An Adjusted Treatment Comparison Comparing Amivantamab Versus Real-World Clinical Practice in Europe and the United States for Patients with Advanced Non-Small Cell Lung Cancer with Activating Epidermal Growth Factor Receptor Exon 20 Insertion Mutations

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ORIGINAL RESEARCH

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ABSTRACT

Introduction: Patients with advanced, epidermal growth factor receptor (*EGFR*)-mutated, non-small cell lung cancer (NSCLC) with Exon 20 insertion mutations (Exon20ins) have poor prognoses, exacerbated by a previous lack of specific treatment guidelines and unmet need for targeted therapies. Amivantamab, an *EGFR* and *MET* bispecific antibody, demonstrated efficacy and tolerability in patients with advanced *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy in CHRYSALIS (NCT02609776; Cohort D+). Since CHRYSALIS was single-arm, individual patient

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data (IPD)-based adjusted analyses versus similar patients in real-world clinical practice (RWCP) were conducted to generate comparative evidence.

Methods: RWCP cohorts were derived from seven European and US real-world sources, comprising patients fulfilling CHRYSALIS Cohort D+ eligibility criteria. Amivantamab was compared with a basket of RWCP treatments. Differences in prognostic characteristics were adjusted for using inverse probability weighting (IPW; average treatment effect among the treated [ATT]). Balance between cohorts was assessed using standardized mean differences (SMDs). Overall response rate (ORR; investigator- [INV] and independent review committee-assessed [IRC]), overall survival (OS), progression-free survival (PFS; INV and IRC) and time-to-next treatment (TTNT) were compared. Binary and time-to-event endpoints were analyzed using weighted logistic regression and proportional hazards regression, respectively.

Results: Pre-adjustment, baseline characteristics were comparable between cohorts. IPW ATT-adjustment improved comparability, giving closely matched characteristics. ORR (INV) was 36.8% for amivantamab versus 17.0% for the adjusted EU + US cohort (response rate ratio [RR]: 2.16). Median OS, PFS (INV) and TTNT were 22.77 versus 12.52 months (hazard ratio [HR]: 0.47; $p < 0.0001$), 6.93 versus 4.17 months (HR: 0.55; $p < 0.0001$) and 12.42 versus 5.36 months (HR: 0.44; $p < 0.0001$) for amivantamab versus the adjusted EU + US cohort, respectively. Results were consistent versus EU- and US-only cohorts, and when using IRC assessment.

Conclusion: Adjusted comparisons demonstrated significantly improved outcomes for amivantamab versus RWCP, highlighting the value of amivantamab in addressing unmet need in patients with advanced *EGFR* Exon20ins NSCLC following platinum-based therapy.

Trial Registration: CHRYSALIS: NCT02609776.

Keywords: Adjusted comparison; Amivantamab; Exon 20 insertion mutations; Non-small cell lung cancer; Real-world clinical practice

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Key Summary Points

Why carry out this study?

The efficacy of amivantamab, an *EGFR* and *MET* antibody licensed for the treatment of adult patients with advanced *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy, was assessed in the phase 1b, single-arm CHRYSALIS trial.

In the absence of a randomized controlled trial, adjusted comparisons versus RWCP are required to provide comparative evidence for the relative efficacy of amivantamab.

What was learned from the study?

Treatment lines for RWCP in Europe and the US were pooled into a single cohort and baseline characteristics were adjusted using ATT methodology to provide an external comparator arm for the CHRYSALIS trial, based on data from 7 cohorts based in EU and US.

Prior to and after adjustment, amivantamab was associated with improved ORR, OS, PFS and TTNT, when compared with RWCP in (1) pooled European (EU) and US, (2) pooled EU-only, and (3) pooled US-only cohorts; all results were statistically significant, and a consistent treatment effect was seen for each comparison.

INTRODUCTION

Lung cancer is one of the most common types of cancer, and is the most common cause of death from cancer worldwide, with non-small cell lung cancer (NSCLC) comprising 85% of all cases [1]. Epidermal growth factor receptor (*EGFR*) mutations are common in NSCLC and are among the most well-established NSCLC driver mutations (genetic mutations which accelerate cancer progression). Approximately 30% of NSCLC tumors harbor a mutation in the *EGFR* gene, with prevalence rates reported to be highest in Asia (38%) and lowest in Europe (14%), with 24% prevalence in the US [2–4]. While the majority of *EGFR* mutations comprise Exon 19 deletions and Exon 21 L858R substitutions, 10–15% consist of uncommon mutations, including Exon 20 insertion mutations (Exon20ins) [2]. Across Europe and the US, the frequency of *EGFR* Exon20ins ranges from 0.3% to 2.6% of all NSCLC cases and from 4% to 12% of all *EGFR* mutations [2, 4]. Patients with *EGFR*-mutated NSCLC with Exon20ins have a poorer prognosis compared with patients with common *EGFR* mutations [5]. For example, real-world evidence demonstrates that patients with *EGFR* Exon20ins have a 75% increased risk of death and a 93% increased risk of disease progression or death compared with patients with common *EGFR* mutations [6]. This poorer prognosis may be attributed to a previous lack of effective, targeted treatments in the *EGFR* Exon20ins population and because *EGFR* Exon20ins may be associated with insensitivity and resistance to currently available *EGFR*-targeted treatments (such as *EGFR* tyrosine kinase inhibitors [TKIs]) [1, 6–8].

Until recently, there was a lack of specific and effective treatment for patients with advanced, *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy at second-line or later (2L+), and thus no treatment guidelines existed for this specific patient population (other than those for patients without an oncogenic driver mutation). This lack of specific recommendations has led to an absence of standard of care, with clinicians prescribing a mix of treatments, including TKI-based regimens, immuno-oncology agent (IO)-based regimens, platinum-based chemotherapy re-treatment, and non-platinum-based chemotherapy. Following the development of targeted treatments for patients with *EGFR* Exon20ins, treatment guidelines now recommend amivantamab and mobocertinib specifically as monotherapy for patients with *EGFR*-mutated NSCLC with Exon20ins who have progressed on platinum chemotherapy [9, 10].

Amivantamab is a novel, fully human, bis-pecific *EGFR* and *MET* antibody. The safety and efficacy of amivantamab for treating patients with locally advanced or metastatic NSCLC with *EGFR* Exon20ins was assessed in the phase 1b, single arm, open-label, multicenter CHRY-SALIS trial (NCT02609776). CHRYSALIS comprised a dose-escalation phase followed by a dose-expansion phase, where patients were assigned to cohorts on the basis of *EGFR* and *MET* mutation status and previous therapy [11]. The primary endpoint for the dose-expansion phase was overall response rate (ORR; the proportion of patients with a partial or complete response). Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Time-to-next treatment (TTNT) was also measured. Results from CHRYSALIS have been published previously, indicating the clinically meaningful efficacy of amivantamab monotherapy and a favorable safety profile for patients who have progressed on platinum-based chemotherapy [11, 12]. Based on these results, regulatory approval was granted by the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency and the Food and Drug Administration, leading to amivantamab being the first targeted treatment approved in this setting [12–14]. Regulatory approval has also been granted in 9 other jurisdictions, and confirmatory data on the efficacy and tolerability of amivantamab are anticipated from the Phase 3 trial, PAPILLON [15].

Notwithstanding regulatory approval based on single-arm trial evidence, there is a requirement to generate comparative evidence to estimate the relative efficacy of amivantamab for patients with advanced *EGFR*-mutated NSCLC with Exon20ins. However, given the severity of the disease and the lack of clinical equipoise, a randomized controlled trial was deemed unethical. In addition, *EGFR* Exon20ins mutations are rare, and identifying these mutations via conventional polymerase chain reaction-based methods is challenging; these factors lead to difficulties in recruiting large patient cohorts for a randomized trial in this setting [16].

As described above, there is substantial heterogeneity in current treatments applied for this specific patient population. Thus, the most relevant comparison was between amivantamab and a pooled basket of diverse treatments that are routinely used in RWCP at 2L+.

Here, we present an individual patient data (IPD)-based adjusted treatment comparison of amivantamab versus RWCP in Europe and the US in patients with advanced *EGFR*-mutated NSCLC with Exon20ins at 2L+.

METHODS

The primary objective of this analysis was to compare the efficacy of amivantamab, as assessed in the CHRYSALIS trial, to RWCP from Europe and the US in patients with advanced *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy at 2L+. As patients in both cohorts may not be fully comparable and/or exchangeable due to lack of randomization, all comparative analyses were adjusted for imbalances in prognostic baseline characteristics between amivantamab- and RWCP-treated patients.

The CHRYSALIS cohort used in this analysis included patients with *EGFR* Exon20ins who had progressed on or after prior platinum-based chemotherapy, as per Cohort D + of the trial (Supplementary Material Table S1). At the data cut-off (30 March 2021; as requested by the EMA) [10], 114 patients had received their first dose of amivantamab. CHRYSALIS was approved by an Independent Ethics Committee, and all patients provided written informed consent.

The real-world evidence portion of the analysis is based on previously collected data which is de-identified of personal health information, so there is no Institutional Review Board or ethics review requirement.

Real-World Data Sources

The real-world data sources used to provide comparative data in the analyses were from Public Health England [PHE (now NHS Digital)]; England, 13 treatment lines) [17–19]; the Network Genomic Medicine (NGM; Germany, 109 treatment lines); the Clinical Research platform

Into molecular testing, treatment and outcome registry of non-Small cell lung carcinoma Patients (CRISP; Germany, 21 treatment lines), the Epidemiological Strategy and Medical Economics (ESME; France, 52 treatment lines) and Flatiron Health Spotlight, ConcertAI and COTA (US; 206 treatment lines [combined, after excluding duplicates]) (Supplementary Material Table S2). To compare patients from CHRYSALIS Cohort D + with similar patients from the external data sources, the same inclusion and exclusion criteria (Supplementary Material Table S1) were applied to all real-world data sources, where possible, depending on data availability. The following eligibility criteria were applied across real-world data sources: age ≥ 18 years; Stage IIIB/C or IV NSCLC; *EGFR* Exon20ins diagnosis prior to start of relevant line of therapy; progression on or after prior platinum-based therapy; and Eastern Cooperative Oncology Group (ECOG) performance status score < 2 (or missing, as described below). Details of criteria applied to individual data sources are provided in Supplementary Material Table S3. Patients from the real-world data sources that satisfied inclusion criteria at multiple times during their follow-up contributed to the analysis with more than one line of therapy [20–22]. Only treatment lines where patients received *EGFR* Exon20ins testing prior to treatment were included, ensuring that treatment was reflective of clinical practice once physicians were aware that a patient had an *EGFR* Exon20ins mutation, and to avoid immortal time bias. Correlation of outcomes across treatment lines for the same patient was accounted for statistically, using the robust sandwich estimator of the covariance matrix [23].

The base case analysis compared CHRYSALIS with a pooled EU and US RWCP cohort (hereafter the "EU + US cohort" [401 treatment lines]). Pooling was considered appropriate given that treatment class distributions of the EU and US cohorts were similar (Tables 2, 3). Sensitivity analyses explored comparisons between CHRYSALIS and a pooled EU RWCP cohort [PHE, NGM, CRISP, and ESME; hereafter the "EU cohort" (195 lines)], and between CHRYSALIS and a pooled US RWCP cohort [Flatiron Health Spotlight, ConcertAI, and COTA; hereafter the "US cohort" (206 lines)].

Adjustment Methodology

To account for differences in patient populations between CHRYSALIS and the real-world data sources, adjustment was carried out for key prognostic variables based on the confounders identified by a systematic literature review, clinical expert opinion. and data availability. The covariates identified for consideration in the adjustment were: age, gender, race (Asian), smoking history, cancer stage at initial diagnosis, number of metastatic locations, brain metastasis, liver metastasis, prior lines of treatment, ECOG performance status, hemoglobin, and body mass index (BMI).

IPD were available for all sources except ESME. For ESME, reconstructed patient-level data were generated. For the EU + US cohort analysis, all common variables across CHRYSALIS and the NGM, CRISP, PHE, and US real-world data sources were included in the adjustment, to maximize sample size (Supplementary Material Table S4). Uncommon prognostic variables (i.e., covariates missing in some sources) were not included in the adjustment of the combined IPD, as sources with missing data would be automatically discarded in the average treatment effect among the treated (ATT) approach (see details below), thus reducing the sample size. For ESME, data were balanced versus CHRYSALIS independent of other data sources. As there were no restrictions regarding the common variables between ESME and other databases, balancing was conducted using all prognostic variables (Supplementary Material Table S4). For analysis of individual data sources (e.g., the US cohort and ESME), all prognostic variables were included. Pooling of all data sources was appropriate to create the EU + US and EU cohorts as identical methodology was used for adjustment (ATT, see below). NGM, CRISP, PHE, US, and ESME data were therefore adjusted similarly to the CHRYSALIS population. For the base case (EU + US cohort) analysis, age, gender, brain metastasis, and prior lines of treatment were included.

ECOG performance status is not routinely captured in clinical practice at the initiation of each treatment line, and thus was not always available for all real-world data sources. To maintain a similar patient population to the CHRYSALIS study while maximizing the sample size, base case analyses included treatment lines for which ECOG was missing only when estimated outcomes for treatment lines with missing ECOG performance status were not worse than those with ECOG performance status of 1, and when results including and excluding missing ECOG performance status were consistent. Overall, observations with missing ECOG were excluded from the US cohort and PHE, and were included for NGM, CRISP, and ESME.

Propensity score (PS) methods were used to mimic the effect of randomization by creating a balance between two treatment groups with respect to important baseline covariates. The IPW approach and ATT weighting scheme was then used to generate a comparative arm reflecting the population enrolled in CHRYSALIS by reweighting the RWCP cohort to match the amivantamab patients of CHRYSALIS. To maintain the original sample size for the adjusted populations and to reflect the associated uncertainty, ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights, making the sum of these recalculated weights equal to the original sample size. The ATT approach was considered the most appropriate as amivantamab was the main intervention of relevance for the analyses. With ATT weights, the amivantamab population from CHRYSALIS was left untouched (as all patients receive a weighting of 1) and the RWCP cohort was reweighted to achieve a similar distribution in baseline characteristics to the amivantamab-treated population from CHRYSALIS. In addition, overlap between PS distributions using ATT was very high [as the observed populations were already very similar to start with (Table 1)] and the standardized mean differences (SMDs) after ATT weighting were small (Supplementary Material Figure S1), representing good balance after ATT IPW. Other

methodologies (such as covariate adjustment) are more appropriate in case of poor overlap.

Endpoint Definitions

The efficacy outcomes evaluated in the analysis were ORR, PFS, OS, and TTNT, although ORR and PFS data were not available from PHE, and ORR data were not available from ESME.

ORR was defined as the proportion of all patients who achieved a partial response or better. For RWCP, this was measured among those with a non-missing record only. OS was defined as the time between index date and date of death (or censoring). PFS was defined as the interval between the index date and the date of disease progression or death (patients initiating subsequent anticancer therapy in the absence of progressive disease were censored on the date of the last disease assessment before the start of subsequent therapy in CHRYSALIS, and at the start of subsequent therapy for real-world data sources). TTNT was defined as the interval between index date and initiation of subsequent systemic anticancer therapy or death (for patients without a record of subsequent anticancer therapy, the interval was censored at the date of last contact with the patient).

For CHRYSALIS patients, response and progression evaluations were based on RECIST v1.1 criteria. For patients in real-world data sources, response and progression were defined as clinically relevant response or progression in the opinion of the investigator; it was generally not possible to check whether RECIST v1.1 criteria were applied. ORR and PFS in CHRYSALIS were assessed by both INV and IRC. INV was considered the key method of assessment in this analysis to align with real-world clinical practice. IRC results (where IRC data from CHRYSALIS only were used) are also presented, where collected, to demonstrate consistency.

For CHRYSALIS patients, the index date was the date of the first amivantamab dose. For patients from the real-world data sources, the index date was the start of any line of therapy

Table 1 Baseline characteristics for CHRYSALIS versus the unadjusted and IPW–ATT adjusted EU + US cohort

Characteristic	CHRYSALIS analysis set	EU + US cohort[a] (unadjusted)	EU + US cohort[a] (adjusted)
n	114	349	349
Prior lines of treatment			
1	48 (42.1%)	155 (44.4%)	147 (42.1%)
2	34 (29.8%)	108 (30.9%)	105 (30.1%)
3	15 (13.2%)	52 (14.9%)	45 (12.9%)
4+	17 (14.9%)	34 (9.7%)	52 (14.9%)
Brain metastasis			
No	85 (74.6%)	217 (62.2%)	260 (74.5%)
Yes	29 (25.4%)	132 (37.8%)	89 (25.5%)
Age			
≤ 55	30 (26.3%)	97 (27.8%)	88 (25.3%)
> 55 to ≤ 60	20 (17.5%)	54 (15.5%)	63 (18.1%)
> 60	64 (56.1%)	198 (56.7%)	198 (56.6%)
Gender			
Male	44 (38.6%)	137 (39.3%)	135 (38.6%)
Female	70 (61.4%)	212 (60.7%)	214 (61.4%)

ATT average treatment effect among the treated, *IPW* inverse probability weighting
[a]Excluding ESME (presented in Supplementary Table S8)

for which inclusion and exclusion criteria were met upon initiation.

Statistical Analysis

PSs were calculated using a multivariable logistic regression model. For the ATT approach, where the RWCP cohort was re-weighted to mimic the amivantamab-treated cohort, treated patients received a weight of 1, while control patients were reweighted by $PS/(1 − PS)$. This allowed for the generation of counterfactual outcomes for RWCP in a patient cohort with similar baseline characteristics to CHRYSALIS.

Binary Endpoint
For the binary endpoint (ORR), adjusted treatment effects, in terms of odds ratio (OR) and the corresponding 95% confidence intervals (CIs), were generated using logistic regression models. A weighted logistic regression model including treatment only was used. To estimate treatment effects in terms of response rate ratio (RR), the same framework was implemented using a generalized linear model with the appropriate link (instead of logistic regression).

Time-to-Event Endpoints
The IPW approach provided weights for estimating the treatment effect of amivantamab versus comparators in a weighted Cox proportional hazards model, in terms of the hazard ratio (HR) with 95% Wald-type CI and corresponding p values. A robust sandwich variance estimator was also used to account for clustering of treatment lines within the same patient. Kaplan–Meier (K–M) curves were generated, based on which median survival with 95% CI was reported for each treatment group.

RESULTS

Baseline Patient and Disease Characteristics

As shown in Table 1, the baseline characteristics for patients in the CHRYSALIS analysis set and EU + US cohort were comparable prior to adjustment. Using the IPW ATT-adjustment, the comparability improved to give two cohorts with closely matched characteristics. These similarities were also evident for the EU cohort (excluding ESME; Supplementary Material Table S6) and the US cohort (Supplementary Material Table S7). Unadjusted data from the ESME database was an exception, differing substantially from the CHRYSALIS data. Adjustment of the ESME data improved the similarities between the two datasets, in particular the data relating to prior lines of treatment (Supplementary Material Table S8). However, some differences in the ages and metastasis status remained.

RWCP Treatments Received

The treatments classes received as part of RWCP are described in Tables 2 and 3, for the EU and US cohorts, respectively. The most common therapy class received in the real-world cohorts was *EGFR* TKIs (21.5% in the EU cohort and 26.7% in the US cohort).

PS Weighting

The use of ATT resulted in good overlap between PS distributions between the CHRYSALIS cohort and the EU + US cohort. Additionally, the SMDs after ATT weighting improved and became closer to 0 (Supplementary Material Figure S1).

Efficacy Assessments

The ORR (INV) estimated for amivantamab was 36.8%. For the EU + US cohort, ORR (INV) pre-adjustment and post-IPW-ATT adjustment was 16.8% and 17.0%, respectively (Table 4). Before

Table 2 Treatments received as part of RWCP for the EU cohort

Treatment class	All lines	% total
IO	37	19.0
EGFR TKI	42	21.5
Non-platinum-based chemotherapy	39	20.0
VEGFi + chemotherapy	35	18.0
Other[a]	42	21.5

EGFR epidermal growth factor receptor, *IO* immuno-oncology agent, *RWCP* real-world clinical practice, *TKI* tyrosine kinase inhibitor, *VEGFi* vascular endothelial growth factor inhibitor

[a]therapies listed as 'other' were those which were either under investigational study at the time of data collection, or alternatively would not usually be considered as an evidencebased treatment for patients with EGFR-mutated non-small cell lung cancer (such as everolimus or pazopanib)

Table 3 Treatments received as part of RWCP for the US cohort

Treatment class	All lines	% total
IO	34	16.5
EGFR TKI	55	26.7
Non-platinum-based chemotherapy	52	25.2
VEGFi + chemotherapy	29	14.1
Other[a]	36	17.5

EGFR epidermal growth factor receptor, *IO* immuno-oncology agent, *RWCP* real-world clinical practice, *TKI* tyrosine kinase inhibitor, *VEGFi* vascular endothelial growth factor inhibitor

[a]therapies listed as 'other' were those which were either under investigational study at the time of data collection, or alternatively would not usually be considered as an evidencebased treatment for patients with EGFR-mutated non-small cell lung cancer (such as everolimus or pazopanib)

adjustment, the OR and RR for amivantamab versus RWCP were 2.88 (95% CI 1.71, 4.86) and 2.19 (95% CI 1.49, 3.21), respectively. The ATT-adjusted OR and RR for amivantamab versus RWCP were 2.84 (95% CI 1.68, 4.79; $p < 0.05$)

Table 4 ORR results; INV, versus EU + US cohort

	ORR		OR (95% CI)	RR (95% CI)
	Amivantamab	RWCP		
Unadjusted	36.8%	16.8%	2.88 (1.71; 4.86)	2.19 (1.49; 3.21)
IPW–ATT approach	36.8%	17.0%	2.84 (1.68; 4.79)	2.16 (1.48; 3.17)

ATT average treatment effect among the treated, *INV* investigator-assessed, *IPW* inverse probability weighting, *OR* odds ratio, *ORR* overall response rate, *RR* response rate ratio, *RWCP* real-word clinical practice

and 2.16 (95% CI 1.48, 3.17), respectively. Improved ORR was also observed for amivantamab versus RWCP for the EU cohort and the US cohort (Supplementary Material Table S9). Results for ORR, based on IRC assessment, versus the EU + US cohort (Supplementary Material Table S10), were also similar to those based on INV assessment.

The median OS of amivantamab was 22.77 months (95% CI 17.48, not estimable [NE]) versus 12.12 (95% CI 10.64, 13.31) for the unadjusted EU + US cohort and versus 12.52 months (95% CI 10.74, 14.09) for the ATT-adjusted EU + US cohort (Fig. 1). Before adjustment, the HR for amivantamab versus RWCP was 0.45 (95% CI 0.32, 0.62; $p < 0.0001$). The adjusted HR for amivantamab versus RWCP was 0.47 (95% CI 0.34, 0.66; $p < 0.0001$). Improved OS was also observed for amivantamab versus ATT-adjusted RWCP for the EU
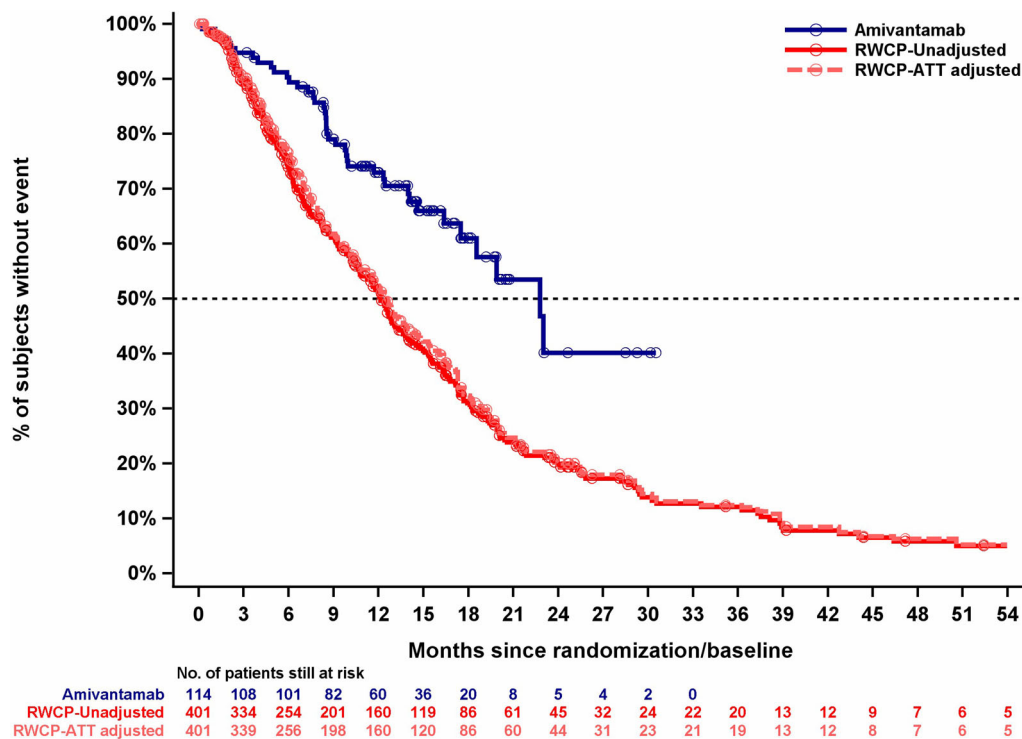
Fig. 1 Kaplan–Meier curve for OS for CHRYSALIS versus EU + US cohort (amivantamab vs. unadjusted and adjusted RWCP). *ATT* average treatment effect among the treated, *HR* hazard ratio, *IPW* inverse probability weighting, *OS* overall survival, *RWCP* real-word clinical practice
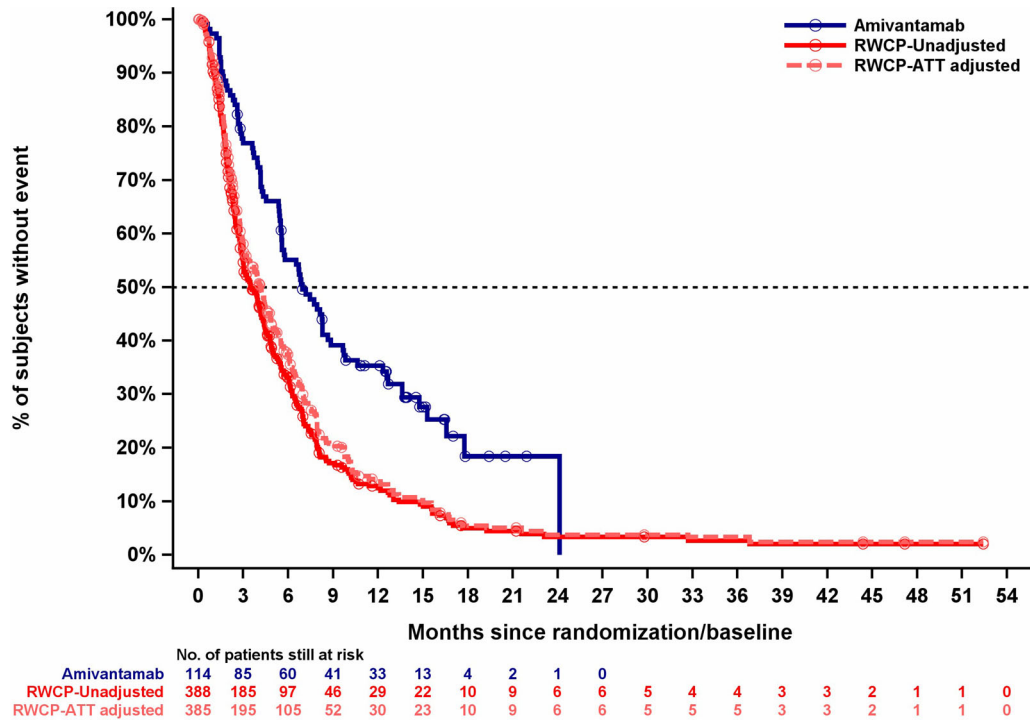
Fig. 2 Kaplan–Meier curve for PFS (INV) for CHRY-SALIS versus EU + US cohort (amivantamab vs. unadjusted and adjusted RWCP). *ATT* average treatment effect among the treated HR: hazard ratio, *INV* investigator-assessed, *IPW* inverse probability weighting, *PFS* progression-free survival, *RWCP* real-word clinical practice

cohort and the US cohort (Supplementary Material Figure S2).

The median PFS (INV) of amivantamab was 6.93 months (95% CI 5.55, 8.64) versus 3.48 (95% CI 2.96, 4.21) for the unadjusted EU + US cohort and versus 4.17 months (95% CI 3.12, 4.86) for the ATT-adjusted cohort (Fig. 2). Before adjustment, the HR for amivantamab versus RWCP was 0.51 (95% CI 0.41, 0.65; *p* < 0.0001). The adjusted HR for amivantamab versus RWCP was 0.55 (95% CI 0.43, 0.70; *p* < 0.0001). Improved PFS was also observed for amivantamab versus RWCP for the EU cohort and the US cohort (Supplementary Material Figure S3). The K–M plots for PFS, based on IRC assessment, versus the EU + US cohort (Supplementary Material Figure S4), were also consistent with those based on INV assessment.

The median TTNT of amivantamab was 12.42 months (95% CI 8.34, 18.79) versus 4.99 (95% CI 4.50, 5.95) for the unadjusted EU + US cohort and versus 5.36 months (95% CI 4.73,

6.41) for the ATT-adjusted cohort (Fig. 3). Before adjustment, the HR for amivantamab versus RWCP was 0.41 (95% CI 0.32, 0.54; *p* < 0.0001). The adjusted HR for amivantamab versus RWCP was 0.44 (95% CI 0.33, 0.57; *p* < 0.0001). Improved TTNT was also observed for amivantamab versus RWCP for the EU cohort and the US cohort (Supplementary Material Figure S5).

DISCUSSION

At present, patients with *EGFR*-mutated NSCLC with Exon20ins face a poor prognosis, and there is a high unmet need for novel and targeted therapies, such as amivantamab, for these patients [8, 24]. Given the regulatory approval of amivantamab based on data from CHRYSA-LIS Cohort D+, the unmet need for new treatments in this setting, and difficulties in identifying large cohorts of patients with *EGFR* Exon20ins, comparative data were generated to
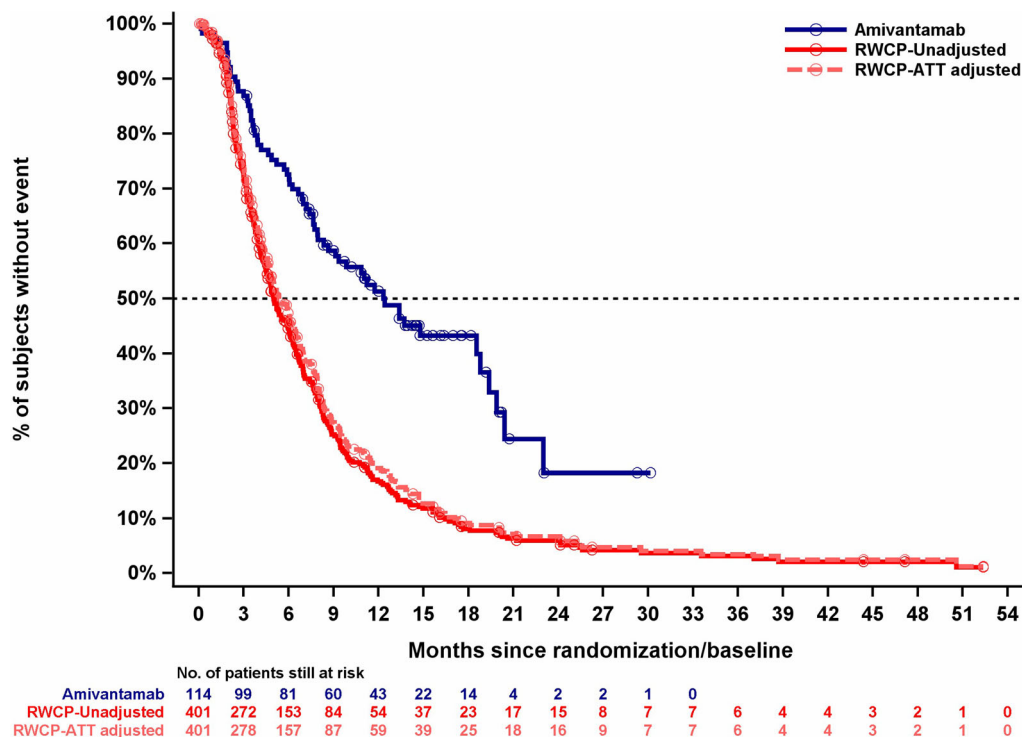
Fig. 3 Kaplan–Meier curve for TTNT for CHRYSALIS versus EU + US cohort (amivantamab vs. unadjusted and adjusted RWCP). *ATT* average treatment effect among the treated, *HR* hazard ratio, *IPW* inverse probability weighting, *RWCP* real-word clinical practice, *TTNT* time-to-next treatment

determine the efficacy of amivantamab compared with RWCP based on an external cohort. This cohort was constructed using data from seven real-world data sources across Europe and the US. The control arm comprised a basket of many different treatment regimens, reflecting the heterogeneous real-world treatment patterns for patients with *EGFR*-mutated NSCLC after diagnosis of Exon20ins following failure of platinum-based chemotherapy.

The most common therapy class received in the RWCP cohorts was *EGFR* TKIs (21.5% in the EU cohort and 26.7% in the US cohort), despite established poor response rates to TKIs among patients with *EGFR* Exon20ins [25]. This treatment class was maintained in the comparator basket as it was the most commonly prescribed treatment class in the available real-world data sources, and, if clinicians had access to sub-mutation status of patients, there would be a small proportion of patients with *EGFR*

Exon20ins mutations (those with the *EGFR*-A763_Y764insFQEA sub-mutation) that may benefit from TKI treatment [26–29]. Although the data described here indicate that *EGFR* TKIs were prescribed in a higher proportion of patients in real-world practice than would be expected if clinicians were only prescribing to patients with the *EGFR*-A763_Y764insFQEA sub-mutation (in the literature, it is reported that 5–6% patients with *EGFR* Exon20ins mutations have this sub-mutation) [9], this is likely reflective of the fact that clinicians may not have access to sub-mutation data to inform treatment decisions, as well as the lack of specific and effective treatments for patients with advanced NSCLC with *EGFR* Exon20ins at 2L+. As such clinicians appear to prescribe a mix of treatments including *EGFR* TKIs, despite known poor response rates, as demonstrated by real-world data presented in this manuscript and in other real-world studies [5, 30, 31].

Pooling of the EU and US cohorts (justified by a comparable treatment distribution and consistency in outcomes across the EU and US individually) provided comparator data with the largest possible sample size. Baseline characteristics between amivantamab- and RWCP-treated patients were similar before adjustment, indicating the comparability between CHRYSALIS Cohort D+ and the real-world cohorts. Using the IPW-ATT adjustment for all clinically important variables which were common to the pooled data sources, the comparability of the cohorts was increased, as indicated by small SMDs post-adjustment.

Compared with both the unadjusted and adjusted RWCP cohorts, amivantamab demonstrated a significant benefit across all endpoints evaluated (ORR, OS, PFS and TTNT) among patients with *EGFR*-mutated NSCLC with Exon20ins following platinum-based therapy at 2L+. Amivantamab showed a consistent treatment benefit versus the EU + US, EU, and US cohorts, and with IRC assessment of ORR and PFS. The consistent and significant treatment effect of amivantamab, along with alignment with previously reported data versus a US-only cohort, confirm the robustness of the results and support the generalizability of these results across multiple geographies [30].

The adjusted treatment comparisons were conducted using robust statistical methodology. The ATT approach was considered the most appropriate, given that it maintained the data from CHRYSALIS and adjusted the RWCP data to the CHRYSALIS population, thus maintaining the balance with CHRYSALIS data when pooling all ATT-weighted data from different sources. In addition, overlap between PS distributions using ATT was high and the SMDs after ATT weighting were small, representing good balance after IPW-ATT. The ATT approach also provided a means of maximizing the data from the relatively small sample size available. Although no IPD were available for the ESME data source for the comparison versus RWCP, aggregated outcomes data from ESME were used to reconstruct unadjusted and ATT-adjusted IPD, thereby maximizing the sample size and enabling a robust statistical analysis. Despite adjustment, some differences between the

baseline characteristics of the CHRYSALIS cohort and ESME remained or were increased. While this may limit comparisons to ESME, pooling all databases minimized the effect of these differences.

In the present manuscript, the efficacy of amivantamab is compared with a pooled basket of diverse treatments that are routinely used in RWCP at 2L+. Further research is required to investigate whether the observed benefit of amivantamab remains applicable when compared to the individual treatment classes which comprise RWCP (i.e., TKI-based regimens, IO-based regimens, non-platinum-based chemotherapy, and VEGFi plus chemotherapy). Such comparisons of amivantamab versus individual treatment classes will be described in an forthcoming publication.

Further limitations of this study include differences which may have arisen from inconsistencies in patient assessments between the CHRYSALIS trial and RWCP. For example, protocol-driven criteria, such as RECIST v1.1, were adhered to during the trial; however, these may not have been used for patients in the RWCP cohorts. INV assessment for ORR and PFS was chosen as the primary analysis to align more closely with real-world clinical practice; however, caution should still be applied when comparing ORR and PFS between trial and real-world cohorts. TTNT and OS are less prone to measurement bias given the variability in time interval for tumor assessment in a RWCP setting; however, the lines of therapy underlying TTNT estimations from the PHE data source were derived via an algorithm such that there was a risk of misclassification of lines and movements between them. Additionally, patients from the PHE cohort may not be fully representative of all Exon20ins patients in England, given the limitations in diagnostic test sensitivity and that only approximately 80% of molecular tests currently feed into the utilized database. Moreover, despite comparative analyses being adjusted for available clinically important prognostic variables, as with any non-randomized comparison, bias due to residual confounding cannot be entirely excluded. Other biases and confounders may also be associated with comparisons between

amivantamab treatment in a clinical trial setting and a range of therapies selected by physicians in real-world practice based on patient characteristics.

In contrast with clinical studies, real-world data sources do not collect extensive baseline disease characteristics. Consequently, not all inclusion/exclusion criteria from CHRYSALIS could be applied, and it was not always feasible to adjust for all baseline characteristics identified as relevant prognostic factors. For example, ECOG performance status was missing for certain treatment lines, and treatment lines were only included if necessary to maintain a reasonable sample size and when estimated outcomes for treatment lines with missing ECOG performance status were not worse than those with ECOG performance status of 1, and when results including and excluding missing ECOG performance status were consistent. In addition, *EGFR* Exon20ins sub-mutation data was not available from all of the relevant real-world data sources discussed in this manuscript. Where these were available, numerous different sub-mutations and inconsistent categorization between data sources prevented the use of sub-mutation status as a covariate in the adjustment. Finally, the lack of systematic adverse event reporting and quality of life measurement in the real-world data sources limits this comparative analysis to efficacy outcomes.

Despite the limitations stated, similar baseline characteristics between amivantamab- and RWCP-treated patients were observed before adjustment and improved using the adjustment methodology which was chosen to make best use of the available real-world data. Consistent comparative outcomes versus adjusted and unadjusted pooled real-world cohorts confirm the robustness of the results. Larger randomized studies for amivantamab could help to validate the findings of these adjusted treatment comparisons in future, such as the ongoing randomized, open-label phase 3 study, PAPILLON, which is investigating amivantamab in combination with chemotherapy versus chemotherapy alone in patients with locally advanced or metastatic *EGFR*-mutated NSCLC with Exon20ins [15].

CONCLUSION

Adjusted treatment comparisons provide robust evidence of a statistically significant clinical benefit of amivantamab versus RWCP treatments from Europe and the US in patients with advanced EGFR-mutated NSCLC with Exon20ins following platinum-based therapy at 2L+.

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Compliance with Ethics Guidelines. CHRYSALIS was approved by an Independent Ethics Committee, and all patients provided written informed consent. The real-world evidence portion of the analysis is based on previously collected data which is de-identified of personal health information, so there is no Institutional Review Board or ethics review requirement.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to CHRYSALIS study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu. The CRISP data included in this study are based on patient-level information collected by CRISP in the German routine care setting. The data are collated, maintained, and quality assured by CRISP. CRISP is an AIO study (project no. AIO-TRK-0315) under the medical leadership of the Executive Committee (Prof. F. Griesinger (Oldenburg), Prof. M. Thomas (Heidelberg), Dr. M. Sebastian (Frankfurt) and PD Dr. W. Eberhardt (Essen)). CRISP is conducted by AIO-Studien-gGmbH (sponsor) in cooperation with iOMEDICO (conception, project management, analysis). CRISP is supported by Amgen Limited, AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, GlaxoSmithKline Research & Development Limited, Janssen-Cilag GmbH, Lilly Deutschland GmbH, MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG and Takeda Pharma Vertrieb GmbH & Co. KG. The EMSE data included in this study are based on patient-level information collected by Unicancer, as part of the care and support of cancer patients. The data are collated, maintained and quality assured by Unicancer. The NGM data included in this study are based on patient-level information collected by NGM in the German routine care setting. The data are collated, maintained, and quality assured by NGM. The PHE data included in this study were collected and analyzed under the National Disease Registries Directions 2021, made in accordance with sections 254(1) and 254(6) of the 2012 Health and Social Care Act. This is data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which

is part of NHS Digital. The US data included in this study were made available by ConcertAI, COTA Healthcare, and Flatiron Health, Inc. and used under license for the current study and so are not publicly available. Other researchers should contact ConcertAI (https://www.concertai.com), COTA Healthcare (https://cotahealthcare.com), and Flatiron Health, Inc. (https://flatiron.com). Flatiron Health, Inc., did not participate in the analysis of this data.

REFERENCES

1. Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5.

2. Van Sanden S, Murton M, Bobrowska A, et al. Prevalence of epidermal growth factor receptor exon 20 insertion mutations in non-small-cell lung cancer in Europe: a pragmatic literature review and meta-analysis. Target Oncol. 2022;17:153–66.

3. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7:78985–93.

4. Burnett H, Emich H, Carroll C, et al. Epidemiological and clinical burden of EGFR exon 20 insertion in advanced non-small cell lung cancer: a systematic literature review. PLoS ONE. 2021;16: e0247620.

5. Chouaid C, Filleron T, Debieuvre D, et al. A real-world study of patients with advanced non-squamous non-small cell lung cancer with EGFR exon 20 insertion: clinical characteristics and outcomes. Target Oncol. 2021;16:801–11.

6. Bazhenova L, Minchom A, Viteri S, et al. Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. Lung Cancer. 2021;162:154–61.

7. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. J Thorac Oncol. 2013;8:179–84.

8. Girard N, Bazhenova L, Minchom A, et al. Comparative clinical outcomes for patients with NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. J Thorac Oncol. 2021;16:S145–6.

9. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-small cell lung cancer. Version 5. 2022. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450. Last accessed: Nov 2022.

10. Leitlinienprogramm Onkologie. S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. 2022. Available at: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/LL_Lungenkarzinom_Langversion_2.01.pdf. Last accessed: July 2022.

11. 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.

12. European Medicines Agency (EMA). European Public Assessment Report: Rybrevant. Available at: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf. Last accessed: Nov 2022.

13. Medicines and Healthcare products Regulatory Agency (MHRA). Rybrevant 50 mg/ml concentrate for solution for infusion SmPC. 2021. Available at: https://mhraproducts4853.blob.core.windows.net/docs/d25ead446a4a1bc2da9f3aa220b0ce8422247ba3. Last accessed: July 2022.

14. U.S. Food and Drug Administration. Prescribing information: ybrevant (amivantamab-vmjw)

injection, for intravenous use. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s000lbl.pdf. Last accessed: July 2022.

15. ClinicalTrails.gov. A study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in participants with advanced or metastatic non-small cell lung cancer characterized by epidermal growth factor receptor (EGFR) exon 20 insertions (PAPILLON). Available at: https://clinicaltrials.gov/ct2/show/NCT04538664. Last accessed: July 2022.

16. Hou J, Li H, Ma S, et al. EGFR exon 20 insertion mutations in advanced non-small-cell lung cancer: current status and perspectives. Biomark Res. 2022;10:21.

17. Herbert A, Wijlaars L, Zylbersztejn A, et al. Data resource profile: hospital episode statistics admitted patient care (HES APC). Int J Epidemiol. 2017;46:1093–1093i.

18. Bright CJ, Lawton S, Benson S, et al. Data resource profile: the systemic anti-cancer therapy (SACT) dataset. Int J Epidemiol. 2020;49:15–15l.

19. Henson KE, Elliss-Brookes L, Coupland VH, et al. Data resource profile: national cancer registration dataset in England. Int J Epidemiol. 2020;49:16–16h.

20. Danaei G, Rodríguez LAG, Cantero OF, et al. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. Stat Methods Med Res. 2011;22:70–96.

21. Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008;19:766–79.

22. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016;183:758–64.

23. Backenroth D. How to choose a time zero for patients in external control arms. Pharm Stat. 2021;20:783–92.

24. Nicolas Girard, Lyudmila Bazhenova, Anna Minchom, et al. Comparative clinical outcomes for patients with NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. In: Presented at the IASLC 2020 World Conference on Lung Cancer. 2021.

25. Remon J, Hendriks LEL, Cardona AF et al. EGFR exon 20 insertions in advanced non-small cell lung cancer: a new history begins. Cancer Treat Rev. 2020;90:102105.

26. Choudhury NJ, Schoenfeld AJ, Flynn J, et al. Response to standard therapies and comprehensive genomic analysis for patients with lung adenocarcinoma with EGFR exon 20 insertions. Clin Cancer Res. 2021;27:2920–7.

27. Vasconcelos P, Gergis C, Viray H et al. EGFR-A763_Y764insFQEA is a unique exon 20 insertion mutation that displays sensitivity to approved and in-development lung cancer EGFR tyrosine kinase inhibitors. JTO Clin Res Rep. 2020;1(3):100051.

28. Coleman N, Woolf D, Welsh L, et al. EGFR exon 20 insertion (A763_Y764insFQEA) mutant NSCLC is not identified by Roche Cobas version 2 tissue testing but has durable intracranial and extracranial response to osimertinib. J Thorac Oncol. 2020;15:e162–5.

29. Gergis C, Rangachari D, Fujii M, et al. EGFR-A763_Y764insFQEA: a unique exon 20 insertion mutation that displays sensitivity to all classes of approved lung cancer EGFR tyrosine kinase inhibitors. J Clin Oncol. 2019;37:e20593–e20593.

30. Minchom A, Viteri S, Bazhenova L et al. Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy. Lung Cancer. 2022;168:74–82.

31. Mountzios G, Planchard D, Metro G et al. Molecular epidemiology and treatment patterns of patients with EGFR exon 20-mutant NSCLC in the precision oncology era: the European EXOTIC registry. JTO Clin Res Rep. 2022:100433. https://doi.org/10.1016/j.jtocrr.2022.100433