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Phase 1b study of ramucirumab in combination with erlotinib or osimertinib for untreated EGFR-mutated non–small cell lung cancer patients with asymptomatic brain metastases

Hiroyasu Kaneda1,*, Kenji Sawa2, Haruko Daga3, Asuka Okada3, Yuki Nakatani3, Shinji Atagi4, Kyoichi Okishio4, Yoko Tani1, Yoshiya Matsumoto2, Koichi Ogawa2, Kenji Nakahama2, Motohiro Izumi2, Shigeki Mitsuoka1, Tomoya Kawaguchi1,2

1Department of Clinical Oncology and 2Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan
3Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan
4Department of Thoracic Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan

*Corresponding author at: Hiroyasu Kaneda, Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abenouku, Osaka 545-8585, Japan. Tel.: +81-6-6645-3793. Fax: +81-6-6646-6170. Email: kaneda.hiroyasu@med.osaka-cu.ac.jp
ABSTRACT

Objectives: The study was designed to investigate the safety of ramucirumab administered in combination with erlotinib or osimertinib for patients with untreated EGFR-mutated non–small cell lung cancer (NSCLC) and asymptomatic brain metastases, a patient subgroup in which these regimens have remained untested.

Materials and methods: This phase 1b study (RELAY-Brain) consisted of two cohorts with three patients each. Patients with asymptomatic brain metastases received ramucirumab every 2 weeks plus either daily oral erlotinib or osimertinib until disease progression or intolerable toxicity. The primary objective was to assess dose-limiting toxicity (DLT), defined as central nervous system (CNS) hemorrhage of grade ≥2.

Results: Six patients were enrolled. Neither DLT nor serious or unexpected adverse events were observed. One treatment-related adverse event of grade ≥3 (hypertension of grade 3) was apparent. Common adverse events were generally manageable. The median number of ramucirumab administrations was 18.5 (range, 13 to 31), and there were no detected episodes of CNS hemorrhage. Five of the six patients showed an objective systemic response. Although only one patient had a measurable CNS lesion at baseline, a confirmed intracranial partial response was observed.

Conclusion: Ramucirumab in combination with erlotinib or osimertinib showed safety for EGFR-mutated NSCLC with brain metastases.

Keywords
EGFR mutation, ramucirumab, brain metastasis, non–small cell lung cancer, antiangiogenic agent, tyrosine kinase inhibitor

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Author Declarations
Availability of data and materials
Data are available.
Authors’ contributions
H.K. and K.S. participated in the conception and design of this study. H.K had a funding acquisition. H.K drafted the article. All authors critically reviewed and contributed to all drafts, approved the final version, and made the decision to submit the report for publication.
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Authors' information
Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, Osaka, Japan
Hiroyasu Kaneda, Yoko Tani, Shigeki Mitsuoka, and Tomoya Kawaguchi
Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan
Kenji Sawa, Yoshiya Matsumoto, Koichi Ogawa, Kenji Nakahama, Motohiro Izumi, and Tomoya Kawaguchi
Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan
Haruko Daga, Asuka Okada, and Yuki Nakatani
Present address: Division of Respiratory Medicine, Saiseikai Suita Hospital, Osaka, Japan
Asuka Okada
Department of Thoracic Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan
Shinji Atagi and Kyoichi Okishio

Compliance with Ethical Standards:
Disclosure of potential conflicts of interest; Dr. Kaneda reports grants from Eli Lilly, during the conduct of the study; personal fees from Chugai, AstraZeneca, Novartis Pharma, Bristol-Myers Squibb, Ono, Boehringer Ingelheim, MSD, Taiho, Pfizer, Nippon KAYAKU, and
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**Ethics approval;**
The study was approved by the institutional review board of each participating institution and was conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guideline, and applicable local regulations.

**Informed consent;**
Informed consent was obtained from all individual participants included in the study.
1. Introduction
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been found to substantially prolong progression-free survival (PFS) compared with chemotherapy as well as to improve overall survival and quality of life in such individuals [1]. Recently, the FLAURA study revealed superior efficacy for osimertinib compared with gefitinib or erlotinib as a first-line treatment for advanced NSCLC [2]. Despite these beneficial effects of EGFR-TKIs, however, disease progression during treatment with these drugs is universal. Strategies to overcome EGFR-TKI resistance, such as the combination of EGFR-TKIs with antiangiogenic or cytotoxic agents, have been developed. Several prospective studies have shown that the antiangiogenic agent bevacizumab enhances the efficacy of erlotinib in patients with EGFR-mutated NSCLC [3].

Ramucirumab is a monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 with high specificity and affinity. The RELAY phase 3 trial recently showed found that ramucirumab plus erlotinib significantly prolonged PFS compared with placebo plus erlotinib in patients with untreated EGFR-mutated NSCLC [4]. Patients with brain metastases were excluded from this trial, however, because of concerns about potential intracranial hemorrhage. The safety of bevacizumab with regard to the induction of central nerve system (CNS) hemorrhage in NSCLC patients with treated or untreated brain metastases has been evaluated in several trials [5, 6]. However, the safety of ramucirumab in combination with EGFR-TKIs for EGFR-mutated NSCLC patients with brain metastases has remained unknown. We therefore performed a phase 1b study to assess the safety and tolerability of ramucirumab administered in combination with erlotinib or osimertinib in patients with untreated EGFR mutation–positive NSCLC and asymptomatic brain metastases.

2. Materials and methods
2.1. Patient eligibility
The study enrolled individuals aged 20 years or older with previously untreated EGFR mutation (exon-19 deletion or L858R)–positive stage IV NSCLC and with brain metastasis. With regard to brain metastases, if the lesion was asymptomatic, untreated, and either had a major diameter of <20 mm or was nonmeasurable according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the patient was allowed to enter the study. Patients with
initially symptomatic or larger brain metastases (major diameter of ≥20 mm) were considered eligible for the study if the lesion had received adequate prior treatment. All patients were required to be neurologically stable, and those with brain metastases with a major diameter of ≥40 mm were excluded. Eligible patients were also required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, at least one measurable lesion according to RECIST, and adequate organ function. Exclusion criteria included a detected T790M mutation of EGFR, clinically relevant interstitial lung disease, uncontrolled hypertension, third-space fluid requiring frequent drainage, and leptomeningeal carcinomatosis. Administration of corticosteroids at a dose of >10 mg/day for the prevention of cerebral edema related to prior treatment was not allowed. The study was approved by the institutional review board of each participating institution and was conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guideline, and applicable local regulations. All patients provided written informed consent. The study was registered with the Japan Registry of Clinical Trials (jRCTs2051190027).

2.2. Study design and treatment
The study was designed as a noncomparative, nonrandomized, multicenter phase 1b trial to assess the safety and tolerability of ramucirumab in patients with previously untreated EGFR mutation–positive NSCLC and with asymptomatic brain metastases. The study was to include two cohorts that were to be assessed independently and not compared. The target enrollment was a total of six patients. Patients received either ramucirumab plus erlotinib or ramucirumab plus osimertinib. Ramucirumab was administered intravenously at a dose of 10 mg/kg on day 1 of each cycle (every 2 weeks). Patients in cohorts 1 or 2 also received erlotinib at 150 mg daily or osimertinib at 80 mg daily, respectively. In both cohorts, patients continued the study treatment until disease progression or the development of unacceptable toxicity.

2.3. Study end points and assessments
The primary objective of the study was to investigate the safety of ramucirumab—in particular, with regard to evaluation of dose-limiting toxicity (DLT)—in evaluable patients according to a conventional 3 + 3 design. DLT was defined as CNS hemorrhage of grade ≥2 (a clinically significant intracranial
hemorrhage), where grade 2 is defined as CNS hemorrhage for which medical intervention is indicated. Secondary end points included safety profile, objective response rate (ORR), and intracranial response. Disease assessment was performed every 6 weeks for 24 weeks, and then every 12 weeks until disease progression. Brain tumor imaging by gadolinium-enhanced magnetic resonance imaging (MRI) was mandated for all patients. All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.4. Statistical analysis
DLT was assessed during the first two cycles (4 weeks) of treatment. DLT-evaluable patients were considered to be individuals who either completed two cycles of treatment or discontinued the study treatment or study participation before completing two cycles as a result of DLT. All patients who received at least one dose of study treatment were assessed for safety. AEs other than CNS hemorrhage were not reassessed as DLT because the safety of ramucirumab plus erlotinib had been thoroughly assessed in phase 1b portion of the RELAY study [4]. Tumor response was assessed according to RECIST version 1.1. Preplanned interim analysis was to be performed 6 months after the start of administration of study treatment.

3. Results
3.1. Patient characteristics
Clinical characteristics of the six patients at baseline are summarized in Table 1. The median age was 63.5 years, and most patients were male, never-smokers, and had stage IV disease at diagnosis as well as an L858R mutation in exon 21 of EGFR. Four patients had undergone surgery or radiotherapy for brain metastasis before study enrollment. At the time of this analysis, the median follow-up time was 9.4 months (range, 8.2 to 14.3 months) and discontinuation of the study drugs had not occurred.

3.2. Assessment of DLT and safety, and treatment exposure
An overview of safety findings including DLT assessment is provided in Table 2. CNS hemorrhage was not detected during the DLT assessment period or as of the time of this analysis. Treatment-emergent AEs (TEAEs) of grade 3 occurred in two patients, hypertension and anaphylaxis in one each. Only the case of
grade 3 hypertension was related to ramucirumab treatment, which was manageable. No serious AEs occurred. The most common (≥50% of patients) TEAEs of any grade were rash, dry skin, stomatitis, diarrhea, paronychia, alanine aminotransferase (ALT) increased, epistaxis, and edema (Table 3). There was no occurrence of interstitial lung disease. In addition, no new safety signals were observed. The median number of ramucirumab administrations was 18.5 (range, 13 to 31). With regard to ramucirumab dose adjustment, four of the six patients experienced at least one dose delay, but dose reduction or dose omission did not occur. In the case of EGFR-TKIs, one patient experienced two dose reductions for erlotinib, whereas one patient had a dose reduction and one patient a dose interruption for osimertinib. AEs were the most common reason for dose modification.

3.3. Efficacy
All patients in the erlotinib plus ramucirumab cohort and two patients in the osimertinib plus ramucirumab cohort had an objective response, resulting in an ORR of 83.3% (Figure 1A). Tumor response during the treatment period for all patients is shown in Figure 1B. With regard to intracranial response, one patient had a measurable untreated CNS lesion associated with brain edema, and this patient showed intracranial tumor shrinkage of 66% as the best response (PR) accompanied by disappearance of the edema.

4. Discussion
Patients with untreated brain metastases have been excluded from clinical trials featuring antiangiogenic agents because of concerns about potential intracranial hemorrhage. Our phase 1b study is the first prospective trial designed to assess the safety of ramucirumab—in particular, with regard to the incidence of CNS hemorrhage—when combined with erlotinib or osimertinib in patients with previously untreated EGFR mutation–positive NSCLC and with asymptomatic brain metastases. No CNS hemorrhage occurred in the study patients treated with ramucirumab and either erlotinib or osimertinib regardless of the baseline status of brain metastases, suggestive of a minimal or low risk for intracranial hemorrhage associated with ramucirumab administration in this patient population. The overall safety profile for both combination therapies was tolerable, consistent with the profiles of each drug in previous trials [2, 4]. Previous studies have suggested that an increased risk of intracranial
hemorrhage might be associated with the size of metastatic brain tumors in patients with advanced NSCLC [7]. Brain tumors have been found to be more numerous and smaller in NSCLC patients with EGFR mutations than in those with wild-type EGFR [8].

The brain is one of the most common sites of distant metastasis in patients with advanced EGFR-mutated NSCLC, with such brain metastasis being associated with shorter survival and increased morbidity [9]. Preclinical studies have revealed an important role for angiogenesis in the development of CNS metastasis as well as a beneficial effect of antiangiogenic agents on such metastasis in NSCLC [10, 11]. The combination of EGFR-TKIs with bevacizumab has shown encouraging results in EGFR mutation–positive NSCLC patients with brain metastases [12, 13]. Our preliminary findings also hint at the efficacy of ramucirumab for brain metastases. The measurable untreated brain lesion was associated with edema and showed shrinkage after treatment for 6 weeks, with the responses of the nontarget brain lesions of the other five patients being classified as non-CR/non-progressive disease. The stability of the brain metastatic lesions of the study patients for at least 6 months suggests a clinically meaningful benefit of study treatment.

Although our results have potentially important implications for ramucirumab administration in patients with brain metastases, the study has several limitations. First, the sample size was small as a result of the study design. Second, brain metastases of all enrolled patients were small, with a major diameter of <20 mm. Finally, the long-term safety of ramucirumab with regard to brain hemorrhage remains to be evaluated definitively. Further clinical investigation of ramucirumab should thus be conducted in patients with brain metastases.

In summary, we found that ramucirumab in combination with EGFR-TKIs was safety in patients with asymptomatic brain metastases.
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**Figure Legend**

**Fig. 1.** Confirmed best response assessed by TRCIST. 

**A)** Overall systemic and intracranial responses. 

**B)** Best change in target tumor burden over time in individual patients. 

ERL, erlotinib; RAM, ramucirumab; OSM, osimertinib.
Figure 1.

A

|                      | Cohort 1 (ERL+RAM, n=3) | Cohort 2 (OSM+RAM, n=3) | Total (n=6) |
|----------------------|-------------------------|-------------------------|-------------|
| **Systemic response**|                         |                         |             |
| Complete response (CR)| 0                       | 0                       | 0           |
| Partial response (PR) | 3                       | 2                       | 5           |
| Stable disease (SD)   | 0                       | 1                       | 1           |
| Progressive disease (PD)| 0                    | 0                       | 0           |
| Overall response      | 3                       | 2                       | 5           |
| **Intracranial response**|                       |                         |             |
| Complete response (CR)| 0                       | 0                       | 0           |
| Partial response (PR) | 1                       | 0                       | 1           |
| Stable disease (SD)   | 0                       | 0                       | 0           |
| Progressive disease (PD)| 0                    | 0                       | 0           |
| Non-CR/non-PD         | 2                       | 3                       | 5           |

B

![Graph showing response over time](image-url)
**Table 1.** Patient characteristics at baseline.

| Characteristic                      | Cohort 1 (ERL+RAM, n = 3) | Cohort 2 (OSM+RAM, n = 3) | Total (n = 6) |
|-------------------------------------|-----------------------------|---------------------------|--------------|
| Median age (range), years           | 64 (59–77)                  | 63 (50–75)                | 63.5 (50–77) |
| Sex                                 |                             |                           |              |
| Male                                | 2                           | 2                         | 4            |
| ECOG performance status             |                             |                           |              |
| 0                                   | 1                           | 2                         | 3            |
| 1                                   | 2                           | 1                         | 3            |
| Smoking                             |                             |                           |              |
| Ever                                | 1                           | 1                         | 2            |
| Never                               | 2                           | 2                         | 4            |
| Disease classification              |                             |                           |              |
| Primary                             | 2                           | 2                         | 4            |
| Recurrent                           | 1                           | 1                         | 2            |
| EGFR mutation                       |                             |                           |              |
| Exon-19 deletion                    | 1                           | 1                         | 2            |
| Exon-21 L858R                       | 2                           | 2                         | 4            |
| Prior treatment of brain metastasis |                             |                           |              |
| None                                | 1                           | 1                         | 2            |
| Resection                           | 1                           | 0                         | 1            |
| Radiotherapy                        | 1                           | 2                         | 3            |

Abbreviations: ERL, erlotinib; RAM, ramucirumab; OSM, osimertinib; ECOG, Eastern Cooperative Oncology Group.
|                                | Cohort 1 (ERL+RAM, n = 3) | Cohort 2 (OSM+RAM, n = 3) | Total (n = 6) |
|--------------------------------|---------------------------|---------------------------|--------------|
| DLT-evaluable patients         | 3                         | 3                         | 6            |
| Patients with DLT              | 0                         | 0                         | 0            |
| Any TEAE                       | 3                         | 3                         | 6            |
| Grade ≥3 TEAE                  | 1                         | 1                         | 2            |
| Any TRAE                       | 3                         | 3                         | 6            |
| Grade ≥3 TRAE                  | 1                         | 0                         | 1            |
| Serious TRAE                   | 0                         | 0                         | 0            |
| Discontinued study             |                           |                           |              |
| treatment because of TRAE      | 0                         | 0                         | 0            |
| TRAEs leading to dose          |                           |                           |              |
| adjustment (EGFR-TKI)          | 1                         | 1                         | 2            |

Abbreviations: ERL, erlotinib; RAM, ramucirumab; OSM, osimertinib; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor.
| Adverse Event          | Cohort 1 (ERL+RAM, n=3) | Cohort 2 (OSM+RAM, n=3) | Total (=6) |
|------------------------|--------------------------|--------------------------|------------|
| Patients with adverse events | 3 (100) 0 | 3 (100) 0 | 6 (100) |
| Rash                   | 2 (66.7) 0 | 3 (100) 0 | 5 (83.3) |
| Dry Skin               | 3 (100) 0 | 0 0 | 3 (50) |
| Stomatitis             | 3 (100) 0 | 0 0 | 3 (50) |
| Diarrhea               | 2 (66.7) 0 | 1 (33.3) 0 | 3 (50) |
| Paronychia             | 2 (66.7) 0 | 1 (33.3) 0 | 3 (50) |
| ALT increased          | 2 (66.7) 0 | 1 (33.3) 0 | 3 (50) |
| Epistaxis              | 2 (66.7) 0 | 1 (33.3) 0 | 3 (50) |
| Edema                  | 1 (33.3) 0 | 2 (66.7) 0 | 3 (50) |
| AST increased          | 2 (66.7) 0 | 0 0 | 2 (33.3) |
| Pruritus               | 2 (66.7) 0 | 0 0 | 2 (33.3) |
| Proteinuria            | 1 (33.3) 0 | 1 (33.3) 0 | 2 (33.3) |
| Platelet Count Decreased | 1 (33.3) 0 | 1 (33.3) 0 | 2 (33.3) |
| Blurred vision         | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Decreased appetite     | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Fatigue                | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Hemorrhoid Bleeding    | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Hypertension           | 1 (33.3) 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Increased Blood Bilirubin | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Injection site Bleeding | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Muscle cramp           | 1 (33.3) 0 | 0 0 | 1 (16.7) |
| Alopecia               | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Stomatotrhagia         | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Dizziness              | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Increased Serum Creatinine | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Myalgia                | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Arthritis              | 0 0 | 1 (33.3) 0 | 1 (16.7) |
| Anaphylaxis            | 0 0 | 1 (33.3) 1 (33.3) | 1 (16.7) |
| Headache               | 0 0 | 1 (33.3) 0 | 1 (16.7) |

Abbreviations: ERL, erlotinib; RAM, ramucirumab; OSM, osimertinib; ALT, alanine aminotransferase; AST, aspartate aminotransferase.