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Late-line Real-world Outcomes of Amivantamab Plus Lazertinib After EGFR-TKI Failure in EGFR-Mutated Non-Small Cell Lung Cancer

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Abstract

Background

Real-world evidence on amivantamab plus lazertinib after EGFR tyrosine kinase inhibitor (EGFR-TKI) failure remains limited, particularly in later-line settings. We evaluated the clinical outcomes, safety, and exploratory genomic findings of this regimen in a single-institution cohort.

Methods

We retrospectively reviewed patients with advanced or recurrent *EGFR*-mutated non-small cell lung cancer, excluding *EGFR* exon 20 insertion mutations, who initiated amivantamab plus lazertinib after EGFR-TKI therapy at a single institution between July 2025 and May 2026. First-line patients were excluded. Time to treatment failure (TTF), adverse events, and comprehensive genomic profiling results from post-EGFR-TKI failure tumor biopsy specimens were evaluated.

Results

Eighteen patients were included. The median treatment line was 3.5, and 16 patients had received osimertinib. Among 13 response-evaluable patients, the best overall response was partial response in 1 patient, stable disease in 4 patients, non-CR/non-PD in 6 patients, and progressive disease in 2 patients, yielding an objective response rate of 7.7% and a disease control rate of 84.6%. The median TTF was 8.5 months. Infusion-related reactions occurred in 5 patients, with no grade 3 or higher events. Grade 3 or higher adverse events occurred in 8 patients, and adverse event-related discontinuation occurred in 1 patient. Comprehensive genomic profiling was available in 6 patients and revealed *EGFR* amplification in 3 patients, *MET* amplification in 1 patient, and *EGFR* C797S in 1 patient.

Conclusion

Amivantamab plus lazertinib showed disease control and manageable safety in a later-line real-world cohort after EGFR-TKI failure. Exploratory genomic findings demonstrated molecular heterogeneity, warranting further study.

Introduction

Molecularly targeted therapies have transformed the treatment landscape of advanced non-small cell lung cancer (NSCLC). *EGFR* mutations are among the most common actionable oncogenic drivers in Asian patients with lung adenocarcinoma, and EGFR tyrosine kinase inhibitors (EGFR-TKIs) have been established as the cornerstone of treatment for patients with *EGFR*-mutated NSCLC through multiple randomized trials [1, 2]. However, despite the substantial clinical benefit of EGFR-TKIs, disease

progression eventually occurs in most patients. Molecular profiling studies after osimertinib have identified a range of acquired resistance mechanisms, including *EGFR*-dependent alterations such as secondary *EGFR* mutations including C797S [3] and *EGFR* amplification, and *EGFR*-independent bypass pathway activation, most notably *MET* amplification [4]. These findings have prompted the development of therapeutic strategies directed at distinct resistance pathways, including agents targeting EGFR-dependent resistance alterations [5, 6] and approaches targeting EGFR-independent bypass signaling such as MET activation.

Amivantamab is a bispecific antibody targeting EGFR and MET, designed to inhibit both EGFR-driven signaling and MET-mediated bypass signaling [7]. In patients with *EGFR*-mutated NSCLC who experience disease progression after osimertinib, amivantamab-based regimens have demonstrated clinical activity in prospective trials. In MARIPOSA-2, amivantamab combined with chemotherapy, with or without lazertinib, improved outcomes compared with chemotherapy alone after progression on osimertinib [8]. In CHRYSALIS-2, the combination of amivantamab and lazertinib showed antitumor activity in patients previously treated with osimertinib and platinum-based chemotherapy [9].

The first-line treatment landscape for *EGFR*-mutated NSCLC has recently expanded to include combination strategies such as amivantamab plus lazertinib [7] and osimertinib plus platinum-based chemotherapy [10], in addition to osimertinib monotherapy. Nevertheless, osimertinib monotherapy remains widely used in routine clinical practice, particularly when tolerability is an important consideration. Therefore, the management of patients who develop disease progression after osimertinib remains a clinically important issue. Given the dual EGFR/MET-targeting mechanism of amivantamab and the involvement of EGFR-dependent alterations and MET-mediated bypass signaling in osimertinib resistance, amivantamab plus lazertinib may represent a biologically rational therapeutic strategy after EGFR-TKI failure.

However, evidence regarding amivantamab plus lazertinib in routine clinical practice remains limited, particularly in heavily pretreated patients treated in later-line settings. In addition, few studies have evaluated clinical outcomes together with comprehensive genomic profiling findings from post-EGFR-TKI failure biopsy specimens. Therefore, we conducted a single-institution retrospective study to evaluate the clinical outcomes, safety, and exploratory pretreatment comprehensive genomic profiling findings of intravenous amivantamab plus lazertinib after EGFR-TKI failure in patients with *EGFR*-mutated NSCLC treated in a later-line setting.

Methods

We retrospectively reviewed patients with advanced or recurrent NSCLC with confirmed EGFR mutations other than exon 20 insertion mutations who initiated amivantamab plus lazertinib after prior EGFR-TKI therapy at a single institution between July 1, 2025, when the regimen became available for clinical use, and May 30, 2026. Patients who received amivantamab plus lazertinib as first-line therapy were excluded. EGFR-TKI failure was defined as discontinuation of prior EGFR-TKI therapy because of disease

progression or treatment intolerance/adverse events. Clinical data were extracted from medical records, including patient characteristics, EGFR mutation subtype, metastatic sites, prior treatments, cumulative duration of prior EGFR-TKI therapy, reason for discontinuation of the last EGFR-TKI, treatment line, treatment duration, best overall response, adverse events, post-EGFR-TKI failure tumor biopsy status, and CGP results.

All patients initiated treatment with intravenous amivantamab in combination with lazertinib. This cohort represents a treatment period before subcutaneous amivantamab became available in routine clinical practice. Premedication for IRR prophylaxis was administered according to our institutional protocol, which was based on previously reported prophylactic strategies [11].

Tumor response was assessed based on radiologic findings. Time to treatment failure (TTF) was defined as the time from initiation of amivantamab plus lazertinib to treatment discontinuation of both agents for any reason. Patients who remained on treatment at the data cutoff were censored at the last follow-up. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Patients who underwent comprehensive genomic profiling using tumor biopsy specimens obtained after EGFR-TKI failure were included in the exploratory molecular analysis. Time to treatment failure was estimated using the Kaplan–Meier method, and Kaplan–Meier curves were generated using GraphPad Prism version 10 (GraphPad Software, Boston, MA, USA). Swimmer plots and oncoprints were generated using R software (version 4.6.1; R Foundation for Statistical Computing, Vienna, Austria). Comprehensive genomic profiling was performed using Rapid-Neo, an in-house DNA-based targeted panel sequencing assay, as previously reported [12].

Results

Eighteen patients with *EGFR*-mutated NSCLC initiated amivantamab plus lazertinib with intravenous amivantamab after EGFR-TKI failure and were included in this study. Patient characteristics and prior treatment are summarized in Table 1. Detailed individual data are provided in Supplementary Table 1. The median age was 67 years, and 16 patients had an ECOG performance status of 0 or 1. *EGFR* mutation subtypes included exon 19 deletion in 11 patients and L858R in 6 patients. One patient had atypical *EGFR* mutations consisting of G719A and S768I. Brain metastases were present in 11 patients.

Table 1
Baseline patient characteristics, prior treatment history, and biopsy status before amivantamab plus lazertinib

Variable	Overall Cohort, n = 18
Patient characteristics	67 (34–85)
Age, median (range), years	
Male sex, n (%)	6 (33.3)
ECOG PS 0–1, n (%)	16 (88.9)
EGFR mutation subtype : exon 19 deletion / L858R / atypical, n (%)	11 (61.1) / 6 (33.3) / 1 (5.6)
Brain metastasis, n (%)	11 (61.1)
Prior treatment and biopsy status	
Prior osimertinib exposure, n (%)	16 (88.9)
Treatment line, median (range)	3.5 (2–9)
Interval since last EGFR-TKI discontinuation, median (range), months	10 (0-109) *
Cumulative duration of prior EGFR-TKI therapy, median (range), months	26.0 (1.9–163)*
Prior platinum-based chemotherapy, n (%)	16 (88.9)
Post-EGFR-TKI failure tumor biopsy with CGP, n (%)	6 (33.3)
* Calculated among 17 patients with available data.	

Amivantamab plus lazertinib was administered in a late-line setting, with a median treatment line of 3.5. Prior osimertinib exposure and prior platinum-based chemotherapy were each documented in 16 patients. The median cumulative duration of prior EGFR-TKI therapy was 26.0 months. The last EGFR-TKI was discontinued because of disease progression in 17 patients; the reason for discontinuation was unknown in 1 patient.

Treatment outcomes are summarized in Table 2. Thirteen patients were evaluable for tumor response. The best overall response was partial response in 1 patient, stable disease in 4 patients, non-CR/non-PD in 6 patients, and progressive disease in 2 patients, resulting in an objective response rate of 7.7% and a disease control rate of 84.6%. The median time to treatment failure (TTF) was 8.5 months, and 7 patients remained on treatment at the data cutoff. The swimmer plot is shown in Fig. 1A. The waterfall plot of the best percentage change in target lesion size in 7 patients with measurable target lesions and the Kaplan–Meier curve for TTF are shown in Supplementary Figs. 1 and 2, respectively.

Table 2
Clinical outcomes

Variable	Overall Cohort, n = 18
Follow-up duration, median (range), months	6.39 (0–11)
Response-evaluable patients, n (%)	13 (72.2)
Best overall response, n (%)	
PR	1 (7.7)
SD	4 (30.8)
non-CR/non-PD	6 (46.2)
PD	2 (15.4)
Non-evaluable patients, n (%)	5 (27.8)
ORR / DCR, %	7.7 / 84.6
Median TTF, months	8.5
Ongoing treatment at data cutoff, n (%)	7 (38.9)

Adverse events are summarized in Table 3. All patients received infusion-related reaction prophylaxis according to an institutional protocol based on a previously reported strategy [11]. Infusion-related reactions occurred in 5 patients, and no grade 3 or higher infusion-related reaction was observed. Grade 3 or higher adverse events occurred in 8 patients. Common adverse events included rash or acneiform dermatitis, paronychia, hypoalbuminemia or edema, and venous thromboembolism. Treatment discontinuation due to adverse events occurred in 1 patient.

Table 3
Adverse events

Hypoalbuminemia or edema	**All grades, n (%)**	**Grade ≥ 3, n**
	14 (77.8)	**2**
Rash / acneiform dermatitis	13 (72.2)	2
Paronychia	8 (44.4)	2
Infusion-related reaction	5 (27.8)	-
Oral mucositis	3 (16.7)	1
Venous thromboembolism	2 (11.1)	1
Anorexia	2 (11.1)	-
Thrombocytopenia	2 (11.1)	1
Drug-induced lung injury	1 (5.6)	-
Liver dysfunction	1 (5.6)	1
Renal dysfunction	1 (5.6)	-
Anemia	1 (5.6)	-
Headache	1 (5.6)	-
Alopecia	1 (5.6)	-
Malaise	1 (5.6)	-

Comprehensive genomic profiling using Rapid-Neo on tumor biopsy specimens obtained after EGFR-TKI failure and before initiation of amivantamab plus lazertinib was available in 6 of 18 patients. The clinically documented original *EGFR* mutation subtype was also detected in all six post-EGFR-TKI failure biopsy specimens. Among these 6 patients, *EGFR* amplification was detected in 3 patients, while *MET* amplification and *EGFR* C797S were each detected in 1 patient. *EGFR* T790M was detected in 1 patient who had previously received erlotinib followed by osimertinib. Additional alterations included *TP53, RB1, PIK3CA, PTEN, CDKN2A/B*, and *STK11*, indicating co-occurring genomic alterations beyond EGFR/MET pathway-related changes.

The best overall response to amivantamab plus lazertinib among these 6 patients was partial response in 1 patient, non-CR/non-PD in 3 patients, and not evaluable in 2 patients. Among the 3 patients with *EGFR* amplification, the best overall response was partial response in 1 patient and non-CR/non-PD in 2 patients. Non-CR/non-PD was also observed in the patient with *MET* amplification and in the patient with both *EGFR* C797S and *EGFR* amplification. In the patient with *MET* amplification, lazertinib was discontinued at 0.85 months, whereas amivantamab was continued thereafter without lazertinib for

most of the treatment period; the TTF for this patient was 8.5 months. These genomic alterations and corresponding clinical annotations are summarized in Fig. 1B.

Discussion

In this single-institution retrospective study, amivantamab plus lazertinib showed disease control with manageable safety in patients with EGFR-mutated NSCLC after EGFR-TKI failure in routine clinical practice, highlighting the real-world feasibility of targeted therapy after acquired resistance. This cohort was characterized by later-line treatment use, with a median treatment line of 3.5, and most patients had previously received both osimertinib and platinum-based chemotherapy. Notably, the last EGFR-TKI had been discontinued because of disease progression in nearly all patients. Although the objective response rate was modest, disease control was observed in 84.6% of response-evaluable patients, and the median TTF was 8.5 months. In CHRYSALIS-2 cohort A, amivantamab plus lazertinib demonstrated antitumor activity in patients previously treated with osimertinib and platinum-based chemotherapy [9]. Our cohort shared this key clinical feature, as most patients had received both treatments before amivantamab plus lazertinib. However, our study differed from CHRYSALIS-2 in its real-world retrospective design, inclusion of heterogeneous later-line patients, and use of TTF rather than trial-defined efficacy endpoints. These findings may also be considered in light of previous reports of EGFR-TKI rechallenge. EGFR-TKI retreatment after intervening therapy or a TKI-free interval has been reported to provide clinical benefit in selected patients with *EGFR*-mutated NSCLC [13, 14]. In the present cohort, the median interval from discontinuation of the last EGFR-TKI to initiation of amivantamab plus lazertinib was 10.0 months. Although this regimen is distinct from simple EGFR-TKI rechallenge because it combines lazertinib with EGFR/MET-directed antibody therapy, re-exposure to EGFR pathway inhibition after a treatment interval may be one possible contributor to the observed disease control. Although direct comparison is therefore limited, our findings suggest that this regimen may provide clinically meaningful treatment durability in selected heavily pretreated patients in routine clinical practice.

The safety profile was generally consistent with that expected for EGFR- and MET-directed therapy [7]. Infusion-related reactions occurred in five patients; however, no grade 3 or higher infusion-related reaction was observed, possibly reflecting the use of institutional prophylaxis based on previously reported preventive strategies [11]. Other adverse events, including rash or acneiform dermatitis, paronychia, hypoalbuminemia or edema, and venous thromboembolism, were manageable in most patients. Treatment discontinuation due to adverse events occurred in only one patient, supporting the feasibility of this regimen with appropriate supportive care.

All patients in the present cohort initiated treatment with intravenous amivantamab. Recently, subcutaneous amivantamab has become clinically available and has been reported to reduce the incidence of infusion-related reactions compared with intravenous administration [15]. Therefore, the burden of infusion-related reactions may be lower in future routine practice with broader use of subcutaneous administration. Nevertheless, the present study provides real-world reference data on the safety and feasibility of intravenous initiation of amivantamab plus lazertinib.

Exploratory comprehensive genomic profiling demonstrated molecular heterogeneity in tumor specimens obtained after EGFR-TKI failure and before initiation of amivantamab plus lazertinib. *EGFR* amplification was detected in three patients, while *MET* amplification and *EGFR* C797S were each detected in one patient. *EGFR* amplification has been implicated as a potential mechanism of resistance to third-generation EGFR-TKIs, including osimertinib, in both preclinical models [16] and clinical molecular profiling studies [17]. In the present cohort, the patient who achieved a partial response harbored *EGFR* amplification, and disease control was also observed in other patients with *EGFR* amplification. *MET* amplification is a well-recognized bypass resistance mechanism after osimertinib failure [18, 19], and non-CR/non-PD was observed in the patient with *MET* amplification. Notably, in this patient, lazertinib was discontinued at 0.85 months, whereas amivantamab was continued without lazertinib for most of the treatment course, with a TTF of 8.5 months from initiation of amivantamab plus lazertinib. Although no conclusion can be drawn from a single case, this clinical course may be informative as a real-world example in which amivantamab was continued after discontinuation of lazertinib in a patient with MET amplification. Beyond EGFR/MET pathway-related alterations, co-occurring alterations in tumor suppressor and cell-cycle–related genes, including *TP53*, *RB1*, and *CDKN2A/B*, were also observed. Co-occurring genomic alterations have been reported to influence tumor evolution and clinical outcomes in *EGFR*-mutant NSCLC [20–22], and concurrent *TP53* and *RB1* alterations have been associated with lineage plasticity, histologic transformation, and inferior outcomes [23, 19, 4]. Although these alterations may reflect the genomic complexity of heavily pretreated EGFR-mutant NSCLC, their clinical significance in relation to amivantamab plus lazertinib could not be determined in this exploratory cohort. Given the small number of patients and the absence of systematic matched molecular profiling before and after EGFR-TKI failure, these alterations could not be definitively classified as acquired resistance mechanisms or predictive biomarkers for amivantamab plus lazertinib.

This study is limited by its retrospective single-institution design and small sample size. Molecular profiling was available only in a subset of patients, which limits the interpretation of exploratory genomic findings. Nevertheless, these findings provide early real-world evidence supporting the feasibility of amivantamab plus lazertinib after EGFR-TKI failure.

In conclusion, amivantamab plus lazertinib demonstrated disease control and manageable safety in a later-line real-world cohort of patients with *EGFR*-mutated NSCLC after EGFR-TKI failure. Exploratory genomic findings suggest molecular heterogeneity in this setting, but larger studies are needed to identify biomarkers associated with clinical benefit.

Declarations

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Conflict of interest

Naoko Maruyama reports stock ownership in Johnson & Johnson, the parent company of Janssen Pharmaceutical, and honoraria from AstraZeneca, outside the submitted work. Tetsuo Tani has received honoraria for lectures or presentations from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Daiichi Sankyo Co., Ltd., and Kyorin Pharmaceutical Co., Ltd., and research grants from the Japan Society for the Promotion of Science (JSPS) KAKENHI (grant number JP 26K11106) and Keio University Academic Development Funds. Shinnosuke Ikemura has received honoraria for lectures or presentations from Janssen Pharmaceutical K.K., AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., MSD K.K., and Pfizer Japan Inc. Hideki Terai has received honoraria for lectures or presentations from Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., MSD K.K., Nippon Kayaku Co., Ltd., Amgen K.K., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyorin Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Company Limited. Hiroyuki Yasuda has received honoraria from AstraZeneca, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, Takeda Pharmaceutical Company Limited, Daiichi Sankyo Co., Ltd., and Boehringer Ingelheim. Kazuhito Horie has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd. All other authors declare no conflict of interest.

Ethics approval

All samples were obtained as part of routine clinical care. Written informed consent was obtained for in-house clinical genomic testing (Rapid-Neo). This retrospective study was approved by the Ethics Committee of Keio University School of Medicine and conducted using an institutional opt-out procedure (IRB No. 20231104, approved on September 26, 2023; and IRB No. 20231123, approved on November 15, 2023).

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy restrictions related to patient confidentiality.

CRediT authorship contribution statement

Naoko Maruyama: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

Tetsuo Tani: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Risako Suzuki: Formal analysis, Visualization.

Kazuhito Horie: Data curation, Investigation, Resources.

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Shinnosuke Ikemura: Supervision.

Hideki Terai: Supervision, Writing – review & editing.

Takahiro Fukushima: Data curation, Investigation, Resources.

Kohei Nakamura: Formal analysis, Investigation.

Hiroshi Nishihara: Formal analysis, Investigation.

Hiroyuki Yasuda: Supervision.

Koichi Fukunaga: Supervision.

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Figures

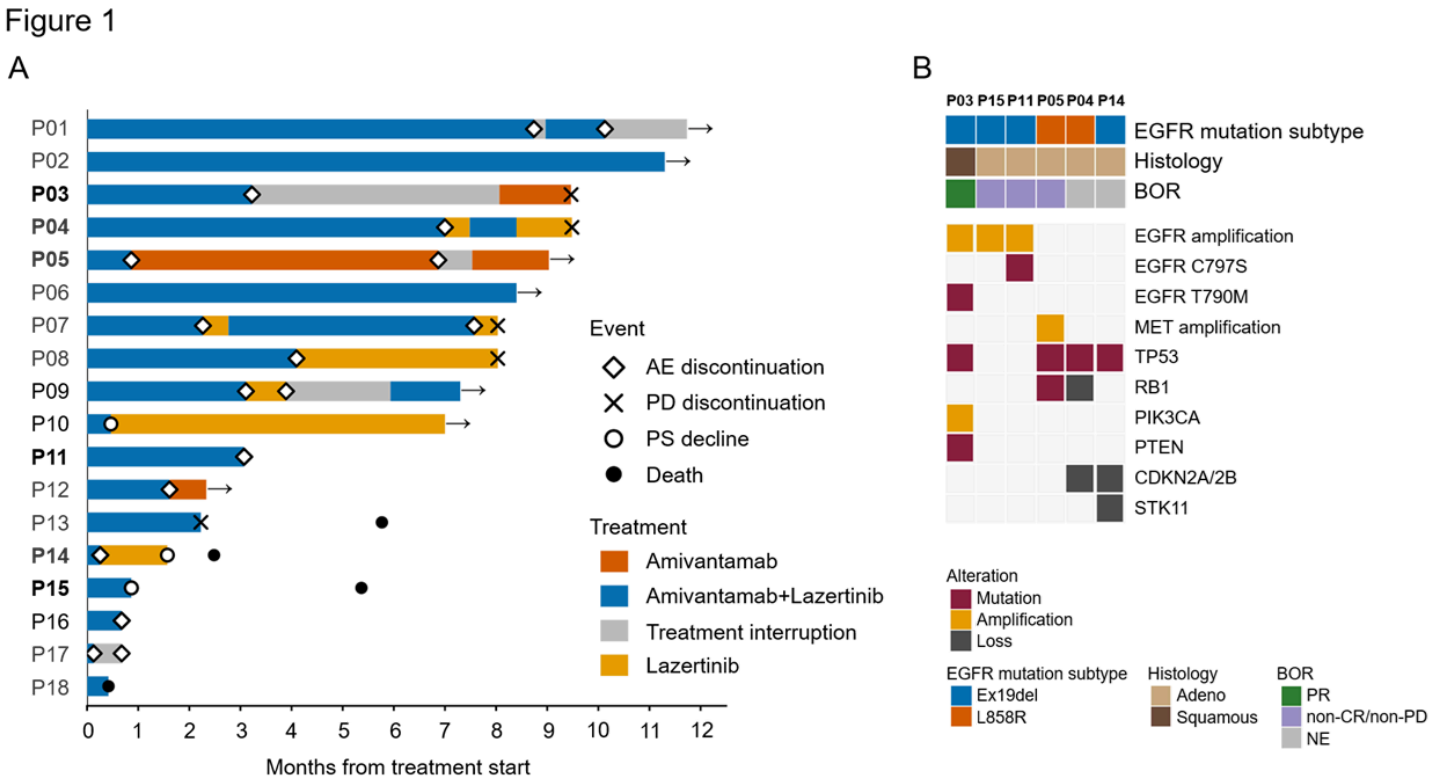


Figure 1

Treatment duration and genomic alterations in patients treated with amivantamab plus lazertinib.

(A) Swimmer plot showing the duration of treatment with amivantamab plus lazertinib in all 18 patients. Bars extend from initiation of amivantamab plus lazertinib to treatment discontinuation or the data cutoff. Arrows indicate patients who remained on treatment at the data cutoff. Patients with CGP data are indicated by bold patient identifiers and correspond to those shown in Figure 1B.

Abbreviations: AE, adverse event; PD, progressive disease; PS, performance status.

(B) Oncoprint showing genomic alterations detected by comprehensive genomic profiling using tumor biopsy specimens obtained after EGFR-TKI failure and before initiation of amivantamab plus lazertinib. Clinical annotations include EGFR mutation subtype, post-EGFR-TKI failure biopsy histology, and best overall response to amivantamab plus lazertinib. EGFR mutation subtype indicates the clinically documented original EGFR mutation subtype, which was also detected in all six specimens. Colors indicate alteration types, including mutation, amplification, and loss. Patient identifiers correspond to those shown in the swimmer plot in Figure 1A.

Abbreviations: BOR, best overall response; NE, not evaluable; non-CR/non-PD, non-complete response/non-progressive disease; PR, partial response; Adeno, adenocarcinoma; Squamous, squamous cell carcinoma.

Supplementary Files

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