Supplementary

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.

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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.

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