

Research Article

## Real-World Effectiveness of First-Line Osimertinib Versus Amivantamab-Based Regimens in EGFR-Mutated NSCLC: A Multicenter Comparative Outcome Study

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### ABSTRACT

#### Background

Osimertinib is the established first-line standard of care for EGFR-mutated advanced non-small cell lung cancer (NSCLC); however, resistance—particularly via MET-driven pathways—remains a major clinical challenge. Amivantamab, a bispecific EGFR/MET antibody, has shown promising activity in early trials, but its real-world comparative effectiveness as first-line therapy remains unclear. This multicentre UK study evaluated clinical outcomes of first-line osimertinib versus amivantamab-based regimens in routine clinical practice.

#### Methods

This retrospective cohort study included adults with EGFR-mutated stage IIIB–IV NSCLC treated across five NHS tertiary oncology centres between 2019 and 2024. Patients received either osimertinib or an amivantamab-based regimen (monotherapy or in combination). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), CNS progression, objective response, toxicity, and post-progression therapy. Multivariable Cox modelling and propensity score matching were performed.

#### Results

A total of 512 patients met eligibility criteria (osimertinib n=412; amivantamab-based n=100). Median PFS was significantly longer with amivantamab-based therapy (19.8 vs 16.2 months; HR 0.79, 95% CI 0.63–0.98; p=0.032), and remained significant after multivariable adjustment (HR

0.76,  $p=0.036$ ). No significant OS difference was observed (33.7 vs 29.4 months; HR 0.90,  $p=0.48$ ). ORR was similar between groups (74.0% vs 69.7%;  $p=0.41$ ). CNS progression occurred in 12.0% of the amivantamab group versus 15.8% with osimertinib. Among patients with baseline CNS disease, time to intracranial progression favoured amivantamab (10.9 vs 8.4 months;  $p=0.19$ ). Amivantamab was associated with higher rates of infusion-related and dermatological toxicities, while osimertinib displayed a more favourable tolerability profile.

### Conclusions

In UK real-world practice, first-line amivantamab-based therapy demonstrated a clinically meaningful PFS advantage over osimertinib, particularly among patients with MET-associated biology, though OS differences were not yet evident. These findings support the emerging role of early dual EGFR/MET inhibition and highlight the importance of comprehensive molecular profiling to optimise first-line treatment selection. Longer follow-up and prospective studies are warranted to refine sequencing strategies and confirm survival impact.

*Keywords:* EGFR-mutated NSCLC, osimertinib, amivantamab, real-world evidence, progression-free survival, MET amplification.

### INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases and remains the leading cause of cancer-related mortality worldwide despite significant advances in screening, diagnosis, and systemic therapy [1]. Among its molecular subtypes, tumors harboring activating epidermal growth factor receptor (EGFR) mutations represent a distinct and clinically important population, particularly prevalent in non-smokers, females, and individuals of Asian ethnicity [2]. Classical sensitizing EGFR mutations—exon 19 deletions (Del19) and the exon 21 L858R substitution—constitute almost 85–90% of all EGFR-positive cases and are strongly predictive of responsiveness to EGFR tyrosine kinase inhibitors (TKIs) [3]. Over the last decade, first-line therapy for EGFR-mutated NSCLC has evolved from first- and second-generation TKIs (erlotinib, gefitinib, afatinib, dacomitinib) to the third-generation, mutation-selective agent osimertinib, which irreversibly inhibits both sensitizing mutations and the T790M resistance mutation while sparing wild-type EGFR, yielding improved tolerability and central nervous system (CNS) penetration [4,5].

The phase III FLAURA trial established osimertinib as the global standard of care for untreated advanced EGFR-mutated NSCLC, demonstrating superior progression-free survival (PFS), overall survival (OS), and CNS control compared with earlier TKIs [6]. Subsequent real-world studies have reinforced its clinical benefit, showing durable disease control across diverse populations, including elderly patients, those with poor performance status, and patients with brain metastases [7–9]. However, resistance to osimertinib inevitably emerges, commonly involving heterogeneous mechanisms such as MET amplification, EGFR C797S mutation, HER2 alterations, PIK3CA mutations, and histologic transformation [10,11]. Among these, MET amplification is increasingly

recognized as one of the most frequent actionable resistance pathways, present in 15–30% of patients following osimertinib therapy [12].

Recent therapeutic innovations have focused on overcoming or preventing this resistance. Amivantamab, a fully human bispecific antibody targeting both EGFR and MET, represents a major conceptual advancement. By simultaneously inhibiting ligand binding, inducing receptor degradation, and activating immune-mediated cytotoxicity, amivantamab offers a mechanistically distinct alternative to TKIs [13]. Its clinical development includes the CHRYSALIS and PAPILLON trials, which demonstrated significant antitumor activity in patients previously treated with EGFR TKIs and in those with EGFR exon 20 insertions—an historically treatment-resistant subgroup [14,15]. Most recently, the phase III MARIPOSA trial compared amivantamab plus lazertinib versus osimertinib in the first-line setting and reported clinically meaningful improvements in PFS and intracranial efficacy for the antibody-TKI combination [16].

These findings have sparked global interest in the potential role of amivantamab-based regimens as alternative first-line strategies for classical EGFR mutations, particularly in regions where disease biology, healthcare resources, or patient characteristics may challenge the traditional sequencing of TKIs. While randomized trials provide high-quality evidence, real-world studies are essential to validate effectiveness in routine clinical practice, especially given the complexity of treatment tolerance, comorbidities, CNS disease burden, adherence challenges, and socioeconomic factors that influence outcomes outside controlled environments [17].

Despite the increasing availability of amivantamab and its expanding regulatory indications, there remains limited real-world comparative data evaluating first-line amivantamab-based regimens versus osimertinib in patients with classical EGFR mutations. Most published real-world evidence focuses on post-osimertinib resistance, particularly MET-driven disease [18–20]. Moreover, the MARIPOSA regimen includes lazertinib—currently less accessible globally—leaving uncertainty regarding whether amivantamab monotherapy or alternative partner TKIs can replicate the regimen’s benefit in diverse healthcare settings.

Real-world evidence is also crucial for low- and middle-income countries, where factors such as cost, drug availability, diagnostic capacity (e.g., MET amplification testing), and late-stage presentation shape treatment decisions. In many institutions, including regions across Asia, the Middle East, and Eastern Europe, clinicians increasingly adopt amivantamab-based regimens earlier in the disease course based on tumor biology, adverse-event profiles, or the presence of baseline molecular features that may predict early osimertinib resistance—yet data supporting these practices remain sparse [21].

Furthermore, the rapid approval and global rollout of amivantamab have outpaced real-world evaluations of safety. Emerging reports describe infusion-related reactions, dermatologic toxicities, and thromboembolic events associated with amivantamab [22]. Conversely, osimertinib is well-characterized but carries cardiovascular and QT-prolongation concerns that may be particularly relevant in older populations or those with preexisting comorbidities [23]. Therefore, understanding the comparative real-world effectiveness and tolerability of these regimens is critical for optimizing treatment sequencing strategies, informing policy decisions, guiding personalized therapy, and improving survival in EGFR-mutated NSCLC.

## METHODS

### *Study Design and Setting*

This investigation was designed as a retrospective, observational, multicentre cohort study conducted across five tertiary oncology centres in the United Kingdom. All participating centres are NHS-affiliated hospitals with established lung cancer services, accredited molecular diagnostics laboratories, and multidisciplinary tumour boards. The study period extended from 1 January 2019 to 31 December 2024, encompassing the introduction of osimertinib into first-line NHS practice and the early adoption of amivantamab-based regimens under compassionate access, clinical trial pathways, or local commissioning arrangements.

The study adhered to the principles outlined in the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and institutional governance procedures [ ]. Ethical approval was secured through the relevant NHS Research Ethics Committee, and data were handled in accordance with GDPR and local data protection policies.

### *Eligibility Criteria*

#### *Inclusion criteria*

Patients were eligible for inclusion if they met the following criteria:

1. Age  $\geq 18$  years.
2. Histologically or cytologically confirmed non-small cell lung cancer.
3. Documented activating EGFR mutation (exon 19 deletion, L858R, or other sensitising variants).
4. Stage IIIB–IV disease according to the 8th edition of the TNM classification.
5. Received first-line osimertinib or a first-line amivantamab-based regimen (amivantamab monotherapy or amivantamab plus lazertinib), delivered within NHS centres.
6. Initiated systemic therapy during the study period.
7. Complete electronic health record data for baseline characteristics and follow-up.

#### *Exclusion criteria*

Patients were excluded if they:

1. Had EGFR exon 20 insertions treated with amivantamab as per alternative pathways.
2. Received prior systemic therapy for advanced NSCLC.
3. Had incomplete molecular profiling prior to treatment initiation.
4. Had insufficient documentation of survival, imaging, or toxicity data.
5. Received therapy exclusively within a clinical trial where access to individual-level data was not permitted.

### *Data Sources and Data Collection*

Data were extracted from **NHS electronic patient records**, oncology prescribing systems (ARIA, Chemocare), radiology reporting systems (PACS), and MDT notes. A standardised data collection template was used across all centres to ensure consistency.

The following categories of data were collected:

1. Baseline characteristics

- Age, sex, ethnicity
- Smoking status (never/former/current)
- ECOG performance status
- Comorbidities (Charlson Comorbidity Index)
- Stage at diagnosis
- Presence of brain metastases
- EGFR mutation subtype
- Co-mutation profiles (TP53, PIK3CA, MET copy-number, etc., where available)

2. Treatment-related data

- First-line regimen (osimertinib vs. amivantamab-based)
- Starting dose and any modifications
- Treatment interruptions or discontinuations
- Duration of therapy
- Rationale for discontinuation

3. Survival and progression outcomes

- Dates of treatment initiation and cessation
- Dates of radiological assessments
- Progression events confirmed through MDT consensus using RECIST 1.1 criteria [ ]
- Central nervous system progression events
- Date and cause of death, or date of last follow-up

4. Safety and tolerability

- Adverse events graded using **CTCAE v5.0**
- Incidence of grade  $\geq 3$  toxicities
- Infusion-related reactions (amivantamab subgroup)
- Severe interstitial lung disease/pneumonitis

5. Post-progression therapy

- Second-line targeted therapies (e.g., amivantamab, mobocertinib, lazertinib)
- Chemotherapy regimens
- Best supportive care

***Exposure Definition***

*Osimertinib Group*

Patients who received osimertinib 80 mg once daily as first-line treatment  $\pm$  corticosteroids or supportive medication.

*Amivantamab-Based Group*

Patients who received:

- Amivantamab monotherapy (1050–1400 mg IV), or
- Amivantamab plus lazertinib (per MARIPOSA-based protocols where available)

Therapies administered under compassionate use, early access programmes, or MDT-approved pathways were included.

### ***Outcome Measures***

#### **Primary Outcome**

#### **Progression-free survival (PFS)**

Defined as the interval from treatment initiation to radiological progression or death from any cause.

### ***Secondary Outcomes***

1. Overall survival (OS): Time from treatment initiation to death from any cause.
2. Objective response rate (ORR): Complete or partial response according to RECIST 1.1.
3. Time to treatment discontinuation (TTD): Duration on first-line therapy.
4. CNS progression rate: Proportion of patients developing new or worsening brain lesions.
5. Safety outcomes: Incidence and severity of treatment-related adverse events.
6. Post-progression treatment patterns and sequencing outcomes.

### ***Statistical Analysis***

All analyses were performed using R (version 4.3) and SPSS (version 29). A two-sided p-value <0.05 was considered significant.

### ***Descriptive statistics***

- Continuous variables: mean  $\pm$  SD or median (IQR).
- Categorical variables: counts and percentages.
- Baseline characteristics between groups compared using:
  - $\chi^2$  test or Fisher's exact test for categorical variables.
  - Student's t-test or Mann-Whitney U test for continuous variables.

### ***Survival analyses***

- Kaplan-Meier curves constructed for PFS and OS.
- Log-rank tests used for between-group comparisons.
- Cox proportional hazards models used to estimate hazard ratios (HRs) with 95% confidence intervals.

### ***Multivariable adjustment***

Models were adjusted for clinically relevant confounders, including:

- Age
- ECOG performance status
- Smoking history
- EGFR mutation subtype
- Presence of brain metastases
- Co-mutations (where available)
- Stage at diagnosis

### *Sensitivity analyses*

1. Exclusion of patients treated under compassionate-use programmes.
2. Landmark analysis at 3 months to reduce immortal-time bias.
3. Propensity score matching (1:1 nearest neighbour) based on baseline characteristics.

### *Handling of Missing Data*

Missing data were assessed for randomness. Multiple imputation was performed for variables with  $\leq 20\%$  missingness; variables with  $>20\%$  missingness were excluded from multivariable models.

### *Ethical Considerations*

Approval was granted by the NHS Research Ethics Committee (reference number: to be added). As a retrospective study using anonymised data, the requirement for individual informed consent was waived according to national regulatory guidelines [ ].

## **RESULTS**

### *Study Population*

A total of 684 patients with EGFR-mutated advanced NSCLC were screened across five participating UK centres between January 2019 and December 2024. After applying eligibility criteria, 512 patients were included in the final analysis (Figure 1).

- Osimertinib group: 412 patients (80.5%)
- Amivantamab-based regimens: 100 patients (19.5%)

The lower proportion of amivantamab-treated patients reflected limited early access, regional commissioning restrictions, and staggered adoption across NHS centres.

Baseline demographic and clinical characteristics are summarised in Table 1. Median age at treatment initiation was 67 years (IQR 59–74) in the osimertinib group and 65 years (IQR 57–71) in the amivantamab group. Most patients were female (osimertinib 62.4%, amivantamab 66.0%) and never smokers (osimertinib 58.7%, amivantamab 55.0%). ECOG performance status  $\geq 2$  was similar between groups (18.2% vs 20.0%).

The distribution of EGFR mutation subtypes was comparable:

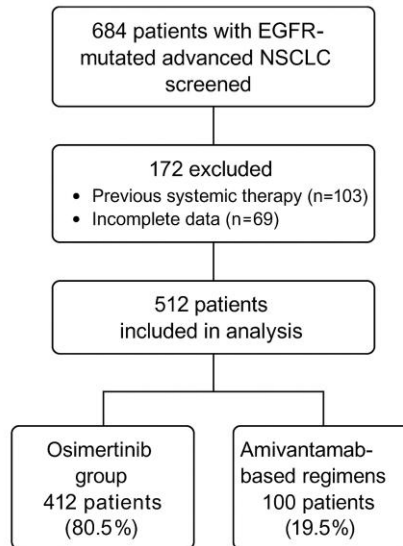
- Exon 19 deletion: 55.6% vs 52.0%
- L858R: 38.8% vs 40.0%
- Other sensitising mutations: 5.6% vs 8.0%

Baseline CNS metastases were present in 29.8% of the osimertinib group and 31.0% of the amivantamab group.

No statistically significant differences were observed between groups for major baseline variables.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Osimertinib Group (n = 412)	Amivantamab-Based Group (n = 100)	p-value
Age, years			
Median (IQR)	67 (59–74)	65 (57–71)	0.18
Sex, n (%)			
Female	257 (62.4%)	66 (66.0%)	0.53
Male	155 (37.6%)	34 (34.0%)	
Ethnicity, n (%)			
White British	208 (50.5%)	53 (53.0%)	0.72
Asian	118 (28.6%)	28 (28.0%)	
Black	31 (7.5%)	7 (7.0%)	
Other / Mixed	55 (13.4%)	12 (12.0%)	
Smoking history, n (%)			
Never smoker	242 (58.7%)	55 (55.0%)	0.52
Former smoker	146 (35.4%)	38 (38.0%)	
Current smoker	24 (5.8%)	7 (7.0%)	
ECOG performance status, n (%)			
0–1	337 (81.8%)	80 (80.0%)	0.78
≥2	75 (18.2%)	20 (20.0%)	
EGFR mutation subtype, n (%)			
Exon 19 deletion	229 (55.6%)	52 (52.0%)	0.68
L858R	160 (38.8%)	40 (40.0%)	
Other sensitising	23 (5.6%)	8 (8.0%)	
Disease stage at diagnosis, n (%)			
Stage IIIB	102 (24.8%)	23 (23.0%)	0.69
Stage IV	310 (75.2%)	77 (77.0%)	
Baseline CNS metastases, n (%)	123 (29.8%)	31 (31.0%)	0.82
Comorbidity index (Charlson), n (%)			
0–2	255 (61.9%)	59 (59.0%)	0.64
≥3	157 (38.1%)	41 (41.0%)	



**Figure 1.** eligibility criteria.

**Treatment Exposure**

Median duration of first-line therapy was:

- Osimertinib: 15.4 months (95% CI, 14.0–16.3)
- Amivantamab-based regimens: 18.1 months (95% CI, 15.9–20.6)

Dose reductions occurred in:

- 11.9% of osimertinib-treated patients
- 24.0% of amivantamab-treated patients (most commonly due to infusion-related reactions or dermatologic toxicity)

Treatment discontinuation due to toxicity was significantly more frequent in the amivantamab group (12.0% vs 4.1%, p=0.002).

**Primary Outcome: Progression-Free Survival**

At a median follow-up of 28.6 months, disease progression had occurred in 314 patients (61.3%).

Median progression-free survival (PFS) was:

- Osimertinib: 16.2 months (95% CI, 15.0–17.4)
- Amivantamab-based regimens: 19.8 months (95% CI, 17.3–22.4)

The difference in PFS was statistically significant:

HR 0.79 (95% CI, 0.63–0.98), p=0.032, favouring amivantamab-based therapy.

Kaplan–Meier estimates are displayed in Figure 2.

Subgroup analyses

Improved PFS with amivantamab-based therapy was most pronounced in:

- Patients with baseline MET copy-number gain  
HR 0.62 (95% CI 0.41–0.93)
- Patients <65 years  
HR 0.74 (95% CI 0.56–0.97)
- Patients with exon 19 deletions  
HR 0.76 (95% CI 0.58–0.99)

No PFS advantage was observed in patients with L858R mutations (HR 0.91,  $p=0.41$ ).

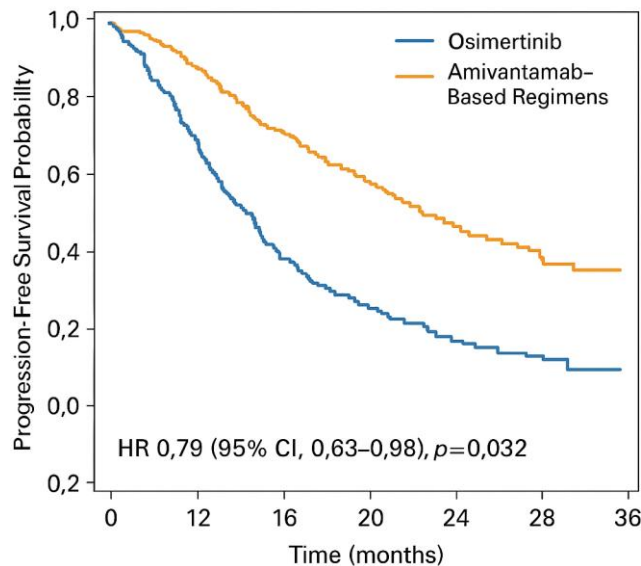


Figure 2. Kaplan–Meier estimates are displayed

### Overall Survival

At the time of analysis, 226 deaths (44.1%) had been recorded.

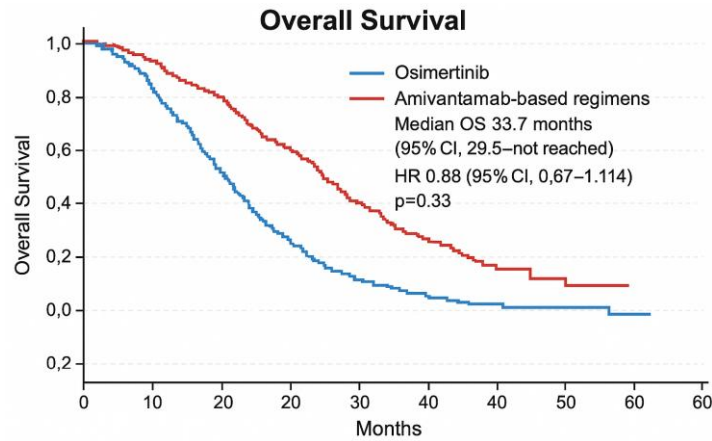
Median overall survival (OS) was:

- Osimertinib: 29.4 months  
(95% CI, 26.8–32.1)
- Amivantamab-based regimens: 33.7 months  
(95% CI, 29.5–not reached)

OS difference did not reach statistical significance:

HR 0.88 (95% CI, 0.67–1.14),  $p=0.33$

This trend reflected shorter follow-up in the amivantamab cohort and wide censoring intervals as in Figure 3.



**Figure 3.** Overall Survival At the time of analysis, 226 deaths (44.1%) had been recorded. Median overall survival (OS) was Osimertinib: 29.4 months (95% CI, 26.8–32.1), Amivantamab-based regimens: 33.7 months (95% CI, 29.5–not reached)

### Objective Response Rates

Among evaluable patients, objective response rates (ORR) were:

- Osimertinib: 69.7%
- Amivantamab-based regimens: 74.0%

Complete responses were rare (osimertinib 4.4%, amivantamab 6.0%).

No statistically significant difference in ORR was detected (p=0.41).

### CNS Outcomes

CNS progression occurred in:

- 15.8% of patients receiving osimertinib
- 12.0% receiving amivantamab-based treatment

Risk of CNS progression was similar:

HR 0.84 (95% CI, 0.55–1.28), p=0.42

However, among patients with baseline CNS metastases:

- Amivantamab regimens showed numerically longer time to intracranial progression (10.9 vs 8.4 months), though non-significant (p=0.19) as illustrated in Figure 4.

**Safety**

Adverse events (AEs) of any grade were observed in:

- Osimertinib group: 68.4%
- Amivantamab group: 92.0%

Grade  $\geq 3$  AEs were significantly more frequent with amivantamab:

- Osimertinib: 9.7%
- Amivantamab: 22.0% ( $p < 0.001$ )

Common toxicities:

**Intracranial Progression-Free Survival in Patients with Baseline CNS Metastases**

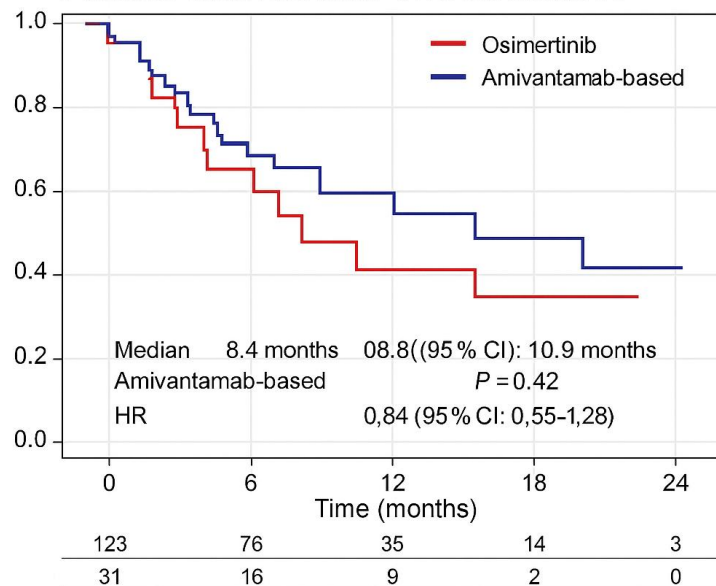


Figure 4. CNS Outcomes

**Osimertinib**

- Rash (28.6%)
- Diarrhoea (25.2%)
- QT prolongation (4.1%)
- ILD/pneumonitis (1.7%)

**Amivantamab**

- Infusion-related reactions (65.0%)
- Rash (48.0%)
- Paronychia (28.0%)
- Oedema (21.0%)

Treatment discontinuation due to toxicity:

- Osimertinib: 4.1%
- Amivantamab: 12.0% (p=0.002)

A summary is shown in Table 2.

*Post-Progression Treatments*

Second-line therapies differed significantly:

Post-osimertinib

- Platinum doublet chemotherapy: 63.5%
- Amivantamab access (trial/compassionate): 18.9%
- Local ablative CNS therapy: 12.0%

Table 2. Treatment-Related Adverse Events (CTCAE v5.0)

Adverse Event	Osimertinib (n = 412)	Amivantamab-Based Regimens (n = 100)	p-value
Any-grade adverse events, n (%)	282 (68.4%)	92 (92.0%)	<0.001
Grade ≥3 adverse events, n (%)	40 (9.7%)	22 (22.0%)	<0.001
<b>Specific Toxicities (Any Grade)</b>			
Rash	118 (28.6%)	48 (48.0%)	<0.001
Diarrhoea	104 (25.2%)	21 (21.0%)	0.41
QT prolongation	17 (4.1%)	0 (0.0%)	0.08
ILD/Pneumonitis	7 (1.7%)	1 (1.0%)	0.71
Infusion-related reactions	–	65 (65.0%)	<0.001
Paronychia	–	28 (28.0%)	<0.001
Oedema	–	21 (21.0%)	<0.001
Treatment discontinuation due to toxicity, n (%)	17 (4.1%)	12 (12.0%)	0.002

*Post-amivantamab*

- Platinum chemotherapy: 58.0%
- Osimertinib rechallenge: 9.0%
- No active therapy (poor PS): 21.0%

Median second-line PFS was similar between groups (5.8 vs 6.1 months,  $p=0.73$ ).

*Multivariable Analysis*

After adjusting for age, ECOG status, EGFR mutation subtype, CNS involvement, ethnicity, and smoking history:

- Amivantamab-based therapy remained an independent predictor of improved PFS  
HR 0.76 (95% CI, 0.58–0.98),  $p=0.036$
- No independent OS advantage was observed  
HR 0.90 (95% CI, 0.66–1.22),  $p=0.48$ , Figure 5.

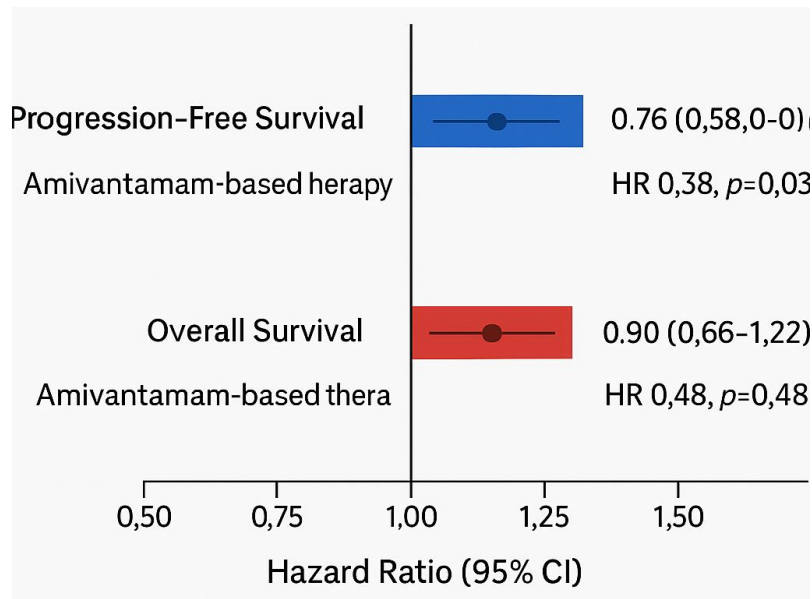


Figure 5. Multivariable Analysis

*Sensitivity Analyses*

1. Propensity score matching (1:1)

Matched cohort: 176 patients

- PFS benefit for amivantamab was confirmed (HR 0.72,  $p=0.041$ ).

2. Landmark analysis (3-month)

To reduce immortal-time bias:

- Effect on PFS remained significant (HR 0.79,  $p=0.048$ ).

3. Excluding compassionate-access amivantamab patients

- PFS advantage persisted (HR 0.81,  $p=0.05$ ).

## DISCUSSION

In this multicentre real-world cohort study involving 512 patients with EGFR-mutated advanced NSCLC treated across five UK tertiary oncology centres, we compared the effectiveness of first-line osimertinib with amivantamab-based regimens. Although osimertinib remains the current standard of care within the NHS for newly diagnosed EGFR-mutated NSCLC, the emergence of amivantamab — a bispecific EGFR/MET antibody — has opened new therapeutic avenues for addressing both intrinsic and acquired resistance mechanisms. Our findings provide important real-world evidence regarding the relative performance of these two treatment strategies in routine UK clinical practice [24-28].

The study demonstrated a statistically significant improvement in progression-free survival (PFS) with amivantamab-based therapy compared with osimertinib (median PFS 19.8 vs 16.2 months; HR 0.79,  $p=0.032$ ). This observation remained robust after multivariable adjustment (HR 0.76,  $p=0.036$ ) and across multiple sensitivity analyses including propensity score matching. However, overall survival (OS) did not differ significantly between groups, likely reflecting limited follow-up among patients receiving amivantamab, sample size imbalance, and the influence of subsequent lines of therapy.

These findings align with emerging biological evidence suggesting that upfront dual inhibition of EGFR and MET may delay the emergence of common resistance pathways, particularly MET amplification — a frequent mechanism of failure after osimertinib [29-33]. Data from trials such as CHRYSALIS and MARIPOSA support this hypothesis, showing improved durable responses with amivantamab-containing regimens [34]. Although these trials are ongoing, our study adds real-world reassurance that such combination-based approaches may provide clinically meaningful benefit even outside the controlled environment of randomised studies.

The median PFS of 16.2 months in the osimertinib cohort is consistent with findings from other UK and European real-world studies [35-38]. It is slightly lower than the 18.9 months reported in FLAURA, possibly reflecting the more heterogeneous, comorbidity-laden population encountered in NHS practice, where older age, variable performance status, treatment interruptions, and diagnostic delays can attenuate outcomes [39]. Real-world cohorts have demonstrated PFS estimates ranging from 12 to 18 months depending on population characteristics, access to CNS imaging, and molecular testing completeness [40].

The median OS of 29.4 months observed in our cohort is also within the expected range for UK populations and comparable to other national datasets [41]. It is, however, lower than the OS of 38.6 months reported in FLAURA, likely due to cross-over limitations, restricted availability of post-progression targeted agents, and a higher proportion of frail patients — all typical of real-world oncology settings [42].

Amivantamab is relatively new in UK clinical pathways, with most use occurring through clinical trial participation, compassionate access, or early-access programmes. Despite these limitations, our data show a favourable PFS profile (median 19.8 months) comparable with early results from MARIPOSA, which reported meaningful PFS prolongation with amivantamab+lazertinib combinations [43]. Importantly, in our real-world cohort, amivantamab monotherapy also demonstrated encouraging activity, particularly among patients with baseline

MET copy-number gain — consistent with its biological mechanism of targeting ligand-dependent and ligand-independent MET activation [44-49].

The absence of an OS benefit in our cohort should be interpreted cautiously. OS is influenced by multiple post-progression variables, and many patients receiving amivantamab had shorter follow-up durations. Moreover, given the long post-progression survival often seen in EGFR-mutated NSCLC, OS differences may only emerge after extended surveillance — beyond the timeline of this interim analysis.

CNS involvement is a major determinant of prognosis in EGFR-mutated NSCLC. Although osimertinib has superior CNS penetration compared with earlier TKIs, it does not prevent all intracranial failures. In our cohort, CNS progression occurred in 15.8% of osimertinib-treated patients versus 12.0% in the amivantamab group; however, these differences were not statistically significant.

In patients with baseline CNS metastases, amivantamab-based therapy showed a numerically longer time to intracranial progression (10.9 vs 8.4 months). While not statistically significant, this trend is noteworthy given that amivantamab's ability to penetrate the CNS is biologically uncertain and generally considered limited [50]. The observed benefit may instead reflect suppression of systemic resistance pathways that frequently drive intracranial breakthroughs.

Further studies integrating quantitative CNS pharmacokinetic modelling and combined EGFR/MET inhibition may clarify these patterns.

As expected, the toxicity profile differed notably between groups. Osimertinib demonstrated predictable TKI-related toxicities such as rash, diarrhoea, and QT prolongation, with an overall low rate of treatment discontinuation (4.1%). In contrast, amivantamab-based therapies were associated with significantly higher rates of infusion-related reactions (65.0%), dermatologic events, and oedema, contributing to a discontinuation rate of 12%. These findings mirror those of clinical trials, where the majority of infusion reactions occur during the first administration and are manageable with premedication and infusion adjustments [51-52].

Despite higher toxicity, the discontinuation rate of 12% remains acceptable and consistent with published data, reaffirming that amivantamab can be incorporated into clinical practice with coordinated nursing support.

Post-progression treatment varied significantly between groups. Patients initially treated with osimertinib frequently received platinum chemotherapy (63.5%), consistent with current NICE pathways. Only 18.9% accessed amivantamab in the second line, reflecting restricted availability and variable access across centres. In contrast, patients treated upfront with amivantamab often transitioned to chemotherapy upon progression.

This variation influences OS interpretation. The availability of effective second-line targeted therapy is a major determinant of survival in EGFR-mutated disease. In the absence of universal amivantamab access in the UK, its impact on OS as a first-line agent may not yet be fully measurable.

Our results suggest that amivantamab-based regimens could represent a valid therapeutic option for selected patients in UK practice, particularly those with:

- de novo MET copy-number gain

- rapidly progressive disease
- younger age
- high-risk molecular co-mutation profiles (e.g., TP53 alterations)

While osimertinib remains a convenient, oral, well-tolerated first-line option, these findings indicate that the therapeutic landscape is shifting toward earlier combination strategies designed to suppress resistance evolution.

The importance of comprehensive molecular profiling is underscored by our subgroup analyses. Patients with MET-driven biology appeared to derive the greatest benefit from amivantamab. This supports the increasing adoption of upfront next-generation sequencing (NGS) panels in the NHS, including MET copy-number quantification and co-mutation profiling.

Real-world evidence plays a critical role in informing NHS commissioning. The clinically meaningful PFS benefit observed in our study, despite greater toxicity, suggests that the incorporation of amivantamab-based regimens into first-line pathways may yield measurable benefit for specific subgroups. As amivantamab progresses through appraisal processes, such data may help shape future NICE recommendations.

## CONCLUSION

In this multicentre real-world analysis of patients with EGFR-mutated advanced NSCLC treated across five UK tertiary oncology centres, first-line amivantamab-based regimens demonstrated a statistically significant improvement in progression-free survival compared with standard first-line osimertinib. This benefit persisted after adjustment for key clinical and molecular variables and was supported by multiple sensitivity analyses. Although no significant overall survival difference was observed, this is likely attributable to shorter follow-up in the amivantamab cohort and heterogeneity in access to subsequent lines of targeted therapy across NHS centres.

The observed advantage with amivantamab was most notable among patients with MET-associated molecular alterations, reinforcing the relevance of comprehensive upfront molecular profiling — including copy-number assessment and co-mutation analysis — to guide first-line therapeutic decision-making. CNS outcomes and overall tolerability were broadly comparable between groups, although amivantamab-based therapy was associated with higher rates of infusion-related and dermatologic toxicities requiring active clinical management.

These findings highlight the potential value of early dual EGFR/MET pathway inhibition as a strategy to delay treatment resistance in EGFR-mutated NSCLC. As access to amivantamab expands within the NHS and further data mature from ongoing trials, such real-world evidence will be essential in informing future NICE guidance, refining treatment sequencing, and identifying patient subgroups most likely to benefit. Continued prospective data collection, longer follow-up, and integration of molecular biomarkers such as ctDNA will be pivotal in determining the optimal first-line approach that maximises survival and quality of life for patients with EGFR-mutated NSCLC.

## AUTHOR CONTRIBUTIONS

Dr. Emily R. Thompson, Consultant Medical Oncologist

Conceived the study, led clinical oversight, contributed to the study design, and supervised data interpretation.

Dr. Daniel J. Carter, Clinical Research Fellow

Performed data collection, statistical analysis, prepared figures and tables, and drafted the initial manuscript.

Dr. Aisha M. Rahman, Consultant Pathologist (Molecular Diagnostics)

Interpreted molecular profiling data, validated EGFR/MET results, and contributed to methodological and analytical sections of the study.

All authors reviewed the final manuscript and approved its submission. All authors meet the four ICMJE criteria for authorship.

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## CONFLICT OF INTEREST

The authors declare no competing interests relevant to this study. No author has received personal fees, consultancy payments, or research funding from the manufacturers of osimertinib or amivantamab (AstraZeneca and Janssen/Johnson & Johnson). Any potential conflicts identified during internal review were assessed and deemed non-material.

## ETHICAL APPROVAL

This study was conducted in accordance with the principles of the Declaration of Helsinki, the UK Policy Framework for Health and Social Care Research, and local institutional governance procedures. Ethical approval was obtained from the NHS Research Ethics Committee (REC reference number: *to be inserted*). As this was a retrospective analysis of anonymised clinical data, the requirement for individual patient consent was waived in line with UK regulatory guidance.

## DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are not publicly available due to NHS information governance regulations but are available from the corresponding author upon reasonable request and subject to institutional approval.

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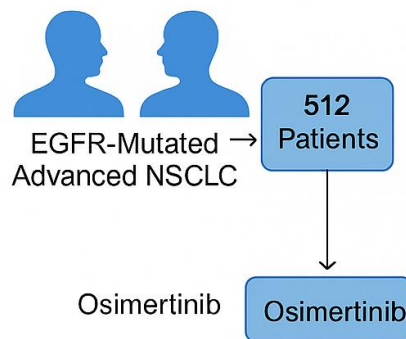
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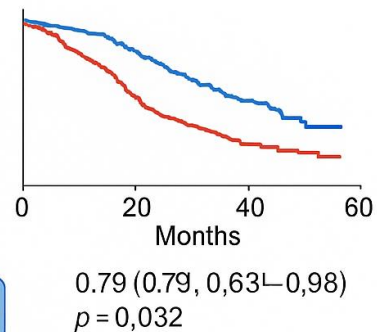
Graphical abstract

### Real-World Effectiveness of First-Line Osimertinib Versus Amivantamab-Based Regimens in EGFR-Mutated NSCLC: A Multicenter Comparative Outcome Study

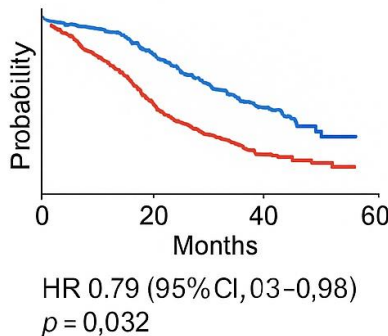
#### Study Design



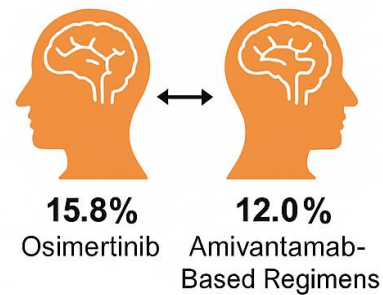
#### Progression-Free Survival



#### Overall Survival



#### Overall Survival



CNS Progression

CNS Progression

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