Supplementary Material: Trial protocol summary

Title of Trial	Randomized controlled trial of S-1 versus docetaxel in patients with non-small cell lung cancer who have received a platinum-based treatment
Sponsor	Taiho Pharmaceutical Co., Ltd.
Clinical Phase	Phase III
Objectives	**Primary objectives:** To establish the non-inferiority in terms of overall survival (OS) of S-1 to standard treatment of docetaxel therapy in previously-treated non-small cell lung cancer (NSCLC) patients. **Secondary objectives:** To compare the two treatment arms in terms of ・ Progression-free survival (PFS) ・ Time to treatment failure (TTF) ・ Response rate (RR) ・ Quality of life (QOL) ・ Time to deterioration of disease-related symptoms (TDS) ・ Incidence and severity of adverse events
Trial Design	Randomized, controlled, multicenter, open-labeled, phase III trial
Eligibility Criteria	**Inclusion criteria:** Patients meeting all the following criteria can be randomized: 1) Histologically or cytologically proven NSCLC 2) Locally advanced or metastatic NSCLC (Clinical Stage IIIB/IV, according to TNM classification ver. 7) for which curative radiotherapy is not indicated 3) Age of 20 years or older 4) ECOG performance status 2 or less 5) Measurable or non-measurable lesions (A lesion confirmed with objective evidence such as CT, MRI images, or X-ray taken within 21 days before randomization, regardless of its measurability). Patients with only pleural effusion cannot be randomized 6) Progression or recurrence after the last treatment is confirmed by radiological image. Previous treatments should include at least one platinum-based regimen. The number of previous regimens must be 3 or less for whom EGFR-TKI (gefitinib/erlotinib) was administered, or 2 or less for whom EGFR-TKI was not administered for metastatic disease ・ Adjuvant chemotherapy is counted as one regimen if the disease recurred within a year after the completion of postoperative adjuvant chemotherapy, or within a year after surgery in patients given preoperative adjuvant

chemotherapy

7) Ability to take drugs orally

8) Adequate major organ functions within 7 days before randomization, as defined below:

- Absolute neutrophil count $\geq 2{,}000/mm^3$
- Platelet count $\geq 100{,}000/mm^3$
- Hemoglobin ≥ 9.0 g/dL
- Aspartate aminotransferase $\leq 2.5 \times$ ULN
- Alanine aminotransferase $\leq 2.5 \times$ ULN
- Total bilirubin $\leq 1.5 \times$ ULN
- $PaO_2 \geq 60$ Torr or $SpO_2 \geq 94\%$
- CCr measured or estimated by the Cockcroft-Gault formula ≥ 60 ml/min.

Measured CCr is preferred if available.

<Cockcroft-Gault formula>

Estimated CCr for men

$= ((140 - \text{age}) \times \text{weight [kg]})/(72 \times \text{serum creatinine [mg/dL]})$

Estimated CCr for women = 0.85 × estimate for men

9) Written informed consent

Exclusion Criteria:

Patients meeting any of the following criteria should be excluded:

1) Previous treatment with docetaxel or fluoropyrimidine
   Patient who experienced recurrence more than one year after completion of postoperative adjuvant chemotherapy with tegafur-uracil capsules/granules (UFT) will be eligible
2) Chemotherapy within 4 weeks and/or EGFR-TKI within 2 weeks before the initial administration of the study drug
3) Curative radiotherapy within 6 weeks before the initial administration of the study drug. Palliative local radiation within 2 weeks before the initial administration of the study drug
4) Major surgery within 4 weeks and/or surgical incision within 2 weeks before the initial administration of the study drug
5) Symptomatic brain metastasis (Patients with known asymptomatic brain metastasis are allowed for randomization if they are clinically stable and no treatment is required.)
6) Pleural, peritoneal or pericardial effusion likely to require surgical intervention
7) Active infection requiring administration of systemic treatment with antibiotics. e.g. Body temperature rose higher than 38°C
8) Patients with Grade 2 or higher diarrhea
9) Severe complication(s), e.g., paresis of intestines, ileus, radiographically confirmed interstitial pneumonitis (except documented radiation pneumonitis)

	or pulmonary fibrosis, poorly-controlled diabetes, cardiac failure, renal failure, liver failure, active gastrointestinal ulceration, myocardial infarction within 6 months, grade 3 or higher angina, known active hepatitis B*, etc. 10) Patients with autoimmune disease requiring treatment with an immunosuppressive agent such as azathiopurine, chlorambucil, cyclophosphamide, ciclosporin, methotrexate, and steroids 11) Active double cancer (synchronous cancer, or metachronous cancer with less than 5 years of disease-free interval), except in situ cervical cancer cured by local treatment, gastric or colon cancer curatively resectable with endoscopy, and resectable non-melanoma skin cancer 12) Confirmed or possible pregnancy, lactation, willingness to become pregnant (for women), or willingness to have a child (for men) 13) Psychiatric disorder or symptom that makes participation of the patient difficult 14) Continuous administration of a steroid 15) History of severe hypersensitivity reaction to polysorbate 80, or to tegafur-uracil capsules/granules (UFT) 16) Current use of flucytosine 17) Participation in other registration trial within one month before randomization in this trial 18) Caucasian 19) Physician concludes that the patient's participation in this trial is inappropriate *: 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.
Trial Medication	Eligible patients will be randomized one of two treatment arms in a ratio of 1:1. **Arm A** (control arm, Docetaxel monotherapy): Indicated dose of Docetaxel (75 mg/m^2 for outside of Japan, 60 mg/m^2 for Japan) by intravenous infusion on day 1 in a 3-week cycle. **Arm B** (experimental arm, S-1 monotherapy): S-1 will be administered orally twice daily after morning and evening meals at a dose of 40-60 mg (80-120 mg/day), depending on BSA on days 1 to 28. The treatment will be followed by a 14-day recovery period. BSA — Dose of S-1 (based on tegafur dose) <1.25 m^2 — 80 mg/day ≥1.25 m^2 to <1.5 m^2 — 100 mg/day ≥1.5 m^2 — 120 mg/day The trial treatment will be continued until the patient meets any of the conditions for discontinuation of the trial treatment.
Concomitant therapy	**Prohibited concomitant medications and therapies** The following concomitant antitumor therapies will be prohibited in this trial: other investigational drugs, bisphosphonates[*1], prophylactic G-CSF[*2], chemotherapy, hormonal therapy, immunotherapy (BRM), antibody therapy, radiation therapy,

	thermotherapy, and surgical therapy. [*1] Patients who are on bisphosphonates before randomization may continue with the bisphosphonates during the trial, if clinically indicated. [*2] G-CSF should be used adhering to the dose/regimen approved in each country and following relevant guidelines. **Drugs not to be used concomitantly with S-1** The following drugs will be prohibited on the basis of known interactions with S-1. a. Sorivudine, brivudine, uracil, cimetidine, Calcium folinate, and dipyridamole, which may enhance toxicity of S-1. b. Allopurinol, which may decrease efficacy of S-1. c. Phenytoin, which may become more toxic. d. Flucytosine and other fluoropyrimidine antifungal agents, which may enhance toxicity of S-1.
Analysis set	**Full analysis set:** The full analysis set consists of all patients who are randomized in this trial and randomized, except those with a major protocol violation such as missing informed consent, randomization outside the contract period, or withdrawal of consent before starting the trial treatment. **Per protocol set:** The per protocol set consists of the FAS patients with none of the following violations: ・ Violation of inclusion criteria ・ Violation of exclusion criteria ・ Use of a prohibited concomitant drug ・ Use of prohibited concomitant therapy **Safety analysis set:** The safety analysis set consists of the patients who were randomized in the trial, and received at least one dose of the assigned trial treatment.
Statistical Consideration	**Non-inferiority margin:** The non-inferiority margin was determined by effect-retention method, guided by the results of the TAX317 trial in previously-treated NSCLC patients, which established the superiority of docetaxel to BSC, with a hazard ratio of docetaxel therapy to BSC of 0.61 (median survival time, 7.5 months vs. 4.6 months). The present trial assumed that up to about 60% of the difference in the effect of docetaxel therapy over that of BSC will be acceptable as a non-inferiority margin, considering the relative convenience of S-1. This corresponds approximately to a hazard ratio of 1.2 and 2 month difference in OS.

	Sample size consideration: The primary objective of this trial is to establish the non-inferiority of the trial treatment, S-1 therapy, to the standard treatment, docetaxel therapy, with respect to the primary endpoint, i.e., OS. With an expected median survival time of 12 months in both arms 1.5 years after the final randomization and a hazard ratio of 1.2 as the non-inferiority margin, a total of 944 events (observed in both arms combined) or 568 patients per arm are required to establish the non-inferiority of S-1 to docetaxel in OS with a 1-sided significance level of 0.025 and an 80% power. Taking into account the exclusion of some of the patients from the analysis, the target number of patients was set to 600 in each arm, or 1200 in a total. **Efficacy:** The primary analyses will be performed with the full analysis set for all efficacy variables; additional efficacy analyses will be performed with the per protocol set.

Schedule of events in arm A (docetaxel therapy)

Activities	Before Randomization		Course 1			Beyond Course 1			Post-Treatment		
	≤21 days	≤7 days	Day1 (-1/+0)	Day8 (-3/+3)	Day15	Day1 (-1/+0)	Day8	Day15	EOT or withdrawal [16]	30 Days Post-treatment (+5days) [17]	Follow-Up period
Informed consent	○	-	-	-	-	-	-	-	-	-	-
Patient background [1]	○	-	-	-	-	-	-	-	-	-	-
Physical examination [2]	-	○	○	-	-	○	-	-	○	-	-
ECOG performance status	-	○	○	○	-	○	-	-	○	○	-
Baseline Signs and symptoms	-	○	-	-	-	-	-	-	-	-	-
Hematology [3]	-	○	○	○	-	○	-	-	○	○	-
Biochemistry [4]	-	○	○	○	-	○	-	-	○	○	-
Urinalysis [5]	-	○	○	-	-	○	-	-	○	○	-
Pregnancy test (if applicable) [6]	-	○	-	-	-	-	-	-	-	-	-
ECG [7]	○	-	-	-	-	-	-	-	-	-	-
Study randomization [8]	-	○	-	-	-	-	-	-	-	-	-
Study medication administration [9]	-	-	○	-	-	○	-	-	-	-	-
Chest X-Ray [10]	○	-	-	-	-	-	-	-	-	-	-
Tumor imaging [11]	○	-	Every 6 weeks (±1 week) until radiological progression is confirmed.								
AE/Toxicity assessment [12]	-	-	○	○	-	○	-	-	○	○	-
Concomitant medications/ Treatments [13]	○	○	○	○	-	○	-	-	○	○	-
EORTC QLQ-C30 [14]	-	○	Every 6 weeks (±1 week)						○	-	-
QLQ-LC13 [14]	-	○	Every 6 weeks (±1 week)						○	-	-
Post-trial survival status & treatment [15]	-	-	-	-	-	-	-	-	-	-	○ Every 6months (±2weeks)

Footnotes for Schedule of Events:

1. **Patient background:** Collection of data within 21 days prior to randomization. Baseline characteristics include demographics, medical history, prior treatments, and information on the target disease.
2. **Physical examination:** To be performed within 7 days prior to randomization, on Day 1 of each course and at the end of treatment (EOT) visit. Includes height (at baseline only), weight, and vital signs (body temperature, systolic/diastolic blood pressure, heart rate).
3. **Hematology:** Include white blood cell count, ANC, platelet count, and hemoglobin content.
   Screening: within 7 days prior to randomization.
   Course 1: Day1: If the tests were not performed within 7days from Day 1, it has to perform on Day 1(-1/+0), Day 8 (± 3 days)
   Course 2 onwards: one day prior to /on Day 1 of each course
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
4. **Biochemistry:** Include albumin, total bilirubin, AST, ALT, serum creatinine, CCr* (measured or estimated), PaO_2 or SpO_2 (at baseline only), and serum electrolytes (Na, K, Ca).
   Screening: within 7 days prior to randomization.

Course 1: Day1: If the tests were not performed within 7days from Day 1, it has to perform on Day 1(-1/+0), Day 8 (± 3 days) Course2 onwards: one day prior to /on Day 1 of each course
EOT: within 14 days after investigator's decision to discontinue the trial treatment.
30 days post-treatment (+5 days window period)

*CCr is optional for patients receiving Docetaxel in subsequent biochemistry assessments after baseline.

5. **Urinalysis:** Include urinary protein, urine sugar.
   Screening: within 7 days prior to randomization.
   Course 1: Day1: If the tests were not performed within 7days from Day1, it has to perform on Day 1(-1/+0)
   Course 2 onwards: one day prior to /on Day 1 of each course
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
6. **Pregnancy test (serum or urine):** Women of reproductive potential must be tested within 7 days prior to randomization.
7. **ECG:** To be performed within 21 days prior to randomization. Additional ECGs may be performed, if clinically indicated.
8. **Study Randomization:** Patient number, treatment arm and planned dose of study drug will be obtained upon successful randomization of patient via the web randomization system. This should be performed after completion of all activities required to determine the eligibility of the patient.
9. **Study Medication Administration:** Course 1 Day 1 should start within 7 days after randomization. Patients randomized to Arm A will receive Docetaxel intravenously at a starting dose of 75 mg/m^2 (60 mg/m^2 in Japan only) on Course 1 Day 1. Each course is 3 weeks cycle. Docetaxel will be administered on Day 1 of every course, until discontinuation criteria are met. The patient must meet all criteria one day before or on the scheduled date of starting a new course. The dose may be adjusted according to the individual patient's tolerance.
10. **Chest X-Ray:** To be performed within 21 days prior to randomization.
11. **Tumor Imaging:** CT, MRI or x-ray of the chest, abdomen and head to be performed within 21 days prior to randomization to assess disease status at baseline. Baseline bone scan is also required when any of the following is observed:
    - known history of bone metastasis
    - detection of bone metastasis by baseline CT or other modalities
    - bone pain suggestive of bone metastasis.

    Subsequent imaging studies should include 6 weekly follow-up of the chest, abdomen, and head lesions identified at baseline and 12 weekly follow-up of the bone lesions starting from Course1 Day 1, to be performed under the same conditions (slice thickness, use of contrast agent) as at baseline. Any baseline lesion other than the above stated and any new lesions later suspected to have arisen will be assessed when appropriate.
    The allowable window for scheduling of imaging studies is ± 1 week. Beyond the window period, re-scheduling of imaging studies due to early discontinuation or delay of the course is not allowed (i.e. fixed by calendar rather than by course duration). Unscheduled imaging may be performed when disease progression is suspected (e.g. symptomatic deterioration) or partial or complete response is confirmed (at least 4 weeks after initial response).
    The patients, who end study drug treatment for reasons other than radiographically-confirmed progressive disease or consent withdrawal, will be followed for tumor response at every 6 weeks interval until progressive disease is documented, even after subsequent antitumor therapy is initiated.

12. **AE/ Toxicity Assessment:** Monitor patients for untoward medical events from the time of randomization, including toxicities from previous treatment and any ongoing or newly reported AEs or SAEs during the protocol treatment period, and until the 30 days after the last dose of study medication.
13. **Concomitant Medications/ Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to randomization, and during the trial. Once the patient had discontinued the study drug treatment, concomitant medications and treatments should only be recorded if used to treat new or unresolved trial treatment related adverse events.
14. **EORTC QLQ-C30 and QLQ-LC13:** These questionnaires should be completed by the patient. However, if the patient is unable to read and write, the questionnaires may be administered by an authorized staff member or caregiver. The questionnaires should be completed within 7 days prior to randomization, at every 6 weeks timepoints (± 1 week window period) after Course1 Day 1, and at EOT: within 14 days after investigator's decision to discontinue the trial treatment or before initiation of post-trial treatment (whichever occurs first).
15. **Post-Trial Survival Status & Treatment:** After discontinuation of trial treatment, post-trial survival status and treatment information will be collected by clinic visit or telephone contact every 6 months (window period ± 2 weeks) starting after the End of Treatment (EOT) of each patient for up to 18 months after randomization of the last patient or until the target number of events (deaths) is met, whichever is earlier.
16. **End of Treatment (EOT) or Withdrawal:** Assessments will be performed at the time of withdrawal of trial treatment. End of treatment procedures will be performed within 2 weeks after investigator's decision to discontinue the trial treatment.
17. **Days Post-Treatment:** At 30 days after the last dose of study medication (with +5 days of allowable window period) or until the start of new antitumor therapy, whichever is earlier, the patient should return to the clinic.

Schedule of events in arm B (S-1 therapy) based on 4 weeks of S-1, 2 weeks rest

Activities	Before Randomization		Course 1						Beyond Course 1						Post-Treatment		
	≤21 days	≤7 days	Day 1 (-1/ +0)	Day 8	Day 15 (±3)	Day 22	Day 29 (±3)	Day 36	Day 1 (-1/ +0)	Day 8	Day 15 (±3)	Day 22	Day 29	Day 36	EOT or Withdrawal [17]	30 Days Post-Treatment (+5days) [18]	Follow-Up Period
Informed Consent	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient background [1]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical Examination [2]	-	○	○	-	-	-	-	-	○	-	-	-	-	-	○	-	-
ECOG performance status	-	○	○	-	○	-	○	-	○	-	○	-	-	-	○	○	-
Baseline Signs and symptoms	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology [3]	-	○	○	-	○	-	○	-	○	-	○	-	-	-	○	○	-
Biochemistry [4]	-	○	○	-	○	-	○	-	○	-	○	-	-	-	○	○	-
Urinalysis [5]	-	○	○	-	-	-	-	-	○	-	-	-	-	-	○	○	-
Pregnancy Test (if applicable) [6]	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECG [7]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Study Randomization [8]	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Study Medication Administration [9]	-	-	D1-D28, twice daily				REST		D1-D28, twice daily				REST		-	-	-
Study Medication Compliance [10]	-	-	-	-	○	-	○	-	○	-	○	-	-	-	○	-	-
Chest X-Ray [11]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tumor Imaging [12]	○	-	Every 6 weeks (±1 week) until radiological progression is confirmed.														
AE/Toxicity Assessment [13]	-	-	○	-	○	-	○	-	○	-	○	-	-	-	○	○	-
Concomitant Medications/ Treatments [14]	○	○	○	-	○	-	○	-	○	-	○	-	-	-	○	○	-
EORTC QLQ-C30 [15]	-	○	Every 6 weeks (±1 week)												○	-	-
QLQ-LC13 [15]	-	○	Every 6 weeks (±1 week)												○	-	-
Post-Trial Survival Status & Treatment [16]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○ Every 6months (±2wk)

Footnotes for Schedule of Events:

1. **Patient background:** Collection of data within 21 days prior to randomization. Baseline characteristics include demographics, medical history, prior treatments, and information on the target disease.
2. **Physical examination:** To be performed within 7 days prior to randomization, on Day 1 of each course and at the EOT visit. Includes height (at baseline only), weight, and vital signs (body temperature, systolic/diastolic blood pressure, heart rate).
3. **Hematology:** Include white blood cell count, ANC, platelet count, and hemoglobin content.
   Screening: within 7 days prior to randomization.
   Course 1: Day 1: If the tests were not performed within 7days from Day 1, it has to perform on Day 1(-1/+0), Day 15 (± 3 days), Day 29 (± 3 days)
   Course 2 onwards: one day prior to /on Day 1, Day 15 (± 3 days)
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)

4. **Biochemistry:** Include albumin, total bilirubin, AST, ALT, serum creatinine, CCr (measured or estimated), PaO_2 or SpO_2 (at baseline only), and serum electrolytes (Na, K, Ca).
   Screening: within 7 days prior to randomization.
   Course 1: Day 1: If the tests were not performed within 7days from Day 1, it has to perform on Day 1 (-1/+0), Day 15 (± 3 days), Day 29 (± 3 days)
   Course 2 onwards: one day prior to /on Day 1, Day 15 (± 3 days)
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
   ***CCr is required at baseline and when significant change in SCr is indicated at the subsequent courses.**
5. **Urinalysis:** Include urinary protein, urine sugar.
   Screening: within 7 days prior to randomization.
   Course 1: Day 1: If the tests were not performed within 7days from Day1, it has to perform on Day 1 (-1/+0) Course 2 onwards: one day prior to /on Day 1
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
6. **Pregnancy test (serum or urine):** Women of reproductive potential must be tested within 7 days prior to randomization.
7. **ECG:** To be performed within 21 days prior to randomization. Additional ECGs may be performed, if clinically indicated.
8. **Study Randomization:** Patient number, treatment arm and planned dose of study drug will be obtained upon successful randomization of patient via the web randomization system. This should be performed after completion of all activities required to determine the eligibility of the patient.
9. **Study Medication Administration:** Course 1 Day 1 should start within 7 days after randomization. All patient randomized to Arm B will receive oral S-1 capsules after morning and evening meals, at a starting dose of 40 mg twice a day or 50 mg twice a day or 60 mg twice a day depending on the patient's BSA. Each course is 6 weeks cycle. The patients will take S-1 orally over 28 consecutive days on Days 1 through 28, followed by a 14-day rest period in each course, and will be repeated until discontinuation criteria are met. Treatment with S-1 will not be permitted to extend beyond Day 28, even if the treatment has been temporarily stopped or the patient has forgotten to take some doses. There is an exception to this. If the patient starts the first dose after evening meal on Day 1, in such a case, the patient is allowed to take S-1 until after morning meal on Day 29. The patient must meet all criteria for starting S-1 therapy. One day before or on the scheduled date of starting a new course. The dose may be stopped temporarily if S-1 suspension criteria are met, and may only resume if criteria for resumption are met. If dose reduction is required, the dose may be adjusted according to the individual patient's tolerance.
10. **Study Medication Compliance:** The patient should bring back all empty packaging and unused S-1 medication, at each visit, for verification by the pharmacist or authorized staff member. In the event of dose adjustment or temporary dose cessation, the patient should be advised on the new instructions of taking the study medications by the pharmacist or authorized staff member.
11. **Chest X-Ray:** To be performed within 21 days prior to randomization.
12. **Tumor Imaging:** CT, MRI or x-ray of the chest, abdomen and head to be performed within 21 days prior to randomization to assess disease status at baseline. Baseline bone scan is also required when any of the following is observed:
    - known history of bone metastasis
    - detection of bone metastasis by baseline CT or other modalities
    - bone pain suggestive of bone metastasis.

Subsequent imaging studies should include 6 weekly follow-up of the chest, abdomen, and head lesions identified at baseline and 12 weekly follow-up of the bone lesions starting from Course 1 Day 1, to be performed under the same conditions (slice thickness, use of contrast agent) as at baseline. Any baseline lesion other than the above stated or any new lesions later suspected to have arisen will be assessed when appropriate.

The allowable window for scheduling of imaging studies is ± 1 week. Beyond the window period, re-scheduling of imaging studies due to early discontinuation or delay of the course is not allowed (i.e. fixed by calendar rather than by course duration). Unscheduled imaging may be performed when disease progression is suspected (e.g. symptomatic deterioration) or partial or complete response is confirmed (at least 4 weeks after initial response).

The patients, who end study drug treatment for reasons other than radiographically-confirmed progressive disease or consent withdrawal, will be followed for tumor response at every 6 weeks interval until progressive disease is documented, even after subsequent antitumor therapy is initiated.

13. **AE/ Toxicity Assessment:** Monitor patients for untoward medical events from the time of randomization, including toxicities from previous treatment and any ongoing or newly reported AEs or SAEs during the protocol treatment period, and until the 30 days after the last dose of study medication.
14. **Concomitant Medications/ Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to randomization, and during the trial. Once the patient had discontinued the study drug treatment, concomitant medications and treatments should only be recorded if used to treat new or unresolved trial treatment related adverse events.
15. **EORTC QLQ-C30 and QLQ-LC13:** These questionnaires should be completed by the patient. However, if the patient is unable to read and write, the questionnaires may be administered by an authorized staff member or caregiver. The questionnaires should be completed within 7 days prior to randomization, at every 6 weeks timepoints after Course 1 Day 1 (± 1 week window period), and at EOT: within 14 days after investigator's decision to discontinue the trial treatment or before initiation of post-trial treatment (whichever occurs first).
16. **Post-Trial Survival Status & Treatment:** After discontinuation of trial treatment, post-trial survival status and treatment information will be collected by clinic visit or telephone contact every 6 months (window period ± 2 weeks) starting after the End of Treatment (EOT) of each patient for up to 18 months after randomization of the last patient or until the target number of events (deaths) is met, whichever is earlier.
17. **End of Treatment (EOT) or Withdrawal:** Assessments will be performed at the time of withdrawal of trial treatment. End of treatment procedures will be performed within 2 weeks after investigator's decision to discontinue the trial treatment.
18. **30 Days Post-Treatment:** At 30 days after the last dose of study medication (with +5 days of allowable window period) or until the start of new antitumor therapy, whichever is earlier, the patient should return to the clinic.

Schedule of events in arm B (S-1 therapy) based on 2 weeks of S-1, 1 week rest (beyond course 1)

Activities	Before Randomization		Course 1 (4w2w)						Schedule Modification (2w1w)						Post-Treatment		
	≤21 days	≤7 days	Day 1 (-1/ +0)	Day 8	Day 15 (±3)	Day 22	Day 29 (±3)	Day 36	Day 1 (-1/ +0)	Day 8	Day 15	Day 22 (-3)	Day 29	Day 36	EOT or Withdrawal [17]	30 Days Post-Treatment (+5days) [18]	Follow-Up Period
Informed Consent	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient background [1]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical Examination [2]	-	○	○	-	-	-	-	-	○	-	-	-	-	-	○	-	-
ECOG performance status	-	○	○	-	○	-	○	-	○	-	-	○	-	-	○	○	-
Baseline Signs and symptoms	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology [3]	-	○	○	-	○	-	○	-	○	-	-	○	-	-	○	○	-
Biochemistry [4]	-	○	○	-	○	-	○	-	○	-	-	○	-	-	○	○	-
Urinalysis [5]	-	○	○	-	-	-	-	-	○	-	-	-	-	-	○	○	-
Pregnancy Test (if applicable) [6]	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECG [7]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Study Randomization [8]	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Study Medication Administration [9]	-	-	D1-D28, twice daily				Rest		D1-14 twice daily		Rest	D22-35 twice daily		Rest	-	-	-
Study Medication Compliance [10]	-	-	-	-	○	-	○	-	○	-	-	○	-	-	○	-	-
Chest X-Ray [11]	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tumor Imaging [12]	○	-	Every 6 weeks (±1 week) until radiological progression is confirmed.														
AE/Toxicity Assessment [13]	-	-	○	-	○	-	○	-	○	-	-	○	-	-	○	○	-
Concomitant Medications/ Treatments [14]	○	○	○	-	○	-	○	-	○	-	-	○	-	-	○	○	-
EORTC QLQ-C30 [15]	-	○	Every 6 weeks (±1 week)												○	-	-
QLQ-LC13 [15]	-	○	Every 6 weeks (±1 week)												○	-	-
Post-Trial Survival Status & Treatment [16]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○ Every 6 months (±2wks)

Footnotes for Schedule of Events:

1. **Patient background**: Collection of data within 21 days prior to randomization. Baseline characteristics include demographics, medical history, prior treatments, and information on the target disease.
2. **Physical examination:** To be performed within 7 days prior to randomization, on Day 1 of each course and at the EOT visit. Includes height (at baseline only), weight, and vital signs (body temperature, systolic/diastolic blood pressure, heart rate).
3. **Hematology:** Include white blood cell count, ANC, platelet count, and hemoglobin content.
   Screening: within 7 days prior to randomization.
   Course 1: Day 1: If the tests were not performed within 7 days from Day 1, it has to perform on Day 1 (-1/+0), Day 15 (± 3 days), Day 29 (± 3 days)
   Course 2 onwards: one day prior to /on Day 1, Day 22 (- 3 days)
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
4. **Biochemistry:** Include albumin, total bilirubin, AST, ALT, serum creatinine, CCr (measured or estimated), PaO_2 or SpO_2 (at baseline only), and serum electrolytes (Na, K, Ca).

Screening: within 7 days prior to randomization.
Course 1: Day 1: If the tests were not performed within 7 days from Day 1, it has to perform on Day 1 (-1/+0), Day 15 (± 3 days), Day 29 (± 3 days)
Course 2 onwards: one day prior to /on Day 1, Day 22 (- 3 days)
EOT: within 14 days after investigator's decision to discontinue the trial treatment.
30 days post-treatment (+5 days window period)
***CCr is required at baseline and when significant change in SCr is indicated at the subsequent courses.**

5. **Urinalysis:** Include urinary protein, urine sugar.
   Screening: within 7 days prior to randomization.
   Course 1: Day 1: If the tests were not performed within 7days from Day1, it has to perform on Day 1 (-1/+0) Course 2 onwards: one day prior to /on Day 1
   EOT: within 14 days after investigator's decision to discontinue the trial treatment.
   30 days post-treatment (+5 days window period)
6. **Pregnancy test (serum or urine):** Women of reproductive potential must be tested within 7 days prior to randomization.
7. **ECG:** To be performed within 21 days prior to randomization. Additional ECGs may be performed, if clinically indicated.
8. **Study Randomization:** Patient number, treatment arm and planned dose of study drug will be obtained upon successful randomization of patient via the web randomization system. This should be performed after completion of all activities required to determine the eligibility of the patient.
9. **Study Medication Administration:** Course 1 Day 1 should start within 7 days after randomization. All patients randomized to Arm B will receive oral S-1 capsules after morning and evening meals, at a starting dose of 40 mg twice a day or 50 mg twice a day or 60 mg twice a day depending on the patient's BSA. Each course is 6 weeks cycle. The patients will take S-1 orally over 28 consecutive days on Days 1 through 28, followed by a 14-day rest period. Treatment with S-1 will not be permitted to extend beyond Day 28, even if the treatment has been temporarily stopped or the patient has forgotten to take some doses. There is an exception to this. If the patient starts the first dose after evening meal on Day 1, in such a case, the patient is allowed to take S-1 until after morning meal on Day 29.
   If the patient meets the criteria for schedule modification, the treatment schedule need to changes from 4w2w to 2w1w. The treatment of the 4w2w course will be cancelled and the next course (2w1w) may start if the patient fulfills the criteria for starting S-1 therapy. Dose escalation is not permitted for a patient for whom the dose has been reduced.
   Treatment with S-1 will be repeated in each course until discontinuation criteria are met.
   The patient must meet all criteria for starting S-1 therapy one day before or on the scheduled date of starting a new course. The dose may be stopped temporarily if suspension criteria are met, and may only be resumed if criteria for resumption are met. If dose reduction is required, the dose may be adjusted according to the individual patient's tolerance.
10. **Study Medication Compliance:** The patient should bring back all empty packaging and unused S-1 medication, at each visit, for verification by the pharmacist or authorized staff member. In the event of dose adjustment or temporary dose cessation, the patient should be advised on the new instructions of taking the study medications by the pharmacist or authorized staff member.
11. **Chest X-Ray:** To be performed within 21 days prior to randomization.
12. **Tumor Imaging:** CT, MRI or x-ray of the chest, abdomen and head to be performed within 21 days prior to randomization to assess disease status at baseline. Baseline bone scan is also required when any of the following is observed:
    · known history of bone metastasis

· detection of bone metastasis by baseline CT or other modalities
· bone pain suggestive of bone metastasis.

Subsequent imaging studies should include 6 weekly follow-up of the chest, abdomen, and head lesions identified at baseline and 12 weekly follow-up of the bone lesions starting from Course 1 Day 1, to be performed under the same conditions (slice thickness, use of contrast agent) as at baseline. Any baseline lesion other than the above stated or any new lesions later suspected to have arisen will be assessed when appropriate.

The allowable window for scheduling of imaging studies is ± 1 week. Beyond the window period, re-scheduling of imaging studies due to early discontinuation or delay of the course is not allowed (i.e. fixed by calendar rather than by course duration). Unscheduled imaging may be performed when disease progression is suspected (e.g. symptomatic deterioration) or partial or complete response is confirmed (at least 4 weeks after initial response).

The patients, who end study drug treatment for reasons other than radiographically-confirmed progressive disease or consent withdrawal, will be followed for tumor response at every 6 weeks interval until progressive disease is documented, even after subsequent antitumor therapy is initiated,

13. **AE/ Toxicity Assessment:** Monitor patients for untoward medical events from the time of randomization, including toxicities from previous treatment and any ongoing or newly reported AEs or SAEs during the protocol treatment period, and until the 30 days after the last dose of study medication.
14. **Concomitant Medications/ Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to randomization, and during the trial. Once the patient had discontinued the study drug treatment, concomitant medications and treatments should only be recorded if used to treat new or unresolved trial treatment related adverse events.
15. **EORTC QLQ-C30 and QLQ-LC13:** These questionnaires should be completed by the patient. However, if the patient is unable to read and write, the questionnaires may be administered by an authorized staff member or caregiver. The questionnaires should be completed within 7 days prior to randomization, at every 6 weeks timepoints after Course 1 Day 1 (± 1 week window period), and at EOT: within 14 days after investigator's decision to discontinue the trial treatment or before initiation of post-trial treatment (whichever occurs first).
16. **Post-Trial Survival Status & Treatment:** After discontinuation of trial treatment, post-trial survival status and treatment information will be collected by clinic visit or telephone contact every 6 months (window period ± 2 weeks) starting after the End of Treatment (EOT) of each patient for up to 18 months after randomization of the last patient or until the target number of events (deaths) is met, whichever is earlier.
17. **End of Treatment (EOT) or Withdrawal:** Assessments will be performed at the time of discontinuation of trial treatment. End of treatment procedures will be performed within 2 weeks after investigator's decision to discontinue the trial treatment.
18. **30 Days Post-Treatment:** At 30 days after the last dose of study medication (with +5 days of allowable window period) or until the start of new antitumor therapy, whichever is earlier, the patient should return to the clinic.