

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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SUPPLEMENTARY MATERIAL

Supplementary Table S1: Inclusion and exclusion criteria applied to CHRYSLIS

Cohort D+

Inclusion criteria	Exclusion criteria
• Stage IIIB/C or IV NSCLC • <i>EGFR</i> Exon20ins • Age ≥ 18 years • Failure of a platinum-based therapy at any point after initial NSCLC diagnosis • Previously received platinum-based therapy after advanced NSCLC diagnosis or in the 12 months before advanced NSCLC diagnosis • ECOG performance status 0 or 1 • Hemoglobin ≥ 10 g/dL, ANC $\geq 1.5 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$, AST and ALT $\leq 3 \times$ ULN, total bilirubin ≤ 1.5 ULN (patients with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits), serum creatinine $< 1.5 \times$ ULN or calculated/measured creatinine clearance > 50 mL/min/1.73m² • No transfusions or use of G-CSF within 7 days prior to testing	• History of particular cardiovascular comorbidities • Deep vein thrombosis or pulmonary embolism within 4 weeks • Myocardial infarction, angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft or any acute coronary syndrome within 6 months • Untreated brain metastases • Other primary cancer diagnoses (with exception of skin cancer other than basal cell or squamous cell skin cancer, or in situ cervical cancer) within 3 years • Leptomeningeal disease • HBV, HCV, other infectious liver disease or HIV • Medical history of ILD, including drug induced ILD or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years

ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Exon20ins: Exon 20 insertion; G-CSF: granulocyte colony stimulating factors; HBV: hepatitis B; HCV: hepatitis C; HIV: human immunodeficiency virus; ILD: interstitial lung disease; NSCLC: non-small cell lung cancer; ULN: upper limit of normal.

Supplementary Table S2: Characteristics of the real-world data sources included in the analyses

Data source	Location	Time period of data collection
Flatiron, ConcertAI and COTA	US	15 December 2009–16 October 2020
PHE ^a	England	01 Jan 2016 to 31 December 2016 and 01 Jan 2018 to 31 December 2018
NGM	Germany	20 Sep 2013–08 July 2021
CRISP	Germany	27 April 2017–30 June 2021
ESME ^b	France	01 Jan 2015–12 July 2021

^aNo ORR/PFS data were available from the PHE cohort; ^bNo ORR data were available for ESME. CRISP: the Clinical Research platform Into molecular testing, treatment, and outcome registry of non-Small cell lung carcinoma Patients; ESME: Epidemiological Strategy and Medical Economics; NGM: Network Genomic Medicine; PHE: Public Health England; US: United States.

Supplementary Table S3: Additional^a inclusion and exclusion criteria applied to individual data sources

Data source	Criteria applied
Flatiron, ConcertAI and COTA	- Previously received platinum-based therapy after advanced NSCLC diagnosis or in the 12 months before advanced NSCLC diagnosis ≥1 LOT after platinum-based chemotherapy - No record of other malignancy in 3 years before start of qualifying therapy
PHE	- Previously received platinum-based therapy after advanced NSCLC diagnosis or in the 12 months before advanced NSCLC diagnosis - Hemoglobin ≥10 g/dL, ANC ≥1.5 x10⁹/L, platelets ≥75 x10⁹/L, AST and ALT ≤3 x ULN, total bilirubin ≤1.5 ULN, serum creatinine <1.5 x ULN or calculated/measured creatinine clearance >50 mL/min/1.73m² - No transfusions or use of G-CSF within 7 days prior to testing
NGM	No transfusions or use of G-CSF within 7 days prior to testing
CRISP	AST and ALT ≤3 x ULN, total bilirubin ≤1.5 ULN
ESME	No other primary cancer diagnosed within 3 years before advanced NSCLC diagnosis

^aThe 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 ECOG performance status score <2 (or missing). ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; CRISP: the Clinical Research platform Into molecular testing, treatment, and outcome registry of non-Small cell lung carcinoma Patients; ECOG: Eastern Cooperative Oncology Group; ESME: Epidemiological Strategy and Medical Economics; G-CSF: granulocyte colony stimulating factors; LOT: line of therapy; NGM: Network Genomic Medicine; NSCLC: non-small cell lung cancer; PHE: Public Health England; ULN: upper limit of normal.

Supplementary Table S4: Baseline characteristics adjusted for in comparative analyses

Baseline characteristics	EU+US cohort ^a	US cohort	EU cohort ^a	ESME ^b
Age	Y	Y	Y	Y
Gender	Y	Y	Y	N
Race (Asian)	N	N	N	N
Smoking history	N	N	N	N
Cancer stage at initial diagnosis	N	Y	N	N
Number of metastatic locations	N	Y	N	Y
Brain metastasis	Y	Y	Y	Y
Liver metastasis	N	N	Y	Y
Prior lines of treatment	Y	Y	Y	Y
ECOG	N	Y	N	N
Hemoglobin	N	Y	N	N
BMI	N	N	N	N

Uncommon prognostic variables could not be included in the adjustment of the combined IPD due to exclusion of sources with missing data in the ATT approach. ^aExcluding ESME.

^bIPD were not available. ATT: average treatment effect among the treated; BMI: body mass index; CRISP: the Clinical Research platform Into molecular testing, treatment, and outcome registry of non-Small cell lung carcinoma Patients; ECOG: Eastern Cooperative Oncology Group; ESME: the Epidemiological Strategy and Medical Economics; IPD: individual patient data; NGM: the Network Genomic Medicine; NSCLC: non-small cell lung cancer; PHE: Public Health England.

Supplementary Table S5: Baseline characteristics not adjusted for in comparative analyses and associated justification

Data source	Characteristic not adjusted for	Justification
EU+US cohort	All characteristics not common to the pooled sources	High rate of missing data
US cohort	Smoking	Not prognostic
	Race (Asian)	Not prognostic High rate of missing data
EU cohort	All characteristics not common to the pooled data sources	High rate of missing data

ECOG: Eastern Cooperative Oncology Group.

Supplementary Table S6: Baseline characteristics for CHRYSALIS versus the unadjusted and IPW–ATT adjusted EU cohort

Characteristic	CHRYSALIS analysis set	EU cohort ^a (unadjusted)	EU cohort ^a (adjusted)
N	114	143	143
Prior lines of treatment			
1	48 (42.1%)	73 (51.0%)	60 (41.8%)
2	34 (29.8%)	44 (30.8%)	43 (30.2%)
3	15 (13.2%)	19 (13.3%)	18 (12.8%)
4+	17 (14.9%)	7 (4.9%)	22 (15.2%)
Brain metastasis			
No	85 (74.6%)	91 (63.6%)	107 (74.9%)
Yes	29 (25.4%)	52 (36.4%)	36 (25.1%)
Liver metastasis			
No	101 (88.6%)	111 (77.6%)	126 (88.3%)
Yes	13 (11.4%)	32 (22.4%)	17 (11.7%)
Age			
≤55	30 (26.3%)	44 (30.8%)	34 (24.0%)
55≤60	20 (17.5%)	17 (11.9%)	27 (18.6%)
>60	64 (56.1%)	82 (57.3%)	82 (57.4%)
Gender			
Male	44 (38.6%)	58 (40.6%)	55 (38.4%)
Female	70 (61.4%)	85 (59.4%)	88 (61.6%)

^aExcluding ESME. ATT: average treatment effect among the treated; IPW: inverse probability weighting.

Supplementary Table S7: Baseline characteristics for CHRYSALIS versus the unadjusted and IPW–ATT adjusted US cohort

Characteristic	CHRYSALIS analysis set	US cohort (unadjusted)	US cohort (adjusted)
N	114	206	206
Prior lines of treatment			
1	48 (42.1%)	82 (39.8%)	91 (44.1%)
2	34 (29.8%)	64 (31.1%)	62 (30.1%)
3	15 (13.2%)	33 (16.0%)	26 (12.8%)
4+	17 (14.9%)	27 (13.1%)	27 (13.0%)
Brain metastasis			
No	85 (74.6%)	126 (61.2%)	155 (75.3%)
Yes	29 (25.4%)	80 (38.8%)	51 (24.7%)
Age			
<60	48 (42.1%)	77 (37.4%)	85 (41.2%)
60–70	38 (33.3%)	63 (30.6%)	68 (33.1%)
≥70	28 (24.6%)	66 (32.0%)	53 (25.7%)
Gender			
Male	44 (38.6%)	79 (38.3%)	81 (39.2%)
Female	70 (61.4%)	127 (61.7%)	125 (60.8%)
ECOG performance status			
0	33 (28.9%)	61 (29.6%)	57 (27.5%)
1	81 (71.1%)	145 (70.4%)	149 (72.5%)
Number of metastatic locations			
1	42 (36.8%)	61 (29.6%)	76 (36.8%)
2	45 (39.5%)	40 (19.4%)	81 (39.4%)
3	18 (15.8%)	44 (21.4%)	33 (15.9%)
4	9 (7.9%)	47 (22.8%)	16 (7.9%)
Missing	0	14 (6.8%)	0
Hemoglobin			
Normal/high	62 (54.4%)	96 (46.6%)	113 (55.0%)
Low	52 (45.6%)	110 (53.4%)	93 (45.0%)
Cancer stage at initial diagnosis			
I	8 (7.0%)	23 (11.2%)	16 (7.7%)

II	6 (5.3%)	10 (4.9%)	11 (5.4%)
IIIA	6 (5.3%)	13 (6.3%)	11 (5.5%)
IIIB/IV	94 (82.5%)	160 (77.7%)	168 (81.4%)

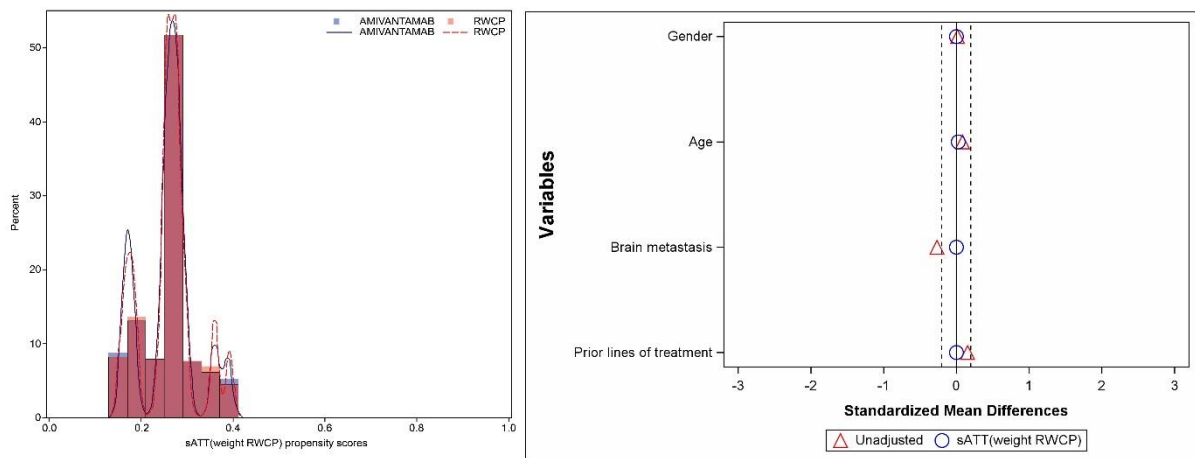
ATT: average treatment effect among the treated; ECOG PS: Eastern Cooperative Oncology Group; IPW: inverse probability weighting.

Supplementary Table S8: Baseline characteristics for CHRYSALIS versus the unadjusted and IPW–ATT adjusted ESME cohort (RWCP)

Characteristic	CHRYSALIS analysis set	ESME cohort (RWCP) (unadjusted)	ESME cohort (RWCP) (adjusted)
N	114	52	52
Prior lines of treatment			
1	48 (42.1%)	40 (76.9%)	24.7 (47.5%)
2	34 (29.8%)	9 (17.3%)	15.2 (29.1%)
3+	32 (28.1%)	3 (5.8%)	12.1 (23.4%)
Brain metastasis			
No	85 (74.6%)	34 (65.4%)	32.7 (62.8%)
Yes	29 (25.4%)	18 (34.6%)	19.3 (37.2%)
Age			
≤60	48 (42.1)	25 (48.1%)	17.4 (33.4%)
60<70	38 (33.3)	18 (34.6%)	23.4 (44.9%)
≥70	28 (24.6)	9 (17.3%)	11.3 (21.7%)
Liver metastasis			
No	101 (88.6%)	38 (73.1%)	35.2 (67.7%)
Yes	13 (11.4%)	14 (26.9%)	16.8 (32.3%)
Number of metastatic locations			
1	42 (36.8%)	19 (36.5%)	15.7 (30.1%)
2	45 (39.5%)	5 (9.6%)	21.6 (41.5%)
3	18 (15.8%)	15 (28.8%)	10.6 (20.4%)
4+	9 (7.9%)	13 (25.0%)	4.1 (8.0%)

ATT: average treatment effect among the treated; ESME: The Epidemiological Strategy and Medical Economics; IPW: inverse probability weighting; RWCP: real-world clinical practice.

Supplementary Figure S1: Distribution of PSs (left) and SMDs (right) for the EU+US cohort



ATT: average treatment effect among the treated; PS: propensity score; SMD: standardized mean difference; RWCP: real-world clinical practice.

Supplementary Table S9: ORR results (INV, versus EU cohort and versus US cohort)

		ORR		OR (95% CI)	RR (95% CI)
		Amivantamab	RWCP		
EU cohort	Unadjusted	36.8%	14.4%	3.46 (1.72, 6.96)	2.55 (1.46, 4.45)
	IPW-ATT approach		15.6%	3.16 (1.56, 6.40)	2.36 (1.36, 4.12)
US cohort	Unadjusted	36.8%	18.5%	2.56 (1.42, 4.63)	1.99 (1.28, 3.08)
	IPW-ATT approach		20.5%	2.26 (1.27, 4.03)	1.80 (1.18, 2.73)

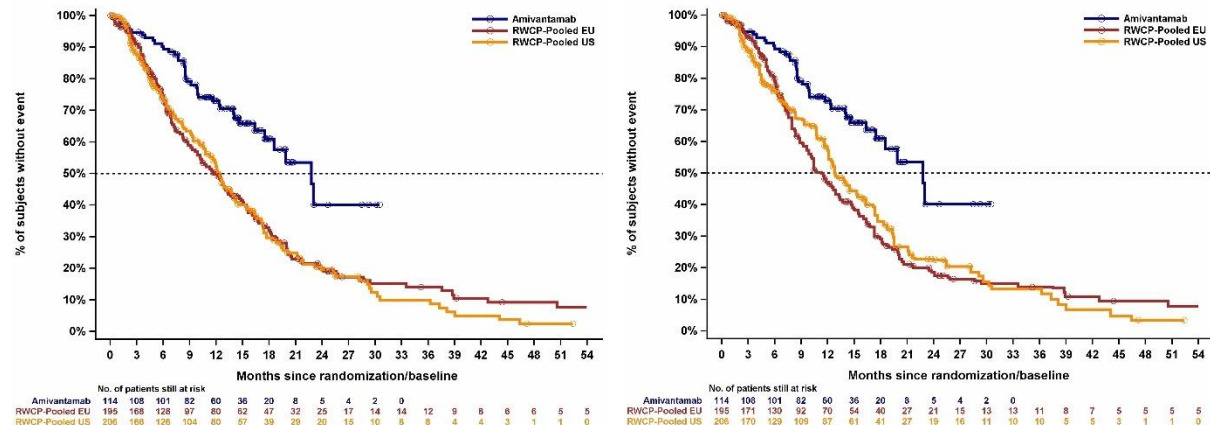
ATT: average treatment effect among the treated; INV: investigator-assessed; IPW: inverse probability weighting; NR: not reported; OR: odds ratio; ORR: overall response rate; RR: response rate ratio; RWCP: real-world clinical practice.

Supplementary Table S10: ORR results (IRC, versus EU+US cohort)

	ORR		OR (95% CI)	RR (95% CI)
	Amivantamab	RWCP		
Unadjusted	43.0%	16.8%	3.73 (2.23, 6.24)	2.56 (1.77, 3.68)
IPW – ATT approach		17.0%	3.67 (2.19, 6.15)	2.52 (1.75, 3.63)

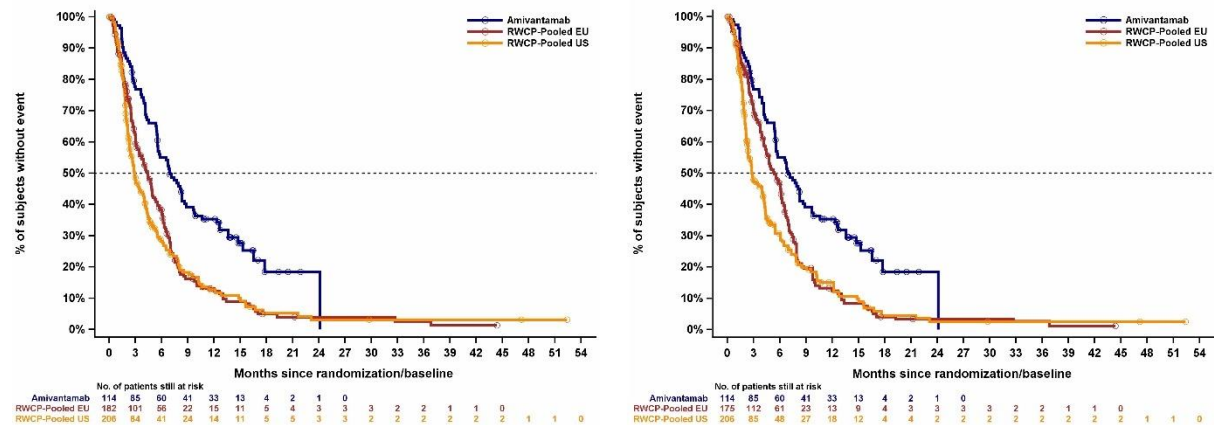
ATT: average treatment effect among the treated; IPW: inverse probability weighting; IRC: independent review committee; OR: odds ratio; ORR: overall response rate; RR: response rate ratio; RWCP: real-world clinical practice.

Supplementary Figure S2: Kaplan-Meier curve for OS for CHRYSALIS versus EU cohort and versus US cohort (amivantamab versus RWCP – unadjusted [left] and IPW–ATT adjusted [right])



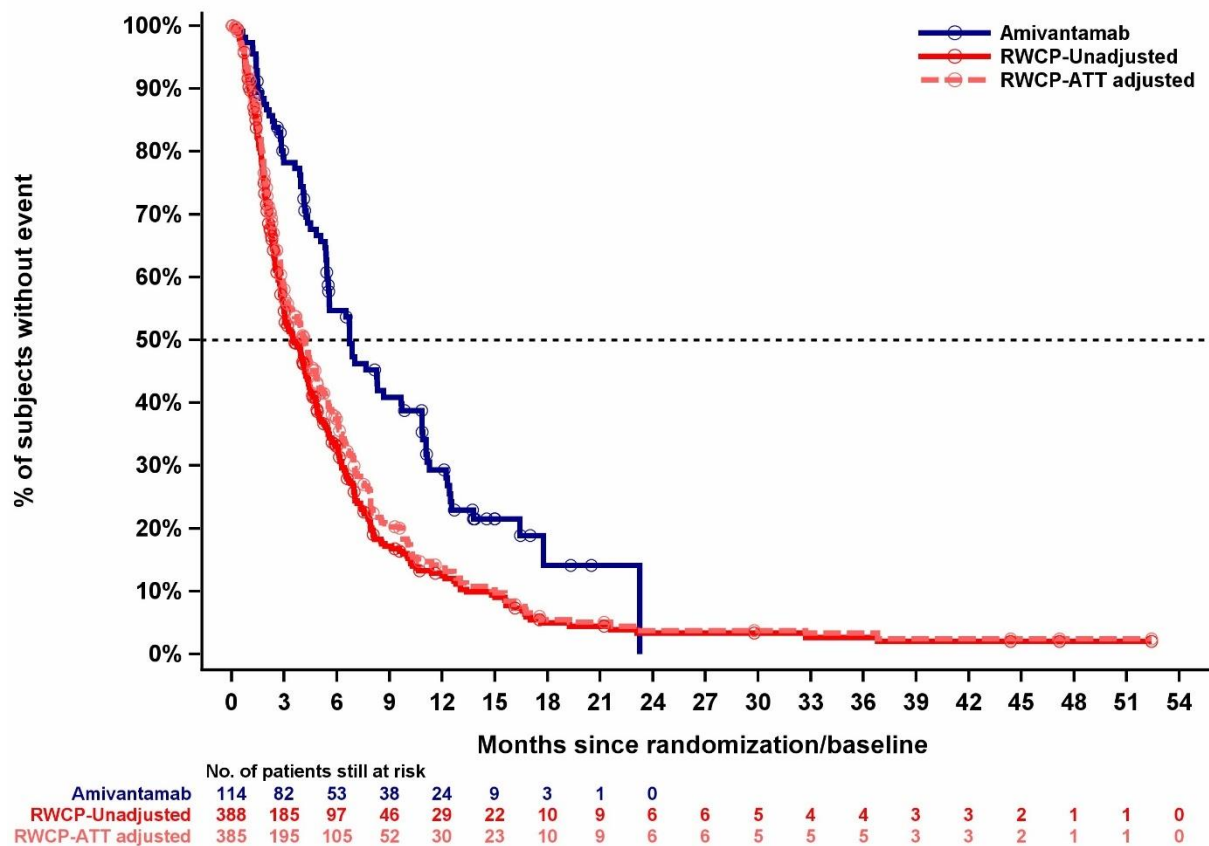
For the EU cohort, the HR for amivantamab versus RWCP was 0.53 (95% CI: 0.40, 0.70; $p < 0.0001$) prior to adjustment and 0.58 (0.44, 0.77; $p = 0.0002$) after adjustment. For the US cohort, the HR for amivantamab versus RWCP was 0.48 (0.37, 0.63; $p < 0.0001$) prior to adjustment and 0.50 (0.38, 0.66; $p < 0.0001$) after adjustment. ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; OS: overall survival; RWCP: real-world clinical practice.

Supplementary Figure S3: Kaplan-Meier curve for PFS (INV) for CHRYSALIS versus EU cohort and versus US cohort (amivantamab versus RWCP – unadjusted [left] and IPW-ATT adjusted [right])



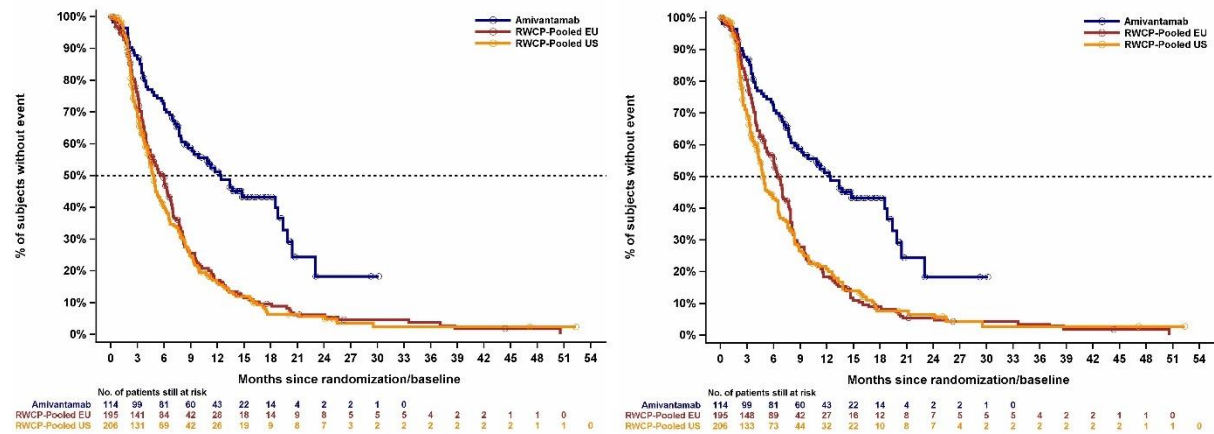
For the EU cohort, the HR for amivantamab versus RWCP was 0.53 (95% CI: 0.41, 0.70; $p < 0.0001$) prior to adjustment and 0.58 (0.44, 0.77; $p = 0.0002$) after adjustment. For the US cohort, the HR for amivantamab versus RWCP was 0.48 (0.37, 0.63; $p < 0.0001$) prior to adjustment and 0.50 (0.38, 0.66; $p < 0.0001$) after adjustment. ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PFS: progression-free survival; RWCP: real-world clinical practice.

Supplementary Figure S4: Kaplan-Meier curve for PFS (IRC) for CHRYSALIS versus EU+US cohort (amivantamab versus unadjusted and IPW–ATT adjusted RWCP)



The HR for amivantamab versus RWCP was 0.51 (95% CI: 0.39, 0.67; $p < 0.0001$) prior to adjustment and 0.53 (0.40, 0.70; $p < 0.0001$) after adjustment. ATT: average treatment effect among the treated; CI: confidence interval; IRC: independent review committee; HR: hazard ratio; PFS: progression-free survival; RWCP: real-world clinical practice.

Supplementary Figure S5: Kaplan-Meier curve for TTNT for CHRYSALIS versus EU cohort and versus US cohort (amivantamab versus RWCP – unadjusted [left] and IPW–ATT adjusted [right])



For the EU cohort, the HR for amivantamab versus RWCP was 0.43 (0.32, 0.58; $p < 0.0001$) prior to adjustment and 0.45 (0.34, 0.61; $p < 0.0001$) after adjustment. For the US cohort, the HR for amivantamab versus RWCP was 0.40 (0.30, 0.53; $p < 0.0001$) prior to adjustment and 0.43 (0.32, 0.58; $p < 0.0001$) after adjustment. ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; RWCP: real-word clinical practice; TTNT: time-to-next treatment.