Original Article

# Effectiveness and safety of amivantamab in EGFR exon 20 insertion (E20I) mutations in non-small cell lung cancer (NSCLC)

**Dae-Ho Choi^, Hyun Ae Jung, Sehhoon Park, Jong-Mu Sun, Jin Seok Ahn, Myung-Ju Ahn, Se-Hoon Lee**

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

*Contributions:* (I) Conception and design: SH Lee, DH Choi; (II) Administrative support: SH Lee; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: DH Choi; (V) Data analysis and interpretation: DH Choi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Se-Hoon Lee, MD. Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. Email: sehoon.lee119@gmail.com.

**Background:** In non-small cell lung cancer (NSCLC), the epidermal growth factor receptor (EGFR) mutation is a representative oncogenic driver mutation. Only about 12% of EGFR mutation patients have the exon 20 insertion mutation, which is the third most frequent mutation among EGFR mutation NSCLC. Amivantamab, an EGFR and MET proto-oncogene, receptor tyrosine kinase (MET) bispecific antibody, was approved for NSCLC patients with the EGFR exon 20 insertion (E20I) mutation. In this study, we described the real-world, single-center efficacy and safety data of amivantamab in E20I mutation patients.

**Methods:** This study included metastatic NSCLC patients with EGFR E20I mutations. From January 2018 to June 2022, patients with EGFR E20I mutations who were treated with amivantamab were analyzed at Samsung Medical Center as part of the clinical trial or the early access program (EAP). We collected the patients' characteristics [age, sex, smoking history, location of mutation, sites of metastasis, programmed death-ligand 1 (PD-L1) expression status, etc.] and analyzed progression-free survival (PFS) and overall survival (OS) stratified by PD-L1 expression status, co-mutation such as tumor protein p53 (TP53), and metastasis sites.

**Results:** A total of 42 patients were analyzed, of which 16 patients were enrolled in the phase 1 study, and 26 patients received amivantamab through EAP. There were 14 (33%) patients with partial remission, 18 (43%) patients with stable disease, and 10 (24%) patients with disease progression. The objective response rate (ORR) was 33%, and the disease control rate (DCR) was 76%. PFS was analyzed by dividing the near and far loop for 31 patients whose mutation location was known. The two groups had no statistically significant difference in PFS [median (range): 11.8 (2.3–21.3) *vs.* 11.3 (3.4–19.2) months, P=0.69]. For 29 patients with TP53 mutation data, there was no significant difference in PFS between the two groups [median (range): 5.9 (0–18.0) *vs.* 12.6 (6.9–18.3) months, P=0.11]. When analyzing PFS in 37 patients with PD-L1 expression data, PD-L1 (+) patients showed a poor prognosis [median (range): 11.3 (5.0–17.6) *vs.* 19.5 (5.3–33.7) months, P=0.04; hazard ratio (HR), 0.44; 95% confidence interval (CI): 0.20–0.98].

**Conclusions:** The efficacy of amivantamab was confirmed for the real-world population for EGFR E20I-mutated NSCLC. PD-L1 status could be a poor predictive factor, which should be further validated.

**Keywords:** Epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC); programmed death-ligand 1 (PD-L1); exon 20; amivantamab

Submitted Oct 08, 2023. Accepted for publication Dec 14, 2023. Published online Dec 22, 2023.
doi: 10.21037/tlcr-23-643
**View this article at:** https://dx.doi.org/10.21037/tlcr-23-643

^ ORCID: 0000-0001-8528-7917.

## Introduction

Lung cancer is one of the most common cancers in the world and has one of the highest mortality rates (1). Lung cancer is classified into non-small cell lung cancer (NSCLC) and small cell lung cancer, and about 85% of lung cancer is classified as NSCLC (2,3). Many of the cases are classified as adenocarcinoma or squamous cell carcinoma, and among them, adenocarcinoma has more oncogenic driver mutations than squamous cell carcinoma (4).

In the Western world, Kirsten rat sarcoma virus (KRAS) mutations are relatively more common than epidermal growth factor receptor (EGFR) mutations (5-7), but in the Eastern world, EGFR mutations are more common than KRAS mutations (8,9). Among EGFR mutation cases, exon 19 deletion and exon 21 point mutations are the two most common types of mutation. The third most common EGFR mutation is the EGFR exon 20 insertion (E20I) mutation (9). In the case of the E20I mutation, the EGFR tyrosine kinase inhibitor (TKI) is less effective, so it is difficult to treat (10,11). The EGFR mutation induces a steric hindrance of the pocket of the adenosine triphosphate (ATP)-binding site and the C-helix, resulting in EGFR activation (12). However, in the case of the E20I mutation, the drug-binding activity with TKI is different from that of the exon 21 mutations and exon 19 deletions, causing many difficulties in treatment (13).

Amivantamab, an EGFR-mesenchymal epithelial transition receptor (MET) bispecific antibody, is a Food and Drug Administration (FDA)-approved drug for E20I mutation patients whose disease has progressed on or after platinum-based chemotherapy (14). Amivantamab binds to EGFR and MET on the cell surface and is downmodulated to exhibit antitumor activity (15).

However, amivantamab has not yet been investigated through subgroup analysis such as biomarker studies, and real-world analysis data is also insufficient. In this study, the real-world data of patients with the E20I mutation were analyzed to determine the efficacy via overall survival (OS) and progression-free survival (PFS), and subgroup analysis was additionally conducted for mutation location and biomarkers such as tumor protein p53 (TP53) and programmed death-ligand 1 (PD-L1). Furthermore, we conducted a subgroup analysis to explore the potential synergistic effects of amivantamab when combined with immune checkpoint inhibitors, leveraging the immune-enhancing effects associated with trogocytosis (16-21). We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-643/rc).

### Highlight box

**Key findings**

- The progression-free survival was inferior in case of programmed death ligand-1 (PD-L1) expression positive EGFR exon 20 insertion (E20I) mutation patients with non-small cell lung cancer (NSCLC).

**What is known and what is new?**

- The Food and Drug Administration has granted approval for amivantamab in patients with NSCLC harboring E20I, and its effectiveness has been validated through the CHRYSALIS trial.
- This study undertook an analysis in a real-world setting to assess the efficacy of amivantamab in NSCLC patients with E20I, including a subgroup analysis focusing on biomarkers.

**What is the implication, and what should change now?**

- When using amivantamab in individuals with NSCLC possessing E20I, PD-L1 may function as a poor predictive marker.

## Methods

### *Data collection*

From January 2018 to June 2022, 42 patients who were treated with amivantamab among patients with the E20I mutation were analyzed at Samsung Medical Center. Sixteen patients were enrolled in the phase 1 study, and 26 patients received amivantamab through early access program (EAP). Baseline characteristics were collected, and pathological, molecular data were extracted and analyzed to investigate any prognostic or predictive factors for treatment outcomes.

Clinical data were obtained from the electronic medical record database. The data collectors are trained to use the standardized case report form. And, to mitigate selection bias, we incorporated all patients with exon 20 insertion mutations who underwent amivantamab treatment into our analysis. We handled unidentifiable data as either 'unknown' or 'censored' in the study.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and the Korea Good Clinical Practice guidelines. This study was approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2023-05-048), and individual consent for this retrospective analysis was waived. Patients in the database were identified by patient

number only, with personally identifiable information kept confidential according to the IRB protocol.

### *Definition of variables*

To investigate the patients' baseline characteristics, age, gender, smoking history, histologic status, previous lines of therapy, central nervous system (CNS) metastasis, liver metastasis, bone metastasis, previous TKI use, previous immunotherapy, and previous platinum-based chemotherapy were investigated. To confirm the molecular profile, EGFR mutation location, PD-L1 expression status, and TP53 were investigated.

The molecular profile was analyzed by next-generation sequencing (NGS), real-time polymerase chain reaction (RT-PCR), and immunohistochemistry (IHC). EGFR mutation-positive NSCLC was analyzed by RT-PCR (PANAMutyper™ EGFR kit; PANAGENE Inc., Daejeon, Republic of Korea) and NGS panel (Trusight™ Oncology 500; Illumina, San Diego, CA, USA), Oncomine™ (ThermoFisher Scientific, Waltham, MA, USA), CancerSCAN® (Twist Biosciences, CA, USA), Guardant360® CDx (GUARDANT, Palo Alto, CA, USA), and FoundationOne® CDx (FOUNDATION MEDICINE, Cambridge, MA, USA). PD-L1 expression was evaluated with various IHC platforms using 22C3, SP263 antibody and determined with a tumor proportion score (TPS). TP53 expression was confirmed by NGS, and by referring to the transcriptional activity of the TP53 database (the TP53 database), it was confirmed whether the mutation was effective.

### *Outcomes*

The primary outcome was PFS, defined as the time from the start of amivantamab administration to radiographic progression or death. The secondary outcomes were OS, defined as the time from the start of amivantamab administration to death, and objective response rate (ORR), defined as the proportion of patients who had the best response of complete response or partial response. Disease progression and tumor response were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

### *Statistical analysis*

For patient characteristics, all categorical variables are presented as frequencies and percentages. Chi-square tests and Fisher's exact tests were used to compare the general characteristics of each subgroup. Survival analysis between the two subgroups was analyzed using the Kaplan-Meier method, and the hazard ratio (HR) between the two subgroups was analyzed using Cox proportional hazards models. Univariable and multivariable analyses were conducted to estimate HR and 95% confidence intervals (CIs). All P values were two-sided, and a P value less than 0.05 was considered statistically significant. We endeavored to mitigate confounding variables by contrasting the characteristics of the two groups in pursuit of meaningful finding (Table S1). All statistical analyses were performed using SPSS version 25 (IBM-SPSS, Armonk, NY, USA).

## Results

### *Characteristics of the study population*

Patients with the NSCLC exon 20 insertion mutation who used amivantamab were analyzed at Samsung Medical Center from January 2018 to June 2022. The data was analyzed as of June 2023. All patients harboring exon 20 insertion mutations and undergoing Amivantamab therapy in our center were included in the analysis. A total of 42 patients were analyzed, of which 16 patients were enrolled in the amivantamab phase 1 study, and 26 patients received amivantamab through EAP. *Table 1* presents the clinical characteristics of the study population, the median age of which was 63 years. Twenty-five (60%) patients were male, and 17 (40%) patients were female. Twenty-two (52%) patients were never-smokers, and 20 (48%) patients had a smoking history. Adenocarcinoma was present in 41 (98%) patients; only 1 (2%) patient had squamous cell carcinoma. Nineteen (45%) patients had CNS metastasis, 7 (17%) patients had liver metastasis, and 22 (52%) patients had bone metastasis. Second lines of anticancer drugs were administered prior to amivantamab: 9 (21%) patients were previously treated with TKIs, 16 (38%) patients were previously treated with immune checkpoint inhibitors, and 40 (95%) patients were previously treated with platinum-based chemotherapy. The methods used for EGFR mutation analysis were as follows: Oncomine for 8 patients (19%), CancerSCAN for 7 patients (17%), Trusight Oncology 500 for 9 patients (21%), Guardant 360 for 4 patients (10%), and FoundationOne for 2 patients (5%). Confirmation through PCR was done for 12 patients (28%) (Figure S1).

**Table 1** Baseline characteristics

| Characteristics | Value (n=42) |
|---|---|
| Age (years) | 63 [48–84] |
| Gender | |
| Male | 25 [60] |
| Female | 17 [40] |
| Smoking history | |
| Never-smoker | 22 [52] |
| Ex/current-smoker | 20 [48] |
| Histologic type | |
| Adenocarcinoma | 41 [98] |
| Squamous cell carcinoma | 1 [2] |
| Metastasis site | |
| CNS | 19 [45] |
| Liver | 7 [17] |
| Bone | 22 [52] |
| Previous lines of chemotherapy | 2 [0–8] |
| Previous chemotherapy | |
| TKI | 9 [21] |
| Immune checkpoint inhibitor | 16 [38] |
| Platinum-based chemotherapy | 40 [95] |
| Methods of EGFR mutation analysis | |
| PCR (PANAMutyper) | 9 [21] |
| PCR (others) | 3 [7] |
| NGS, CancerSCAN | 7 [17] |
| NGS, Oncomine | 8 [19] |
| NGS, Trusight Oncology 500 | 9 [21] |
| NGS, Guardant 360 | 4 [10] |
| NGS, FoundationOne | 2 [5] |
| Site of EGFR mutation | |
| C-helix | 2 [5] |
| A763_Y764insFQEA | 2 |
| Near loop | 21 [50] |
| A767_S768insTLA | 1 |
| S768_V769insLDS | 1 |
| V769_D770insASV | 7 |
| D770_N771insP | 1 |
| D770_N771insSVD | 8 |
| D770_N771insNPH | 1 |
| D770delinsGY | 1 |
| P772_H773insT | 1 |
| Far loop | 8 [19] |
| H773_V774insPH | 3 |
| H773_V774insANPH | 1 |
| H773_V774insNPH | 1 |
| H773_V774insH | 1 |
| V774_C775insCPHV | 1 |
| V774_C775insNPHV | 1 |
| Unknown | 11 [26] |
| Biomarkers | |
| TP53 | |
| Positive | 14 [33] |
| Negative | 15 [36] |
| Unknown | 13 [31] |
| PD-L1 | |
| Positive | 24 [57] |
| Negative | 13 [31] |
| Unknown | 5 [12] |

Values are presented as median [range], n [%], or n. CNS, central nervous system; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; PCR, polymerase chain reaction; NGS, next-generation sequencing; TP53, tumor protein p53; PD-L1, programmed death ligand-1.

### *Locations of exon 20 insertion mutation and concurrent alterations*

There were 31 patients for whom the mutation location was known, among which 2 (5%) patients corresponded to the C-helix (EGFR codons 761–766) mutation, 21 (50%) patients corresponded to the near loop (EGFR codons 767–772), and 8 (19%) patients were in the far loop (EGFR codons 773–775). In biomarker analysis, there were 14 (33%) patients with TP53 positive, 15 (36%) patients with TP53 negative, and 13 (31%) patients with unknown TP53 expression status. There were 24 (57%) patients with PD-L1 expression positive, 13 (31%) patients with PD-L1 expression negative, and 5 (12%) patients with unknown PD-L1 expression status.

### *Overall outcomes*

There were no patients with complete remission, 14 (33%) patients with partial remission, 18 (43%) patients with stable

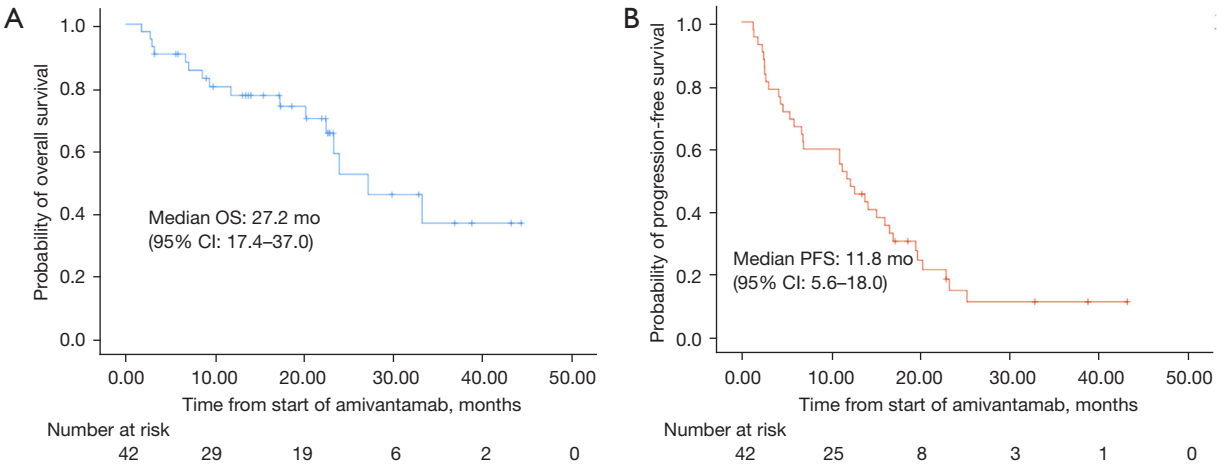


**Figure 1** OS and PFS of all patients. (A) OS of all patients. (B) PFS of all patients. OS, overall survival; mo, months; CI, confidence interval; PFS, progression-free survival.

disease, and 10 (24%) patients with disease progression. The ORR was 33%, and the disease control rate (DCR) was 76%. The OS of the entire patient population was 27.2 months (95% CI: 17.4–37.0), and the PFS was 11.8 months (95% CI: 5.6–18.0) (*Figure 1*).

### *Outcomes according to clinical parameters*

We analyzed OS and PFS according to metastasis site at the time of administration of amivantamab. When analyzed by dividing subgroups according to CNS metastasis [CNS meta (–) *vs.* CNS meta (+)], there was no statistically significant difference between OS and PFS {OS: 33.2 [not available (NA)] *vs.* 23.9 (22.1–25.7) months, P=0.74, HR, 1.19, 95% CI: 0.44–3.20; PFS: 6.9 (0–14.0) *vs.* 13.8 (10.4–17.2) months, P=0.43, HR, 1.32, 95% CI: 0.67–2.62}. In cases without CNS metastasis, the ORR was 35%. For cases with CNS metastasis, the ORR was 32%. There was no significant difference between the two groups (P=0.83). OS tended to be worse in the presence of liver metastasis, but there was no statistically significant difference in either OS or PFS [for liver meta (–) *vs.* liver meta (+)] [OS: 33.2 (23.9–NA) *vs.* 22.5 (3.0–NA) months, P=0.07, HR, 2.56, 95% CI: 0.89–7.41; PFS: 12.2 (9.0–15.4) *vs.* 4.2 (0.5–7.9) months, P=0.80, HR, 1.12, 95% CI: 0.46–2.74]. In cases without liver metastasis, the ORR was 29%. For cases with liver metastasis, the ORR was 57%. There was no significant difference between the two groups (P=0.14). When analyzed by dividing subgroups according to bone metastasis, both OS and PFS showed no statistically significant difference [for bone meta (–) *vs.* bone meta (+)] [OS: NA *vs.* 23.9 (17.4–30.5) months, P=0.52, HR, 1.40, 95% CI: 0.51–3.87; PFS: 13.8 (7.0–20.6) *vs.* 11.0 (4.2–17.8) months, P=0.22, HR, 1.52, 95% CI: 0.77–2.97]. In cases without bone metastasis, the ORR was 32%. For cases with bone metastasis, the ORR was 35%. There was no significant difference between the two groups (P=0.83) (*Table 2* and *Figure 2*).

When analyzing based on gender and smoking status, no significant differences were observed in OS and PFS between the two groups (Figure S2).

In the context of the analysis of survival outcomes based on the history of prior treatments, the OS for cases without any previous treatment or with only one prior treatment was 33.2 months (95% CI: 19.0–47.4), in contrast to 23.3 months (95% CI: 15.5–31.1) for those who had undergone two or more prior treatments (P=0.05). The PFS was 14.2 (95% CI: 9.8–18.6) and 6.7 months (95% CI: 0.0–16.2) respectively (P=0.21) (Figure S3).

### *Outcomes according to locations of exon 20 insertion mutation and concurrent alterations*

The OS and PFS were analyzed by dividing the near loop and the far loop for the 29 people whose mutation location was known, except for two patients who had helical area mutations. There was no statistically significant difference in PFS and OS between the two groups (near loop *vs.* far loop) [OS: 23.3 (19.1–27.5) months *vs.* NA, P=0.50, HR, 0.60, 95% CI: 0.13–2.75; PFS: 11.8 (2.3–21.3) *vs.* 11.3 (3.4–19.2) months, P=0.69, HR, 0.83, 95% CI: 0.33–2.01]. In

**Table 2** Comparing ORR between subgroups

| Clinical characteristics | ORR, n/N [%] | P value |
|---|---|---|
| Metastasis site | | |
| CNS | | 0.83 |
| Metastasis (+) | 6/19 [32] | |
| Metastasis (–) | 8/23 [35] | |
| Liver | | 0.14 |
| Metastasis (+) | 4/7 [57] | |
| Metastasis (–) | 10/35 [29] | |
| Bone | | 0.83 |
| Metastasis (+) | 7/20 [35] | |
| Metastasis (–) | 7/22 [32] | |
| Mutation site | | 0.83 |
| Near loop | 7/21 [33] | |
| Far loop | 3/8 [38] | |
| Biomarkers | | |
| TP53 | | 0.004 |
| (+) | 2/14 [14] | |
| (–) | 10/15 [67] | |
| PD-L1 | | 0.30 |
| (+) | 7/24 [29] | |
| (–) | 6/13 [46] | |
| Kinds of previous therapy | | |
| TKI | | 0.36 |
| Previous use | 2/9 [22] | |
| No | 12/33 [36] | |
| ICI | | 0.55 |
| Previous use | 5/16 [31] | |
| No | 9/26 [35] | |

ORR, overall response rate; CNS, central nervous system; TP53, tumor protein p53; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; ICI, immune-checkpoint inhibitor.

the case of near-loop, the ORR was 33%, while for far-loop, the ORR was 38%, and there was no significant difference between the two groups (P=0.83) (*Table 2* and *Figure 3*).

For the 29 patients with TP53 mutation data, we analyzed OS and PFS according to TP53 existence. There was no significant difference in OS and PFS between the two groups, but the PFS tended to poor prognosis in the case of TP53 (+) [for TP53 (+) *vs.* TP53 (–)] [OS: 22.5 (12.6–32.3) *vs.* 23.3 (18.7–28.0) months, P=0.84, HR, 0.88, 95% CI: 0.27–2.87; PFS: 5.9 (0–18.0) *vs.* 12.6 (6.9–18.3) months, P=0.11, HR, 0.51, 95% CI: 0.21–1.19]. For TP53 (–) cases, the ORR was 67%, whereas for TP53 (+) cases, the ORR was 14%, indicating a significant difference between the two groups (P=0.004) (*Table 2* and *Figure 4*).

When analyzing the 37 patients with PD-L1 expression data, there was no significant difference in OS, but in the case of PFS, patients who had PD-L1 showed statistically significantly poorer outcomes [for PD-L1 (+) *vs.* PD-L1 (–)] [OS: 23.9 (19.3–28.6) *vs.* 33.2 (21.8–44.6) months, P=0.15, HR, 0.42, 95% CI: 0.13–1.41; PFS: 11.3 (5.0–17.6) *vs.* 19.5 (5.3–33.7), P=0.04, HR, 0.44, 95% CI: 0.20–0.98]. For PD-L1 (–) cases, the ORR was 46%, while for PD-L1 (+) cases, the ORR was 29%. There was no significant difference between the two groups (P=0.30) (*Table 2* and *Figure 4*).

In addition, we conducted further investigations into survival outcomes based on the level of PD-L1 expression. PD-L1 expression levels were divided into three groups using cutoff values of 0, 1–49, and 50 or more. Each group included 13, 15, and 9 patients, respectively. Figure S4 depicts the survival outcomes based on PD-L1 expression levels using Kaplan-Meier curves. The observed variations in OS with respect to the degree of expression yielded a P value of 0.26, and similarly, the differences in PFS also resulted in a P value of 0.26.

### *Safety*

Amivantamab is associated with several adverse events, with rash being the most common. Among the 42 patients in this study, 29 (69%) experienced a rash. Out of these, 2 patients (5%) had grade 3 rash. Nail toxicity occurred in 14 patients (33%), while edema was observed in 9 patients (21%).

Additionally, stomatitis occurred in 5 patients (12%), mucositis in 3 patients (7%), pruritus in 2 patients (5%), and hypertrichosis in 2 patients (5%). One patient (2%) experienced drug-induced pneumonitis, which was graded as 2 and managed with the use of steroids (*Table 3*).

These results are similar to the known adverse events of amivantamab, which include rash (84%) and nail toxicity (50%) (22).

## Discussion

This study identified real-world data on patients who were administered amivantamab among those who had exon

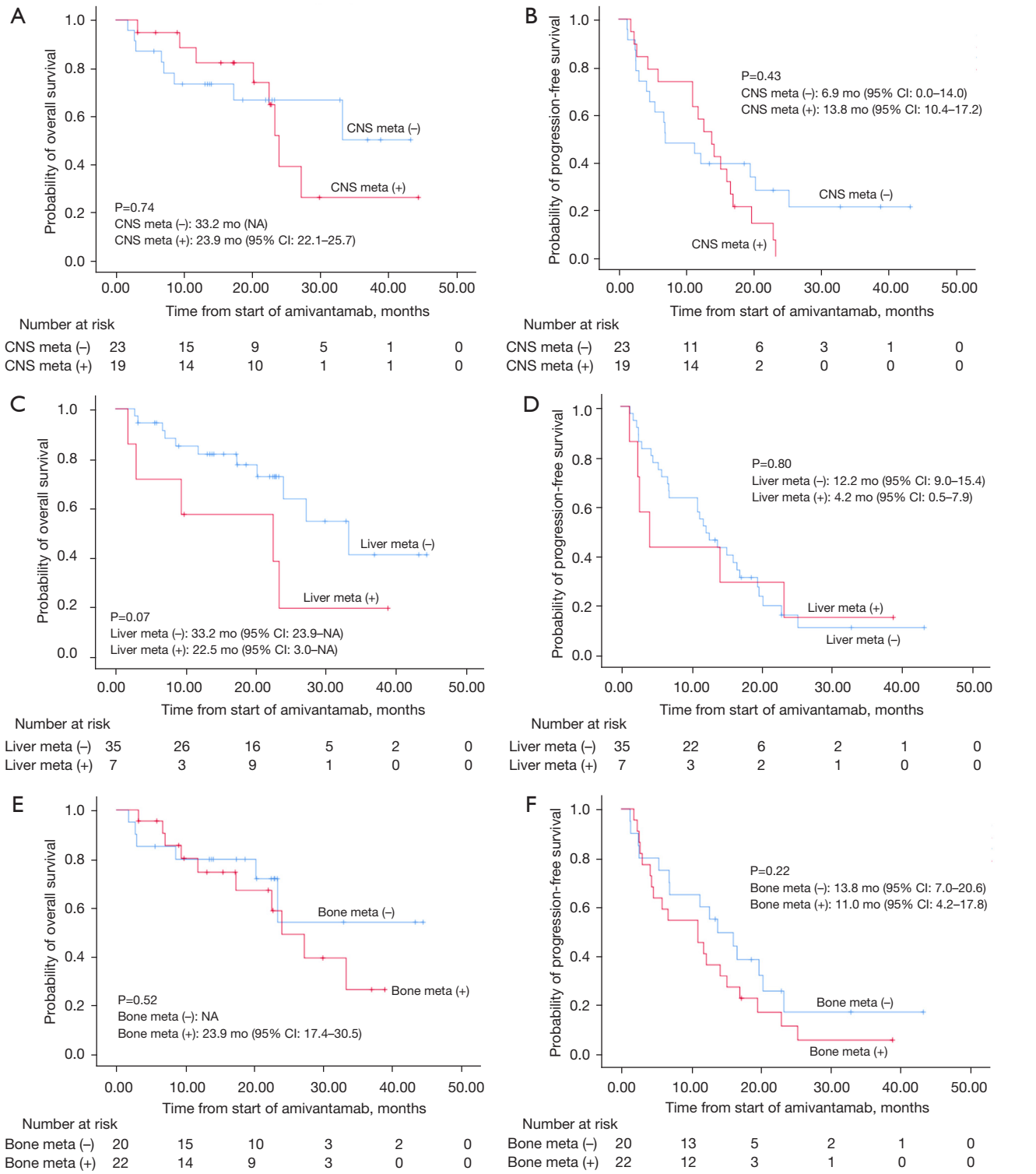


**Figure 2** OS and PFS according to metastasis sites. (A) OS according to CNS metastasis. (B) PFS according to CNS metastasis. (C) OS according to liver metastasis. (D) PFS according to liver metastasis. (E) OS according to bone metastasis. (F) PFS according to bone metastasis. CNS, central nervous system; meta, metastasis; mo, months; NA, not available; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

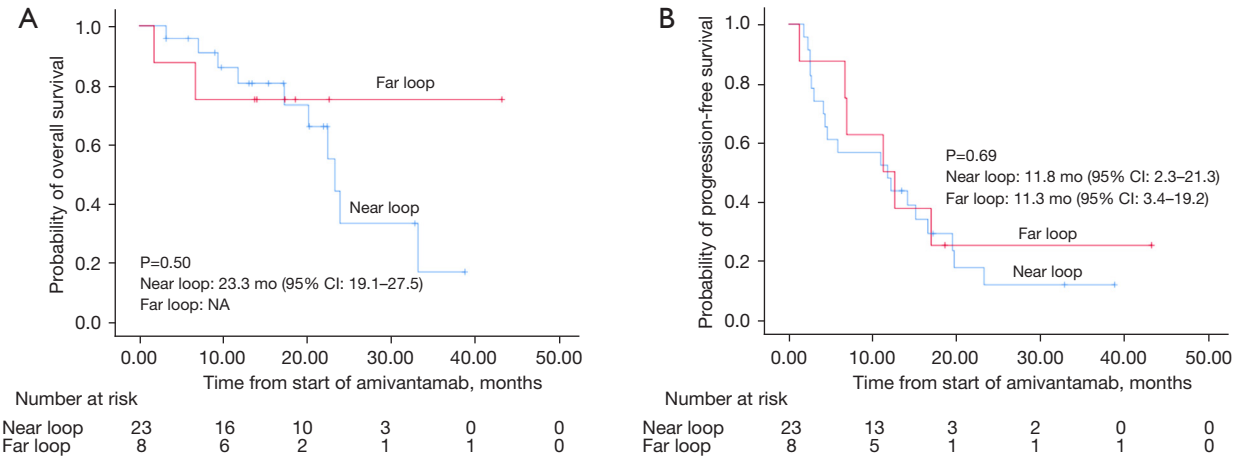


**Figure 3** OS and PFS according to mutation locations. (A) OS according to mutation locations [blue line: near loop (EGFR codons 767–772), red line: far loop (EGFR codons 773–775)]. (B) PFS according to mutation locations [blue line: near loop (EGFR codons 767–772), red line: far loop (EGFR codons 773–775)]. mo, months; CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival; EGFR, epidermal growth factor receptor.

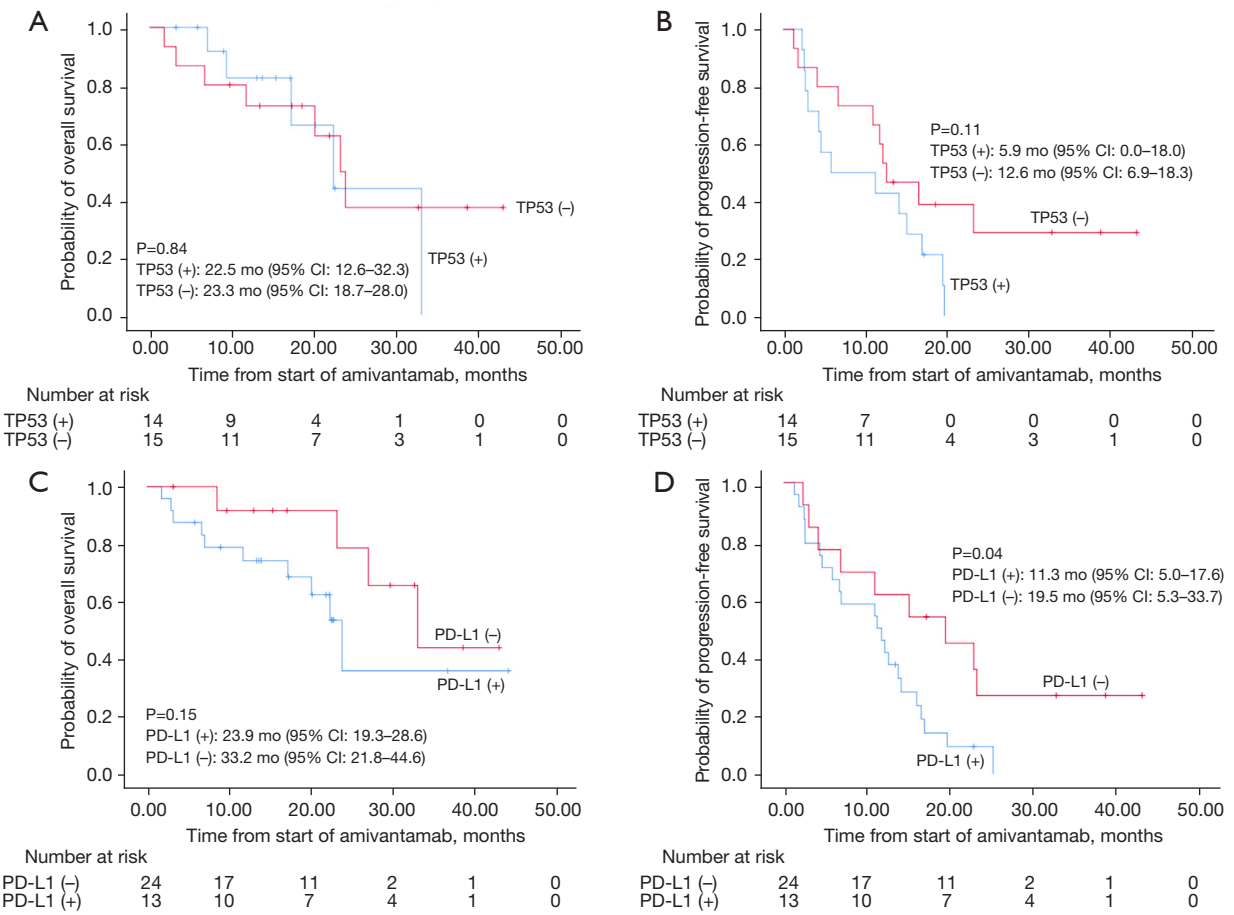


**Figure 4** OS and PFS according to biomarkers (TP53, PD-L1). (A) OS according to TP53 mutation. (B) PFS according to TP53 mutation. (C) OS according to PD-L1 expression. (D) PFS according to PD-L1 expression. TP53, tumor protein p53; mo, months; CI, confidence interval; PD-L1, programmed death ligand-1; OS, overall survival; PFS, progression-free survival.

20 insertion mutation with NSCLC. The real-world data (ORR, 34%) confirmed that the treatment was sufficiently effective as it showed no significant difference from the CHRYSALIS trial (ORR, 40%). We observed a median PFS of 11.8 months, somewhat higher than the PFS of 8.3 months (95% CI: 6.5 to 10.9) reported in the previous study (22).

There was no significant difference in OS or PFS in the presence of CNS metastasis, liver metastasis, or bone metastasis. The noteworthy point here is that there were no significant differences in OS, PFS or ORR between patients with and without CNS metastasis. Although most patients with CNS metastasis received local therapies such as gamma knife surgery (GKS) or whole brain radiation therapy (WBRT), it is important to note that two patients showed partial response in brain lesions with amivantamab. Amivantamab, a bispecific antibody, has a larger molecular weight and generally does not penetrate the blood-brain barrier (BBB) well (7). However, unlike the conventional EGFR antibody cetuximab, amivantamab has enhanced Fc function, which enables effective immune effector cell activity (18). Trogocytosis refers to the phenomenon where immune effector cells strip membrane fragments from cells bound by antibodies, which can have both anti-cancer effects and immune evasion mechanisms (21). When immune effector cells recognize the stripped membrane fragments as new antigens, they may fail to recognize cells carrying these antigens or may intensify attacks against cells carrying them (19,20). Amivantamab can induce sufficient anti-cancer effects through macrophage-mediated trogocytosis (18). This suggests that, despite its high molecular weight, amivantamab can provide some anti-cancer effect in the brain through immune responses. Therefore, it appears that there are no significant differences in OS, PFS, and ORR regardless of the presence of CNS metastasis.

In some studies, the efficacy decreased as the distance from the helix increased (22). However, in this study, there was no difference in OS or PFS. It is likely that the structural disruption caused by the E20I mutation is due to changes in the tyrosine kinase domain, which may not significantly affect the binding affinity between the extracellular domain and amivantamab. Therefore, it appears that the distance from the helix may not have a significant impact on the prognosis. However, additional research is needed because the sample size is small. Analysis according to the presence or absence of TP53 mutation did not show a statistically significant difference, but TP53 mutation positive cases showed numerically inferior results in PFS compared to negative cases (P=0.11). Furthermore, patients with the TP53 mutation showed a statistically significantly lower ORR compared to patients without the mutation (P=0.004). This suggests that mutations in TP53, a tumor suppression gene, are involved in tumor growth through pathways other than the EGFR pathway (23,24).

PD-L1-positive patients showed inferior results to negative cases, and these results were consistent with what is known about the poor prognosis when PD-L1 expression is positive in EGFR mutation. Presumably, the tumor mutation burden is generally higher when the PD-L1 expression is positive, and it is likely to contribute to tumor growth through other pathways in addition to the pathway by the E20I mutation (25,26). Despite studies showing that immunotherapy does not respond well to patients with driver mutations (27), it was established in a small cohort that immunotherapy is helpful for rare EGFR mutations such as the E20I mutation (28). Therefore, additional studies are needed to determine the efficacy of immunotherapy when PD-L1 expression is present in patients with the E20I mutation (29). Alternatively, additional studies are needed to determine the effectiveness of the amivantamab plus immunotherapy combination in patients with E20I mutations with PD-L1 expression.

This study has several limitations. Firstly, it is a retrospective study. While we aimed to mitigate selection bias by analyzing all patients with exon 20 insertion mutations who received amivantamab, it was challenging to eliminate other inherent biases in the study. However, in this study, we conducted correlation analyses for various variables between the groups to mitigate confounding factors, especially when demonstrating significant results in survival outcomes based on PD-L1 expression. Secondly, due to the limited number of patients with exon 20 insertion mutations, the sample size in the study is insufficient as we could not administer amivantamab extensively. In the case of TP53 mutations, it is possible that if there were more cases, we could have achieved statistically significant results in survival outcomes. Lastly, to the best of our knowledge, there is currently no available subgroup analysis data regarding the utilization of amivantamab in patients with exon 20 insertion mutations; thus, it is imperative to undertake further research to amass such data.

## Conclusions

In conclusion, in the case of E20I mutation patients with NSCLC, the efficacy of amivantamab was confirmed

**Table 3** Safety profiles with amivantamab

| Common adverse events | Total (n=42) | Grade 1 | Grade 2 | Grade ≥3 |
|---|---|---|---|---|
| Rash | 29 [69] | 17 [40] | 10 [24] | 2 [5] |
| Nail toxicity | 14 [33] | 11 [26] | 3 [7] | 0 [0] |
| Edema | 9 [21] | 7 [17] | 2 [5] | 0 [0] |
| Stomatitis | 5 [12] | 5 [12] | 0 [0] | 0 [0] |
| Mucositis | 3 [7] | 3 [7] | 0 [0] | 0 [0] |
| Pruritis | 2 [5] | 1 [2] | 1 [2] | 0 [0] |
| Hypertrichosis | 2 [5] | 1 [2] | 0 [0] | 0 [0] |
| Pneumonitis | 1 [2] | 0 [0] | 1 [2] | 0 [0] |

Data are presented as n [%].

through real-world data. In cases where PD-L1 expression was positive, PFS was inferior, which should be further validated in the future.

## Acknowledgments

The abstract was published in *Annals of Oncology* https://www.annalsofoncology.org/article/S0923-7534(23)04861-5/fulltext. The authors acknowledge the Korea Research Environment Open Network (KREONET) service and the usage of the Global Science Experimental Data Hub Center (GSDC) provided by the Korea Institute of Science and Technology Information (KISTI).
*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-643/rc

*Data Sharing Statement:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-643/dss

*Peer Review File:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-643/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-643/coif). S.H.L. and M.J.A. serve as unpaid editorial board members of *Translational Lung Cancer Research* from October 2021 to September 2023. S.H.L. has disclosed receiving research funding for his institution from Merck, AstraZeneca, and Lunit. Additionally, he serves as a consultant or advisor to AstraZeneca, Roche, Merck, Pfizer, Lilly, BMS/Ono, Takeda, Janssen, IMBdx, and Novartis. 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. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and the Korea Good Clinical Practice guidelines. This study was approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2023-05-048), and individual consent for this retrospective analysis was waived. Patients in the database were identified by patient number only, with personally identifiable information kept confidential according to the IRB protocol.



## References

1. de Groot PM, Wu CC, Carter BW, et al. The

 

epidemiology of lung cancer. Transl Lung Cancer Res 2018;7:220-33.
2. Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. Lancet 2021;398:535-54.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
4. Jin R, Peng L, Shou J, et al. EGFR-Mutated Squamous Cell Lung Cancer and Its Association With Outcomes. Front Oncol 2021;11:680804.
5. Chevallier M, Borgeaud M, Addeo A, et al. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. World J Clin Oncol 2021;12:217-37.
6. Esposito Abate R, Frezzetti D, Maiello MR, et al. Next Generation Sequencing-Based Profiling of Cell Free DNA in Patients with Advanced Non-Small Cell Lung Cancer: Advantages and Pitfalls. Cancers (Basel) 2020;12:3804.
7. Meador CB, Sequist LV, Piotrowska Z. Targeting EGFR Exon 20 Insertions in Non-Small Cell Lung Cancer: Recent Advances and Clinical Updates. Cancer Discov 2021;11:2145-57.
8. Riess JW, Gandara DR, Frampton GM, et al. Diverse EGFR Exon 20 Insertions and Co-Occurring Molecular Alterations Identified by Comprehensive Genomic Profiling of NSCLC. J Thorac Oncol 2018;13:1560-8.
9. Li K, Yang M, Liang N, et al. Determining EGFR-TKI sensitivity of G719X and other uncommon EGFR mutations in non-small cell lung cancer: Perplexity and solution (Review). Oncol Rep 2017;37:1347-58.
10. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med 2013;5:216ra177.
11. Kobayashi IS, Viray H, Rangachari D, et al. EGFR-D770>GY and Other Rare EGFR Exon 20 Insertion Mutations with a G770 Equivalence Are Sensitive to Dacomitinib or Afatinib and Responsive to EGFR Exon 20 Insertion Mutant-Active Inhibitors in Preclinical Models and Clinical Scenarios. Cells 2021;10:3561.
12. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. Lancet Oncol 2012;13:e23-31.
13. Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. Nat Med 2018;24:638-46.
14. Yun J, Lee SH, Kim SY, et al. Antitumor Activity of Amivantamab (JNJ-61186372), an EGFR-MET Bispecific Antibody, in Diverse Models of EGFR Exon 20 Insertion-Driven NSCLC. Cancer Discov 2020;10:1194-209.
15. Brazel D, Nagasaka M. Spotlight on Amivantamab (JNJ-61186372) for EGFR Exon 20 Insertions Positive Non-Small Cell Lung Cancer. Lung Cancer (Auckl) 2021;12:133-8.
16. Lim SM, Synn CB, Kang S, et al. Combinatorial activity of amivantamab and pembrolizumab in head and neck squamous cell carcinoma and lung squamous cell carcinoma expressing wild-type EGFR and MET. Cancer Res 2023;83:5865.
17. Lindorfer MA, Taylor RP. FcγR-Mediated Trogocytosis 2.0: Revisiting History Gives Rise to a Unifying Hypothesis. Antibodies (Basel) 2022;11:45.
18. Vijayaraghavan S, Lipfert L, Chevalier K, et al. Amivantamab (JNJ-61186372), an Fc Enhanced EGFR/cMet Bispecific Antibody, Induces Receptor Downmodulation and Antitumor Activity by Monocyte/Macrophage Trogocytosis. Mol Cancer Ther 2020;19:2044-56.
19. Taylor RP, Lindorfer MA. Fcγ-receptor-mediated trogocytosis impacts mAb-based therapies: historical precedence and recent developments. Blood 2015;125:762-6.
20. Miyake K, Karasuyama H. The Role of Trogocytosis in the Modulation of Immune Cell Functions. Cells 2021;10:1255.
21. Joly E, Hudrisier D. What is trogocytosis and what is its purpose? Nat Immunol 2003;4:815.
22. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 2021;39:3391-402.
23. Canale M, Andrikou K, Priano I, et al. The Role of TP53 Mutations in EGFR-Mutated Non-Small-Cell Lung Cancer: Clinical Significance and Implications for Therapy. Cancers (Basel) 2022;14:1143.
24. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. J Biomed Biotechnol 2011;2011:583929.
25. Brody R, Zhang Y, Ballas M, et al. PD-L1 expression in advanced NSCLC: Insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer 2017;112:200-15.
26. Chen K, Cheng G, Zhang F, et al. PD-L1 expression and T cells infiltration in patients with uncommon EGFR-

 

mutant non-small cell lung cancer and the response to immunotherapy. Lung Cancer 2020;142:98-105.
27. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc 2019;94:1623-40.
28. Metro G, Baglivo S, Bellezza G, et al. Sensitivity to Immune Checkpoint Blockade in Advanced Non-Small Cell Lung Cancer Patients with EGFR Exon 20 Insertion Mutations. Genes (Basel) 2021;12:679.
29. Qiao M, Jiang T, Liu X, et al. Immune Checkpoint Inhibitors in EGFR-Mutated NSCLC: Dusk or Dawn? J Thorac Oncol 2021;16:1267-88.

**Cite this article as:** Choi DH, Jung HA, Park S, Sun JM, Ahn JS, Ahn MJ, Lee SH. Effectiveness and safety of amivantamab in EGFR exon 20 insertion (E20I) mutations in non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2023;12(12):2448-2459. doi: 10.21037/tlcr-23-643

## Supplementary

**Table S1** Comparing baseline characteristics according to PD-L1 expression status

| Characteristics | PD-L1 positive (n=24) | PD-L1 negative (n=13) | P value |
|---|---|---|---|
| Age (years) | 63 [49–84] | 65 [50–78] | – |
| Gender | | | 0.95 |
| Male | 15 [63] | 8 [62] | |
| Female | 9 [38] | 5 [38] | |
| Smoking history | | | 0.64 |
| Never-smoker | 13 [54] | 6 [46] | |
| Ex/current-smoker | 11 [46] | 7 [54] | |
| Histologic type | | | 0.17 |
| Adenocarcinoma | 24 [100] | 12 [92] | |
| Squamous cell carcinoma | 0 [0] | 1 [8] | |
| Metastasis site | | | |
| CNS | 12 [50] | 6 [46] | 0.82 |
| Liver | 3 [13] | 3 [23] | 0.41 |
| Bone | 12 [50] | 9 [69] | 0.26 |
| Previous lines of chemotherapy | 2 [0–8] | 1 [1–6] | – |
| Previous chemotherapy | | | |
| TKI | 6 [25] | 1 [8] | 0.20 |
| Immune checkpoint inhibitor | 10 [42] | 3 [23] | 0.26 |
| Platinum-based chemotherapy | 22 [92] | 13 [100] | 0.29 |
| Methods of EGFR mutation analysis | | | 0.86 |
| PCR (PANAMutyper) | 3 [13] | 3 [23] | |
| PCR (others) | 3 [13] | 0 [0] | |
| NGS, CancerSCAN | 2 [8] | 5 [38] | |
| NGS, Oncomine | 6 [25] | 2 [15] | |
| NGS, Trusight Oncology 500 | 5 [21] | 2 [15] | |
| NGS, Guardant 360 | 3 [13] | 1 [8] | |
| NGS, FoundationOne | 2 [8] | 0 [0] | |
| Site of EGFR mutation | | | 0.42 |
| C-helix | 1 [4] | 1 [8] | |
| A763_Y764insFQEA | 1 | 1 | |
| Near loop | 12 [50] | 8 [62] | |
| A767_S768insTLA | 1 | 0 | |
| S768_V769insLDS | 1 | 0 | |
| V769_D770insASV | 4 | 2 | |
| D770_N771insP | 0 | 1 | |
| D770_N771insSVD | 4 | 4 | |
| D770_N771insNPH | 1 | 0 | |
| D770delinsGY | 1 | 0 | |
| P772_H773insT | 0 | 1 | |
| Far loop | 6 [25] | 1 [8] | |
| H773_V774insPH | 1 | 1 | |
| H773_V774insANPH | 1 | 0 | |
| H773_V774insNPH | 1 | 0 | |
| H773_V774insH | 1 | 0 | |
| V774_C775insCPHV | 1 | 0 | |
| V774_C775insNPHV | 1 | 0 | |
| Unknown | 5 [21] | 3 [23] | |
| TP53 status | | | 0.90 |
| Positive | 8 [33] | 5 [38] | |
| Negative | 9 [38] | 5 [38] | |
| Unknown | 7 [29] | 3 [23] | |

Data are presented as median [range], n [%], or n. PD-L1, programmed death ligand-1; CNS, central nervous system; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; PCR, polymerase chain reaction; NGS, next-generation sequencing; TP53, tumor protein p53.


https://dx.doi.org/10.21037/tlcr-23-643

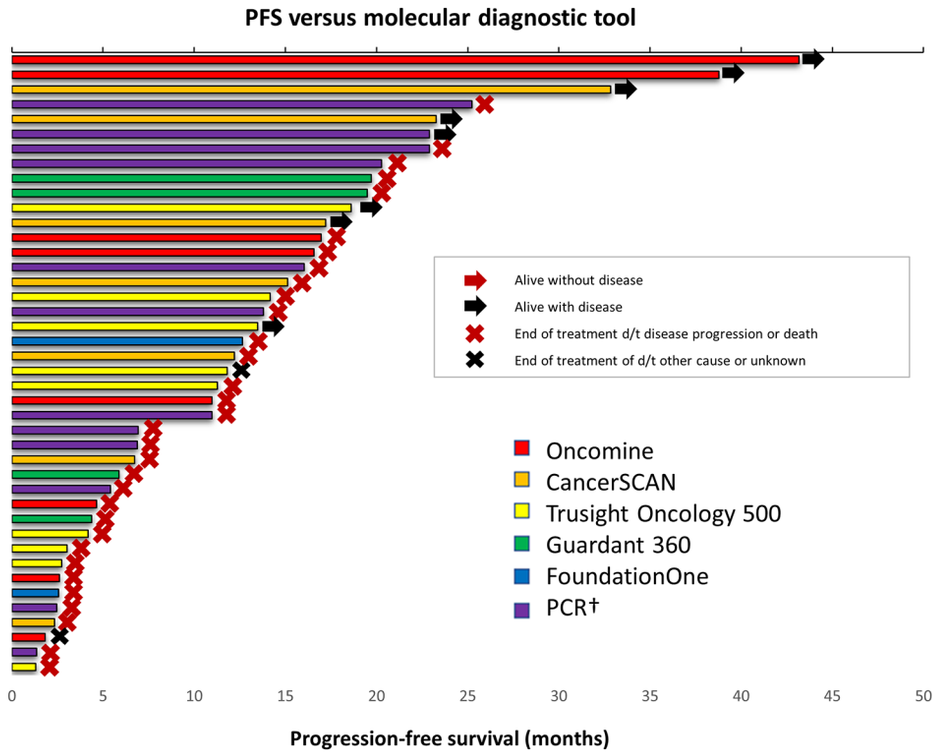


**Figure S1** PFS *vs.* molecular diagnostic tools. †, PCR means the patient was confirmed to have an exon 20 insertion mutation through the use of RT-PCR (PANAMutyper™ EGFR kit). PFS, progression-free survival; RT-PCR, real-time polymerase chain reaction; EGFR, epidermal growth factor receptor.

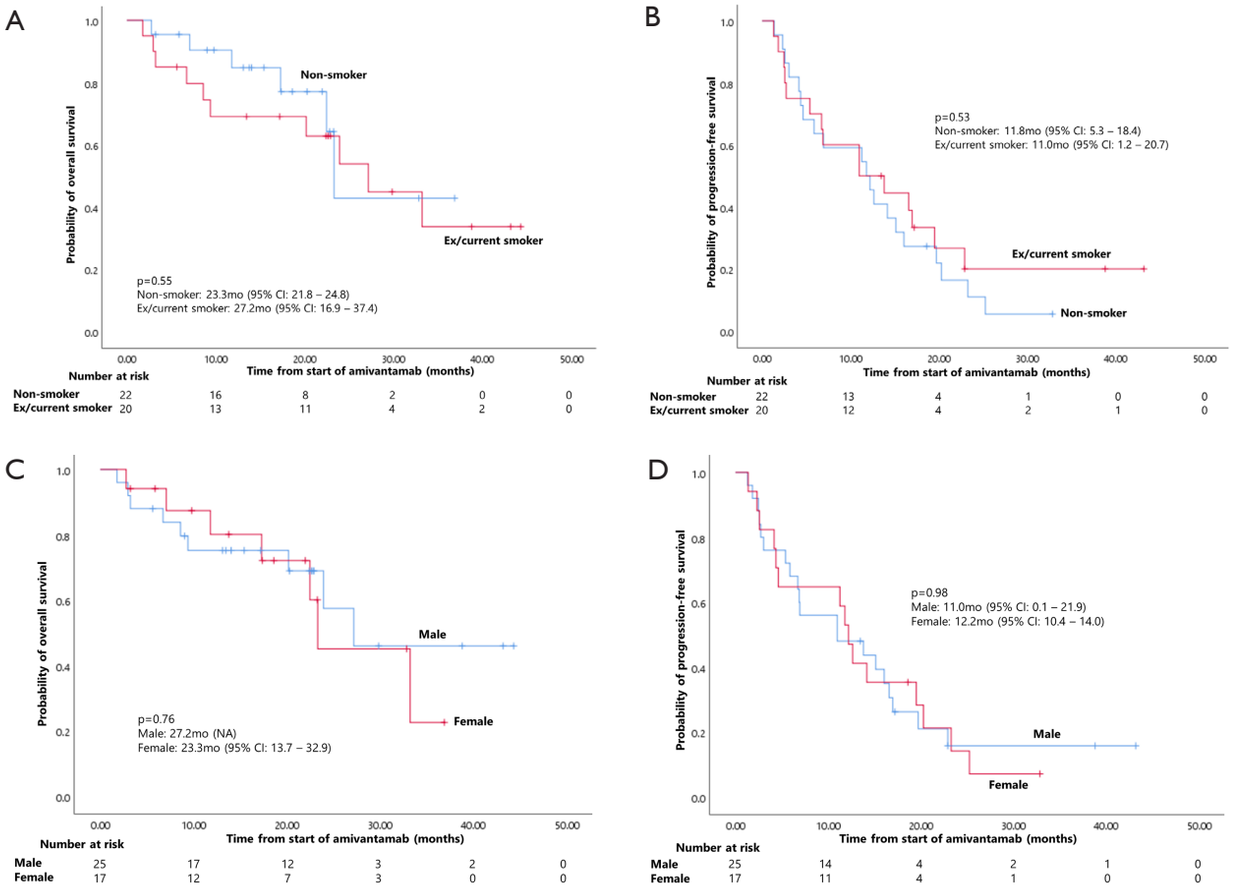


**Figure S2** OS and PFS according to smoking status and gender. (A) OS according to smoking status. (B) PFS according to smoking status. (C) OS according to gender. (D) PFS according to gender. mo, months; CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.


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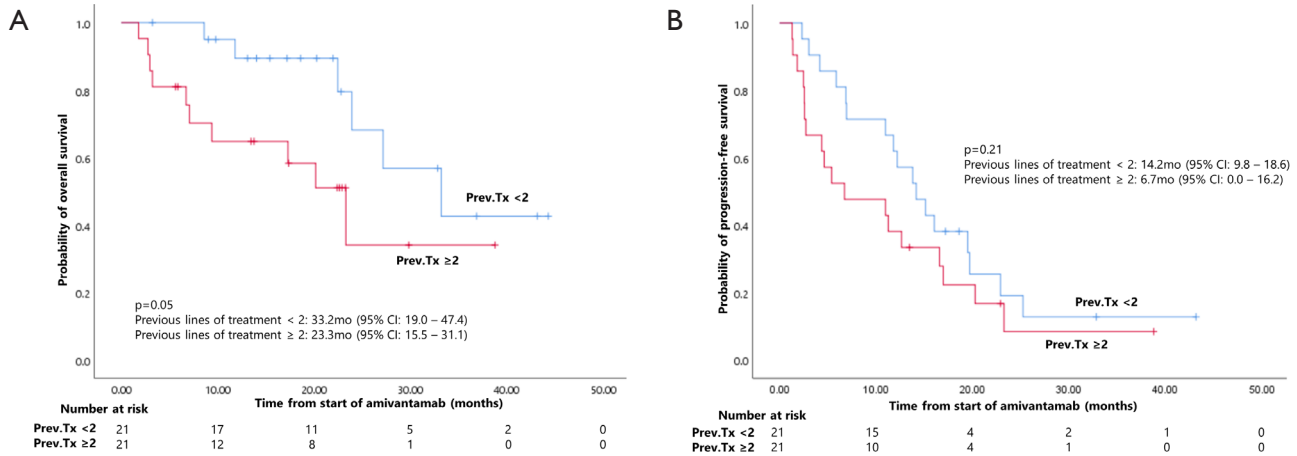


**Figure S3** OS and PFS according to previous lines of treatment (first and second line amivantamab *vs.* third line or more advanced line amivantamab). (A) OS according to previous lines of treatment. (B) PFS according to previous lines of treatment. Prev.Tx, previous lines of treatment; mo, months; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

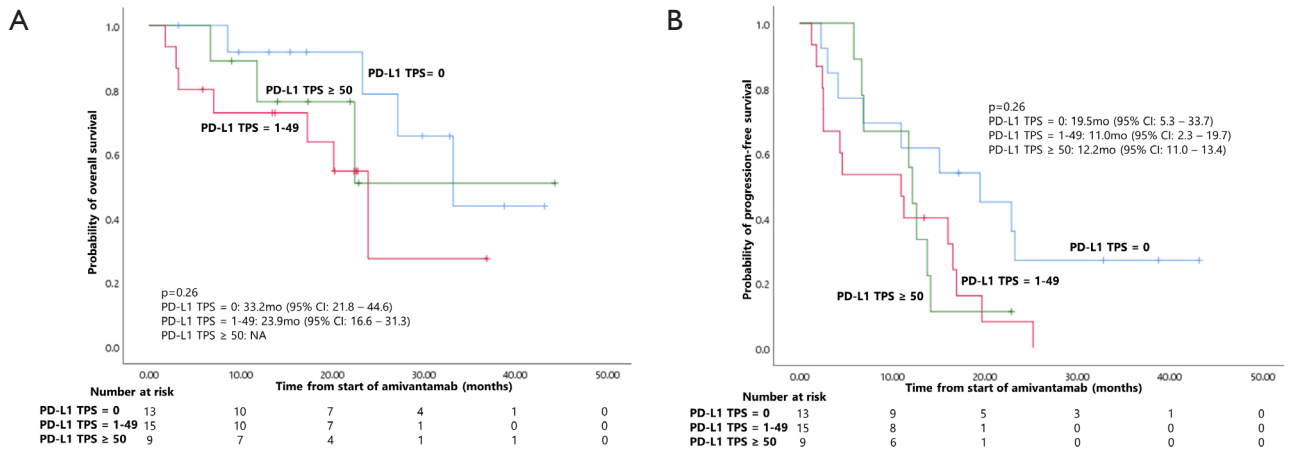


**Figure S4** OS and PFS according to PD-L1 expression status (PD-L1 TPS less than 0 *vs.* 1–49% *vs.* 50% and more than 50%). (A) OS according to PD-L1 expression. (B) PFS according to PD-L1 expression. PD-L1, programmed death-ligand 1; TPS, tumor proportion score; mo, months; CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.


https://dx.doi.org/10.21037/tlcr-23-643