Amivantamab Versus Real-World Clinical Practice in Europe and the US for Patients with Advanced Non-Small Cell Lung Cancer with Activating Epidermal Growth Factor Receptor Exon 20 Insertion Mutations

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INTRODUCTION

- Patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion (Exon20ins) mutations have a poor prognosis and high unmet need for targeted therapies.[1,2]
- Amivantamab, an EGFR and MET bispecific antibody, has demonstrated efficacy and tolerability in these patients after prior platinum-based therapy in the phase 1/2 single-arm CHRYSALIS study (NCT02609776).[3]
- Based on these results, regulatory approval was granted by the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA), amongst others.[4–6]
- In the absence of a randomised controlled trial, comparative data are required to evaluate the relative effectiveness of amivantamab versus real-world clinical practice (RWCP) in patients with advanced EGFR-mutated NSCLC with Exon20ins mutations following platinum-based therapy.

OBJECTIVES

- To compare the efficacy of amivantamab, as assessed in the CHRYSALIS trial, with the effectiveness of RWCP from Europe and the US, in patients with advanced NSCLC with EGFR Exon20ins mutations following platinum-based therapy at second line or later (2L+).
- To provide a complementary analysis for previous analyses comparing amivantamab data from CHRYSALIS with US registry data,[7] and European chart review data.[8]

METHODS

- The amivantamab-treated patient cohort used in this analysis comprised patients with locally advanced or metastatic NSCLC with EGFR Exon20ins mutations who had progressed on or after prior platinum-based therapy (Cohort D+ from CHRYSALIS; 30 March 2021 data cut-off; N=114).
- Patients who fulfilled the main inclusion criteria from CHRYSALIS were identified from real-world data sources including European and US registries, and a pan-European chart review, to generate an external control arm for CHRYSALIS.
- Registry data were obtained from the **C**linical **R**esearch platform **I**nto molecular testing, treatment and outcome registry of non-**S**mall cell lung carcinoma **P**atients (**CRISP**; Germany; for patients treated 27 April 2017 to 30 June 2021), **N**etwork **G**enomic **M**edicine (**NGM**; Germany; 20 September 2013 to 08 July 2021), **E**pidemiological **S**trategy and **M**edical **E**conomics (**ESME**; France; 01 January 2015 to 12 July 2021), **P**ublic **H**ealth **E**ngland (**PHE** [now NHS Digital]; years 2016 and 2018), and Flatiron Health Spotlight, ConcertAI and COTA (US; 15 December 2009 to 16 October 2020).
- Chart review data were obtained from CATERPILLAR-RWE, a non-interventional, multicentre study conducted across England, France, Germany, Italy, the Netherlands, Portugal and Spain, for patients treated 01 January 2011 to 31 May 2021.
- Given the rarity of EGFR Exon20ins mutations, and to increase the sample size, all RWCP sources were pooled, and all eligible RWCP treatment lines within each individual patient were used.
- Overall response rate (ORR; RWCP-unadjusted N=260), overall survival (OS; N=456), progression-free survival (PFS; N=443) and time-to-next-treatment (TTNT; N=456) were compared between cohorts. Differences in patient numbers across endpoints are caused by non-availability of endpoints in some data sources.
  - Investigator (INV) and independent review committee (IRC) assessed ORR and PFS were available from CHRYSALIS. For RWCP, response and progression were INV assessed, in line with real-world treatment monitoring practices.
  - Adjustment of outcomes was conducted to address differences in patient and disease characteristics between cohorts, using both inverse probability weighting (IPW; average treatment effect among the treated [ATT]) and covariate adjustment.
  - Binary endpoints were analysed using logistic regression and time-to-event endpoints via proportional hazards regression, leading to the generation of relative risk ratios (RRs; binary) and hazard ratios (HRs; time-to-event).
- For the pooled cohort analyses, all common variables between CHRYSALIS and the real-world data sources with direct access to individual patient data (IPD; all except ESME) were included in the adjustment (prior lines of treatment, age, gender and presence of brain metastases).
  - For ESME, data were balanced versus CHRYSALIS independent of other data sources using all prognostic variables (prior lines of treatment, age, presence of brain metastases, presence of liver metastases and number of metastatic locations).

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RESULTS

- Pre-adjustment baseline characteristics are presented in Table 1. After adjustment, baseline characteristics were well-balanced between cohorts (average standardised mean difference: ≤0.25).
- Table 2 contains unadjusted and adjusted RRs, HRs and p values for the assessed endpoints (CHRYSALIS versus RWCP), with adjusted results summarised for both the IPW-ATT and covariate adjustment approaches.
  - The ORR (INV) estimated for amivantamab was 36.8% (95% CI: 28.5, 46.0) versus 17.2% (13.1, 22.2) for the ATT-adjusted RWCP cohort. The corresponding RR was 2.14 (1.50, 3.06), meaning that patients receiving amivantamab were more than twice as likely to achieve an overall response, compared with RWCP.
- Kaplan-Meier curves for OS, PFS (INV), PFS (IRC) and TTNT for CHRYSALIS versus the unadjusted and ATT-adjusted RWCP data are presented in Figure 1, alongside median values and HRs.
- Results were consistently, significantly superior for amivantamab versus RWCP across endpoints, methodologies and geographies.

TABLE 1: Observed baseline characteristics for CHRYSALIS and RWCP

Characteristic	CHRYSALIS (N=114)	RWCP (N=404)[a]	ATT-adjusted RWCP (N=404)[a]
Prior lines of treatment			
1	48 (42.1%)	179 (44.3%)	171 (42.3%)
2	34 (29.8%)	125 (30.9%)	121 (30.0%)
3	15 (13.2%)	64 (15.8%)	52 (13.0%)
4+	17 (14.9%)	36 (8.9%)	60 (14.8%)
Age			
≤55	30 (26.3%)	106 (26.2%)	103 (25.5%)
55 to ≤60	20 (17.5%)	66 (16.3%)	73 (18.1%)
>60	64 (56.1%)	232 (57.4%)	228 (56.4%)
Gender			
Male	44 (38.6%)	152 (37.6%)	156 (38.6%)
Female	70 (61.4%)	252 (62.4%)	248 (61.4%)
Presence of brain metastases			
No	85 (74.6%)	256 (63.4%)	301 (74.4%)
Yes	29 (25.4%)	139 (34.4%)	103 (25.6%)
Missing	0	9 (2.2%)	0

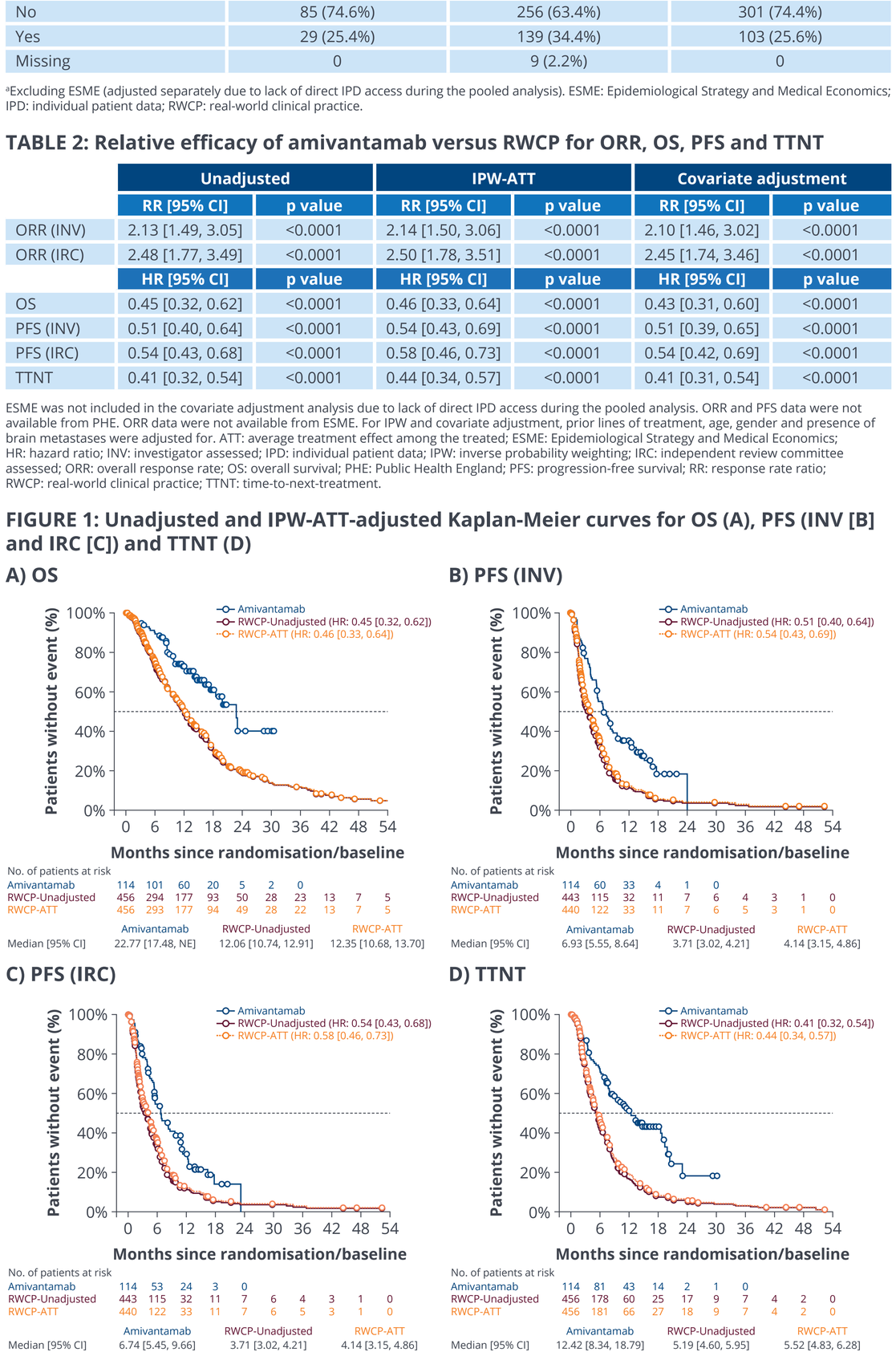
[a]Excluding ESME (adjusted separately due to lack of direct IPD access during the pooled analysis). ESME: Epidemiological Strategy and Medical Economics; IPD: individual patient data; RWCP: real-world clinical practice.

TABLE 2: Relative efficacy of amivantamab versus RWCP for ORR, OS, PFS and TTNT

	Unadjusted		IPW-ATT		Covariate adjustment	
	RR [95% CI]	p value	RR [95% CI]	p value	RR [95% CI]	p value
ORR (INV)	2.13 [1.49, 3.05]	<0.0001	2.14 [1.50, 3.06]	<0.0001	2.10 [1.46, 3.02]	<0.0001
ORR (IRC)	2.48 [1.77, 3.49]	<0.0001	2.50 [1.78, 3.51]	<0.0001	2.45 [1.74, 3.46]	<0.0001
	HR [95% CI]	p value	HR [95% CI]	p value	HR [95% CI]	p value
OS	0.45 [0.32, 0.62]	<0.0001	0.46 [0.33, 0.64]	<0.0001	0.43 [0.31, 0.60]	<0.0001
PFS (INV)	0.51 [0.40, 0.64]	<0.0001	0.54 [0.43, 0.69]	<0.0001	0.51 [0.39, 0.65]	<0.0001
PFS (IRC)	0.54 [0.43, 0.68]	<0.0001	0.58 [0.46, 0.73]	<0.0001	0.54 [0.42, 0.69]	<0.0001
TTNT	0.41 [0.32, 0.54]	<0.0001	0.44 [0.34, 0.57]	<0.0001	0.41 [0.31, 0.54]	<0.0001

ESME was not included in the covariate adjustment analysis due to lack of direct IPD access during the pooled analysis. ORR and PFS data were not available from PHE. ORR data were not available from ESME. For IPW and covariate adjustment, prior lines of treatment, age, gender and presence of brain metastases were adjusted for. ATT: average treatment effect among the treated; ESME: Epidemiological Strategy and Medical Economics; HR: hazard ratio; INV: investigator assessed; IPD: individual patient data; IPW: inverse probability weighting; IRC: independent review committee assessed; ORR: overall response rate; OS: overall survival; PHE: Public Health England; PFS: progression-free survival; RR: response rate ratio; RWCP: real-world clinical practice; TTNT: time-to-next-treatment.

FIGURE 1: Unadjusted and IPW-ATT-adjusted Kaplan-Meier curves for OS (A), PFS (INV [B] and IRC [C]) and TTNT (D)



Prior lines of treatment, age, gender and presence of brain metastases were adjusted for. ATT: average treatment effect among the treated; INV: investigator assessed; IPW: inverse probability weighting; IRC: independent review committee assessed; OS: overall survival; PFS: progression-free survival; RWCP: real-world clinical practice; SoC: standard of care; TTNT: time-to-next-treatment.

CONCLUSIONS

As demonstrated by the poor survival outcomes experienced by those receiving RWCP in this study, patients with advanced NSCLC with EGFR Exon20ins mutations have a high unmet need for more effective and tolerable targeted treatment options following progression on or after platinum-based therapy.

The presented adjusted comparisons consistently demonstrate a statistically significant clinical benefit across outcomes for amivantamab versus RWCP pooled from a range of US and European cohorts.

These analyses highlight the value of amivantamab for addressing the unmet need in patients with advanced NSCLC with EGFR Exon20ins mutations following platinum-based therapy and are aligned with previously published analyses of amivantamab versus RWCP from Europe and the US separately.[7,8]

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The datasets generated and analysed during the current study are available from the presenting 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. The ESME 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 analysed 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. These are data that have 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.

DISCLOSURES

CC: Consulting/advisory role for Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, GSK, Ipsen, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda; travel/accommodation expenses from AstraZeneca, BMS, Pfizer; research funding from AstraZeneca, Pfizer, Roche, Takeda. **NG:** Consulting/advisory role for AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, GSK, Janssen, Lilly, MSD, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Takeda; travel/accommodation expenses from AstraZeneca, BMS, MSD Oncology, Roche; research funding from AstraZeneca, Boehringer Ingelheim, Roche. **AK, CK:** No disclosures to declare. **MSc:** Speaker/advisory role for Amgen, Boehringer Ingelheim, Janssen, Novartis, Pfizer, Roche, Sanofi-Aventis, Siemens Healthineers, Takeda; research support (institutional) from Amgen, BMS, Dracen Pharmaceuticals, Janssen, Novartis, Takeda. **LB:** Employee of Unicancer. **JT:** Speaker/advisory role for AstraZeneca, BMS, Merck, Takeda; travel expenses from MSD; research funding (institutional) from BMS. **SV:** Consulting/advisory role for BMS, Janssen, Merck KGaA, Puma Biotechnology, Reddy Pharma Iberia, Roche, Sanofi, Takeda; speaker role for AstraZeneca Spain, BMS, MSD, Roche, Takeda; travel/accommodation expenses from Merck KGaA, MSD, OSE Immunotherapeutics, Roche. **MSe:** Honoraria from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Janssen Oncology, Lilly, MSD, Novartis, Pfizer/EMD Serono, Roche/Genentech, Sanofi, Takeda; consulting/advisory role for AstraZeneca, BMS, Boehringer Ingelheim, Janssen Oncology, Lilly, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Takeda; research funding (institutional) from AstraZeneca; travel/accommodation expenses from Pfizer, Takeda. **SP:** Consultancy/honoraria from Amgen, AstraZeneca, Bayer, BeiGene, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, EQRx, GSK, Guardant Health, Janssen, Lilly, Merck KGaA, MSD, Novartis, Pfizer, Roche, Sanofi, Seattle Genetics, Takeda and Turning Point Therapeutics; direct funding from Elsevier, Medscape, Touch Medical and VJ Oncology; research funding (institutional) from Amgen, AstraZeneca, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, GSK, Guardant Health, Janssen, Lilly, MSD, Roche, Takeda, Seattle Genetics, Trizel and Turning Point Therapeutics. **NR, RT, BR, JC, JD, CAS, NJP, JS, NE, JM, MNS, CMF, JP, IP, TL, PM, AA:** Employees of Janssen and shareholders of Johnson & Johnson. **CPL:** Employee of Janssen. **JW:** Honoraria from Abbvie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Chugai Pharma Europe, Daiichi Sankyo Europe GmbH, Janssen, Lilly, Loxo, Merck, MSD, Novartis, Nuvalent, Pfizer, Roche, Seattle Genetics, Takeda, Turning Point; consulting/advisory role for Abbvie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Chugai Pharma, Daiichi Sankyo Europe GmbH, Janssen, Lilly, Loxo, Merck, MSD Oncology, Novartis, Nuvalent, Pfizer, Roche, Seattle Genetics, Takeda, Turning Point; research funding from BMS, Janssen, Novartis, Pfizer.

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