Supplementary Information for

Amivantamab-Chemotherapy in Non-small Cell Lung Cancer with *EGFR* Exon 20 Insertions: Impact of Treatment Crossover and Other Endpoints from the Phase III PAPILLON Study

Rachel E. Sanborn[1] Caicun Zhou[2] Ke-Jing Tang[3] Byoung Chul Cho[4] Susanna Cheng[5] Sanjay Popat[6] Akira Ono[7] Shun Lu[8] Margarita Majem[9] Andres Aguilar[10] Maria Del Rosario Garcia Campelo[11] Hidetoshi Hayashi[12] Kang-yun Lee[13] Se-Hoon Lee[14] Angelo Delmonte[15] Jorge Alatorre-Alexander[16] Gary Richardson[17] Victor Santos[18] Christophe Dooms[19] Joshua K. Sabari[20] Catherine A. Shu[21] Nicolas Girard[22] Aaron S. Mansfield[23] Keunchil Park[14,24] Yichuan Xia[25] Archan Bhattacharya[26] Nasuh Buyukkaramikli[27] Nolen Perualila[27] Joris Diels[27] Sandip Acharya[28] Conor Chandler[29] Irina Proskorovsky[29] Lindsay Dearden[26] Honeylet Wortman-Vayn[30] Parthiv J. Mahadevia[30] Roland E. Knoblauch[31] Trishala Agrawal[31] Mahadi Baig[30] Enriqueta Felip[32]

Affiliations

[1]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA

[2]Shanghai East Hospital/Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

[3]Division of Pulmonary and Critical Care Medicine, Sun Yat-sen University First Affiliated Hospital, Guangzhou, China

[4]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

[5]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

[6]Royal Marsden Hospital NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, UK

[7]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

[8]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[9]Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[10]Dexeus University Hospital, Barcelona, Spain

[11]Hospital Universitario de A Coruña, Coruña, Spain

[12]Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama City, Japan

[13]Taipei Medical University Shuang Ho Hospital, New Taipei, Taiwan

[14]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[15]IRCCS Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori” (IRST), Meldola (FC), Italy

[16]Health Pharma Professional Research, México City, Mexico

[17]Cabrini Health, Melbourne, Australia

[18]Instituto Nacional de Câncer, Rio de Janeiro, Brazil

[19]Respiratory Oncology Unit, University Hospitals KU Leuven, Leuven, Belgium

[20]NYU Langone Health, New York, NY, USA

[21]Columbia University Irving Comprehensive Cancer Center, New York, NY, USA

[22]Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France; Paris Saclay University, Versailles, France

[23]Mayo Clinic, Rochester, MN, USA

[24]MD Anderson Cancer Center, Houston, TX, USA

[25]Johnson & Johnson, Wayne, PA, USA

[26]Janssen-Cilag Ltd, a Johnson & Johnson company, High Wycombe, UK

[27]Janssen Pharmaceutica NV, a Johnson & Johnson company, Beerse, Belgium

[28]Johnson & Johnson, Mumbai, India

[29]Evidera, Waltham, MA, USA

[30]Johnson & Johnson, Raritan, NJ, USA

[31]Johnson & Johnson, Spring House, PA, USA

[32]Medical Oncology Service, Vall d'Hebron Institute of Oncology Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain

Table of Contents

Supplementary Methods

The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidance was used to inform the inverse probability of censoring weighting (IPCW), two-stage estimation (TSE), and rank-preserving structural failure time (RPSFT) methods described below [1,2].

IPCW

Feasibility Assessment

The absence of the unmeasured confounder assumption cannot be directly tested; however, a systematic approach was used to identify candidate prognostic variables. First, a parent list of covariates was obtained using a systematic literature review and a Delphi panel. Then, the final list of prognostic factors was identified after an extensive medical review and determination of data availability, and included the following: age group, sex, Asian race, history of brain metastasis, history of liver metastasis, Eastern Cooperative Oncology Group performance status, history of tobacco use, EQ-5D UK utility, time to disease progression, ongoing serious treatment-emergent adverse events (TEAEs), ongoing TEAE (febrile neutropenia), prior major surgery, and best overall response. However, time to disease progression and the best overall response could not be included as baseline or time-varying covariates (TVCs) for the IPCW method.

Statistical Methods

The IPCW method was implemented following three general steps: 1) creation of panel data, 2) estimation of stabilized, time-dependent weights for the chemotherapy arm, and 3) estimation of an adjusted treatment effect on overall survival (OS).

For the creation of panel data, the follow-up time from randomization to crossover or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into time intervals. Daily time intervals were used, as they were expected to provide the most reliable results that leverage all available information. Individual participant-level data were then restructured to create panel data, with one record per participant per time interval. The baseline covariates were repeated across the time intervals for a given participant, and TVCs were specific to each time interval. In the absence of TVC values specific to a particular time period, the last observation was used. Time-dependent outcome binary variables were then created for the crossover status and death, with participants censored at the time of crossover (implemented in the panel data structure by omitting all observations after crossover occurred).

After artificially censoring participants at the time of treatment crossover, progressed participants who did not switch (yet) to second-line (2L) amivantamab were assigned weights over time, such that these accounted not only for themselves but also for participants with similar characteristics (both baseline and time-varying), to adjust for informative censoring. This step involved the estimation of stabilized time-dependent weights as follows:

1) Participants not at risk of crossover (i.e. participants in the amivantamab-chemotherapy arm and chemotherapy participants who did not progress) were assigned a probability of crossover of 0 and received a weight of 1.

2) The probability of crossover within each time period was estimated using two logistic regression models (including splines with three knots to ensure that time-dependent relationships were sufficiently flexible):

    a. Model 1 (conditional on baseline covariates and TVCs) was fitted to all participants who received chemotherapy and had disease progression and included all the above-mentioned time-varying and baseline covariates. A reduced model was also derived using the stepwise variable selection method with a significance level of 25%. The inverse probability of not crossing over up to the current timepoint was used for non-stabilized weights.

    b. Model 2 (conditional on the baseline variables selected, if any, in Model 1) was fitted to all participants who received chemotherapy, and stabilized weights for each timepoint were then calculated by the ratio of the probabilities of not crossing over up to the current timepoint from Model 2 (numerator) and Model 1 (denominator). As suggested by Latimer, et al., [3] an additional analysis using non-stabilized weights was conducted, and the results were similar to those obtained using stabilized weights.

An IPCW-adjusted hazard ratio and p-value for OS were calculated using a Cox proportional hazards model, including the time-dependent stabilized weights. The variance estimate was obtained using a robust sandwich variance estimator to account for the induced correlation among weighted individuals. The weighted Cox proportional hazards model was also conducted while including the same set of baseline

characteristics (with baseline correction) using stepwise variable selection at a 10% level of statistical significance.

TSE

Feasibility Assessment

The TSE method necessitates the use of a disease-related secondary baseline to precede treatment crossover. This is aligned with the PAPILLON study design, in which the time of disease progression was a prerequisite for crossover. Similar to IPCW, the TSE method assumes that there are no unmeasured confounders, no time-dependent confounding after secondary baseline until crossover, and all identified/measured confounders are included and correctly specified in the regression adjustment based on a relatively well-fitting parametric accelerated failure time (AFT) model to the observed post-progression survival (PPS) data. The absence of an unmeasured confounder assumption cannot be directly tested; however, a systematic approach was used to identify relevant prognostic variables as already outlined for IPCW.

Statistical Methods

The model was selected based on a stepwise approach. In step 1, the best-fitting distribution model was selected (fitting parametric survival regression models for the following accelerated failure time distributions: exponential, Weibull, log-logistic, log-normal, generalized gamma, and gamma). Based on this model, a multivariate model was derived using stepwise variable selection with a significance level of 25% in step 2. The best-fitting model was used to estimate an acceleration factor, which represents the treatment effect on PPS that is associated with 2L amivantamab monotherapy.

The PPS endpoint was used in the TSE analyses while determining the treatment effect of 2L amivantamab. The survival times of PPS (in days) were derived as $PPS = OS - PFS_{\mathrm{BICR}} + 1$ by blinded independent central review (BICR), and the same censoring variable used for OS was used for PPS.

The TSE method [4,5] compares survival between participants that crossed over or did not cross over in the same control treatment arm studied within one clinical trial, in this case the chemotherapy arm. The TSE adjustment method for OS was implemented in the following general steps:

1) In stage 1 of the TSE, parametric survival analyses of PPS were conducted to compare the chemotherapy participants who crossed over to 2L amivantamab monotherapy versus those who did not. Time of disease progression was used as a secondary baseline within the chemotherapy treatment arm using AFT models, including exponential, Weibull, log-logistic, log-normal, generalized gamma, and gamma distributions. In particular, the prognostic factors available at secondary baseline were included in the AFT model to adjust for differences between the 2L amivantamab monotherapy crossover cohort versus those who did not cross over, and crossover to 2L treatment was used as a TVC. The best-fitting AFT model was then used to estimate an acceleration factor, denoted γ_B, which represents the treatment effect on PPS that is associated with 2L amivantamab monotherapy (vs no 2L amivantamab monotherapy).
2) In stage 2 of the TSE, the observed PPS survival for the participants who crossed over to 2L amivantamab monotherapy was replaced by the counterfactual PPS estimated from the AFT model in stage 1. The counterfactual

PPS from the crossover cohort was added to the time progression, to obtain the counterfactual OS of those participants.

Following the estimation of counterfactual survival, subsequent statistical analyses were conducted to compare the relative efficacy of amivantamab-chemotherapy versus chemotherapy with regard to OS. The relative efficacy of amivantamab-chemotherapy versus chemotherapy on adjusted/counterfactual OS was estimated by fitting a Cox proportional hazards model with randomized treatment as a covariate. The conventional estimators of standard error and 95% confidence intervals (CIs) in the Cox model do not account for the uncertainty around the estimated acceleration factor (or shrinkage parameter) from the preceding TSE analysis. This additional source of uncertainty was properly propagated in subsequent analyses by bootstrapping the entire two-step procedure as follows: by first conducting a TSE analysis and then fitting a Cox regression model to the counterfactual OS to estimate the relative effect of amivantamab-chemotherapy versus chemotherapy. TSE was also tested using g-estimation, which relies on the assumption that the treatment effect in the crossover cohort is the same as in the participants originally randomized to the experimental arm [1,2] Analyses were conducted both without recensoring (primary analysis) and with recensoring (sensitivity analyses). The *p*-value was estimated using the Cox PH model with the counterfactual OS data, while propagating the additional source of uncertainty around the acceleration factor estimate.

RPSFT

Feasibility Assessment

The RPSFT method depends on the common treatment effect assumption. A previously conducted comparative efficacy analysis of 2L amivantamab monotherapy (CHRYSALIS trial) versus an external cohort receiving 2L amivantamab-chemotherapy resulted in an OS hazard ratio (HR 0.55-0.59) similar to those observed in the adjusted first-line (1L) amivantamab-chemotherapy versus 1L chemotherapy analyses in PAPILLON and provides supportive evidence for the underlying common treatment effect assumption.

Statistical Methods

The RPSFT model involved two stages: 1) estimating the treatment effect of 2L amivantamab monotherapy based on a counterfactual survival model, and 2) estimating counterfactual OS in the chemotherapy arm in the absence of 2L amivantamab monotherapy by reducing the observed survival benefit based on the treatment effect from stage 1.

In the first step, the RPFST method estimates a shrinkage factor, using g-estimation, in such a way that when shrinking all survival post the initiation of amivantamab, both in the chemotherapy arm as in the active amivantamab-chemotherapy arm, the OS in both arms become similar. As these shrunken estimates are expected to reflect the OS, when none of the participants in the trial would have been exposed to amivantamab, their OS should be identical due to randomization.

This shrinkage factor is then applied to the OS observed after 2L amivantamab only in the chemotherapy arm, to estimate the counterfactual survival under the assumption

that none of the patients would have been exposed and benefited from 2L amivantamab. The adjusted OS is then estimated comparing the observed OS in the amivantamab-chemotherapy arm with the counterfactual OS in the chemotherapy arm.

In the primary analysis, the RPSFT model was configured with “treatment grouping” assuming lagged treatment effect if a participant initiated 2L amivantamab monotherapy. Scenario analyses under an “on-treatment” configuration, where treatment effect disappears upon discontinuation, are presented as sensitivity analyses.

The specific steps in the first stage of the RPSFT process were as follows, where T_E denotes a participant’s time of death if the participant always received amivantamab-chemotherapy, and T_S denotes the same participant’s time of death if the participant always received chemotherapy:

1) A tentative value for φ was set, where φ is a (non-negative) treatment effect parameter, called an acceleration or delay factor, that stretches or shrinks survival times by some fixed factor.
2) For all participants in PAPILLON, the counterfactual survival times were calculated assuming that the participants were only randomized to the chemotherapy arm (T_S).
    a. The observed OS time (T_E) using the following structural model: $T_S = T_E \times \exp(\varphi)$ were adjusted for participants randomized to the amivantamab-chemotherapy arm.
    b. For participants randomized to the chemotherapy arm who never crossed over to 2L amivantamab monotherapy, T_S was observed directly.

c. For participants in the chemotherapy arm who crossed over to 2L amivantamab monotherapy, a portion of T_s was observed directly as the time from randomization to crossover ($T_{pre.sw}$). The remaining survival time (i.e. the time after treatment crossover until death [$T_{post.sw}$]) was adjusted to reflect what would have occurred if the participant continued to receive chemotherapy alone, which is given by $T_{post.sw} \times \exp(\varphi)$; hence, the total counterfactual OS time in the chemotherapy arm was as follows: $T_s = T_{pre.sw} + T_{post.sw} \times \exp(\varphi)$.

3) G-estimation was used to search for the optimal treatment effect (φ) over a grid of potential values that balanced the counterfactual survival (T_s) between the amivantamab-chemotherapy and chemotherapy arms. In this analysis, the metric used to measure "balance" in the counterfactual survival times between the arms was a chi-square test of significance of a study arm indicator in a Cox proportional hazards regression model (i.e. target *p*-value of 1) [6] That is, the value of φ that produces the strongest equivalence metric (i.e. largest *p*-value [or *p*-value closest to 1]) was considered the optimal value.

In the second stage of RPSFT, the counterfactual OS distribution (i.e. Kaplan–Meier curves) with chemotherapy was estimated by 1) plugging in the optimal value of φ (from step 3) to the counterfactual survival model described in step 2c for those who crossed over and 2) retaining the observed OS for those who did not. The counterfactual survival with chemotherapy was compared with the observed OS with amivantamab-chemotherapy using a Cox proportional hazards model to estimate an adjusted HR. To account for the additional uncertainty in the estimation of φ, the RPSFT model retained

the *P*-value from the corresponding intention-to-treat (ITT) analysis by adjusting the conventional estimate of the standard error. The *p*-value associated with the RPSFT method reflects the *p*-value from the ITT analysis.

Sensitivity Analyses

Sensitivity analyses for IPCW included no baseline correction with non-stabilized weights, baseline correction with stabilized weights, and baseline correction with non-stabilized weights. Sensitivity analyses for TSE included Weibull distribution with recensoring, gamma distribution without recensoring, and Weibull distribution without recensoring full covariates. Sensitivity analyses for RPSFT included recensoring and treatment grouping, and no recensoring and on-treatment analysis.

Supplementary Results

Outcomes in the Per-protocol Crossover Cohort After 2L Amivantamab Monotherapy Initiation

A total of 65 participants crossed over from the chemotherapy arm to amivantamab monotherapy every 3 weeks (Q3W) as part of the per-protocol crossover cohort. Among participants who crossed over, 57% were female and 72% were Asian (Supplementary Table 2). Participants in the per-protocol crossover cohort were exposed to amivantamab for a median duration of 4.9 months (range 0–18.2; Supplementary Fig. 1). In addition to the per-protocol crossover cohort, six participants received amivantamab off-protocol, with four participants initiating treatment before the OS censoring date.

After a median follow-up of 9.8 months from 2L amivantamab initiation, participants in the per-protocol crossover cohort had a median progression-free survival (PFS) of 6.8 months (95% CI, 4.4-9.6) and a median OS of 17.7 months (95% CI, 12.1-not estimable [NE]; **Supplementary Figure 2**). Median post-crossover time to treatment discontinuation (TTD) was 9.7 months (95% CI, 6.7-11.0), and median post-crossover time to subsequent therapy (TTST) was 9.7 months (95% CI, 7.7-12.1). Of the 65 participants in the per-protocol crossover cohort, 46% (30/65) discontinued 2L amivantamab monotherapy.

Supplementary Table 1 Sensitivity analyses for participants receiving 2L amivantamab

Sensitivity analysis	OS HR (95% CI)
IPCW	
No baseline correction with non-stabilized weights	0.51 (0.29–0.90)
Baseline correction with stabilized weights	0.54 (0.30–0.97)
Baseline correction with non-stabilized weights	0.53 (0.30–0.95)
TSE	
Weibull distribution with recensoring	0.64 (0.32–1.28)
Gamma distribution without recensoring	0.55 (0.34–0.89)
Weibull distribution full model without recensoring	0.55 (0.34–0.89)
RPSFT	
Recensoring and treatment grouping	0.59 (0.31–1.12)
No recensoring and on-treatment analysis	0.61 (0.34–1.11)

monotherapy per protocol

2L, second-line; CI, confidence interval; HR, hazard ratio; IPCW, inverse probably of censoring weight; OS, overall survival; RPSFT, rank-preserving structural failure time; TSE, two-stage estimation.

Supplementary Table 2 Baseline characteristics of participants whose disease progressed

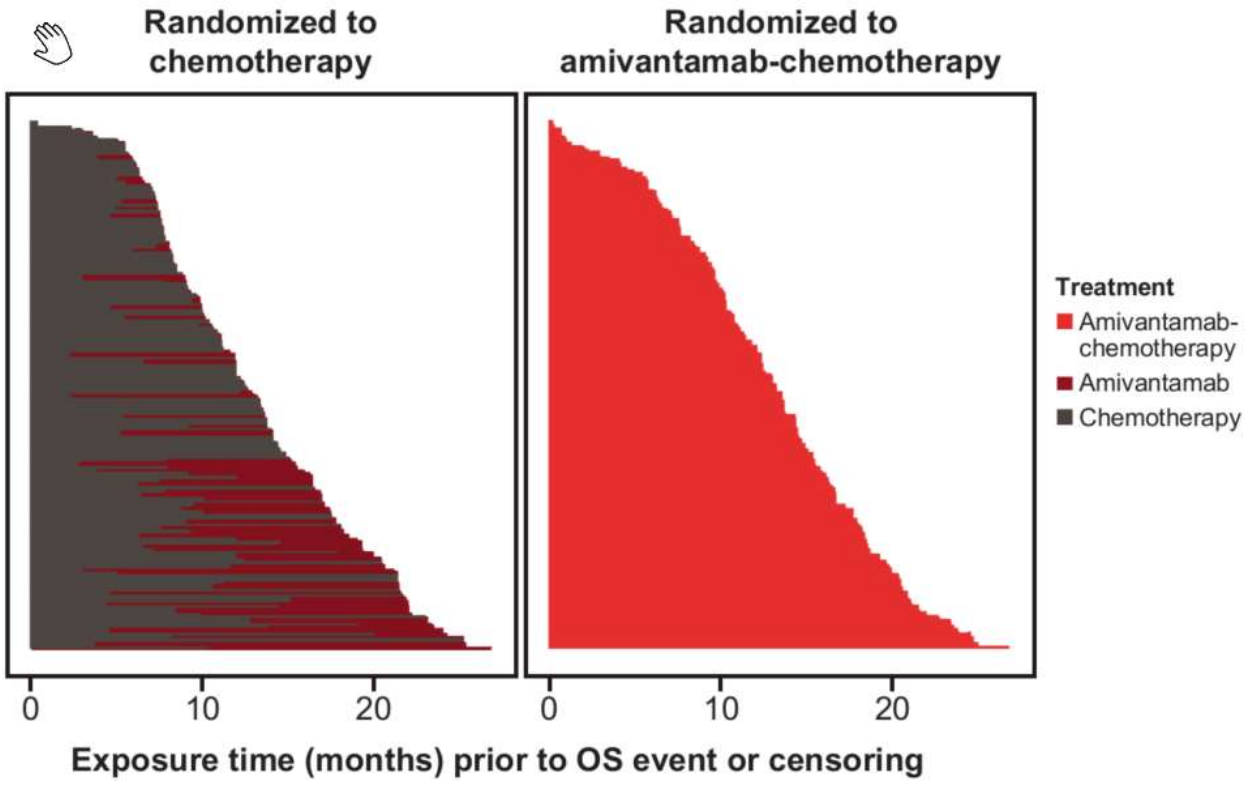
Characteristic, *n* (%)	**Progressed on chemotherapy: did not cross over to 2L amivantamab (*N* = 61) *n* (%)**	**Progressed on chemotherapy: crossed over to 2L amivantamab (*N* = 65) *n* (%)**	**All disease progressions on chemotherapy (*N* = 126) *n* (%)**	**Progressed on amivantamab-chemotherapy (*N* = 75) *n* (%)**
Sex				
Female	41 (67)	37 (57)	78 (62)	37 (49)
Male	20 (33)	28 (43)	48 (38)	38 (51)
Race				
Asian	28 (46)	47 (72)	75 (60)	52 (69)
Non-Asian	29 (48)	18 (28)	47 (37)	21 (28)
Unknown	4 (7)	0	4 (3)	2 (3)
History of brain metastases	13 (21)	19 (29)	32 (25)	26 (35)
History of liver metastases	14 (23)	13 (20)	27 (21)	8 (11)
History of tobacco use	24 (39)	29 (45)	53 (42)	31 (41)
Prior major surgery	9 (15)	9 (14)	18 (14)	7 (9)
Best overall response (BICR)				
Complete response	1 (2)	0	1 (1)	2 (3)

Partial response	30 (49)	27 (42)	57 (45)	53 (71)
Stable disease	24 (39)	26 (40)	50 (40)	16 (21)
Progressive disease	5 (8)	11 (17)	16 (13)	4 (5)
Not evaluable	1 (2)	1 (2)	2 (2)	0
Responder[a]	31 (51)	27 (42)	58 (46)	55 (73)
Non-responder[b]	30 (49)	38 (58)	68 (54)	20 (27)

[a]Complete or partial. [b]Stable, progressive, or not evaluable.

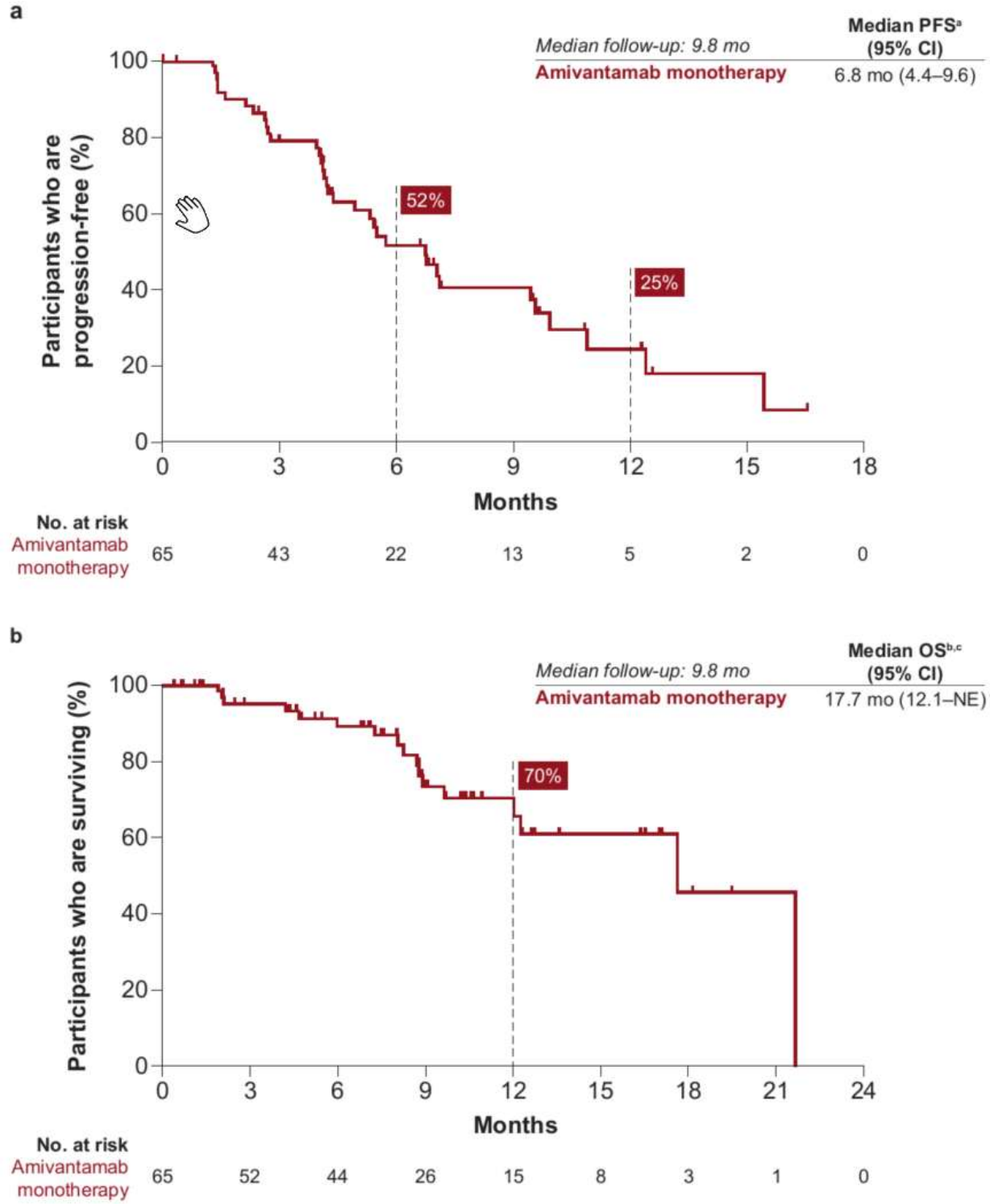
2L, second-line; BICR, blinded independent central review.

Supplementary Fig. 1 Swim-lane plot of exposure times to chemotherapy and amivantamab in PAPILLON



OS, overall survival.

Supplementary Fig. 2 Efficacy of amivantamab monotherapy in the per-protocol crossover cohort for (A) post-crossover PFS and (B) post-crossover OS



[a]PFS was defined as the time from first administration of amivantamab monotherapy until the date of objective disease progression or death, whichever occurred first. [b]OS was defined as the time from first administration of amivantamab monotherapy until the date of death. [c]There were 17 deaths reported in the crossover cohort.

CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.