SUPPLEMENTARY MATERIALS

Supplementary Table 1. Univariable analyses of progression-free and overall survival.

Variable[a]	Progression-free survival		Overall survival	
	HR (95% CI)	P value[b]	HR (95% CI)	P value[b]
Age (≥63 years vs. <63 years)	1.05 (0.30-6.00)	0.56	1.01 (0.71-1.48)	0.33
Gender (male vs. female)	0.98 (0.43-2.23)	0.96	1.01 (0.78-2.23)	0.46
Zubrod performance status (0 vs. 1-2)	0.37 (0.12-0.88)	0.01	0.01 (0.01-0.37)	0.009
Clinical T classification (T3-4 vs. T1-2)	3.18 (1.36-7.40)	0.007	3.52 (1.19-7.62)	0.001
Clinical N classification (N2-3 vs. N0-1)	1.01 (1.00-1.03)	0.07	2.45 (1.32-5.96)	0.01
Number of metastases (3-5 vs. 1-2)	2.92 (1.41-4.42)	0.001	2.13 (1.32-3.44)	0.002
EGFR mutation (exon 19 deletion vs. exon 21 mutation)	0.75 (0.57-0.99)	0.04	0.72 (0.12-0.91)	0.001
Randomization arm (TKI only vs. TKI+RT)	2.75 (1.42-3.79)	0.002	3.58 (1.94-7.62)	<0.001

[a]The notation in parentheses refers to comparator group vs. reference group. HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; RT, radiation therapy

[b] All tests were 2-sided.

TKI combined with SBRT in the treatment of stage IV oligometastatic EGFRm non-small cell lung cancer Research Program

Principal investigators: Yu Ruilian, Zeng Ming

Cancer Center

Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital

Research Summary

Study Name	TKI combined with SBRT in the treatment of stage IV oligometastasis non-small cell lung cancer
Clinical Trials Registration Number	
Organizer	Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital
Principal investigators	Yu Ruilian, Zeng Ming
Research phase	III phase
Plan the research cycle	First patient enrollment: January 2016 Last patient enrollment time: June 2017 End of last patient treatment: December 2018 Analysis period during the first data period: December 2018
Research purposes	the main purpose: Progression-free survival, through TKI combined with SBRT in the treatment of stage IV oligometastatic EGFRm non-small cell lung cancer Secondary purpose: Overall survival

Study Design and Planning	This is a prospective, randomized controlled case study This study was designed to use TKI combined with SBRT to treat stage IV oligometastatic non-small cell lung cancer. Radiotherapy uses SBRT (Body Stereotactic Large Segmentation Radiation Therapy) technology, CT simulation positioning, 3D TPS (treatment planning system) optimization, and DVH (dose volume (Histogram) to evaluate tumor and normal tissue doses, plan GTV 25GY-40GY. Radiotherapy was given at the same time as TKI once daily (except to lung which requested one week prior till one week after SBRT). Then observe and evaluate the efficacy. The research treatment flowchart is detailed in Appendix 1. Efficacy was evaluated by imaging and clinical examinations at 4 and 8 weeks after the start of treatment. The safety and toxicity of the combination therapy, including acute and chronic toxicity, will be continuously evaluated during treatment and during follow-up. Any serious adverse drug reaction will be promptly reported to the hospital ethics committee.
Number of planned patients	A total of 200 patients will participate in this experiment.
Visit schedule and evaluation	Screening and first visit: (within two weeks before treatment begins) -Sign informed consent -Meets the criteria for inclusion and does not meet the exclusion criteria -General patient information -Primary tumor diagnosis and staging (AJCC 2010 7th edition staging, Appendix 2) -EGFR status -Previous medical history -Physical examination -vital signs -ECOG physical state -First tumor imaging evaluation (CT / MRI / PET-CT) -ECG -Laboratory testing of blood samples (blood routine and biochemical, etc.) The first day of the first week to the 2nd week:

	-Human body surface area -Examination of the treatment area and other body parts -Blood samples and other laboratory evaluations (blood routine and biochemical tests) -TKI QD at the same time Observe and record adverse reactions during treatment First to fifth days of the first week to the 2nd week（daily or every other day） -Radiation Therapy -Record adverse reactions -CBCT before each treatment during radiotherapy, CT / MRI examination after completion (GTV 25GY-40GY). Evaluation after treatment -Physical examination -Vital signs check -ECOG physical state -Oncology assessment (thoracic and abdominal CT / MRI / PET-CT) -Observe and record adverse reactions Follow-up and study end observations (every 6 weeks / 1 year, every 3 months / 2, 3 years, 6 months / 4, 5 years) -Medical examination and vital signs examination -ECOG physical state -Oncology assessment (whole abdominal, chest enhanced CT / MRI / PET-CT) -Blood samples and other laboratory evaluations (blood routine and biochemical)
Enrollment criteria	-In the case of informed consent, the subjects were ≥18 years old and ≤75 years old. -Newly diagnosed oligo mets with EGFR mutant non-small cell lung cancer. -Eastern Cooperative Oncology Group (ECOG) performance status score 0-1 (see Appendix 3). -oligo mets defined as less than two lesions in one organ, and total lesions less than 5 including primary site.

	-According to RECIST 1.1 (see Appendix 3), there is at least one measurable lesion during the follow up. -consents obtained prior treatment must return to normal before randomization. -Laboratory examination to evaluate bone marrow function, liver and kidney function within 1 week before randomization: HB ≥ 90g / L; ANC ≥ 1.5 × 10E + 9 / L; PLT ≥ 80 × 10E + 9 / L; ALT and AST <2.5 × normal upper limit; TBIL ≤1.25 × normal upper limit; Cr ≤1.25 × normal upper limit; CL> 45 ml / min. - life expectancy of at least 6 months. -Sign informed consent and have the will and ability to comply with the requirements of the experimental protocol
Exclusion criteria	-The pathological types are small cell lung cancer, squamous cell carcinoma, and adenosquamous cell lung cancer. -Pregnant or lactating women. - with brain mets identified by enhanced MRI. -prior history of radiation to the sit at diagnosis - Those unable obtain SBRT treatment for any reason. -Second or higher myocardial ischemia or myocardial infarction, uncontrolled arrhythmia (including prolonged QT interval, male ≥450ms, female ≥470ms). Severe or uncontrolled systemic diseases, such as clinically significant hypertension (systolic blood pressure ≥140mmHg and / or diastolic blood pressure ≥90mmHg), cardiac insufficiency of III-IV, according to NYHA standard or echocardiography: LVEF <50% . -Factors affecting oral administration (inability to swallow tablets, gastrointestinal resection, chronic diarrhea, intestinal obstruction, etc.). -Coagulation dysfunction, bleeding tendency or receiving anticoagulant therapy within 4 weeks ≥ CTCAE 2 pulmonary bleeding or ≥ CTCAE 3 bleeding in other organs. -Fracture or trauma has not healed. Arterial or venous thrombosis occurred within -12 months, and anticoagulant medication was taken. -Mental illness and psychotropic substance abuse. -Received other test drugs within 4 weeks. -Previously received treatments such as VEGFR, platelet-derived growth factor receptor (PDGFR), etc.

	-Proteinuria ≥ (++) or 24 hours urine protein> 1.0g. -Other coexisting malignant diseases (except basal cell carcinoma and cervical carcinoma in situ).
TKI combined with SBRT treatment	Patients with advanced lung adenocarcinoma with EGFR mutations receive of TKI daily (except to lung which requested one week prior till one week after SBRT). Radiation Therapy Technology used: SBRT (Body Stereotactic Large Segmentation Radiation Therapy) Strength: GTV 25GY—40GY GTV from CT, PET or MRI
Duration of treatment planned for each treatment modality	Overall treatment duration: long-term TKI combined with SBRT treatment duration: 4 weeks Radiation therapy duration: within 2 weeks per sit total RT time less than 4 weeks..
Main target variable	PFS at 6 month
Secondary target variable	OS
Tolerance / safety variables	Types and frequency of all adverse reactions (including serious adverse reactions) Death event
Pharmacokinetic	Not inspected
Genomic or genetic pharmacodynamics	Not inspected
Quality of Life	Not inspected
Pharmacoeconomics	Not inspected

statistical methods	definition: Main end point is PEF at 6 month. Alternative hypthesis two sides. Power 0.8 and alpha 0.05. Group allocation: 1:1 S1, (proportion Survival-Control) : 0.75 S2 (proportion Survival- Experimental) : 0.9 T0 (Survival Time): 16 Accural Time (Integers Only) :17 Total Time (Integers only): 24 Evaluate the effect by imaging examination at 4 and 8 weeks after treatment The time window for the observation of local recurrence is 1 year. From the first review after treatment, observe the tumor for signs of recurrence. The time window for distant metastasis observation is 1 years. From the first review after treatment, observe whether there is distant metastasis. Estimate of survival time will be analyzed by Kaplan-Meier method method: Kaplan-Meier analysis of overall and progression-free survival The incidence and severity of safety were assessed according to NCI-CTCAE (v4.0), and specific cases and proportions were listed. Chi-square test and Fisher's exact (probability) test will be used to analyze clinical results and toxic reactions.
Sample size calculation and basis	1. Primary end point is PFS, 2ndary is OS. 2. The case enrollment time was 1-2 year, and the follow-up time was 5 years. The rate of lost follow-up was 5%.
Starting time	January 2016

1. Researchers and Research Management Institutions

The main investigators of this clinical trial are Professor Zeng Ming The unit is Sichuan Academy of Medical Sciences and Provincial People's Hospital.

The trial was coordinated by the main investigator, and data management and statistical analysis were the responsibility of the main investigator also.

The principal investigator will monitor the safety of the drug and the timely reporting of adverse events (AEs) and severe adverse events (SAEs). Leading investigators will regularly review the safety of the data to ensure that this trial continues to be performed reasonably.

This study should meet the test protocol, GCP, and applicable management requirements.

2. Research background

Lung cancer is one of the most common malignant tumors. Globally, lung cancer has the highest incidence and mortality rate. The World Cancer Organization's International Cancer Research Agency (IARC) GLOBOCAN 2008 cancer report released in 2010 shows that in 2008 there were approximately 1.61 million new cases of lung cancer worldwide, accounting for 13% of all new cases of malignant tumors, and approximately 1.38 million deaths. Cases, accounting for 18% of all deaths from malignant tumors, and the morbidity and mortality are the first in malignant tumors. The incidence of lung cancer in China is increasing year by year. According to the data released by China's 36 tumor registration sites in 2008, the number of new cases of lung cancer in China in 2008 was about 522,000, accounting for 18.5% of all new cases of malignant tumors. 453,000 cases, accounting for 23.1% of all malignant tumor deaths, the morbidity and mortality are the first in all malignant tumors. Based on the biological characteristics, treatment and prognosis of lung cancer, the World Health Organization (WHO) divides it into two categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (non-small cell lung cancer, NSCLC). Among them, non-small cell lung cancer accounts for more than 85% of all lung cancer cases, and it mainly includes two types: (1) non-squamous cell carcinoma (including adenocarcinoma, large cell carcinoma, and other cell types); (2) squamous cells cancer. Decades ago, the ratio of adenocarcinoma to squamous cell carcinoma was 1:17. Due to environmental pollution, industrial pollution and other factors, the incidence of adenocarcinoma and squamous cell carcinoma is nearly the same. Due to the lack of special clinical symptoms in the early stages of most lung cancers, early detection and diagnosis are difficult. About 30% to 40% of patients are locally advanced at the time of diagnosis while 40% of patients have distant metastases at the time of diagnosis. The 5-year survival rate of patients with advanced non-small cell lung cancer is only about 15.8%, which seriously harms human health.

The treatment of lung cancer requires comprehensive treatment methods such as surgery, radiotherapy and TKI. For patients with advanced non-small cell lung cancer, platinum-based chemotherapy can benefit patients. Currently widely used chemotherapy drugs include: cisplatin, carboplatin, paclitaxel, docetaxel, vinorelbine, etoposide, pemetrexed, irinotecan, and gemcitabine. The use of platinum-containing two-drug combination chemotherapy has improved the quality of life of patients with advanced non-small cell lung cancer and improved disease-free survival, but the one-year survival rate is still only 30% to 40%. In recent years, with the in-depth study of tumor pathogenesis and the rapid development of molecular biology technology, molecular targeted therapy targeting specific genes has become an important strategy for the treatment of advanced non-small cell lung cancer. Breakthrough progress has been made in targeted therapy for epidermal growth factor receptor (EGFR) mutations, which has brought new hope to advanced non-small cell patients.

TKI is an EGFR signaling inhibitor and has been widely used in patients with advanced lung adenocarcinoma with exon 19, 20 mutations. TKI can increase the PFS of stage IV lung adenocarcinoma and may increase OS. However, after TKI-targeted therapy, some patients still have brain and bone metastases, which improves the efficacy and survival rate of oligometastatic advanced non-small cell lung cancer, which has become one of the important research topics in clinical treatment of lung cancer.

Advances in radiation therapy technology over the past 20 years have ensured that tumor target locations are more accurately located and surrounding normal tissues are better protected, such as the combination of modern imaging technology and radiation therapy technology. Stereotactic radiation therapy (SBRT) is a short-course, low-fraction, high-dose irradiation technique for tumors using modern radiotherapy techniques. Unlike conventional segmented radiotherapy (daily dose of 1.8-2.5Gy) or large

segmented radiotherapy (daily dose of -6Gy, often used in hospice palliative care), SBRT can be ablated up to 8-30Gy per day with the support of complex image guidance technology Dose for treatment. Such high doses can invalidate the tumor repair mechanisms that cause other treatments to fail, but the potential risk is that they can produce intolerable severe late reactions. The key to ensuring the success of treatment lies in the strict implementation of treatment and the active support of symptomatic treatment. The standard treatment for early non-small cell lung cancer is surgical resection, with a 5-year overall survival rate of 60% -80%. However, many patients with early non-small cell lung cancer cannot accept surgery due to heart, lung or other medical complications, and patients who cannot receive surgery due to medical reasons and receive conventional segmented external irradiation have a 5-year overall survival of approximately 10% -30% . SBRT is one of the standard treatments for stage I non-small cell lung cancer, especially for patients who cannot be have surgery. In the past 10 years, the results of a large number of retrospective studies and clinical trials have shown that SBRT has taken full advantage of flexibility, safety and efficiency in the treatment of stage I NSCLC. In recent years, with the progress of phase II clinical trials, everyone has gained a new understanding of the radio-biological characteristics, clinical characteristics, and clinical effects and adverse reactions of SBRT in the treatment of phase I NSCLC, Providing more reliable evidence and guidance. SBRT has been used in some patients with stage IV NSCLC [2-10], which has extended PFS and OS.

Targeted therapy is a commonly used method for the treatment of advanced non-surgical non-small cell lung cancer in recent years. However, the shortcomings of targeted drugs are that it has a poor effect on large lesions and drug-resistant lesions, and has a good effect on multiple small lesions. It can make up for the shortcomings of targeted therapy. The combined use of TKI and radiotherapy in the international and domestic literature has started to increase. Studies have found that [10] targeted therapy combined with SBRT in patients with oligometastasis improves their survival.

Although Shanghai and Guangzhou are currently conducting research on TKI and conventional radiotherapy for advanced non-small cell lung cancer, this study combined with SBRT treatment has reduced the size of measurable lesions. By reducing the tumor burden, it is possible to further improve the efficacy. There are similar studies in the United States but a small sample, one-arm study, and the radiation dose is small, only to 21 Gy [11] while our initial measurement is 25 Gy. At the same time, the scope of SBRT does not only include isolated lesions in the lung.

This study intends to use TKI combined with SBRT to treat all sites at diagnosis of stage IV EGFRm non-small cell lung cancer in order to evaluate the effectiveness and safety of the combined treatment regimen.

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3. Test purpose

3.1 main purpose

To observe the PFS of TKI combined with SBRT in the treatment of stage IV oligometastatic non-small cell lung cancer.

3.2 secondary objectives

Total survival OS (time window: 5 years)

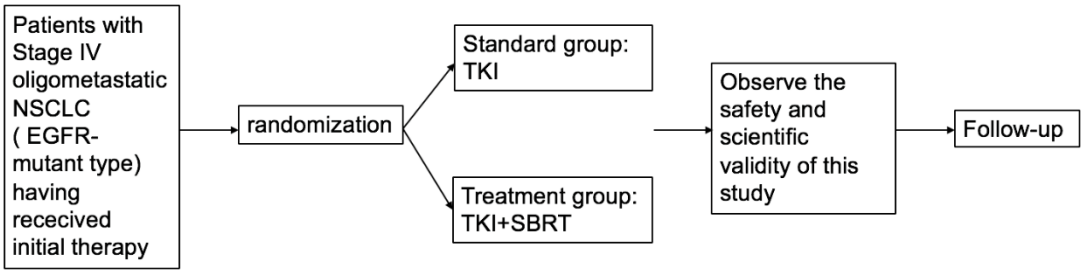
Side effects

4. Test design

4.1 Overall design of the test

This trial is a prospective, randomized controlled case study. Patients with EGFRm oligometastasis non-small cell lung cancer who meet the eligibility criteria are given TKI treatment: daily. Patients in the experimental group combined with SBRT to treat all sits including metastases: SBRT (body stereo-tactic large segmentation radiotherapy) technology, CT simulation positioning, IGRT TPS (treatment planning system) optimization, and DVH (dose volume histogram) to evaluate tumor and normal Tissue dose, planned GTV 25GY-40GY in tumor area. The efficacy was evaluated by CT / MRI observation at various time after the treatment. During the follow up, chest ± whole abdominal CT / MRI / PET-CT was performed to comprehensively evaluate the tumor remission. Follow-up thereafter: once every 4 months in the first year, once every 6 months in the second and third years, and once a year in the fourth and fifth years

4.2 Workflow Chart



4.3.1 Inclusion Criteria

1. Provision of informed consent prior to any study specific procedures, Age ≥18 years, and ≤75 years.

2. Newly diagnosed oligo mets with EGFR mutant non-small cell lung cancer

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 3)

4. According to the RECIST 1.1(Appendix 4), there is at least one measurable tumor lesion.

5. Adverse effects from the prior therapy should be resolved before randomization.

6. Lab test including assessment of bone marrow, liver and kidney function should be done in a week before the randomization: HB ≥ 90g/L; ANC≥1.5×10E+9/L; PLT≥80×10E+9/L; ALT and AST < 2.5-fold ULN; TBIL ≤1.25-fold ULN; Cr ≤1.25-fold ULN;CL>45 ml/min.

7. Life expectancy at lease 6 months

8. Signed written informed consent, subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing

4.3.2 Exclusion Criteria

1. Patients with histopathologic subtype, such as small cell lung carcinoma (SCLC), squamous cell carcinoma, adenosquamous carcinoma

2. women in pregnancy or breast-feeding

3. brain mets identified by MRI of brain.

4. prior history of radiation to the site at diagnosis

5. Stage II or above myocardial ischemia or myocardial infarction, unresolved arrhythmia(including QT interval (QTc) ≥480 msecs in males, ≥450 msecs in females); severe or uncontrolled systematic diseases, such as symptomatic hypertension(often defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), stage III-IV cardiac insufficiency, LVEF<50%(according to the NYHA Classification or by the echocardiograms.

6. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to: difficulty swallowing tablets, gastrointestinal resection, chronic diarrhea, bowel obstruction

7. Bleeding disorders, bleeding tendency or receiving anticoagulant treatment within 4 weeks ≥ CTCAE 2 pulmonary bleeding or ≥ CTCAE 3 bleeding in other organs.

8. Bone fracture or trauma is not healed

9. Arterial or venous thrombosis occurred within 12 months, and taking anticoagulant drugs

10. Mental illness and psychotropic substance abuse

11. Received other test drugs within 4 weeks

12. Prior use of an investigational or licensed drug that targets VEGF receptors or Platelet-derived growth factor receptors (PDGF-R)

13. Proteinuria ≥ (++) or 24-hour urine protein excretion> 1.0g

14. Prior malignancy

4.4 Outcome Measures

4.4.1 Response evaluation criteria

1. Validity: assessed by post-treatment imaging

2. Progression-free survival: The time from date of randomization to tumor progression or death will be analyzed by the Kaplan-Meier method.

3. Overall survival: Estimate of OS will be analyzed by Kaplan-Meier method.

Define the endpoint to be time to death if the patient has died;

Missing cases will be treated as censored data at the last date of contact;

Survival cases will be treated as censored data at the time of the last visit.

4. Determine ECOG performance status according to the following criteria

0 Fully active, able to carry on all pre-disease performance without restriction（karnofsky90-100）

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work（karnofsky70-80）

2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours （karnofsky50-60）

3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours （karnofsky30-40）

4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair （karnofsky<30）

4.4.2 Evaluation of Baseline Characteristics

contents	Time before the treatment

1. Informed consent	Signed	Before enrollment
2. Medical history and physical examination	Medical history, past history, including concomitant diseases. Symptoms and signs, vital signs, height, weight, ECOG score	14 days
3. Pathological examination	EGFR mutant NSCLC	14 days
4. Imaging	Chest ± abdominal CT/MRI/PET-CT	14 days
5. Blood test	Hemoglobin, platelets, white blood cells, neutrophils	14 days
6. Biochemical test	Biochemistry and electrolytes	14 days
7.ECG	18-lead ECG	14 days
8. Pregnancy test	Pregnancy test (serum or urine β-HCG)	14 days
Every laboratory must have quality certification and normal value range		

4.4.3 Evaluation during the TKI+SBRT treatment

Content		Frequency
1. physical examination	Height, weight, and ECOG performance status scores during treatment	Once a week
2. Blood test	Hemoglobin, platelets, white blood cells, neutrophils	Once a week
3. Biochemical test	Biochemistry and electrolytes	Once every 2 weeks
4.Imaging	CBCT	Before every fractions during radiation therapy
5.ECG	18-lead ECG	based on needs
6.others	based on clinical needs	based on needs

7. Adverse events assessment		based on needs
Window period(-2/+0)should be adopted during the follow-up。From the first cycle of combined TKI and RT, window period(±2days)should be adopted. The observation period for collecting adverse events was from the day of the first treatment to 30 days after the end of TKI and radiotherapy, however, enteritis should be followed up for 1 year after the last treatment is completed. Serious adverse events should be carried out in accordance with the program.		

4.4.4 Evaluation after completion of treatment

Thoracic ± abdominal enhanced CT / MRI / PET-CT was performed 4 weeks after the end of all treatments to evaluate the final efficiency, and adverse events were collected at the same time. But enteritis should be followed up for 1 year after treatment is completed.

4.4.5 research termination

4.4.5.1 the standard of research termination

Patients are free to discontinue the study at any time and need to explain the reasons.

Withdraw informed consents

Events affecting patient's safety are occurred, and researchers think the study must be stopped.

Disease progression

Toxicity of delayed treatment ≥ 2 weeks during treatment

Adverse events occur and the investigator or patient believe that the study must be stopped

Patients undergo other studies during our clinical trial

Patients unwilling to continue the research

At the discretion of the researchers

Lost follow-up

pregnancy

Inadequate patient compliance

4.4.5.2 Criteria for early withdrawal of trials (stopping treatment and no longer collecting data)

Medical or ethical reasons continue to influence this trial

Difficulty in enrolling patients

No previous knowledge of the characteristics, severity and duration of adverse events

All reasons and dates for stopping the study should be recorded on the CRF form.

The investigator will begin the study termination step at the time of termination.

5. Treatment research

5.1 Radiotherapy

All patients were treated with SBRT (body stereotactic large fractionation radiotherapy).

5.1.1

SBRT radiotherapy dose regulation

(1) GTV25GY-40GY in tumor area.

(2) At the same time, TKI was given to start radiotherapy within one week.

(3) The prescription dose covers 95% of the planned target (PTV).

5.1.2 Technical factors of radiotherapy

(1)Ray energy: X-ray with 6-10MV energy.

(2)Beam shaping: MLC (multi-leaf grating, multi-leaf collimator) is used to protect the normal tissue outside the target area.

5.1.3 Postural fixation and simulated positioning

（1） Postural fixation: each patient was fixed with an individual fixation device.

（2） Simulated positioning: all patients were lying on a fixed plate, positioned for treatment, and performed enhanced scanning under the CT simulator under quiet breathing (plain scan was optional for allergy to contrast media or special problems). The scanning range was determined according to the location of the transfer, and the slice thickness was 3mm. The scanned images were transmitted to the three-dimensional treatment planning system through the network, and the doctors sketched GTV, CTV and important dose-restricted organs layer by layer.

5.1.4 Treatment plan / target area

（1） Gross tumor volume (GTV) is defined as all known gross tumors found by imaging examination (CT/MRI/PET-CT, etc.). GTV includes primary tumor or distant metastasis

（2） The clinical tumor volume (CTV) includes GTV and its surrounding subclinical area.

（3） Dosimetric requirements of tumor target: the dose calculation adopts the correction of inhomogeneous tissue, and 95% of the PTV is required to accept the prescription dose: the continuous volume of ≥ 120% prescription dose within the PTV < 2cm3 × PTV ≥ 110% of the prescription dose < 1cm3. Record the maximum point dose and minimum point dose (within PTV).

5.1.5 Delineation and limitation of normal tissue

（1） A sketch of normal tissue.

（2） Dose limitation in normal tissues

When making a treatment plan, it is necessary to take into account the limitation of radiation dose to normal tissues and the priority of these tissues.

5.1.6 Adverse events of radiotherapy

The normal tissue around the focus should be protected as far as possible.

（1）Radiation enteritis

Patients are advised to avoid alcohol, hot and sour food or drinks during treatment.

Mucosal protective agents such as calf serum and riboflavin can be given prophylactically.

Acute radiation enteritis may last for 4 weeks. If grade 3 enteritis occurs, consider giving antibiotics and corticosteroids, interrupting radiotherapy if necessary, and limiting the interruption time to 5 days or less as much as possible, not more than 2 weeks.

（2）Radiation cystitis

One hour before treatment, the patient was told to take 500ml water and then start radiotherapy.

Acute cystitis can be considered to be treated with antibiotics, if necessary to interrupt radiotherapy, as far as possible to limit the interruption time to 5 days or less, not more than 2 weeks.

（3）Radiation penumonitis

To avoid pneumonitis, TKI was restricted one week prior to, during RT and one week post RT. The breath holding is preferred. Dose constrains to OAR based up the TG101 SBRT dose constrain. Steroid choice based up physician preference.

（4）Interruption of treatment:

Interruption of treatment should be avoided as far as possible except for the interruption of regular holidays.

Note: fever, hemocytopenia, or grade 2 enteritis usually does not need to be interrupted.

Radiotherapy is allowed to be interrupted or delayed only in febrile neutropenia and ≥ grade 3 enteritis / cystitis. If febrile neutropenia occurs, radiotherapy should be suspended and G-CSF can be used to accelerate neutrophil recovery. The reason for the interruption of treatment must be recorded in the CRF table.

The interruption time is limited to 5 days or less, and the cumulative interruption time is not allowed to exceed 2 weeks. If the interruption time is more than 2 weeks, resulting in the discontinuity of radiotherapy, the patient is considered to have violated the regimen, but continues to be followed up. The total number of times and missed dates should be reported carefully.

All acute and late adverse events of radiotherapy must be reported, the severity of which is based on the NCI Common Adverse Event Judgment Criterion (CTCAE) (V4.0) score.

CTCAE can be downloaded from the CTEP homepage (http://ctep.Info.nih.gov).

5.2 TKI

TKI is an EGFR signaling inhibitor and is now widely used in patients with advanced lung adenocarcinoma with exon19,20 and other mutations. TKI can increase the PFS of stage IV lung adenocarcinoma and may increase OS.

Protocol: In this study, first generation TKI allowed, dose depends type of TKI, once daily.

5.3 Side effects and dose adjustment

All patients are given the planned drug dose in principle and can be adjusted according to the most severe hematology or other toxicity if necessary. Any patient who needs to reduce the dose will continue to receive reduced dose treatment for the rest of the treatment cycle. If the patient has multiple toxicities and the dose adjustment principles are different from each other, choose the minimum dose. If any patient has reduced the dose twice and needs to reduce the dose for the third time due to toxic reaction, the treatment must be stopped. Treatment can be delayed for up to 2 weeks, otherwise it should be discontinued in principle, unless the researchers consider it necessary to continue the treatment.

5.3.1 Hematological toxicity

Patients can only receive combined therapy when neutrophils ≥ 1.5×109 /L and platelets ≥ 80×109 /L, the delay time of treatment should not exceed 2 weeks, otherwise it should be discontinued in principle, unless the researchers consider it necessary to continue treatment.

5.3.2 Non-hematological toxicity

Rash, dry skin, itchy skin

5.4 Concomitant treatment

Supportive treatment will be provided if necessary.

Available medication:

^■Antibiotic

■Antiemetic drug

■G-CSF, GM-CSF

6. Methodology

6.1 Curative effect evaluation

The objective evaluation of curative effect was based on the criteria of RECIST solid tumor, as detailed in schedule 3.

6.2 Safety evaluation

6.2.1 Definition

Adverse events (or adverse experiences):

▲An adverse event refers to any adverse medical event that occurs in clinical subjects, and there is not necessarily a causal relationship between the event and treatment.

▲Adverse events may be adverse and unexpected signs (for example, including abnormal laboratory results), symptoms, or diseases briefly associated with combination therapy.

▲Due to regulatory requirements, events before and after treatment should be designated as adverse events. As a result, the patient enrollment trial began safety monitoring (adverse event reports) until the completion of follow-up at the end of the study.

▲Adverse events may include the following:

●Emerging disease

●With the deterioration of the disease

●The effect of combined therapy

●Include the above two or three articles at the same time

Serious adverse events

▲A serious adverse event is an adverse medical event that occurs at any dose of combination therapy

●Cause death

●Threaten life1

●Request hospitalization or extended stay

●Cause permanent or serious disability or disability 2

●Congenital malformation or birth defect

●Serious medical events3

1 " Threatening life " refers to the risk of immediate death of patients when serious adverse events occur, rather than serious adverse events that may lead to death if they are more serious.

2" Cause permanent or serious disability or disability " means that it substantially affects the patient's ability of daily living.

3 Medical and scientific judgement should be made to determine whether urgent reporting is required in the absence of any of the above. Serious medical events may not immediately threaten life or cause death or require hospitalization, but all medical events that may endanger patients or require intervention to prevent the above situations are serious medical events. If the allergic bronchospasm needs emergency rescue in the emergency room or home, it will not lead to the in-hospital blood cachexia or convulsion, or drug dependence or drug abuse. The diagnosis of cancer in the process of treatment should be regarded as of medical importance. The key terms list (who key terms list of adverse events revised in 1998, see "guidance for filling in the" clinical trial serious adverse events / emergency report "form") should be used as a guide to judge the events of medical importance that may be reported as serious adverse events.

▲The difference between "severe" and "severe": the word "severe" is usually used to describe the severity of adverse events (such as mild, moderate, severe myocardial infarction). Severe adverse events themselves may not be medically important (such as severe headaches). Unlike "serious", the latter is often associated with adverse events that affect life or ability. "Serious" (rather than "severe") adverse events must be accurately reported ".

▲Other events treated as serious adverse events

Exposure to drugs during pregnancy / lactation

In principle, pregnancy and lactation are excluded criteria. If pregnancy occurs during the study, the patient must discontinue the study drug immediately. The sponsor must be informed immediately that the patient should be followed up during the whole pregnancy and postpartum period. Parents and newborns

must be recorded, even if they are completely normal and have no adverse events. Even if pregnancy is not considered a serious adverse event, it should be recorded in the severe adverse event alert report form (ARF). Instead of detecting "severity criteria," ARF is only used to ensure rapid reporting.

▲Events not treated as serious adverse events

Serious adverse event of disease progression omission.

6.2.2 Methods of recording and evaluating adverse events

▲All adverse events should be recorded in an appropriate place in the CRF. In these adverse events, all serious adverse events must be recorded separately in ARF or as follow-up data in "serious adverse event alarm report follow-up".

▲Deaths within 60 days after the start of treatment and within 30 days after the end of treatment and the cause of death will be listed.

▲The results of the physical examination will be listed at baseline. Abnormal results with clinical significance in physical examination will be reported as adverse events.

The following aspects of each event must be recorded in the CRF:

●Adverse events are described in medical terms and cannot be reported by patients

●Date of onset (start date)

●Onset time (start time)

●Recovery date (stop date)

● Recovery time (stop time)

● Levels evaluated by researchers based on the definition of NCI-CTC version 4.0 (http://ctep.info.nih.gov)

Level 1 = Mild

Level 2 = moderate

Level 3 = severe

Level 4 = life threatening or disabled

Level5 = Death

● The causal relationship with combination therapy is evaluated by the investigator; the determining factor in the document is the temporary relationship between treatment and adverse events. The causal relationship between treatment and research is judged as follows:

No correlation = There is a temporary relationship with the combination therapy, or a reasonable causal relationship with other drugs, complications, or the environment.

Impossible correlation = There is a temporary relationship with combination therapy, but there is no reasonable causal relationship with adverse events in combination therapy.

Maybe = there is a reasonable causal relationship between the combination therapy and the adverse event, which improves after discontinuation. No suspension of treatment is required.

Affirmative / clear relationship = There is a reasonable causal relationship between the combination therapy and the adverse event. When clinically feasible, it improves after discontinuation and relapses after retreatment.

●Take measures (none, combined administration, new or prolonged admission, conventional surgery, postponed TKI, discontinued TKI, reduced TKI dose)

● Consequences determined according to the following definitions:

Recovery with sequelae.

Recovery without sequelae.

No treatment in progress.

Ongoing, treatment.

Is dead.

Change in toxicity level / severity

● Severe: Yes or No

▲ If the same adverse event occurs under different circumstances in any patient, the adverse event in question must be recorded and re-evaluated each time.

▲ The CRF records listed above must also be recorded in the ARF as serious adverse events. Only adverse events that meet the criteria for serious adverse events need to be listed.

6.2.3 Procedures for reporting serious adverse events

▲ No matter what kind of treatment the patient receives during the research process or after treatment, if there is a serious or medically important clinical adverse event or abnormal laboratory test value, the researcher is obliged to immediately notify the sponsor by phone or fax.

▲ After the telephone report, the written information must be submitted by fax, and the written report must use ARF (initiation of serious adverse events or "follow-up" information of previous serious adverse events).

▲ As a principle, serious adverse events must be recorded and medically evaluated by the researcher. The consequences are described in the ARF and CRF adverse reactions section. If required, the ARF should be faxed with the relevant pages of the CRF (eg medical history, adverse events, and concomitant medications).

6.2.4 Monitoring of patients with adverse events

▲ Any adverse events that occur during clinical research must be monitored and followed up, and serious adverse events must be reported through ARF.

▲ All existing toxic reactions at the end of the study visit should be followed up in the follow-up evaluation every 3 months until the results are clear. Moreover, investigators can report any serious adverse events or follow-up information directly after the visit.

The investigator is obliged to implement any necessary further treatment measures and follow-up procedures.

6.2.5 Laboratory inspection

At baseline, weekly, at the end of the combination therapy and at the time of the last tumor evaluation visit, laboratory examinations were performed (blood routine tests were performed once a week during the combined therapy, and blood biochemical tests were performed every 2 weeks). The following variables are required to be checked:

● Hematology: Hemoglobin, blood cell count (neutrophil) and platelet count

● Clinical biochemistry: total bilirubin, alanine aminotransferase, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, chlorine, serum calcium, blood urea and lactate dehydrogenase.

6.2.6 Vital signs, body surface area and physical examination

▲ vital signs: including body temperature, heart rate, blood pressure, weight, will be measured at all visits.

▲ Vital signs will be recorded in the CRF at the following visits:

● Baseline

● Last visit of tumor evaluation

▲ Physical examination: At baseline, weekly and at the time of the last tumor evaluation visit, a physical examination was performed and recorded. Physical examination includes whole body appearance, skin, head / neck, lungs, cardiovascular, gastrointestinal tract, genitourinary, lymph / musculoskeletal system, and extremities.

6.3 Pharmacokinetic evaluation

No pharmacokinetic evaluation

6.4 Pharmacodynamic Evaluation

No pharmacodynamic evaluation

6.5

Evaluation plan

6.6.1 Screening and baseline visits

If patients are not enrolled after screening, for whatever reason, they must be recorded in the CRF. Baseline visits must be completed within 14 days of enrollment. The following will be implemented and documented:

▲ Get informed consent

▲ Check the entry and exclusion criteria

▲ Existing related diseases except lung cancer

Except for cancer, previous treatments given within 14 days before the start of the study

▲ Concomitant medication and operation

▲ ECOG's physical condition

▲ physical examination

▲ vital signs

▲ ECG

▲ Chest CT

▲ Evaluation of tumor by MRI / PET-CT (chest + whole abdomen)

▲ serum HCG test

▲ Adverse events

Based on the results of these tests, the investigator will determine whether the patient is eligible for the study. If eligible, patients will be enrolled in this study.

6.6.2

Weekly visit evaluation during combination therapy

The following will be completed and recorded weekly during the combination therapy:

▲ ECOG's physical condition

▲ physical examination

▲ vital signs

▲ Laboratory examination (blood routine and biochemical)

▲ Adverse events

▲ Concomitant medication

6.6.3 Follow-up after treatment

▲ The last tumor evaluation visit was performed after the combined treatment, and a comprehensive evaluation was performed, and the following examinations were recorded:

▲ ECOG physical condition

▲ physical examination

▲ vital signs

▲ ECG

▲ blood samples for laboratory testing

▲ Chest CT

▲ CT / MRI / PET-CT

▲ Adverse events

▲ Concomitant medication

The patient death report form must be completed when the patient dies. All deaths and withdrawal of consent from patients who suspend the study must also complete the "Patient Death Report" form.

6.6.4 Follow-up

At the end of the study visits (every 6 weeks / 1 year, every 3 months / 2, 3 years, every 6 months / 4, 5 years) the following will be recorded:

▲ Living conditions

▲ ECOG physical condition

▲ physical examination

▲ vital signs

▲ ECG

▲ Chest CT

▲ CT / MRI / PET-CT

When a patient dies, the researcher must fill out a "Patient Death Report" form.

7. Data Management

7.1 Completion and transfer of case report form

The case report form is in triplicate, without carbon copy, and the researcher filled it with a black (blue-black) pen and a black signature pen. When correcting mistakes, you need to mark the center line with a mark, then fill in the correct data above it and sign the name and date of the amendment. A case report form must be completed for each selected case. After the completed case report form was reviewed by the clinical supervisor, the first unit was handed over to the data manager for data entry and management. After the first transfer, the contents of the case report form will not be modified.

7.2 Database Establishment and Data Locking

▲ Database establishment: DAS electronic data management system (DAS for EDC) is used for data management. The data administrator constructs the database according to the research plan and CRF. At the same time, the validity of the data is checked and set logically. System access to verify data and answer questions.

▲ Data entry and double verification: During the clinical trial, the inspector should (in batches) send the CRF to the data management unit, and the data administrator will perform independent double entry and double verification, and check the inconsistent results. CRF checks and corrects item by item. Then randomly select several case report tables and the data in the database for manual comparison to ensure that the data in the database are consistent with the results in the original CRF table.

▲ At the same time of data entry, the system automatically issues questions, such as date, entry criteria, exclusion criteria, shedding, missing values, etc. In particular, important indicators for statistical analysis are checked in detail using a computer program. Researchers can answer questions directly online, or they can be inspected After downloading the data questionnaire, the researcher answers the questions in the

questionnaire in writing and signs it, and then enters the system by the research assistant. Researchers should answer system questions as soon as possible. After answering the questions, the data can be re-issued if necessary.

▲Data audit and database locking: after all data questions in the system are solved, "clean" data is exported to the statistician, and the data is audited by the main investigator, sponsor and statistical analyst. After the data is audited, the data will be locked, the statistical plan will be finalized, and the statistical analysis will be performed according to the statistical analysis plan.。

7.3 Special data processing principles

▲For the purpose of effectiveness evaluation, if there is a month, a year but no day, it is recorded as the 15th day of the month. Although it does not happen frequently, on the day when there is only year but no month or date, the date and month are recorded as the middle point between the end of the year and the last known date.

▲If the date is missing, and there is a year and month, the incomplete start date will be recorded as the first day of the month; if both the month and the dates are missing, it will be recorded as January 1. If the recovery date is missing, the incomplete recovery date will be recorded as the last day of this month.

▲The following conversion factors will be used to convert from day to year or month: : 1month=30.4375 day ; 1year=365.25 day

7.4 Medical encoding

▲Adverse events will be coded as required by MedDRA.

▲The severity of adverse events is classified according to NCI-CTC classification standard.

8. Statistical analysis

8.1 Analysis of main efficacy indicators

Analysis of effectiveness and safety according to the post-treatment imaging examination.

8.2 Analysis of secondary efficacy indicators

The time window for progression-free survival observation is 6 - 60 months, starting with the first review after treatment, observe whether the tumor has progressed.

Estimate of survival time will be analyzed by Kaplan-Meier method.

According to NCI-CTCAE (v4.0), the incidence and severity of safety are evaluated, and the specific cases and proportion are listed.

Chi square test and Fisher exact (probability) test will be used to analyze clinical results and toxic reactions.

8.3 Security analysis

▲Vital signs analysis.

▲Incidence of adverse events, grade 3 or above grade 3 adverse events(CTC grade 3+4+5).

▲Incidence of serious adverse events.

▲Mortality rate.

▲Number of cases leading to discontinuation of treatment.

▲The frequency and counts of adverse events and associated adverse events are listed in the subsystem.

▲Grade (CTC grade 3 + 4 + 5) lists the frequency and counts of adverse events and those related to combination therapy.

▲Detailed list of adverse event cases.

▲Detailed list of adverse reaction cases.

▲Detailed list of severe adverse event cases.

▲Detailed list of causes of death.

▲Detailed list of cases leading to discontinuation of treatment.

▲The number and rate of "normal to abnormal" or "abnormal aggravation" of laboratory indicators and ECG after the test.

▲List laboratory indicators, electrocardiograms, abnormal cases of physical examination cases, and clinical explanations.

8.4 Statistics software and general requirements

▲Using SPASS 21 software analysis.

▲$P \leq 0.05$ is considered statistically significant。

8.5 Interim analysis

Intermediate analysis of the validity variable will be performed when 68% of the total sample size is included. At the interim analysis, and a P value less than the critical value 0.05 ($p < 0.05$) indicates statistical significance. The enrollment can stop earlier than planned because of the result of an interim analysis showing larger than expected benefit or harm on the experimental intervention.

8.6 Sample size

Main end point is PES rate at 6 month.

Alternative hypothesis two sides.

Power 0.8 and alpha 0.05.

Group allocation: 1:1

S1, (proportion Survival-Control) : 0.75

S2 (proportion Survival- Experimental) : 0.9

T0 (Survival Time): 16

Accural Time (Integers Only) :17

Total Time (Integers only): 24

Lost follow up rate 3%

Total patient number is 200

9. Ethics and supervision

9.1 Responsibility of investigators

It is the responsibility of the investigator to ensure that clinical trials are conducted according to the ethical principles in the declaration of Helsinki (Declaration of the World Medical Association Helsinki, latest revision) and the requirements of GCP (ICH, topic e61995) and applicable laws and regulations approved by the international drug registration coordination meeting on July 17, 1996. These documents suggest that the informed consent of patients is a necessary prerequisite for participation in clinical trials.

9.2 Patient data

It is absolutely necessary for patients to sign the informed consent. Therefore, investigators should provide patients with sufficient information before signing the informed consent. The words and sentences of informed consent should make it easier for non-professional patients to understand their actual meaning.

Whenever important new patient related information is obtained, the patient information will be modified.

9.3 Informed consent

Patients must obtain informed consent before treatment in this clinical trial begins. It must be signed and dated by the subject or immediate family, and the investigator / investigator designator is responsible for discussing the informed consent with the patient. The signed informed consent must be securely archived by the investigator so that it can be used for monitoring, auditing and inspection at any times. Copies should be provided to patients prior to their participation in the trial.

9.4 Ethics committee or institutional review board

Before the trial begins, the trial specifications and relevant documents (patient information form, consent, current investigator's manual) will be submitted to the relevant ethics committee and institutional review committee for their approval / approval. The approval / approval of the relevant ethics committee and institutional review committee will be archived in the research base file, and the copies will be kept in the sponsor's main research file.

The test can only be started with written approval / approval. Written evidence is required to clearly indicate the trial, protocol version and consent document for the review. Any program supplement will be submitted to the relevant ethics committee / institutional audit committee. As required by the State, the Commission should be informed serious adverse events

10. Research management

10.1 Management of case report forms

The main goal is to obtain the data needed in the trial plan completely, accurately and timely. The information in CRF should be consistent with the relevant original documents. The data recorded during the trial should be recorded in the CRF and must be forwarded to the sponsor. The assessment is then processed and maintained in accordance with the data custody regulations。

The CRF must be completed completely and clearly (using a black or blue ballpoint pen approved by official documents). Any required supplement and modifications must be made and confirmed by the investigator, indicating the date of the change / correction. Errors must be guaranteed to be readable and cannot be deleted with modifiers. The investigator must state the reasons for the modification of important information.

10.2 Raw data and patient files

The investigators should keep a written or electronic file of each patient participating in the clinical trial. In the patient file, general information and medical information of the patient should be recorded, in particular: name, date of birth, gender, height, weight, medical history, concomitant diseases and concomitant medications (including changes during the trial), and statements during enrollment, trial description, enrollment number, date of informed consent, date of all trial visits, pre-planned examinations and clinical results, observed adverse events, and reasons for withdrawal from the trial. Inclusion and exclusion criteria for trials should be verified from the data existing in the archives.

Each patient can be identified through the patient file.

In addition, any other original data files, especially the original data printing paper tapes, must be archived. It includes electrocardiographic drawings, X-ray films, CT and MRI, PET-CT scanning images, and a list of laboratory test values. All documents shall at least have the patient identification number printed out by the recorder and the date printed to indicate which patient the document belongs to and which research procedure. These medical tests must be archived and signed and dated by the investigator. All data recorded in the CRF must also be part of the patient's original data.

10.3 Changes to the trial plan

Any change or formal description of the trial plan must be recorded in written form.

Major changes to the program will be described in the “supplement program”. It will be submitted to the relevant ethics committee and institutional review committee, as well as the local authorities required. Approval / support from ethics committee and institutional review committee is required before the amendments are completed.

Any patient-impacting changes require patient informed consent before implementation.

Changes in management and technology will be recorded in a document entitled "management changes in the trial program". The information will be sent to the relevant ethics committee and institutional review committee or the department required by the authority.

All the signers of the scheme should sign the supplements and changes in management. By signing on the management supplement and changes signature page, all investigators indicated that they knew and insisted on the supplements and changes in management. Copies of the form will be distributed, one signed copy will be filed in the ISF and one copy will be filed in the SMF.

Appendix 1

Step	Before Research	The 1st week	The 2nd week	The 3rd week	The 4th week	End of the treatment
Informed consent	X					
collect medical history	X					
Physical examination	X	X	X	X	X	X
Results of the histologic	X					
General condition evaluation	X	X	X	X	X	X
Weight(Kg)	X	X	X	X	X	X
Chest and belly CT/MRI/PET-CT	X					X
ECG	X					
Blood routine	X	X	X	X	X	X
Blood biochemistry (including liver,kidney function and the electrolyte)	X			X		X
EGFR test results	X					
Adverse event assessment (CTC4.0)		X	X	X	X	X
Adverse radiological reaction assessment (RTOG)		X	X	X	X	X
The quality of life（QOL）	X	X	X	X	X	X

NOTE：Time is calculated by starting treatment

The laboratory inspection time window is ±2 days

The imaging and efficacy evaluation window was ±3 days

Appendix 2

The 7th lung cancer TNM classification and staging system （AJCC 7TH ,2010）

T: Tumour

TX:Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0:No evidence of primary tumour

T1:Tumour < 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1a:Tumour < 2 cm in greatest dimension

T1b:Tumour > 2 cm but < 3 cm in greatest dimension

T2:Tumour > 3 cm but < 7 cm or tumour with any of the following features :Invades visceral pleura;Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a:Tumour > 3 cm but < 5 cm in greatest dimension

T2b:Tumour > 5 cm but < 7 cm in greatest dimension

T3:Tumour > 7 cm or one that directly invades any of the following:Chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium;Tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina;Associated atelectasis or obstructive pneumonitis of the entire lung;Separate tumour nodule(s) in the same lobe

T4:Tumour of any size that invades any of the following:Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina;Separate tumour nodule(s) in a different ipsilateral lobe.

N: Regional lymph node

NX:Regional lymph nodes cannot be assessed

N0　　No regional lymph node metastasis

N1:Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2:Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3:Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M:Metastases

MX:Distant metastasis cannot be assessed

M0:No distant metastasis

M1:Distant metastasis

M1a:Separate tumour nodule(s) in a contralateral lobe

tumour with pleural nodules or malignant pleural/ pericardial effusion

M1b:Distant metastasis

T/M	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

Appendix 3

ECOG Performance Status

GRADE	Syndrome
0	No symptoms, no effect of activity
1	Symptomatic, but almost entirely mobile
2	Sometimes in bed, but not more than 50% during the day
3	Stay in bed for more than 50% of the day
4	bedridden

Appendix 4. RECIST 1.1

CR：All lesions disappeared and no new lesions appeared. Tumor markers were reduced to normal and maintained for at least 4 weeks

PR：The maximum diameters of the tumor were reduced by more than 30% and maintained for at least 4 weeks

SD：The sum of the maximum diameters of the tumor decreased PR or increased PD

PD：Maximum diameter increased ≥20%, or new lesions appeared. But the division of the original lesion should not be counted

★Lymph nodes with short diameter < 10mm were considered normal and were not recorded and followed up. Lymph nodes with short diameters ≥10mm and < 15mm were considered to be pathologically

significant unmeasurable non-target lesions. Lymph nodes with short diameter ≥15mm in CT scan can be used as measurable target lesions with pathological significance, and the total number of target lesions can be included in the evaluation of efficacy.