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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

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ABSTRACT

Background: In the single-arm CHRYSALIS study, amivantamab showed durable responses and manageable safety in patients with advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 insertion mutations (ex20ins) who progressed on prior platinum-based chemotherapy. External controls can provide context for interpreting amivantamab efficacy.

Methods: External controls were selected from three US-based databases (ConcertAI, COTA, and Flatiron). Key inclusion criteria were diagnosis of EGFR ex20ins advanced NSCLC, prior platinum-based chemotherapy, and performance status score ≤ 1. Duplicate external controls were identified using a tokenization procedure and removed, and adjustment for differences in baseline characteristics between amivantamab-treated and external control cohorts was achieved using propensity score weighting.

Results: Amivantamab-treated and pooled external control cohorts included 81 and 125 patients, respectively. Baseline characteristics were generally similar across cohorts, except more amivantamab-treated patients were Asian (56% vs 13%). Most common therapies received by external controls were non-platinum-based chemotherapy (25.1%), immuno-oncology therapies (24.2%), EGFR tyrosine kinase inhibitors (16.3%), and platinum-based chemotherapy (16.3%). Overall response rate was 40% among amivantamab-treated patients and 16% among external controls. Amivantamab-treated patients had longer progression-free survival (median 8.3 vs 2.9 months; hazard ratio [HR; 95% CI]: 0.47 [0.34–0.65]), time to next therapy (median 14.8 vs 4.8 months; HR [95% CI]: 0.40 [0.28–0.57]), and overall survival (median 22.8 vs 12.8 months; HR [95% CI]: 0.49 [0.31–0.77]) than external controls. Results were consistent in sensitivity analyses comparing each external control dataset against the amivantamab-treated group separately.

Conclusion: Among post-platinum patients with EGFR ex20ins advanced NSCLC, those treated with amivantamab had improved outcomes, including 10-month longer overall survival, versus external controls.

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1. Introduction

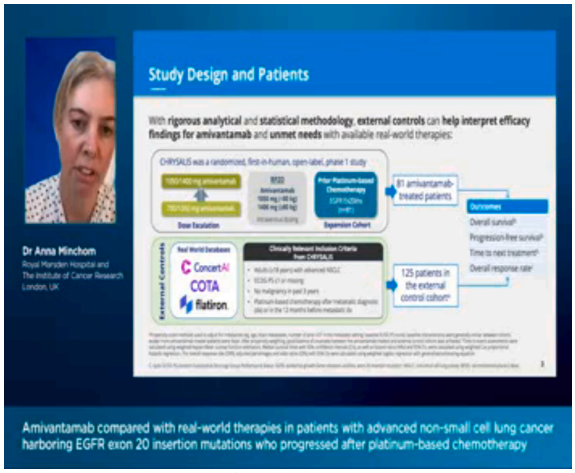
Activating epidermal growth factor receptor (EGFR) mutations are some of the most common mutations in non-small cell lung cancer (NSCLC) and represent targetable oncogenic driver events. EGFR exon 20 insertion mutations (ex20ins) are the third most common EGFR mutations after the common mutations, exon 19 deletions and the exon 21 point mutation L858R.[1] While patients with NSCLC harboring common EGFR mutations respond well to approved EGFR tyrosine kinase inhibitors (TKIs),[2–4] patients with EGFR ex20ins NSCLC are generally refractory to these agents[1,5–11] owing to altered conformation at the kinase active site, which restricts TKI binding.[2,6,11] Standard first-line treatment for EGFR ex20ins NSCLC is platinum-based chemotherapy,[12–15] but prognosis remains poor.[2,7,16,17] A high unmet need exists for safe and effective treatments for patients with advanced NSCLC harboring EGFR ex20ins because all patients will eventually progress after platinum-based chemotherapy.[18,19]

Amivantamab (RYBREVANT™ injection for intravenous use; Janssen Biotech, Inc.) was the first treatment approved by the Food and Drug Administration (FDA) for patients with advanced NSCLC harboring EGFR ex20ins whose disease has progressed on or after platinum-based chemotherapy.[20] Amivantamab is a fully human, bispecific EGFR-directed and MET receptor-directed antibody that targets activating and resistance EGFR mutations, as well as MET mutations and amplifications.[19,21–23] Amivantamab is hypothesized to not be affected by mutations that affect affinity in the EGFR TKI binding pocket because it binds to the extracellular domains of EGFR and MET.[19] As a result, amivantamab is able to overcome the inherent resistance of EGFR ex20ins NSCLC to targeted therapies. Once bound to its target, the antitumor activity of amivantamab includes inducing trogocytosis from macrophages, eliciting antibody-dependent cellular cytotoxicity from natural killer cells, and causing receptor-antibody complex endocytosis and removal via lysosomal trafficking.[19,22–24]

In CHRYSALIS (NCT02609776)—a first-in-human, open-label, dose-escalation, phase 1 study—the safety, pharmacokinetics, and efficacy of amivantamab is being evaluated in adults with advanced NSCLC as monotherapy and in combination with the EGFR TKI lazertinib, as well as with chemotherapy.[25–28] An expansion cohort in CHRYSALIS included patients with EGFR ex20ins advanced NSCLC who received amivantamab at the recommended phase 2 dose (RP2D; 1050 mg, $<$ 80 kg; 1400 mg, $\geq$ 80 kg). Among 81 patients who experienced disease progression after platinum-based chemotherapy, amivantamab showed durable responses and manageable safety.[28] Confirmed overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 40% with a median duration of response (DOR) of 11.1 months; median progression-free survival (PFS) was 8.3 months; and median overall survival (OS) was 22.8 months.

Because CHRYSALIS is a non-randomized, single-arm study, external controls can add valuable context in interpreting efficacy findings for amivantamab and appreciating unmet needs with available real-world therapies. We conducted a protocol-driven, treatment comparison of amivantamab and real-world therapies in patients with advanced NSCLC harboring EGFR ex20ins in whom platinum-based chemotherapy failed using data from the subset of patients from CHRYSALIS and external controls from three US-based, real-world data sources.

To view a summary of the study presented by Dr Anna Minchom please follow the link found in the supplementary material.



Video Summary.

2. Methods

The primary objective of this study was to evaluate the effectiveness of amivantamab versus physicians' choice of anticancer treatment in real-world settings among patients with advanced NSCLC harboring EGFR ex20ins in whom platinum-based chemotherapy failed. A secondary objective was to describe real-world treatment patterns for these patients.

2.1. Patients

The CHRYSALIS (amivantamab-treated) cohort included a subset of patients from CHRYSALIS (n = 81) who were $\geq$ 18 years old with EGFR ex20ins advanced NSCLC, disease progression on or after platinum-based chemotherapy (receipt of adjuvant platinum-based chemotherapy must have been $\leq$ 12 months from metastatic diagnosis to be included), Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of $\leq$ 1, no prior treatment with a TKI with known activity against EGFR ex20ins NSCLC, and no other malignancy within three years of screening, as well as adequate organ and bone marrow function; no uncontrolled comorbidity or comorbid leptomeningeal disease, HIV, hepatitis B or C, and/or interstitial lung disease; no untreated brain metastases; and no clinically significant cardiovascular disease. The CHRYSALIS study was approved by an Independent Ethics Committee and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients provided written informed consent.

The external control cohort comprised patients in real-world data sources who met clinically relevant eligibility criteria for CHRYSALIS (Table 1), including age $\geq$ 18 years at advanced NSCLC diagnosis, an ECOG PS score $\leq$ 1, no other malignancy within the prior three years (with exceptions consistent with those in CHRYSALIS), and evidence of prior exposure to platinum-based chemotherapy after metastatic NSCLC diagnosis or in the 12 months before metastatic NSCLC diagnosis. Lines(s) of therapy (LOT) from external controls with missing ECOG PS scores were excluded in the primary (pooled) analyses but were included in some of the sensitivity analyses.

2.2. Real-world data sources

Custom-curated, real-world data abstracting clinically relevant measures (eg, brain metastases, real-world tumor response, and real-world PFS [rwPFS]) from 2011 to 2020 were obtained from three de-identified, retrospective databases (ConcertAI [ConcertAI], COTA [COTA Healthcare], and Flatiron [Flatiron Health Inc.]) that included patients in the United States with NSCLC and confirmed EGFR ex20ins (Supplementary Table 1). The ConcertAI and Flatiron Health Spotlight datasets each contained aggregate data for patients with EGFR ex20ins advanced NSCLC from US cancer clinics, primarily in the community oncology setting. The datasets included electronic health record (EHR) data derived from structured fields, and data abstracted from physicians' notes and other documents (eg, biomarker reports). The COTA dataset contained data for patients with confirmed EGFR ex20ins NSCLC from five US healthcare sites (79% academic medical centers; 21% community oncology setting).

2.3. Efficacy assessments

Efficacy endpoints were ORR, PFS, time to next treatment (TTNT), and OS. Because follow-up and surveillance for events are different in clinical trials than in real-world settings, endpoints for the external control cohort were defined as rwORR, rwPFS, rwTTNT, and rwOS.

For the amivantamab-treated cohort, ORR was defined as the percentage of patients who achieved a confirmed best overall response of complete response (CR) or partial response (PR) based on RECIST v1.1 criteria and was determined by blinded independent central review. rwORR was based on human abstraction of physician evaluation of tumor scans in the EHR, not on RECIST criteria, and confirmation of response was required. A confirmed best real-world overall response of CR or PR in a particular line setting required a scan associated with a physician-noted CR or PR during that LOT, as well as a subsequent scan during the same line setting associated with a physician notation of stable disease (SD), PR, or CR without an intervening scan associated with a physician-noted response of progressive disease (PD). If the intervening scan was missing, the next non-missing scan was used. To avoid underestimation of rwORR, LOT without available responses were removed from the analyses.

For the amivantamab-treated cohort, PFS was defined as the interval between the index date (date of first amivantamab dose) and the date of PD (based on RECIST v1.1) or death, whichever occurred first. Patients with no post-baseline assessments were censored on the index date. rwPFS was based on human abstraction of physician evaluation of tumor progression, not on RECIST criteria (PD within 14 days of the index date was not included). Amivantamab-treated patients and external controls who started a subsequent anticancer therapy in the absence of PD were censored on the date of the last disease assessment before the start of subsequent therapy and at the start of subsequent therapy, respectively. TTNT, censored at loss to follow-up, was compared to rwTTNT in the real-world data sources. Death was treated as an event for purposes of calculating TTNT.

OS was defined as the interval between the index date and the date of death for the amivantamab-treated cohort. For patients who were alive, or for whom vital status was unknown, OS was censored on the date the patient was last known to be alive. rwOS was based on information in the EHR and external sources (eg, social security records and obituaries), and was censored on the last-known-alive date.

Because CHRYSALIS included patients at any time after receipt of platinum-based chemotherapy, an approach recommended by Hernan et al.[29,30] was used to identify suitable external controls. This approach accepts all qualifying LOT; therefore, a given external control could have been included in the analysis multiple times, once each time they qualified based on inclusion criteria. The index date was considered the start of each LOT. Appropriate adjustments[31] were made for correlated data within patients.

2.4. Analyses

Analyses were conducted using individual, patient-level data. The amivantamab-treated efficacy dataset included patients from CHRYSALIS with EGFR ex20ins advanced NSCLC who received prior platinum-based chemotherapy, received the RP2D of amivantamab on or before February 5, 2020, and had $\geq$ 2 post-baseline disease efficacy assessments, or discontinued treatment for any reason, or had PD or death before the second post-baseline disease assessment. The external control efficacy dataset included patients in the real-world data sources who satisfied key inclusion-exclusion criteria for the CHRYSALIS study.

Propensity score weighting (average treatment effects on the treated) [32] was used to weight external controls in each real-world dataset to the distribution of baseline covariates in CHRYSALIS (eg, age, brain metastases, number of prior LOT in the metastatic setting, and [in pooled analyses] baseline ECOG PS score). Standardized mean differences (SMDs) between external controls and amivantamab-treated patients were plotted on a love plot before and after baseline covariate adjustment. An absolute SMD of $<$ 10% after adjustment for each baseline covariate in the propensity score model was considered to indicate good balance.[33]

Treatment effects were compared between amivantamab-treated patients and external controls, separately as individual datasets and as a pooled dataset after de-duplication. De-duplication using a tokenization procedure allowed for Health Insurance Portability and Accountability Act of 1996-compliant identification of duplicate patients across the three real-world datasets. Patients in the Flatiron database were

Table 1
Real-world Data Source Disposition After Applying Key CHRYSALIS Inclusion Criteria and After De-duplication.

		Pooled		ConcertAI		COTA		Flatiron	
		n	Reduction	n	Reduction	n	Reduction	n	Reduction
Key CHRYSALIS criteria	Received from vendor	391	–	99	–	92	–	200	–
	Advancved NSCLC and EGFR ex20ins	371	5.1%	96	3.0%	75	18.5%	200	0.0%
	$\geq$ 18 years at advanced NSCLC diagnosis	371	0.0%	96	0.0%	75	0.0%	200	0.0%
	Platinum-based chemotherapy after metastatic diagnosis or in 12 months prior	282	24%	75	21.9%	63	16.0%	144	28.0%
	$\geq$ 1 LOT after platinum-based chemotherapy	193	31.6%	54	28.0%	42	33.3%	97	32.6%
	ECOG PS score of 0 or 1 (or missing) at start of qualifying therapy	180	6.7%	50	7.4%	42	0.0%	88	9.3%
	No record of other malignancy in 3 years before start of qualifying therapy	174	3.3%	48	4.0%	42	0.0%	84	4.5%
	After de-duplication	125[a]	28.2%	35	27.1%	39	7.1%	84	0.0%

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion mutations; LOT, line(s) of therapy; NSCLC, non-small cell lung cancer

[a] Excludes LOT from patients with missing ECOG PS scores.

removed from ConcertAI and COTA databases, and patients in the ConcertAI database were removed from the COTA database. LOT from patients with missing ECOG PS scores were excluded in analyses of real-world pooled data. Study power was not formally assessed because sample sizes were fixed according to the number of patients in the amivantamab-treated and external control cohorts meeting key inclusion criteria.

External controls who qualified for inclusion and had ≥ 1 LOT after platinum-based chemotherapy were included in analyses once for each qualifying LOT. Appropriate adjustments were made to confidence intervals (CIs) to account for correlation of outcomes within patients using the grouped jackknife for time-to-event outcomes[31] and generalized estimating equations for binary outcomes.[34]

For ORR, adjusted percentages and odds ratios (ORs) with 95% CIs were calculated using weighted logistic regression with generalized estimating equations. The robust variance estimator was used to account for average treatment effects on the treated and overlapping weights. Time-to-event assessments (OS, PFS, and TTNT) were calculated using weighted Kaplan-Meier survival function estimation. Median survival times with 95% CIs, as well as hazard ratios (HRs) and 95% CIs, were calculated using weighted Cox proportional hazards regression. Left truncation adjustment was applied for OS analyses to account for bias arising from the inclusion of LOT starting before EGFR ex20ins results were available.[35] The database cut-off for the amivantamab group was October 8, 2020. However, to allow more time for OS maturity, the OS analysis was refreshed using an April 19, 2021 snapshot.

2.5. Sensitivity analyses

Sensitivity analyses were conducted to evaluate the impact of certain criteria and analytic methods on differences in outcomes (ORR, PFS, TTNT, and OS) between groups. Analyses were conducted (1) with and without LOT from patients with missing ECOG PS scores; (2) only including external controls in their second LOT (if that was a qualifying LOT)—to be conservative, where external controls had the longest possible survival, and external controls were each included only once in the analyses; (3) for OS, stratified by the number of prior LOT in the metastatic setting; (4) including only LOT from external controls who started ≥ 30 days before EGFR ex20ins results were first available, and no left truncation adjustment was applied—this landmark analysis strategy is robust against violations of the assumption required for the left truncation adjustment (ie, the "independent delayed entry" assumption that survival does not depend on when a patient is sequenced); and (5) for PFS and OS, taking timing of treatment (received on or before December 31, 2015 vs on or after January 1, 2016) of external controls into consideration given treatment options changed during the 10-year, real-world data collection period.

Table 2
Baseline Demographics and Clinical Characteristics (All Qualifying LOT for Each Patient [Without Weighting]).

	CHRYSALIS n = 81 81 LOT	Real-world pooled dataset[a] n = 125 227 LOT	ConcertAI n = 48 102 LOT	COTA n = 42 98 LOT	Flatiron n = 84 168 LOT
Age, median [min; max]	62.0 [42.0;84.0]	62.0 [31.0;84.0]	61.5 [36.0;84.0]	61.0 [31.0;78.0]	65.0 [40.0;82.0]
Sex, n (%)					
Female	48 (59.3)	137 (60.4)	64 (62.7)	59 (60.2)	90 (53.6)
Male	33 (40.7)	90 (39.6)	38 (37.3)	39 (39.8)	78 (46.4)
Race, n (%)					
Asian	40 (55.6)	27 (13.0)	0 (0.0)	7 (7.5)	20 (12.8)
Black or African American	2 (2.8)	11 (5.3)	11 (12.2)	8 (8.5)	5 (3.2)
White	30 (41.7)	140 (67.3)	62 (68.9)	75 (79.8)	100 (64.1)
Other	0 (0.0)	30 (14.4)	17 (18.9)	4 (4.26)	31 (19.9)
Missing	9 (11.1)	19 (8.4)	12 (11.8)	4 (4.1)	40 (23.8)
Smoking history, n (%)					
No	43 (53.1)	133 (58.8)	62 (62.0)	53 (54.1)	89 (53.0)
Yes	38 (46.9)	93 (41.2)	38 (38.0)	45 (45.9)	79 (47.0)
Missing	0 (0.00)	1 (0.44)	2 (1.96)	0 (0.0)	0 (0.0)
ECOG PS score, n (%)					
0	26 (32.1)	69 (30.4)	35 (43.2)	6 (7.9)	35 (33.3)
1	54 (66.7)	158 (69.6)	46 (56.8)	70 (92.1)	70 (66.7)
2[b]	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	21 (20.6)	22 (22.4)	63 (37.5)
Brain metastasis at baseline, n (%)					
No	63 (77.8)	137 (60.4)	64 (62.7)	57 (58.2)	108 (64.3)
Yes	18 (22.2)	90 (39.6)	38 (37.3)	41 (41.8)	60 (35.7)
Prior lines in metastatic setting,[c] n (%)					
0–1	29 (35.8)	100 (44.1)	47 (46.1)	38 (38.8)	77 (45.8)
2	23 (28.4)	63 (27.8)	25 (24.5)	32 (32.7)	42 (25.0)
3+	29 (35.8)	64 (28.2)	30 (29.4)	28 (28.6)	49 (29.2)
Time from advanced diagnosis to LOT (months), median [min; max]	14.1 [0.66;116]	14.8 [0.23;85.6]	13.5 [0.10;55.2]	15.3 [0.69;85.6]	14.6 [0.39;54.5]

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LOT, line(s) of therapy
[a] After de-duplication and exclusion of patient LOT with missing ECOG PS scores.
[b] One enrolled patient was reclassified as having an ECOG PS score 2 rather than 1.
[c] Does not include neo-adjuvant/adjuvant platinum-based chemotherapy (or any other therapy) before date of metastatic non-small cell lung cancer diagnosis.

2.6. Real-world treatment patterns

Treatments received in real-world settings were categorized as non-platinum chemotherapies (eg, paclitaxel, docetaxel, gemcitabine, pemetrexed, vinorelbine, and mitomycin); immuno-oncology (IO) therapies (eg, nivolumab, pembrolizumab, atezolizumab, durvalumab) with or without vascular endothelial growth factor inhibitors (VEGFi); platinum-containing regimens, which included platinum alone, platinum and a TKI, platinum and an IO therapy, platinum and an IO therapy and a VEGFi, and platinum and a VEGFi; TKI (eg, afatinib, gefitinib, erlotinib and osimertinib) with or without VEGFi; VEGFi alone; and other (clinical study drugs, anaplastic lymphoma kinase [ALK] inhibitors, multi-kinase inhibitors, anti-EGFR monoclonal antibodies, mammalian target of rapamycin (mTOR) inhibitors, and estrogen modulators). Analyses were conducted after de-duplication and exclusion of LOT from patients with missing ECOG PS scores.

3. Results

3.1. Patients

The amivantamab-treated efficacy analysis set included 81 patients treated with amivantamab at the RP2D (81 LOT; Table 2). The external control efficacy analysis set included 174 patients (368 LOT): 48 from ConcertAI (102 LOT), 42 from COTA (98 LOT), and 84 from Flatiron (168 LOT). The external control pooled analysis set, after de-duplication and exclusion of patient LOT with missing ECOG PS scores, included 125 unique patients (227 LOT; Table 1).

Before propensity weighting, baseline characteristics were generally comparable across datasets, except for more patients of Asian descent in the amivantamab-treated cohort (55.6%) than among the external control cohorts (pooled dataset: 13.0%; Table 2). Among amivantamab-treated and pooled external control cohorts, median age was 62 years (range: 42–84 and 31–84 years, respectively), approximately 60% of patients in each cohort were female, and less than half were smokers (46.9% and 41.2%, respectively). Most patients had an ECOG PS score of ≤ 1 (98.8% and 100.0%, respectively) and had adenocarcinoma histology (95.1% and 96.0%, respectively). Fewer amivantamab-treated patients than external controls had brain metastases at baseline (22.2% vs 39.6%, respectively), as expected given the inclusion criteria in

Table 3
Real-world Treatment Patterns for EGFR ex20ins Advanced NSCLC by LOT After Platinum-based Chemotherapy (Real-world Pooled Dataset).

	After platinum-based chemotherapy		
	Line 1	Line 2	Line ≥ 3
Unique patients, n[a]	125	53	27
Lines of therapy	125	53	49[f]
Real-world treatments, n (%)			
IO	36 (28.8)	12 (22.6)	7 (14.3)
Platinum-containing regimen[b,c]	23 (18.4)	9 (17.0)	5 (10.2)
TKI	21 (16.8)	8 (15.1)	8 (16.3)
Non-platinum chemo[d]	19 (15.2)	17 (32.1)	21 (42.9)
Others[e]	15 (12.0)	1 (1.9)	5 (10.2)
VEGFi alone	11 (8.8)	6 (11.3)	3 (6.1)

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ex20ins, exon 20 insertion mutations; IO, immuno-oncology; LOT, line(s) of therapy; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor

[a] After de-duplication and exclusion of patient LOT with missing ECOG PS scores.

[b] Includes platinum alone, platinum plus TKI, platinum plus IO, platinum plus IO plus VEGFi plus platinum plus VEGFi.

[c] Reflects either re-treatment of a patient with platinum after an intervening LOT or a combination of platinum with a different agent(s) that triggered a LOT change.

[d] Includes paclitaxel, docetaxel, gemcitabine, pemetrexed, vinorelbine, etoposide, and mitomycin.

[e] Includes clinical study drugs, ALK inhibitors, multi-kinase inhibitors, anti-EGFR monoclonal antibodies, mTOR inhibitors, and estrogen modulators.

[f] Includes unique patients who received multiple LOT.

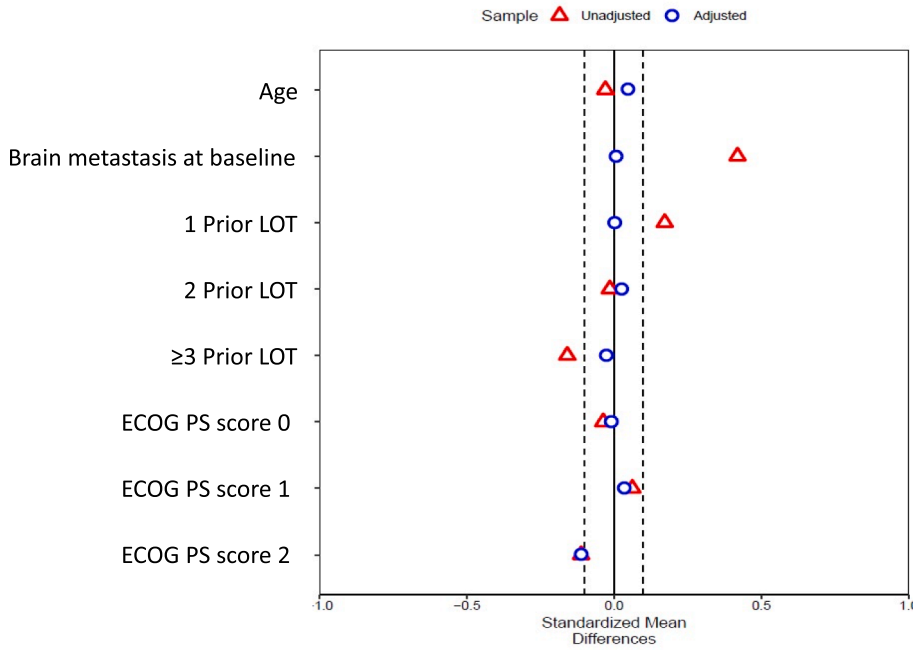


Fig. 1. Love plot displaying baseline covariate balance before and after adjustment (external controls [pooled dataset] vs amivantamab-treated patients). A good balance was considered an absolute standardized mean difference of < 10% after adjustment for each baseline covariate included in the propensity score model.[33] ECOG PS, Eastern Cooperative Oncology Group Performance Status; LOT, line(s) of therapy.

CHRYSALIS. Compared to first qualifying LOT for external controls, more amivantamab-treated patients had ≥ 2 prior LOT in the metastatic setting (55.9% vs 64.2%, respectively), and the median time from advanced diagnosis to treatment was 14.1 [0.66;116] for amivantamab-treated patients versus 14.8 [0.23;85.6] for external controls.

After propensity weighting, good balance of covariates between the amivantamab-treated and external control cohorts was achieved. For example, absolute SMDs of < 10% were achieved for external controls (pooled dataset) versus amivantamab-treated patients after adjustment for each baseline covariate included in the model (Fig. 1).

3.2. Real-world therapies

Most common therapies received by external controls across their qualifying LOT in the post-platinum setting were non-platinum-based chemotherapy (25.1%), IO therapies with or without VEGFi (24.2%), platinum-containing regimens (16.3%), and TKIs with or without VEGFi (16.3%). Most common therapies received by ECs in their first LOT after platinum-based chemotherapy were IO therapies with or without VEGFi (28.8%), platinum-containing regimens (18.4%), and TKIs with or without VEGFi (16.8%; Table 3).

3.3. Treatment outcomes

Confirmed ORR was 40% (95% CI: 29.5%, 50.5%) among amivantamab-treated patients and 16% (95% CI: 11.2%, 22.0%) for the external control pooled dataset (OR [95% CI]: 3.47 [1.90, 6.33]). ORRs were 13% (95% CI: 6.4%, 25.1%; OR: 4.32 [1.73, 10.77]) for external controls in ConcertAI, 18% (95% CI: 11.1%, 27.6%; OR: 3.00 [1.46, 6.13]) in COTA, and 15% (95% CI: 10.3%, 21.8%; OR: 3.64 [1.94, 6.83]) in Flatiron (Supplementary Fig. 1).

Amivantamab-treated patients had longer PFS (HR [95% CI]: 0.47 [0.34, 0.65]; median: 8.3 vs 2.9 months) and longer TTNT (HR [95% CI]: 0.40 [0.28, 0.57]; median: 14.8 vs 4.8 months) than external controls (pooled dataset; Fig. 2A and B). Furthermore, amivantamab-treated patients had longer OS (HR [95% CI]: 0.49 [0.31, 0.77]; median: 22.8 vs 12.8 months [data cut-off April 19, 2021]) than external controls (pooled dataset; Fig. 2C). Findings for each outcome were consistent across real-world datasets (Supplementary Fig. 2).

Results of sensitivity analyses for ORR, PFS, TTNT, and OS were consistent with those from the main analyses (Supplementary Figs. 3–7).

4. Discussion

With standard treatment options, patients with advanced NSCLC harboring EGFR ex20ins have poor prognoses, with a median OS of approximately 16 months.[14,36] The standard of care for these patients is platinum-based chemotherapy; however, all patients will eventually experience disease progression, with limited treatment options in subsequent LOT.[2,7,11,36] In a real-world analysis, median OS was 12.5 months and median PFS was 3.5 months in the relapsed setting, [37] emphasizing the high unmet need associated with EGFR ex20ins advanced NSCLC.

Amivantamab, the first treatment approved by the FDA for patients with advanced NSCLC harboring EGFR ex20ins whose disease progressed on or after platinum-based chemotherapy,[20] is a new targeted therapy in the treatment armamentarium for these patients. In this protocol-driven analysis using three US-based, real-world datasets, treatment outcomes of amivantamab were compared with those of real-world therapies among patients with EGFR ex20ins advanced NSCLC in whom platinum-based chemotherapy failed. Demographics and baseline characteristics of amivantamab- and real world-treated patients were well balanced across datasets and consistent with known traits of patients with advanced NSCLC harboring EGFR ex20ins; most patients had tumors of adenocarcinoma histology and with overrepresentation of females and non-smokers relative to the broader advanced NSCLC population.[1,6] Of note, however, Asian patients were more prevalent in the amivantamab-treated cohort than in the US-based, real-world datasets because CHRYSALIS initiated in Korea before expanding to the United States and other countries.[28] Still, the efficacy of chemotherapy or immune checkpoint inhibitors has never been reported as being different across ethnicities. Clinical outcomes were better with amivantamab than with real-world therapies in patients with EGFR ex20ins advanced NSCLC post platinum-based chemotherapy. Amivantamab-treated patients had a 10-month longer median OS (median: 22.8 vs 12.8 months [data cut-off April 19, 2021]), as well as improved PFS (median 8.3 vs 2.9 months), TTNT (median 14.8 vs 4.8 months), and ORR (median 40% vs 16%). The poor performance of the external controls substantiates the ineffectiveness of currently available real-world treatments and highlights the potential treatment advantage with amivantamab in this patient population.

In the present study, the real-world treatment pattern of patients with advanced NSCLC harboring EGFR ex20ins confirms the limited options after failure of platinum-based chemotherapy, with no clear standard in the post-platinum setting.[14] After progression on platinum-based chemotherapy, most commonly used first LOT were IO therapies (28.8%), followed by platinum-based chemotherapy (18.4%) and TKIs (16.8%), despite established poor response rates to immune checkpoint inhibitors and EGFR TKIs among patients with EGFR ex20ins NSCLC.[38] As the external controls used in this study comprised patients from three independent real-world datasets, the findings corroborate and strengthen prior reports on the lack of and ineffectiveness of real-world treatments using just the Flatiron database.[14,37] Meanwhile, findings from the external control cohort show that patients with EGFR ex20ins may actually receive multiple lines of therapy, highlighting the need to optimize treatment sequences.

The trajectory of treatment options for patients with EGFR ex20ins NSCLC who progressed on or after platinum-based chemotherapy likely will change as the FDA-approved therapies such as amivantamab and mobocertinib become more widely prescribed in real-world clinical practice. Availability of these therapies and potentially other investigational treatments, such as the EGFR ex20ins-specific TKIs TAS6417/CLN-081 and DZD9008, may lead to modifications in treatment sequencing protocols and improvements in clinical outcomes.

A strength of this protocol-driven study was comparison of individual, patient-level data from three disease-specific, real-world data sources with clinical trial data. The real-world datasets were curated to provide additional key prognostic information (eg, brain metastases, progression events) and outcomes that are not typically available in off-the-shelf datasets. Another strength of the study was the conduct of sensitivity analyses to substantiate the robustness of the results. Consistency of results across the three real-world datasets, among the four efficacy outcomes, and across sensitivity analyses raises confidence in the robustness of our findings.

Limitations of this study include the potential that real-world data sets lacked consistency in assessments such as physician assessment of performance status and physician assessment of radiological response in comparison to protocol-driven trial assessments, including RECIST radiological assessment. In addition, comparisons were between amivantamab treatment in a clinical trial setting and a range of therapies selected by physicians in real-world practice based on patient characteristics. Supportive care in real-world settings was also likely different from that received by clinical trial patients. Further, findings from prior studies indicate that patients in clinical trials may be healthier than the general population.[39,40] Finally, formal statistical comparisons across cohorts were not carried out because this was not a randomized study; thus, the potential for unmeasured confounding cannot be ruled out.

In conclusion, patients with advanced NSCLC harboring EGFR ex20ins whose disease progressed on or after platinum-based chemotherapy have poor prognoses and are in need of more effective therapies. Amivantamab improved ORR, OS, PFS, and TTNT compared to real-

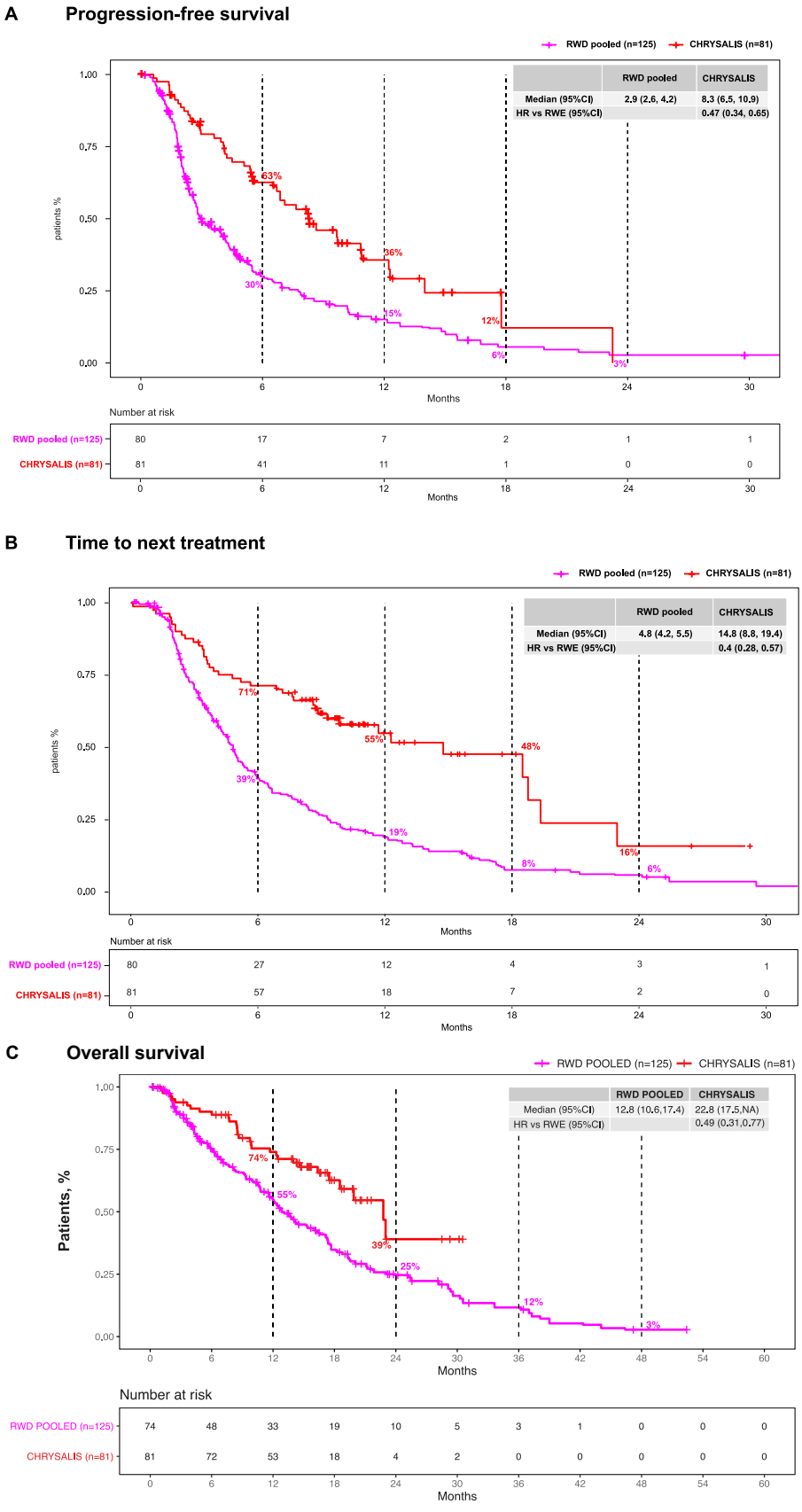


Fig. 2. Kaplan-Meier Curves (after weighting) for amivantamab-treated patients (CHRYSALIS) and external controls* (pooled dataset). *(A)* Progression-free survival, *(B)* Time to next treatment, and *(C)* Overall survival.[†] *Excludes LOT from patients with missing ECOG PS scores. [†]Left truncation adjustment was applied to account for bias arising from inclusion of patients whose EGFR ex20ins results were only available after the start of a qualifying LOT. Data cut-off was October 8, 2020 for analyses of progression-free survival and time to next treatment and April 19, 2021 for analysis of overall survival. CI, confidence interval; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion mutations; HR, hazard ratio; LOT, line(s) of therapy; RWD, real-world data; RWE, real-world evidence.

world therapies.

Data sharing statement

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 real-world data 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).

CRediT authorship contribution statement

Anna Minchom: Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Santiago Viteri:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Lyudmila Bazhenova:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Shirish M. Gadgeel:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Sai-Hong Ignatius Ou:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **José Trigo:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Joshua M. Bauml:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Daniel Backenroth:** Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Archan Bhattacharya:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Tracy Li:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Parthiv Mahadevia:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Nicolas Girard:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing.

Declaration of Competing Interest

Anna Minchom reports a consulting/advisory role for Janssen Oncology; travel, accommodations, and expenses for Amgen; honoraria for Faron Pharmaceuticals, Bayer, Novartis Pharmaceuticals UK Ltd., Merck, and Chugai Pharma.

Santiago Viteri reports a consulting/advisory role for Roche, Bristol-Myers Squibb, and Janssen; Speakers' Bureau for Roche, Bristol-Myers Squibb, and AstraZeneca; and travel, accommodations, and expenses for MSD.

Lyudmila Bazhenova reports a consulting/advisory role for AstraZeneca, Genentech/Roche, Takeda, Blueprint Medicines, BeyondSpring Pharmaceuticals, G1 Therapeutics, Bayer, Boehringer Ingelheim, Novartis, Regeneron, Merck, Johnson & Johnson, BMS, Daiichi Sankyo, and neovogen; stock and other ownership interests for Epic Sciences; and research funding from BeyondSpring Pharmaceuticals.

Shirish M. Gadgeel reports a consulting/advisory role for Genentech/Roche, AstraZeneca, Bristol-Myers Squibb, Takeda, Xcovery, Boehringer Ingelheim, Novicure, Daiichi Sankyo, Novartis, Jazz Pharmaceuticals, Blueprint Medicines, Lilly, and Pfizer; travel, accommodations, and expenses for Genentech/Roche and Merck; honoraria for AstraZeneca, Merck, and Genentech/Roche; and research funding from Merck, Genentech/Roche, Blueprint Medicines, ARIAD/Takeda, Aeglea Biotherapeutics, Astellas Pharma, G1 Therapeutics, Lycera, Daiichi Sankyo, I-Mab, and Nektar.

Sai-Hong Ignatius Ou reports a consulting/advisory role for Pfizer, Genentech/Roche, AstraZeneca, Takeda, and TP Therapeutics; Speakers' Bureau for Genentech, AstraZeneca, and Takeda; stock and other ownership interests for Turning Point Therapeutics and Elevation Oncology; honoraria from Pfizer, Roche Pharma AG, Genentech/Roche, ARIAD/Takeda, AstraZeneca, Foundation Medicine, and Merck; and research funding from Pfizer, Roche Pharma AG, AstraZeneca/MedImmune, AstraZeneca, ARIAD, Ignyta, Astellas Pharma, Chugai Pharma, and Revolution Medicines.

José Trigo reports a consulting/advisory role for Takeda, Boehringer Ingelheim, Bristol-Myers Squibb, and Merck Serono; Speakers' Bureau for MSD Oncology, AstraZeneca, Merck Serono, and Roche; and travel, accommodations, expenses for MSD Oncology, Bristol-Myers Squibb, and AstraZeneca.

Joshua M. Bauml is a current employee of Johnson & Johnson/Janssen and reports previous consulting/advisory role for Bristol-Myers Squibb, Merck, AstraZeneca, Genentech, Celgene, Boehringer Ingelheim, Guardant health, Takeda, Novartis, Janssen, Ayala Pharmaceuticals, Regeneron, Inivata, Novartis, and Foundation Medicine; and research funding from Merck, Carevive Systems, Novartis, Incyte, Bayer, Janssen, AstraZeneca, Takeda, Amgen, Pfizer, and Mirati Therapeutics.

Nicolas Girard reports a consulting/advisory role for Roche, Lilly, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Bristol-Myers Squibb, MSD, Takeda, GlaxoSmithKline, AbbVie, PharmaMar, Janssen, and Sanofi; travel, accommodations, expenses for Roche, AstraZeneca, Bristol-Myers Squibb, MSD Oncology; research funding from Roche, AstraZeneca, Boehringer Ingelheim; and that a family member is an employee of AstraZeneca.

Daniel Backenroth, Archan Bhattacharya, Tracy Li, Parthiv Mahadevia, are employees of Johnson & Johnson/Janssen and report stock or ownership interests for Johnson & Johnson.

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Appendix A. Supplementary data

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