THERAPEUTIC ADVANCES in
Medical Oncology

Study Protocol

Rationale and design of phase II clinical trial of dual inhibition with ramucirumab and erlotinib in *EGFR* exon 19 deletion-positive treatment-naïve non-small cell lung cancer with high PD-L1 expression (SPIRAL-3D study)

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Abstract

Background: Osimertinib is a standard treatment option for epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC). However, osimertinib monotherapy yields poor clinical outcomes in some patients, necessitating the development of novel treatment strategies. In addition, several studies have suggested that high programmed cell death-ligand 1 (PD-L1) expression is associated with poor progression-free survival (PFS) for osimertinib monotherapy in patients with advanced NSCLC harboring *EGFR* mutations.

Objective: To evaluate the clinical efficacy of erlotinib plus ramucirumab for *EGFR* exon 19 deletion-positive treatment-naïve NSCLC with high PD-L1 expression.

Design: A single-arm, prospective, open-label, phase II study

Methods and Analysis: Patients with treatment-naïve *EGFR* exon 19 deletion-positive NSCLC with high PD-L1 expression and a performance status of 0–2 will receive combination therapy with erlotinib plus ramucirumab until evidence of disease progression or development of unacceptable toxicity. High PD-L1 expression is defined as a tumor proportion score of 50% or higher, as determined by PD-L1 immunohistochemistry 22C3 pharmDx testing. The Kaplan–Meier method and the Brookmeyer and Crowley method with the arcsine square-root transformation will be used with PFS as the primary endpoint. The secondary endpoints include overall response rate, disease control rate, overall survival, and safety. A total of 25 patients will be enrolled.

Ethics: The study has been approved by the Clinical Research Review Board, Kyoto Prefectural University of Medicine, Kyoto, Japan, and written informed consent will be obtained from all patients.

Discussion: To the best of our knowledge, this is the first clinical trial to focus on PD-L1 expression in *EGFR* mutation-positive NSCLC. If the primary end point is met, combination therapy with erlotinib and ramucirumab could become a potential treatment option for this clinical population.

Trial Registration: This trial was registered with the Japan Registry for Clinical Trials on 12 January 2023 (jRCTs 051220149).

Keywords: epidermal growth factor receptor, programmed cell death-ligand 1, tyrosine kinase inhibitor, vascular endothelial growth factor

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Introduction

Oncogenic alterations in the epidermal growth factor receptor (*EGFR*) gene are observed in a certain subset of patients with non-small cell lung cancer (NSCLC). The development of molecular-targeted therapy in the form of tyrosine kinase inhibitors (TKIs) has markedly improved the clinical outcomes of these patients.[1] The FLAURA study demonstrated that osimertinib, a third-generation EGFR–TKI, resulted in significantly longer progression-free survival (PFS) and overall survival (OS) compared to first-generation EGFR–TKIs, such as gefitinib or erlotinib, for patients with untreated advanced *EGFR* mutation-positive NSCLC.[2,3] Therefore, osimertinib has been approved as a standard pharmacotherapeutic modality for treatment-naïve *EGFR* mutation-positive NSCLC in several countries. Moreover, various clinical studies have attempted to confirm the efficacy and safety of novel treatment approaches based on EGFR–TKIs, including combination therapy and alternative therapy.[4–6] Of these, several randomized studies have reported the synergistic effect of first-generation EGFR–TKIs and angiogenesis inhibitors in the initial phase.[7–10] In the RELAY study, combination therapy with erlotinib and ramucirumab, a fully human recombinant IgG1 monoclonal antibody that specifically binds to the vascular endothelial growth factor receptor (VEGFR)-2 extracellular domain with high affinity, resulted in significantly longer PFS than that with erlotinib plus placebo; hence, this combination is considered an alternative initial treatment strategy for *EGFR* mutation-positive NSCLC.[7]

Since several treatment options are available for treatment-naïve *EGFR* mutation-positive advanced NSCLC, it is important to identify predictive biomarkers to ascertain the optimal treatment for this patient population. Thus, other treatment options are warranted for patients in whom osimertinib is considered to yield a poor prognosis. Subgroup analysis of survival in the FLAURA study revealed that the OS for osimertinib was significantly longer than that for first-generation EGFR–TKIs in the subgroup harboring the exon 19 deletion mutation [hazard ratio (HR), 0.68 (95% CI: 0.51–0.90)], while the OS did not differ significantly in the subgroup harboring the EGFR–L858R mutation [HR, 1.00 (95% CI: 0.71–1.40)].[3] These discrepancies in the treatment outcomes of osimertinib by *EGFR* mutation subtype are also apparent in real-world data from patients with advanced treatment-naïve *EGFR* mutation-positive NSCLC who were administered osimertinib.[11–13] In contrast, the RELAY study showed that the PFS extending the effect of combination therapy exhibited a similar trend in patients with exon 19 deletion [HR, 0.65 (95% CI: 0.47–0.90)] and L858R mutation [HR, 0.62 (95% CI: 0.44–0.87)].[4] These results suggest that combination therapy with erlotinib plus ramucirumab may be superior to osimertinib monotherapy in L858R mutation-positive patients, and a phase III clinical trial for this population is currently underway.[14]

Several clinical observational studies on predictive biomarkers of osimertinib sensitivity, including our prospective analysis, revealed that elevated programmed cell death-ligand 1 (PD-L1) expression in tumors was associated with poor clinical outcomes for osimertinib monotherapy when used as first-line treatment in patients with advanced treatment-naïve *EGFR* mutation-positive NSCLC.[11,12] Moreover, the efficacy of osimertinib is reportedly limited in patients with NSCLC with exon 19 deletion in *EGFR* with high expression of PD-L1, although osimertinib monotherapy yields good therapeutic effects in patients with NSCLC with *EGFR* exon 19 deletion.[11,12]

Thus, the formulation of novel treatment strategies is needed to improve clinical outcomes in this population. A previous study reported that high PD-L1 expression in lung adenocarcinoma was associated with missense and nonsense mutations in the tumor protein P53 (*TP53*) gene.[15] Concomitant *TP53* mutation is considered a negative prognostic factor and is associated with poorer outcomes in patients treated with EGFR–TKI monotherapy, including osimertinib.[16,17] Conversely, the analysis in the RELAY study showed that the PFS was prolonged in the subgroup with baseline *TP53* co-mutation after treatment with ramucirumab plus erlotinib compared to placebo plus erlotinib, irrespective of the *EGFR* mutation subtype.[16,18] Furthermore, the RANGE study, which evaluated the additional efficacy of ramucirumab in patients with platinum-refractory advanced urothelial carcinoma, reported that the OS was longer in the subgroup with higher PD-L1 expression than in the subgroup with lower PD-L1 expression.[19] A preclinical study showed that tumor PD-L1 regulates angiogenesis and metastasis of ovarian cancer via VEGFR2 signaling.[20] Hence, we hypothesized that combination therapy with ramucirumab plus erlotinib would be more effective than osimertinib monotherapy for *EGFR* exon 19

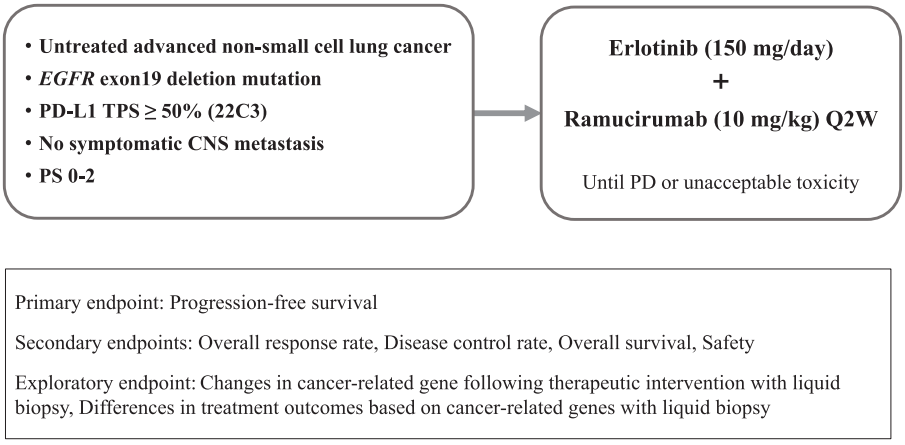

Figure 1. SPIRAL-3D trial design.

deletion mutation-positive NSCLC with high PD-L1 expression.

Therefore, we have planned a single-arm phase II trial to investigate the efficacy and safety of combination therapy with ramucirumab plus erlotinib in *EGFR* exon 19 deletion-positive treatment-naïve advanced NSCLC with high PD-L1 expression.

Study protocol

Study design and objective

This single-arm, prospective, open-label, multicenter, phase II trial aims to evaluate the efficacy and safety of the combination of ramucirumab plus erlotinib therapy in patients with *EGFR* exon 19 deletion-positive treatment-naïve advanced/recurrent NSCLC with high tumor PD-L1 expression (Figure 1).

Eligibility criteria

The key inclusion and exclusion criteria are enumerated in Table 1. Based on the safety results of a phase I study examining the combination therapy of ramucirumab with erlotinib for *EGFR* mutation-positive NSCLC patients with asymptomatic brain metastases, these patients are eligible for this study.[21]

Interventions

Eligible patients will be administered erlotinib 150 mg/day orally and ramucirumab 10 mg/kg intravenously biweekly until disease progression, withdrawal of consent, death, or unacceptable toxicity, whichever occurs first. Efficacy assessment will be conducted first at 6 weeks ± 1 week, and at 6 weeks ± 2 weeks thereafter. From week 24 onward, it will be conducted 8 weeks ± 2 weeks after the preceding evaluation. An interval of 4 weeks or more needs to be interposed between two sessions of evaluation.

Outcomes

The primary endpoint is PFS, as determined by the investigators' review. The secondary endpoints include the overall response rate, disease control rate, OS, and safety. Treatment response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[22] The incidence of adverse events will be assessed according to the Common Terminology Criteria for Adverse Events, version 5.0.[23] Furthermore, changes in the cancer-related genes after therapeutic intervention and differences in treatment outcomes based on the cancer-related genes are designated as exploratory endpoints, which will be assessed using liquid biopsy at baseline and after discontinuation of the treatment protocol.

Sample size

A total of 20 participants are necessary to achieve a statistical power of 80% with a one-sided significance level of 5%, assuming enrollment and follow-up periods of 1.5 years each. A total of 25 participants would be expected in anticipation of the exclusion of some patients from the analysis after enrollment.[24]

Table 1. Eligibility criteria for this study.

Inclusion criteria
1. Patients rated histologically or cytologically to have non-small cell lung carcinoma.
2. Stage IV or postoperative recurrence not amenable to radical treatment.
3. Having received no chemotherapy for 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.
4. *EGFR* gene exon19 deletion mutation-positive (excluded if they have T790M mutation).
5. PD-L1 high expression in tumors (Tumor PD-L1 ⩾ 50%, determined by PD-L1 IHC 22C3 pharmDx testing at each individual laboratory)
6. Patients can take oral-dose drugs.
7. Age of 20 years old or older at the time of consent obtainment.
8. ECOG performance status 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). • Neutrophils ⩾1500/mm^3 • Hemoglobin ⩾9.0 g/dL • Platelets ⩾100,000/mm^3 • AST, ALT ⩽ 3.0 × ULN (upper limit of normal range) (Patients with liver metastasis: ⩽5.0 × ULN) • Total bilirubin ⩽1.5 × ULN • Serum creatinine ⩽1.5 × ULN or creatinine clearance ⩾40 mL/min with Cockcroft-Gault formula • SpO2 (Room air) ⩾90% • PT-INR ⩽ 1.5 and APTT longer by 5 s or less than the upper limit of the normal range (unless receiving anticoagulant therapy) *In patients receiving anticoagulant therapy, such as warfarin, the anticoagulant therapy should be replaced with low-molecular-weight heparin before starting the protocol treatment, and then PT-INR ⩽ 3.0 should be confirmed. • Urinary protein ⩽1 + (test paper method, or less than 1000 mg/day in 24 h pooled urine)
10. No restriction about the presence/absence of measurable lesions according to RECIST1.1.
11. Patients are 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 specified period of time has elapsed since the completion of the prior treatments or procedures before registration: • Higher invasive surgery (open abdominal/thoracic surgery): 4 weeks or more has elapsed. • Thoracic drainage: 1 week or more has elapsed after postoperative removal of sutures. • Stereotactic radiation/γknife therapy for brain metastasis Passage of one or more days from the final irradiation day (final irradiation day on the registration day will not be accepted).
13. 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 T790M *EGFR* mutation in tumor specimens.
2. Spinal cord compression, symptomatic and unstable brain metastasis (symptomatic brain metastases stable for at least 1 week with systemic steroids [prednisolone ⩽ 40 mg/day equivalent] are allowed).
3. 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.
4. Patients with imaging findings suggestive of macrovascular tumor invasion, tumor encasement, or hollowing within the tumor.
5. Patients with tumor exposure in the central airway up to the segmental branch.

(Continued)

Table 1. (Continued)

Inclusion criteria
6. Patients having developed severe uncontrollable coagulation disorder or severe hemorrhagic complication within 6 months before registration.
7. Patients who have developed deep vein thrombus or pulmonary embolism within 3 months before registration.
8. 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.
9. 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. (Except for carcinoma in situ undergone potentially curative therapy with no evidence of disease recurrence.)
10. Patients confirmed by MRI or cerebrospinal fluid test to have meningeal dissemination.
11. 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.
12. Patients judged to have developed gastrointestinal perforation within 6 months before registration or to have a risk for perforation (gastrointestinal invasion, metastasis).
13. 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) despite appropriate management.
14. Patients having unhealed wounds or peptic ulcers.
15. Patients having developed fractures within 1 month before registration.
16. Patients with poorly controlled metabolic disease (diabetes mellitus) or other nonmalignant organ or systemic diseases or secondary effects of cancer that induce a high medical risk and/or make an assessment of survival uncertain. Provided, patients on continued insulin use are eligible if the condition is rated as being well controlled.
17. Local infection or systemic active infection requiring surgical treatment, such as drainage.
18. Periodical users of nonsteroidal 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.
19. Patients rated as Child-Pugh B or severer liver cirrhosis or having hepatic encephalopathy or symptomatic hepatic ascites.
20. 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.)
21. Interstitial pulmonary disease evident on CT scan at the time of registration (positive history or organization of radiation pneumonitis is acceptable).
22. Patients judged to be difficult to register with this study because of clinically significant psychiatric disease.
23. Complication by clinically significant ophthalmic disease [e.g., severe dry eye syndrome (including Sjögren's syndrome), dry keratoconjunctivitis, keratitis].
24. Patients requiring oral treatment with CYP3A4-inducing drugs or inhibitors.
25. Hypersensitivity to any ingredient or additive in ramucirumab or erlotinib.
26. The patient has elective or planned major surgery to be performed during the course of the clinical trial.
27. 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 the first dose of protocol therapy.
28. Other patients were judged by the clinical investigator to be inappropriate for the study.

APTT, Activated partial thromboplastin time; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferease; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; hCG, Human chorionic gonadotropin; PD-L1, programmed cell death-ligand 1; PT-INR, Prothrombin Time Test and International Normalized Ratio; RECIST1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TKI, tyrosine kinase inhibitor.

Statistical methods

The FLAURA and RELAY studies did not report the efficacy results for *EGFR* exon 19 deletion-positive NSCLC with high PD-L1 expression. Only a few prospective and retrospective observational studies have reported the efficacy of osimertinib or first-generation EGFR –TKIs in this patient population.[11,12] The primary objective of this study is to evaluate the efficacy of the combination of ramucirumab plus erlotinib in patients with treatment-naïve *EGFR* exon 19 deletion-positive NSCLC with high tumor PD-L1 expression. This objective is achieved when the lower limit of a 2-sided 90% confidence interval on the median PFS is greater than the median PFS assumed under the null hypothesis. In our previous prospective observational study, the estimated median PFS was 5.0 months for patients with NSCLC harboring *EGFR* exon 19 deletion with high tumor PD-L1 expression who were administered osimertinib as first-line treatment.[12] The median PFS for erlotinib monotherapy was 6.6 months in a similar patient population.[25] In the RELAY trial, the addition of ramucirumab to erlotinib improved the median PFS by 7.0 months with an HR of 0.594.[4] On the basis of these results, the null hypothesis that the median PFS is 5 months will be tested against the alternative hypothesis that the median PFS is 13 months. As the main analysis for the primary endpoint, the median PFS and its confidence interval will be estimated using the Kaplan–Meier method and the Brookmeyer and Crowley method with the arcsine square-root transformation.[26]

Ethical consideration and registration

The study received ethical approval from the Clinical Research Review Board, Kyoto Prefectural University of Medicine, Kyoto, Japan (approval number: 2022013). The trial is subject to the supervision and management of the Ethics Committee. Written informed consent will be obtained from all patients before registration, and the study will be conducted in accordance with the Declaration of Helsinki. The study results will be disseminated via publication in a peer-reviewed journal.

Discussion

To the best of our knowledge, this is the first clinical trial to focus on PD-L1 expression in *EGFR* mutation-positive NSCLC. The results of this prospective phase II study will provide evidence on the safety and antitumor activity of combination therapy with ramucirumab plus erlotinib in patients with *EGFR* exon 19 deletion-positive treatment-naïve NSCLC with high PD-L1 expression. If the primary endpoint is met, combination therapy with erlotinib and ramucirumab has the potential to become a treatment option for this clinical population, but further randomized controlled trials are warranted.

Declarations

Ethics approval and consent to participate

The study received ethical approval from the Clinical Research Review Board, Kyoto Prefectural University of Medicine, Kyoto, Japan. The trial is subject to the supervision and management of the Ethics Committee. Written informed consent will be obtained from all patients before registration, in accordance with the Declaration of Helsinki.

Consent for publication

None.

Author contributions

Hayato Kawachi: Conceptualization; Investigation; Visualization; Writing – original draft; Writing – review & editing.

Tadaaki Yamada: Conceptualization; Funding acquisition; Investigation; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Akihiro Yoshimura: Investigation; Writing – review & editing.

Kenji Morimoto: Investigation; Writing – review & editing.

Masahiro Iwasaku: Investigation; Writing – review & editing.

Shinsaku Tokuda: Investigation; Writing – review & editing.

Young Hak Kim: Investigation; Writing – review & editing.

Takayuki Shimose: Formal analysis; Methodology; Writing – review & editing.

Koichi Takayama: Investigation; Supervision; Writing – review & editing.

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Competing interests

H. Kawachi received personal fees from Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., AstraZeneca KK, Taiho Pharmaceutical Co. Ltd., Eli Lilly Japan KK, and MSD KK, outside the purview of the submitted work. T. Yamada received research grants from Ono Pharmaceutical, Janssen, AstraZeneca, and Takeda Pharmaceutical, and has received speaking honoraria from Eli Lilly that are outside the purview of the submitted work. K. Takayama received research grants from Chugai Pharmaceutical and Ono Pharmaceutical and personal fees from AstraZeneca, Chugai Pharmaceutical, MSD-Merck, Eli Lilly, Boehringer-Ingelheim, and Daiichi-Sankyo, that are outside the purview of the submitted work. The other authors declare no potential conflicts of interest.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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References

1. Recondo G, Facchinetti F, Olaussen KA, *et al.* Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation tki? *Nat Rev Clin Oncol* 2018; 15: 694–708.
2. Soria JC, Ohe Y, Vansteenkiste J, *et al.* Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New Engl J Med* 2018; 378: 113–125.
3. Ramalingam SS, Vansteenkiste J, Planchard D, *et al.* Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *New Engl J Med* 2020; 382: 41–50.
4. Gijtenbeek RGP, van der Noort V, Aerts JGJV, *et al.* Randomised controlled trial of first-line tyrosine-kinase inhibitor (TKI) *versus* intercalated TKI with chemotherapy for *EGFR*-mutated nonsmall cell lung cancer. *ERJ Open Res* 2022; 8: 00239–02022.
5. Cheng Y, Murakami H, Yang PC, *et al.* Randomized phase II trial of gefitinib with and without pemetrexed as first-line therapy in patients with advanced nonsquamous non-small-cell lung cancer with activating epidermal growth factor receptor mutations. *J Clin Oncol* 2016; 34: 3258–3266.
6. Passiglia F, Bironzo P, Bertaglia V, *et al.* Optimizing the clinical management of *EGFR*-mutant advanced non-small cell lung cancer: a literature review. *Transl Lung Cancer Res* 2022; 11: 935–949.
7. 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: 1655–1669.
8. Seto T, Kato T, Nishio M, *et al.* Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014; 15: 1236–1244.
9. Saito H, Fukuhara T, Furuya N, *et al.* Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019; 20: 625–635.
10. Stinchcombe TE, Jänne PA, Wang X, *et al.* Effect of erlotinib plus bevacizumab vs erlotinib alone on progression-free survival in patients with advanced EGFR-mutant non-small cell lung cancer: a Phase 2 randomized clinical trial. *JAMA Oncol* 2019; 5: 1448–1455.
11. Sakata Y, Sakata S, Oya Y, *et al.* Osimertinib as first-line treatment for advanced epidermal growth factor receptor mutation–positive non–small-cell lung cancer in a real-world setting (OSI-FACT). *Eur J Cancer* 2021; 159: 144–153.
12. 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: 3582–3593.
13. Gijtenbeek RGP, Damhuis RAM, van der Wekken AJ, *et al.* Overall survival in advanced epidermal growth factor receptor mutated non-small cell lung cancer using different tyrosine kinase inhibitors

in the Netherlands: a retrospective, nationwide registry study. *Lancet Reg Health Eur* 2023; 27: 100592.

14. Haratake N, Hayashi H, Shimokawa M, *et al.* Phase III clinical trial for the combination of erlotinib plus ramucirumab compared with osimertinib in previously untreated advanced or recurrent non-small cell lung cancer positive for the L858R mutation of EGFR: REVOL858R (WJOG14420L). *Clin Lung Cancer* 2022; 23: e257–e263.
15. Sun H, Liu SY, Zhou JY, *et al.* Specific TP53 subtype as biomarker for immune checkpoint inhibitors in lung adenocarcinoma. *EBioMedicine* 2020; 60: 102990.
16. Qin K, Hou H, Liang Y, *et al.* Prognostic value of TP53 concurrent mutations for EGFR-TKIs and ALK-TKIs based targeted therapy in advanced non-small cell lung cancer: a meta-analysis. *BMC Cancer* 2020; 20: 328.
17. 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.
18. 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: 5258–5271.
19. van der Heijden MS, Powles T, Petrylak D, *et al.* Predictive biomarkers for survival benefit with ramucirumab in urothelial cancer in the RANGE trial. *Nat Commun* 2022; 13: 1878.
20. Yang Y, Xia L, Wu Y, *et al.* Programmed death ligand-1 regulates angiogenesis and metastasis by participating in the c-Jun/VEGFR2 signaling axis in ovarian cancer. *Cancer Commun* 2021; 41: 511–527.
21. Kaneda H, Sawa K, Daga H, *et al.* 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. *Investig New Drugs* 2021; 39: 1598–1603.
22. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* *Eur J Cancer* 2009; 45: 228–247.
23. Freites-Martinez A, Santana N, Arias-Santiago S, *et al.* Using the common terminology criteria for adverse events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr* 2021; 112: 90–92.
24. Nagashima K, Noma H, Sato Y, *et al.* Sample size calculations for single-arm survival studies using transformations of the Kaplan-Meier estimator. *Pharm Stat* 2021; 20: 499–511.
25. Liu J, Itchins M, Nagrial A, *et al.* Relationship between PD-L1 expression and outcome in EGFR-mutant lung cancer patients treated with EGFR tyrosine kinase inhibitors. *Lung Cancer* 2021; 155: 28–33.
26. Brookmeyer R and Crowley J. A confidence interval for the median survival time. *Biometrics* 1982; 38: 29–41.