Study Protocol

A protocol of a single arm, prospective, open-label, multicenter, phase II study of ramucirumab and erlotinib in treatment-naïve non-small cell lung cancer patients with *EGFR* mutation and brain metastases (SPIRAL-BRAIN study)

Ryo Sawada[1], Naoya Nishioka[1,2], Young Hak Kim[1], Fumiaki Kiyomi[3], Junji Uchino[1,4], Koichi Takayama[1]

[1]Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Department of Respiratory Medicine, Fukuchiyama City Hospital, Kyoto, Japan; [3]Department of Statistics and Data Center, Clinical Research Support Center Kyushu, Fukuoka, Japan; [4]Department of Internal Medicine, Bannan Central Hospital, Shizuoka, Japan

Contributions: (I) Conception and design: J Uchino, K Takayama; (II) Administrative support: F Kiyomi; (III) Provision of study materials or patients: R Sawada, YH Kim, J Uchino, K Takayama; (IV) Collection and assembly of data: R Sawada, YH Kim, J Uchino, K Takayama; (V) Data analysis and interpretation: R Sawada, N Nishioka, F Kiyomi, K Takayama; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Naoya Nishioka, MD, PhD. Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan; Department of Respiratory Medicine, Fukuchiyama City Hospital, Kyoto, Japan. Email: g4h4n93w@koto.kpu-m.ac.jp.

Background: The combination of erlotinib, a first-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), and ramucirumab, an anti-vascular endothelial growth factor receptor (VEGFR) antibody, is one of the most effective treatments for patients with non-small cell lung cancer (NSCLC) and *EGFR* mutation. However, little is known about the safety and efficacy of this combination treatment for patients with brain metastases.

Methods: This single arm, prospective, open-label, multicenter, phase II study will recruit 32 NSCLC patients with *EGFR* mutation (except for T790M mutation) and brain metastases (asymptomatic or mild symptoms). Patients will be treated with erlotinib at a dose of 150 mg/body once daily and ramucirumab at a dose of 10 mg/kg once every 2 weeks. The primary endpoint is intracranial overall response rate (iORR) and the secondary endpoints are intracranial disease control rate, intracranial progression-free survival (iPFS), extracranial ORR, extracranial PFS, ORR, overall PFS, overall survival (OS), and safety. The planned number of enrollments was calculated based on a one-sample binomial test (normal approximation) with a two-sided α level of 5% and 80% power, assuming that the expected iORR is 65% and the iORR threshold is 40%.

Discussion: A prospective study to confirm the safety and efficacy of the combined erlotinib plus ramucirumab treatment for NSCLC patients with *EGFR* mutation and brain metastases is ongoing.

Trial Registration: Japan Registry of Clinical Trials, jRCTs051220059.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor mutation (*EGFR* mutation); epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI); brain metastasis; vascular endothelial growth factor or vascular endothelial growth factor receptor inhibitor (VEGF or VEGFR inhibitor)

Submitted Feb 23, 2023. Accepted for publication Jul 20, 2023. Published online Aug 14, 2023.
doi: 10.21037/tlcr-23-109
View this article at: https://dx.doi.org/10.21037/tlcr-23-109

Introduction

Epidermal growth factor receptor (*EGFR*) gene mutation has been known to be closely involved in the onset, growth and metastases of non-small cell lung cancer (NSCLC). Discovery of *EGFR* mutation and development of tyrosine kinase inhibitors (TKIs) for EGFR marked the beginning of molecularly targeted treatment in patients with NSCLC (1), and a 3rd-generation EGFR-TKI (osimertinib) is now available on the market.

In the FLAURA study, a phase III study compared osimertinib with first-generation EGFR-TKIs in advanced, previously untreated NSCLC patients with *EGFR* mutation, exon 19 deletion (ex 19del) or exon 21 Leu858Arg mutation (L858R), both progression-free survival (PFS) and overall survival (OS) were significantly better for the osimertinib arm [18.9 *vs.* 10.2 months; hazard ratio (HR), 0.46; 95% confidence interval (CI): 0.37 to 0.57; P<0.001 and 38.6 *vs.* 31.8 months; HR, 0.80; 95% CI: 0.64 to 1.00; P=0.046, respectively] (2,3).

Combination treatment with EGFR-TKI and vascular endothelial growth factor (VEGF) or VEGF-receptor (VEGFR) inhibitor is another treatment option for NSCLC patients with *EGFR* mutation. Angiogenesis, the process leading to the formation of new blood vessels, is one of the hallmarks of cancer. The study established that VEGF, a key driver of sprouting angiogenesis, is overexpressed in NSCLC and inhibition of VEGF can suppress tumor growth (4).

Recently, in the RELAY study, combination with ramucirumab, a human monoclonal IgG1 antibody selectively targeting VEGFR2, and erlotinib achieved significantly better PFS compared with erlotinib alone (19.4 *vs.* 12.4 months; HR, 0.59; 95% CI: 0.46 to 0.76; P<0.0001) (5). This study indicates that dual blockade of the *EGFR* and VEGFR pathways in *EGFR* mutation-positive NSCLC has demonstrated improved tumor control compared with *EGFR* inhibition alone.

Osimertinib shows excellent efficacy for *EGFR*-mutated NSCLC; however, a subgroup analysis of the FLAURA study revealed that there was no significant OS difference in patients with L858R mutation, while those with ex 19del derived significant OS benefit from osimertinib (3). A following observational study also suggested that the efficacy of osimertinib for L858R mutation might be inferior to that for ex 19del (6). On the other hand, in RELAY study, the benefit was similar between patients with L858R and ex 19del, although OS data is not yet mature to date (5). Therefore, ramucirumab plus erlotinib is a promising treatment option regardless of ex 19del or L858R mutation status.

TP53 is common co-mutation with *EGFR* mutation in NSCLC (7) and the p53 family members regulates VEGF expression (8). Previous study demonstrates that the existence of *TP53* co-mutation is negative prognostic factor for treatment of osimertinib in 2nd line or later line settings (9), whereas *TP53* co-mutation leads to more additional efficacy of ramucirumab to erlotinib in RELAY study subgroup analysis (10,11).

Central nervous system (CNS) metastases are a common poor prognostic factor in patients with advanced NSCLC with *EGFR* mutations (occurring in approximately 30% of patients during treatment with an EGFR-TKI) (12). Osimertinib has shown favorable CNS penetration and FLAURA study also revealed the high CNS efficacy of osimertinib. Fewer patients in the osimertinib arm developed new brain lesions compared with the control arm (12% *vs.* 30%), supporting the protective role of osimertinib in the development of new CNS lesions (13). There also have been several reports that bevacizumab may improve the efficacy of EGFR-TKI in NSCLC patients with *EGFR* mutation and brain metastases (14,15). In a retrospective study, for example, combination of EGFR-TKI and bevacizumab demonstrated significantly better intracranial overall response rate (iORR) (66.1% *vs.* 41.6%, P=0.001), PFS (14.4 *vs.* 9.0 months; P<0.001), and OS (29.6 *vs.* 21.7 months; P<0.001) compared with EGFR-TKI alone (14). However, no data have been available for the combination with ramucirumab and erlotinib because the RELAY study excluded patients with brain metastases (5).

Thus, we aim to investigate prospectively the efficacy and the safety of erlotinib plus ramucirumab as the first-line therapy for advanced or recurrent *EGFR*-mutated NSCLC patients with brain metastasis. We present this article in accordance with the SPIRIT reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-109/rc).

Methods

Study design

This study is a single arm, prospective, open-label, multicenter, phase II study. The present study has begun in July 2022 and is currently in progress. The schema of this study is shown in *Figure 1*. Participating

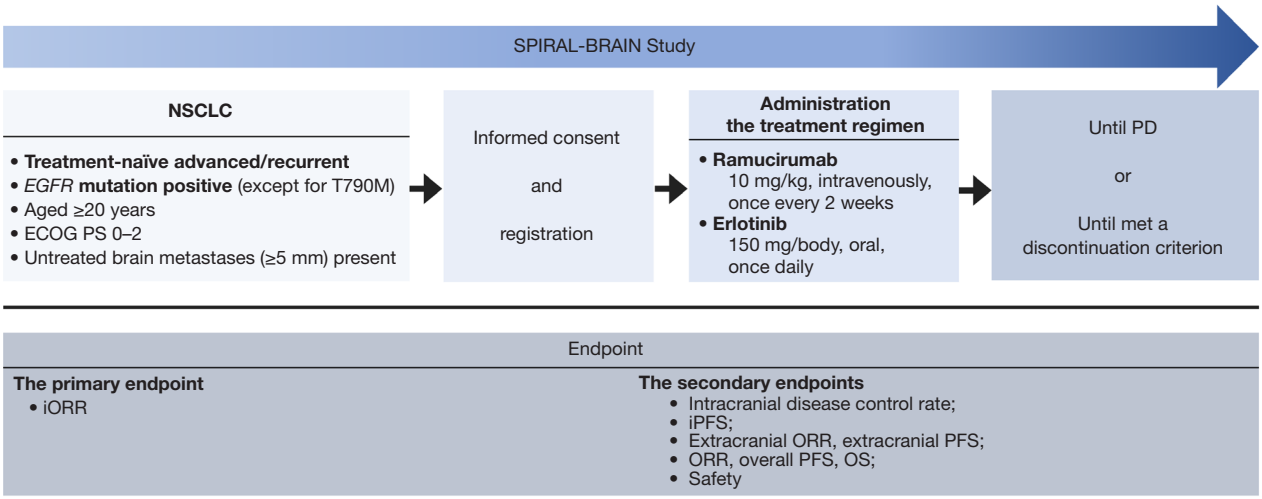

Figure 1 Schema of this study. NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD, progressive disease; iORR, intracranial overall response rate; iPFS, intracranial progression-free survival; OS, overall survival.

institutions are following: Kyoto Prefectural University of Medicine (Kyoto, Japan), Uji-Tokushukai Medical Center (Kyoto, Japan), Japanese Red Cross Kyoto Daini Hospital (Kyoto, Japan), North Medical Center Kyoto Prefectural University of Medicine (Kyoto, Japan), Izumi City General Hospital (Osaka, Japan), Saiseikai Suita Hospital (Osaka, Japan), Japan Community Health care Organization Kobe Central Hospital (Hyogo, Japan), Iizuka Hospital (Fukuoka, Japan), Asahi General Hospital (Chiba, Japan), Nagasaki University Hospital (Nagasaki, Japan), Omi Medical Center (Shiga, Japan), University of Fukui Hospital (Fukui, Japan), Hyogo Medical University Hospital (Hyogo, Japan), Teikyo University Hospital (Tokyo, Japan), Fujita Health University Hospital (Aichi, Japan), Okinawa National Hospital (Okinawa, Japan), Kobe Minimally Invasive Cancer Center (Hyogo, Japan), Kyoto Yamashiro General Medical Center (Kyoto, Japan), Shonan-Fujisawa Tokushukai Hospital (Kanagawa, Japan), Kanazawa Medical Center (Ishikawa, Japan), Fukuchiyama City Hospital (Kyoto, Japan), Rakuwakai Otowa Hospital (Kyoto, Japan), Kanazawa University Hospital (Ishikawa, Japan), Kitakyushu Municipal Medical Center (Fukuoka, Japan), Himeji Medical Center (Hyogo, Japan), Otsu City Hospital (Shiga, Japan), Osaka Metropolitan University Hospital (Osaka, Japan), and Japanese Red Cross Kyoto Daiichi Hospital (Kyoto, Japan). The ethical committees of the Clinical Research Review Board of Kyoto Prefectural University of Medicine (No. 2022001-3) approved the study protocol and informed consent documents. The other participating hospitals were informed about the study and provided their agreement. All patients will be required to provide informed consent. The study will be conducted in compliance with the provisions of the Declaration of Helsinki (as revised in 2013).

Eligibility criteria

The inclusion and exclusion criteria of this study are shown in Table S1.

Dose and treatment regimen

Erlotinib at a dose of 150 mg will be administered orally once daily and ramucirumab at a dose of 10 mg/kg intravenously once every 2weeks. The treatment regimen will be continued until disease progression or until a discontinuation criterion (Table S2) is met. We also set a discontinuation criterion for ramucirumab. Even after discontinuation of ramucirumab, treatment with erlotinib may be continued at the discretion of the clinical investigator. If treatment with erlotinib has been discontinued, the protocol treatment will be discontinued.

Statistical analysis

This trial is based on the following clinical hypothesis: the combined ramucirumab plus erlotinib therapy is safe and effective for treatment-naïve advanced/recurrent NSCLC

patients with *EGFR* mutation and brain metastases. Therefore, the primary endpoint of this study is iORR. Secondary endpoints are intracranial disease control rate, intracranial progression-free survival (iPFS), extracranial ORR, extracranial PFS, ORR, overall PFS, OS, and safety. The efficacy of this therapy is judged as positive if the lower bound of the 95% confidence interval for the iORR exceeds 40%. The threshold level of 40% was set based on the data from the FLAURA study, in which iORR for the first-generation EGFR-TKI arm was 40% [95% confidence interval (CI): 41–81%] in all patients with brain metastases (n=67) and 63% (95% CI: 41–81%) in the patients having a 10-mm or larger brain metastases (n=19). The expected iORR was set to be 65% because iORR for the osimertinib arm was 57% (95% CI: 45–69%) in all patients with brain metastases (n=61) and 77% (95% CI: 57–90%) in the patients having a 10-mm or larger brain metastases (n=22). The number of subjects needed for a valid study with the use of one-sample binomial test (normal approximation) is 30 under the assumption of the threshold level 40%, the expected level 65%, the significance level 5% (two-tailed) and the detective power 80%. With possible dropout before the start of treatment taken into consideration, the planned number of patients to be registered was thus set as 32.

Discussion

Ramucirumab plus erlotinib is one of the treatment options for previously untreated NSCLC patients with *EGFR* mutation, and the efficacy of which is independent with *EGFR* subtypes, L858R or ex 19del. Considering that osimertinib might be less effective for patients with L858R subtype, ramucirumab plus erlotinib should be a viable alternative for this population; however, efficacy of the combination treatment is still unclear for patients with brain metastases. We believe that our study will pave the way for developing the new treatment option for these patients.

Acknowledgments

Funding: This work was supported by "Externally sponsored scientific research" in Eli Lilly and Company to Koichi Takayama.

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-109/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-109/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-109/coif). KT reports honoraria (lecture fee) and research funds from Chugai-Roche and Eli Lilly and Company that are outside of the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol and informed consent documents were approved by the ethical committees of Clinical Research Review Board of Kyoto Prefectural University of Medicine (No. 2022001-3). The other hospitals were informed and agreed with the study. Informed consent will be obtained from all patients. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
2. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
3. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
4. Le X, Nilsson M, Goldman J, et al. Dual EGFR-VEGF Pathway Inhibition: A Promising Strategy for

Patients With EGFR-Mutant NSCLC. J Thorac Oncol 2021;16:205-15.
5. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:1655-69.
6. Yoshimura A, Yamada T, Okuma Y, et al. Impact of tumor programmed death ligand-1 expression on osimertinib efficacy in untreated EGFR-mutated advanced non-small cell lung cancer: a prospective observational study. Transl Lung Cancer Res 2021;10:3582-93.
7. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer 2019;19:495-509.
8. Farhang Ghahremani M, Goossens S, Haigh JJ. The p53 family and VEGF regulation: "It's complicated". Cell Cycle 2013;12:1331-2.
9. Roeper J, Christopoulos P, Falk M, et al. TP53 co-mutations as an independent prognostic factor in 2nd and further line therapy-EGFR mutated non-small cell lung cancer IV patients treated with osimertinib. Transl Lung Cancer Res 2022;11:4-13.
10. Nakagawa K, Nadal E, Garon EB, et al. RELAY Subgroup Analyses by EGFR Ex19del and Ex21L858R Mutations for Ramucirumab Plus Erlotinib in Metastatic Non-Small Cell Lung Cancer. Clin Cancer Res 2021;27:5258-71.
11. Nishio M, Paz-Ares L, Reck M, et al. RELAY, Ramucirumab Plus Erlotinib (RAM+ERL) in Untreated Metastatic EGFR-Mutant NSCLC (EGFR+ NSCLC): Association Between TP53 Status and Clinical Outcome. Clin Lung Cancer 2023;24:415-28.
12. Heon S, Yeap BY, Britt GJ, et al. Development of central nervous system metastases in patients with advanced non-small cel lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin Cancer Res. 2010;16:5873-82.
13. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018. [Epub ahead of print]. doi: 10.1200/JCO.2018.78.3118.
14. Jiang T, Zhang Y, Li X, et al. EGFR-TKIs plus bevacizumab demonstrated survival benefit than EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. Eur J Cancer 2019;121:98-108.
15. Chen F, Chen N, Yu Y, et al. Efficacy and Safety of Epidermal Growth Factor Receptor (EGFR) Inhibitors Plus Antiangiogenic Agents as First-Line Treatments for Patients With Advanced EGFR-Mutated Non-small Cell Lung Cancer: A Meta-Analysis. Front Oncol 2020;10:904.

Cite this article as: Sawada R, Nishioka N, Kim YH, Kiyomi F, Uchino J, Takayama K. A protocol of a single arm, prospective, open-label, multicenter, phase II study of ramucirumab and erlotinib in treatment-naïve non-small cell lung cancer patients with *EGFR* mutation and brain metastases (SPIRAL-BRAIN study). Transl Lung Cancer Res 2023;12(8):1802-1806. doi: 10.21037/tlcr-23-109

Table S1 Eligibility criteria

Inclusion criteria

[1] Patients revealed by head MRI (contrast-enhanced MRI as far as possible) within 28 days before registration (28-day earlier on the same day of the week is acceptable) to have treatment-naïve brain metastases (major axis double the slice thickness or more and 5 mm or more). Symptom-free patients and patients with mild symptoms (remaining controlled for 1 week or more by anti-brain edema therapy with steroid at dose levels not exceeding 40 mg when converted into prednisolone dose level) are eligible. Patients having undergone stereotactic radiotherapy are eligible if their clinical symptoms are stable and they have recovered from all treatment-related adverse events by the time of registration. Patients planned to receive radiotherapy for brain metastasis must have at least one lesion not covered by irradiation

[2] Patients rated histologically or cytologically to have non-small cell lung cancer

[3] Stage IV disease or postoperative recurrence not amenable to radical treatment

[4] Having received no chemotherapy for the cancer covered by this study. Patients having received preoperative or postoperative chemotherapy are eligible if the final chemotherapy dose is given 6 months or more before the date of registration with this study. Provided patients having received EGFR-TKI during preoperative or postoperative chemotherapy are not eligible

[5] *EGFR* mutation positive (excluding patients confirmed to have T790M mutation). Patients with exon 20 insertion mutations are eligible

[6] Patients able to take oral-dose drugs

[7] Age of 20 years old or older at the time of consent obtainment

[8] ECOG PS of 0–2

[9] Patients free of severe disorder of major organs (bone marrow, heart, lungs, liver) and satisfying the criteria given below (the latest data collected within 14 days before registration are used for judgment of eligibility. The 14-day period is counted from the date of registration and includes the same day of the preceding week)

Neutrophil count ≥1,500/mm^3

Hemoglobin ≥9.0 g/dL

Platelet count ≥100,000 /mm^3

AST ≤3.0× ULN (patients with liver metastasis: ≤5.0× ULN)

ALT ≤3.0×ULN (patients with liver metastasis: ≤5.0× ULN)

Total bilirubin ≤1.5× ULN

Serum creatinine ≤1.5× ULN or creatinine clearance ≥40 mL/min

SpO_2 (room air) ≥90%

PT-INR ≤1.5

Urinary protein ≤1+ (paper test method, or less than 1,000 mg/day in 24-hour pooled urine)

[10] No restriction about presence/absence of lesions other than brain lesions (no restriction about presence/absence of measurable lesions according to RECIST1.1). However, thoracic/abdominal CT performed within 28 days before registration is essential (28-day earlier on the same day of the week is acceptable)

[11] Patients expected to survive for at least 3 months

[12] The absence of any of the prior treatments or procedures described below, or if any prior treatments or procedures had been done, the prespecified period of the time has elapsed since the completion of the prior treatments or procedures before registration:

1) Stereotactic radiation or γ-knife therapy for brain metastases

Passage of 1 or more days from the final irradiation day (final irradiation day on the registration day will not be accepted).

2) Surgery for brain metastases

Passage of 7 or more days after surgery (surgery on the registration day will be accepted)

The presence of untreated brain metastasis meeting the criterion [1] other than lesions treated with 1) or 2) is required

[13] Restriction on other prior treatments (other than local treatment for brain metastases)

1) Invasive surgery (open abdominal/thoracic surgery): 1 month or more has elapsed

2) Thoracic drainage: 1 week or more has elapsed after postoperative removal of sutures.

[14] Obtainment of written consent from the patient himself/herself after sufficient explanation of the study content before registration in this study

Exclusion criteria

[1] The patient has known to have *EGFR* T790M mutation

[2] Having developed grade 3 or higher gastrointestinal bleeding within 3 months before registration or hemoptysis (defined as bright red blood or ≥1/2 teaspoon, regardless of grade) within 2 months before registration

[3] Patients with imaging findings suggestive of macrovascular tumor invasion, tumor encasement, or hollowing within the tumor

[4] Patients having developed severe uncontrollable coagulation disorder or severe hemorrhagic complication within 6 months before registration

[5] Patients who have developed deep vein thrombus, pulmonary embolism within 3 months before registration

[6] Patients having undergone surgery within 4 weeks before registration (surgery on the same day of week 4 weeks before registration is acceptable). Provided, skin tumor resection and endoscopic surgery are acceptable if 1 week or more has elapsed after surgery

[7] Patients having active double cancer. Synchronous double cancer and metachronous double cancer with disease-free survival of within 2 years requiring treatment will be regarded as double cancer

[8] Patients confirmed to have meningeal dissemination by MRI or cerebrospinal fluid test

[9] Patients having developed cerebrovascular or neurovascular disease (including myocardial infarction, cerebral infarction, and transient ischemic attack) or other arterial thromboembolic events within 6 months before registration

[10] Patients judged to have developed gastrointestinal perforation within 6 months before registration or to have a risk for perforation (gastrointestinal invasion or metastasis)

[11] Patients having poorly controlled hypertension (systolic blood pressure remaining 160 mmHg or higher and diastolic blood pressure remaining 100 mmHg or higher for 4 weeks or more)

[12] Patients having unhealed wound or peptic ulcer

[13] Patients having developed fracture within 1 month before registration

[14] Patients with poorly controlled metabolic disease (e.g., diabetes mellitus) or other nonmalignant organ or systemic diseases or secondary effects of cancer that induce a high medical risk and/or make assessment of survival uncertain. Provided, patients on continued insulin use are eligible if the condition is rated as been well controlled

[15] Local infection or systemic active infection requiring surgical treatment, such as drainage

[16] Periodical users of non-steroidal anti-inflammatory drugs (NSAIDs: indomethacin, ibuprofen, naproxen or analogous drugs) or anti-platelet drugs (aspirin, dipyridamole, ticlopidine, clopidogrel or analogous drugs). Provided, low-dose aspirin (325 mg/day or less) is acceptable. NSAIDs are acceptable if 7 days or more have elapsed after switching to acetaminophen

[17] Patients rated as Child-Pugh B or severer liver cirrhosis or having hepatic encephalopathy or symptomatic hepatic ascites

[18] Active hepatitis B or hepatitis C (patients testing positive for HBs antibody, HBc antibody or HBs antigen are eligible if the virus level is lower than the detection limit and hepatitis is inactive. Patients testing positive for HCV antibody are eligible if hepatitis is inactive)

[19] Interstitial pulmonary disease evident on CT scan at the time of registration (positive history or organization of radiation pneumonitis is acceptable)

[20] Patients judged to be difficult for registration with this study because of clinically significant psychiatric disease

[21] Complication by clinically significant ophthalmic disease [e.g., severe dry eye syndrome (including Sjögren's syndrome), dry keratoconjunctivitis, or keratitis]

[22] Patients requiring oral treatment with CYP3A4-inducing drugs or inhibitors

[23] Hypersensitivity to any ingredient or additive in ramucirumab or erlotinib

[24] The patient has elective or planned major surgery to be performed during the course of the clinical trial

[25] Pregnant women, lactating women or women unwilling to take contraceptive measures. Males desiring pregnancy of their partner. Because the teratogenicity of ramucirumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods). Female patients of childbearing potential must have a negative qualitative urinary hCG test within 7 days prior to first dose of protocol therapy

[26] Other patients judged by the clinical investigator to be inappropriate for the study

MRI, magnetic resonance imaging; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AST, aspartate amino transferase; ALT, alanine aminotransferase; ULN, upper limit of normal range; PT-INR, prothrombin time-international normalized ratio; SpO_2, peripheral capillary oxygen saturation; CT, computing tomography; hCG, human chorionic gonadotropin.

https://dx.doi.org/10.21037/tlcr-23-109

Table S2 Discontinuation criteria

Discontinuation criteria for ramucirumab
[1] When the Grade 4 hypertension occurs
[2] When proteinuria with the following findings occurs
One-day urinary protein: ≥3 g/24 hours
Qualitative urine test: ≥3+ and urine protein/creatinine ratio of 2.0 or higher, or proteinuria with a protein content of 2 g or higher in 24 hours on three occasions
[3] When the Grade 3 or severer infusion-related reactions occurs
[4] When the following adverse events with any grades occurs
Thromboembolism
Gastrointestinal perforation/fistulation
Reversible posterior leukoencephalopathy
Discontinuation criteria for protocol treatment (both erlotinib and ramucirumab)
[1] When the protocol treatment is judged to be ineffective:
Systemic aggravation with the PD on the basis of the diagnostic imaging
Systemic aggravation not possible to be confirmed by the diagnostic imaging; clinically judged systemic aggravation
If the clinical investigator judges that continuation of the regimen after progressive disease is expected to benefit the patient, the treatment can be continued as the post-treatment
[2] When the protocol treatment cannot be continued because of adverse events below:
When the Grade 4 non-hematological toxicity causally related to the protocol treatment occurs
When the Grade 2 or severer interstitial pneumonia occurs
When the erlotinib cessation period has exceeded 28 days
When the third dose reduction of erlotinib is needed
When the clinical investigator judges it necessary to discontinue the protocol treatment for a reason of adverse events other than the criteria for discontinuation of protocol treatment
[3] When a patient requests discontinuation of protocol treatment due to a reason with which adverse events may associate.
[4] When a patient requests discontinuation of protocol treatment due to a reason with which adverse events do not associate.
[5] When a patient dies during protocol treatment
[6] When a treatment is changed due to other reasons, such as aggravation before treatment initiation after registration, protocol violation, revision of pathological diagnosis after registration
[7] When the clinical investigator judges the validity of discontinuation of the protocol treatment

PD, progressive disease.

https://dx.doi.org/10.21037/tlcr-23-109