administration schedule 35
10.1.1 Dose 35
10.1.1.1 Arm A (TAS-118/L-OHP)....35
10.1.1.2 Arm B (S-1/CDDP)....35
10.1.2 Administration schedule 37
10.1.2.1 Arm A (TAS-118/L-OHP)....37
10.1.2.2 Arm B (S-1/CDDP) [CDDP on Day 1] (Korea) 38
10.1.2.3 Arm B (S-1/CDDP) [CDDP on Day 8] (Japan)....39
10.1.3 Criteria for Modification of Treatment Schedule....41
10.1.3.1 Criteria for Dose Initiation in Each Cycle 41
10.1.3.2 Criteria for Dose Interruption and Resumption within Treatment Cycle 42
10.1.3.3 Criteria for Dose Reduction (Arm A) 43
10.1.3.4 Criteria for Dose Reduction (Arm B) 44
10.1.4 Criteria for Dose Increase 45
10.2 Medication and Treatments Prohibited during Study....45
10.2.1 Medication and Treatments Prohibited during Study 45
10.2.2 Concomitant Medications Requiring Precautions....45
10.2.3 Expected Adverse Drug Reactions and Treatment Options 45
10.3 Supportive therapy and other points to be considerd....46
10.4 Instruction to Patients for Handling Study Medication (TAS-118 or S-1)....46
11. Data Items and Schedule for Testing and Monitoring....48
11.1 Data Items and schedule for Testing and Monitoring 48
11.1.1 Collection and Submission of Images....49
11.2 Testing and Monitoring Schedule 50
11.3 Tests at Randomization or before Initiation of Study Treatment 52
11.4 Tests during Study Treatment....52
11.5 End of Treatment....54
11.6 Safety Follow-up....54
11.7 Tumor Follow-up 55
11.8 Survival Follow-up....55
12. Pharmacokinetics and Pharmacogenomics 55
13. Discontinuation of study....56
13.1 Discontinuation criteria for individual subject....56
13.1.1 Study Treatment Discontinuation Criteria 56
13.1.2 Safety Follow-up Discontinuation Criteria....56
13.1.3 Tumor Follow-up Discontinuation Criteria 56
13.1.4 Survival Follow-up Discontinuation Criteria....56

13.2 Criteria for Discontinuation of Study in Individual Institutions 57
13.3 Criteria for Termination of Entire Study 57
13.4 Post Treatment 57
14. Efficacy Assessment 58
14.1 Assessment of Antitumor Efficacy (RECIST Guideline Version 1.1) 58
14.1.1 Evaluation of lesions 58
14.1.1.1 Measurement of Lesions 58
14.1.1.2 Tumor Definitions 58
14.1.1.3 Evaluation of Response in Target Lesions 59
14.1.1.4 Evaluation of Response in Non-Target Lesions 60
14.1.2 Assessment of Overall Response 61
14.1.3 Best Overall Response Assessment 62
14.2 Overall Response Rate (ORR) 62
14.3 Disease Control Rate (DCR) 62
14.4 Progression Free Survival (PFS) 62
14.5 Time to Treatment Failure (TTF) 63
14.6 Overall Survival (OS) 63
15. Reporting Safety Information 64
15.1 Adverse Events/Serious Adverse Events 64
15.1.1 Adverse Events 64
15.1.2 Adverse Drug Reactions 65
15.1.3 Serious Adverse Events (SAE) 65
15.1.4 Disease Progression 66
15.1.5 Pregnancy 67
15.1.6 Other Information 67
15.1.7 Breaking the Study Blind 67
15.2 Laboratory Evaluations 67
15.2.1 Reporting and Evaluation of Laboratory Test Results 67
15.2.2 Repeat Testing 68
15.3 Physical Examination and Performance Status 68
15.4 Body Temperature, Blood Pressure and Body Weight 68
16. Statistical Analysis 69
16.1 Timing of Statistical analyses 69
16.1.1 Interim Analyses 69
16.1.2 Primary Evaluation 69
16.1.3 Final Evaluation 69
16.2 Populations and Criteria for Handling Patient Data 69
16.2.1 Analysis Populations 69
16.2.2 Criteria for Handling Patient Data 70
16.3 Statistical Methods 70
16.3.1 Patient Disposition, Baseline and Treatment Characteristics 71
(1) Patient Disposition 71
(2) Patient Baseline Characteristics 71
(3) Evaluation of Comparability 71
16.3.2 Primary Endpoint Analyses 71
16.3.3 Secondary Endpoints Analyses 72

16.3.3.1 Efficacy Endpoints 72
16.3.3.2 Treatment Status 72
16.3.3.3 Safety Analyses 73
16.4 Determination of Sample Size 73
17. Case Report Form 75
17.1 Preparation of CRF 75
18. Protocol Compliance, Deviation and Amendment 76
18.1 Protocol Compliance 76
18.2 Protocol Deviation 76
18.3 Revision of Protocol, etc. 76
19. Direct Access to Source Documents 78
19.1 Identification of Source Documents 78
19.2 Method of Direct Access to Source Documents 79
20. Quality Control and Quality Assurance for the Study 80
20.1 Conduct of the study 80
20.2 Quality Control of the Study 80
20.2.1 Monitoring Procedures 80
20.2.2 Curriculum Vitae 80
20.3 Sponsor's Audits and Regulatory Inspections 80
21. Archiving of Records 81
21.1 Archiving of Records 81
21.1.1 Investigator 81
21.1.2 Sponsor 81
22. Compensation to Subjects and Investigators 81
23. Confidentiality 82
24. Publication policy 82
25. Study Period 82
26. Rationales 83
26.1 Validity of the clinical study design 83
26.2 Rationale for endpoints 83
26.3 Rationale for doses 83
26.4 Rationale for administration methods 84
26.5 Rationale for inclusion criteria 85
26.6 Rationale for exclusion criteria 86
26.7 Rationale for prohibited concomitant drugs and therapies 87
26.8 Rationale for precautions for concomitant drugs and therapies 87
26.9 Rationale for contraception period 87
27. References 88

LIST OF IN-TEXT FIGURES

Figure 6.1-1 Study period 27
Figure 10.1.2.1-1 Study regimen of TAS-118/L-OHP 37
Figure 10.1.2.1-2 Study regimen of TAS-118 37
Figure 10.1.2.2-1 Study regimen of S-1/CDDP 38
Figure 10.1.2.2-2 Study regimen of S-1 (1) 38
Figure 10.1.2.2-3 Study regimen of S-1 (2) 39
Figure 10.1.2.2-4 Study regimen of S-1 (3) 39
Figure 10.1.2.3-1 Study regimen of S-1/CDDP 40
Figure 10.1.2.3-2 Study regimen of S-1 (1) 40
Figure 10.1.2.3-3 Study regimen of S-1 (2) 40
Figure 10.1.2.3-4 Study regimen of S-1 (3) 40

LIST OF IN-TEXT TABLES

Table 2.3.1-1 [redacted] .....
Table 2.3.1-2 [redacted] .....
Table 2.3.2.1-1 [redacted] .....
Table 7.1.1-1 Description of TAS-118 28
Table 7.1.2-1 Description of S-1 29
Table 10.1.1.1-1 Initial Dose of TAS-118 35
Table 10.1.1.2-1 Initial Dose of S-1 36
Table 10.1.3.1-1 Dose initiation criteria in each cycle for TAS-118 and L-OHP (Arm A) 41
Table 10.1.3.1-2 Dose initiation criteria in each cycle for S-1 and CDDP (Arm B) 41
Table 10.1.3.2-1 Dose interruption criteria within treatment cycle 42
Table 10.1.3.2-2 Dose resumption criteria within treatment cycle 42
Table 10.1.3.3-1 Dose reduction criteria for TAS-118 and L-OHP 43
Table 10.1.3.3-2 Dose reduction scheme for TAS-118 and L-OHP 43
Table 10.1.3.3-3 Reduced dose of administration for TAS-118 43
Table 10.1.3.4-1 Dose reduction criteria for S-1 and CDDP 44
Table 10.1.3.4-2 Dose reduction scheme for S-1 and CDDP 44
Table 10.1.3.4-3 Reduced dose of administration for S-1 44
Table 11.1-1 Data items for testing and monitoring 48
Table 11.2-1 A Study Schedule Arm A (TAS-118/L-OHP) 50
Table 11.2-2 A Study Schedule Arm B (S-1/CDDP) 51
Table 14.1.2-1 Time Point Response for Patients with Target (+/- Non-target) Disease . 61
Table 14.1.2-2 Time Point Response for Patients with only Non-target Disease 61
Table 16.2.1-1 Definitions of Analysis Populations 70
Table 16.4-1 Powers(%) at various situations where expected MSTs of each arm change 74

ABBREVIATIONS

Abbreviation	Definition
5,10-methylene-THF	5,10-methylene tetrahydrofolate
5-FU	5-fluoropyrimidine-2,4(1*H*, 3*H*)-dione 5-fluorouracil, fluorouracil
5-HT_3	5-hydroxytryptamine receptor subtype 3
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	as-treated
BID	bis in die; twice a day
BSA	body surface area
CA19-9	carbohydrate antigen 19-9
CDDP	(*SP* -4-2)-diamminedichloroplatinum, Cisplatin
CDHP	5-chloro-2,4-dihydroxyprimidine, Gimeracil
CEA	carcinoembryonic antigen
CI	confidence intervals
CPH	cox proportional hazards
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
CRC	clinical research coordinator
CRO	contract research organization
CRP	c-reactive protein
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DCR	disease control rate
DLT	dose limiting toxicity
DPD	dihydropyrimidine dehydrogenase
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FAS	full analysis set
FdUMP	5-fluoro-2'-deoxyuridine-5'-monophosphate
FT	5-fluoro-1-[(2*RS*)-tetrahydrofuran-2-yl] uracil, Tegafur
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	international conference on harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IWRS	interactive web response system

JCOG	Japan clinical oncology group
LDH	lactate dehydrogenase
LV	calcium folinate (*dl*-LV), Leucovorin
l-LV	levofolinate calcium
L-OHP	(*SP*-4-2)-[(1*R*, 2*R*)-Cyclohexane-1, 2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κO^1, κO^2] platinum, Oxaliplatin
MASCC	Multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
MST	median survival time
MTS	maximum tolerated schedule
NCCN	national comprehensive cancer network
NCI	national cancer institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
Oxo	monopotassium 1,2,3,4-tetrahydro-2,4- dioxo-1,3,5-triazine-6-carboxylate, oteracil potassium
PD	progressive disease
PFS	progression free survival
PS	performance status
PR	partial response
PT-INR	prothrombin time international normalized ratio
PTP	press-through package
QOL	quality of life
RD	recommended dose
RECIST	response evaluation criteria in solid tumors
RS	recommended schedule
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedures
TR	tumor response
TS	thymidylate synthase
TTF	time to treatment failure
TTP	time to progression
UFT	Tegafur･Uracil

PROTOCOL SYNOPSIS

Title of Study:	An open-label randomized multi-center phase III study of TAS-118 plus Oxaliplatin (L-OHP) versus S-1 plus Cisplatin (CDDP) as first-line therapy in patients with advanced gastric cancer
Phase:	Phase III
Study Objectives:	To compare the following endpoints for the TAS-118/L-OHP (experimental arm) with the S-1/CDDP (control arm) in patients with advanced gastric cancer: **Primary** - Overall Survival (OS) **Secondary** - Progression Free Survival (PFS) - Time to Treatment Failure (TTF) - Overall Response Rate (ORR) - Disease Control Rate (DCR) - Safety
Indication:	Advanced Gastric cancer
Inclusion Criteria:	Patients must fulfil all of the following criteria at the time of randomization in this study: (1) Histologically confirmed adenocarcinoma of the stomach or esophagogastric junction with metastatic or recurrent disease. (2) Measurable or evaluable metastatic lesion (s), according to RECIST version 1.1 detected by CT or MRI for response evaluation within 21 days prior to randomization. (3) Negative or unknown for HER2 testing. (4) No prior treatment (e.g. radiotherapy, chemotherapy, hormonal therapy) for gastric cancer. ・ Adjuvant chemotherapy is permitted if more than 180 days has elapsed between the end of adjuvant therapy and first recurrence. Adjuvant chemotherapy with platinum agent is not permitted. (5) ECOG PS of 0 to 1. (6) At least 20 years of age[*1] at the time of informed consent. (7) The following bone marrow, liver, and kidney function parameters measured within 14 days prior to randomization: 1) Neutrophil count ≥ 1500/mm^3 [*2] 2) Hemoglobin ≥ 8.0 g/dL [*2] 3) Platelet count ≥ 100000/mm^3 [*2] 4) Total bilirubin ≤ 1.5 mg/dL 5) AST, ALT levels ≤ 3 x ULN, or ≤ 5 x ULN in the presence of liver metastasis 6) ALP levels ≤ 2.5 x ULN, or ≤ 5 x ULN in the presence of liver metastasis 7) Creatinine clearance ≥ 60 mL/min [*3] (8) Life expectancy of at least 90 days after randomization. (9) Capable of oral intake. (10) Written informed consent to participate as a subject in this clinical study. [*1]: For 75 years of age or older patient, pay careful attention to manage adverse events. [*2]: If patients received blood transfusion or treatment with any blood product or hematopoietic factor such as G-CSF, it must be confirmed the data is obtained more than 14 days after the last blood transfusion or treatment.

	[*3]: A value obtained from a urine collection, if available. Otherwise an estimate by the Cockcroft-Gault formula: Estimated creatinine clearance (mL/min) = (140 - age) x Body weight (kg) / [72 x Serum creatinine (mg/dL)] For women, the obtained value is multiplied by a factor of 0.85.
Exclusion Criteria:	Patients who meet any of the following criteria at the time of randomization will be excluded from this study: (1) Serious hypersensitivity to any ingredients of S-1 or LV. (2) Treated with other investigational agents within 4 weeks before randomization. (3) Remain affected by a surgery performed before randomization. (4) Blood transfusion, treatment with blood products, or hematopoietic growth factors such as G-CSF within 2 weeks before randomization. (5) Ongoing treatment with flucytosine at the time of randomization. (6) Unmanageable Diarrhea (e.g. watery stool, difficulty in controlling bowel movements despite the medication, grade 2 or higher, 5 stools or more per day). (7) Current peripheral sensory neuropathy or paresthesia (grade 2 or higher). (8) Current or past severe lung disease (e.g. interstitial pneumonia, pulmonary fibrosis, or severe emphysema). (9) Any other active illness such as severe (e.g. grade 3 or higher) cardiac disease[*1] (e.g. myocardial infarction, angina pectoris, arrhythmia, or cardiac failure). Any of the following events within the 6 months prior to randomization: any episode of myocardial infarction or angina pectoris. (10) Diabetic patients who have poorly controlled despite the medication or severe diabetic complication. (11) Any other severe (e.g. Grade 3 or higher) complications (e.g. severe enteritis, severe stomatitis, gastrointestinal ulceration /perforation, ileus, renal failure, nephrosis syndrome, liver failure or cerebrovascular disorder). (12) Known human immunodeficiency virus (HIV) or active hepatitis. (13) Active infection, inflammatory diseases, or connective tissue disease (e.g. administration of intravenous antibiotics, fever of 38°C or higher). (14) Current use or anticipated need for continuous systemic steroid administration (oral or intravenous). (15) Active gastrointestinal bleeding (e.g. Grade 3 or higher). (16) Brain metastasis, present or suspected from clinical symptoms. (17) Extensive bone metastasis (e.g. whole pelvis, or 50% of spine). (18) Accumulation of pleural, ascitic, or pericardial fluid requiring drainage within 2 weeks prior to randomization. (19) Other concurrent active cancer (synchronous double cancer or heterochronous double cancer with a disease-free interval of 5 years or shorter, excluding lesions consistent with intraepithelial cancer, i.e., carcinoma *in situ*, or intramucosal cancer that are assessed as cured by local treatment). (20) Pregnant, breast-feeding[*2], possibly pregnant women or patients wishing to have children during the study period or a certain period (6 months) after stopping study treatment. Women of childbearing potential have to take a pregnancy test[*3]. (21) Concurrent mental disorder or psychiatric symptoms assessed as interfering with study participation. (22) Ineligible for participating in this study according to the investigator. [*1]: Patients with a cardiac pacemaker, or valve replacement are impossible to be randomized. [*2]: Women who stop breast-feeding are impossible to be randomized. [*3]: Women of childbearing potential are defined as any women who are

	premenopausal, less than 1 year after last menses, more than 1 year with no menses due to medical causes, or not permanently sterilized and so on.
Treatment Regimens:	**[Arm A (TAS-118/L-OHP)]** L-OHP will be administered intravenously at dose of 85 mg/m^2 on day 1, and TAS-118 will be administered 30-60 mg orally twice daily for 7 days (day 1 through day 7), repeated every 2 weeks. Treatment will be continued during the study period unless any of Study Treatment Discontinuation Criteria (see Section 13.1.1) is met. **[Arm B (S-1/CDDP)]** CDDP will be administered intravenously at dose of 60 mg/m^2 on day 1 (Korea) or day 8 (Japan), and S-1 will be administered 40-60 mg orally twice daily for 21 days (day 1 through day 21), repeated every 5 weeks (rest period can be shorten from 14 days to 7 days). Treatment will be continued during the study period unless any of Study Treatment Discontinuation Criteria (see Section 13.1.1) is met.
Registration	Central registration
Study drugs	TAS-118 (granules): 30 mg, 40 mg, 50 mg, 60 mg L-OHP (infusion solution): 100 mg S-1 (capsule): 20 mg, 25 mg CDDP (infusion solution): 50 mg
Allocation	Treatment assignment will be done centrally using a dynamic allocation method (minimization method) via an IWRS stratified by: - ECOG PS: (0, 1) - Measurable lesion: (Yes, No) - Country: (Japan, Korea)
Observation/ examination items and study schedule	See Tables in the following page.
Evaluation method	Evaluation of anti-tumor effects - RECIST criteria version 1.1 Evaluation of adverse events - CTCAE version 4.03
Planned Sample Size:	686 patients will be enrolled in the study using a treatment allocation of 1:1 (TAS-118/L-OHP: S-1/CDDP).
Study period	December 2014 to May 2020

Table 1 A Study Schedule Arm A (TAS-118/L-OHP)

Procedure	Pretreatment Period				Study Treatment Period		Post-treatment Follow-up Period			
					Arm A					
	within 28 days prior to randomization	within 21 days prior to randomization	within 14 days prior to randomization	within 7 days prior to Day 1 of the first treatment cycle [e]	Day 1	Before Initiation of next treatment cycle [h, i] **Day15 (Day 14 to 18)**	End of Treatment [j] **(+14 days)**	**Safety Follow-up [k] 30 days after last dose of study treatment (+14 days)**	**Tumor Follow-up Every 6 weeks (+/- 1 week)**	Survival Follow-up **Every 12 weeks (+/-2 weeks)**
TAS-118 treatment					X [f] (Day 1 - 7)					
L-OHP treatment					X [f]					
Signed ICF	X									
Patient Background	X									
Height			X							
Pregnancy Test [a]			X							
Weight			X	X	→[g]		X	X		
ECOG PS			X	X	→[g]		X	X		
Blood Pressure			X	X	→[g]		→[g]			
Body Temperature			X	X	→[g]		→[g]			
ECG			X		→[g]		→[g]			
Physical Examination			X	X		X	X	X		
Hematology			X	X		X	X	X		
Serum Chemistry [b]			X	X		X	X	X		
Urinalysis [b]			X	X		X	X	X		
Tumor Markers [c]			X	→	→	→	→	→	X	
Tumor Measurements [c]		X		→	→	→	→	→	X	
Concomitant Medications [d]	X			→	→	→	→	X		
AE/SAE Assessment [d]	X			→	→	→	→	X		
Post Treatment										X
Survival Status					→	→	→	→	→	X [l]

a. If the patient is female and of childbearing potential, a pregnancy test (serum or urine) must be done and the results must be negative at baseline.
b. Creatinine clearance is mandatory only at prior to randomization.
c. Every 6 weeks starting on the day of randomization (the data may be collected within 1 week before or after the scheduled date). Patients without progressive disease (PD) defined by RECIST version 1.1 must be followed for tumor assessment.
d. Monitor patients for any medications and untoward medical events from the time of signed ICF through the safety follow-up period.
e. These data may be collected within 7 day prior to Day 1 of the first treatment cycle. These tests may be substituted by the data obtained within 14 days prior to randomization if screening data is obtained within 7 days prior to Day 1 of the first treatment cycle.
f. Study drug administration is to be initiated within 8 days after randomization.
g. If abnormalities are indicated by other physical examination or tests, it must be performed.
h. These data may be collected 15 days after Day 1 (from Day 14 to Day 18 if not feasible on Day 15) of each treatment cycle.
i. Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date). Examination is mandatory on Day 1 or the day before starting the study treatment specified in this protocol.
j. End of treatment assessments must be completed within 14 days from the date of last dose of study drug.
k. These data may be collected 30 days after last dose of study drug or until the start of new anti-tumor therapy, whichever comes first. In cases an AE/SAE related to study drug is not resolving, the safety follow-up period will be extended.
l. Obtain survival status (alive/ dead) at scheduled 12-week time intervals from randomization until death, and at the cutoff date for second interim analysis and primary evaluation (the data may be collected within 2 weeks before or after the scheduled date).

Table 2　A Study Schedule　Arm B (S-1/CDDP)

Procedure	Pretreatment Period				Study Treatment Period				Post-treatment Follow-up Period			
					Arm B							
	within 28 days prior to randomization	within 21 days prior to randomization	within 14 days prior to randomization	within 7 days prior to Day 1 of the first treatment cycle [e]	Day 1	Day 8 [i] **(Day 6 to 15)** (Japan)	Day 15 [j] **(Day 8 to 22)**	Before Initiation of next treatment cycle [k,l] **Day36 (Day 29 to 43)**	End of Treatment [m] **(+14 days)**	**Safety Follow-up [n] 30 days after last dose of study treatment (+14 days)**	**Tumor Follow-up Every 6 weeks (+/- 1 week)**	Survival Follow-up **Every 12 weeks (+/-2 weeks)**
S-1 treatment					X [f] (Day 1 - 21)							
CDDP treatment (Korea)					X [f]							
CDDP treatment (Japan)						X [g]						
Signed ICF	X											
Patient Background	X											
Height			X									
Pregnancy Test [a]			X									
Weight			X	X	→[h]				X	X		
ECOG PS			X	X	→[h]				X	X		
Blood Pressure			X	X	→[h]				→[h]			
Body Temperature			X	X	→[h]				→[h]			
ECG			X		→[h]				→[h]			
Physical Examination			X	X		X[i]	X	X	X	X		
Hematology			X	X		X[i]	X	X	X	X		
Serum Chemistry [b]			X	X		X[i]	X	X	X	X		
Urinalysis [b]			X	X		X[i]	X	X	X	X		
Tumor Markers [c]			X	→	→	→	→	→	→	→	X	
Tumor Measurements [c]		X		→	→	→	→	→	→	→	X	
Concomitant Medications [d]	X			→	→	→	→	→	→	X		
AE/SAE Assessment [d]	X			→	→	→	→	→	→	X		
Post Treatment												X
Survival Status					→	→	→	→	→	→	→	X [o]

a. If the patient is female and of childbearing potential, a pregnancy test (serum or urine) must be done and the results must be negative at baseline.
b. Creatinine clearance is mandatory only at prior to randomization.
c. Every 6 weeks starting on the day of randomization (the data may be collected within 1 week before or after the scheduled date). Patients without PD defined by RECIST version 1.1 must be followed for tumor assessment.
d. Monitor patients for any medications and untoward medical events from the time of signed ICF through the safety follow-up period.
e. These data may be collected within 7 day prior to Day 1 of the first treatment cycle. These tests may be substituted by the data obtained within 14 days prior to randomization if screening data is obtained within 7 days prior to Day 1 of the first treatment cycle.
f. Study drug administration is to be initiated within 8 days after randomization.
g. CDDP administration shall be permitted within 2 days before and 7 days after the reference day.
h. If abnormalities are indicated by other physical examination or tests, it must be performed.
i. When administering CDDP, the examination on the day before administration or on the day of administration until the start of administration (hematology, serum chemistry, urinalysis, and physical examination) shall be mandatory.
j. These data may be collected 15 days after Day 1 (from Day 8 to Day 22 if not feasible on Day 15) of each treatment cycle. Collect this data after the data of day8 and don't put the data of day 8 together in Japan.
k. These data may be collected 36 days (from Day 29 to Day 43 if not feasible on Day 36) after Day 1 of each treatment cycle.
l. Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date). Examination is mandatory on Day 1 or the day before starting the study treatment specified in this protocol.
m. End of treatment assessments must be completed within 14 days from the date of last dose of study drug.
n. These data may be collected 30 days after last dose of study drug or until the start of new anti-tumor therapy, whichever comes first. In cases an AE/SAE related to study drug is not resolving, the safety follow-up period will be extended.
o. Obtain survival status (alive/ dead) at scheduled 12-week time intervals from randomization until death, and at the cutoff date for second interim analysis and primary evaluation (the data may be collected within 2 weeks before or after the scheduled date).

1. Study Administrative Structure

1.1 Title of Protocol, Protocol Number and Date of Preparation

Title of study: An open-label randomized multi-center phase III study of TAS-118 plus Oxaliplatin versus S-1 plus Cisplatin as first-line therapy in patients with advanced gastric cancer

Protocol number: [redacted] (Ver.P05)

Date: 07 Nov 2019

1.2 Sponsor

Company name: Taiho Pharmaceutical Co., Ltd.

Location: 1-27, Kandanishiki-cho, Chiyoda-ku, Tokyo

1.3 Contract Research Organization

Company name: ICON Clinical Research Limited

Location: South County Business Park, Leopardstown, Dublin 18, Ireland

2. Background Information

2.1 Background of disease

Gastric cancer is the third most common cancer on incidence of mortality worldwide (second common in Japan and third common in Korea)[1]. Surgical therapy is indicated for early gastric cancer. Based on the results of previously conducted clinical trials[2,3,4]which had shown the prolongation of overall survival (OS) in the chemotherapy group compared with the untreated group (Best Supportive Care: BSC), chemotherapy had been indicated for unresectable advanced, recurrent gastric cancer.

2.2 Current standard treatment

Chemotherapy for patients with unresectable, advanced/recurrent gastric cancer

For chemotherapy in patients with unresectable, advanced/recurrent gastric cancer, 5-fluorouracil (5-FU)-based combination therapy has been the most widely used. MacDonald et al. reported FAM therapy [the median survival time (MST), 5.5 months][5], a triple combination therapy with 5-FU, doxorubicin, and mitomycin C in 1980. The recommended treatment regimens vary from region to region. In the Europe, ECF [epirubicin/cisplatin (CDDP)/5-FU] therapy and EOX [epirubicin/oxaliplatin (L-OHP)/capecitabine] therapy are recommended, according to the result of the REAL2 study[6], which showed the non-inferiority of EOX therapy to ECF therapy. In the US, DCF (docetaxel/CDDP/5-FU) therapy is recommended, in accordance with the result of the V325 study[7], which showed the superiority of DCF therapy to CF (CDDP/5-FU) therapy. In regions other than Europe and the US, FP (5-FU/CDDP) therapy is recommended.

Both in Japan and Korea, the combination therapy with fluoropyrimidine antitumor agents and platinum preparations is recommended as a standard therapy. The results of the JCOG9912 study[8] (5-FU vs. CPT-11/CDDP vs. S-1) conducted in Japan showed that the OS of S-1 monotherapy was non-inferior to that of 5-FU continuous intravenous infusion, which was the standard therapy at that time. Moreover, in the SPIRITS study[9] (S-1 vs. S-1/CDDP), S-1/CDDP combination therapy showed a significant prolongation of OS compared with S-1 monotherapy. In addition, the ToGA study[10] in patients with HER2 positive gastric cancer showed a significant OS prolongation when Trastuzumab, a molecular target agent, was added to capecitabine (or 5-FU)/CDDP therapy. On the basis of these results, the Japanese Gastric Cancer Treatment Guidelines (ver. 4) (revised in May 2014)[11] recommends capecitabine (or 5-FU)/CDDP/Trastuzumab therapy for patients with HER2-positive advanced/recurrent gastric cancer and S-1/CDDP combination therapy and S-1 monotherapy for patients with HER2-negative gastric cancer who can receive oral drugs. Clinical practice guidelines for gastric cancer in Korea published in 2014[12] recommends fluoropyrimidines (5-FU, capecitabine, or S-1)/CDDP combination therapy and (5-FU or capecitabine)/L-OHP combination therapy as a treatment regimen for first-line chemotherapy.

Compared with L-OHP, CDDP requires hydration for the prevention of renal toxicity before treatment. Therefore replacement of CDDP by L-OHP requiring no hydration is under investigation.

As the REAL2 study (ECF vs. ECX vs. EOF vs. EOX)[6] demonstrated the non-inferiority of OS in the L-OHP and CDDP groups, the efficacy of CDDP is considered to be similar to that of L-OHP. To evaluate non-inferiority of S-1/CDDP therapy to S-1/L-OHP therapy, the phase III clinical study (G-SOX study[13,14]) (S-1/CDDP vs. S-1/L-OHP) was performed in Japan. This result showed that the progression free survival (PFS) of S-1/L-OHP therapy was non-inferior to that of S-1/CDDP therapy but did not show the non-inferiority of OS. Oxaliplatin has not been approved for gastric cancer yet in Japan.

2.3 Introduction of novel anti-cancer therapy

2.3.1 TAS-118

TAS-118 is an anti-cancer drug in which the components of TS-1 (S-1), i.e. tegafur (FT), gimeracil (CDHP), and oteracil potassium (Oxo), are combined with calcium folinate (*dl*-LV, hereafter LV).

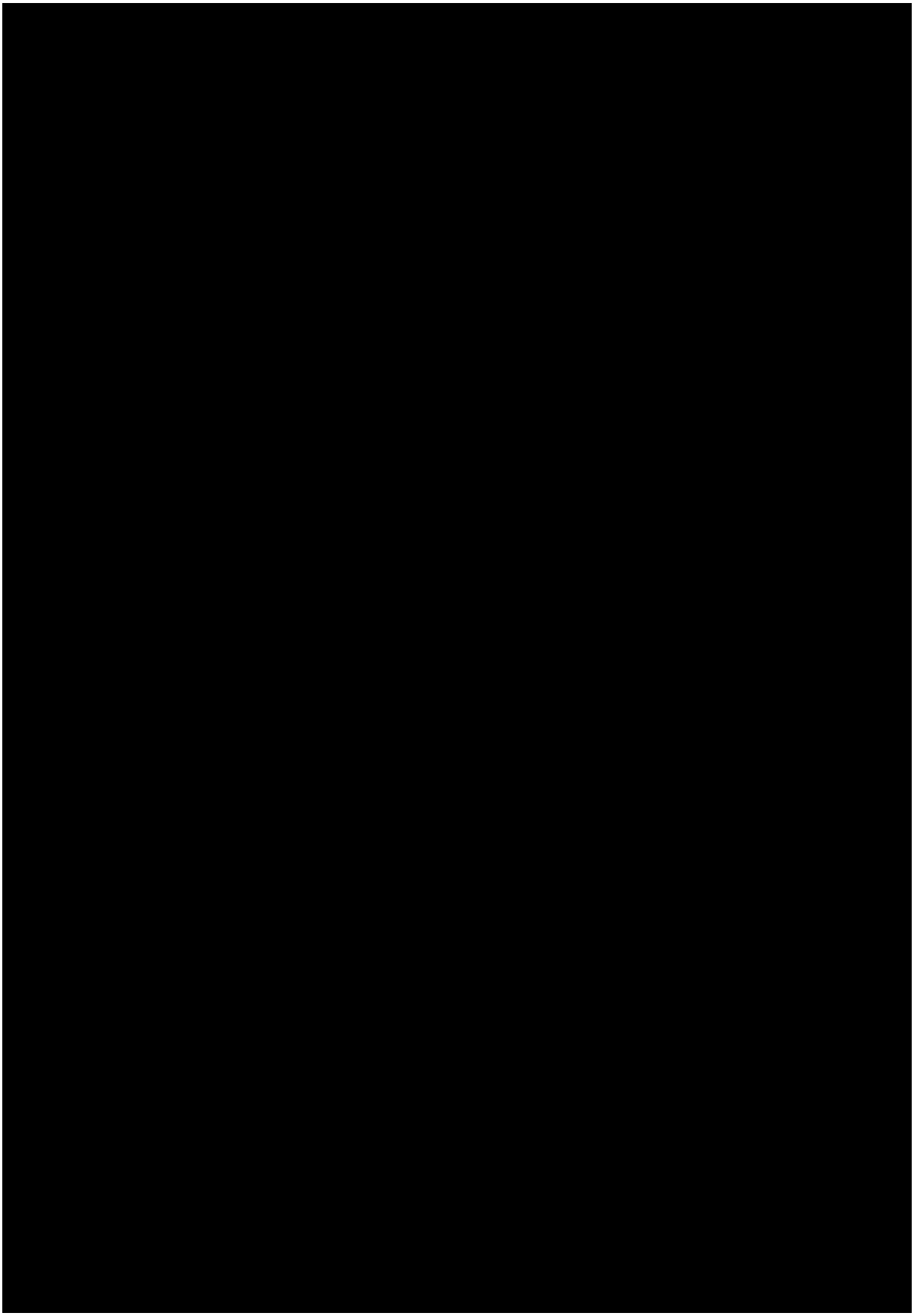
S-1 is a combination product containing FT, a prodrug of Fluorouracil (5-FU), and 2 modulators, CDHP and Oxo, in a molar ratio of 1:0.4:1. CDHP increases 5-FU concentration by reversible inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme that degrades 5-FU, while Oxo, densely distributed in gastrointestinal tissues, prevents gastrointestinal toxicity of 5-FU by inhibiting its local activation.

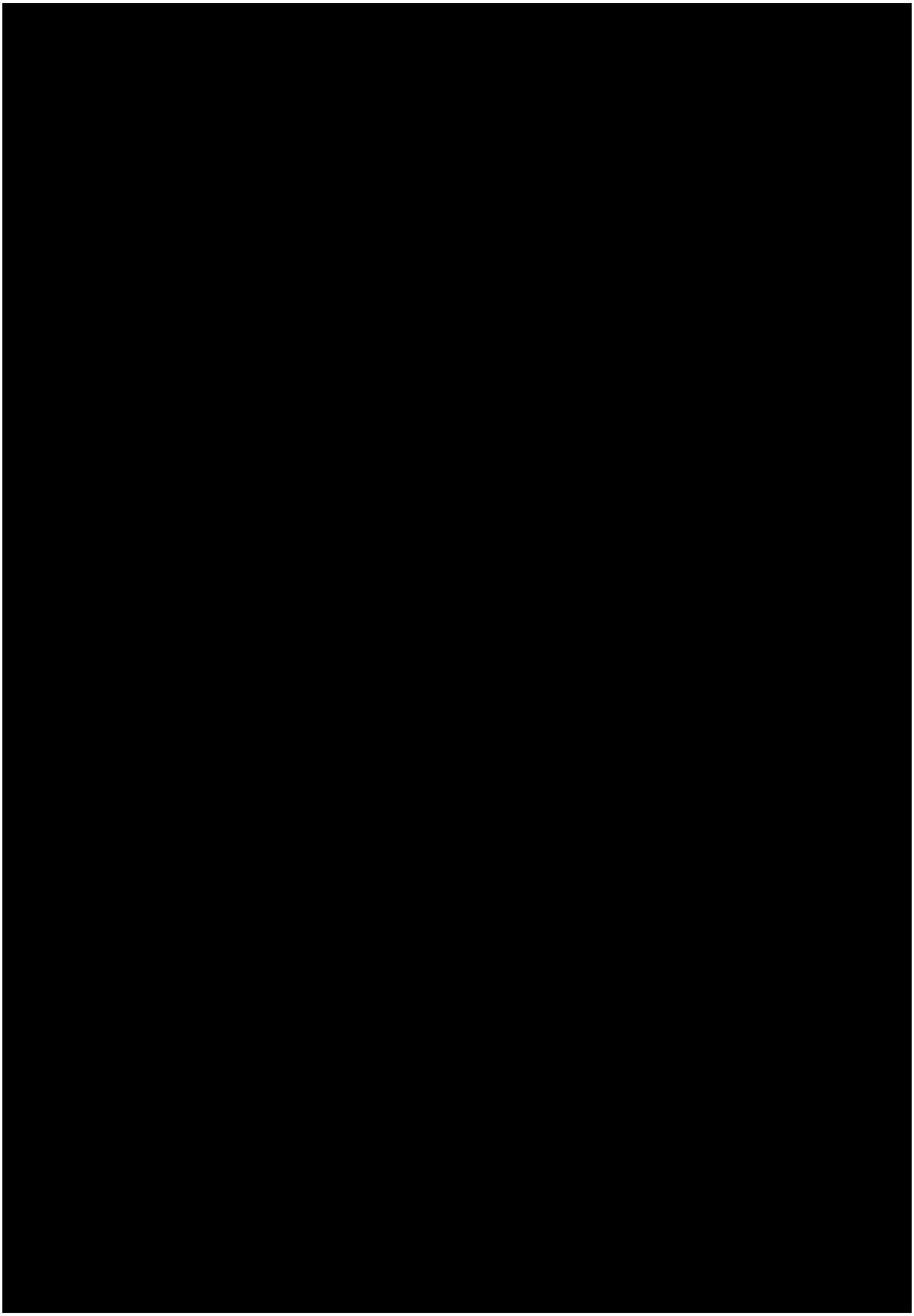
S-1 is an oral anticancer treatment, which has been developed by combining the three components to enhance therapeutic efficacy in comparison with conventional 5-FU products and also to reverse the resulting increase in adverse drug reactions. In Japan, the initial marketing authorization was granted in 1999 for S-1 capsules as a treatment for gastric cancer. Thereafter the indications have been extended to include head and neck cancer, colorectal cancer, non-small-cell lung cancer, unresectable or recurrent breast cancer, pancreatic cancer, and biliary tract cancer. In addition, fast-dissolving granules and orally disintegrating tablets were developed as an additional dosage form to provide a new option to diverse patients. S-1 is approved in Korea for the treatment of gastric cancer and head and neck cancer, in China for the treatment of advanced gastric cancer, in Singapore for postoperative adjuvant chemotherapy for locally advanced gastric cancer, in Taiwan for the treatment of gastric cancer and locally advanced or metastatic pancreatic cancer, in Hong Kong for postoperative adjuvant chemotherapy for locally advanced gastric cancer, in Thailand for treatment of advanced gastric cancer in adult by combination use with CDDP and use as monotherapy for adjuvant treatment for locally advanced gastric cancer, and in Malaysia for the treatment of advanced gastric cancer when given in combination with CDDP and postoperative adjuvant chemotherapy for locally advanced gastric cancer. In the EU, Norway, Iceland and Liechtenstein, S-1 has been approved in adults for the treatment of advanced gastric cancer when given in combination with CDDP.

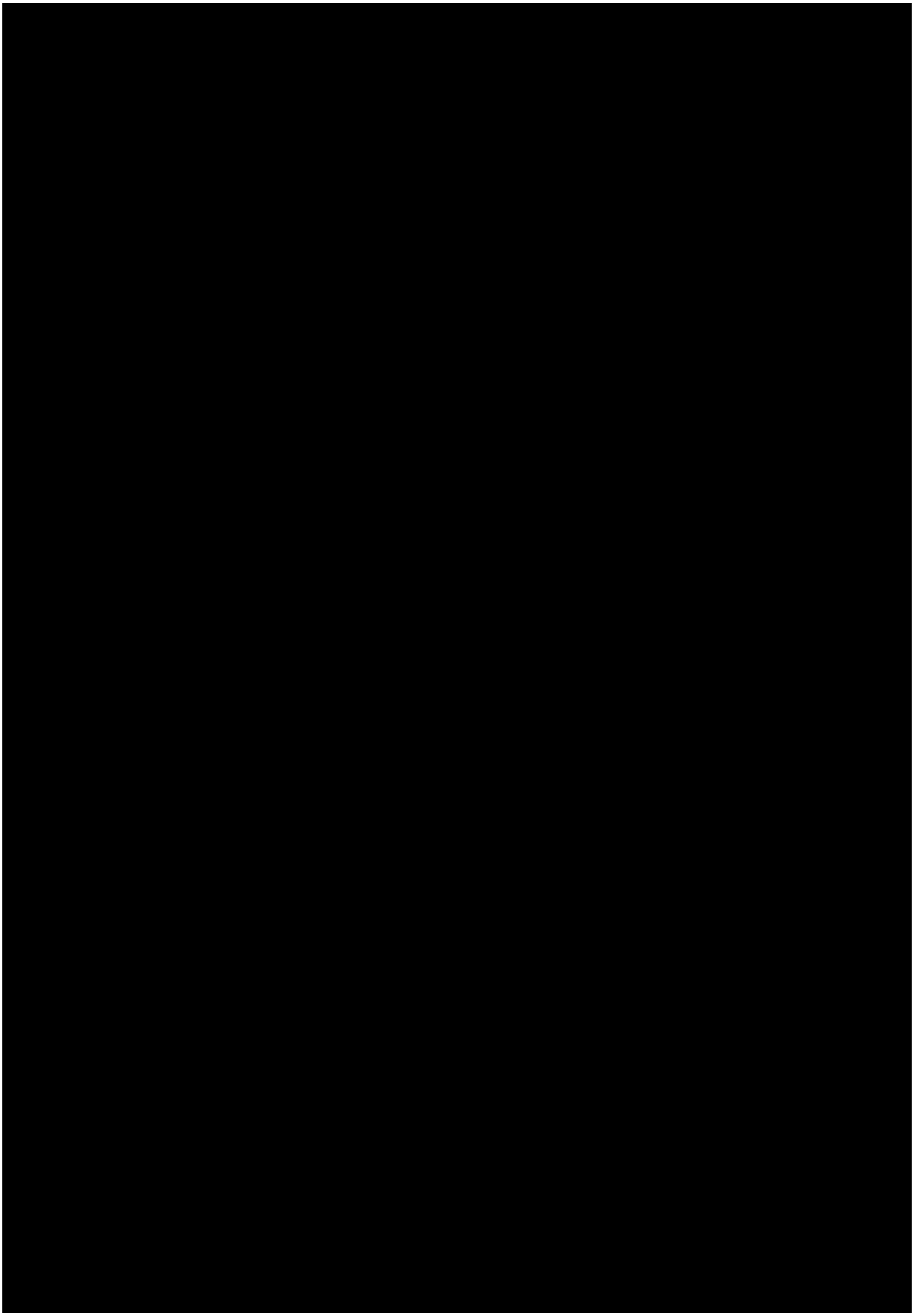
LV is an equal mixture of *d*- and *l*-diastereomers, among which the *l*-form is biologically active, e.g. in enhancing the antitumor efficacy of 5-FU. A number of basic studies have shown that coadministration of LV potentiates the inhibition by 5-FU of thymidylate synthase (TS), an enzyme that catalyzes thymidylate biosynthesis. LV is reduced to 5,10-methylene tetrahydrofolate (5,10-methylene-THF), which serves as a methyl donor in the pathway to

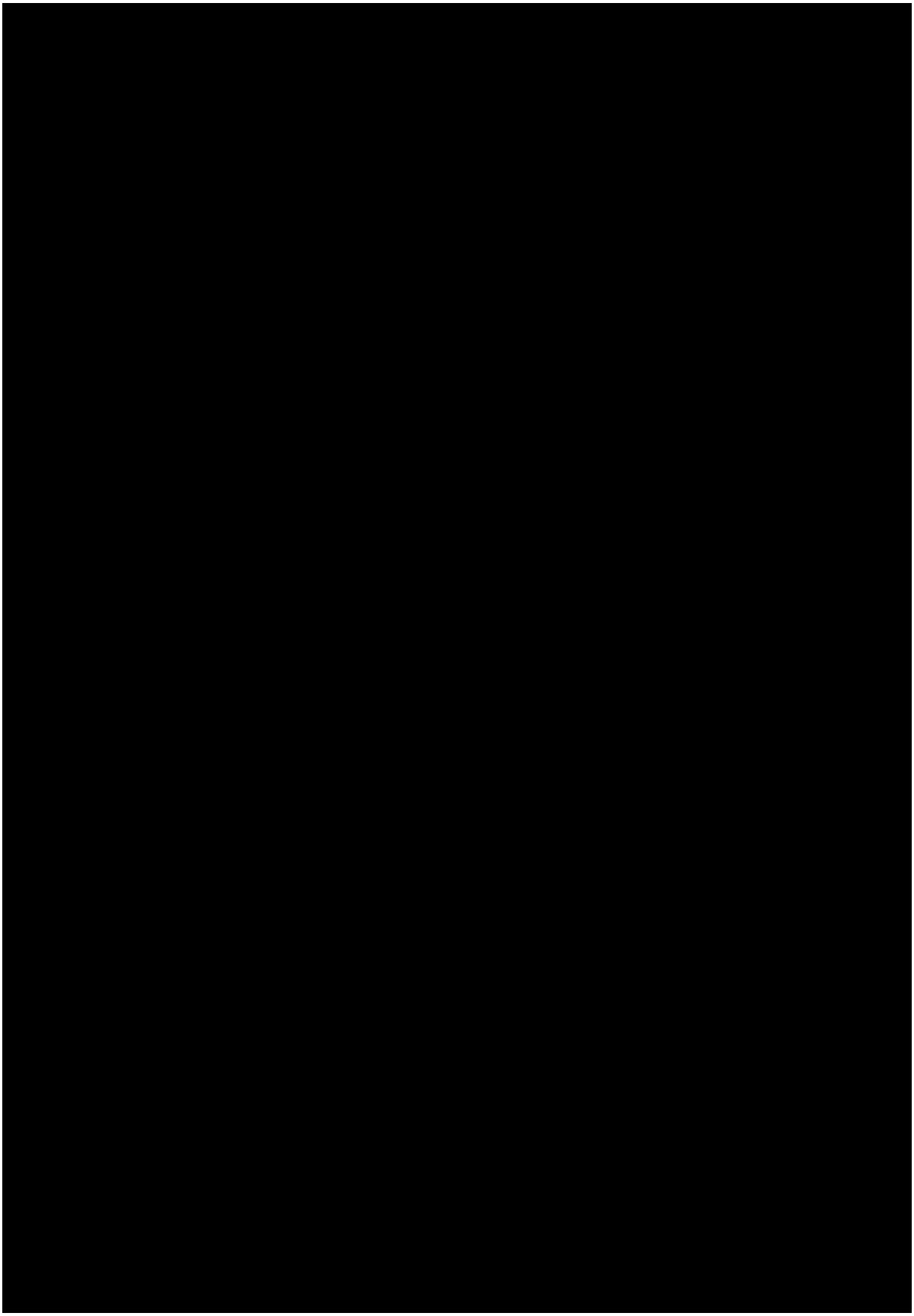
synthesize thymidylate, a substance essential for nucleic acid production, while 5-FU is phosphorylated to 2'-deoxy-5-fluorouridine-5'-monophosphate (FdUMP), which forms a stable ternary complex with TS and 5,10-methylene-THF, resulting in inhibition of nucleic acid synthesis. LV, when combined with 5-FU, is thus believed to enhance the formation of the ternary complex, and to thereby potentiate the antitumor efficacy of 5-FU. The benefits of combining 5-FU and LV in the treatment of colon cancer have been reported in many clinical researches, including a meta-analysis of more than 3000 subjects, which reported that coadministration of 5-FU and LV produced an increased response rate and prolonged survival in comparison with 5-FU alone[15], and *l*-LV for injection has been in clinical use since being approved for "Enhancement of the antitumor efficacy of 5-FU for treatment of gastric cancer (unresectable or recurrent) and colorectal cancer" in Japan. In Korea, *l*-LV for injection has been approval for "advanced colorectal cancer with 5-FU" and "reduction of the toxicity of anti-folate agent". Meanwhile, combination therapy with UFT, an oral agent, and oral LV was developed to improve ease of use in comparison with 5-FU/LV, and oral LV preparations were approved for "Enhancement of the antitumor efficacy of UFT for treatment of colorectal cancer" in Japan. In Korea, oral LV is approval for "reduction of the toxicity of anti-folate agent".

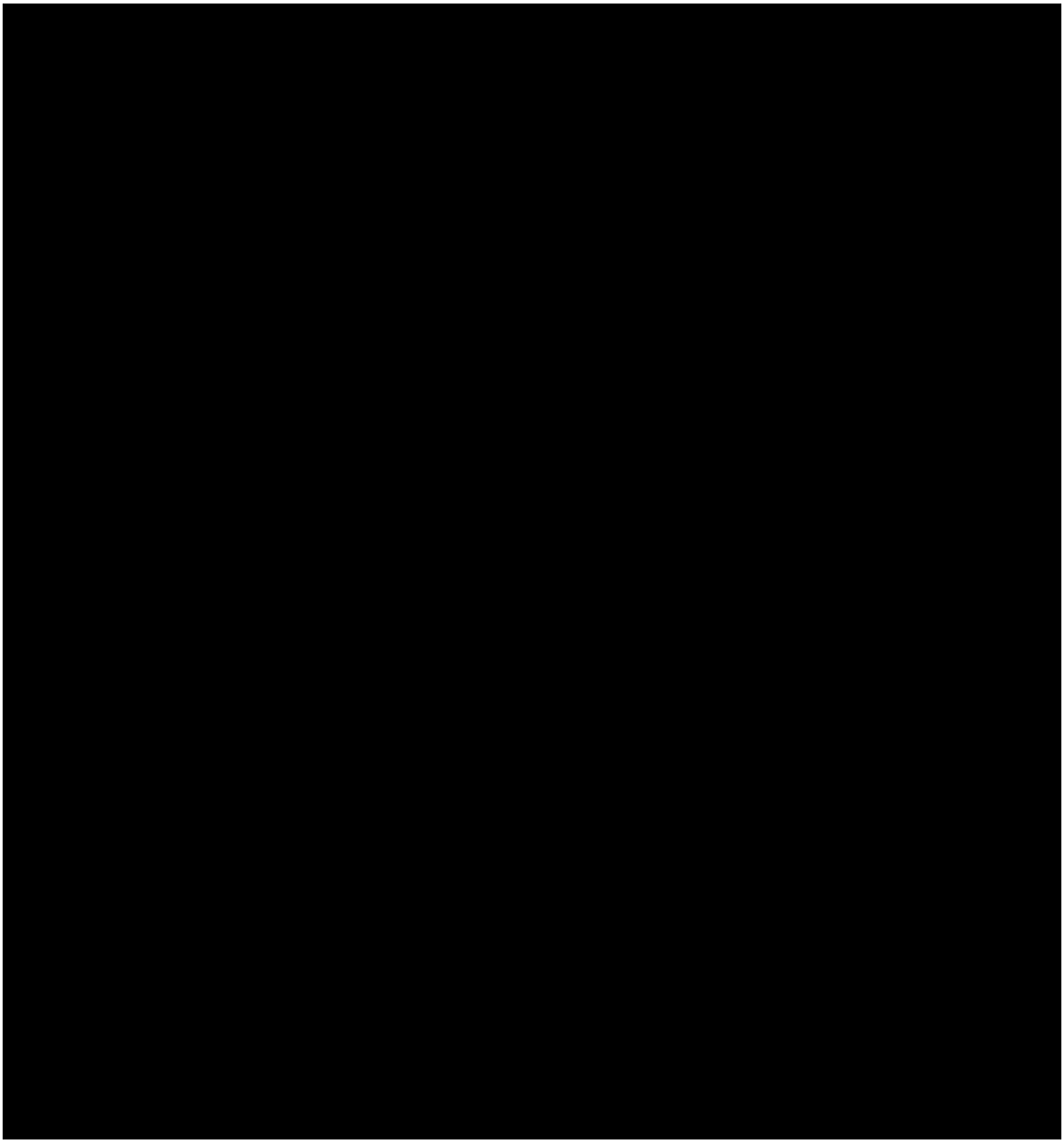
Given that LV has been shown to enhance the antitumor efficacy when coadministered with 5-FU or its prodrug, FT, LV was expected to produce a further enhancement in efficacy when combined with S-1, which also contains FT in combination with CDHP, a more potent DPD inhibitor than uracil, a component of UFT.











2.4 Rationale for considering the new therapy as promising

Efficacy of TAS-118 and L-OHP against gastric cancer

In the [redacted] for patients with unresectable, advanced, recurrent gastric cancer conducted in Japan (see section 2.3.2.4), RR was highest at 66% for the S-1/LV/L-OHP group and PFS was 8.3 months, and OS was 18.4 months. On the other hand, RR was 46%, PFS was 5.6 months and OS was 12.6 months for one of the standard therapy, S-1/CDDP group, and S-1/LV/L-OHP group showed high efficacy. In addition, the efficacy of S-1/CDDP group was similar to other studies[9, 13, 24]. Therefore S-1/LV/L-OHP was suggested as promising regimen to show high efficacy. Regarding safety, tolerability was also

shown. From these results, TAS-118/L-OHP therapy using TAS-118 containing S-1 and LV is expected to be promising as the first-line therapy in patients with gastric cancer.

3. GCP Compliance and Ethical Conduct of the Study

3.1 GCP Compliance

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the protocol, Good Clinical Practices (GCP), ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

3.2 Protection of Subjects' Privacy

When processing and archiving personal data pertaining to the investigator and or to the patients, the sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

3.3 Institutional Review Board/Independent Ethics Committee Approval

The study must be approved by an appropriately constituted Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), as required in Chapter 3 of the ICH E6 Guidelines.

The IRB/IEC must provide written approval of the study. The written approval/favorable opinion should include protocol (title, protocol number and version number), list of documents reviewed (e.g., protocol, ICF, IB, curriculum vitae, etc), and the date of the review.

The investigator is required to submit a copy of the written and dated IRB/IEC approval/favorable opinion to the sponsor or its representative prior to initiation of this study.

Investigational product will not be released to the trial site and the investigator will not start the trial until this written IRB/IEC approval/favorable opinion is received by the sponsor or its representative.

The investigator is responsible for obtaining renewal of approval throughout the duration of the study. Timeframes for renewal will be based on IRB/IEC requirements but renewal at least annually is required by regulations.

At the end of the trial, the IRB/IEC will be notified of the conclusion of the trial and its outcome.

4. Study Objectives

4.1 Primary objective

To compare the overall survival (OS) in patients with advanced gastric cancer treated with TAS-118/L-OHP versus S-1/CDDP.

4.2 Secondary objective

To compare the efficacy and safety of TAS-118/L-OHP versus S-1/CDDP in patients with advanced gastric cancer.

5. Study Design

5.1 Endpoints

5.1.1 Primary

Overall Survival：OS

5.1.2 Secondary

Progression Free Survival：PFS
Time to Treatment Failure：TTF
Overall Response Rate：ORR
Disease Control Rate：DCR
Safety

5.2 Study Type

5.2.1 Study Type by Objectives

Type: Confirmatory trial
Objectives: Assessment of the evidence of efficacy

5.2.2 Study Type by Design

Multinational, multicenter, open-label, active-controlled, randomized, parallel-group, comparative study using central registration

5.3 Description of Study Design

This trial is confirmatory trial to evaluate the superiority of TAS-118/L-OHP therapy against S-1/CDDP therapy in the OS.

Patients with advanced gastric cancer will be enrolled using the central registration method on a multicenter basis, randomized to two treatment groups, and treated/evaluated on

an open-label basis.

5.4 Patient Numbering and Randomization

Once patient have been confirmed to be eligible, patients will be centrally randomized in a 1:1 ratio to TAS-118/L-OHP (experimental arm) or S-1/CDDP (control arm) via an Interactive Web Response System (IWRS) based on a dynamic allocation method (minimization method). Detailed instructions for randomization are provided as a separate document.

The IWRS will assign a unique patient number as well as identification corresponding to the patient's treatment assignment.

No patients will be replaced at any time during this study.

Patient will be stratified by the following factors:

- ECOG PS: (0, 1)
- Measurable lesion: (Yes, No)
- Country: (Japan, Korea)

5.5 Blinding

This is an open-label study.

Maintenance of blinding would require a double-dummy design because of the difference between treatment procedures, but in this study with cancer patients, double-dummy blinding may reduce treatment compliance of subjects and thereby affect the assessment of efficacy and safety. Therefore an open-label design was selected.

6. Study Procedures

6.1 Explanation of Study Schedule to Individual Subjects

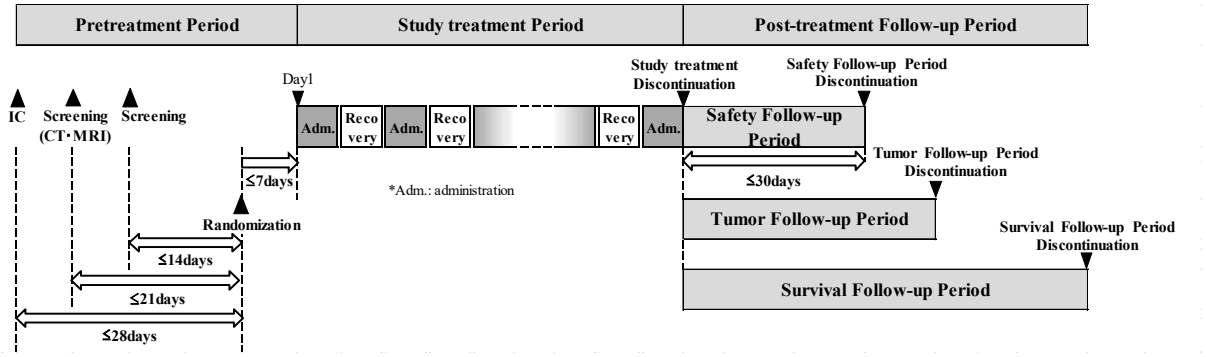


Figure 6.1-1 Study period

6.1.1 Definition of Study Period

Study periods for each patient are defined below:

- Pretreatment Period: Commences on the day the ICF is signed and lasts until the day prior to initiation study treatment.
- Study Treatment Period: Commences on the day of initiation study treatment and lasts until the day the patient meets any of the study treatment discontinuation criteria (see. 13.1.1 Study Treatment Discontinuation Criteria).
- Safety Follow-up Period: Defined as the day after the end of study treatment (i.e. last dose of study drug) until 30 days or until the start of new anti-tumor therapy, whichever comes first. (see. 13.1.2 Safety Follow-up Discontinuation Criteria).
- Tumor Follow-up Period: Applicable only to patients who have had no progressive disease (PD) defined by RECIST version 1.1 until the end of study treatment and defined as the day after the end of study treatment until patients meet tumor follow-up discontinuation criteria (see. 13.1.3 Tumor Follow-up Discontinuation Criteria).
- Survival Follow-up Period: Defined as the day after the end of study treatment until patients meet survival follow-up discontinuation criteria (see. 13.1.4 Survival Follow-up Discontinuation Criteria). The patient will be followed for survival and the use of new anti-tumor therapy.
- Post-Treatment Follow-up Period: Defined as the day after the end of study treatment.

7. Study Drug

The sponsor will supply TAS-118 (30, 40, 50, 60 mg), S-1 (20, 25 mg), L-OHP (100 mg), CDDP (50 mg) during study period.

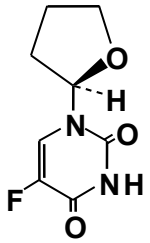
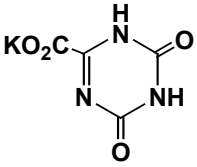
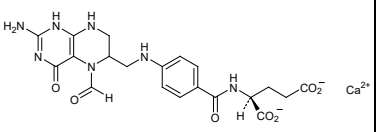
TAS-118 will be packed in sachet packages in a box. S-1 will be packed in a press through package (PTP) in a box.

7.1 Study Drug

7.1.1 TAS-118

TAS-118 is an anti-cancer drug in which the components of S-1, i.e. tegafur (FT), gimeracil (CDHP), and oteracil potassium (Oxo), are combined with calcium folinate (LV). Physical and chemical characteristics of the active ingredients are shown in Table 7.1.1-1.

Table 7.1.1-1 Description of TAS-118

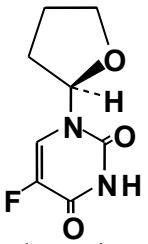
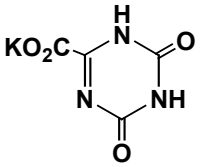
Code name	TAS-118			
Generic name	Tegafur	Gimeracil	Oteracil potassium	Calcium Folinate
Chemical name	5-fluoro-1-[(2*RS*)-tetrahydrofuran-2-yl]uracil	5-chloro-2,4-dihydroxypyridine	monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate	monocalcium *N*-{4-[(2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl)methylamino]benzoyl}-L-glutamate
Chemical structure	 and enantiomer			
Molecular formula	$C_8H_9FN_2O_3$ (200.17)	$C_5H_4ClNO_2$ (145.54)	$C_4H_2KN_3O_4$ (195.17)	$C_{20}H_{21}CaN_7O_7$ (511.50)
Dosage form	Combination granules			
Description	TAS-118 (30 mg):	white granules and white to yellowish white granules in one pack		
	TAS-118 (40 mg):	white granules and white to yellowish white granules in one pack		
	TAS-118 (50 mg):	white granules and white to yellowish white granules in one pack		
	TAS-118 (60 mg):	white granules and white to yellowish white granules in one pack		
Compounds and unit dose	TAS-118 (30 mg):	[redacted]		
	TAS-118 (40 mg):	[redacted]		

	TAS-118 (50 mg):	[redacted]
	TAS-118 (60 mg):	[redacted]
Composition	TAS-118 is a combination of S-1 and LV. S-1 is a combination of FT, CDHP and Oxo with a molar ratio of 1: 0.4: 1. S-1 (as FT 30mg, 40 mg, 50 mg and 60 mg) is combined with LV 25 mg (as folinate). TAS-118 drug product is immediate release granules packed in a sachet. [redacted]	
Storage condition	Room temperature (1-30°C)	
Package form	30mg/dose 1 pack: TAS-118 (30) x 14 (Color: pink) 40mg/dose 1 pack: TAS-118 (40) x 14 (Color: yellow) 50mg/dose 1 pack: TAS-118 (50) x 14 (Color: blue) 60mg/dose 1 pack: TAS-118 (60) x 14 (Color: gray) Two aluminum pouches with desiccant in a box	

7.1.2 **S-1**

S-1 is an anti-tumor nucleoside drug that combines Tegafur, Gimeracil and Oteracil potassium. Physical and chemical characteristics of the active ingredients are shown in Table 7.1.2-1.

Table 7.1.2-1 Description of S-1

Code name	S-1		
Generic name	Tegafur	Gimeracil	Oteracil potassium
Chemical name	5-fluoro-1-[(2*RS*)-tetrahydrofuran-2-yl]uracil	5-chloro-2,4-dihydroxypyridine	monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate
Chemical structure	 and enantiomer		
Molecular formula	$C_8H_9FN_2O_3$ (200.17)	$C_5H_4ClNO_2$ (145.54)	$C_4H_2KN_3O_4$ (195.17)
Dosage form	Capsule		
Description	S-1 (20mg):	An opaque, hard-shell capsule with a white cap and white body containing white powder and granules	
	S-1 (25mg):	An opaque, hard-shell capsule with an orange cap and white body containing white powder and granules	
Compounds	S-1 (20mg):	Tegafur (20 mg), gimeracil (5.8 mg) and oteracil potassium (19.6 mg)	

and unit dose	S-1 (25mg):	Tegafur (25 mg), gimeracil (7.25 mg) and oteracil potassium (24.5 mg)
Composition	S-1 is an immediate release dosage form contained in a capsule in which FT, CDHP, and Oxo are combined at a molar ratio of 1:0.4:1. The capsule excipients are lactose monohydrate and magnesium stearate.	
Storage condition	room temperature (1-30°C)	
Package form (1)	40 mg/dose	1 sheet:S-1 (20) x 2 CAP x 2 x 7 (PTP board color: copper)
	50 mg/dose	1 sheet:S-1 (25) x 2 CAP x 2 x 7 (PTP board color: blue)
	60 mg/dose	1 sheet:S-1 (20) x 3 CAP x 2 x 7 (PTP board color: silver)
	Four sheets in a box	
Package form (2)	40 mg/dose	1 sheet:S-1 (20) x 2 CAP x 2 x 7 (PTP board color: copper)
	50 mg/dose	1 sheet:S-1 (25) x 2 CAP x 2 x 7 (PTP board color: blue)
	60 mg/dose	1 sheet:S-1 (20) x 3 CAP x 2 x 7 (PTP board color: silver)
	Three sheets in a box	

7.2 Oxaliplatin (L-OHP)

Oxaliplatin will be provided in this clinical study. See the current package insert for handling, treatment, and storage of L-OHP.

7.3 Cisplatin (CDDP)

Cisplatin will be provided in this clinical study. See the current package insert for handling, treatment, and storage of CDDP.

7.4 Packaging and Labeling of Study Drug

Required information will be printed on the label(s) according to local regulatory requirements.

7.5 Delivery, Storage, Control, Retrieve of Study Drug

In accordance with International Conference on Harmonization (ICH) and local regulatory requirements, the investigator and/or the person responsible for dispensing study drug must be able at all times to account for all study drug provided to the site. The study drug administrator of the study site follows “study drug management procedures”. Record the use of all study drug on the appropriate Drug Accountability Record.

Dose reductions, interruptions, and reasons for these actions must be recorded in the patient’s source documents.

At the conclusion of the study, all unused study drug shipped to the investigator must be returned to the sponsor or its representative.

No study drug is to be used outside of this study.

8. Criteria for Inclusion and Exclusion of Patients

8.1 Inclusion Criteria

Patients must fullfil all of the following criteria at the time of randomization in this study: The rationale is provided in “26.5 Rationale for inclusion criteria”.

(1) Histologically confirmed adenocarcinoma of the stomach or esophagogastric junction with metastatic or recurrent disease.

(2) Measurable or evaluable metastatic lesion(s), according to RECIST version 1.1 detected by CT scan or MRI for response evaluation within 21 days prior to randomization.

(3) Negative or unknown for HER2 testing.

(4) No prior treatment (e.g. radiotherapy, chemotherapy, hormonal therapy) for gastric cancer.

- Adjuvant chemotherapy is permitted if more than 180 days has elapsed between the end of adjuvant therapy and first recurrence. Adjuvant chemotherapy with platinum agent is not permitted.

(5) ECOG PS of 0 to 1.

(6) At least 20 years of age[*1] at the time of informed consent.

(7) The following bone marrow, liver, and kidney function parameters measured within 14 days prior to randomization:

1) Neutrophil count ≥ 1500/mm^3 [*2]
2) Hemoglobin ≥ 8.0 g/dL [*2]
3) Platelet count ≥ 100000/mm^3 [*2]
4) Total bilirubin ≤ 1.5 mg/dL
5) AST, ALT levels ≤ 3 x ULN, or ≤ 5 x ULN in the presence of liver metastasis
6) ALP levels ≤ 2.5 x ULN, or ≤ 5 x ULN in the presence of liver metastasis
7) Creatinine clearance ≥ 60 mL/min [*3]

(8) Life expectancy of at least 90 days after randomization.

(9) Capable of oral intake.

(10) Written informed consent to participate as a subject in this clinical study.

[1*] : For 75 years of age or older patient, pay careful attention to manage adverse events.

[2*] : If patients received blood transfusion or treatment with any blood product or hematopoietic factor such as G-CSF, it must be confirmed the data is obtained more than 14 days after the last blood transfusion or treatment.

[3*] : A value obtained from a urine collection, if available. Otherwise an estimate by the Cockcroft-Gault formula:

Estimated creatinine clearance (mL/min)
= (140 - age) x Body weight (kg) / [72 x Serum creatinine (mg/dL)]
For women, the obtained value is multiplied by a factor of 0.85.

8.2 Exclusion Criteria

Patients who meet any of the following criteria at the time of randomization will be excluded from this study:

The rationale is provided in "26.6 Rationale for exclusion criteria".

(1) Serious hypersensitivity to any ingredients of S-1 or LV.

(2) Treated with other investigational agents within 4 weeks before randomization.

(3) Remain affected by a surgery performed before randomization.

(4) Blood transfusion, treatment with blood products, or hematopoietic growth factors such as G-CSF within 2 weeks before randomization.

(5) Ongoing treatment with flucytosine at the time of randomization.

(6) Unmanageable Diarrhea (e.g. watery stool, difficulty in controlling bowel movements despite the medication, grade 2 or higher, 5 stools or more per day).

(7) Current peripheral sensory neuropathy or paresthesia (grade 2 or higher).

(8) Current or past severe lung disease (e.g. interstitial pneumonia, pulmonary fibrosis, or severe emphysema).

(9) Any other active illness such as severe (e.g. grade 3 or higher) cardiac disease[*1] (e.g. myocardial infarction, angina pectoris, arrhythmia, or cardiac failure). Any of the following events within the 6 months prior to randomization: any episode of myocardial infarction or angina pectoris.

(10) Diabetic patients who have poorly controlled despite the medication or severe diabetic complication.

(11) Any other severe (e.g. Grade 3 or higher) complications (e.g. severe enteritis, severe stomatitis, gastrointestinal ulceration/perforation, ileus, renal failure, nephrosis syndrome, liver failure or cerebrovascular disorder).

(12) Known human immunodeficiency virus (HIV) or active hepatitis.

(13) Active infection, inflammatory diseases, or connective tissue disease (e.g. administration of intravenous antibiotics, fever of 38°C or higher).

(14) Current use or anticipated need for continuous systemic steroid administration (oral or intravenous).

(15) Active gastrointestinal bleeding (e.g. Grade 3 or higher).

(16) Brain metastasis, present or suspected from clinical symptoms.

(17) Extensive bone metastasis (e.g. whole pelvis, or 50% of spine).

(18) Accumulation of pleural, ascitic, or pericardial fluid requiring drainage within 2 weeks prior to randomization.

(19) Other concurrent active cancer (synchronous double cancer or heterochronous double cancer with a disease-free interval of 5 years or shorter, excluding lesions consistent with intraepithelial cancer, i.e., carcinoma *in situ*, or intramucosal cancer that are assessed as cured by local treatment).

(20) Pregnant, breast-feeding[*2], possibly pregnant women or patients wishing to have children during the study period or a certain period (6 months) after stopping study treatment. Women of childbearing potential have to take a pregnancy test[*3].

(21) Concurrent mental disorder or psychiatric symptoms assessed as interfering with study participation.

(22) Ineligible for participating in this study according to the investigator.

*1 : Patients with a cardiac pacemaker, or valve replacement are impossible to be randomized.

*2 : Women who stop breast-feeding are impossible to be randomized.

*3 : Women of childbearing potential are defined as any women who are premenopausal, less than 1 year after last menses, more than 1 year with no menses due to medical causes, or not permanently sterilized and so on.

8.3 Informed Consent

Patients will indicate their consent to participate in the study by signing and dating an ICF prior to study procedures.

Patients must be provided a signed and dated copy of the ICF prior to any study-related procedures that are outlined in the consent.

8.3.1 Procedure for obtaining informed consent

Obtaining informed consent must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for GCP, and local regulations.

The investigator (according to applicable regulatory requirements) or a person designated by the investigator should fully inform patients of all pertinent aspects of the clinical trial. All participants should be informed to the fullest extent possible about the study in a language and in terms they are able to understand.

Prior to participation in the trial, the written ICF is to be signed and personally dated by the patient and the person who conducted the ICF discussion. A copy of the signed and dated ICF will be provided to the patient. The ICF used must have had prior approval by the IRB/ IEC.

9. Subject Registration

All subjects will be enrolled into this study using the central registration (IWRS).

(1) The investigator (subinvestigator) evaluates and verifies the eligibility of each subject candidate according to the inclusion and exclusion criteria.
(2) The subject will be centrally randomized to one of the two treatment arms and received the subject number via an IWRS.
(3) The subject number will be "TAS-118 GC-" and 3 digits; these 3 digits will be consecutive number for study (not each site).
(4) The subject number will be maintained throughout the study and will not be reassigned.
(5) Study drug administration should be initiated within 8 days of randomization.
(6) If the investigator (subinvestigator) does not enroll any patient for more than 6 months from initial supply of study drug to the site, randomization procedure can not be performed in the site.

10. Administration

10.1 Dose, administration schedule

10.1.1 Dose

10.1.1.1 Arm A (TAS-118/L-OHP)

For the initial dose, TAS-118 shall be administered orally twice daily after breakfast and after dinner according to the reference daily dose in the following table depending on the body surface area (See Table 10.1.1.1-1).

Even if body weight change at subsequent cycle, dose of TAS-118 is not modified.

Table 10.1.1.1-1 Initial Dose of TAS-118

Body Surface Area (m^2)	Dosage in each dose	Number of sachet package	Total daily dose (Number of sachet packages)
< 1.25	40 mg	Morning: 1 Evening: 1	80 mg (2)
≥ 1.25 – < 1.5	50 mg	Morning: 1 Evening: 1	100 mg (2)
≥ 1.5	60 mg	Morning: 1 Evening: 1	120 mg (2)

L-OHP shall be administered via intravenous drip for 2 hours on Day 1 of each cycle, with an initial dose of 85 mg/m^2 (acceptable within ± 10%).

5-HT_3 receptor antagonist and steroid are recommended to be administered as pretreatment. However, for patients considered inappropriate for steroid treatment, such as patients with hepatitis virus infection or diabetes mellitus, steroid treatment is not essential.

See the current package insert for other precautions for the preparation and treatment of L-OHP.

The dose shall not be recalculated by body weight fluctuation in principle, but for 10% or higher fluctuation of body weight, recalculation is possible at the discretion of the investigator (or subinvestigator). When recalculation, the body surface area (BSA) will be calculated using the DuBois formula.

10.1.1.2 Arm B (S-1/CDDP)

For the initial dose, S-1 shall be administered orally twice daily after breakfast and after dinner according to the reference daily dose in the following table depending on the body surface area (See Table 10.1.1.2-1).

Even if body weight change at subsequent cycle, dose of S-1 is not modified.

Table 10.1.1.2-1 Initial Dose of S-1

Body Surface Area (m^2)	Dosage in each dose	Number of capsules		Total daily dose (Number of capsules)
		20 mg (white)	25 mg (orange/white)	
< 1.25	40 mg	Morning: 2 Evening: 2	Morning: - Evening: -	80 mg (4)
≥ 1.25 – < 1.5	50 mg	Morning: - Evening: -	Morning: 2 Evening: 2	100 mg (4)
≥ 1.5	60 mg	Morning: 3 Evening: 3	Morning: - Evening: -	120 mg (6)

CDDP shall be administered via intravenous drip for 2 hours or longer on Day 1 (Korea) or Day 8 (Japan) of each cycle, with an initial dose of 60 mg/m^2 (acceptable within ± 10%).

Before and after treatment of CDDP, hydration shall be performed to maintain sufficient urinary volume, and 5-HT_3 receptor antagonist, Neurokinin (NK)1 receptor antagonist, and steroid are recommended to be administered as pretreatment for nausea and vomiting. Care must be taken to avoid overhydration for patients with suspected heart disease or with pleural effusion or ascites. Pretreatment with steroid are not recommended for the patients who are inappropriate for administration of steroid (e.g. active hepatitis or diabetes mellitus).

See the current package insert for other precautions for the preparation and treatment of CDDP.

The dose shall not be recalculated by body weight fluctuation in principle, but for 10% or higher fluctuation of body weight, recalculation is possible at the discretion of the investigator (or subinvestigator). When recalculation, the BSA will be calculated using the DuBois formula.

10.1.2 Administration schedule

The administration schedule for each treatment group is shown below. The administration period is until 31 Jan 2020.

10.1.2.1 Arm A (TAS-118/L-OHP)

L-OHP will be administered on Day 1, and TAS-118 will be administered orally twice daily in a administration period from Day 1 through Day 7 followed by a recovery period from Day 8 through Day 14. This regimen is to be repeated every 2 weeks until study treatment discontinuation criteria (Section 13.1.1). If TAS-118 administration is initiated from evening on Day 1, it will be continued until morning on Day 8, and recovery period will be from evening on Day 8 through morning on Day 15 (see Figure 10.1.2.1-1).

- A recovery period is not allowed to be shortened (e.g. even if the dosing is interrupted due to some reasons, such as adverse events after the morning of Day 6, the subsequent dosing should be started as a new treatment cycle after the morning/evening meal on Day 15).
- Any unused doses are not allowed to be administered in a recovery period (see Figure 10.1.2.1-2).
- If any of dose initiation criteria (see Table 10.1.3.1-1) for L-OHP did not meet, administration of L-OHP may be skipped and start each treatment cycle only with TAS-118.

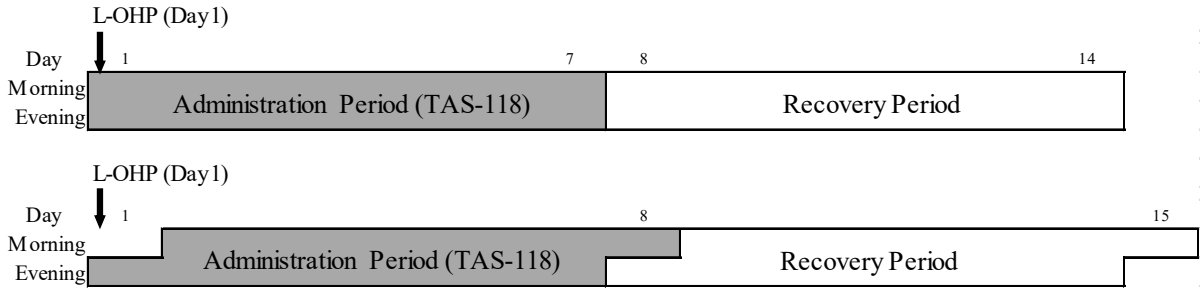


Figure 10.1.2.1-1 Study regimen of TAS-118/L-OHP

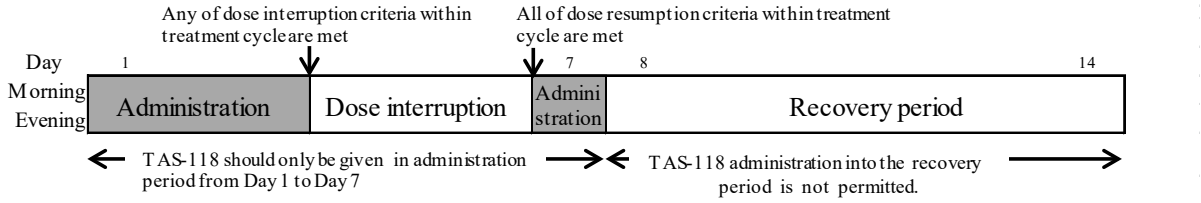


Figure 10.1.2.1-2 Study regimen of TAS-118

10.1.2.2 **Arm B (S-1/CDDP) [CDDP on Day 1] (Korea)**

CDDP will be administered on Day 1, and S-1 will be administered orally twice daily in a administration period from Day 1 through Day 21 followed by a recovery period from Day 22 through Day 35. This regimen is to be repeated every 5 weeks until study treatment discontinuation criteria (Section 13.1.1). If S-1 administration is initiated from evening on Day 1, it will be continued until morning on Day 22, and recovery period will be from evening on Day 22 through morning on Day 36 (see Figure 10.1.2.2-1).

- A recovery period may be shortened down to 7 days after the administration period which has been finished either without AE/SAE related to study drug or with AE/SAE related to study drug that are of no safety concern and assessed as allowing the subsequent recovery period to be shortened (see Figure 10.1.2.2-2Figure 10.1.2.2-3).
- Any unused doses are not allowed to be administered in a recovery period (see Figure 10.1.2.2-3).
- If the dose interruption continues 14 days and over in the administration period, drug administration has to be discontinued in the cycle. After confirmation of being met criteria for starting new treatment cycle (see Table 10.1.3.1-2), drug administration can be restarted as the next treatment cycle (see Figure 10.1.2.2-4).
- If any of dose initiation criteria for CDDP(see Table 10.1.3.1-2) did not meet, administration of CDDP may be skipped and start each treatment cycle only with S-1.

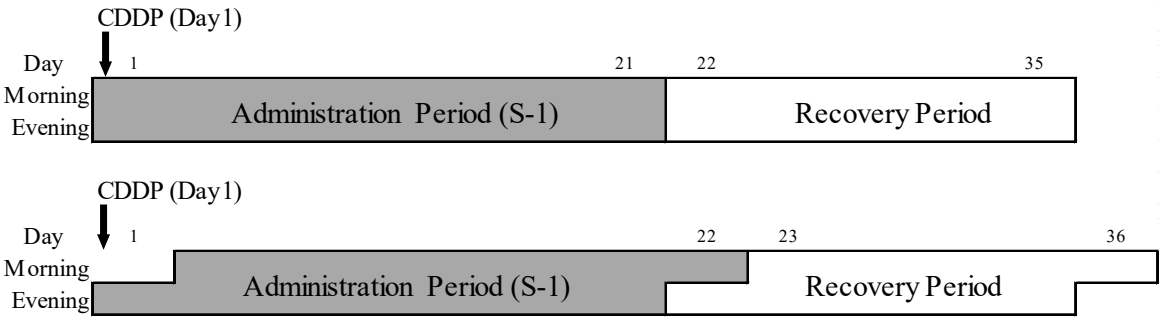


Figure 10.1.2.2-1 Study regimen of S-1/CDDP

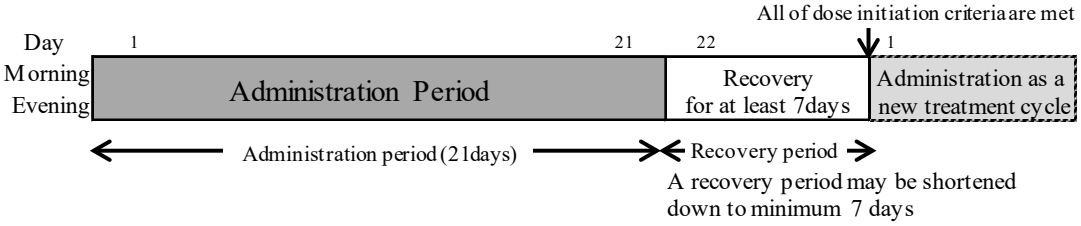


Figure 10.1.2.2-2 Study regimen of S-1 (1)

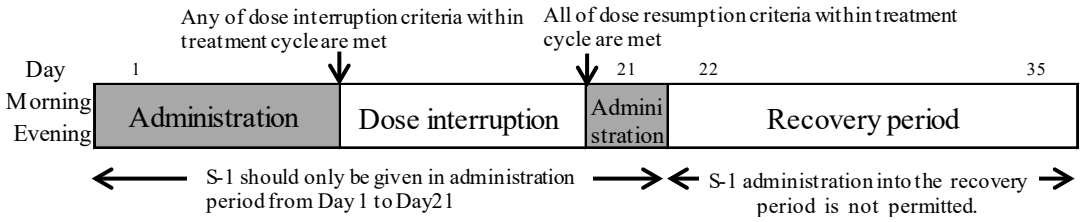


Figure 10.1.2.2-3 Study regimen of S-1 (2)

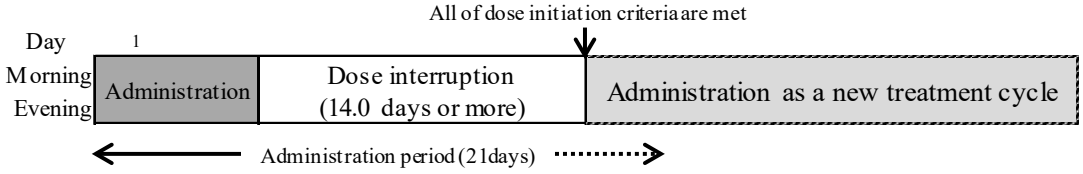


Figure 10.1.2.2-4 Study regimen of S-1 (3)

10.1.2.3 **Arm B (S-1/CDDP) [CDDP on Day 8] (Japan)**

CDDP will be administered on Day 8 (Day 6 to Day 15), and S-1 will be administered orally twice daily in a administration period from Day 1 through Day 21 followed by a recovery period from Day 22 through Day 35. This regimen is to be repeated every 5 weeks until study treatment discontinuation criteria (Section 13.1.1). If S-1 administration is initiated from evening on Day 1, it will be continued until morning on Day 22, and recovery period will be from evening on Day 22 through morning on Day 36 (see Figure 10.1.2.3-1).

- A recovery period may be shortened down to 7 days after the administration period which has been finished either without AE/SAE related to study drug or with AE/SAE related to study drug that are of no safety concern and assessed as allowing the subsequent recovery period to be shortened (see Figure 10.1.2.3-2).
- Any unused doses are not allowed to be administered in a recovery period (see Figure 10.1.2.3-3).
- If the dose interruption continues 14 days and over in the administration period, drug administration has to be discontinued in the cycle. After confirmation of being met criteria for starting new treatment cycle (see Table 10.1.3.1-2), drug administration can be restarted as the next treatment cycle (see Figure 10.1.2.3-4).
- If any of dose initiation criteria (see Table 10.1.3.1-2) for CDDP did not meet, administration of CDDP may be skipped and start each treatment cycle only with S-1.

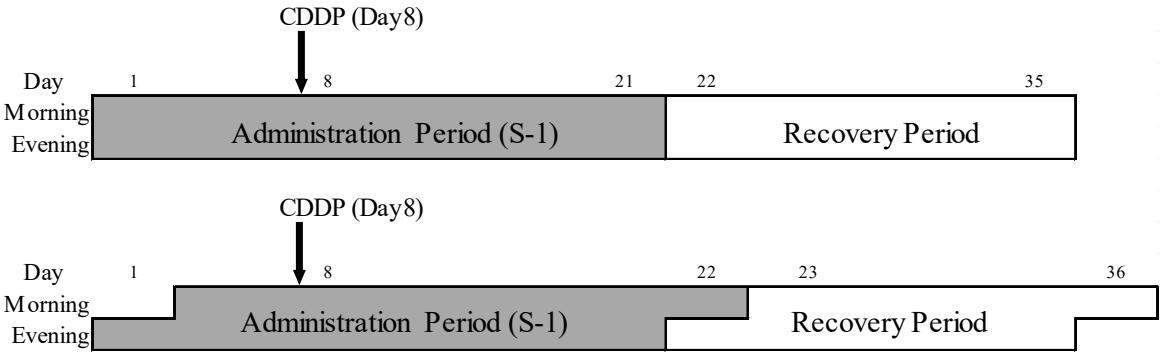


Figure 10.1.2.3-1 Study regimen of S-1/CDDP

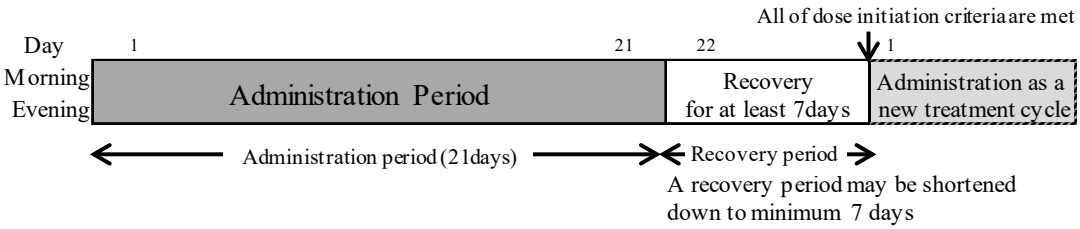


Figure 10.1.2.3-2 Study regimen of S-1 (1)

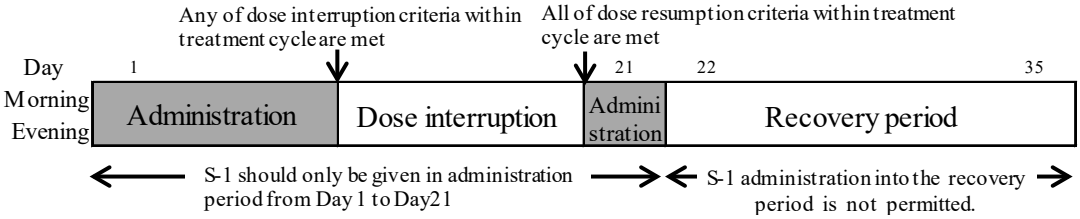


Figure 10.1.2.3-3 Study regimen of S-1 (2)

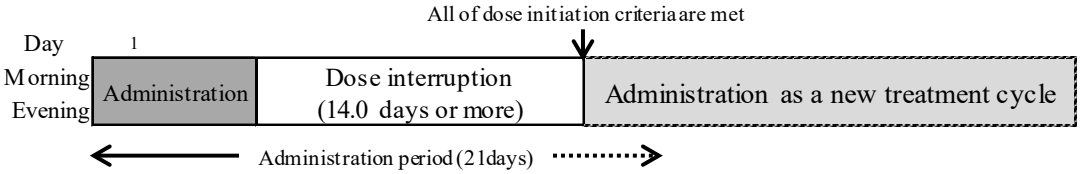


Figure 10.1.2.3-4 Study regimen of S-1 (3)

10.1.3 Criteria for Modification of Treatment Schedule

10.1.3.1 Criteria for Dose Initiation in Each Cycle

Cycle 1 will be started after completion of the scheduled examination and the confirmation of being met all of dose initiation criteria in each cycle (Table 10.1.3.1-1, Table 10.1.3.1-2), which may be substituted by the test at randomization performed within 7 days prior to Day 1 treatment start. Cycle 2 and later cycles will be started if the results of the scheduled examination on or one day before Day 1 meet all the following criteria (Table 10.1.3.1-1, Table 10.1.3.1-2). No treatment cycle can be started if any of these criteria are not met. Even if a subject meets all the following criteria, dose initiation can be postponed at the investigator's discretion. Even if all of dose initiation criteria were met, administration of L-OHP or CDDP may be skipped and each treatment cycle can be started only with TAS-118 or S-1 at the investigator's discretion.

Table 10.1.3.1-1 Dose initiation criteria in each cycle for TAS-118 and L-OHP (Arm A)

Item	TAS-118	L-OHP
Neutrophil count	≥ 1000 /mm^3 (≤ Grade2) *1	≥ 1500 /mm^3 (≤ Grade1) *1
Platelet count	≥ 75000 /mm^3 (≤ Grade1) *2	
Serum creatinine*3	< 1.5 mg/dL (1.2 -< 1.5 mg/dL: 1 level down)	-
Infection	No infection with fever (< 38°C)	
Diarrhea, Stomatitis, Anorexia	≤ Grade1	
Peripheral sensory neuropathy	—	≤ Grade2*4

*1 : If the patients received G-CSF, it must be confirmed the data is obtained more than 48 hours after the last administration.

*2 : If the patients received platelet transfusion, it must be confirmed the data is obtained more than 48 hours after the last transfusion.

*3 : New treatment cycle would be initiated with creatinine clearance ≥ 50 mL/min, as a reference.

*4 : Even if the grade is ≤ 2, administration of L-OHP may be skipped at the investigator's discretion.

Table 10.1.3.1-2 Dose initiation criteria in each cycle for S-1 and CDDP (Arm B)

Item	S-1	CDDP
Neutrophil count	≥ 1000 /mm^3 (≤ Grade2)*1	≥ 1500 /mm^3 (≤ Grade1)*1
Platelet count	≥ 75000 /mm^3 (≤ Grade1)*2	
Serum Creatinine*3	< 1.5 mg/dL (1.2 -< 1.5 mg/dL: 1 level down)	< 1.5 mg/dL (1.2 – < 1.5 mg/dL: 10 mg/mm^2 reduction from previous cycle)
Infection	No infection with fever (< 38°C)	
Diarrhea, Stomatitis, Anorexia	≤ Grade1	

*1 : If the patients received G-CSF, it must be confirmed the data is obtained more than 48 hours after the last administration.

*2 : If the patients received platelet transfusion, it must be confirmed the data is obtained more than 48 hours after the last transfusion.

*3 : New treatment cycle would be started with creatinine clearance ≥ 50 mL/min, as a reference.

10.1.3.2 **Criteria for Dose Interruption and Resumption within Treatment Cycle**

The study treatment must be interuppted if any of the following dose interruption criteria (Table 10.1.3.2-1) is met during administration period of the study agent (TAS-118 or S-1), and will be resumed after the confirmation of being met all the following dose resumption criteria (Table 10.1.3.2-2). After dose resumption, the dose must be the same as before dose interruption.

Table 10.1.3.2-1 Dose interruption criteria within treatment cycle

Item	Criterion
Neutrophil count	< 1000/mm^3 (Grade 3 ≤)
Platelet count	< 50000/mm^3 (Grade 3 ≤)
Infection	Infection with fever (≥ 38°C)
Diarrhea, Stomatitis	Grade 3 ≤
Other	Difficulty in continuing treatment as assessed by the investigator (subinvestigator)

Table 10.1.3.2-2 Dose resumption criteria within treatment cycle

Item	Criterion
Neutrophil count	≥ 1000/mm^3 (≤ Grade 2)*[1]
Platelet count	≥ 50000/mm^3 (≤ Grade 2)*[2]
Serum Creatinine*[3]	< 1.5 mg/dL
Infection	No infection with fever (< 38°C)
Diarrhea, Stomatitis	≤ Grade 1
Other	Acceptability of resuming treatment as assessed by the investigator (subinvestigator)

*[1] : If the patients received G-CSF, it must be confirmed the data is obtained more than 48 hours after the last administration.

*[2] : If the patients received platelet transfusion, it must be confirmed the data is obtained more than 48 hours after the last transfusion.

*[3] : The study treatment would be resumed with creatinine clearance ≥ 50 mL/min, as a reference.

10.1.3.3 **Criteria for Dose Reduction (Arm A)**

If the patients suffered any adverse drug reaction that meets any of the following dose reduction criteria, a new treatment cycle will be started after confirmation that the subject meets "Section 10.1.3.1 criteria for dose initiation in each cycle", with the dose of TAS-118 or L-OHP reduced 1 level in each step according to the scheme for dose reduction criteria. Dose reduction is not allowed in the same treatment cycle.

Table 10.1.3.3-1 Dose reduction criteria for TAS-118 and L-OHP

Item	Criterion		TAS-118	L-OHP
Neutrophil count	< 500/mm^3 (Grade 4)	Worst grade observed in last cycle	1 step	1 step
Platelet count	< 25000/mm^3 (Grade 4)		1 step	1 step
Febrile neutropenia	Grade 3 ≤		1 step	1 step
Stomatitis	Grade 3 ≤		1 step	-
Diarrhea	Grade 3 ≤*1		1 step	-
Peripheral sensory neuropathy	Grade 3 ≤*2		-	1 step
Serum creatinine	1.2 - < 1.5 mg/dL	The value observed before the initiation of new treatment cycle	1 step	-
Others*3	Difficulty in continuing treatment without reducing the study drug dose as assessed by the investigator (subinvestigator)			

*1: In the event of a Grade 3 or greater adverse drug reaction in spite of the best treatment possible.

*2: Even if the grade is ≤ 2, the dose can be reduced at the investgator's discretion.

*3: If the patient suffers from anorexia or other remarkable adverse drug reactions, the dose can be reduced at the investigator's discretion.

Table 10.1.3.3-2 Dose reduction scheme for TAS-118 and L-OHP

Investigational product	Initial dose	Step 1	Step 2	Step 3
TAS-118	60 mg/dose	50 mg/dose	40 mg/dose	30 mg/dose
	50 mg/dose	40 mg/dose	30 mg/dose	None*
	40 mg/dose	30 mg/dose	None*	None*
L-OHP	85 mg/m^2	65 mg/m^2	50 mg/m^2	None*

* : In this case, the dose reduction cannot be done for the subjects, but there is no necesssity that the study treatment is terminated. After confirmation that the patients meet all of dose resumption criteria, the study treatment can be restarted at minimum dose.

Table 10.1.3.3-3 Reduced dose of administration for TAS-118

Dosage in each dose	Number of sachet package	Total daily dose (Number of sachet packages)
30 mg	Morning: 1 Evening: 1	60 mg (2)
40 mg	Morning: 1 Evening: 1	80 mg (2)
50 mg	Morning: 1 Evening: 1	100 mg (2)

10.1.3.4 **Criteria for Dose Reduction (Arm B)**

If the patients suffered any adverse drug reaction that meets any of the following dose reduction criteria, a new treatment cycle will be started after confirming that the subject meets "Section 10.1.3.1 criteria for dose initiation in each cycle", with the dose of S-1 or CDDP reduced 1 level in each step according to the scheme for dose reduction criteria.

Dose reduction is not allowed in the same treatment cycle.

Table 10.1.3.4-1 Dose reduction criteria for S-1 and CDDP

Item	Criterion		S-1	CDDP
Neutrophil count	< 500/mm^3 (Grade 4)	Worst grade observed in last cycle	1 step	Reduced by 10 mg/m^2
Platelet count	< 25000/mm^3 (Grade 4)		1 step	Reduced by 10 mg/m^2
Febrile neutropenia	Grade 3 ≤		1 step	Reduced by 10 mg/m^2
Stomatitis	Grade 3 ≤		1 step	-
Diarrhea	Grade 3 ≤*1		1 step	-
Serum creatinine	1.2 - < 1.5 mg/dL	The value observed before the initiation of new treatment cycle	1 step	Reduced by 10 mg/m^2
Others*2	Difficulty in continuing treatment without reducing the study drug dose as assessed by the investigator (subinvestigator)			

*1: In the event of a Grade 3 or greater adverse drug reaction in spite of the best treatment possible.
*2: If the patient suffers from anorexia or other remarkable adverse drug reactions, the dose can be reduced at the investigator's discretion.

Table 10.1.3.4-2 Dose reduction scheme for S-1 and CDDP

Investigational product	Initial dose	Step 1	Step 2
S-1	60 mg/dose	50 mg/dose	40 mg/dose
	50 mg/dose	40 mg/dose	None*
	40 mg/dose	None*	None*
CDDP	60 mg/m^2	Reduced by 10 mg/m^2	

* : In this case, the dose reduction cannot be done for the subjects, but there is no necessity that the study treatment is terminated. After confirmation that the patients meet all of dose resumption criteria, the study treatment can be restarted at minimum dose.

Table 10.1.3.4-3 Reduced dose of administration for S-1

Dosage in each dose	Number of capsules		Total daily dose (Number of capsules)
	20 mg (white)	25 mg (orange/white)	
40 mg	Morning: 2 Evening: 2	Morning: - Evening: -	80 mg (4)
50 mg	Morning: - Evening: -	Morning: 2 Evening: 2	100 mg (4)

10.1.4 Criteria for Dose Increase

The dose of study drugs (TAS-118, L-OHP, S-1, and CDDP) must not be increased even after dose reduction.

10.2 Medication and Treatments Prohibited during Study

10.2.1 Medication and Treatments Prohibited during Study

The following concomitant therapies are not permitted during the study treatment period.

(1) Any other anti-tumor therapy, including chemotherapy, radiotherapy, immunotherapy, biological response modifiers (BRMs) with antitumor effect, or endocrine therapy
(2) Other investigational drugs
(3) Uracil, Cimetidine and Calcium folinate
(4) Flucytosine
(5) Prophylactic use of G-CSF

10.2.2 Concomitant Medications Requiring Precautions

(1) Warfarin potassium
Changes in coagulation profile should be monitored e.g. by INR when relevant abnormalities are indicated by other tests or findings, and the warfarin dose should be adjusted as needed.
(2) Phenytoin
Subjects receiving phenytoin should be monitored. If abnormalities are noted, appropriate measures should be taken including dose reduction or discontinuation.
(3) Aminoglycoside antibiotics, vancomycin hydrochloride, and furosemide (Arm B: S-1/CDDP therapy only)
(4) Amphotericin B for injection (Arm B: S-1/CDDP therapy only)
(5) Piretanide (Arm B: S-1/CDDP therapy only)

10.2.3 Expected Adverse Drug Reactions and Treatment Options

The following medications may be given concomitantly under the following guidelines. In case that dose reduction should be taken, see section 10.1.3-3 or 10.1.3-4.

(1) Neutrophil count decrease: Appropriate measures, such as dose change (reduction) or dose interruption, should be taken. Any accompanying fever should be treated with appropriate agent (e.g. antibiotics).
(2) Stomatitis: Severe Stomatitis interfering with continuation of oral drug treatment should be managed by appropriate measures such as dose change (reduction) or dose interruption.
(3) Nausea/vomiting: Severe nausea/vomiting interfering with continuation of oral drug treatment should be treated by appropriate agent (e.g. antiemetics).

(4) Anorexia: Appropriate measures, such as dose change (reduction) or dose interruption, should be taken. Taken actions for causal disease of Anorexia such as Nausea/vomitings should be taken as well.
(5) Diarrhea: Severe diarrhea should be managed by dose interruption of TAS-118 and S-1 and appropriate fluid replacement as needed while adequately monitoring fluid and electrolyte balance. Antidiarrheal treatment (e.g. loperamide hydrochloride) should be considered while diarrhea is still mild if prevention of its exacerbation is required on the basis of careful monitoring.
(6) Skin eruption: Skin eruption should be managed by appropriate measures such as dose reduction or dose interruption.
(7) Platelet decrease: Appropriate measures, such as dose change (reduction) or dose interruption, should be taken.
(8) Peripheral sensory neuropathy: Paresthesia or dysesthesia of hands, feet or area surrounding the mouth and lips (peripheral neuropathy) occurs in almost all patients from immediately after the administration of L-OHP. Carefully observe the patient's state because a constricted feeling of the larynx and pharynx (dysesthesia of the larynx and pharynx) may appear, and take appropriate measures such as dose reduction/interruption if such abnormalities occur.
(9) Hypersensitivity: Appropriate measures, such as antihistamic agent or steroid, should be taken.
(10) Renal disorder: Before and after treatment with CDDP, adequate hydration and coadministration of diuretics to maintain sufficient urinary volume shall be performed in order to prevent renal disorder. When renal insufficiency occurs, careful fluid management, electrolyte replacement, and if required, renal dialysis shall be performed to restore urinary volume.

10.3 Supportive therapy and other points to be considerd

- Therapies required for study drug (L-OHP or CDDP) administration (supportive therapies)
  - administration of 5-HT_3 receptor antagonist, NK1 receptor antagonist, and steroid as prophylaxis of nausea and vomiting
  - hydration for prophylaxis of renal disorder
- In patients with past medical history of Hepatitis B infection, attention should be paid to signs or symptoms of the reactivation of Hepatitis B, and regular monitoring for liver function tests or viral markers are recommended.

10.4 Instruction to Patients for Handling Study Medication (TAS-118 or S-1)

The patient must be instructed in the handling of study medication as follows:

- To store the study medication at room temperature
- To only open the indicated sachet at the time of dosing (TAS-118)
- To only take out the indicated dose from the PTP sheet at the time of dosing (S-1)

- Not to take out study drugs in advance of the next scheduled dosing
- Take the study drugs within 1 hour after the morning and evening meals, and to keep at least about 8 hours between the two meals
- To make every effort to take doses on schedule
- Not to take any missed doses, and report it
- If the patient vomits after taking study medication, the patient should not take another dose
- To take study medication after completing a meal (morning and evening meal) with a glass of water
- To keep study medication in a safe place and out of reach of children
- To bring all unused study medication to the site at each visit

11. Data Items and Schedule for Testing and Monitoring

11.1 Data Items and schedule for Testing and Monitoring

Table 11.1-1 Data items for testing and monitoring

Data items for testing and monitoring	
Informed consent	Date of informed consent
Patient background	Sex, age, country, race, past medical history, complications, date of first diagnosis, site of primary lesion, clinical stage, distant metastasis, histological type, whether or not past treatment included any of the following: gastrectomy (surgical site, procedure, date, outcome); previous treatment (regimen, start/end dates), HER2 status
Height, body temperature, blood pressure	Height (only at randomization), body temperature, blood pressure (systolic/diastolic)
ECOG PS, weight	ECOG PS, body weight
Hematology	Hemoglobin, white blood cell count, white blood cell fractions (percentages of neutrophils and lymphocytes), platelet count
Serum chemistry	Serum AST (GOT), serum ALT (GPT), serum ALP, serum albumin, total serum bilirubin, serum creatinine, creatinine clearance (only at randomization), LDH, serum CRP, serum electrolytes (Na, K, Ca)
Urinalysis	Urine protein (qualitative)
Physical examination	Stomatitis, diarrhea, anorexia, peripheral sensory neuropathy
Electrocardiography	Resting 12-lead electrocardiography
Pregnancy test	Pregnancy test
Tumor measurement	CT, MRI
Tumor markers	CA19-9, CEA
Compliance with study treatment	Compliance with treatment, missed doses, non-compliance e.g. with dose level, discontinuation (dose interruption) during treatment cycle, changes in recovery period
Concomitant medications/regimen	Concomitant medications (regimen, reason)
Post treatment	Whether or not a post treatment is performed (if yes, regimen and start date and end date)
Hospitalization	Date of admission, reason for admission, date of discharge
Survival status	Survival date, date of death, cause of death

11.1.1 Collection and Submission of Images

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded.

Contrast enhanced CT is the preferred method for tumor assessments. If contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and magnetic resonance imaging (MRI) of the abdomen and pelvis. Spiral CT should be performed using a 5 mm or less continuous reconstruction algorithm. Images must be acquired of the chest, abdomen and pelvis at each time point. Only CT and MRI may be used for tumor measurement.

Imaging data of baseline and requested for submission by sponsor must be captured according to the format of Digital Imaging and Communication in Medicine (DICOM) be submitted to the sponsor.

11.2 Testing and Monitoring Schedule

Table 11.2-1 A Study Schedule Arm A (TAS-118/L-OHP)

Procedure	Pretreatment Period				Study Treatment Period		Post-treatment Follow-up Period			
					Arm A					
	within 28 days prior to randomization	within 21 days prior to randomization	within 14 days prior to randomization	within 7 days prior to Day 1 of the first treatment cycle [e]	Day 1	Before initiation of next cycle [h, i] **Day15 (Day 14 to 18)**	End of Treatment [j] **(+14 days)**	**Safety Follow-up [k] 30 days after last dose of study treatment (+14 days)**	**Tumor Follow-up Every 6 weeks (+/- 1 week)**	Survival Follow-up **Every 12 weeks (+/-2 weeks)**
TAS-118 treatment					X [f] (Day 1 - 7)					
L-OHP treatment					X [f]					
Signed ICF	X									
Patient Background	X									
Height			X							
Pregnancy Test [a]			X							
Weight			X	X	→[g]		X	X		
ECOG PS			X	X	→[g]		X	X		
Blood Pressure			X	X	→[g]		→[g]			
Body Temperature			X	X	→[g]		→[g]			
ECG			X		→[g]		→[g]			
Physical Examination			X	X		X	X	X		
Hematology			X	X		X	X	X		
Serum Chemistry [b]			X	X		X	X	X		
Urinalysis [b]			X	X		X	X	X		
Tumor Markers [c]			X	→	→	→	→	→	X	
Tumor Measurements [c]		X		→	→	→	→	→	X	
Concomitant Medications [d]	X			→	→	→	→	X		
AE/SAE Assessment [d]	X			→	→	→	→	X		
Post Tratment										X
Survival Status					→	→	→	→	→	X [l]

a. If the patient is female and of childbearing potential, a pregnancy test (serum or urine) must be done and the results must be negative at baseline.
b. Creatinine clearance is mandatory only at prior to randomization.
c. Every 6 weeks starting on the day of randomization (the data may be collected within 1 week before or after the scheduled date). Patients without PD defined by RECIST version 1.1 must be followed for tumor assessment.
d. Monitor patients for any medications and untoward medical events from the time of signed ICF through the safety follow-up period.
e. These data may be collected within 7 day prior to Day 1 of the first treatment cycle. These tests may be substituted by the data obtained within 14 days prior to randomization if screening data is obtained within 7 days prior to Day 1 of the first treatment cycle.
f. Study drug administration is to be initiated within 8 days after randomization.
g. If abnormalities are indicated by other physical examination or tests, it must be performed.
h. These data may be collected 15 days after Day 1 (from Day 14 to Day 18 if not feasible on Day 15) of each treatment cycle.
i. Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date). Examination is mandatory on Day 1 or the day before starting the study treatment specified in this protocol.
j. End of treatment assessments must be completed within 14 days from the date of last dose of study drug.
k. These data may be collected 30 days after last dose of study drug or until the start of new anti-tumor therapy, whichever comes first. In cases an AE/SAE related to study drug is not resolving, the safety follow-up period will be extended.
l. Obtain survival status (alive/ dead) at scheduled 12-week time intervals from randomization until death, and at the cutoff date for second interim analysis and primary evaluation (the data may be collected within 2 weeks before or after the scheduled date).

Table 11.2-2 A Study Schedule Arm B (S-1/CDDP)

Procedure	Pretreatment Period				Study Treatment Period				Post-treatment Follow-up Period			
					Arm B							
	within 28 days prior to randomization	within 21 days prior to randomization	within 14 days prior to randomization	within 7 days prior to Day 1 of the first treatment cycle [e]	Day 1	Day 8 [i] **(Day 6 to 15)** (Japan)	Day 15 [j] **(Day 8 to 22)**	Before Initiation of next treatment cycle [k,l] **Day36 (Day 29 to 43)**	End of Treatment [m] **(+14 days)**	**Safety Follow-up [n] 30 days after last dose of study treatment (+14 days)**	**Tumor Follow-up Every 6 weeks (+/- 1 week)**	Survival Follow-up **Every 12 weeks (+/-2 weeks)**
S-1 treatment					X [f] (Day 1 - 21)							
CDDP treatment (Korea)					X [f]							
CDDP treatment (Japan)						X [g]						
Signed ICF	X											
Patient Background	X											
Height			X									
Pregnancy Test [a]			X									
Weight			X	X	→[h]				X	X		
ECOG PS			X	X	→[h]				X	X		
Blood Pressure			X	X	→[h]				→[h]			
Body Temperature			X	X	→[h]				→[h]			
ECG			X		→[h]				→[h]			
Physical Examination			X	X		X[i]	X	X	X	X		
Hematology			X	X		X[i]	X	X	X	X		
Serum Chemistry [b]			X	X		X[i]	X	X	X	X		
Urinalysis [b]			X	X		X[i]	X	X	X	X		
Tumor Markers [c]			X	→	→	→	→	→	→	→	X	
Tumor Measurements [c]		X		→	→	→	→	→	→	→	X	
Concomitant Medications [d]	X			→	→	→	→	→	→	X		
AE/SAE Assessment [d]	X			→	→	→	→	→	→	X		
Post Treatment												X
Survival Status					→	→	→	→	→	→	→	X [o]

a. If the patient is female and of childbearing potential, a pregnancy test (serum or urine) must be done and the results must be negative at baseline.
b. Creatinine clearance is mandatory only at prior to randomization.
c. Every 6 weeks starting on the day of randomization (the data may be collected within 1 week before or after the scheduled date). Patients without PD defined by RECIST version 1.1 must be followed for tumor assessment.
d. Monitor patients for any medications and untoward medical events from the time of signed ICF through the safety follow-up period.
e. These data may be collected within 7 day prior to Day 1 of the first treatment cycle. These tests may be substituted by the data obtained within 14 days prior to randomization if screening data is obtained within 7 days prior to Day 1 of the first treatment cycle.
f. Study drug administration is to be initiated within 8 days after randomization.
g. CDDP administration shall be permitted within 2 days before and 7 days after the reference day.
h. If abnormalities are indicated by other physical examination or tests, it must be performed.
i. When administering CDDP, the examination on the day before administration or on the day of administration until the start of administration (hematology, serum chemistry, urinalysis, and physical examination) shall be mandatory.
j. These data may be collected 15 days after Day 1 (from Day 8 to Day 22 if not feasible on Day 15) of each treatment cycle. Collect this data after the data of day8 and don't put the data of day 8 together in Japan.
k. These data may be collected 36 days (from Day 29 to Day 43 if not feasible on Day 36) after Day 1 of each treatment cycle.
l. Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date). Examination is mandatory on Day 1 or the day before starting the study treatment specified in this protocol.
m. End of treatment assessments must be completed within 14 days from the date of last dose of study drug.
n. These data may be collected 30 days after last dose of study drug or until the start of new anti-tumor therapy, whichever comes first. In cases an AE/SAE related to study drug is not resolving, the safety follow-up period will be extended.
o. Obtain survival status (alive/ dead) at scheduled 12-week time intervals from randomization until death, and at the cutoff date for second interim analysis and primary evaluation (the data may be collected within 2 weeks before or after the scheduled date).

11.3 Tests at Randomization or before Initiation of Study Treatment

The investigator (subinvestigator) should obtain written informed consent from each subject candidate before randomization. Then the investigator (subinvestigator) or the CRC prepares the following findings and test results, and verifies the eligibility of the candidate. In addition to the inclusion and exclusion criteria, the results of tests such as CT or MRI should be included in the eligibility assessment on an as-needed basis. The results of unscheduled tests performed before informed consent, if available, may be used as the basis for randomization. Participation of a patient being treated in another hospital/department at the time of randomization should be notified to his or her attending physician.

Eligibility for randomization in this study will be determined from review of results of the baseline assessments in relation to the inclusion/exclusion criteria (see Section 8.1, 8.2). Obtain the following at baseline:

(1) Within 28 days prior to randomization
- Informed consent, patient background, AE/SAE assessment, concomitant medications

(2) Within 21 days prior to randomization
- Tumor measurement, AE/SAE assessment, concomitant medications

(3) Within 14 days prior to randomization
- Height, weight, body temperature, blood pressure, ECOG PS, hematology, serum chemistry, urinalysis, tumor markers, pregnancy test, electrocardiography, physical examination, AE/SAE assessment, concomitant medications

(4) Within 7 days prior to Day 1 of the first treatment cycle
- Weight, body temperature, blood pressure, ECOG PS, hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- These tests may not be needed, if it is overlapped with the test date which is "(3) within 14 days prior to randomization".

11.4 Tests during Study Treatment

Arm A (TAS-118/L-OHP)

(1) Before initiation of next treatment cycle (Day15) (from Day 14 to Day 18 if not feasible on Day 15)
- Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- Examination is mandatory on Day1 or the day before starting study treatment specified in this protocol.

(2) If initiation of next treatment cycle is postponed
- ☐ Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- Every 1 week starting on Day 1 of each treatment cycle (the data may be collected within 7 days before the scheduled date).

(3) If any of abnormality is suspected (if necessary)
- Weight, body temperature, blood pressure, ECOG PS, electrocardiography

(4) Every 6 weeks from the day of randomization (within 1 week before or after the scheduled date)
- Tumor measurement, tumor markers

If PD is strongly suspected by any symptoms or signs, preform extra tumor measurement objectively at the discretion of the investigator (or subinvestigator) even if not the scheduled date.
In case of performing extra tumor measurement, the measurement of the tumor marker is not mandatory.

Arm B (S-1/CDDP) [CDDP on Day1] (Korea)

(1) Day 15 in each cycle (from Day 8 to Day 22 if not feasible on Day 15)
- Physical examination, hematology, serum chemistry, urinalysis, AE/SAE assessment, concomitant medications

(2) Before initiation of next treatment cycle (Day36) (from Day 29 to Day 43 if not feasible on Day 36)
- Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- Examination is mandatory on Day1 or the day before starting study treatment specified in this protocol.

(3) If initiation of next treatment cycle is postponed
- ☐ Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- ☐ Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date).

(4) If any of abnormality is suspected (if necessary)
- Weight, body temperature, blood pressure, ECOG PS, electrocardiography

(5) Every 6 weeks from the day of randomization (within 1 week before or after the scheduled date)
- Tumor measurement, tumor markers

If PD is strongly suspected by any symptoms or signs, preform extra tumor measurement objectively at the discretion of the investigator (or subinvestigator) even if not the scheduled date.
In case of performing extra tumor measurement, the measurement of the tumor marker is not mandatory.

Arm B (S-1/CDDP) [CDDP on Day8] (Japan)

(1) Day 8 in each cycle (on the day before administration or on the day of administration until the start of administration) (from Day 6 to Day 15 if not feasible on Day 8)
- Physical examination, hematology, serum chemistry, urinalysis, AE/SAE assessment, concomitant medications

(2) Day 15 in each cycle (from Day 8 to Day 22 if not feasible on Day 15)
- Physical Examination, Hematology, serum chemistry, urinalysis, AE/SAE assessment, concomitant medications

(3) Before initiation of next treatment cycle (Day36) (from Day 29 to Day 43 if not feasible on Day 36)
- Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- Examination is mandatory on Day1 or the day before starting study treatment specified in this protocol.

(4) If initiation of next treatment cycle is postponed
- ☐ Hematology, serum chemistry, urinalysis, physical examination, AE/SAE assessment, concomitant medications
- ☐ Every 1 week starting on Day 1 of each treatment cycle if the next treatment cycle is delayed (the data may be collected within 7 days before the scheduled date).

(5) If any of abnormality is suspected (if necessary)
- Weight, body temperature, blood pressure, ECOG PS, electrocardiography

(6) Every 6 weeks from the day of randomization (within 1 week before or after the scheduled date)
- Tumor measurement, tumor markers

If PD is strongly suspected by any symptoms or signs, preform extra tumor measurement objectively at the discretion of the investigator (or subinvestigator) even if not the scheduled date.

In case of performing extra tumor measurement, the measurement of the tumor marker is not mandatory.

11.5 End of Treatment

An end of treatment visit will be conducted at the date of last dose of study drug (+14 days).

Perform the following assessments:
- ECOG PS, weight, physical examination, hematology, serum chemistry, urinalysis, AE/SAE assessment, concomitant medications (including new anti-tumor therapy)

As needed (when abnormalities are indicated):
- Body temperature, blood pressure, electrocardiography

11.6 Safety Follow-up

A Safety Follow-up visit will be conducted 30 days (+ 14 days) after the last dose of study drug. Moreover, if an adverse drug reaction due to the study drug occurs after the end of the safety follow-up period, this information should be reported. If the patient starts new anti-tumor therapy within 30 days of the last dose of study treatment, the Safety Follow-up Visit should be performed prior to the start of new anti-tumor therapy. If the patient is unable to return to the site prior to the initiation of new treatment, a follow-up phone call can be

conducted by the site to collect any new safety information that occurred between the “11.5 End of Treatment Visit” and the initiation of the new treatment.

Perform the following assessments:

- ECOG PS, weight, physical examination, hematology, serum chemistry, urinalysis, AE/SAE assessment, concomitant medications (including new anti-tumor therapy)

As needed (when abnormalities are indicated):

- Body temperature, blood pressure, electrocardiography

11.7 Tumor Follow-up

For patients who discontinued treatment for reasons other than radiologic disease progression defined by RECIST version 1.1, tumor follow-up visit will be performed every 6 weeks (+/-1 week) from randomization until the patient develops radiologic disease progression defined by RECIST version 1.1, or initiation of new anti-tumor therapy.

Perform the following assessments:

- Tumor measurement, tumor markers

11.8 Survival Follow-up

All treated patients will be followed for survival status (alive/dead) and new anti-tumor therapy at scheduled 12-week (+/- 2 weeks) time intervals from randomization until death, and at the cutoff date for second interim analysis and primary evaluation. Patients will be followed until the target number of events (deaths) is met. The investigator (subinvestigator) should make every effort to contact the patient or primary caregiver to determine his/her survival status. Survival information must be documented in the patient’s records. If patient wishes to discontinue the study treatment (including withdrawal of consent), survival follow-up will be continued.

12. Pharmacokinetics and Pharmacogenomics

Not included in this study.

13. Discontinuation of study

13.1 Discontinuation criteria for individual subject

13.1.1 Study Treatment Discontinuation Criteria

Discontinue the study treatment if any of the following occur:

- Disease progression defined by RECIST version 1.1
- Patient has an adverse event (AE) that in the opinion of the investigator (subinvestigator) requires the study treatment to be discontinued
- Patient has not taken the study drug for more than 28 consecutive days
- Application for curative surgery due to tumor shrinkage
- Patient has a critical protocol deviation
- Pregnancy
- Patient request to discontinue the study treatment
- The investigator (subinvesitigator) concludes that the patient needs to discontinue the study treatment
- Study is completed

13.1.2 Safety Follow-up Discontinuation Criteria

In the case of follows, safety follow-up is discontinued.

- 30 days after the last dose study treatment
- The start of new anti-tumor therapy
- Patient meets one of the survival follow-up discontinuation criteria
- Safety follow-up becomes impossible due to changing hospital or other reasons
- Patient wishes to discontinue the safety follow up (including withdrawal of consent)

If an AE/SAE related to study drug occurs after the end of the safety follow-up period, this information should be reported.

13.1.3 Tumor Follow-up Discontinuation Criteria

Only patients who discontinued study treatment without PD defined by RECIST version 1.1 will be followed for tumor assessments every 6 weeks (+/- 1 week) from randomization until one of the following occurs:

- Disease progression defined by RECIST version 1.1
- The starts of new anti-tumor therapy
- Patient meets one of the survival follow-up discontinuation criteria
- Patient wishes to discontinue the imaging and tumor marker measurement
- Tumor follow-up becomes impossible due to changing hospital or other reasons
- The investigator (subinvestigator) judges it necessary to discontinue the imaging for the safety of the patient

13.1.4 Survival Follow-up Discontinuation Criteria

A patient is considered “Discontinued from Survival Follow-up” only if one of the following occurs:

- Patient dies

· Study is completed or terminated by the sponsor or regulatory agencies.

13.2 Criteria for Discontinuation of Study in Individual Institutions

The sponsor may discontinue the study in a study institution where significant or continued non-compliance with GCP or the study protocol by an investigator (subinvestigator) is found to be compromising the proper conduct of the study. In that case, the sponsor will notify the discontinuation of the study to the investigator and the head of the institution in question.

If an investigator takes the initiative to discontinue the study, he/she should notify his or her intention and reasons in writing to the head of the study institution, who should then forward the notified intention and reasons for discontinuation/interruption in writing to the Institutional Review Board.

13.3 Criteria for Termination of Entire Study

The sponsor may terminate the study either entirely or partially at any time for whatever reason. In that case, the sponsor will notify the termination of the study and reasons in writing to the heads of the institutions, who should then forward the notification of termination and reasons to the Institutional Review Boards and investigators. The investigators (subinvestigators) should immediately advise subjects of the termination of the study, and initiate another treatment. The sponsor should notify the regulatory authorities of the termination of the study.

13.4 Post Treatment

Post treatments depend on investigator’s choice.

14. Efficacy Assessment

14.1 Assessment of Antitumor Efficacy (RECIST Guideline Version 1.1)

14.1.1 Evaluation of lesions

14.1.1.1 Measurement of Lesions

The diameters of individual lesions, the long axis for non-nodal lesions and the short axis for nodal lesions, should be measured (in mm) using objective diagnostic techniques.

14.1.1.2 Tumor Definitions

(1) Measurable Lesions

Measurable tumor lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT or MRI scan if using slice thickness of 5 mm or less, or at least double the slice thickness of CT or MRI scan if the slice thickness is >5 mm.

Measurable malignant lymph nodes: A lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT or MRI scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Only measurable lesions can be selected as target lesions.

(2) Non-measurable Lesions

Non-measurable lesions include:

- Small metastatic tumor lesions that have a longest dimension less than 10 mm or if slice thickness is greater than 5 mm less than twice the slice thickness.
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis.
- Truly non-measurable lesions (e.g., ascites).
- Primary lesion (in case primary lesion is not able to be evaluated as non-measurable lesion, evaluation of the lesion will not be performed.)

All non-measurable lesions can only be selected as non-target lesions.

(3) Target Lesions

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs should be identified as target lesions.
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
- When recording tumor measurements the longest diameter will be measured for

tumor lesions. For pathological lymph nodes, the short axis will be measured.

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded, even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response (CR) criteria are met.
- The sum of the diameters for all target lesions at beseline will be calculated as the beseline sum. The baseline sum will be used as a reference for follow-up tumor assessment.
- An option of 'Not Assessable' for a lesion will only apply to lesions that cannot be read due to technical reasons, for example:
  - CT artifact.
  - Patient positioning where the lesions are obstructed or cannot be seen.
  - Lesion that may not be seen in their entirety due to CT slice thickness.
- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

(4) Non-target Lesions

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded.
- All lesions (or sites of disease) other than target lesions, including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed until tumor follow-up discontinuation.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).

14.1.1.3 **Evaluation of Response in Target Lesions**

The response in target lesions should be evaluated using the 5-grade scale shown below.

Complete Response (CR):

Complete disappearance of non-nodal target lesions, and the short axes of all nodal target lesions below 10 mm (an assessment of CR with the sum of diameters being above 0 is possible if nodal lesions have been included in target lesions before the study treatment).

Partial Response (PR):

A decrease of at least 30% in the sum of the diameters of target lesions in comparison with the baseline value.

Stable Disease (SD):

The absence not only of tumor shrinkage corresponding to CR or PR but also of tumor growth corresponding to PD.

Progressive Disease (PD):

An increase of at least 20% and at least 5 mm in length in the sum of the diameters of target lesions in comparison with the smallest value among the sums obtained previously (including the baseline value).

Not Evaluable (NE):

Lack of examination for any reason; response corresponding to none of CR, PR, SD, and PD.

The diameters of target lesions should have their actual measurements recorded even when they have become very small (e.g. 2 mm). When the diameter has become "too small to measure", the measurement should be recorded as 0 mm if the lesion is considered to have disappeared, or a default value of 5 mm should be assigned if the lesion is believed to be present.

14.1.1.4 **Evaluation of Response in Non-Target Lesions**

The response in non-target lesions should be evaluated using the 4-grade scale shown below.

Complete Response (CR):

Complete disappearance of non-nodal non-target lesions, the short axes of all nodal non-target lesions below 10 mm, and all tumor marker levels at or below the institutional upper normal limits.

Non-Complete Response/Non-Progressive Disease (Non-CR/non-PD):

The presence of at least one non-nodal non-target lesion; or the short axis not less than 10 mm in at least one nodal non-target lesion; or any tumor marker levels above the institutional upper normal limits.

Progressive Disease (PD):

Clear progression of existing non-target lesions, where "clear progression" is, in the presence of target lesions, an increase in overall tumor volume which is assessed as warranting discontinuation of the study treatment despite SD or PR in the target lesions but does not apply to a "modest increase" in tumor volume, and in the presence of only non-measureable lesions, e.g. a 73% increase in tumor volume (equivalent to a 20% increase in the diameters of measurable lesions).

Not Evaluable (NE):

Lack of examination for any reason; response corresponding to none of CR, Non-CR/non-PD, and PD.

Examination of Pleural, Ascitic, and Pericardial Fluids: Any fluid in body cavities that has collected or increased in the absence of progression in both target and non-target lesions should be examined for cytology as needed, and assessed to determine whether its collection/increase represents an adverse event or PD.

Although this protocol specifies no procedures for confirmation of the appearance of new lesions, it is advisable that any findings suggesting development of new lesions be promptly investigated using appropriate diagnostic instruments.

14.1.2 Assessment of Overall Response

Assessments will be based on the definitions provided in Table 14.1.2-1 and Table 14.1.2-2 below.

Table 14.1.2-1 Time Point Response for Patients with Target (+/- Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR *
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* For CR, tumor marker must have been under upper limit of normal.

Table 14.1.2-2 Time Point Response for Patients with only Non-target Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR *
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* For CR, tumor marker must have been under upper limit of normal.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not

change the assigned time point response.

14.1.3 Best Overall Response Assessment

The best overall response as per RECIST Criteria (version 1.1) is the best response recorded from the start of the study treatment until the end of tumor follow-up period. The confirmation of tumor response for CR or PR is not required, but the duration of SD (or Non-CR/Non-PD) is set as 6 weeks from randomization (the data may be collected within 1 week before or after the scheduled date).

14.2 Overall Response Rate (ORR)

ORR is defined as the proportion of patients with the best overall response of CR or PR in tumor response evaluable population.

14.3 Disease Control Rate (DCR)

The assessment of DCR will parallel that of ORR, with DCR defined as the proportion of patients with objective evidence of CR, PR, or SD.

14.4 Progression Free Survival (PFS)

Progression free survival is defined as the time (in months) from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause, whichever comes first. Patients who receive post treatment before disease progression will be censored at the date of the last evaluable tumor assessment before post treatment is initiated.Patients who are alive with no disease progression at the time of the analysis will be censored at the date of the last confirmation as non-PD.

Event / Censoring	Case	Event date
Event	PD	the date of disease progression
	Death (without PD)	the date of death
Censoring	Non-PD at the time of analysis	the date of the last tumor assessment
	The date of PD is unknown	the date of the last tumor assessment
	Patient without any tumor assessment after randomization	the date of randomization
	Patient receive other post treatment for a reason other than PD	the date of the last tumor assessment
	Other	the date of the last tumor assessment

14.5 Time to Treatment Failure (TTF)

Time to treatment failure is defined as the time from the date of randomization until the date of last dose of study treatment. Patients who are still on study treatment as of the cut-off date will be censored at the last date of study treatment, or the cut-off date, whichever is earlier.

14.6 Overall Survival (OS)

Survival is defined as the time from the date of randomization to the date of death due to any cause. In the absence of death confirmation or for patients alive as of the cut-off date, patient will be censored at the date of last study follow-up, or the cut-off date, whichever is earlier.

15. Reporting Safety Information

15.1 Adverse Events/Serious Adverse Events

15.1.1 Adverse Events

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in a clinical study and does not necessarily have a causal relationship with the use of the product.

Treatment emergent adverse events are AEs that occur from the initiation of any study medication administration, and do not necessarily have a causal relationship to the use of the study medication.

Provide a complete and specific clinical diagnosis as an AE term. If a diagnosis is not available, then report physical examination. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03) terms are to be used to assess severity/provide the grade for each adverse event that is reported.

Refer to Sections 15.1.5 and 15.1.6 for definitions and reporting of pregnancy, medication errors, and overdose, respectively.

Symptoms or laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, should not be considered an AE. However, occurrences of new symptoms as well as worsening of pre-existing medical conditions are considered AEs. In addition, a new laboratory or instrumental abnormality that has a clinical impact on a patient (e.g., resulting in study medication dose reduction, treatment delay, treatment discontinuation, requires treatment due to abnormal values, or is considered medically important by the investigator) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

AEs will be reported from the time a patient signs informed consent through the period of patient follow-up (30 days after the last dose of study medication or until the start of new anti-tumor therapy, whichever is earlier). Document all AEs in the source documents. Documentation should include onset and resolution dates, severity/grade, relationship to study medication, and outcome of the event.

Any untoward medical event that occurs outside the period of patient follow-up (30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier) is not considered an AE. If any AEs are observed after the patient follow-up period has ended, only those AEs determined to have a causal relationship with the investigational drug will be recorded in the case report form.

Causal relationship:

(1) Related: The AE is related if it follows a reasonable temporal sequence from administration of study medication.

(2) Not related: The AE is not related when there is no reasonable possibility that the study medication caused the event. For the purposes of safety reporting, “no

reasonable possibility" means there is no evidence to suggest a causal relationship between the drug and the adverse event and one or more of the following conditions are true:

- Disease Under Study
- Medical Condition(s)
- Previous or Concomitant Medication
- Protocol-related Procedure
- Other

Outcome:

- Resolved without sequelae
- Resolved with sequelae
- Resolving (Should be used only in the reporting SAE)
- Unresolved
- Death
- Unknown

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- AE has resolved
- Although the AE has not yet resolved, the Investigator considers that the AE is stable or no further improvement is expected. An AE cannot be considered stabilized while the patient is on study medication. Ongoing AEs must be assessed for stabilization 30 days post after the last dose of study medication
- The start of new anti-tumor therapy
- Patient meets one of the survival follow-up discontinuation criteria
- Safety follow-up becomes impossible due to changing hospital or other reasons
- Patient wishes to discontinue the safety follow up (including withdrawal of consent)

15.1.2 Adverse Drug Reactions

Adverse drug reactions are concern noxious and unintended responses to a medicinal product within adverse events.

15.1.3 Serious Adverse Events (SAE)

A Serious Adverse Event (experience) or reaction is any untoward medical occurrence that at any dose:

(a) Results in death.

(b) Is life-threatening.
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(c) Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness:
- Emergency room visits less than 24 hours.
- Hospitalizations for preplanned procedures.
- Hospitalization for study-related treatment and procedures.

(d) Results in persistent or significant disability or incapacity.

(e) Is a congenital anomaly/birth defect.

(f) Is any other important medical event.
- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Serious adverse events must be reported to Taiho Drug Safety or designee within 24 hours from the time the investigator first becomes aware of the SAE. The SAE reporting process and contact information for reporting SAEs are provided in the CRF and SAE Completion Guidelines.

After the initial SAE notification to Taiho Drug Safety or designee, follow-up SAE information will be submitted each time that important follow-up information (e.g., diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

All SAEs within the follow-up window (e.g., within 30 days after the last dose of study medication or until the start of new anti-tumor therapy, whichever is earlier) established in the protocol will be reported to Taiho Drug Safety or designee.

If serious medical occurrences including deaths outside the follow-up window established by the protocol are reported to or observed by the investigator that he/she believes are related to the administration of the investigational product, it is the investigator's responsibility to report this occurrence to Taiho Drug Safety or designee.

15.1.4 **Disease Progression**

Disease progression is not an acceptable AE term. In cases of disease progression the relevant signs, symptoms and complications should be reported as an AE unless they meet the serious criteria. If any of the signs, symptoms and complications meets any of the serious criteria, they should be reported as an SAE. In both cases it should be indicated whether the signs, symptoms and complications are related to disease progression.

In cases of death due to clinical disease progression, clinical disease progression may only be reported as an SAE term if none of the relevant signs or symptoms support a fatal

outcome.

Radiological disease progression without relevant signs, symptoms and complications will not be reported as an AE or SAE.

15.1.5 Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for a female patient or for the female partner of the male patient should be reported within 24 hours from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and emailing or faxing it to Taiho Drug Safety or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted by emailing or faxing an updated Pregnancy Form to Taiho Drug Safety or designee.

If outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to Taiho Drug Safety or designee.

15.1.6 Other Information

Any information about overdose, or medication error, which was defined below, should be forwarded to the sponsor regardless of whether it is associated with an adverse event (even if not fulfilling seriousness criterion).

- Overdose: Administration at a dose above the dose specified in “section 10.1 Dose, administration method, and administration period”;
- Medication error: Any errors in administration of the study treatment, including the wrong agent, wrong route of administration, wrong dose/dosing interval, and accidental ingestion;

15.1.7 Breaking the Study Blind

This is an open-label study. Both investigators and patients will be aware of which treatment regimen the patient is receiving, TAS-118/L-OHP or S-1/CDDP.

15.2 Laboratory Evaluations

15.2.1 Reporting and Evaluation of Laboratory Test Results

Laboratory tests are to be performed as required per protocol. All laboratory values that are out of the normal range are to be evaluated for their clinical significance before exposing the patient to the next dose of study medication.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that is clinically significant, e.g., results in delay of study

medication dosing, study discontinuation, requires treatment due to abnormal values, or is considered by the investigator to be medical important, must be reported as an AE, unless it is considered a supporting lab to a clinical diagnosis that is already reported as an AE. All laboratory data will be analyzed using NCI CTCAE grade criteria (version 4.03).

15.2.2 Repeat Testing

Repeat the evaluation of any clinically significant laboratory test, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until new anti-tumor therapy is given.

15.3 Physical Examination and Performance Status

Perform physical examinations and performance status evaluations as described in the Study Procedures section of the protocol. If changes are observed, determine whether they meet the definition of an AE. Document all observations and evaluations.

15.4 Body Temperature, Blood Pressure and Body Weight

Verify and document body temperature, blood pressure (systolic/diastolic) and body weight. If a clinically significant change is observed, repeat the measurement as clinically indicated and evaluate for its clinical relevance and whether it meets the definition of an AE.

16. Statistical Analysis

The data obtained during this clinical trial will be analyzed following the details provided below. In addition to this document, we will also prepare a Statistical Analysis Plan (SAP), which will include further technical details and descriptions of the planned statistical analyses and summaries of the results.

16.1 Timing of Statistical analyses

Four analyses will be performed at the times of two interim analyses, time of primary evaluation, and time of final analysis as follows.

16.1.1 Interim Analyses

The Independent Data Monitoring Committee (IDMC) will perform two interim analyses. In order to evaluate the safety data, first interium analysis will be performed by the IDMC. At second interim analysis, the IDMC will evaluate the safety and efficacy data based on these analyses. The IDMC will propose whether the trial should stop earlier based on the results obtained to that point. Further details of the role and responsibility of IDMC and the review process are provided in the IDMC charter. The interim analyses will be performed with the data gathered up to following cutoff point.

(1) Data cutoff for the first interim analysis

・In safety analyses, the cutoff data will be defined on the basis of the date when 100 death events are confirmed.

(2) Data cutoff for second interim analysis

・The cutoff date for primary endpoint is the date when 219 death, which is the 50% required number of death events, are confirmed.

・In safety analyses, the cutoff data will be defined on the basis of the date when 219 death events are confirmed.

16.1.2 Primary Evaluation

The primary analysis will be performed when the cutoff date is determined, and CRFs, dispositions and adoptions of all patients are fixed again.

(1) Data cutoff for primary evaluation

・The cutoff date for primary endpoint will be set at the date when 491 death events are confirmed, representing the final number of events required.

・In safety analyses, the cutoff data will be defined on the basis of the date when 491 death events are confirmed.

16.1.3 Final Evaluation

At the end of the trial, statistical analyses will be performed using all the data gathered to this point.

16.2 Populations and Criteria for Handling Patient Data

16.2.1 Analysis Populations

The analysis populations are defined in Table 16.2.1-1.

The sponsor, in collaboration with the medical specialists, will determine the overall disposition of the patients if there are any problems except the following criteria for patient's disposition.

FAS will be included only in the primary analysis.

Table 16.2.1-1 Definitions of Analysis Populations

Analysis Population	Definition
Enrolled Population	All patients enrolled in this trial.
As Treated (AT) Population	Enrolled patients who received at least one dose of the study drug.
Full Analysis Set (FAS)	Patients in AT population who have gastric cancer at randomization.
Tumor Response (TR) Evaluable Population	Patients in FAS population presenting measurable lesions (at least one target lesion), evaluated for tumor responses at least once during treatment with the study drug.

16.2.2 Criteria for Handling Patient Data

The criteria for handling patient data are described below.

The sponsor, in collaboration with the medical specialists, will determine the approach to handle data if there are problematic patients for handling except the criteria listed below:

(1) Handling of missing values and abnormal values

・No specific measures will be implemented. Analyses will be performed using all the data gathered for each time frame. For each analysis proportions will be estimated on the basis of the whole population analyzed.

・The analyses will include all data points unless the laboratory tests, such as the effect of hemolysis during blood collection, showed obvious abnormal values. In the presence of excluding abnormal laboratory results from analysis, these values will still be provided and the reasons for exclusion clearly stated.

(2) Patients with violations of study drug randomization

・For those analyses involving the AT population, the data of patients who have been administered study drug of different treatment arm from allocated treatment arm will be treated as that arms based on actual administored study drug.

・In the analyses for FAS or TR population, data will be treated as allocated treatment arm.

16.3 Statistical Methods

The main statistical methods to evaluate the primary and secondary objectives of the trial are described below.

All the details of the analyses performed in the trial are described in the statistical analysis

plan and a report analysis plan will be separately developed.

16.3.1 Patient Disposition, Baseline and Treatment Characteristics

(1) Patient Disposition

The number of patients included in each population, the reasons for exclusion, and any randomization and/or stratification errors will be summarized schematically.

(2) Patient Baseline Characteristics

The distribution of data such as main patient background characteristics, disease characteristics, and baseline laboratory values will be summarized.

(3) Evaluation of Comparability

Deviation between study drugs will be evaluated using the appropriate statistical test depending on the characteristics of the data.

16.3.2 Primary Endpoint Analyses

Main methods of primary endopoint (OS) analysis are shown below.

(1) Primary analysis

- OS in the FAS will be compared between the two study treatment arms using stratified log-rank test by three stratification factors (significance level is 5% for 2 sided test). 0.305% and 4.899% are set at the time of second interim and main evaluation respectively by alpha spending function with O'Brien-Fleming form and considering correlation between each test statistic to maintain significance level throughout the study less than or equal to 5%. Superiority of efficacy of TAS-118/L-OHP arm to S-1/CDDP arm is statistically considered valid when either p-values are less than or equal to each significance level in each statistical test. Also, a confirmation of the superiority in the first interim analysis will not be done.

(2) Sensitivity analyses of primary analysis

- OS in the FAS will be compared between the two study treatment arms using unstratified log-rank test. In addition, Cox Proportional Hazard (CPH) model will be performed with the study drug as covariate.

(3) Secondary analysis of primary endpoint

Following analyses will be performed in FAS population.

- Hazard ratio of OS with 95% confidence interval will be estimated by CPH model with the study drug and three stratification factors as covariates.
- In each study treatment, survival curves of OS will be estimated and Median Survival Time (MST) with 95% confidence interval using the Kaplan-Meier method will be presented. Otherwise the number at risk and cumulative event free rate every three months will be presented.

・In each stratification factor and each study treatment, survival curves of OS will be estimated and MST with 95% confidence interval using the Kaplan-Meier method will be presented. Otherwise the number at risk and cumulative event free rate every three months will be presented.

16.3.3 Secondary Endpoints Analyses

Main methods of secondary endpoints analyses are shown below.

16.3.3.1 Efficacy Endpoints

(1) Overall Response Rate (ORR)

Following analyses will be performed in TR population.

・In each study treatment, best overall responses will be summarized and ORRs with 95% confidence interval will be estimated. The treatment comparison will be done using Fisher's exact test.

・In each study treatment, onset date, duration of response (duration of overall response and duration of overall complete response) for antitumor effect will be summarized in patients with responses.

(2) Disease Control Rate (DCR)

・In each study treatment and TR population, DCR based on the best overall response will be estimated. The treatment comparison will be done by Fisher's exact test.

(3) Progression Free Survival (PFS)

・In each study treatment and FAS population, survival curves of PFS will be estimated and MST with 95% confidence interval using the Kaplan-Meier method will be presented. Otherwise the number at risk and cumulative event free rate every three months will be presented.

・PFS in the FAS will be compared between the two study treatment arms using stratified log-rank test by three stratification factors. In addition, hazard ratio of PFS with 95% confidence interval will be estimated by CPH model with the study drug as covariates.

(4) Time to Treatment Failure (TTF)

・In FAS population, TTF analyses will be performed by the same ways as PFS analyses.

16.3.3.2 Treatment Status

(1) Treatment discontinuation

・For each study treatment and FAS population, treatment discontinuations and their reasons will be summarized.

(2) Dose Intensity

・For each study treatment and FAS population, actual dose intensity and relative dose intensity of each patient will be summarized.

16.3.3.3 Safety Analyses

Following analyses will be performed in AT population. However, same analyses will be done in FAS population if AT population doesn't correspond to FAS population.

(1) Adverse event

・Rate of adverse event will be summarized.

・For maximum grade of each adverse event in each patient, the number of patient and rate of adverse event by grade will be summarized.

・For all adverse events between onset of study drug administration and end of the trial, tables of their class, grade, onset date, causal relationship, outcome and treatment contents will be described.

(2) Adverse drug reaction

・For adverse drug reaction, same analyses as adverse events will be performed.

(3) Laboratory test

・Transition of main hematological laboratory values (White Blood Cell, Lymphocyte, Neutrophil, Hemoglobin, Platelet) at each point of each patient will be described as graph.

(4) Clinical findings

・For clinical findings (stomatitis, anorexia, diarrhea, peripheral sensory neuropathy), onset date of each patient, date of occurrence for maximum grade, first date of condition with grade 3 or higher, and time to recovery will be presented as list in each study treatment arm.

16.4 Determination of Sample Size

Number of target patients: 686 subjects

(TAS-118/L-OHP arm: 343 subjects, S-1/CDDP arm: 343 subjects)

Number of target patients as FAS: 650 subjects

(TAS-118/L-OHP arm: 325 subjects, S-1/CDDP arm: 325 subjects)

In a randomized phase II study of S-1/LV therapy, S-1/LV/L-OHP therapy, and S-1/CDDP therapy in patients with unresectable, advanced, recurrent gastric cancer ([redacted]), MST of the S-1/LV/L-OHP therapy was 18.4 months and MST of S-1/CDDP therapy was 12.6 months, respectively. In SOS trial which conducted in Japan and Korea,

MST of the S-1/CDDP (5-week-interval administration) was 13.9 months, although the Japanese subgroup showed an MST of 15.5 months. Taking the difference on the ratio of target number of randomized patient between Japan and Korea and on the target popuration in this trial into consideration, MST of the S-1/CDDP is assumed to be 14.5 months for this trial and MST of TAS-118/L-OHP is set 19.33 months (hazard ratio : 0.75).

In the condition that MST is exponentially distributed and 2-sided 4.899% significance level and 85% power, the required number of death events is 437 for logrank test in the primary analysis which compares OS of TAS-118/L-OHP arm with of S-1/CDDP for primary evaluation. In the case that patients are uniformally enrolled in accrual period of 19 months and follow-up period is 19 months, the total required number of patients can be estimated 686 including expectation of 5% exclusion from FAS. Patients can be additionally enrolled when the number of events is less than expectation in the evaluation during the trial. The sponsor will determine, in collaboration with the statistics advisor, the final number of patients if the number of patient increases.

Null and alternative hypotheses of statistial test are as follows

Null hypothesis H_0 : $\lambda_T / \lambda_C = 1$

Alternative hypothesis H_1 : $\lambda_T / \lambda_C \neq 1$

λ_C : Hazard of S-1/CDDP arm

λ_T : Hazard of TAS-118/L-OHP arm

Powers at various situations where expected MSTs of each arm change are shown in Table 16.4-1.

Table 16.4-1 Powers(%) at various situations where expected MSTs of each arm change

		MST of S-1/CDDP arm						
		12	13	14	14.5	15	16	17
MST of TAS-118/L-OHP arm	17	95.3	79.8	52.4	38	25.4	9.1	2.4
	18	98.8	92.4	74.5	61.5	47.5	23	8.5
	19	99.8	97.7	88.9	80.4	69.2	43.2	21
	19.33	99.9	98.5	92	<u>85</u>	75.2	50.3	26.6
	20	100	99.4	96.1	91.8	85	64.2	39.4
	21	100	99.9	98.8	97.1	93.9	80.9	59.5
	22	100	100	99.7	99.2	97.9	91.3	76.6

Note: Powers are estimated in the condition that the number of death events are 437 and 2-sided significance level is 4.899%. The underline is the power set in this trial.

17. Case Report Form

17.1 Preparation of CRF

The investigator shall be provided with standardized eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given.

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them, and when the data should be documented.

It is the responsibility of the investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All eCRFs should be fully completed to ensure accurate data interpretation.

The investigator should record all the data on eCRFs in accordance with time limit in the following items (Except the sponsor request to stop recording the data);

- Patient background：Within 14 days after randomization
- Administration record：Within 14 days after last administration of each cycle
- Hematology, serum chemistry, urinalysis：Within 14 days after the test date
- Survival, post treatment：14 days after getting the information
- Other items：Within 14 days after end of treatment

The computerized handling of the data by the sponsor after receipt of the eCRFs may generate additional requests via electronic queries or other means to which the investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be appended to the eCRFs held by the investigator and the sponsor.

18. Protocol Compliance, Deviation and Amendment

18.1 Protocol Compliance

(1) The investigator agrees with the sponsor the contents of a sample of the protocol and the case report form; in addition, to certify that he/she has agreed with compliance with this protocol, the investigator shall, together with the sponsor, sign and/or seal and date the protocol or other document in lieu of the protocol.

(2) In the event of revision of a sample of the protocol and the case report form, and in the event of revision of a sample of the protocol and the case report form pursuant to the instructions of the head of the medical institution in accordance with the institutional review board, the same as mentioned in above (1) shall apply.

18.2 Protocol Deviation

In attempting to change a protocol, the investigator and subinvestigators shall agree in writing in advance to obtain written approval in accordance with pre-review of the IRB.

The investigator must report promptly every change of the protocol that will have a significant effect on the conduct of the study or will increase the hazard to study subjects to the sponsor, the head of the medical institution and the IRB via the head of the medical institution. Where there is some medically compelling reason such as to eliminate an immediate hazard to a study subject, the investigator or subinvestigator may make a deviation from or a change of the protocol without prior written agreement with the sponsor and without prior approval of the IRB. In such a case, the investigator shall promptly report the content of deviation or change and the reason for it to the sponsor and the head of the medical institution, and submit the report to the IRB via the head of the medical institution to obtain written approval of the IRB.

The investigator is to record any deviation from the protocol, irrespective of any reasons whatsoever.

18.3 Revision of Protocol, etc.

(1) When the sponsor deems it necessary to revise the samples of the protocol and the case report form, the sponsor will provide the investigator with the proposed revisions of the protocol and the case report form.

(2) The investigator will fully consider the proposed revisions.

(3) In revising the samples of the protocol and the case report form, the sponsor shall obtain agreement of the investigator on the contents of the revised protocol and the case report form.

(4) The sponsor shall promptly submit the revised protocol and case report form to the head of the medical institution and obtain the approval of the IRB via the head of the medical institution.

However, when the revisions are made to the protocol, etc., due to the changes in administrative aspects of the study (e.g., change in organization or structure of the sponsor, change in name or name of diagnosis and treatment department of other medical institutions, change in location or telephone number(s) of other medical institutions and the sponsor, change in the title of the investigator, change in monitors, change in layout of a sample of the case report form, etc.), no new agreements are required.

19. Direct Access to Source Documents

The investigator and the head of the medical institution must provide direct access to all the study related records including source documents during monitoring and auditing relating to the study, and at the investigations by the IRB and regulatory authorities.

19.1 Identification of Source Documents

Items listed in (1) through (7) below will be handled as source documents related to the present study. Items (8) through (12) will be handled as "data that should be directly entered in the case report form and regarded as source data." A list of source documents, etc. stipulated in the monitoring plan will be prepared at each medical institution based on the prior confirmation by the investigator or subinvestigator and their copy will be submitted to the investigator and subinvestigators.

(1) Medical records (chart): registration form, informed consent form, records for oral consent, patient background characteristics examined, subjective symptoms and objective findings, vital signs, height, body weight, PS, records for concomitant medication/therapy (other than reasons for concomitance), start date and contents of post-treatment performed, records of incharge and out discharge from the hospital, and outcomes.
(2) Examination reports (pathological examinations, image analysis): Name of histopathological diagnosis and evaluation of lesions (results of cytological diagnosis of ascites/pleural effusion).
(3) Diagnostic images including CT, MRI, X-ray, echo, etc.
(4) Recording data of automated apparatuses (blood chemistry tests, urinalysis, etc.) and clinical laboratory values or clinical laboratory results
(5) Electrocardiogram waves: Electrocardiography
(6) Records of dosing of study drug
(7) Drug accountability log, delivery forms of study drug, receipt of study drug returned
(8) Pre-dosing subjective symptoms and objective findings/grades
(9) Records for images evaluation
(10) Reasons for concomitance, concomitant medication/therapy prescribed at other hospitals
(11) Presence or absence of adverse events, name of adverse events, serious/non-serious, clinical course (date, grade, outcome, etc.), treatment on study therapy, causal relationship with study drug, and reasons for terminating follow-up.
(12) Reasons for incharge and discharge from the hospital, reasons for discontinuation or termination from the study, and reasons for death.

19.2 Method of Direct Access to Source Documents

The monitor of the sponsor should cross-check the entries in the case report forms and source documents to confirm that descriptions are accurate with regard to the following. If there are any discrepancies between the entries in case report forms, etc., and source documents, the monitor will obtain from the investigator records explaining such discrepancies.

(1) Data required by the protocol have been accurately recorded in the case report form and the report on serious adverse events, and are consistent with the descriptions in the source documents.
(2) All changes in dosage regimen or treatment method, if any, have been recorded in the case report form for each patient.
(3) Adverse events have been recorded in the case report form in accordance with the protocol.
(4) All discontinued or drop-out cases among registered patients have been recorded in the case report form together with the reasons for discontinuation or drop-out.

20. Quality Control and Quality Assurance for the Study

20.1 Conduct of the study

The sponsor/CRO will implement and maintain quality control and quality assurance (QA) procedures with written standard operating proceduers (SOPs).

20.2 Quality Control of the Study

20.2.1 Monitoring Procedures

The sponsor will control the quality of the study by performing the main services as the follows in accordance with each study-related SOP and the monitoring plan of the study.

- To hold a briefing on study protocol for the investigator, subinvestigators, or clinical research coordinators to explain the method of screening subjects, examination on efficacy or safety, the methods of evaluation thereof.
- To perform periodic monitoring of participating medical institutions, in order to confirm the performance of the study in compliance with the protocol and GCP.
- To inspect the source documents so that the entries into the CRFs are accurate. To prepare a guidance for change or revision in the CRFs; if any CRF requires any change or revision, to request the investigator (subinvestigator) or clinical research coordinators to revise the relevant CRF.
- To check the entries into CRFs.
- To confirm whether required documents to be stored at the medical institutions are properly stored.
- To record or report the management of the study, data collection, data control, statistical analysis, analysis on adverse events, etc., in accordance with the sponsor's SOP, and check and confirm the foregoing.

20.2.2 Curriculum Vitae

All investigators and any subinvestigator(s) must provide Taiho Pharmaceutical Co., Ltd. with current signed and dated copies of their own curriculum vitae listing the experience, qualifications, and training prior to the beginning of the study.

20.3 Sponsor's Audits and Regulatory Inspections

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the investigator will permit auditing by the sponsor or its representative and inspections by regulatory authorities.

The investigator agrees to allow the auditors and inspectors to have direct access to the study records for review. The people performing these activities will not disclose any personal identity or personal medical information assessed.

The investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical trial. As soon as the investigator is notified of a planned inspection by the regulatory authorities or IRB/IEC, the investigator will inform the sponsor. Any results arising from

such inspections will be immediately communicated by the investigator to the sponsor. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during audits and or inspections.

21. Archiving of Records

21.1 Archiving of Records

21.1.1 Investigator

The investigator is responsible for the retention of all study documents according to institutional policies, local laws and ICH Parts 4.9.4 and 4.9.5 and for studies conducted under an Investigational New Drug (IND) application.

The investigator agrees to inform Taiho Pharmaceutical Co., Ltd. in writing of the intention to remove or destroy any study-related records. Prior to contacting Taiho Pharmaceutical Co., Ltd., the investigator must ensure that institutional and local requirements (for example, ICH Guidelines) have been satisfied. Taiho Pharmaceutical Co., Ltd. will provide authorization for destruction of such records to the investigator in writing.

In the event that all retention of records requirements have been fulfilled, but Taiho Pharmaceutical Co., Ltd. requests that the investigator maintain the records for a longer period of time, additional arrangements will be made.

21.1.2 Sponsor

The sponsor must retain all sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the sponsor intends to apply for approvals.

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor must maintain all sponsor-specific essential documents in conformance with the applicable regulatory requirements.

22. Compensation to Subjects and Investigators

If required by the applicable regulatory requirements, Taiho Pharmaceutical Co., Ltd. should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

Taiho Pharmaceutical Co., Ltd.'s policies and procedures should address the costs of treatment of patients in the event of trial-related injuries in accordance with the applicable regulatory requirements.

When patients receive compensation, the method and manner of compensation should comply with applicable regulatory requirements.

23. Confidentiality

All information provided to the investigator by the sponsor or sponsor's representatives, information produced during the clinical trial included, but not limited to the protocol, CRF, IB, and the results obtained during the course of the trial is confidential. Taiho Pharmaceutical Co., Ltd. has exclusive rights to access and use the data regarding this trial. The members of the research team agree not to discuss such information in any way without prior written permission from Taiho Pharmaceutical Co., Ltd.

However, the submission of the protocol and necessary documentation to the IRB/IEC is permitted. The IRB/IEC members have the same obligation of confidentiality.

The patient's personal data and investigator's personal data which may be included in the sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the investigator and or to the patients, the sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

24. Publication policy

All unpublished documentation (including the protocol, CRF, and IB) given to the investigator is strictly confidential. All recipients must agree not to disclose the information contained herein to any person without the prior written authorization of Taiho Pharmaceutical Co., Ltd. The submission of these documents to the IRB/IEC is permitted.

The investigator agrees that Taiho Pharmaceutical Co., Ltd. maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by Taiho Pharmaceutical Co., Ltd. in accordance with the guidelines set forth in the applicable publication or financial agreement.

The steering committee and sponsor discuss and determine the first presenter and time of the primary results at a major medical meeting in this study.

25. Study Period

Study period (Plan): December 2014 to May 2020

Patient recruitment period (Plan): December 2014 to June 2016

Study treatment period: Until 31 Jan 2020

26. Rationales

26.1 Validity of the clinical study design

Rationale for setting S-1/CDDP combination therapy as the control group

The standard first-line treatment for unresectable, with HER2-negative advanced recurrent gastric cancer was S-1/CDDP therapy in the 2014 Japanese Gastric Cancer Treatment Guidelines (ver. 4)[11]. In the 2014 Korean guidelines[12], the recommended regimen listed for patients previously untreated with chemotherapy is (5-FU, Capecitabine or S-1)/CDDP combination therapy or (5-FU or Capecitabine) /L-OHP combination therapy. From the above, it was determined appropriate to set the control group as S-1/CDDP therapy, the recommended regimen in both Japan and Korea.

Furthermore, the results of the Japanese-Korean phase III clinical study (SOS study[16])(S-1/CDDP therapy: 3-week-interval administration vs. 5-week-interval administration) have been published and MST for S-1/CDDP therapy (5-week-interval administration) was reported to be 13.9 months. The MST for S-1/CDDP therapy in the Japanese SPIRITS study was 13.0 months. Since the repeatability was fairly high for results on clinical performance obtained in different countries, it was determined appropriate to set the control group as S-1/CDDP therapy. The standard schedule for CDDP administration is commonly on Day 8 in Japan, whereas it is on Day 1 in Korea in dailiy practice. Almost all treatment methods (dose of S-1 and CDDP, schedule of S-1 administration) except for the schedule of CDDP administration are same between Japan and Korea. In addition, there were no difference in S-1/CDDP treatment group of SOS study between two countries in terms of efficacy and toxicity to be ignorable for conducting multinational trial. Therefore the CDDP administration day was set differently for each country.

Rationale for allocation adjustment factors

- PS (0, 1): PS is generally considered to be a factor that greatly affects the prognosis of patients.
- Measurable lesion (Yes, No): The difference of tumor volume between mesualable lesion and non-measurable lesion may affects the prognosis of patients.
- Country (Japan, Korea): Country was estimated due to multinational study.

26.2 Rationale for endpoints

According to the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan, survival rate or OS is recommended as primary endpoint in phase III trial to evaluate the clinical usefulness of antitumor agent.

Secondary endpoints used for this study are commonly used endpoints for the evaluation of the safety and efficacy of anticancer drugs.

26.3 Rationale for doses

(1) Rationale for TAS-118 dose selection

TAS-118 is a preparation containing S-1 and LV. Because LV alone has no antitumor effect, it is considered important to not reduce but to maintain the blood concentration of 5-FU, which is the active body of S-1, in the combination therapy of S-1 and LV in order to maintain the RR of S-1 alone and enhance the effect of LV. Therefore, S-1 will be administered at the usual dose in this study. The single dose of 25 mg of LV was considered appropriate on the basis of the experiences of the combination treatment with UFT, an oral fluoropyrimidine drug similar to S-1.

(2) Rationale for L-OHP dose selection

For regimens, including L-OHP used in foreign countries (FOLFOX, etc.), the recommended dose (RD) is usually 85 mg/m^2 every 2 weeks, which is the same as the approved dose of L-OHP for corolectal cancer in Japan. For the combination regimen of three drugs, S-1, LV, and L-OHP, the RD was also 85 mg/m^2 every 2 weeks; therefore, the dose of L-OHP in this study was also set at 85 mg/m^2 every 2 weeks.

(3) Rationale for CDDP dose selection

The RD of CDDP was 60 mg/m^2 in the phase I/II study of S-1 combined with CDDP in patients with gastric cancer[17]; and the phase III study (SPIRITS study[9]), the SOS study[24], G-SOX[13, 14] study, and the phase II study ([redacted]) were performed using the same RD. Thus, the same dose of CDDP will also be used in this study.

26.4 Rationale for administration methods

[redacted]

For S-1/CDDP therapy, S-1 shall be administered for 21 days followed by 14 days rest and CDDP shall be administered on Day 8 of each cycle, similarly to the regimens in the phase I/II study[25], phase II study[redacted], and phase III study[9, 13] of S-1/CDDP in patients with gastric

cancer. The CDDP administration day was set differently for each country (Day 1 in Korea and Day 8 in Japan). The standard schedule for CDDP administration is commonly on Day 8 in Japan, whereas it is on Day 1 in Korea in dailiy practice. Almost all treatment methods (dose of S-1 and CDDP, schedule of S-1 administration) except for the schedule of CDDP administration are same between Japan and Korea. In addition, there were no difference in S-1/CDDP treatment group of SOS study between two countries in terms of efficacy and toxicity to be not ignorable for conducting multinational trial. Therefore the CDDP administration day was set differently for each country.

26.5 Rationale for inclusion criteria

(1) As it is stated that "the confirmation of malignancy with histological examination or cytology is necessary" in the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan, this criterion has been established as an inclusion criterion to select the target disease of this study.
(2) In the Guidelines for Clinical Evaluation Methods of anti-cancer Drugs in Japan, it is stated that "RECIST guideline is recommended to be used as a standard for assessment of antitumor efficacy, and appropriate guideline is necessary to be used for more appropriate assessment of the investigational drug taking scientific progress into account."
(3) To evaluate the efficacy of the study drugs appropriately, this criterion has been established.
(4) To evaluate the efficacy of the study drugs appropriately, this criterion has been established.
(5) To evaluate the safety of the study drugs as appropriate as possible, patients are included with reference to the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan.
(6) In the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan, it is stated that "the age of subjects is not limited in principle, but it shall be determined based on physiological functions and ability to give consent." Therefore, patients aged 20 years or older are included based on the ability to give consent. Besides, an annotation is set referring to the criteria of SOS study[24] and the phase II study ([redacted]) which showed higher rate of treatment discontinuation due to adverse event in the group consist of the subject who were 75 years or higher at randomization compare with other group.
(7) Since it is described that "it is necessary that the physiological functions (such as hematopoietic, cardiac, pulmonary, hepatic and renal functions) of patients are retained sufficiently" in the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan, this criterion has been established to evaluate the safety of the study drugs as appropriately as possible. The criteria for each laboratory data are established based on Phase II ([redacted]), investigator's brochure, and package insert.
(8) Expected survival duration of 90 days or longer is determined as the inclusion criterion because the period is considered to be necessary to evaluate the efficacy and safety of the study drugs, with reference to the Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs in Japan.

(9) Since TAS-118 and S-1 are oral drugs, this criterion has been established to include patients who are able to take drugs orally.
(10) This criterion is established according to the guideline for ICH-GCP.

26.6 Rationale for exclusion criteria

(1) Since serious drug hypersensitivity may affect the evaluation of the safety of study drugs, this criterion has been established.
(2) This criterion has been established to exclude the effect of another study drug which safery evaluation have not been done.
(3) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(4) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(5) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(6) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(7) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(8) Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(9) Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(10) Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(11) Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(12) Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(13) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(14) This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.

(15)This criterion has been established because the inclusion of those patients is considered to be inappropriate to ensure the safety of subjects and to evaluate the safety of the study drugs.
(16)This criterion has been established because the inclusion of those patients is considered to be inappropriate to evaluate the efficacy and safety of the study drugs.
(17)Since patients with those severe complications may not have stable physiological function and such patients are considered to be inappropriate for evaluating the safety of the study drugs, this criterion has been established.
(18)Since the PS of those patients is expected to be worsened and such patients are considered to be inappropriate for evaluating the efficacy and the safety of the study drugs, this criterion has been established.
(19)This criterion has been established because the inclusion of those patients is considered to be inappropriate to evaluate the efficacy and safety of the study drugs.
(20)This criterion has been established because the teratogenicity of S-1 has been observed in nonclinical studies.
(21)This criterion has been established from ethical aspects for subjects.
(22)This criterion has been established to exclude other inappropriate subjects to ensure the safety of subjects and evaluate the efficacy and safety of the study drugs appropriately.

26.7 Rationale for prohibited concomitant drugs and therapies

(1) The use of those drugs is considered inappropriate to evaluate the efficacy of the study drugs.
(2) Safety information is not available for drug-drug interactions between the study treatment and other study drugs. This criterion has been established to ensure the safety of subjects.
(3) Those drugs may enhance the side effect of TAS-118 and S-1.
(4) Those drugs may enhance the side effect of TAS-118 and S-1.
(5) The use of those therapies is considered inappropriate to evaluate the efficacy of the study drugs.

26.8 Rationale for precautions for concomitant drugs and therapies

(1) Tegafur may enhance the effect of warfarin potassium.
(2) Tegafur may inhibit the metabolism of phenytoin to increase the blood phenytoin concentration, so that phenytoin toxicities may occur (such as queasy/vomiting, nystagmus, and movement disorder).
(3) Concomitant administration of these drugs with CDDP may enhance renal disorder and ototoxicity.
(4) Concomitant administration of the drug with CDDP may enhance renal disorder.
(5) Concomitant administration of the drug with CDDP may enhance ototoxicity.

26.9 Rationale for contraception period

Since the teratogenicity of S-1 has been observed in nonclinical studies, the same contraception period as that generally used for an antitumor agent known to be teratogenic is set in this study.

27. References

[1] International Agency for Research on Cancer, World Health Organization. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available from: http://globocan.iarc.fr/fact-sheets-population.aspx.

[2] Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer.1995; 71: 587-591.

[3] Murad AM, Santiago FF, Petroianu A, Rocha PRS, Rodrigues MAG, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer. 1993;72:37-41.

[4] Glimelius B, Hoffman K, Haglund U, Nyrén O, Sjödén PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol. 1994; 5: 189-190.

[5] MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, et al. 5-fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med. 1980;93:533-536.

[6] Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and Oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36-46.

[7] Cutsem EV, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991-4997.

[8] Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063-1069.

[9] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215-221.

[10] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-697.

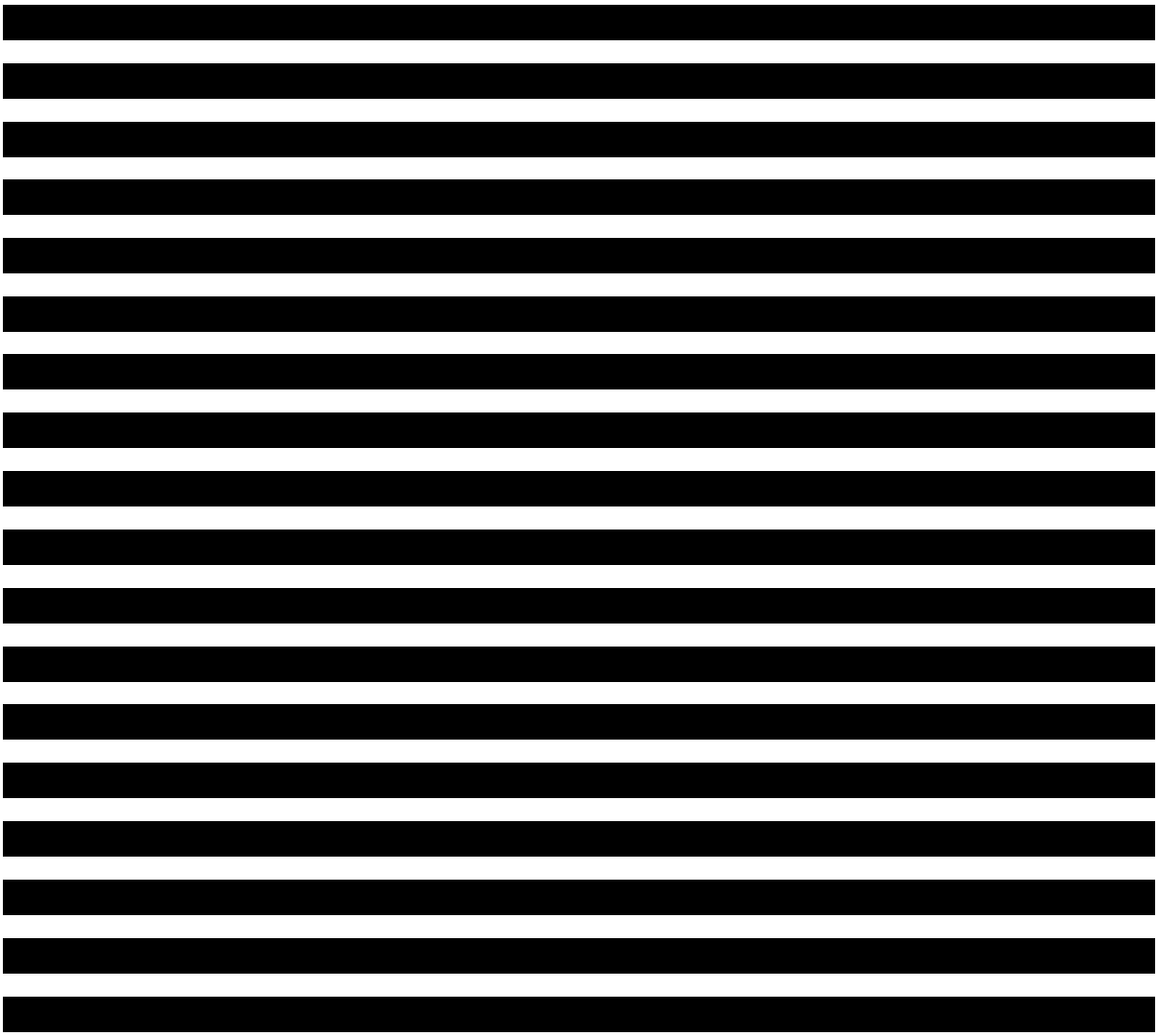
[11] The Japanese Gastric Cancer Treatment Guidelines Revised in May 2014 (ver. 4), edited by the Japanese Gastric Cancer Association, Kanehara & Co., Ltd.

[12] Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, et al. Clinical Practice Guidelines for Gastric Cancer in Korea:An Evidence-Based Approach. J Gastric Cancer. 2014;14:87-104.

[13] Higuchi K, Koizumi W, Yamada Y, Nishikawa K, Gotoh M, Fuse N, et al. Randomized phase III study of S-1 plus oxaliplatin versus S-1 plus cisplatin for first-line treatment of advanced gastric cancer. J Clin Oncol. 2013;31 (suppl 4; abstr 60).

[14] Gotoh M, et al; Abstract PD7-7, The 86th Annual Meeting of Japanese Gastric Cancer Association 2014.

[15] Thirion P, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol. 2004;22:3766-3775.



[16] Ryu MH, Baba E, Lee KH, Boku N, Park YI, Hyodo I, et al. Phase III trial of a 3-weekly versus 5-weekly schedule of S-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOS study. J Clin Oncol. 2013;31 (suppl; abstr LBA4024).

[17] Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer. 2003;89:2207-2212.

Appendix 1. Definition of EGJ

The area extending 2 cm above to 2 cm below the esophagogastric junction (EGJ) is designated the EGJ area. Tumors having their epicenter in this area are designated EGJ carcinomas irrespective of histological type.

Appendix 2. Definition of HER2 status[11]

HER2 status	Criteria
Positive (Meet either criteria)	1. Score as 3+ on immunohistochemistry (IHC) 2. Score as 2+ on IHC and Positive on fluorescence in situ hybridization (FISH)
Negative	Other

Using Silver *in situ* hybridization (SISH) or other tests instead of FISH test for confirmation of HER2 status are allowed.

Appendix 3. Cockcroft-Gault formula

The Cockcroft-Gault formula:

Estimated creatinine clearance (mL/min)
= (140 - age) x Body weight (kg) / [(72 x Serum creatinine (mg/dL)]

For women, the obtained value is multiplied by a factor of 0.85.

Appendix 4. Du Bois formula

The BSA will be calculated by the IWRS using the following DuBois formula. All BSA calculations are rounded down, so the number must be set to 2 decimal places.

$$BSA\ (m^2) = \ ([Body\ Weight\ (kg)\ ]^{0.425} \times [Height\ (cm)]^{0.725}) \times 0.007184$$

Appendix 5. ECOG Performance status (PS)

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.	