Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende amivantamab i kombination med kemoterapi til 1. linjebehandling af ikke-småcellet lungekræft med EGFR exon 20-insertion

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. amivantamab + kemo til førstelinjebehandling af NSCLC
2. Forhandlingsnotat fra Amgros vedr. amivantamab + kemo til førstelinjebehandling af NSCLC
3. Ansøgers endelige ansøgning vedr. amivantamab + kemo til førstelinjebehandling af NSCLC

Johnson&Johnson

Response letter
February 17th, 2025

Dear Medicines Council

Johnson & Johnson appreciates the opportunity to review the assessment report concerning first line treatment with amivantamab (Rybrevant) + CP (AMI+CP) of patients with advanced non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) exon 20 insertion (exon20ins) mutations. We acknowledge the effort put into the report but wish to challenge specific aspects of the analysis, particularly in relation to the following points:

1. Choice of extrapolation for overall survival (OS)
2. Estimation of proportion of patients weighing above 80 kg

Choice of extrapolation for OS

The DMC base case adopts a very conservative OS extrapolation by using the Generalized Gamma distribution, which we believe does not reflect the potential long-term benefits of AMI+CP. Using the OS extrapolations suggested by DMC would mean that there are no survivors in the neither the AMI+CP treatment arm nor comparator arm after 6,5 years. We acknowledge the uncertainty about the true survival benefit of AMI+CP, however we find it implausible that all patients will be dead within 6,5 years with AMI+CP. The survival projected by Generalized Gamma beyond 5.5 years is also more conservative than the DMC base case for the OS extrapolation of amivantamab monotherapy in the 2L setting which was assesed in 2023[i]. We don't find it clinically plausible that long term survival in the 2L setting is greater than in the 1L setting and therefore a more optimistic distribution for AMI+CP, e.g. Weibull, would be more clinically plausible in relation to the assumed survival for amivantamab monotherapy in the 2L setting.

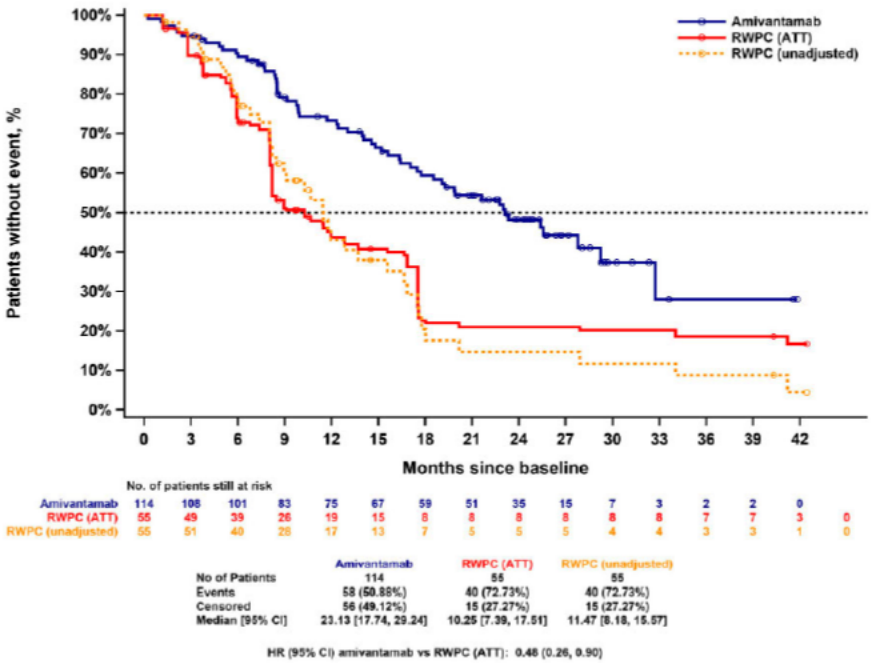
We propose that the DMC changes the base case to use the Weibull OS extrapolation to more accurately reflect the AMI+CP treatment effect. A pragmatic approach could also be to instead of having one base case, the DMC presents two scenarios as the main result of the analysis to address the uncertainty of the long-term benefit of AMI+CP; OS extrapolation of AMI+CP based on 1) the Weibull model (used in a sensitivity analysis in the assessment report), and 2) the Generalized Gamma model.

In the scenario with the Weibull distribution chosen for extrapolating data for both the AMI+CP and the CP arm, it aligns with the NICE guidelines (NICE TSD14) to use the same parametric model for both treatment arms, unless substantially justified, as different models allow very different shaped distributions.

In the assessment report on page 23 it is stated that "*it is also unlikely that the survival will be on a par with or longer than for patients with the classic mutations treated with osimertinib. On this basis, generalized gamma is assessed to be better reflect the expected survival*." Making a naïve comparison of the OS data for the AMI+CP arm from PAPILLON (exon20ins) with OS data for the Osimertinib arm from MARIPOSA-1 (common EGFR mutations – request for assessment has been submitted to DMC), it indicates, that the survival is comparable in these two patient groups (see Figure 1), even though the exon20ins patients' prognosis is considerably worse. We therefore disagree with the statement in the assessment report and believe that there's reason to believe that AMI+CP is as effective in patients with exon20ins patients as osimertinib in the classic mutations.

The amivantamab trial with the longest follow-up data available is currently the CHRYSALIS trial which evaluated amivantamab as a 2L treatment after platinum-based chemotherapy. Figure 2 below shows that approximately 25% of the patient population is still alive 3 years after 2L treatment was initiated[ii].

Figure 2: OS from the CHRYSALIS study (2L amivantamab) and CATERPILLAR-RWE cohort (Real World Physicians Choice)[iii]



If wanted, more information about the analyses can be provided.

[redacted]

Overestimation of proportion of patients weighing above 80 kg

After we submitted the application to DMC in October we have received RWE from a Danish physician. The data contains information on different patient characteristics of exon20ins patients in Region Midtjylland including the patients' weight at diagnosis. The data shows that 25 out of 32 patients with data on weight is above 80 kg corresponding to 78%. In our application we assumed 84% in line with the trial data. DMC assumes only 65% which, according to the data on Danish patients that we have received, appears to be too low. DMC states the data comes from Sundhedsplatformen but given the large discrepancies from the data we have received we considered if the data from Sundhedsplatformen is coming from another patient population e.g. NSCLC in general. If this is the case, we kindly ask you to consider using the exon20ins specific data from the table below.

Table 1: Weight at diagnoses, data on file

[redacted]

[redacted]

Conclusion

To conclude we have illustrated the importance of the DMC choice on OS extrapolation and patient weight assumptions. The QALY gain and ICERs presented in the table is based on the DMC choice of cross-over analysis and DMC assumptions regarding treatment until PFS.

Table 2: QALY gains and ICERs with different choice of OS extrapolation and weight assumptions

	QALY gain	ICER, DKK*	
OS extrapolation AMI+CP/CP		**65% <80kg DMC assumption**	**78% <80kg DK RWE**
Generalized Gamma/Weibull (DMC base case)	[redacted]		
Weibull/Weibull (DMC sensitivity analysis)			
Gamma/Weibull			
Gamma/Gamma (submission base case)			
[redacted]			

We sincerely hope that the DMC will reconsider their view on choice of OS extrapolation making it possible to make amivantamab available to exon20ins patients in Denmark.

[i] https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/a/amivantamab-rybrevant-lungekraeft

[ii] Christopoulos, P., Girard, N., Proto, C., Soares, M., Lopez, P. G., van der Wekken, A. J., Popat, S., Diels, J., Schioppa, C. A., Sermon, J., Rahhali, N., Pick-Lauer, C., Adamczyk, A., Penton, J., & Wislez, M. (2023). Amivantamab Compared with Real-World Physician's Choice after Platinum-Based Therapy from a Pan-European Chart Review of Patients with Lung Cancer and Activating *EGFR* Exon 20 Insertion Mutations. *Cancers*, *15*(22), 5326. https://doi.org/10.3390/cancers15225326

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03.03.2025

KLE/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.03.2025
Leverandør	Johnson & Johnson
Lægemiddel	Rybrevant (amivantamab)
Ansøgt indikation	Amivantamab + kemoterapi til 1. linje behandling af ikke-småcellet lungekræft med aktiverende EGFR exon 20-insertion
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Rybrevant (amivantamab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Rybrevant	350 mg (1 stk.)	9.582,84	[redacted]	[redacted]	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted] Leverandøren har mulighed for at sænke prisen fra dag til dag i hele aftaleperioden.

Information fra forhandlingen

[redacted]

Lægemiddeludgift pr. patient

Tabel 2 viser lægemiddeludgiften for et års behandling med Rybrevant. Komparator er kemoterapi med en minimal udgift, og derfor ikke beregnet.

Tabel 2: Sammenligning af lægemiddeludgift pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Rybrevant Kropsvægt < 80 kg	350 mg (1 stk.)	Uge 1-4: 1.400 mg iv./uge Derefter: 1.750 mg iv. hver 3. uge*	[redacted]	[redacted]
Rybrevant Kropsvægt > 80 kg	350 mg (1 stk.)	Uge 1-4: 1.750 mg iv./uge Derefter: 2.100 mg iv. hver 3. uge*	[redacted]	[redacted]

*Kilde: Udkast: Medicinrådets anbefaling vedr. amivantamab + kemoterapi til 1. linje-behandling af ikke-småcellet lungekræft med EGFR exon20 insertion. Tabel 1. s. 12.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	Endnu ikke anbefalet	Link til status
England	Under vurdering	Endnu ikke anbefalet	Link til status
Sverige	Under vurdering	Endnu ikke anbefalet	Link til status

Opsummering

[redacted]

Application for the assessment of Rybrevant® (amivantamab) + chemotherapy (carboplatin and pemetrexed) for the first line treatment of patients with advanced non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) exon 20 insertion (exon20ins) mutations

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Tables and Figures

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Abbreviations

Abbreviations	Explanation
1L	First line
ADA	Drug antibodies
AE	Adverse events
AFT	Accelerated failure time
AIP	Pharmacy purchase price
ASCO	American society of clinical oncology
BICR	Blinded independent central review
BSA	Body surface area
BSC	Best supportive care
CEM	Cost effectiveness model
CI	Confidence interval

Abbreviations	Explanation
CP	Carboplatin plus pemetrexed
Cmax	Maximum serum concentration
DHFR	Dihydrofolate reductase
DLCG	Danish Lung Cancer Group
DOR	Duration of response
DSU	NICE decision support unit
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
INV	Investigator
IO	Immuno-oncology
IPCW	inverse probability of censoring weight
IPW	inverse probability weighting
IRRs	infusion-related reactions
ITT	Intention to treat
MMRM	mixed-model repeated measures
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PD	Progressed disease
PF	Progression free

Abbreviations	Explanation
PFS	Progression-free survival
PFS2	Survival after subsequent therapy
PH	Proportional hazard
PSM	Partitioned survival model
RDI	Relative dose intensity
RPSFT	rank-preserving structural failure time
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMD	Standardized mean difference
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TS	Thymidylate synthase
TSE	two-stage estimation
TTDD	Time to treatment discontinuation or death
TTF	Time to treatment failure
TTO	Time trade-off
TTSP	Time to symptomatic progression
TTST	Time to subsequent therapy
WCLC	World Conference on Lung Cancer

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Rybrevant®
Generic name	amivantamab
Therapeutic indication as defined by EMA	Rybrevant® is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations.
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	L01FX18
Combination therapy and/or co-medication	In combination with chemotherapy carboplatin and pemetrexed (CP)
(Expected) Date of EC approval	27 June 2024
Has the medicine received a conditional marketing authorization?	As for the indication relevant for the submission there is no conditional approval specified by EMA. A conditional marketing authorization EU/1/21/1594/001 for Rybrevant® as monotherapy for treatment of adult patients with advanced NSCLC with EGFR exon20ins, after failure of platinum-based therapy was issued on 09/12/2021 [1].
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	A conditional marketing authorization EU/1/21/1594/001 for Rybrevant® as monotherapy for treatment of adult patients with advanced NSCLC with EGFR exon 20-ins, after failure of platinum-based therapy was issued on 09/12/2021[1]. Combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of

Overview of the medicine	
	prior therapy including an EGFR tyrosine kinase inhibitor (approval date 22 Aug 2024)
Other indications that have been evaluated by the DMC (yes/no)	Yes. On April 26th 2023, the Danish Medical Council (DMC) did not recommend Rybrevant® as monotherapy for the treatment of adult patients with advanced NSCLC with EGFR exon20ins, after failure of platinum-based therapy [2].
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE): Yes Is the product suitable for a joint Nordic assessment: It is not possible for J&J to coordinate our resources cross-Nordic currently since we are separate country organizations (as aligned in FINOSE/Janssen dialogue meeting March 19th, 2024). Additionally, amivantamab is not a new active substance, and the assessment is for an indication extension which is less suitable for joint assessment through JNHB. Finally, due to the small patient population and the significant unmet need (no available targeted therapies for patients with EGFR exon 20ins-positive NSCLC), not all Nordic countries expect to be doing a full CUA-based assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Rybrevant® 350 mg concentrate for solution for infusion x 1 vial. One mL of concentrate for solution for infusion contains 50 mg amivantamab. One 7 mL vial contains 350 mg of amivantamab.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Amivantamab in combination with chemotherapy (carboplatin and pemetrexed) for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations (exon20ins).
Dosage regiment and administration	When used in combination with chemotherapy, amivantamab should be administered after carboplatin and pemetrexed in 21-days Cycles [3]. Amivantamab: 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3 [3]. Chemotherapy: Carboplatin: Area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles [3]. Pemetrexed: 500 mg/m2 (with vitamin

Summary	
	supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression [3].
Choice of comparator	The comparator is platinum-based chemotherapy, which is composed of carboplatin + pemetrexed (CP), in line with Danish treatment guidelines and the PAPILLON trial [3]. Dose and administration are in line with the treatments administered with the intervention (according to SmPC).
Prognosis with current treatment (comparator)	The current SoC in the Danish clinical practice [2] is CP which has shown not to provide durable treatment benefit in the targeted population [4, 5].
Type of evidence for the clinical evaluation	PAPILLON (NCT04538664) - A randomized, open-label phase 3 study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in patients with EGFR exon20ins mutated locally advanced or metastatic NSCLC.
Most important efficacy endpoints (Difference/gain compared to comparator)	Progression-Free Survival (PFS): 60% reduction of progression, median PFS 11.4 vs. 6.7 months. Overall survival (OS): 33% maturity; median not estimable vs. 24.4 months.
Most important serious adverse events for the intervention and comparator	The overall incidence of serious adverse events (SAEs) was comparable, with SAEs reported in 56 participants (37.1%) in the amivantamab+CP arm and 48 participants (31.0%) in the CP arm. The most frequently reported treatment-emergent SAEs were pneumonia, COVID-19, vomiting, pneumonitis, pulmonary embolism, dyspnea, pleural effusion, hypokalemia, thrombocytopenia, and anemia (see further section 9).
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L data were collected in the PAPILLON clinical study in line with the clinical study protocol. Progress free (PF) state utilities were estimated at each cycle, using pooled cohort to estimate health state specific mean utility values. The area under the curve of the time-specific PF state utilities was used as the PF state utility. Progressed disease (PD) state utilities were estimated from patients who progressed in PAPILLON data, using a mixed-model repeated measures (MMRM) model that accounted for correlations between PRO measurements from the same patients. Mean values [95%CI]: PF = 0.8851 [0.8784, 0.8918], PD = 0.8256 [0.7836, 0.8676]. Health economic model: The health economic model uses health state specific utilities for progression free and progressed disease. In addition, a separate calculation related to Adverse Events disutilities.

Summary	
Type of economic analysis that is submitted	Cost-utility analysis, with a partitioned survival model (PSM) approach with three health states: progression-free, post-progression and death. Endpoints: Key clinical inputs are PFS and OS, which ultimately drives the aggregated costs, LYs, QALYs.
Data sources used to model the clinical effects	The head-to-head trial PAPILLON (NCT04538664)
Data sources used to model the health-related quality of life	The head-to-head trial PAPILLON (NCT04538664)
Life years gained	2.13 years
QALYs gained	1.79 QALY
Incremental costs	1,004,213 DKK
ICER (DKK/QALY)	559,873 DKK/QALY
Uncertainty associated with the ICER estimate	The ICER was robust in most scenarios tested. In the OWSA, the most impactful parameters on the ICER were utility for progressed disease, patients <80 kg and use and proportion of patients receiving subsequent lines of treatments (see 12.2)
Number of eligible patients in Denmark	Incidence: 10-16 patients per year, BIM assume 16 eligible Prevalence: Not applicable
Budget impact (in year 5)	12,642,859 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Lung cancer is the most common malignancy and the leading cause of cancer mortality [6]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all advanced lung cancer cases [6, 7]. NSCLC is further classified into three distinct histological types:

squamous cell carcinoma, adenocarcinoma and large cell carcinoma, of which adenocarcinoma is the most common comprising around 40% to 43% of all lung cancer cases [7-9]. Patients with NSCLC are often diagnosed with advanced disease (63%) [10], defined as locally advanced disease that may have spread to the lymph nodes (Stage III) or metastatic disease that has spread to other organs (Stage IV) [11].

Epidermal growth factor receptor (EGFR) mutations are the most common activating pathway event (genetic mutations which accelerate cancer progression) in NSCLC and therefore presents an important therapeutic target. Among patients with NSCLC, mutations in the EGFR gene typically occur in exons 18 to 21, with a majority of these mutations (90%) comprising exon 19 deletions and L858R point mutations in exon 21 [7], referred to as common or sensitising EGFR mutations [6]. The remaining EGFR mutations are made up of other less frequent mutations, such as exon 20 insertions (exon20ins), S768I, L861Q and G719X [12].

EGFR exon20ins mutations, is a rare type of NSCLC, and account for 0.1% to 4% of NSCLC cases overall and 1% to 12% of EGFR-mutated NSCLC cases, with reported frequencies among patients with NSCLC varying by geographic region [13-20].

The clinical characteristics of patients with NSCLC and EGFR exon20ins are similar to patients with classical EGFR mutations. Multiple studies have found that patients with EGFR exon20ins-positive NSCLC are typically female, younger, non-smokers and diagnosed with metastatic disease [21-26].

Patients with EGFR exon20ins in the first line (1L) setting have a markedly worse prognosis than those with EGFR-mutated NSCLC (real-world 5-year overall survival [OS] 8% vs. 19%, respectively) [27]. Compared to patients with common EGFR mutations, those with exon20ins have a 75% increased risk of death (median overall survival [mOS] 16.2 vs. 25.5 months) and 93% increased risk of disease progression or death (median progression-free survival [mPFS] 5.1 vs. 10.3 months)[1] [27, 28].

No targeted therapy has been approved for patients with EGFR exon20ins-positive NSCLC in the 1L setting in Denmark. Patients typically receive doublet platinum-based chemotherapy as standard of care (SoC), as recommended by 2023 guidelines from ASCO, NCCN and ESMO and the 2024 Danish treatment guidelines developed by DLCG [29-32]. In addition, recommendation of treatment with amivantamab plus carboplatin and pemetrexed for patients with stage IV metastatic NSCLC has been recently added to the most recent ESMO guidelines [33].

While being the most effective treatment available for this population, platinum-based chemotherapy is associated with poor survival outcomes in the 1L setting in patients with exon20ins (mPFS ranging from 3.0 to 8.9 months and mOS from 16.1 to 38.4 months) and chemotherapy alone does not provide a durable treatment benefit [24, 26, 27, 34-44]. EGFR tyrosine kinase inhibitors (TKIs) are unsuitable for patients with

[1] Data based on a follow-up period of 34 months.

exon20ins due to *de novo* resistance [5, 6, 45, 46], and real-world outcomes with immuno-oncology (IO) drugs are consistently poor in this population [36, 43, 44, 46].

Patients therefore face a high level of attrition after 1L therapy, with literature demonstrating that 54% to 56% of advanced NSCLC patients do not receive 2L therapy [47, 48]. Thus, highlighting the urgent unmet need for a targeted treatment upfront that can improve efficacy and HRQoL, providing patients with the best possible survival outcomes from the start of their treatment journey.

For the population with the rare exon20ins mutations, the unmet need is high [49, 50], despite advances in treatment for EGFR-mutated patients, there remains an ongoing need for effective, well-tolerated treatments for exon20ins [49, 50]. The prognosis is poor compared with other, more common mutations. Newly diagnosed patients with metastatic NSCLC and EGFR exon20ins require an upfront targeted therapy to improve their rapid disease progression and dismal outcomes that exist with the current SoC [13, 35-39, 44].

3.2 Patient population

The patient population relevant for the assessment are adult patients with NSCLC with EGFR exon20ins mutations in Denmark. Globally, the frequency of EGFR exon20ins varies by geographic region ranging from 0.1% to 4% of NSCLC cases overall and accounting for between 1% to 12% of NSCLC EGFR mutations [13-19, 51].

According to the Danish Lung Cancer Group (DLCG) [52], 4,820 people were diagnosed with lung cancer in Denmark in 2018. Approximately, 81% (3,880) being NSCLC [52]. Data shows that 58% of the NSCLC patients had adenocarcinoma (non-squamous NSCLC), 24% had squamous NSCLC and the rest of the cases were attributed to other types of NSCLC. With an EGFR testing coverage of 85% among adenocarcinoma patients (48% coverage across all lung cancer patients), 180 patients with EGFR mutations were identified in 2018 (approx. 9.3% of the tested adenocarcinoma patients had EGFR mutations) [52]. As previously described, EGFR exon20ins is a rare type of mutation overall as well as among the other EGFR mutations in NSCLC [5, 7, 45, 53].

With current estimates, approximately 140 patients have been estimated to have NSCLC with EGFR mutations [54]. In the DMC evaluation of amivantamab as monotherapy for the treatment of adult patients with advanced NSCLC with EGFR exon20ins, after failure of platinum-based therapy, Johnsson & Johnsson internal estimations through interviews with key opinion leaders from the Nordics were that 10-16 patients per year will be diagnosed with EGFR exon20ins-positive NSCLC [55]. The number of estimated patients per year was validated by DMC expert committee since they were included in the assessment report of amivantamab mentioned above [55].

The incidence is shown in Table 1, while the number of patients eligible for treatment in the following five years is presented in Table 2. For the number of patients in Denmark who are eligible for treatment in the coming years, the upper bound of 16 patients, from the clinical expert estimation was used.

Table 1. Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	10-16	10-16	10-16	10-16	10-16
Prevalence in Denmark	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A: Not applicable

Table 2. Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	16	16	16	16	16

3.3 Current treatment options

There is limited clinical guidance for treatment of patients with EGFR exon20ins-positive NSCLC. In the latest published ASCO [29] and ESMO [31] treatment guidelines from 2023, platinum doublet chemotherapy for patients with EGFR exon20ins NSCLC in the 1L setting is recommended, due to the limited sensitivity of exon20ins mutations to EGFR TKIs and immunotherapies [29-31]. Platinum-based doublet chemotherapy is the most commonly used treatment option for patients with exon20ins-positive NSCLC in the 1L setting [23, 27, 43, 56, 57]. Most recently, the recommendation of treatment with amivantamab plus carboplatin and pemetrexed for patients with stage IV metastatic NSCLC has been included in the ESMO guidelines [33].

Patients with exon20ins mutations (unlike other EGFR mutations), do not respond to current standard treatment for EGFR and Danish, international and European guidelines do not recommend EGFR TKIs for NSCLC with EGFR exon20ins since available EGFR TKI therapies are ineffective against exon20ins, as described in the literature [5, 6, 45, 46]. In addition, IO therapies used in the treatment of advanced NSCLC have not demonstrated a survival benefit for patients with EGFR mutations when added to 1L therapy or given alone as a 2L treatment [58, 59] which limits the evidence supporting their use for the treatment of patients with EGFR exon20ins [36, 43, 44, 46].

In Denmark, there are currently no approved targeted therapies for patients with EGFR exon 20ins-positive NSCLC in the 1L setting. The DMC have developed guidelines for 1L treatment for patients with NSCLC [54], but with no specific guidelines for 1L NSCLC with EGFR exon20ins mutations. However, the DLCG in Denmark has recently developed guidelines for the palliative oncological treatment of oncogene-driven NSCLC [32], which include treatment of patients with activating EGFR exon20ins. These guidelines

recommend offering platinum-based chemotherapy as 1L treatment to patients with activating exon20ins and performance status 0-2 [32]. As 2L treatment for this patient population with performance status 0-1, guidelines recommend offering treatment according to EMA approved treatment of amivantamab after approval in regional medical councils [32].

As there are currently no targeted treatments for patients with activating EGFR exon20ins mutations available, the current SoC in Denmark is platinum-based chemotherapy, carboplatin in combination with pemetrexed, hereafter referred to as CP, in line with the International, European and Danish guidelines developed by DLCG [29-32]. Newly diagnosed patients with EGFR exon20ins mutations, require an upfront targeted therapy to improve their rapid disease progression and dismal outcomes with current SoC [13, 35-39, 44].

3.4 The intervention

Rybrevant® (amivantamab) is approved in Europe as monotherapy for treatment of adult patients with advanced NSCLC with EGFR exon20ins mutations, after failure of platinum-based therapy. On April 26th 2023, the DMC did not recommend amivantamab as monotherapy for the treatment of adult patients with advanced NSCLC with EGFR exon20ins, after failure of platinum-based therapy due to uncertainty about the efficacy as the submission was based on a phase 1b study [2]. The European commission granted an extension of the indication for amivantamab in combination with carboplatin and pemetrexed for the 1L treatment of adult patients with NSCLC with EGFR exon20ins mutations, which is the relevant indication in this assessment, issued on 27th of June 2024 [1]. The European Commission granted a further extension of the indication for amivantamab on 27 August 2024. The indication now includes amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy, including a third-generation EGFR TKI. This indication is not included in this STA [1].

Amivantamab, is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumours with activating EGFR exon 20 insertion mutations (exon20ins). Amivantamab binds to the extracellular domains of EGFR and MET. Amivantamab disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression [1].

Administering amivantamab and chemotherapy together is expected to provide several potential benefits with improved outcomes over those demonstrated with either agent alone [60]:

- Amivantamab will provide targeted inhibition of the EGFR pathway, while the chemotherapy may eliminate potential tumour cell populations with inherent EGFR TKI resistance, thereby delaying disease recurrence [60]
- The immune cell-directing activity of amivantamab (not associated with EGFR TKIs) may provide additional benefit arising from disruption of an inhibitory

tumour microenvironment and targeting of Fc receptor-bearing immune cells to tumour cells [60].

An overview of the intervention given in Table 3.

Table 3. Overview of intervention

Overview of intervention	
Indication relevant for the assessment	Amivantamab is indicated in combination with chemotherapy (carboplatin and pemetrexed) for the first-line treatment of adult patients with advanced NSCLC with EGFR exon20ins.
ATMP	N/A
Method of administration	Intravenous infusion Subcutaneous injection expected in [redacted]
Dosing	When used in combination with chemotherapy, amivantamab should be administered after carboplatin and pemetrexed in 21-days Cycles [3]. Amivantamab: 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3 [3]. Carboplatin: Area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles [3]. Pemetrexed: 500 mg/m2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression [3].
Dosing in the health economic model (including relative dose intensity)	1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3. Based on the PAPILLON patient characteristics, validated to be representative of the Danish patients, the health economic model assumes an average patient weight of 65.8 kg with 84% of the population to weigh less than 80 kg. The percentage of dose administrations that are skipped was derived from PAPILLON study and was calculated by dividing the number of doses that were observed to be given in PAPILLON by the doses expected to be given based on the label dosing using the time to treatment discontinuation. Based on the dose reductions observed in PAPILLON, a relative dose intensity (RDI) value was applied.

Overview of intervention	
Should the medicine be administered with other medicines?	Prior to the initial infusion of amivantamab on Week 1 (Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of infusion-related reactions (IRRs). For all subsequent doses, antihistamines and antipyretics should be administered. Glucocorticoid administration is required for Week 1, Days 1 and 2 doses only and as necessary for subsequent infusions. Antiemetics should be administered as needed. Amivantamab is used in combination with chemotherapy, CP.
Treatment duration / criteria for end of treatment	It is recommended that patients are treated with amivantamab until disease progression or unacceptable toxicity. In the PAPILLON study, carboplatin was administered up to 12 weeks, while pemetrexed was administered until progression or unacceptable toxicity. Amivantamab + CP are treat-to-progression therapies. Patients with BICR-confirmed disease progression were optionally allowed to switch to 2L amivantamab monotherapy.
Necessary monitoring, both during administration and during the treatment period	Amivantamab should be administered by a healthcare professional with access to appropriate medical support to monitor and manage any IRRs.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Before initiation of amivantamab therapy, EGFR exon20ins mutation-positive status must be established by NGS testing. NGS testing is a standard method used in the Danish clinical praxis [2], thus, no new testing routine needs to be implemented in Denmark with amivantamab. Testing of mutation are not integrated in the CE-model as it is assumed all the patients have already been diagnosed with NSCLC with EGFR exon20ins.
Package size(s)	Amivantamab 350 mg concentrate for solution for infusion x 1 vial. One mL of concentrate for solution for infusion contains 50 mg amivantamab. One 7 mL vial contains 350 mg of amivantamab.

3.4.1 The intervention in relation to Danish clinical practice

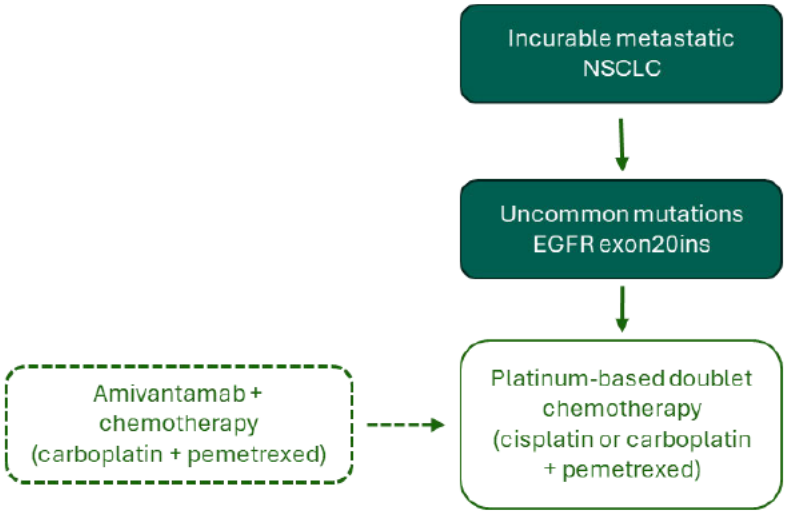
According to the indication and the PAPILLON trial, amivantamab in combination with CP is expected to be relevant for adult Danish patients with advanced NSCLC with EGFR exon20ins mutations in the 1L setting and will be an additional treatment option to the current standard of care (SoC), which consist of CP alone (Figure 1).

As previously mentioned, as there is no recommended targeted therapy for EGFR exon20ins in Denmark, platinum-based doublet chemotherapy is the SoC in the Danish

clinical practice aligned with international, European and Danish guidelines [29-32], as the currently preferred 1L treatment [2].

Amivantamab in combination with CP is expected to be the first targeted regimen in Denmark for patients with exon20ins in the 1L setting, that demonstrated superior efficacy versus CP alone in newly diagnosed patients in the PAPILLON trial, the first and only positive phase III RCT conducted in patients with rare, poor prognosis EGFR exon20ins mutations [61, 62].

Figure 1. Treatment algorithm incurable NSCLC in Denmark



Note: Based on Danish treatment guidelines for first line treatment of oncogene-driven non-small cell lung cancer [32].

Abbreviations: exon20ins, exon 20 insertion mutations; NSCLC, non-small cell lung cancer.

3.5 Choice of comparator

As previously described, there are no approved targeted therapies for patients with EGFR exon20ins-positive NSCLC in the 1L setting in Denmark [54] and the current preferred 1L treatment is platinum doublet chemotherapy consisting of carboplatin plus pemetrexed.

The relevant comparator in Denmark for this assessment is CP, as it reflects the current SoC for this patient population according to treatment practice and it is in line with the PAPILLON trial. An overview of the comparator is given below.

Table 4. Overview of comparator

Overview of comparators	Carboplatin	Pemetrexed
Generic name	Carboplatin "Accord"	Pemetrexed "Fresenius Kabi"
ATC code	L01XA02	L01BA04
Mechanism of action	Carboplatin, induces changes in the super helical conformation	Pemetrexed works by inhibiting three enzymes used in purine

	of DNA, interfering with the replication and suppressing growth of the cancer cell	and pyrimidine synthesis—thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA, which are required for the growth and survival of both normal cells and cancer cells.
Method of administration	Intravenous infusion	Intravenous infusion
Dosing	The recommended dosage of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m² as a single short-term IV dose administered by a 15 to 60 minutes infusion. Alternatively, the Calvert formula shown below may be used to determine dosage: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]	In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of pemetrexed is 500 mg/m2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	Carboplatin: Area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles [3]	Pemetrexed: 500 mg/m^2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression [3] Based on the PAPILLON patient characteristics, validated to be representative of the Danish patients, the health economic model assumes an average patient weight of 65.8 kg with a BSA of 1.7 m². The percentage of dose administrations that are skipped was derived from PAPILLON study and was calculated by dividing the number of doses that were observed to be given in PAPILLON by the doses expected to be given based on the label dosing using the time to treatment discontinuation.

		Based on the dose reductions observed in PAPILLON, a relative dose intensity (RDI) value was applied.
Should the medicine be administered with other medicines?	No	To reduce risk of skin reactions, a corticosteroid should be given the on the day of pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day. To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.
Treatment duration/ criteria for end of treatment	In the PAPILLON study, carboplatin was administered until progression or unacceptable toxicity. Carboplatin is a treat-to-progression therapy.	In the PAPILLON study, pemetrexed was administered until progression or unacceptable toxicity. Pemetrexed is a treat-to-progression therapy.
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No
Package size(s)	10 mg/ml in a vial of 45 ml	25 mg/ml in a vial of 20 ml

3.6 Cost-effectiveness of the comparator(s)

The comparator regimen CP used in the present submission is in line with the clinical trial PAPILLON and is a well-established chemotherapy regimen for advanced metastatic NSCLC in the Danish clinical practice. Moreover, DMC have previously stated that in EGFR exon20ins NSCLC, most patients receive CP in 1L [2]. Furthermore, the cost of CP is low compared to amivantamab. Amivantamab in the 1L setting is given in combination with chemotherapy composed of carboplatin + pemetrexed (CP), thus, it is an addition to the already existing SoC, and no supplementary analysis for the comparator is therefore provided.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The key efficacy outcomes considered relevant to evaluate the effect of amivantamab + CP compared to CP alone are based on the PAPILLON clinical trial [3] and include progression free survival (PFS), PFS after first subsequent therapy (PFS2) and overall survival (OS) (Table 5). Other important efficacy outcomes measured in PAPILLON are objective response rate (ORR), and duration of response (DOR) (see Appendix B). PFS and OS is included in the health economic analysis and PFS2 are included as an important outcome in this application, clinical experts in Denmark recognised the importance of disease progression to prevent morbidity of the disease [63].

Table 5. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression free survival (PFS) PAPILLON	Median follow-up of 14.9 months (range 0.3-27)	PFS is defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurs first).	PFS was investigated using RECIST v1.1 guidelines, as assessed by blinded independent central review (BICR).
PFS after first subsequent treatment (PFS2) PAPILLON	Median follow-up of 14.9 months - the median PFS2 was not evaluable.	Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.	Analysed using the same method as the analysis of PFS.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) PAPILLON	Evaluated at median follow-up of 14.9 and 20.9 months (October 2023)	OS was defined as the time from randomization to death.	Analysed using the same methodology and model as for the analysis of PFS. Conducted at 2 timepoints: at the time of the primary analysis of PFS and at 20.9 months median follow-up.

*Based on data cut-off 3rd May 2023, except for OS (31st October 2023).

Validity of outcomes

Treatment objectives for patients with advanced NSCLC include prolongation of PFS and OS and maintaining/improving HRQoL. All the relevant efficacy outcomes were sourced from the PAPILLON trial. The primary objective of the PAPILLON trial was to assess the efficacy, as indicated by BICR-assessed PFS, of amivantamab + CP compared to CP alone as a 1L treatment in patients with locally advanced or metastatic NSCLC and EGFR exon20ins [3]. The key efficacy outcomes presented in the submission were presented in previous assessments [2] and are relevant endpoints used to evaluate clinical efficacy in oncology, including NSCLC. OS and PFS are relevant clinical endpoints used to evaluate the efficacy of treatment and useful to model the disease progression.

4. Health economic analysis

A cost-utility analysis was performed for this submission, in line with standard methodology as described by NICE and DMC guidelines [64] through the use of a cost effectiveness model (CEM).

4.1 Model structure

A *de novo* CEM was developed to conduct a cost-effectiveness analysis for amivantamab + CP, reflecting the clinical trial evidence and patient pathway.

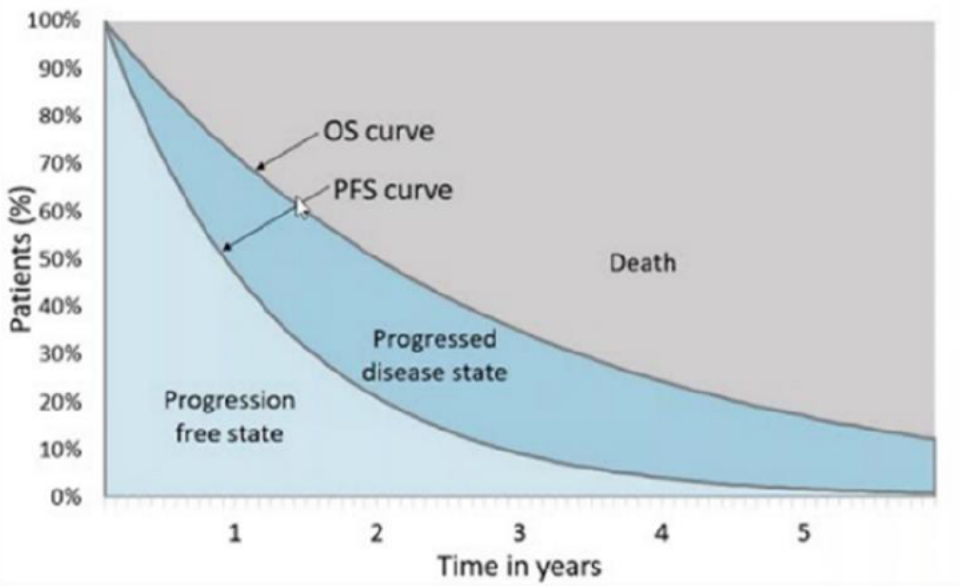
The CEM uses a partitioned survival model (PSM) approach with three health states: progression-free, post-progression and death. It is assumed that all patients start in the progression-free state. From the progression-free health state, patients may transition to the other health states or remain in this health state at each model cycle. Following progression, patients are unable to transition back to the progression-free health state and can only transition to the 'dead' state, an absorbing health state, or stay in the post-progression state.

This approach aligns with standard health economics practices concerning oncology [65]. This structure is appropriate for the Danish model adaptation where PFS and OS are

modelled independently, and the proportions of patients in each health state over time are derived directly from the PFS and OS projections using an area under the curve approach (Figure 2).

The approach also represents the clinical pathway for NSCLC in that a patient's treatment course and outcomes will depend primarily on whether their disease has progressed or if they remain progression-free, which is in line with the Danish treatment guidelines [54].

Figure 2. Model structure



Abbreviations: OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model.

4.2 Model features

The model features are described in Table 6.

Table 6. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with locally advanced or metastatic NSCLC with EGFR exon20ins mutations	Same population as described in section 3.2
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	30 years	Based on the starting cohort age, assumed to be sufficient length to capture all differences in costs and outcomes between the technologies being compared,

Model features	Description	Justification
		in line with the DMC guidelines.
Cycle length	1 week	Allows capturing the varied dosing schedules of comparators
Half-cycle correction	Yes	To account for the transition of patients from one health state to another happening in a continuous process
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Amivantamab + CP	The technology being assessed
Comparator(s)	CP alone	Current standard of care in Danish treatment praxis, as recommended in clinical treatment guidelines and, Danish clinical expert [63, 66]
Outcomes	OS and PFS assessed by BICR	PFS and OS are used to calculate patients' time in each model health state over time derived directly from the PFS and OS projections As the intervention and comparator are treat until progression therapies, the duration of treatment should be based on PFS.

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment and health economic analysis are based on the head-to-head study PAPILLON, an ongoing, phase III, randomised, open-label, parallel, multicentre trial in treatment-naïve patients with locally advanced or metastatic NSCLC and EGFR exon20ins conducted to assess the efficacy and safety of amivantamab + CP vs. CP alone [3, 60, 67].

As the submission is based on the head-to-head study that included the relevant comparison, a systematic literature review (SLR) was not conducted, and not deemed relevant for the decision problem.

Table 7 includes an overview of the relevant literature used in this assessment.

Table 7. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. New England Journal of Medicine. 2023;doi:10.1056/NEJMoa2306441[60] Janssen Research & Development. (Data on File). Clinical Study Report (Primary Analysis-Final). A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (PAPILLON). 5	PAPILLON	NCT04538664	Start: 13/10/20. Completion (estimated): 31/1/26. Data cut-off: 03/05/23 and 31/10/23 (OS) Future data cut-offs: September 2025	Amivantamab plus Chemotherapy (carboplatin and pemetrexed) vs. Chemotherapy alone (carboplatin and pemetrexed) for adult patients with NSCLC with EGFR Exon 20 Insertions.

Reference (Full citation incl. reference number)*	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
September. 2023. [68]				

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Patients' functioning and overall HRQoL were assessed in the PAPILLON study. In the trial, patients completed patient-reported outcome measures related to their HRQoL, including the EuroQol Questionnaire, Five Dimensions, Five Levels (EQ-5D-5L), European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Patient-Reported Outcomes Measurement Information System Physical Function (short-form; PROMIS-PF) and EQ-VAS instruments [3].

The health economic analysis included health state specific utilities for progression free and progressed disease based on the PAPILLON with EQ-5D-5L utility scores derived using Danish specific utility weights. In addition, utility decrements associated with AEs were sourced from the relevant literature and from previous NICE appraisals.

The relevant literature for HRQoL is presented in Table 8.

Table 8. Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. New England Journal of Medicine. 2023;doi:10.1056/NEJMoa2306441[60], Analysis of PAPILLON data on file. Janssen Research & Development. (Data on File). Clinical Study Report (Primary Analysis-Final). A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed	Progression-free: 0.885 Progressed disease: 0.826 Death: 0	Section 10

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (PAPILLON). 5 September. 2023 [68]		
Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84. doi: 10.1186/1477-7525-6-84 [published Online First: 2008/10/23] [69].	Anaemia: -0.073 Paronychia:-0.032 (assumed) Asthenia: -0.073 Neutropenia:-0.090 Leukopenia:-0.090 (assumed) Rash:-0.032	Section 10.4.2
National Institute for Health and Care Excellence (NICE). Osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer [TA653] 2020 [Available from: https://www.nice.org.uk/guidance/ta653 accessed 8 November 2023 [70].	Hypokalaemia: -0.050	Section 10.4.2
Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ* 2013;14(5):749-59. doi: 10.1007/s10198-012-0419-2 [published Online First: 2012/09/04][71].	Thrombocytopenia: -0.108	Section 10.4.2

5.3 Literature used for inputs for the health economic model

The clinical inputs (OS and PFS) were based on the head-to-head trial, PAPILLON, and were extrapolated over time, see further section 8.1.1. Unit cost inputs were based on publicly available literature relevant for Denmark for 2024, medicinpriser.dk, the DMC "Catalogue for estimating unit costs" (Katalog for værdisætning af enhedsomkostninger) and AE cost from Sundhedsdatastyrelsen using the relevant Danish DRGs costs. Resource use was estimated by a Danish clinical expert and not based on literature.

The relevant model inputs and associated literature used in the health economic model are listed in Table 9.

Table 9. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. New England Journal of Medicine. 2023;doi:10.1056/NEJMoa2306441[60] Janssen Research & Development. (Data on File). Clinical Study Report (Primary Analysis-Final). A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (PAPILLON). 5 September. 2023. [68]	OS and PFS	Based on PAPILLON	See section 6.1.4
Publicly available literature	Cost inputs	Drug costs were sourced from medicinpriser.dk, administration, monitoring cost and patient cost from the DMC report of valuation of unit costs and AE cost from relevant Danish DRGs. Resource used were estimated by clinical	See further section 11

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
		experts and not based on literature.	

6. Efficacy

6.1 Efficacy of amivantamab in combination with platinum-based chemotherapy compared to platinum-based chemotherapy alone for 1L treatment of patients with advanced NSCLC and EGFR exon20ins mutation

6.1.1 Relevant studies

The main clinical trial to inform the efficacy of amivantamab + CP versus CP alone, for the 1L treatment of adult patients with advanced NSCLC with activating EGFR exon20ins mutations, is the PAPILLON trial.

PAPILLON (NCT04538664) is an ongoing, phase III, randomised, open-label, parallel, multicentre trial in treatment-naïve patients with locally advanced or metastatic NSCLC and EGFR exon20ins conducted to assess the efficacy and safety of amivantamab + CP vs. CP alone [3, 67]. PAPILLON is the first and only phase III randomised controlled trial for patients with exon20ins in the 1L setting.

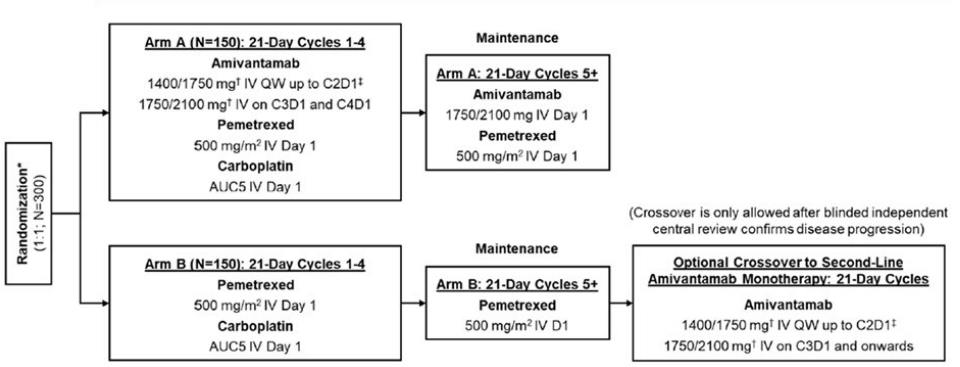
Patients were randomised in a 1:1 treatment ratio to Arms A (amivantamab + CP) and B (CP alone) (Figure 4), stratified by history of brain metastases (yes vs. no), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) and prior EGFR TKI use (yes vs. no) [3]. Treatment was administered in cycles of 21 days until disease progression or treatment discontinuation [3]. The dosing of the two arms; Arm A (amivantamab + CP) and Arm B (CP alone) have previously been described in Table 3 and Table 4.

Patients in CP arm with BICR-confirmed disease progression were optionally allowed to switch to 2L amivantamab monotherapy. As per 31 October 2023, among the 155 patients randomly assigned to the CP arm, 136 (88%) had progressive disease (an additional 7 patients died without prior assessed PD), 78 (57%) switched to amivantamab monotherapy in the 2L, these patients are hereafter referred to as 'per-protocol amivantamab switchers'.

Amivantamab monotherapy in the 2L setting is not recommended in Denmark, and therefore, an intention-to-treat (ITT) analysis of OS may be biased when patients switch to a treatment that is not available in real-world settings. To adjust for crossover in PAPILLON, three advanced methods commonly accepted as valid approaches including inverse probability of censoring weighting (IPCW), two-stage estimation (TSE) methods, and rank-preserving structural failure time (RPSFT) models to generate unbiased estimates of OS in case of treatment switching were applied to PAPILLON OS data (31 October 2023 data cut). This enabled the estimation of the OS benefit for amivantamab + CP versus CP in the absence of treatment switching to 2L amivantamab from the CP arm. In general, the results from the crossover analyses demonstrate the actual OS benefit of amivantamab + CP versus CP to be more apparent in comparison to the ITT analysis.

Both the IPCW approach and TSE method had greater face validity compared to the RPSFT method. The IPCW approach in, was used in the base case in the cost-effectiveness analysis, particular showcased consistent results when compared to real-world evidence (NECTAR) compared with the rest of the others treatment switching adjustment methods used.

Figure 3. PAPILLON Study Design [3]



* Stratification based on brain metastases (yes vs. no), ECOG performance status (0 vs. 1), prior EGFR TKI use (yes vs. no). † Doses shown by body weight (<80 kg/≥80 kg). ‡ Cycle 1: Days 1/2 (split dose), 8 and 15; Cycle 2: Day 1. Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; D = day; IV = intravenously; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; QW = once weekly; TKI = tyrosine kinase inhibitor.

PAPILLON study results for the ITT analysis for the primary endpoint PFS by BICR and PFS after first subsequent treatment (PFS2), based on investigator assessment were based on the clinical data cut-off of 03 May 2023 with a median follow up of 14.92 months. OS data ITT analysis was based on a later data cut-off of 31 of October 2023 with a median follow-up time in the interim analysis of OS is 20.9 months (see section 6.1.4). This additional interim analysis was conducted due to a request by EMA and was only done for OS.

Crossover adjusted OS among patients who crossed over to 2L amivantamab after treatment with CP (n=78) are presented in section 6.1.4.4 and Appendix D.2.9.

PFS by investigator, ORR and DoR were based on the clinical data cut-off 3 May 2023, results are presented in Appendix B.

An overview of the trial design is shown in below, Table 10. Further details are described in Appendix A.

The ongoing trials for amivantamab are listed in Appendix A (Table 55).

Table 10. Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
PAPILLON (NCT04538664)	Phase III, randomised, open-label, parallel, multicentre trial	Ongoing, data cut-off date of 3rd May 2023, and interim analysis (OS only) with data cut-off 31st of October 2023.	Adult treatment-naïve patients with locally advanced or metastatic NSCLC and EGFR ex20ins.	Amivantamab + chemotherapy (carboplatin + pemetrexed) **Cycles 1 through 4:** • Amivantamab 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly up to Day 1 of Cycle 2 (i.e., for the first 4 weeks), followed by 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of Cycle 3 and Cycle 4. The first infusion of amivantamab was split between Day 1 and Day 2 of Cycle 1 (350 mg on Day 1 and the remainder on Day 2). • Carboplatin area under the concentration time curve 5 mg/mL per minute (AUC 5) by IV infusion and pemetrexed 500 mg/m^2 (with vitamin supplementation) and on Day 1 of each cycle, for up to 4 cycles.	Chemotherapy (carboplatin + pemetrexed) alone. **Cycles 1 through 4:** • Carboplatin AUC 5 by IV infusion and pemetrexed 500 mg/m^2 (with vitamin supplementation) and on Day 1 of each cycle, for up to 4 cycles **Cycle 5 until disease progression:** • Pemetrexed 500 mg/m^2 by IV infusion on Day 1 of each cycle (i.e., every 3 weeks) as maintenance.	PFS as determined by BICR using RECIST 1.1, median follow-up of 14.9 months. ORR BICR-assessed. OS assessed at 2 timepoints: at 14.9 months and approximately at 20.9 months follow-up. PFS2 as determined by BICR using RECIST 1.1, median follow-up of 14.9 months. DOR determined with KM plot. TTD as determined by BICR, median follow-up 14.9 months. HRQOL; Patients' functioning and overall HRQoL Was measured by the

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				Cycle 5 until disease progression: • Amivantamab 1,750 mg (2,100 mg if body weight is ≥ 80 kg) and pemetrexed 500 mg/m^2 by IV infusion on Day 1 of each cycle (i.e., every 3 weeks) as maintenance.		EORTC-QLQ-C30 health status and functioning scales, Patient-Reported Outcomes Measurement Information System – Physical Function (PROMIS-PF) and EQ-5D VAS Overall safety and tolerability All efficacy outcomes presented as per 03/05/2023 data cut-off, with the integration of OS data from the 31/10/2023 data cut-off.

6.1.2 Comparability of studies

Not relevant as the only study included in the comparison is the head-to-head trial PAPILLON, the first clinical trial to evaluate amivantamab + CP compared to the current SoC consisting of CP in the relevant population.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients included in the PAPILLON study are presented in Table 11. Since the comparison is based on a head-to-head study, differences in baseline characteristics are presented between the different study arms. Among all randomised patients in PAPILLON, demographics and baseline characteristics were well-balanced between the study arms (Table 11). The median age of patients in the amivantamab + CP and the CP alone arms was 61 years (range 27 to 86) and 62 years (range 30 to 92), respectively [61]. Most patients in the amivantamab + CP and CP arms were female (56% and 60%, respectively), weighed <80 kg (86% and 83%, respectively), were Asian (64% and 59%, respectively) and had an ECOG performance status of 1 (65% of both arms) [61].

Table 11. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	PAPILLON	
	Amivantamab + CP (N = 153)	**CP alone (N = 155)**
Median age, years (range)	61 (27 to 86)	62 (30 to 92)
Female n (%)	85 (56)	93 (60)
Race or ethnic group,† n (%)		
Asian	97 (64)	89 (59)
Black	2 (1)	0
American Indian or Alaska Native	1 (1)	2 (1)
White	49 (32)	60 (39)
Multiple	1 (1)	0
Unknown	1 (1)	1 (1)
Body weight, n (%)		
<80 kg	132 (86)	128 (83)
ECOG performance status, n (%)		

0	54 (35)	55 (36)
1	99 (65)	100 (65)
History of smoking, n (%)		
Yes	65 (43)	64 (41)

ECOG = Eastern Cooperative Oncology Group; †Reported by patients. In some regions, reporting of race was not required. Multiple includes one patient who selected Black or African American and White.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population in the health economic model aligns with the PAPILLON trial inclusion criteria, encompassing adult patients with locally advanced or metastatic NSCLC characterised by EGFR exon20ins mutations, who are treatment naïve and not amenable to curative therapy. The patient characteristics used in the health economic model, relevant for Denmark, are described in Table 12 based on the PAPILLON trial.

The model inputs used included patient age, percentage of female, and inputs relating to dosing of the intervention and comparator i.e. kg body weight, body surface area (BSA) and percentage of patients below 80 kg (Table 12). According to a Danish clinical expert [63], Danish patients in a real-world setting are expected to be slightly older than the trial population in PAPILLON as it is usually the case with real-world vs trial settings, but the baseline characteristics were confirmed to be relevant for Denmark.

Baseline characteristics inputs were varied in the sensitivity analysis.

Table 12. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population	Value used in health economic model [3]
Age (mean)	59.6 years	59.6 years
Gender (% of female)	58%	58%
Patient weight (mean)	65.8 kg	65.8 kg
Body surface area (mean)	1.7 m^2	1.7 m^2
Percentage of <80 kg	84%	84%

6.1.4 Efficacy – results per PAPILLON

The results from the ITT analysis are presented below for the latest available data cut-off, May 03, 2023 for PFS and PFS2, and the October 31, 2023 data cut-off for OS.

Cross over adjusted OS among patients who crossed over to amivantamab 2L after treatment with CP are presented in from the October 31, 2023 data cut-off.

Table 15 in the comparative analysis section 7.1.3, presents the summary results for the key outcomes used in this assessment and relevant differences between the treatment arms, including PFS, PFS2 and OS and the results from the cross over adjusted OS. Further details have been included in Appendix B.

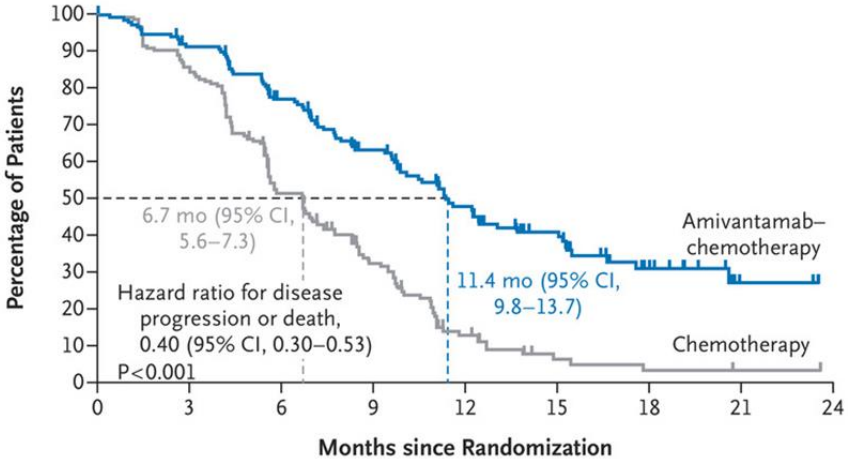
The results for other outcomes in PAPILLON, from the ITT analysis, which are ORR, DOR and TTDD from the May 03, 2023 data cut-off, are presented in Appendix B.

6.1.4.1 Progression free survival (Intention-to-treat analysis)

The results presented are from the ITT analysis, with the May 03 2023, data cut-off. The analysis was performed after 216 BICR-assessed PFS events had been observed. Of the 216 BICR-assessed PFS events, there were 84 events in the amivantamab + CP arm and 132 events in the CP arm [68]. The results showed that the primary endpoint was met, with amivantamab + CP demonstrating a longer median PFS (mPFS) by BICR of 11.4 months (95% CI: 9.8, 13.7) compared with 6.7 months (95% CI: 5.6, 7.3) with CP [61]. The event-free rates in the amivantamab + CP and CP alone arms were 48% and 13%, respectively, at 12 months and 31% and 3% at 18 months [61].

Amivantamab + CP significantly reduced the risk of disease progression or death by 60% vs. CP alone (HR 0.40 [95% CI: 0.30, 0.53]; p<0.001) (Figure 4). The Kaplan-Meier plot of PFS in Figure 4 shows a distinct early separation between the treatment arms favouring amivantamab + CP following the second disease assessment (i.e., after completion of 4 cycles of treatment) [68].

Figure 4. Primary endpoint: PFS by BICR for amivantamab + CP versus CP at data cut-off 03 May 2023 (Intention-to-treat analysis) [61]

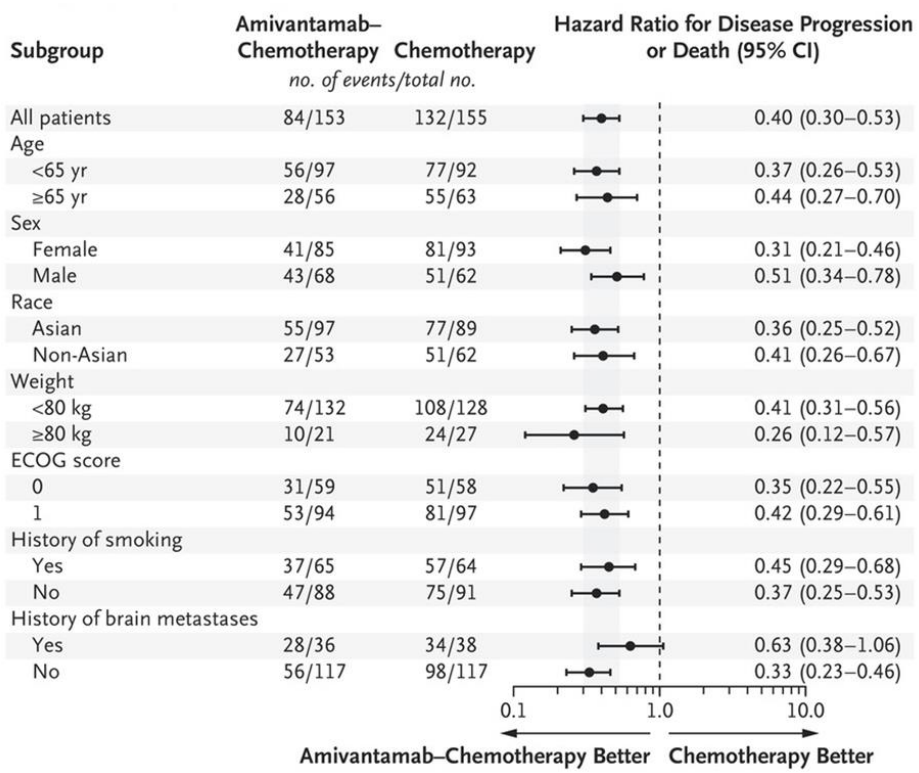


No. at Risk									
Amivantamab–chemotherapy	153	135	105	74	50	33	15	3	0
Chemotherapy	155	131	74	41	14	4	2	1	0

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CP = carboplatin + pemetrexed; PFS = progression-free survival. Censoring of data is indicated by tick marks and median PFS is indicated by dashed lines.

Amivantamab + CP also demonstrated consistent PFS benefit by BICR across all prespecified clinically relevant subgroups, although the 95% CI included 1 in the subgroup of patients aged ≥75 years (n=27) and among patients with a history of brain metastases at baseline (n=71)(Figure 5)[68]. Notably, the treatment benefit was independent of race and age [68].

Figure 5. PFS by BICR across prespecified clinically relevant subgroups [61] at data cut-off 03 May 2023



BICR = blinded independent central review; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival. The grey box indicates the 95% confidence intervals for the overall hazard ratio in all the patients.

Additionally, results of the unstratified analysis of BICR-assessed PFS were consistent with the primary stratified analysis, demonstrating a treatment benefit with amivantamab + CP (HR 0.389 [95% CI: 0.293, 0.516]) [68].

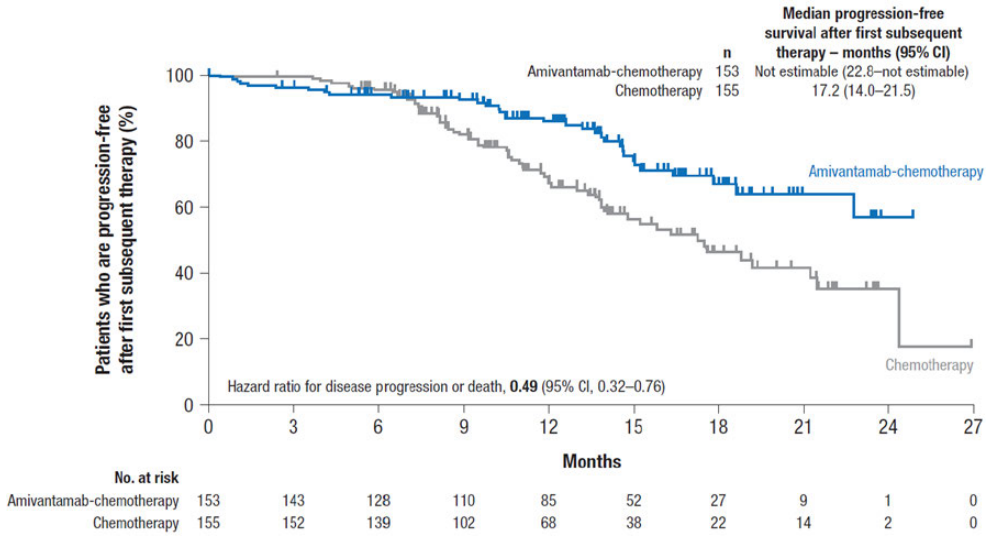
6.1.4.2 Progression free survival after subsequent therapy (Intention-to treat analysis)

Progression free survival after subsequent therapy (PFS2) was defined as the progression free survival after first subsequent therapy. Results are presented from the ITT analysis, at the May 03 2023, data cut-off. After a median follow-up of 14.92 months, there were

more PFS2 events in the CP arm compared with ACP arm 61 (39.4%) of participants versus 33 (21.6%)[68].

At a median follow-up of 14.9 months, the mPFS2 was not evaluable (95% CI: 22.8, not evaluable) for amivantamab + CP compared with 17.3 months (95% CI: 14.0, 21.5) for CP [61]. Amivantamab + CP led to a significant reduction of 51% in the risk of progression or death after first subsequent therapy compared with CP (HR 0.493 [95% CI: 0.320, 0.759]; nominal p=0.001), demonstrating a clinically meaningful improvement [68]. The event-free rate was 67% with amivantamab + CP and 46% with CP at 18 months [68].

Figure 6. PFS after first subsequent therapy (PFS2) for amivantamab + CP vs. CP at data cut-off 03 May 2023 (Intention-to-treat analysis)[61]



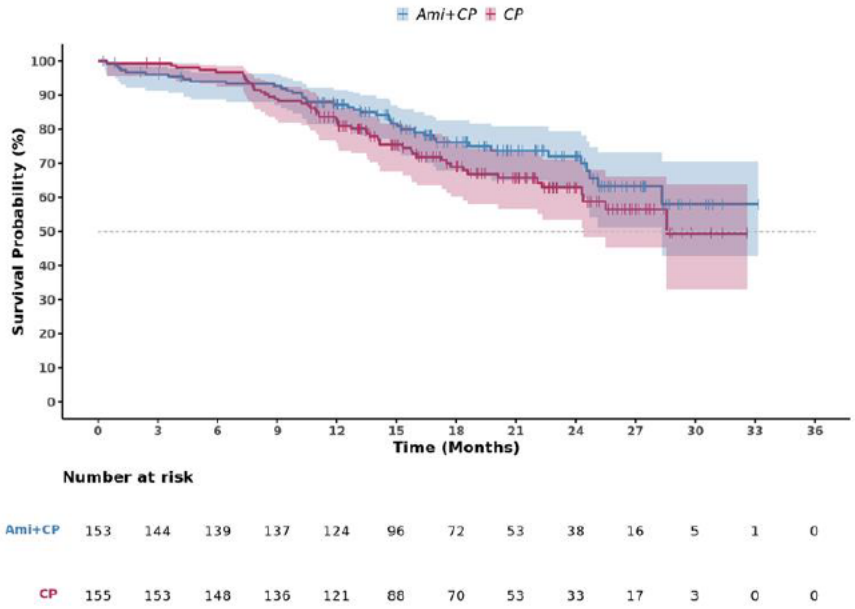
CI = confidence interval; CP = carboplatin + pemetrexed; NE = not evaluable; PFS = progression-free survival. Censoring of data is indicated by tick marks. Definitive treatment effects cannot be inferred by the 95% CI because widths have not been adjusted for multiplicity.

6.1.4.3 Overall survival (Intention-to-treat-analysis)

There was a total of 70 death events reported across both arms combined; 28 in the amivantamab + CP arm and 42 in the CP arm [68]. Results at the interim ITT OS analysis (33% maturity) with the May 03 2023 data cut-off there was a trend towards improved OS in the amivantamab + CP arm (HR 0.67 [95% CI: 0.42, 1.09]; p=0.11), despite 71 of 107 (66%) patients with disease progression in the CP arm receiving subsequent amivantamab monotherapy [68].

These data have been further updated with a new data cut-off from the October 31 2023 (Figure 7)[61]. The new OS shows a similar trend, with a HR of 0.756 [95% CI: (0.50, 1.140); p=0.18].

Figure 7. PAPILLON OS KM Curves for amivantamab + CP and CP at data cut-off 31 October 2024 (Intention-to-treat analysis)



Abbreviations: ACP = amivantamab + carboplatin + pemetrexed; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; OS = overall survival

Results of the unstratified interim OS analysis are presented in Table 13 [61]. At 24 months, 72% of patients were alive in the amivantamab + CP arm vs. 54% in the CP arm [61].

Table 13. Interim unstratified OS analysis for amivantamab + CP versus CP [61] at data cut-off 31 October 2024 (Intention-to-treat analysis)

OS	Amivantamab + CP (n=153)	CP (n=155)
No. of months, median (95% CI)	NE (NE, NE)	28.6 (24.3, NE)
Proportion of patients alive, % (95% CI)		
At 12 months	86 (79, 91)	82 (74, 87)
At 18 months	74 (64, 82)	68 (58, 76)
At 24 months	72 (61, 81)	54 (37, 68)
p value*	0.18	
HR (95% CI)*	0.756 (0.50, 1.140)	

CI = confidence interval; CP = carboplatin + pemetrexed; NE = not evaluable; OS = overall survival. * p value is from a log-rank test. HR is from proportional hazards model. HR <1 favours amivantamab + chemotherapy.

6.1.4.4 Cross over adjusted overall survival

The OS HR from the ITT analysis was 0.76 (0.50,1.14). From all patients randomized to the CP arm in PAPILLON, 78 patients (50%) switched to AMI in the 2L. Using the IPCW method, the method used in the base case of the health economic analysis, with stabilized weights led to an adjusted HR for OS of [redacted] comparing amivantamab + CP versus CP, in the absence of treatment switching (Table 14).

In the TSE method, the OS HR for amivantamab + CP versus CP with counterfactual OS for the 2L amivantamab switchers estimated using multivariable Weibull regression model was [redacted]). Finally, based on the RPSFT method, the adjusted HR for amivantamab + CP versus CP [redacted] Results were generally consistent across a range of sensitivity analyses. These results indicate that patients switching from CP to 2L AMI benefit from 2L AMI, and thus, the ITT-based estimate of the OS benefit likely underestimates the true survival benefit of amivantamab + CP versus CP (in the absence of treatment switching).

A summary of the unadjusted and adjusted OS HRs is presented in Table 14 and more detailed results obtained using each method are reported in Appendix D.2.9.

Table 14. Comparative Efficacy of amivantamab + CP versus CP on OS

Method	OS HR (95% CI)	*P*-value	Setting
ITT	0.76 [0.50, 1.14]	0.1839	No adjustment for switching
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

*Based on bootstrapping

Abbreviations: CI = confidence interval; HR = hazard ratio; IPCW = inverse probability of censoring weight; ITT = intention to treat; OS = overall survival; RPSFT = rank-preserving structural failure time; TSE = two-stage estimation

7. Comparative analyses of efficacy

A head-to-head study comparing the intervention and comparator was used as evidence of efficacy, hence some of the sections in chapter 7 have been omitted, as per the guideline [64]. Results from the comparative analysis are presented in Table 15 below.

7.1.1 Differences in definitions of outcomes between studies

Not relevant.

7.1.2 Method of synthesis

Not relevant.

7.1.3 Results from the comparative analysis

Results from the comparative analysis from the ITT analysis in PAPILLON for 1L EGFR ex20ins-positive NSCLC, amivantamab + CP demonstrated superior efficacy versus CP alone (Table 15). A significant mPFS benefit (11.4 vs. 6.7 months; p<0.001), long-term benefits in terms of prolonged PFS2, and a strong trend towards improved OS with amivantamab + CP (median not estimable vs. 28.6 months), despite the high proportion in the CP arm that crossed over to amivantamab monotherapy, which highlights the need to use the best regimen first.

Table 15. Results from the comparative analysis of amivantamab + CP versus CP for adult patients with NSCLC with EGFR exon20ins mutations

Outcome measure	Amivantamab + CP (N=153)	CP (N=153)	Result
PFS	Median: 11.4 mo. (95% CI: 9.8, 13.7)	Median: 6.7 mo. (95% CI: 5.6, 7.3)	4.7 mo. HR 0.40 (95% CI: 0.30, 0.53); p<0.001
PFS2	Median: NE (95% CI: 22.8, NE)	Median: 17.3 mo. (95% CI: 14.0, 21.5)	NE HR 0.493 (95% CI: 0.320, 0.759); nominal p=0.001
OS	Median: NE (95% CI: 28.3, NE)	Median: 28.6 mo. (95%CI: 24.3, NE)	NE HR: 0.756 (95% CI:0.50, 1.140); p=0.18

Abbreviations: CI=Confidence interval, CP=carboplatin + pemetrexed, HR=Hazard ratio, mo=months, NE=not estimable, OS=overall survival, PFS=Progression free survival. Note:* *p value* is from a logistic regression model stratified by ECOG performance status and history of brain metastases.† OR >1 favours amivantamab + chemotherapy.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Clinical data from the PAPILLON trial were used to model PFS and OS for amivantamab + CP and CP. The results are presented for the latest data cut of 03 May 2023 for PFS, with

additional OS data from the later data cut of 31 October 2023. Survival models were fitted to individual subject data from the trial. The standard survival models—the exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, and generalised gamma were fitted to the trial data.

The process of selecting a distribution was in line with NICE Decision Support Unit guidance [72, 73]. The process involves visual inspection of models against KM curves, statistical fit through AIC and BIC, and consideration of the extrapolation's clinical plausibility.

To ensure that parametric curves do not cross, PFS could not exceed OS; PFS hazards could not be less than OS hazards at any point. To ensure that PFS and OS extrapolations did not provide implausible estimates of mortality, mortality in the model was bound by the age- and gender-specific natural mortality of the general population, calculated using Danish life tables [74].

8.1.1 Extrapolation of efficacy data

8.1.1.1 Adjusting for cross-over

Cross-over occurs when patients switch from the control arm to the experimental arm during a trial, which can bias the OS analyses. As of the 31st of October 2023, data cut-off in PAPILLON, per protocol (n=78) patients received 2L amivantamab monotherapy as subsequent treatment after disease progression in the CP arm.

The NICE Decision Support Unit (DSU) advise that an intention-to-treat (ITT) analysis of OS is inappropriate when cross-over is allowed or subsequent treatment is not used (or used less frequently) in real-world settings [75]. To correct for this bias, statistical methods such as the two-stage estimation (TSE), rank preserving structural failure time (RPSFT), and inverse probability of censoring weight (IPCW) may be used. The key characteristics and assumptions of these methods are provided in Appendix D.

IPCW is particularly effective in adjusting for crossover because it weights patients based on the probability of remaining uncensored, thereby correcting for bias without making strong parametric assumptions and accounting for time-varying factors. The IPCW method can handle time-varying censoring and is less prone to problems when patient dropout or crossover occurs at various stages of the trial and is often the method of choice in oncology trials where long-term survival and dynamic treatment switching are common.

The IPCW per protocol method has been chosen for the base case, with the ITT population analysis (not adjusted for cross-over) presented in the Appendix D.

8.1.1.2 Extrapolation of PFS (BICR)

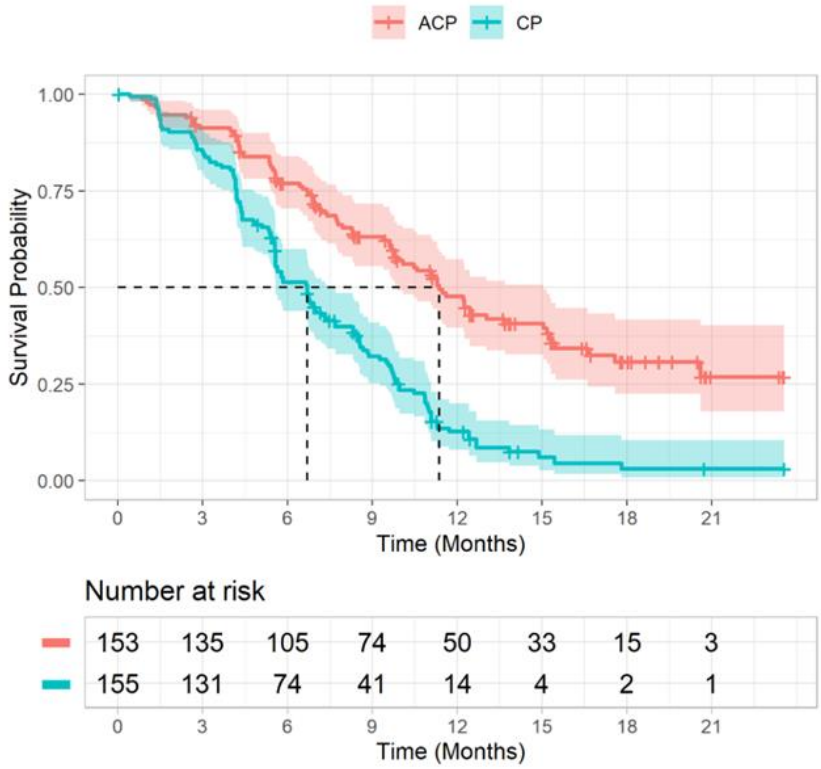
A summary of assumptions associated with the extrapolation of PFS as measured by BICR is presented in Table 16.

Table 16. Summary of assumptions associated with extrapolation of PFS (BICR)

Method/approach	Description/assumption
Data input	Clinical data from the PAPILLON trial (NCT04538664)[3], data cut 3rd May 2023
Model	The seven standard survival models were fitted to the individual subject data in PAPILLON. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No (D.1.3)
Function with best AIC fit	Intervention: Log-logistic Comparator: Gamma Best stratified fit: Gamma
Function with best BIC fit	Intervention: Log-logistic Comparator: Gamma Best stratified: Gamma
Function with best visual fit	Intervention: Gamma Comparator: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gamma Comparator: Gamma
Validation of selected extrapolated curves (external evidence)	Not available
Function with the best fit according to external evidence	Not available
Selected parametric function in base case analysis	Intervention: Gamma Comparator: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

PFS was the primary endpoint of the PAPILLON trial. Further details concerning the extrapolations of PFS can be found in Appendix D. Figure 8 shows the PFS (BICR) KM curves for amivantamab + CP and CP alone based on the clinical cut-off date of 03 May 2023.

Figure 8. PAPILLON PFS (BICR) KM curves for amivantamab + CP and CP



Abbreviations: ACP = amivantamab + carboplatin + pemetrexed; BICR = blinded independent central review; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; PFS = progression-free survival.

The long-term PFS extrapolations for amivantamab + CP and CP are presented in Figure 9Figure 12 and Figure 10Figure 11, respectively.

Figure 9. Long-term PFS (BICR) projections of CP

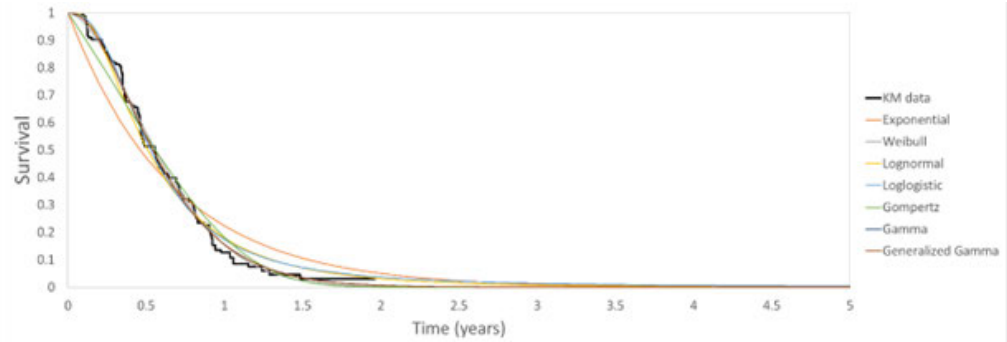
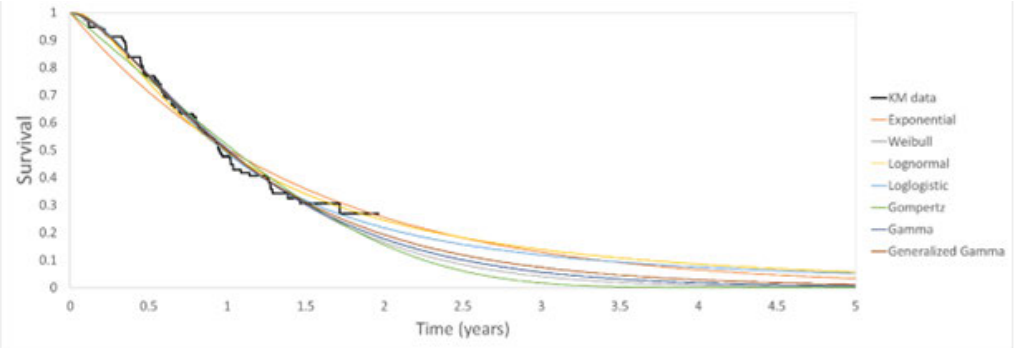


Figure 10. Long-term PFS (BICR) projections of amivantamab + CP

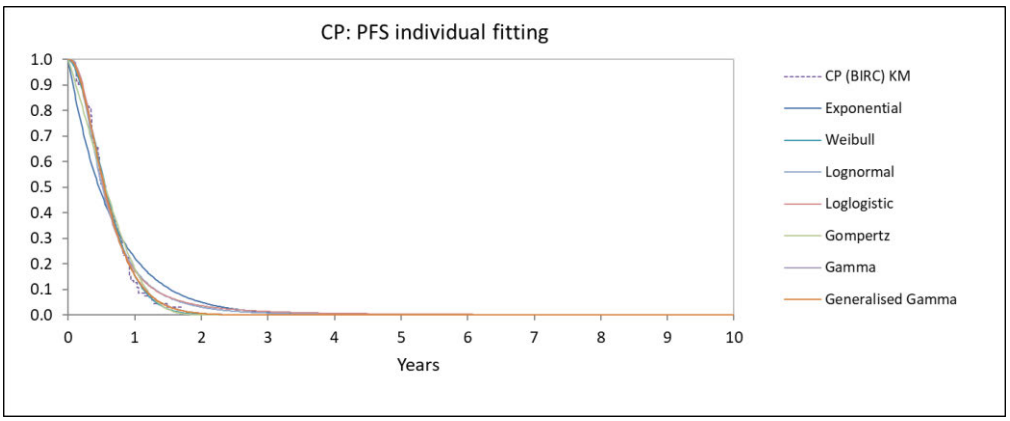


Section D.1 presents details on the goodness-of-fit, predicted landmark PFS rates, median, and estimated mean for each distribution for the amivantamab + CP and CP arm, respectively.

The PFS KM curve was mature for CP alone, and the decision on the base-case parametric distribution was based on the statistical fit and the clinical plausibility of the predictions. According to AIC and BIC, the gamma curve was the best-fitting distribution for the more mature CP arm (Table 60).

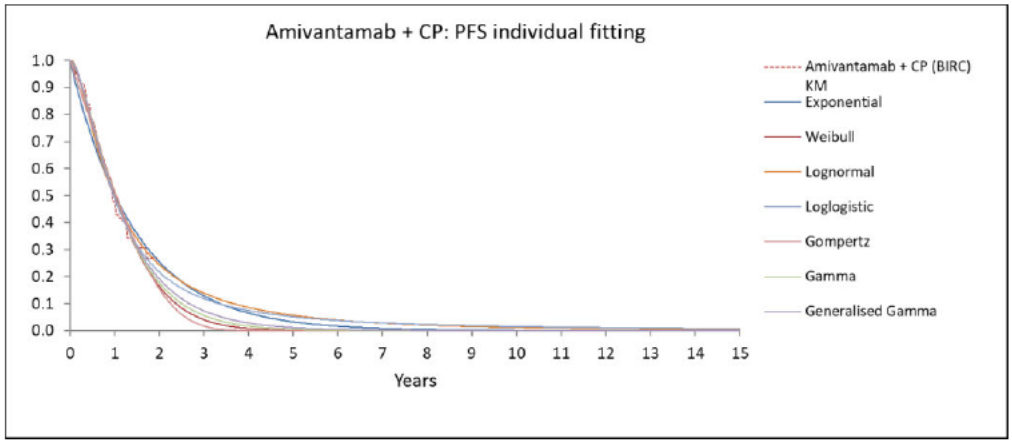
The gamma distribution was also a good fit for amivantamab + CP (Table 61). As there is no reason to expect different hazard shapes for the two arms in the model [72, 73], coupled with clinically plausible extrapolation (close to all subjects progressed at five years) the gamma distribution was selected for the base case. Alternative distributions were tested in scenario analyses.

Figure 11. Long-term PFS projections of CP alone



Abbreviations: BICR = blinded independent central review; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 12. Long-term PFS projections of amivantamab + CP



Abbreviations: BICR = blinded independent central review; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; PFS = progression-free survival

8.1.1.3 Extrapolation of OS

Table 17 shows a summary of assumptions associated with the extrapolation of OS.

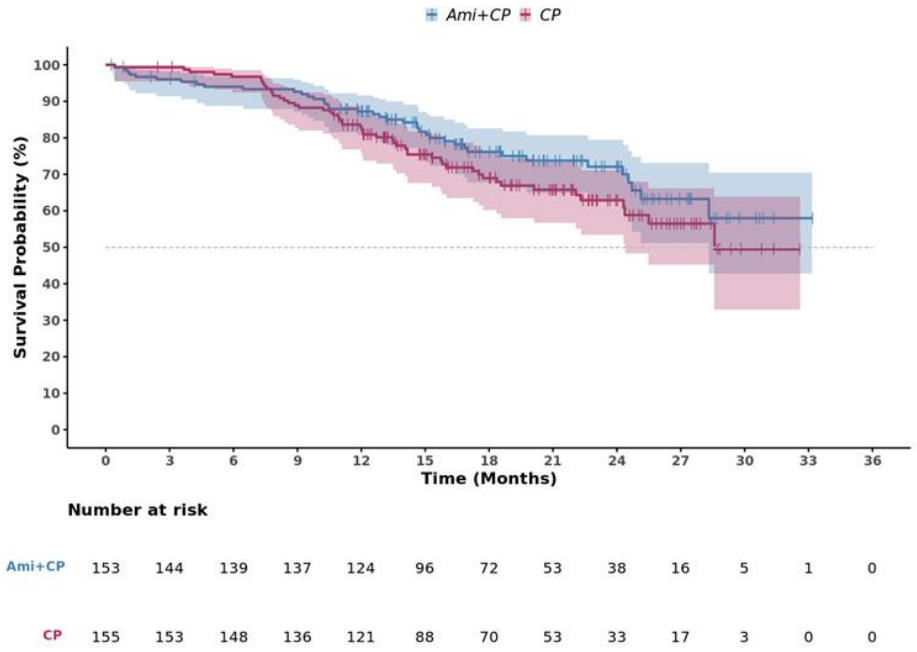
Table 17. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	Clinical data from the PAPILLON trial (NCT04538664)[3], data cut 31st October 2023
Model	The seven standard survival models were fitted to the individual subject data from PAPILLON. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No (see D.2.3)
Function with best AIC fit	Intervention: Gompertz Comparator: Log-logistic Stratified: Log-logisitic
Function with best BIC fit	Intervention: Exponential Comparator: Log-logistic Stratified: Log-logistic
Function with best visual fit	Intervention: Gamma Comparator: Gamma

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gamma Comparator: Gamma
Validation of selected extrapolated curves (external evidence)	Gamma, validated by a Danish clinician [66]
Function with the best fit according to external evidence	Not available
Selected parametric function in base case analysis	Intervention: Gamma Comparator: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Yes, IPCW as described in section D.2.9
Assumptions of waning effect	No
Assumptions of cure point	No

The extrapolation of OS from PAPILLON was based on data from the 31 October 2023 data cut. Figure 13 shows the OS KM curves for amivantamab + CP and CP based on the clinical cut-off date of October 2023.

Figure 13. PAPILLON OS KM Curves for amivantamab + CP and CP – October 2023.



Abbreviations: ACP = amivantamab + carboplatin + pemetrexed; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; OS = overall survival.

The base case analysis used the IPCW estimation for per protocol switches (n=78) to extrapolate OS in the CP arm. The IPCW was chosen for the base case because minimising bias, the flexibility in handling trial complexities, and provides clear, interpretable results.

Figure 14 shows the OS KM curves for CP and CP adjusted for treatment switch to amivantamab per protocol (n=78) using different adjustment methods.

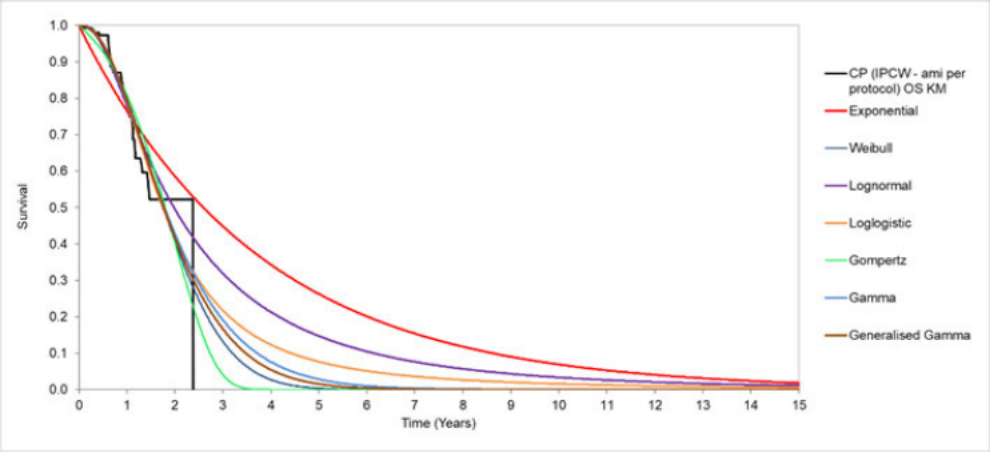
[redacted]

For CP, the log-logistic, gamma, and Weibull curves fit best according to AIC and BIC (Table 63). The Weibull appears overly pessimistic, with no survivors at five years (5-year survival has been reported to be 8% in this population [27]). The log-logistic, known to have a fat tail, predicts survivors beyond ten years for a population with a poor prognosis. The gamma distribution lies between these two, with an OS rate of 3% at five years and no survivors after ten years.

The gamma distribution shows good visual fit to the KM curves (Figure 15 and Figure 16) and the smoothed hazards (Figure 38 and Figure 39). Combining statistical fit, visual fit, and clinical plausibility, the gamma distribution was deemed the most suitable for extrapolating OS for the CP arm. A Danish clinician also considered the gamma distribution the most suitable for extrapolation OS in a Danish setting [66].

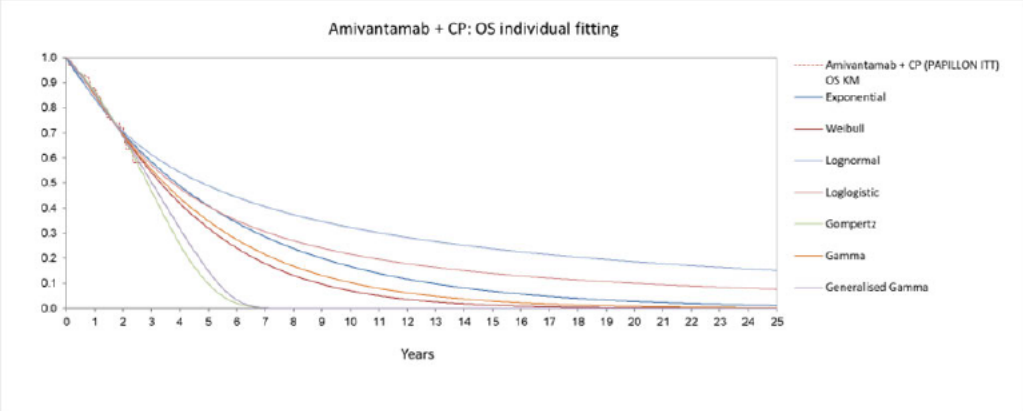
As for PFS there is no reason to assume different shapes for hazards between the two arms [72, 73]. The gamma distribution was selected for the base case extrapolation of OS. Given the statistical fit, the log-logistic and Weibull distributions were used in scenario analyses.

Figure 15. Long-term OS Projections of CP Using IPCW, amivantamab per protocol (n=78) – October 2023



Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; IPCW: inverse probability of censoring weight; OS = overall survival.

Figure 16. Long-term OS Projections of amivantamab + CP – October 2023



8.1.2 Calculation of transition probabilities

Not applicable.

Table 18. Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference

8.2 Presentation of efficacy data from [additional documentation] N/A

Not applicable.

8.3 Modelling effects of subsequent treatments N/A

Not applicable.

8.4 Other assumptions regarding efficacy in the model N/A

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

The overview of the treatment length and estimates in the model are described in Table 19 (undiscounted).

Table 19. Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
PFS			
Amivantamab + CP	15.26 months ("Engine Ami+CP" Cell P7)	12 months ("Engine Ami+CP" Cell P8)	11.4 months
CP only	7.68 months (Engine CP" Cell N7)	6.48 months (Engine CP" Cell n7)	6.7 months
OS			
Amivantamab + CP	55.68 months ("Engine Ami+CP" Cell R7)	41.4 months ("Engine Ami+CP" Cell R7)	Not estimable
CP only	24.6 months (Engine CP" Cell P7)	21.36 months (Engine CP" Cell P8)	28.6 months

Abbreviations: CP = carboplatin + pemetrexed; OS = overall survival; PFS = Progression-free survival.

In Table 20 the modelled average treatment length and time in each model health state are described, undiscounted and with no half cycle correction.

Table 20. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length (months)	Average time in PF state	Average time in PD state (Average time alive - average time in PFS)	Average time alive
Amivantamab + CP	15.00 months	15.00 months	40.56 months	55.56 months
CP only	7.56 months	7.56 months	16.92 months	24.48 months

Abbreviations: CP = carboplatin + pemetrexed; PD = progressed disease; PFS = progression-free survival.

9. Safety

PAPILLON safety results presented in this section are reported for the safety population (N=306; all treated patients who received 1L amivantamab + CP or CP alone) with a median follow-up of 14.9 months [61]. The definition of a safety event was from initial treatment until 30 days after discontinuation or start of secondary anticancer treatment.

Amivantamab + CP demonstrated a well-defined and tolerable safety profile that was consistent with the safety profile of the individual components and with the on-target activity of amivantamab against the EGFR and MET pathways [62]. Overall, treatment-emergent adverse events (TEAEs) occurred in 100% of patients treated with amivantamab + CP and 98% of patients treated with CP [61]. Serious adverse events (SAEs) were comparable between treatment arms: 37% for amivantamab + CP and 31% for CP [61]. TEAEs were manageable in both treatment arms with treatment interruptions and dose reductions [61]. Events leading to death within 30 days of the last study dose were low and comparable between treatment arms [61]. More specifically, 7 (4.6%) out of the 151 patients included in the safety analysis set died due to AEs in the amivantamab + CP arm, while 4 (2.6%) out of the 155 did in the CP arm [68].

9.1 Safety data from the clinical documentation

Table 21 present an overview of safety events from the clinical trial PAPILLON.

Table 21. Overview of safety events – DCO 3rd May 2023.

	Amivantamab + CP (n=151)[61]	CP (n=155)[61]	Difference, % (95 % CI)
Number of adverse events, n	N/A	N/A	N/A
Number and proportion of patients	151 (100)	152 (98)	2% (-0.20%, 4.20%)

	Amivantamab + CP (n=151)[61]	CP (n=155)[61]	Difference, % (95 % CI)
with ≥1 adverse events, n (%)			
Number of serious adverse events*, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	56 (37)	48 (31)	6% (-4.60%, 16.60%)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	114 (75)	83 (54)	21% (10.55%, 31.45%)
Number of adverse reactions, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	151 (100)	146 (94)	6% (2.26%, 9.74%)
Number and proportion of patients who had a dose reduction, n (%)	73 (48)	35 (23)	25% (14.64%, 35.36%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	36 (24)	16 (10)	14% (5.71%, 22.29%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0

Abbreviations: CP = carboplatin + pemetrexed; N/A = not available.

The most frequent TEAEs (any grade TEAEs occurring in ≥25% of patients and/or grade ≥3 TEAEs occurring in ≥5% of patients) regardless of grade and grade ≥3 are presented in Table 22 [61].

- In the amivantamab + CP arm, the most common all grade TEAEs were neutropenia (59%), paronychia (56%) and rash (54%), with neutropenia being the most common grade ≥3 TEAE (33%) [61].
- In the CP arm, the most common all grade TEAEs were anaemia (55%), neutropenia (45%) and nausea (42%), with neutropenia being the most common grade ≥3 TEAE (23%) [61].

Table 22. Any grade TEAEs occurring in ≥25% of patients and/or grade ≥3 TEAEs occurring in ≥5% of patients [61]

TEAE, n (%)	Amivantamab + CP (n=151)		CP (n=155)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Paronychia	85 (56)	10 (7)	0	0
Anaemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reactions	63 (42)	2 (1)	2 (1)	0
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
ALT increased	50 (33)	6 (4)	56 (36)	2 (1)
AST increased	47 (31)	1 (1)	51 (33)	1 (1)
Peripheral oedema	45 (30)	2 (1)	16 (10)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0

Hypokalaemia	32 (21)	13 (9)	13 (8)	2 (1)
Asthenia	30 (20)	8 (5)	29 (19)	4 (3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

The most frequent reasons for AE-related treatment discontinuation were the following [68]:

- In the amivantamab + CP arm, anaemia (3 patients [2.0%]), neutropenia (3 patients [2.0%]), pneumonitis (4 patients [2.6%]), infusion related reaction (3 patients [2.0%]), and decreased appetite (3 patients [2.0%]).
- In the CP arm, neutropenia (2 patients [1.3%]), and thrombocytopenia (3 patients [1.9%])[68].

The overall incidence of SAEs was comparable between treatment arms, with SAEs reported in 56 participants (37.1%) in the amivantamab + CP arm and 48 participants (31.0%) in the CP arm [62].

The most frequently reported treatment-emergent SAEs (reported in ≥2% of participant in any of the arms) were pneumonia (4.0% in the amivantamab + CP arm versus 2.6% in the CP arm), COVID-19 (2.0% in the amivantamab + CP arm versus 0.6% in the CP arm), vomiting (2.0% in the amivantamab + CP arm versus 0.6% in the CP arm), pneumonitis (2.6% in the amivantamab + CP arm versus 0% in the CP arm), pulmonary embolism (2.6% in both the amivantamab + CP and CP arms), dyspnea (0.7% in the amivantamab + CP arm versus 3.2% in the CP arm), pleural effusion (0.7% in the amivantamab + CP arm versus 3.2% in the CP arm), hypokalemia (2.0% in the amivantamab + CP arm versus 0.6% in the CP arm), thrombocytopenia (2.0% in the amivantamab + CP arm versus 3.2% in the CP arm), and anemia (0.7% in the amivantamab + CP arm versus 3.9% in the CP arm).

Of note, there was no preferred term reported with a frequency ≥5% [62]. Since there was no preferred term reported with a frequency ≥5%, the SAEs by system organ class with frequency of ≥ 5% recorded in PAPILLON are presented in Table 23. A list of all SAEs observed in PAPILLON are reported in Appendix F.

Table 23. Serious adverse events by system organ class (DCO 3rd May 2023)

Adverse events	Amivantamab + CP (N= 151)		CP (N=155)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Infections and infestations, n (%)	18 (11.9%)	N/A	10 (6.5%)	N/A
Gastrointestinal disorders	10 (6.6%)	N/A	4 (2.6%)	N/A

Adverse events	Amivantamab + CP (N= 151)		CP (N=155)	
Respiratory, thoracic and mediastinal disorders	8 (5.3%)	N/A	14 (9.0%)	N/A
Blood and lymphatic system disorders	5 (3.3%)	N/A	11 (7.1%)	N/A

Abbreviations: CP = carboplatin + pemetrexed.

In the model, AEs affect both the costs and the HRQoL of patients receiving treatment. AE costs are considered both for 1L treatment (i.e. amivantamab + CP or CP) and for subsequent treatment. The AE impact on HRQoL is only considered for 1L treatment, given that utility decrements for AEs are not expected to be a key model driver.

AEs are limited to treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the PAPILLON trial [76]. Table 24 presents the incidence of AEs associated with the first treatment, used as model inputs.

In the cost effectiveness analysis, the management of Grade 3–4 AEs were included in the costs of subsequent therapy. The AE incidence rates for each subsequent treatment regimen is presented in section 11.6.4.

Table 24. Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Anaemia	10.60%	12.26%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Paronychia	6.62%	0.00%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Hypokalaemia	8.61%	1.29%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of

Adverse events	Intervention	Comparator		
				patients in either treatment arm of the trial
Asthenia	5.30%	2.58%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Neutropenia	33.11%	22.58%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Leukopenia	11.26%	3.23%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Rash	11.26%	0.00%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial
Thrombocytopenia	9.93%	10.32%	PAPILLON	Treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the trial

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 25. Adverse events that appear in more than X % of patients N/A

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with	Number of adverse events	Frequency used in economic model	Number of patients with	Number of adverse events	Frequency used in economic model	Number of patients with	Number of adverse events

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	adverse events		for intervention	adverse events		for comparator	adverse events	
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Table 26 presents the included HRQoL instruments for the submitted application.

Table 26. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L questionnaire and EQ-VAS	PAPILLON	The EQ-VAS instrument was used to assess health-related quality of life in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone. Data from the EQ-5D-5L questionnaire was used to derive utilities for the model.
EORTC-QLQ-C30	PAPILLON	The EORTC-QLQ-C30 instrument was used to evaluate functioning domains and overall health, as well as common cancer symptoms. The instrument was not used in the model.
PROMIS-PF	PAPILLON	The 8 items of the PROMIS-PF v2.0 short form 8c were used to evaluate physical ability levels and daily living activities. The instrument was not used in the model.

In PAPILLON, patients completed patient-reported outcome measures related to their HRQoL, including the EuroQol Questionnaire, Five Dimensions, Five Levels (EQ-5D-5L), European Organization of Research and Treatment of Cancer Quality of Life

Questionnaire Core 30 (EORTC QLQ-C30), Patient-Reported Outcomes Measurement Information System Physical Function (short-form; PROMIS-PF)[3].

The EQ-5D-5L is a validated tool to measure health status and health utility, including mobility, self-care, usual activities, pain, discomfort, and anxiety/depression[77], and it was the tool used to assess HSUV in the model. The EORTC-QLQ-C30 assesses functioning domains and common cancer symptoms with recall in the past week[78]. PROMIS-PF is used to characterize and better understand overall health, level of physical disability, and general well-being. These two instruments were used to support the main EQ-5D-5L analysis.

PAPILLON PRO results presented in the following sections are reported for randomised patients who received at least one dose of study treatment and have at least one evaluable post-baseline PRO measurement [62, 79, 80]. Compliance at baseline was high (>97%) across all PRO measures in both the amivantamab + CP and the CP alone arms, with rates of compliance exceeding 80% through Cycle 31 [80].

A higher number of patients in the CP alone arm discontinued treatment, especially at later cycles, resulting in greater attrition rates in expected PRO assessments compared with the amivantamab + CP arm[80]. A notable decrease in sample sizes was observed in both treatment arms (after Cycle 13 for the CP arm and after Cycle 19 for the amivantamab + CP arm) which led to <25% of the baseline sample still remaining on treatment at later PRO assessments[80]. Overall, the PRO results suggest that the clinical benefits of treatment with amivantamab + CP were achieved without compromising patient HRQoL[79].

10.1 Presentation of the health-related quality of life EQ-5D-5L and EQ VAS

10.1.1 Study design and measuring instrument – EQ-5D-5L

The EQ-5D-5L instrument was used to evaluate overall HRQoL of the patients in both treatment arms[79]. The EQ-5D-5L is a self-administered questionnaire consisting of five dimensions (i.e., mobility, self-care, pain, usual activities, and anxiety/depression) and a health status rating scale. Each dimension has five levels of severity" corresponding to the degree of problems encountered: "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems." The instrument provides a simple descriptive profile for each participant.

EQ-5D-5L data were collected in the PAPILLON clinical study in line with the study protocol. All patients in the ITT population who had filled out the EQ-5D-5L questionnaire at baseline, as well as at least one other observation on a later date (i.e., the EQ-5D-5L evaluable population) were considered eligible for the utility analyses. Missing observations were excluded from the main analysis.

Similar positive baseline overall HRQoL scores were reported for patients receiving amivantamab + CP and CP alone, which were maintained while on treatment.

10.1.2 Data collection – EQ-5D-5L

In PAPILLON, EQ-5D-5L data were collected at the following time points[3]:

- Cycle 1, Day 1
- First day of every other following cycle (Cycle 3, 5, 7, etc.) ± 3 days
- 30 days after last dose ± 7 days
- Every 12 weeks ± 14 days during study follow-up for 1 year

EQ-5D-5L utility scores were derived using DK-specific utility weights, in alignment with DMC guidelines [64]. Table 27 shows the pattern of missing data and completion for both amivantamab + CP combined with CP alone. Separate values for amivantamab + CP and CP alone are shown in Appendix L.

Table 27. Pattern of missing data and completion for amivantamab + CP and CP alone, EQ-5D-5L

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	306	8(3%)	**306**	298(97%)
3	306	28(9%)	**292**	278(95%)
5	306	38(12%)	**276**	268(97%)
7	306	64(21%)	**250**	242(97%)
9	306	103(34%)	**218**	203(93%)
11	306	144(47%)	**176**	162(92%)
13	306	177(58%)	**141**	129(91%)
15	306	205(67%)	**108**	101(94%)
17	306	236(77%)	**75**	70(93%)
19	306	257(84%)	**56**	49(88%)
21	306	268(88%)	**44**	38(86%)
23	306	274(90%)	**33**	32(97%)
25	306	286(93%)	**21**	20(95%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
27	306	291(95%)	**17**	15(88%)

10.1.3 HRQoL results – EQ-5D-5L

The descriptive summary statistics of EQ-5D-5L utility scores within the EQ-5D-5L evaluable population are presented in Table 28. A unique EQ-5D-5L health state was derived by concatenating the levels, or response options, from each of the five dimensions included in the questionnaire. Further details are available in Appendix G.

Observed utility estimates for progression free patients in PAPILLON over time, separately for patients randomized to amivantamab + CP and to CP, as well as the pooled cohort, are plotted in Figure 17 and provided in Table 28. Pooled cohort was used to estimate health state specific mean utility values. Figure 18 shows the mean utilities values for EQ VAS score.

Responses to the five items were converted to a health state. Various established methods exist for computing utility index scores for use in cost-effectiveness analyses according to EQ-5D-5L responses obtained from patient-level data of clinical trials. The following analyses evaluated the EQ-5D-5L responses extracted from the PAPILLON trial, where EQ-5D-5L utility scores were computed according to the EQ-5D-5L value set for Denmark. If one or more questions were not answered on the five dimensions of the EQ-5D, the health utility score was set to missing.

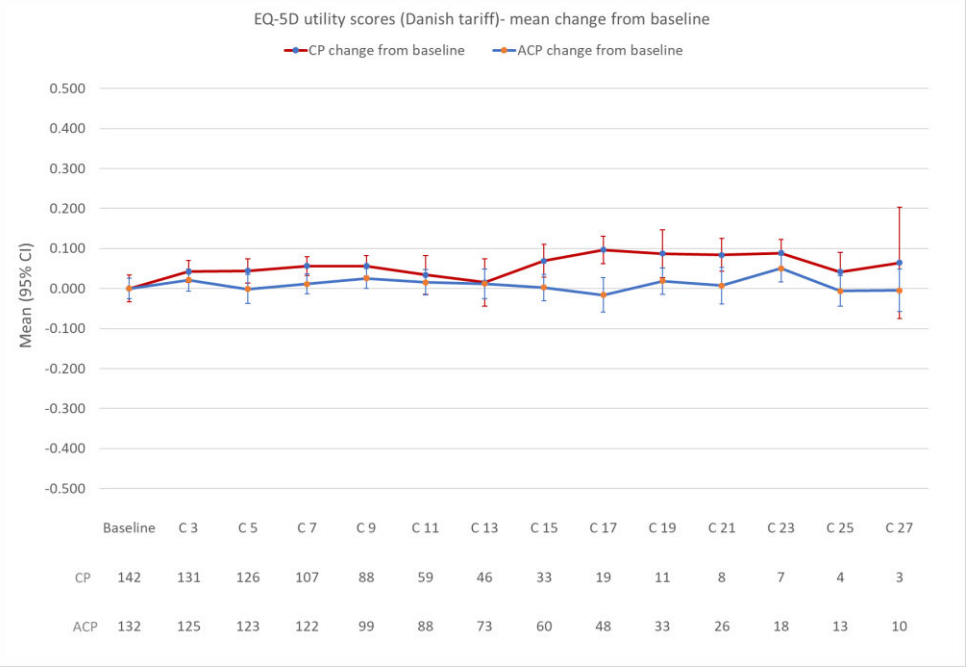
To give an illustration of the descriptive summary presented in Table 28, the mean utility and the associated SE are presented in Figure 17 by treatment arm for the Danish tariff and in Figure 18 for the EQ-VAS.

Table 28. HRQoL: EQ-5D-5L utility weights (Danish tariff) by measurement timepoint, summary statistics

	Amivantamab + CP		CP		Amivantamab + CP vs CP alone
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) *p*-value
Baseline	132	0.8715 (0.0132)	142	0.8315 (0.017)	0.0399 (-0.00284;0.0827)
3	125	0.8931 (0.0141)	131	0.874 (0.0138)	0.0191 (-0.0198;0.0579)
5	123	0.8703 (0.0187)	126	0.8758 (0.0154)	-0.00547 (-0.0531;0.0422)
7	122	0.883 (0.0128)	107	0.8876 (0.0119)	-0.0046 (-0.0395;0.0303)
9	99	0.897 (0.0126)	88	0.8877 (0.0131)	0.00925 (-0.0266;0.0451)

11	88	0.8871 (0.016)	59	0.8654 (0.0246)	0.0217 (-0.0337;0.0771)
13	73	0.8833 (0.019)	46	0.8467 (0.0303)	0.0366 (-0.0306;0.1039)
15	60	0.8742 (0.0168)	33	0.9008 (0.0211)	-0.0267 (-0.0813;0.028)
17	48	0.8556 (0.0217)	19	0.9279 (0.0174)	-0.0723 (-0.1449;0.000193)
19	33	0.8899 (0.0168)	11	0.9187 (0.0304)	-0.0288 (-0.0972;0.0396)
21	26	0.8785 (0.0232)	8	0.9153 (0.021)	-0.0368 (-0.126;0.0524)
23	18	0.9218 (0.0172)	7	0.9203 (0.0175)	0.00149 (-0.0604;0.0633)
25	13	0.8656 (0.0196)	4	0.873 (0.0251)	-0.00738 (-0.089;0.0742)
27	10	0.8667 (0.027)	3	0.896 (0.0711)	-0.0293 (-0.1648;0.1062)

Figure 17. Mean change from baseline EQ-5D utility scores (Danish tariff)



Abbreviations: C: cycle; CI: confidence interval;EQ-5D: EuroQol instrument 5 dimensions

Figure 18. Mean change from baseline EQ VAS scores

Abbreviations: C: cycle; CI: confidence interval;EQ VAS: EuroQol visual analogue scale.

10.2 Presentation of the health-related quality of life EORTC-QLQ-C30

10.2.1 Study design and measuring instrument – EORTC-QLQ-C30

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) was used in the PAPILLON study to assesses functioning domains and common cancer symptoms with recall in the past week. Similar baseline functioning and global health status scores were reported for patients receiving amivantamab + chemotherapy and chemotherapy alone, which were maintained while on treatment [80]. For global health status and all functioning scales, the mean change from baseline was <10 points up to Cycle 15 in each trial arm [80].

10.2.2 Data collection - EORTC-QLQ-C30

In PAPILLON, EORTC-QLQ-C30 data, together with the other HRQoL instruments, were collected at the following time points [3]:

- Cycle 1, Day 1
- First day of every other following cycle (Cycle 3, 5, 7, etc.) ± 3 days
- 30 days after last dose ± 7 days
- Every 12 weeks ± 14 days during study follow-up for 1 year

Table 29 shows the pattern of missing data and completion for both amivantamab + CP combined with CP alone. EORTC-QLQ-C30 data were collected in the PAPILLON clinical

study in line with the study protocol. All patients in the ITT population who had filled out the questionnaire at baseline, as well as at least one other observation on a later date, were considered eligible for the utility analyses. Missing observations were excluded from the main analysis.

Table 29. Pattern of missing data and completion for amivantamab + CP and CP alone, EORTC-QLQ-C30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	306	8(3%)	306	298(97%)
3	306	27(9%)	292	279(96%)
5	306	37(12%)	276	269(97%)
7	306	64(21%)	250	242(97%)
9	306	103(34%)	218	203(93%)
11	306	144(47%)	176	162(92%)
13	306	176(58%)	141	130(92%)
15	306	205(67%)	108	101(94%)
17	306	236(77%)	75	70(93%)
19	306	257(84%)	56	49(88%)
21	306	268(88%)	44	38(86%)
23	306	274(90%)	33	32(97%)
25	306	286(93%)	21	20(95%)
27	306	291(95%)	17	15(88%)

10.2.3 HRQoL results - EORTC-QLQ-C30

Although no statistically significant differences (p>0.05) in time to deterioration were observed between treatment arms, modelled event-free rates at 12 months from baseline across all global health and functioning scales were numerically higher for

patients receiving amivantamab + chemotherapy compared to patients receiving chemotherapy alone [80].

At 6 months and 12 months post-baseline, the chemotherapy group had a larger proportion of “Off Treatment” patients compared to the amivantamab + chemotherapy group [81]. Consequently, a larger proportion of patients in the amivantamab + chemotherapy group reported improved or stable global health status and functioning at these landmarks.

Patients reported low symptom burden at baseline that was maintained while on treatment with amivantamab + chemotherapy or chemotherapy alone, as measured by the EORTC-QLQ-C30 symptom scales[79, 80]. Mixed-model repeated measures (MMRM) analyses were performed to identify differences in the change from baseline for each symptom scale between the amivantamab + chemotherapy vs. chemotherapy alone arm [80].

When significant differences in symptoms were observed between the amivantamab + chemotherapy and chemotherapy alone arms, these tended to favour amivantamab + chemotherapy; however, results should be interpreted with caution as data observed at later timepoints are limited by smaller numbers of patients receiving treatment [80]. A summary of the significant differences in symptoms is reported below:

- Patients receiving chemotherapy alone experienced a statistically significant worse change in diarrhoea symptoms compared to patients receiving amivantamab + chemotherapy at Cycle 9 (LS mean score difference: -4.3 [95% CI: -7.6, -0.9]; p=0.014) and Cycle 15 (LS mean score difference: -5.2 [95% CI: -10.0, -0.4]; p=0.035)[80].
- Worsening in nausea and vomiting symptoms was significantly greater for patients treated with chemotherapy alone compared to patients treated with amivantamab + chemotherapy at Cycle 3 (LS mean score difference: -6.3 [95% CI: -9.6, -3.1]); p<0.001 and Cycle 13 (LS mean score difference: -5.1 [95% CI: -9.7, -0.5]; p=0.029)[80].
- Patients receiving chemotherapy alone experienced a statistically significant worse change in appetite loss from baseline compared to patients receiving amivantamab + chemotherapy at Cycle 13 (LS mean score difference: -7.7 [95% CI: -15.3, -0.1]; p=0.046) [80].
- Patients receiving amivantamab + chemotherapy experienced a significantly greater improvement in insomnia compared to patients receiving chemotherapy alone at Cycle 9 (LS mean score difference: -7.0 [95% CI: -12.8, -1.2]; p=0.019) and Cycle 13 (LS mean score difference: -7.3 [95% CI: -14.5, -0.2]; p=0.044) [80].
- Patients receiving chemotherapy alone reported greater worsening in fatigue compared to patients receiving amivantamab + chemotherapy at Cycle 13 (LS mean score difference: -7.9 [95% CI: -14.2, -1.5]; p=0.015) and Cycle 23 (LS mean score difference: -14.0 [95% CI: -27.9, -0.1]; p=0.049) [80].
- Improvement in dyspnoea was significantly greater for patients treated with amivantamab + chemotherapy compared to patients treated with chemotherapy alone at Cycle 7 (LS mean score difference: -6.7 [95% CI: -12.2, -

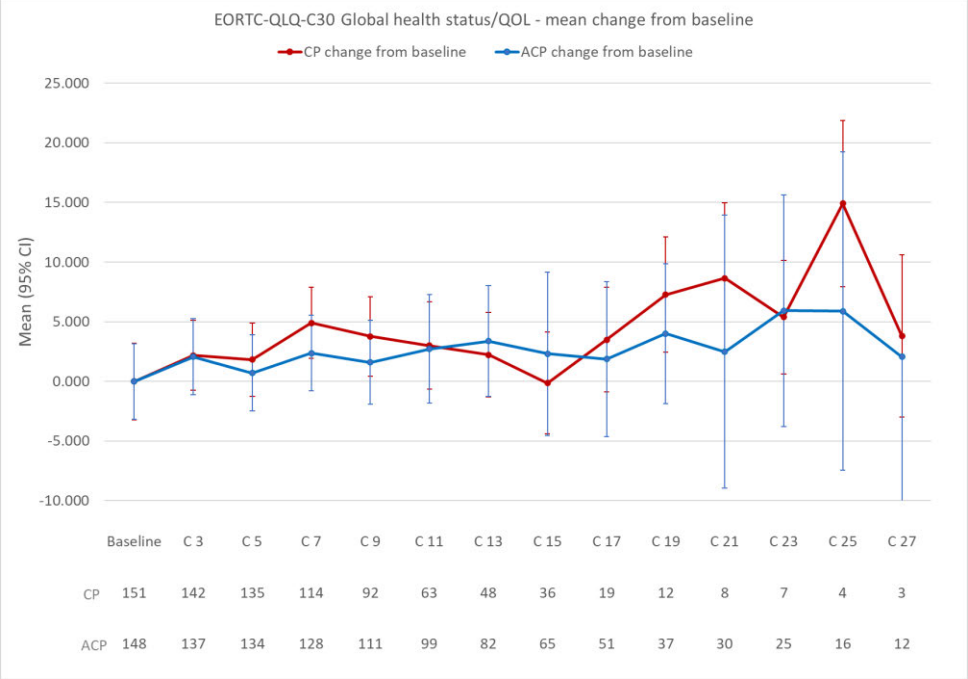
1.2]; p=0.017), Cycle 9 (LS mean score difference: -8.1 [95% CI: -13.9, -2.2]; p=0.007), Cycle 11 (LS mean score difference: -6.7 [95% CI: -13.2, -0.2]; p=0.042) and Cycle 13 (LS mean score difference: -10.7 [95% CI: -17.8, -3.5]; p=0.004) [80].

Statistically significant worsening of constipation symptoms were reported for patients receiving amivantamab + chemotherapy compared to patients receiving chemotherapy alone at Cycle 5 (LS mean score difference: 6.5 [95% CI: 0.6, 12.3]; p=0.031) [80]. No difference was reported in pain from baseline to the end of the treatment phase between the treatment arms. The main EORTC-QLQ-C30 results from the Global Health Status/QOL are shown in Table 30, since it integrates both physical and psychological dimensions, as well as symptoms, providing a broad overview of the patient's overall quality of life. The the mean change from baseline through the different data collection time points for both the intervention and comparator for the same index are presented in Figure 19.

Table 30. EORTC-QLQ-C30 Global health status/QOL measurement timepoint, summary statistics

	Amivantamab + CP		CP		Amivantamab + CP vs CP alone
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	148	68.07 (1.636)	151	68.43 (1.617)	-0.360 (95%CI:-4.87, 4.15)
3	137	70.13 (1.497)	142	70.6 (1.631)	-0.470 (95%CI:-4.81, 3.87)
5	134	68.78 (1.573)	135	70.25 (1.619)	-1.470 (95%CI:-5.89, 2.95)
7	128	70.44 (1.521)	114	73.32 (1.613)	-2.880 (95%CI:-7.23, 1.47)
9	111	69.67 (1.692)	92	72.19 (1.8)	-2.520 (95%CI:-7.36, 2.32)
11	99	70.79 (1.874)	63	71.43 (2.315)	-0.640 (95%CI:-6.48, 5.20)
13	82	71.44 (1.8)	48	70.66 (2.367)	0.780 (95%CI:-5.05, 6.61)
15	65	70.38 (2.17)	36	68.29 (3.495)	2.090 (95%CI:-5.97, 10.15)
17	51	69.93 (2.239)	19	71.93 (3.324)	-2.000 (95%CI:-9.86, 5.86)
19	37	72.07 (2.464)	12	75.69 (2.983)	-3.620 (95%CI:-11.20, 3.96)
21	30	70.56 (3.215)	8	77.08 (5.84)	-6.520 (95%CI:-19.59, 6.55)
23	25	74 (2.421)	7	73.81 (4.956)	0.190 (95%CI:-10.62, 11.00)
25	16	73.96 (3.558)	4	83.33 (6.804)	-9.370 (95%CI:-24.42, 5.68)
27	12	70.14 (3.472)	3	72.22 (11.111)	-2.080 (95%CI:-24.90, 20.74)

Figure 19. Mean change from baseline - EORTC-QLQ-C30 Global health status/QOL



Abbreviations: C: cycle; CI: confidence interval; EORTC-QLQ-C30: The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

10.3 Presentation of the health-related quality of life PROMIS-PF

10.3.1 Study design and measuring instrument – PROMIS-PF

Patient-Reported Outcomes Measurement Information System - Physical Functioning (PROMIS-PF) assesses physical function, including upper, central, and lower extremity functions and instrumental activities of daily living. The 8 items of the PROMIS-PF v2.0 short form 8c were used to evaluate physical ability levels and daily living activities [80]. Similar baseline PROMIS-PF scores were reported for patients in both treatment arms, which remained high throughout the treatment phase [80]. The questionnaire was administered per study protocol, in line with the others HRQoL instruments.

10.3.2 Data collection – PROMIS-PF

In PAPILLON, PROMIS-PF data, together with the other HRQoL instruments, were collected at the following time points [3]:

- Cycle 1, Day 1
- First day of every other following cycle (Cycle 3, 5, 7, etc.) ± 3 days
- 30 days after last dose ± 7 days
- Every 12 weeks ± 14 days during study follow-up for 1 year

Table 31 shows the pattern of missing data and completion for both amivantamab + CP combined with CP alone. In line with the study protocol, PROMIS-PF data were collected in the PAPILLON clinical. All patients in the ITT population who had filled out the questionnaire at baseline, as well as at least one other observation on a later date, were considered eligible for the utility analyses. Missing observations were excluded from the main analysis.

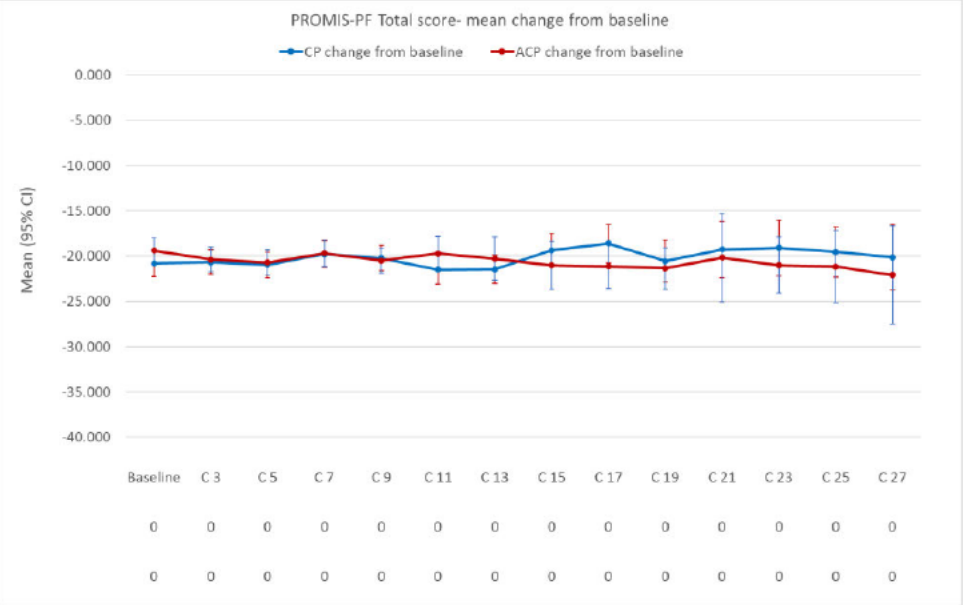
Table 31. Pattern of missing data and completion for amivantamab + CP and CP alone, PROMIS-PF

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	306	7(2%)	306	299(98%)
3	306	25(8%)	292	281(96%)
5	306	38(12%)	276	268(97%)
7	306	65(21%)	250	241(96%)
9	306	204(67%)	218	102(47%)
11	306	144(47%)	176	162(92%)
13	306	176(58%)	141	130(92%)
15	306	205(67%)	108	101(94%)
17	306	236(77%)	75	70(93%)
19	306	257(84%)	56	49(88%)
21	306	268(88%)	44	38(86%)
23	306	274(90%)	33	32(97%)
25	306	286(93%)	21	20(95%)
27	306	291(95%)	17	15(88%)

10.3.3 HRQoL results – PROMIS-PF

No differences in the MMRM analysis during the treatment phase or in median time to deterioration were detected [80]. In the time to deterioration analysis, the model-estimated event-free rates at 12 months from baseline were higher for amivantamab + chemotherapy (0.33 [95% CI: 0.25, 0.42]) compared to chemotherapy alone (0.21 [95% CI: 0.13, 0.29])[80]. The mean changes from baseline total score are presented in Figure 20, while the HRQoL results summary from the PROMIS-PF total score are presented in Table 32.

Figure 20. Mean change from baseline – PROMIS-PF total score



Abbreviations: C: cycle; CI: confidence interval; PROMIS-PF: Patient-Reported Outcomes Measurement Information System - Physical Functioning.

Table 32. PROMIS-PF Total score by measurement timepoint, summary statistics

	Amivantamab + CP		CP		Amivantamab + CP vs CP alone
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) *p*-value
Baseline	149	48.67 (0.734)	151	47.63 (0.706)	1.040 (95%CI:-0.96, 3.04)
3	138	47.7 (0.702)	143	47.76 (0.689)	-0.060 (95%CI:-1.99, 1.87)
5	134	47.37 (0.722)	134	47.48 (0.717)	-0.110 (95%CI:-2.10, 1.88)
7	127	48.37 (0.731)	113	48.64 (0.752)	-0.270 (95%CI:-2.33, 1.79)
9	111	47.57 (0.705)	91	48.2 (0.711)	-0.630 (95%CI:-2.59, 1.33)
11	99	48.36 (0.819)	63	46.93 (0.975)	1.430 (95%CI:-1.07, 3.93)

13	82	47.79 (0.807)	48	46.98 (1.225)	0.810 (95%CI:-2.07, 3.69)
15	65	47.06 (0.934)	36	49.08 (1.334)	-2.150 (95%CI:-5.34, 1.04)
17	51	46.93 (1.085)	19	49.83 (1.234)	-3.100 (95%CI:-6.32, 0.12)
19	37	46.73 (1.192)	12	47.86 (1.168)	0.040 (95%CI:-3.23, 3.31)
21	30	47.9 (1.572)	8	49.15 (2.503)	-2.080 (95%CI:-7.87, 3.71)
23	25	47.07 (1.59)	7	49.33 (1.584)	-2.410 (95%CI:-6.81, 1.99)
25	16	46.92 (1.408)	4	48.9 (2.045)	-2.920 (95%CI:-7.79, 1.95)
27	12	45.98 (1.847)	3	48.3 (2.762)	-2.320 (95%CI:-8.83, 4.19)

10.4 Health state utility values (HSUVs) used in the health economic model

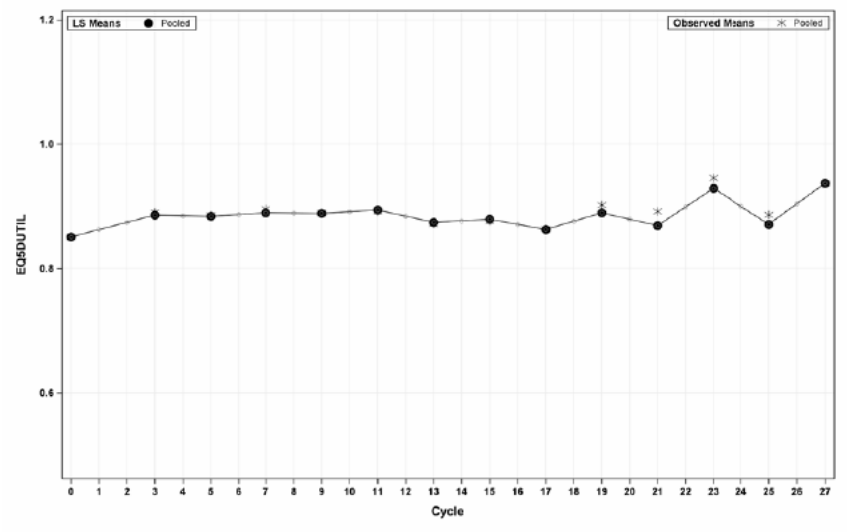
10.4.1 HSUV calculation

A pooled cohort was used to estimate health state specific mean utility values. Cycle specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a cycle do not influence the utility estimate for that cycle. First, for each EQ-5D-5L collection time point, a separate MMRM was fit using information only from patients who stayed progression-free until that time point, including all their available EQ-5D-5L results up to and including that time point, and using the visit as a categorical predictor, to get time specific utility estimates. Second, from each of these MMRMs, the least squares (LS) mean estimate of the last time point was used as the utility estimate for that time point. These time-specific LS estimates (each obtained from a different MMRM) are plotted in Figure 21. Each MMRMs had the compound symmetry correlation structure, assuming variances are homogenous. This means that the variability of utility measurements is constant at each cycle. Compound symmetry (CS) structure was selected based on the correlation structure with the lowest AIC from an MMRM that included all PRO values during PFS (the area under the curve of the progression-free estimates presented in Figure 21 (0.8851, standard error 0.00343) was used as the mean state utility in the progression-free state.

Progressed disease (PD) state utilities were estimated from patients who progressed in PAPILLON data, using a mixed-model repeated measures (MMRM) model that accounted for correlations between PRO measurements from the same patients.

Preference weights based on the general Danish population (Jensen et al. [82]) was used to calculate EQ-5D-5L index scores as utility weights in the model. Furthermore, the health-related utilities in the states have been age-adjusted according to the DMC guidelines.

Figure 21. Mean utility estimates, progression-free over time



10.4.1.1 Mapping

Not applicable.

10.4.2 Disutility calculation

The model includes detrimental impact of Grade 3 or 4 treatment-related AEs on HRQoL. AE-specific durations were derived from PAPILLON study by calculating the average AE duration per patient based on the start and end dates of recorded AE episodes. Duration of AE episodes with missing end dates were imputed as the average of the duration of the AE records with known end dates.

Utility decrements were sourced from literature. For each AE, this decrement is multiplied by the corresponding AE incidence (see Table 24) and mean AE duration and then applied as a one-time utility decrement in baseline utility value to each treatment arm at the start of the PSM. The AE disutility values are shown in Table 34 while the total disutility by treatment is shown in Table 33.

Table 33. Total AE-related Disutility by Treatment Arm

Comparator	Total Disutility
Amivantamab + CP	-0.0033
CP	-0.0020

10.4.3 HSUV results

The health state utility values and disutilities used in the model are listed in Table 34.

Table 34. Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free	0.8851 [0.878-0.892]	EQ-5D-5L	Danish	Calculated as the area under the curve of the time-specific PF state utilities from MMRM. Amivantamab + CP and CP arms were pooled together.
Progressed disease	0.8256 [0.782-0.866]	EQ-5D-5L	Danish	PD utilities were estimated from patients who progressed in PAPILLON data, using a MMRM model that accounted for correlations between PRO measurements from the same patients
Disutilities				
Anaemia	-0.073 [-0.110,0.037]	EQ-5D-3L	UK	NICE TA850,[83] based on fatigue disutility in Nafees 2008[69]
Paronychia	-0.032 [-0.055,-0.010]	EQ-5D-3L	UK	Assumed equal to rash
Hypokalaemia	-0.050			NICE TA653[70], page 50/56 of Cancer Drugs Fund update of TA416
Asthenia	-0.073 [-0.110,0.037]	EQ-5D-3L	UK	NICE TA850,[83] based on fatigue disutility in Nafees 2008[69]
Neutropenia	-0.090 [-0.120,-0.060]	EQ-5D-3L	UK	NICE TA850,[83] based on Nafees 2008[69]
Leukopenia	-0.090 [-0.120,-0.060]	EQ-5D-3L	UK	Assumption: same as neutropenia
Rash	-0.032 [-0.055,-0.010]	EQ-5D-3L	UK	NICE TA850,[83] based on Nafees 2008[69]
Thrombocytopenia	-0.108	Time trade-off (TTO)	UK	NICE TA850,[83] based on Tolley 2013[71]

10.5 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.5.1 Study design

Not applicable.

10.5.2 Data collection

Not applicable.

10.5.3 HRQoL Results

Not applicable.

10.5.4 HSUV and disutility results

Not applicable.

Table 35. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

Table 36. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

11. Resource use and associated costs

Costs considered in the base case include drug acquisition costs, co-medications, drug monitoring, drug administration, subsequent treatment, disease management, and AE management. Indirect costs were included as well in line with the limited societal perspective. All costs are reported in DKK. Resource use was verified to be relevant to the Danish setting by a Danish clinical expert.

11.1 Medicine costs - intervention and comparator

Amivantamab + CP are treat-to-progression therapies. The percentage of dose administrations that are skipped was derived from PAPILLON study and was calculated

by dividing the number of doses that were observed to be given in PAPILLON by the doses expected to be given based on the label dosing using the time to treatment discontinuation. The dosing schedules modelled are based on the PAPILLON study in combination with clinical expertise (Table 81 and Table 82 in the Appendix M).

Unit drug costs were sourced from the relevant publicly available Danish source, medicinpriser.dk [84], for both amivantamab and the carboplatin and pemetrexed combination. The costs are expressed in pharmacy purchase price (AIP) and are shown in Table 37 and in the model sheet. The model is flexible to consider vial sharing (i.e. no wastage). Vial sharing is not considered in the base case, therefore, wastage is assumed; the dosing consumption per administration was rounded up to the closest integer number of vials.

A relative dose intensity (RDI) value was applied to required number of vials for amivantamab, based on the dose reductions observed in the trial. Table 83 and Table 84 present the drug acquisition costs applied in the model, taking into account the relevant dosing details.

Table 37. Pharmaceutical costs used in the model

Treatment	Units Per Pack	Unit Strength	Price Per Pack (DKK)	Dose	Relative dose intensity	Frequency
Amivantamab	1	350 mg	9582.84	1,400 mg <80kg patients: 4 weeks (up to C2D1)	93.70%	1.00 (0.85) per week in cycle 1 and 0.33 (0.29) per week in cycle 2
					93.45%	
				1,750 mg ≥80kg patients: 4 weeks (up to C2D1)	93.70%	1.00 (0.88) per week in cycle 1 and 0.33 (0.29) per week in cycle 2
					93.45%	
				1,750 mg < 80 kg patients: C3D1 until progression		0.33 (0.28) per week in Cycle 3–4 and 0.33 (0.28) per week in subsequent cycles (until progression)
				2,100 mg ≥ 80 kg patients: C3D1 until progression		0.33 (0.29) per week in Cycle 3–4 and 0.33 (0.29) per week in subsequent cycles (until progression)
Carboplatin	1	450 mg	226.00	AUC 5, 550 mg	97.96%	0.33 (0.32) per week in Cycle 1-4

Treatment	Units Per Pack	Unit Strength	Price Per Pack (DKK)	Dose	Relative dose intensity	Frequency
Pemetrexed	1	500 mg	552.49	500 mg/m^2	94.93%	0.33 (0.29) per week until progression

Costs were sourced on 30/08/2024 from medicinpriser.dk [84].

11.2 Medicine costs – co-administration

The cost of concomitant medications was considered in the model. Concomitant medications were defined as any drugs given in addition to the active treatment regimens, and inputs are consistent with the PAPILLON trial where co-medications were given with amivantamab and pemetrexed [3]. Table 38 lists the drug acquisition unit costs for the co-medications included in the model.

Table 38. Concomitant medications – unit costs

Treatment	Units Per Pack	Unit Strength	Price Per Pack (DKK)	Cost Per Unit (DKK)	Source*
Dexamethasone	20	4 mg	214.00	2.14	Medicinpriser.dk[84]
Paracetamol	300	500 mg	85.00	0.28	Medicinpriser.dk[84]
Diphenhydramine	1	350 mg	66.02	66.02	Medicinpriser.dk[84]
Vitamin B12 (hydroxocobalamin)	3	1 mg	513.61	171.20	Medicinpriser.dk[84]
Folic acid	100	5.00 mg	61.59	0.62	Medicinpriser.dk[84]

*Prices accessed on 30/08/2024.

11.3 Administration costs

Table 39 presents the drug administration unit costs used in the model. The frequencies of drug administrations used to calculate total administration costs are shown in Table 39. Base case assumes IV administrations throughout the modelled time horizon.

A subcutaneous formulation of amivantamab is expected to become available in near future[redacted]). The subcutaneous administration is predicted to reduce the burden of administration, therefore reducing the cost profile of the intervention, but is not included in the health economic assessment.

Table 39. Administration costs used in the model

Administration type	Frequency*	Unit cost [DKK]	DRG code	Reference
IV	As per respective product dosing schedule (see Appendix M)	1,311.00	04MA98 "MDC04 1-dagsgruppe, pat. mindst 7 år	Sunhedsdatastyrelsen DRG-takster 2024
Oral	N/A	0.00	Assumption	Assumption

*The frequency varies depending on the treatment. Abbreviations: IV, intravenous infusion; N/A, not applicable.

11.4 Disease management costs

The model captures health-state specific routine monitoring and follow-up care costs. Table 40 presents the types, costs, and frequencies of disease management by health state. The frequencies of resources were based on a Danish clinical expert, and unit costs were sourced from Sunhedsdatastyrelsen DRG-takster 2024.

Table 40. Disease management costs used in the model

Activity	Frequency – progression free	Frequency – progressed	Unit cost [DKK]	DRG code	Reference
Oncology outpatient visit	Once every three months	Once every three months	1,311	04MA98 "MDC04 1-dagsgruppe, pat. mindst 7 år	Sunhedsdatastyrelsen DRG-takster 2024
Disease management	Once every three months	Once every three months			Sunhedsdatastyrelsen DRG-takster 2024
CT scan (chest)	Once every three months	Once every three months	3,468	30PR05, CT-scanning af hjertet med angiografi	Sunhedsdatastyrelsen DRG-takster 2024
CT scan (other)	Once every three months	Once every three months	2,585	30PR07, CT-scanning, ukompliceret,	Sunhedsdatastyrelsen DRG-takster 2024

11.5 Costs associated with management of adverse events

The costs associated with AEs are included in the analysis. The analysis base case estimated the costs due to AEs for each treatment arm by considering the percentage of patients experiencing AEs in each treatment arm, and the cost per each AE episode. The relevant frequencies are described in Table 24. All AE unit costs are detailed in Table 41. Based on the treatment-specific incidence rates of AEs (see Table 24) and the unit costs, the total one-off AE cost in 1L is DKK 1,922 for amivantamab + CP and DKK 1,095 for CP.

Table 41. Cost associated with management of adverse events

AEs	DRG code	Unit cost/DRG tariff (DKK)
Anaemia	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Paronychia	09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år[85]	1,625
Hypokalaemia	10MA98,MDC10 1-dagsgruppe, pat. mindst 7 år[85]	1,847
Asthenia	01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år[85]	1941
Neutropenia	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Leukopenia	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Rash	09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år[85]	1,625
Thrombocytopenia	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Febrile neutropenia	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Neutrophil count decreased	16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år[85]	2,111
Diarrhea	06MA98, MDC06 1-dagsgruppe, pat. mindst 7 år[85]	1,561
Fatigue	23MA03, Symptomer og fund, u. kompl. Bidiag [85]	5,103

11.6 Subsequent treatment costs

Subsequent treatment inputs directly impact costs but not the survival outcomes in the model; the clinical impact of subsequent treatment is already accounted for indirectly in the OS curves. The cost of subsequent treatment is applied as a one-off cost at disease progression and includes drug acquisition, co-medications, monitoring, administration, and AE management.

Subsequent treatment is broken down into 2L and 3L+ treatments, based on a proportion of patients receiving each subsequent line, a distribution of treatments composing each line of therapy, and a duration for each treatment and line. In the base case, the proportion of patients receiving 2L and 3L treatment after discontinuing 1L treatment is based on interviews with a Danish clinical expert [63]. The proportion 1L amivantamab + CP and CP alone patients receiving 2L or 3L+ treatments are assumed equal (Table 42). There is also an optional one-off cost for a proportion of patients receiving best supportive care (BSC) for each line of subsequent treatment.

This cost is set to DKK 0 in the base case analysis.

Table 42. Proportion of Patients Receiving Subsequent Lines of Treatments by 1L Regimen

1L Regimen	% Receiving 2L Treatment	% Receiving BSC in 2L	% Receiving 3L+ Treatment	% Receiving BSC in 3L+
Amivantamab + CP	55%	45%	27.5%	72.5%
CP	55%	45%	27.5%	72.5%

Abbreviations: 1L = first-line; 2L = second line; 3L = third line; BSC = best supportive care; CP = carboplatin + pemetrexed.

The base case selection for the type of subsequent therapy and the distribution of 2L and 3L+ treatments in health economic analysis was based on Danish clinical expert input and included non-platinum based chemotherapy (docetaxel), TKI monotherapy (osimertinib) and IO combination (pembrolizumab+CP) [66] (Table 43). The same distribution in 2L and 3L was assumed for amivantamab + CP and CP alone. The duration of each subsequent treatment regimen is based on the mPFS for that regimen, as reported in the literature.

Table 43. Distribution and duration of 2L and 3L subsequent treatments

Regimen	Distribution 2L & 3L	Duration of 2L Treatments (based on mPFS)		Duration of 3L+ Treatments (based on mPFS)	
		mPFS (months)	Calculated mean duration (weeks)	mPFS (months)	Calculated mean duration (weeks)

Non-platinum chemotherapy	80%	4.3 [27]	18.7	2.5 [86]	10.9
TKI	10%	2.5 [27]	10.9	2.9 [86]	12.6
IO combination	10%	2.3 [27]	10.0	4.2 [87]	18.3

*Source: Nordic KOL, data on file. Abbreviations: 2L = second-line; 3L = third line IO = immuno-oncology drug; mPFS = median progression-free survival; TKI = tyrosine kinase inhibitor

The dosing details divided by treatment category are described in Table 85 in Appendix M. Table 44 presents the unit costs of all the different drugs used for the subsequent treatments in the model.

Table 44. Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Carboplatin	450 mg	1	226.00	Depending on the treatment category – See Table 85	Depending on the treatment category – See Table 85
Cisplatin	50 mg	1	100.00	Depending on the treatment category – See Table 85	Depending on the treatment category – See Table 85
Docetaxel	20 mg	1	35.00	Depending on the treatment category – See Table 85	Depending on the treatment category – See Table 85
Osimertinib	80 mg	30	38,585.29	Depending on the treatment category – See Table 85	Depending on the treatment category – See Table 85
Pembrolizumab	100 mg	1	22,058.88	Depending on the treatment category – See Table 85	Depending on the treatment category – See Table 85
Pemetrexed	500 mg	1	552.49	Depending on the	Depending on the

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
				treatment category – See Table 85	treatment category – See Table 85

11.6.1 Subsequent treatments – concomitant medications

Pemetrexed treatment requires co-medication with vitamin B12 (hydroxocobalamin), folic acid, and dexamethasone. The related unit costs have been described in section 11.1.

11.6.2 Subsequent treatments – administration cost

The administration costs for subsequent treatments used in the model are presented in Table 39 in section 11.3. The frequencies used to calculate total administration costs vary depending on the respective product dosing schedule (see Appendix K).

11.6.3 Subsequent treatments – monitoring cost

Drug monitoring is required for subsequent treatment regimens containing pemetrexed. The monitoring costs and requirements are the same as from pemetrexed given in 1L treatment (see section 11.4).

11.6.4 Subsequent treatments – AEs cost

The management of Grade 3–4 AEs were included in the costs of subsequent therapy. AE unit costs are presented in Table 41 while Table 45. displays the AE incidence rates for each subsequent treatment regimen.

Table 45. Subsequent treatments AEs incidence

Grade 3–4 AE	Platinum-based Chemotherapy	Non-platinum Chemotherapy	Amivantamab	TKI	IO Combination
Anaemia	11.8	3.8	1.3	0.0	11.8
Diarrhoea	11.0	24.4	13.7	69.9	15.4
Fatigue	0.7	3.5	0.7	1.3	1.6
Febrile neutropenia	0.0	9.4	0.0	0.0	0.0
Neutropenia	11.8	14.6	2.6	0.0	11.8
Neutrophil count decreased	0.0	11.1	0.0	0.0	0.0
Rash	0.0	0.0	1.0	5.9	0.0
Thrombocytopenia	7.4	0.0	0.7	0.0	7.4
Source	NICE TA850 (CHRYSALIS trial)[83]	NICE TA850 (CHRYSALIS trial)[83]	NICE TA850 (CHRYSALIS trial)[83]	NICE TA850 (CHRYSALIS trial) [83]	Assumed the maximum incidence for each AE between those associated with IO alone and platinum-based chemotherapy

Abbreviations: AE = adverse event; IO = immuno-oncology drug; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; TKI = tyrosine kinase inhibitor; VEGFi = vascular endothelial growth factor inhibitor

11.7 Patient costs

The health economic analysis adopts a limited societal perspective. This includes non-medical cost for the patients including patient time 188 DKK/hour and the transportation cost to and from treatment (roundtrip 140 DKK). The costs were based on Værdisætning af Enhedsomkostninger v 1.8 [88] (Table 46).

Table 46. Patient costs used in the model

Activity	Time spent/ Cost
Patient cost	DKK 188 per hour
Travel cost	DKK 140 per round trip
Hours per drug administration	4 hours

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

Table 47 provide an overview of the base case, and results are shown in Table 48.

Table 47. Base case overview

Feature	Description
Comparator	CP
Type of model	Partitioned survival model
Time horizon	30 years (lifetime)
Treatment line	1st line. Subsequent treatment lines included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study PAPILLON. Danish population

Feature	Description
	weights were used to estimate health-state utility values.
Costs included	Medicine costs Hospital costs Costs of adverse events Monitoring costs Patient costs
Dosage of medicine	Based on weight
Average time on treatment	Intervention: 1.26 years Comparator: 0.74 years
Parametric function for PFS	Intervention: Gamma Comparator: Gamma
Parametric function for OS	Intervention: Gamma Comparator: Gamma
Inclusion of waste	Not included
Average time in model health state	Progression free: Ami + CP = 1.26 years; CP=0.64 years. Progressed: Ami + CP =3.27 years; CP= 1.41 years. Overall survival: Ami + CP = 4.64 years; CP= 2.05 years

12.1.1 Base case results

The base results for health benefits and costs, respectively, over a lifetime (30-year time horizon) from a limited societal perspective is presented in Table 48.

Over the lifetime time horizon, there was a substantial gain in QALYs for patients who received amivantamab + CP compared with those who received CP only. The base case result showed that amivantamab + CP resulted in an additional 1.79 QALYs (2.13 LYs), compared to CP alone. The incremental cost of the amivantamab + CP arm compared to CP alone was DKK 1,004,213. The ICER value of amivantamab + CP was estimated to DKK 559,873/QALY (DKK 470,520 DKK/LY) compared to CP alone.

Table 48. Base case results, discounted estimates

	Amivantamab + CP (DKK)	CP alone (DKK)	Difference (DKK)
Medicine costs			
Medicine costs – co-medications	4,215	1,477	2.738
Administration	26,745	13,103	13641.13
Treatment monitoring	0	0	0
Costs associated with management of adverse events	1,922	1,095	827.09
Subsequent treatment costs	22,729	26,142	-3,413
Routine costs - PF	40,543	21,071	19,472
Patient costs - PF	18,419	9,215	9,204
Routine costs - PD	95,059	44,347	50,711
Patient costs - PD	2,299	2,645	-345
Total costs	**1,136,072**	**131,858**	**1,004,213**
Life years gained (PF)	1.23	0.64	0.59
Life years gained (PD)	2.89	1.35	1.54
Total life years	**4.12**	**1.99**	**2.13**
QALYs (PF)	1.09	0.57	0.52
QALYs (PD)	2.38	1.11	1.27
QALYs (adverse reactions)	0.00	0.00	0.00
Total QALYs	**3.47**	**1.68**	**1.79**
Incremental costs per life year gained			**470,520 DKK**
Incremental cost per QALY gained (ICER)			**559,873 DKK**

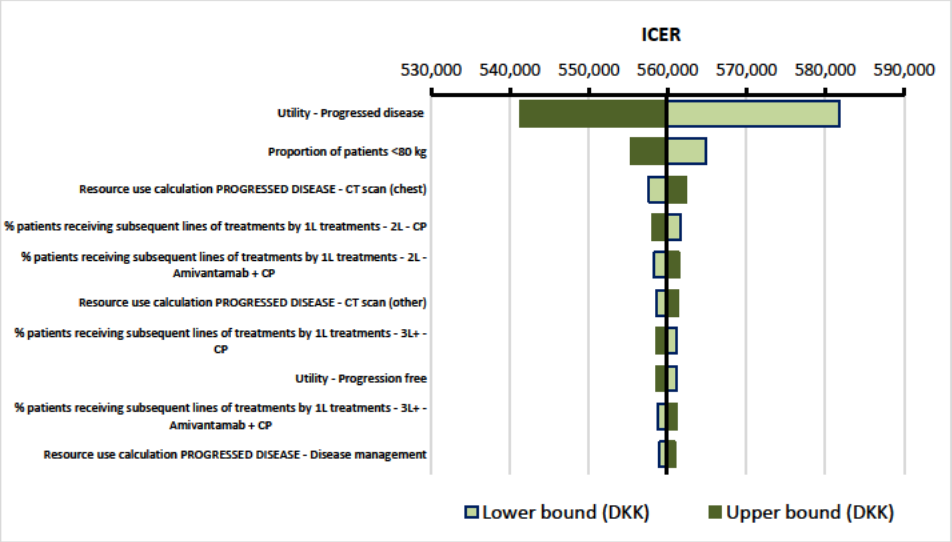
12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The results obtained from the deterministic one-way sensitivity analyses (OWSA) for the ten most impactful parameters on the ICER are presented in Figure 22 and Table 49. In the absence of confidence intervals or published ranges, upper and lower bounds tested in the OWSA were calculated assuming a standard error (SE) of 0.1.

The utility for progressed disease has the most significant impact on ICER with an absolute difference of 40,513 DKK. The proportion of patients <80 kg, that influences dosage, affecting ICER with a difference of 9,433 DKK. The other top parameters that have impact on the ICER, but to a lesser extent included resource use and proportion of patients receiving subsequent lines of treatments.

Figure 22. OWSA Tornado diagram



Abbreviations: CP = carboplatin + pemetrexed, CT = computer tomography

Table 49. Deterministic one-way sensitivity analysis

Parameter	Lower bound	Upper bound	Lower bound (DKK)	Upper bound (DKK)	Absolute difference (DKK)
Utility - PD	0.78	0.87	581,810	541,297	40,513
Proportion of patients <80 kg	0.80	0.88	564,818	555,385	9,433
Resource use calculation PD - CT scan (chest)	3.25	4.82	557,650	562,321	4,671

% patients receiving subsequent lines of treatments by 1L treatments - 2L - CP	0.44	0.66	561,710	558,075	3,635
% receiving subsequent lines of treatments by 1L treatments - 2L - Amivantamab + CP	0.44	0.66	558,275	561,436	3,160
Resource use calculation PD - CT scan (other)	3.25	4.82	558,578	561,300	2,722
% receiving subsequent lines of treatments by 1L treatments - 3L+ - CP	0.22	0.33	561,155	558,511	2,643
Utility - PF	0.88	0.89	561,134	558,649	2,485
% patients receiving subsequent lines of treatments by 1L treatments - 3L+ - Amivantamab + CP	0.22	0.33	558,758	561,057	2,298
Resource use calculation PD - Disease management	3.25	4.82	558,962	560,876	1,914

12.2.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) shows the overall uncertainty of the incremental cost-effectiveness results for amivantamab + CP compared with CP. For all inputs, when possible, the CI or SE from the data source was used to define parameter uncertainty. Otherwise, when not reported, the SE was assumed to be 10% of the default value. This was assumed to represent a reasonable degree of uncertainty and provided realistic values. Further details are listed in Appendix H.

Table 50 presents the mean incremental QALYs and costs from the PSA, which was run for 1,000 simulations, were 1.82 and 1,005,502 DKK, respectively, resulting in a mean ICER of 553,477 DKK per QALY (Table 50). The results from the PSA were similar to those of the deterministic results.

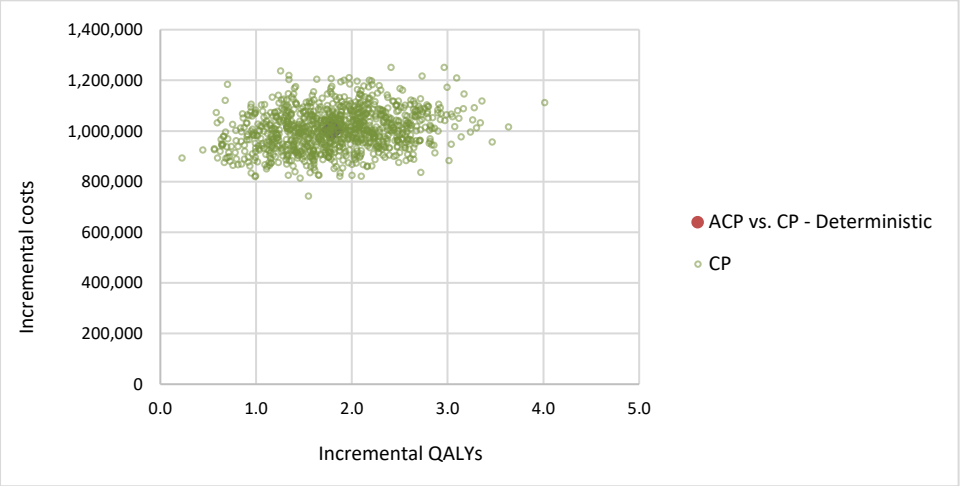
Table 50. PSA results

Comparator	Total Costs (DKK)	Total QALYs	Mean Incremental Results (amivantamab + CP vs. CP)	
			Costs (DKK)	QALYs
Amivantamab + CP	1,135,060	3.50	1,005,502	1.82
CP	129,557	1.68		

Abbreviations: CP = carboplatin + pemetrexed, QALYs =Quality adjusted life years

Figure 24 presents the incremental cost and effectiveness results obtained from the PSA on the cost-effectiveness plane, showing that consistent with the deterministic results, amivantamab + CP was more effective and more expensive in the majority of simulations.

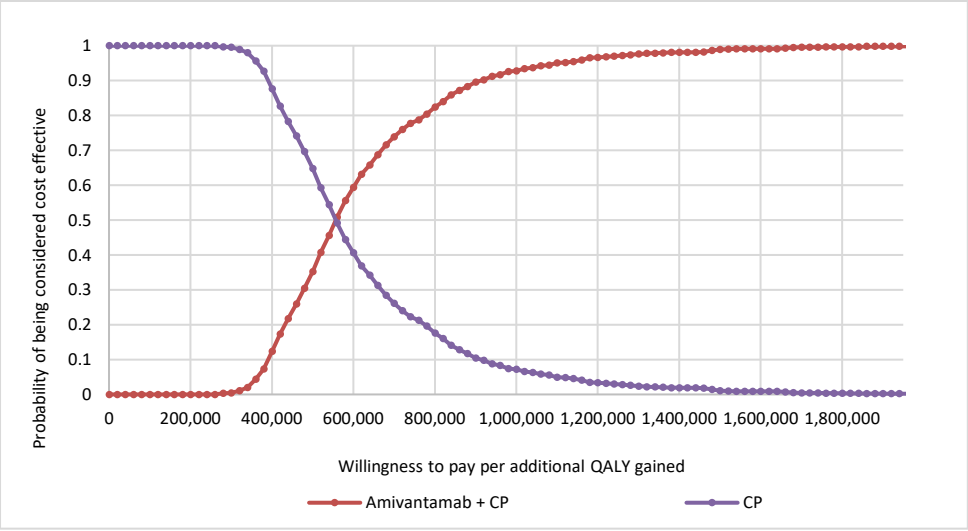
Figure 23. Incremental Cost-effectiveness Scatterplot



Abbreviations: CP = carboplatin + pemetrexed; QALY = quality-adjusted life year.

Table 21 presents the cost-effectiveness acceptability curves for the two treatment arms. The horizontal axis represents a cost-effectiveness threshold in terms of cost per QALY, while the vertical axis represents the probability of a given treatment being the optimal therapy at the given threshold.

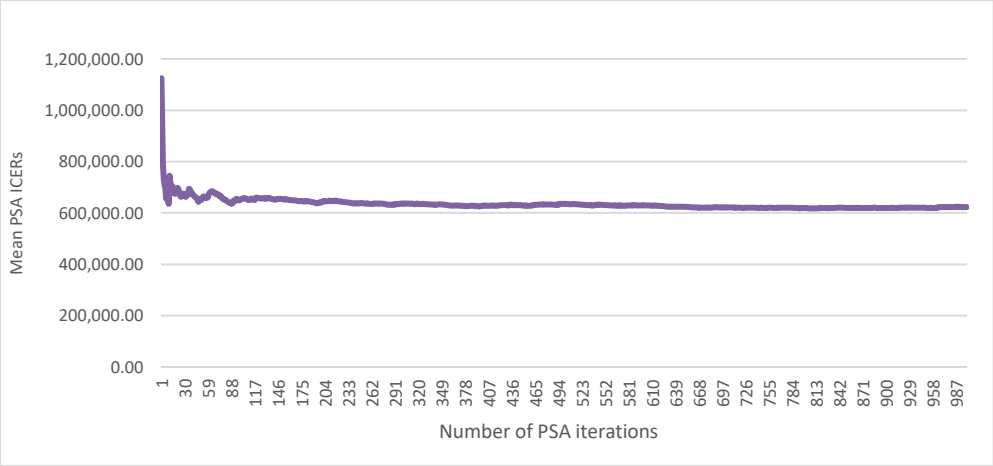
Figure 24. Cost-effectiveness Acceptability Curve



Abbreviations: CP = carboplatin + pemetrexed; QALY = quality-adjusted life year.

The stability of the ICER based on the number of probabilistic sensitivity analysis (PSA) simulations conducted is shown in Figure 25. As the number of PSA iterations increases, the mean ICER values begin to stabilize, indicating that the mean ICER is converging to a more stable estimate. After approximately 300-500 iterations, the curve flatten and beyond this point, increasing the number of simulations has minimal impact on the mean ICER value.

Figure 25. Convergence plot



Abbreviations: ICER = Incremental cost effectiveness ratio; PSA: probabilistic sensitivity analysis

12.2.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties relevant for the Danish clinical setting (Table 51). These included assumptions around:

- Treatment-switching adjustment
- Discount rate
- Time horizon
- Parametric distributions used to extrapolate amivantamab + CP and CP PFS, OS,
- Treatment duration

The ICER was robust in most scenarios tested, as the variations in the results across different scenarios do not show extreme or unreasonable fluctuations.

Table 51. Scenario analysis

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	**Base case**	-	**1,004,213**	**1.79**	**1,004,213**
Treatment switching adjustment	ITT (no adjustment)	To test the impact of no adjustment ITT or different treatment switch adjustment approaches on CP OS	978,328	1.17	978,328
	RPSFT - nrc		987,736	1.40	987,736
	2-stage - nrc		997,149	1.62	997,149
	RPSFT - rc		992,424	1.51	992,424
	2-stage - rc		1,015,181	2.04	1,015,181
Discount rate (Benefits, Costs)	0%,0%	To explore the impact of no discount rate or a higher discount rate	1,036,707	2.17	1,036,707
	5%,5%		992,075	1.67	992,075
	0%,3.5%		1,004,213	2.17	1,004,213
Time Horizon	10	To explore the impact of shorter or longer time horizon	995,729	1.58	995,729
	20		1,003,772	1.78	1,003,772
	40		1,004,236	1.79	1,004,236
OS distribution Amivantamab + CP and CP	Weibull Weibull	To address uncertainty in OS extrapolation	999,087	1.67	999,087
	Loglogistic Loglogistic		1,042,805	2.73	1,042,805
PFS distribution Amivantamab + CP and CP	Exponential Exponential	To address uncertainty in PFS extrapolations	1,152,371	1.80	1,152,371
	Weibull Weibull		977,931	1.79	977,931
	Lognormal Lognormal		1,257,781	1.81	1,257,781

	Loglogistic Loglogistic		1,223,768	1.81	1,223,768
	Gen Gamma Gen Gamma		1,038,465	1.80	1,038,465
Treatment duration	TTDD	To test the impact of TTDD to define treatment duration	1,075,336	1.79	1,075,336
Patient cost	No	To explore the Danish health care perspective	996,745	1.79	996,745

12.2.4 Conclusion

Lung cancer is the leading cause of cancer mortality worldwide, and NSCLC composes 85% of lung cancer cases. EGFR exon20ins is a rare mutation associated with poor prognosis and HRQoL, for which no approved targeted therapies are available in the 1L setting. There is a clear and urgent unmet need for a targeted treatment that can improve efficacy and HRQoL upfront, providing patients with the best possible survival outcomes from the start of their treatment journey.

Over the lifetime time horizon, there was a substantial gain in QALY, 1.79 incremental QALYs and higher total costs, incremental cost 1,004,213 DKK of the amivantamab + CP arm compared to CP alone. The ICER was estimated to 559,873 DKK per QALY gained compared to CP alone.

Similarly, in the sensitivity analysis and scenarios run, amivantamab + CP is more effective but costlier than CP alone. In the OWSA, the utility for progressed disease, proportion of patients <80 kg, resource use and proportion of patients receiving subsequent lines of treatments impacted the results the most. It is relevant to highlight that resource use, hour rates and patients cost related to the lengthy administration of amivantamab is driving the costs. In the near future, the subcutaneous administration for amivantamab would be available, which is predicted to reduce the burden of administration, therefore reducing the cost profile of the intervention.

The overall pattern of the scenario analysis suggested that the ICER is reasonably stable and robust across most scenarios tested, although there are some variations based on specific factors. The robustness is especially evident in the base case and under typical adjustments like treatment switching or discount rates.

The economic model has several strengths. The pathways upon which it was based reflect the current clinical practice for NSCLC in Denmark. The model was designed to provide extensive flexibility in estimating comparative efficacy and OS, including adjustment for treatment switching, which are key areas of uncertainty. Finally, the model's approach and programming were thoroughly validated.

Funding amivantamab + CP in Denmark would address the urgent unmet therapeutic need in EGFR exon20ins-positive NSCLC in the 1L setting and give patients access to an approved, effective therapy that provides improved clinical and quality of life outcomes.

The economic evaluation indicates that treatment with amivantamab + CP is associated with increased survival, more QALYs, and higher costs than treatment with CP, driven by the gains in PFS and OS compared to CP.

13. Budget impact analysis

Below in Table 52 and Table 53, the estimated eligible patients and the budget impact are presented.

All the relevant costs have been included, per DMC guidelines. A market share of 80% yearly for amivantamab was assumed, with eligible patients in line with those described in section 3.2.

Number of patients (including assumptions of market share)

Table 52. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Amivantamab + CP	13	13	13	13	13
CP alone	3	3	3	3	3
			Non-recommendation		
Amivantamab + CP	0	0	0	0	0
CP alone	16	16	16	16	16

Budget impact

Table 53. Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	9,062,632	12,594,908	13,949,777	14,504,893	14,775,679
The medicine under consideration is NOT recommended (DKK)	1,451,342	1,878,553	2,040,107	2,106,929	2,132,820
Budget impact of the recommendation (DKK)	**7,611,291**	**10,716,355**	**11,909,671**	**12,397,964**	**12,642,859**

14. List of experts

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Appendix A. Main characteristics of studies included

Intravenous and subcutaneous administration of amivantamab as monotherapy, and with other agents in different lines of treatment, are being evaluated in a comprehensive clinical development programme for multiple indications within NSCLC.

The IV formulation of amivantamab is currently being investigated in several trials for 1L and 2L+ treatment of patients with locally advanced or metastatic NSCLC and EGFR mutations.

Table 54. Main characteristic of studies included

Trial name: PAPILLON	**NCT number: NCT04538664**
Objective	The purpose of this study is to compare the efficacy, as demonstrated by progression-free survival (PFS), in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) characterized by EGFR Exon 20ins mutations.
Publications – title, author, journal, year	Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. New England Journal of Medicine. 2023;doi:10.1056/NEJMoa2306441[60] Janssen Research & Development. (Data on File). Clinical Study Report (Primary Analysis-Final). A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (PAPILLON). 5 September. 2023 [68].
Study type and design	Ongoing, phase III, randomised, open-label, parallel, multicentre trial in treatment-naïve patients with locally advanced or metastatic NSCLC and EGFR exon20ins conducted to assess the efficacy and safety of amivantamab + chemotherapy vs. chemotherapy alone. PAPILLON includes three study phases (screening, treatment, and follow-up), with an anticipated duration of approximately 48 months. Patients in comparator arm with BICR-confirmed disease progression are allowed to crossover to 2L amivantamab monotherapy.
Sample size (n)	Amivantamab + CP arm: n=153 CP arm: n=155 Total = 308
Main inclusion criteria	• Participant must have histologically or cytologically confirmed, locally advanced or metastatic, nonsquamous non-small cell

Trial name: PAPILLON	NCT number: NCT04538664
	lung cancer (NSCLC) with documented primary epidermal growth factor receptor (EGFR) Exon 20ins activating mutation • Participant must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. • Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Participant must agree to genetic characterization of tumor status through the required pretreatment tumor biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumor mutations in the bloodstream • A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study
Main exclusion criteria	• Participant has evidence of synchronous NSCLC disease (as suggested by genetic characterization or radiographic appearance) • Participant has untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization is eligible) • Participant has history of spinal cord compression that has not been treated definitively with surgery or radiation • Participant has a medical history of interstitial lung disease (ILD), including drug-induced ILD, or radiation pneumonitis • Participant has a contraindication to the use of carboplatin or pemetrexed (refer to local prescribing information for each agent). Participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid
Intervention	Amivantamab + chemotherapy (pemetrexed + carboplatin). **Cycles 1 through 4:** Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by IV infusion once weekly up to Day 1 of Cycle 2 (i.e., for the first 4 weeks), followed by 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of Cycle 3 and Cycle 4. The first infusion of amivantamab was split between Day 1 and Day 2 of Cycle 1 (350 mg on Day 1 and the remainder on Day 2). Pemetrexed 500 mg/m^2 (with vitamin supplementation) and carboplatin AUC5 by IV infusion on Day 1 of each cycle, for up to 4 cycles.

Trial name: PAPILLON	NCT number: NCT04538664
	Cycle 5 until disease progression: Amivantamab 1,750 mg (2,100 mg if body weight is ≥80 kg) and pemetrexed 500 mg/m^2 by IV infusion on Day 1 of each cycle (i.e., every 3 weeks) as maintenance. (N = 153)
Comparator(s)	Chemotherapy (pemetrexed + carboplatin) alone • **Cycles 1 through 4:** Pemetrexed 500 mg/m^2 (with vitamin supplementation) and carboplatin AUC5 by IV infusion on Day 1 of each cycle, for up to 4 cycles. • **Cycle 5 until disease progression:** Pemetrexed 500 mg/m^2 by IV infusion on Day 1 of each cycle (i.e., every 3 weeks) as maintenance. N = 155
Follow-up time	Median follow-up time 14.9 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary: PFS (using RECIST v1.1 guidelines), as assessed by BIC Secondary: Objective response, Duration of response, Overall survival. Time to subsequent therapy, PFS after first subsequent therapy ,Time to symptomatic progression, Incidence and severity of adverse events and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities, Serum amivantamab concentrations and anti-amivantamab antibodies, EORTC-QLQ-C30, PROMIS-PF. Exploratory: Time to treatment discontinuation, Tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, on therapy, and at progression, Circulating mutant allele frequencies by NGS of ctDNA at baseline, on therapy, and at progression, Tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression, Changes in tumor genetics, relative to baseline, by NGS of ct, DNA and genetic analysis of tumor biopsy material at progression, EQ-5D-5L **Endpoints included in this application:** The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1. Secondary endpoints were overall survival, confirmed objective response according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life (HRQoL) as assessed by QLQ-C30 and , EQ-5D-5L, safety, PFS after first subsequent therapy. **Other endpoints:**

Trial name: PAPILLON	NCT number: NCT04538664
	N/A
Method of analysis	All efficacy analyses were intention-to-treat analyses, while the extrapolation of OS was carried with a two stage estimation which assumed disease progression as the secondary baseline and first estimated the effect of receiving a subsequent therapy on the post-progression survival. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons. Hazard ratios were estimated with Cox proportional hazards regression. The proportional hazards assumption was assessed by looking for trends in the scaled Schoenfeld residuals.
Subgroup analyses	Not applicable
Other relevant information	Not applicable

Table 55. Ongoing studies

	CHRYSALIS	MARIPOSA	MARIPOSA-2
Study ID (NCT number)	NCT02609776	NCT04487080	NCT04988295
Study design	An ongoing, phase Ib, non-randomised, single-arm, first-in-human, open-label, parallel, multicentre, 2-part, dose escalation study in adult patients (aged ≥18 years) with advanced NSCLC.	An ongoing, phase III, randomised, Triple-masked (Participant, Investigator, Outcomes Assessor), parallel, multicentre trial.	An ongoing, phase III, randomised, open-label, parallel, multicentre trial.
Study location(s)	The regions of enrolment included Australia, Canada, China, France, Japan, Korea, Republic of, Spain, Taiwan, United Kingdom and United States.	The regions of enrolment included Argentina, Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Russian Federation, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom and United States.	The regions of enrolment included Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Republic of, Malaysia, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Russian Federation, Spain, Sweden, Taiwan, Turkey, United Kingdom and United States.
Population *important inclusion and exclusion criteria,*	Adult patients histologically or cytologically confirmed non-small cell lung cancer (NSCLC) that is metastatic or unresectable.	Adult patients with newly diagnosed histologically or cytologically confirmed, locally advanced or metastatic NSCLC that is treatment naive and not amenable to curative therapy including surgical resection or chemoradiation.	Adult patients with at least 1 measurable lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, that has not been previously irradiated and with histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC, characterized at or

stratification factors, n			after the time of locally advanced or metastatic disease diagnosis by either EGFR Exon 19del or Exon 21 L858R mutation.
Intervention	Part 1: Amivantamab Monotherapy + Combination Dose Escalations. Combination treatments: Lazertinib + Amivantamab or carboplatin + pemetrexed + Amivantamab. Part 2: Amivantamab Monotherapy + Combination Dose Expansion. Combination treatments: Lazertinib + Amivantamab.	Amivantamab and Lazertinib	Lazertinib + Amivantamab + Pemetrexed + Carboplatin
Comparator		Osimertinib + Placebo Lazertinib + Placebo	Carboplatin + Pemetrexed

Primary endpoint	• Part 1:
	  ○ Number of Participants With Dose Limiting Toxicity (DLT).
	• Part 2:
	  ○ Number of Participants With Adverse Events (AEs) and Serious AEs.
	  ○ Overall Response Rate (ORR)
	  ○ Duration of Response (DOR)
	  ○ Percentage of Participants With Clinical Benefit
		Progression-Free Survival (PFS) According to RECIST v1.1 by Blinded Independent Central Review (BICR)	Progression-Free Survival (PFS) According to RECIST v1.1 by Blinded Independent Central Review (BICR)

	• Trough Serum Concentration (Ctrough) of Amivantamab • Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Amivantamab		
Key secondary endpoints	• Maximum Serum Concentration (Cmax) of Amivantamab • Time to Reach Maximum Observed Serum Concentration (Tmax) of Amivantamab • Area Under the Serum Concentration-Time Curve From t1 to t2 Time (AUC[t1-t2]) of Amivantamab • Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Amivantamab • Trough Serum Concentration (Ctrough) of Amivantamab • Maximum Serum Concentration (Cmax) of Lazertinib • Time to Reach Maximum Observed Serum Concentration (Tmax) of Lazertinib • Trough Serum Concentration (Ctrough) of Lazertinib • Accumulation ratio (R) of Amivantamab • Number of Participants With Anti-Drug Antibodies (ADA)	• Overall Survival (OS) • Objective Response Rate (ORR) • Duration of Response (DOR) • Progression-Free Survival After First Subsequent Therapy (PFS2) • Time to Symptomatic Progression (TTSP) • Intracranial PFS • Incidence and Severity of Adverse Events (AEs) • Number of Participants with Clinical Laboratory Abnormalities • Number of Participants with Vital Signs Abnormalities • Number of Participants with Physical Examination Abnormalities • Serum Concentration of Amivantamab • Plasma Concentration of Lazertinib • Number of Participants with Anti-Amivantamab Antibodies • Change from Baseline in Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NCSLC-SAQ) • Change from Baseline in European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)	• Objective Response as Assessed by BICR • Overall Survival (OS) • Duration of Response (DoR) • Time to Subsequent Therapy (TTST) • Progression-Free Survival After First Subsequent Therapy (PFS2) • Time to Symptomatic Progression (TTSP) • Intracranial PFS • Intracranial Objective Response Rate (ORR) as Assessed by BICR • Intracranial Duration of Response (DOR) as Assessed by BICR • Time to Intracranial Disease Progression as Assessed by BICR • Number of Participants with Adverse Events (AEs) • Number of Participants with Clinical Laboratory Abnormalities • Serum Concentration of Amivantamab • Plasma Concentration of Lazertinib • Number of Participants with Anti-Amivantamab Antibodies • Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ) • European Organization of Research and Treatment of Cancer Quality of

	• Progression-Free Survival (PFS) • Time to Treatment Failure (TTF) • Overall Survival (OS)		Life Questionnaire Core 30 (EORTC-QLQ-C30) Score • Patient Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF)
Primary data cut	2024-01-31	2024-04-30 (estimated)	2023-07-10
Estimated completion date	2025-06-30	2027-06-09	2025-12-08
Relevance of this study for the decision problem	Supportive evidence of the efficacy. Not used in the health economic analysis.	Supportive evidence of the efficacy. Not used in the health economic analysis.	Supportive evidence of the efficacy. Not used in the health economic analysis.

Appendix B. Efficacy results per study

B.1 Results per study - PAPILLON

Table 56. Results per study - PAPILLON

Results of PAPILLON (NCT04538664)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95%CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS, months (BICR assessed)	Amivantamab + CP	153	11.37 months (9.79, 13.70)	4.67 months	(2.53, 6.81)	NA	HR: 0.395	0.296, 0.528	<0.0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for	PAPILLON [61]
	CP alone	155	6.70 months (5.59, 7.33)								PAPILLON [61]

										randomization, and study arm.	
Median PFS, months (INV assessed)	Amivantamab + CP	153	12.9 months (11.4, 16.7)	6.0 months	(3.15, 8.85)	NA	HR:			Analysed using the same method as the analysis of BICR assessed PFS	PAPILLON [61]
	CP alone	155	6.9 months (6.2, 8.3)								PAPILLON [61]
PFS2, median months	Amivantamab + CP	153	NE (22.77, NE)	NE	NE	NE	HR: 0.493	0.320, 0.759	0.001	Analyzed using the same method as the analysis of PFS	PAPILLON [61]
	CP alone	155	17.25 months (13.96, 21.52)								PAPILLON [61]
OS, median months (31st Ocotber 2023 DCO)	Amivantamab + CP	153	NE (28.3, NE)	NE	NE	NE	HR: 0.756	0.50, 1.140	0.18	Analyzed using the same methodology and model as for the analysis of PFS. Conducted at 2 timepoints (at the time of the primary	PAPILLON [61]
	CP alone	155	28.6 months (24.3, NE)								PAPILLON [61]

										analysis of PFS and at a follow-up dated 31st of October 2023)	
ORR (BICR assessed)	Amivantamab + CP	153	73.0% (65.2%, 79.9%)	25.6%	(15%, 37%)	NA	Odds ratio: 2.971	1.844, 4.787	<0.0001	Analysed using a logistic regression model stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no). Results presented in terms of an odds ratio together with its associated 95% confidence intervals	PAPILLON [61]
	CP alone	155	47.4% (39.2,% 55.6%)								PAPILLON [61]
DOR, median months	Amivantamab + CP	153	10.09 months (8.48, 13.90)	4.54	(1.56, 7.52)	NA	NA	NA	NA	A Kaplan-Meier plot and median DOR with 95%	PAPILLON [61]

(BICR assessed)	CP alone	155	5.55 months (4.44, 6.93)							confidence interval (calculated from the Kaplan-Meier estimate) presented by treatment group.	PAPILLON [61]
TTST, median, months	Amivantamab + CP	153	17.71 months (13.67, NE)	7.82 months	NE	NE	HR: 0.348	0.250, 0.486	<0.0001	Analyzed using the same method as the analysis of PFS.	PAPILLON [61]
	CP alone	155	9.89 months (8.57, 11.07)								PAPILLON[61]
TTSP, median months	Amivantamab + CP	153	NE (18.63, NE)	NE	NE	NE	HR: 0.669	0.456, 0.982	0.0387	Analyzed using the same method as the analysis of PFS	PAPILLON [61]
	CP alone	155	20.07 months (13.11, NE)								PAPILLON [61]
TTD, median months	Amivantamab + CP	153	13.17 months (11.76, 15.24)	5.71	(3.83, 7.59)	NA	HR: 0.378	0.283, 0.505	<0.001	Analysed using the same method as the analysis of PFS.	PAPILLON [61]

CP alone	155	7.46 months (6.97, 8.38)		PAPILLON[61]

Appendix C. Comparative analysis of efficacy – not applicable

No additional meta-analyses nor indirect comparisons have been performed for the submitted application. Therefore, this appendix is not applicable.

Table 57. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]/N/A

Outcome	Absolute difference in effect				Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No

Appendix D. Extrapolation

D.1 Extrapolation of PFS

D.1.1 Data input

PFS was extrapolated from the subject-level data from the PAPILLON trial (Figure 8).

D.1.2 Model

Standard parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalised gamma were used, see Table 58.

Table 58. Parametric Survival Functions in use in the model

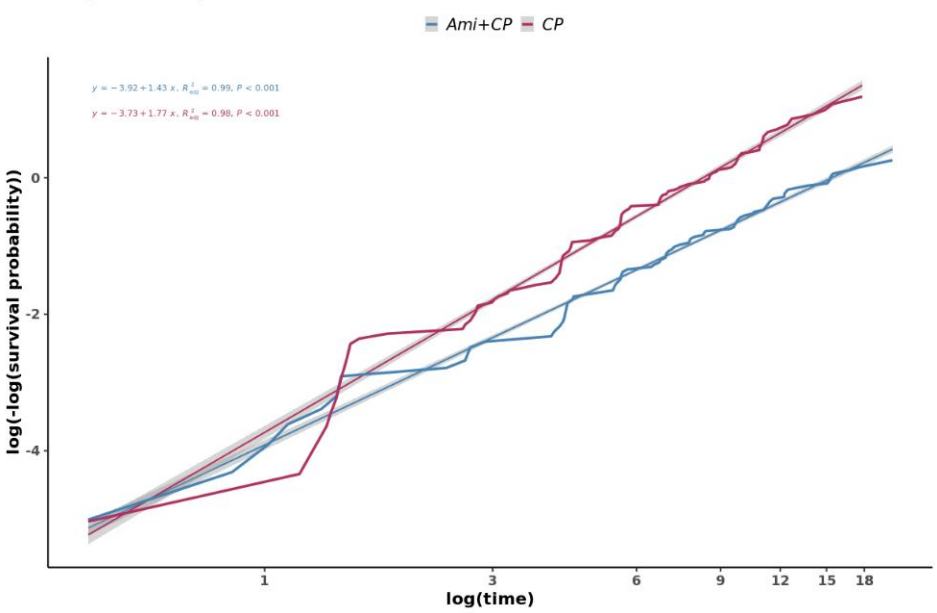
Distribution	Equation
Exponential	*S(t) = EXP(-1*(t* EXP(rate)))*
Weibull	*S(t) = EXP(-1*((t/exp(scale))^ EXP(shape)))*
Lognormal	*S(t) = 1-LOGNORM.DIST(t,meanlog,EXP(sdlog),TRUE)*
Loglogistic	*S(t) = (1/(1+(t/EXP(scale))^(EXP(shape))))*
Gompertz	*S(t) =EXP(-(EXP(rate)/shape)*(EXP(shape*t)-1))*
Gamma	*S(t)=IF(,GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2), 1,TRUE) when SQRT(1/EXP((shape-rate)))<0,* *S(t) = 1-GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2), 1,TRUE)) when SQRT(1/EXP((shape-rate)))≥0*
Generalised gamma	*S(t) = GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE) when Q<0* *S(t) = 1-GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE)) when Q≥0*

D.1.3 Proportional hazards

The proportional hazard (PH) assumption for PFS was assessed graphically by the cumulative hazard plot (Figure 26) and the Schoenfeld residuals (Figure 27). For the cumulative hazard plot, non-parallel lines indicate a potential violation of the PH assumption. For the Schoenfeld residuals plot, random scatter around a flat line indicates PH, while systematic patterns indicate a violation of the PH assumption.

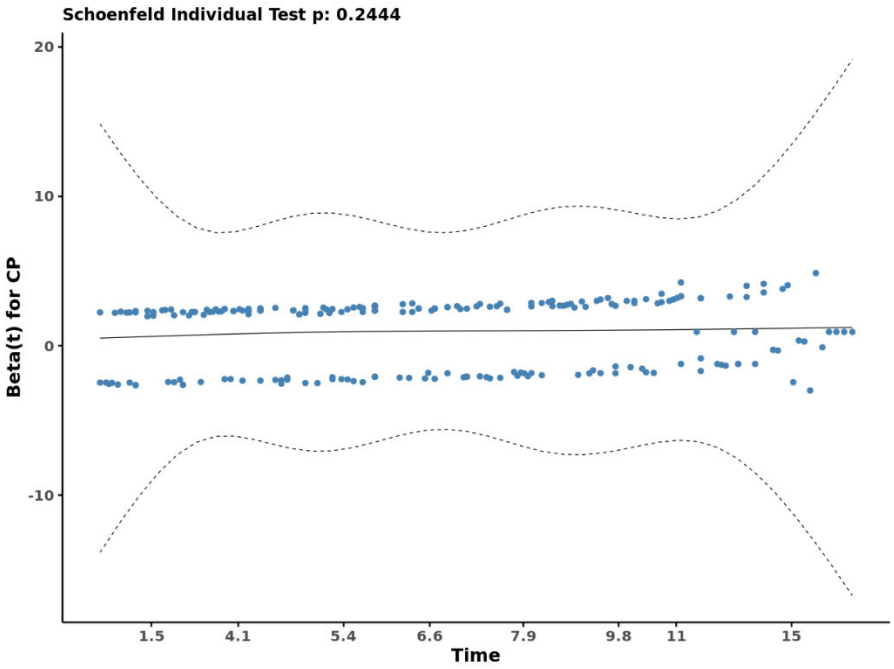
If either plot shows signs of a violation, it suggests that the hazard ratios are not constant over time. While the Shoenfeld plot (and individual test, checking for time-dependence of a treatment covariate) shows no substantial violation of the PH assumption, the log cumulative hazard plot indicates crossing of hazards, i.e. a violation of the PH assumption. Thus, independent survival models were used for the extrapolation of OS.

Figure 26. Log cumulative hazard (log-log) plot for amivantamab + CP and CP PFS (BICR)



Abbreviations: BICR = blinded independent central review; CP = carboplatin + pemetrexed; PFS = progression-free survival

Figure 27. Schoenfeld plot and test for amivantamab + CP and CP PFS – October 2023



D.1.4 Evaluation of statistical fit (AIC and BIC)

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for amivantamab +CP (Table 59) and CP alone (Table 60) are presented below. The total fit and difference between the two arms is presented in (Table 61).

Table 59. Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for amivantamab+CP PFS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1 year	2 years	3 years	5 years	10 years	15 years	20 years	30 years	Median PFS (months)	Mean PFS (months)
Exponential	651.52	654.55	12.20	9.17	50%	25%	13%	3%	0%	0%	0%	0%	12.19	17.68
Weibull	**641.45**	**647.52**	**2.13**	**2.13**	**50%**	**16%**	**4%**	**0%**	**0%**	**0%**	**0%**	**0%**	**12.19**	**14.48**
Lognormal	643.31	649.38	3.99	3.99	49%	24%	14%	6%	1%	0%	0%	0%	11.96	20.08
Loglogistic	**639.32**	**645.38**	**0.00**	**0.00**	**48%**	**22%**	**12%**	**5%**	**2%**	**1%**	**0%**	**0%**	**11.73**	**20.29**
Gompertz	647.68	653.74	8.36	8.36	51%	15%	2%	0%	0%	0%	0%	0%	12.65	13.93
Gamma	**640.41**	**646.47**	**1.09**	**1.09**	**49%**	**17%**	**6%**	**1%**	**0%**	**0%**	**0%**	**0%**	**12.19**	**14.96**
Generalised Gamma	642.15	651.24	2.82	5.85	49%	19%	7%	1%	0%	0%	0%	0%	11.96	15.59

Table 60. Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for CP PFS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median PFS (months)	Mean PFS (months)
Exponential	815.42	818.46	47.94	44.89	22%	5%	1%	0%	0%	0%	0%	0%	5.75	8.13
Weibull	**769.78**	**775.87**	**2.30**	**2.30**	**15%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**6.90**	**7.54**
Lognormal	776.07	782.16	8.59	8.59	17%	3%	1%	0%	0%	0%	0%	0%	6.21	8.13
Loglogistic	**771.73**	**777.82**	**4.25**	**4.25**	**17%**	**4%**	**1%**	**0%**	**0%**	**0%**	**0%**	**0%**	**6.44**	**8.59**
Gompertz	789.60	795.69	22.12	22.12	17%	0%	0%	0%	0%	0%	0%	0%	6.90	7.44
Gamma	**767.48**	**773.56**	**0.00**	**0.00**	**15%**	**1%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**6.67**	**7.60**
Generalised Gamma	769.47	778.60	1.99	5.03	15%	1%	0%	0%	0%	0%	0%	0%	6.67	7.59

Table 61. Total (stratified) goodness-of-fit statistics and incremental difference in landmark survival rates, estimated median, and estimated mean survival for CP and amivantamab + CP PFS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1 year	2 years	3 years	5 years	10 years	15 years	20 years	30 years	Median PFS (months)	Mean PFS (months)
Exponential	1466.94	1473.01	59.05	52.97	28%	20%	12%	3%	0%	0%	0%	0%	6.44	11.58
Weibull	**1411.24**	**1423.38**	**3.35**	**3.35**	**35%**	**16%**	**4%**	**0%**	**0%**	**0%**	**0%**	**0%**	**5.29**	**6.94**
Lognormal	1419.39	1431.53	11.50	11.50	31%	21%	13%	6%	1%	0%	0%	0%	5.75	11.96
Loglogistic	**1411.05**	**1423.20**	**3.16**	**3.16**	**31%**	**18%**	**10%**	**5%**	**1%**	**1%**	**0%**	**0%**	**5.29**	**11.70**
Gompertz	1437.28	1449.43	29.39	29.39	34%	15%	2%	0%	0%	0%	0%	0%	5.75	6.49
Gamma	**1407.89**	**1420.04**	**0.00**	**0.00**	**34%**	**17%**	**6%**	**1%**	**0%**	**0%**	**0%**	**0%**	**5.52**	**7.36**
Generalised Gamma	1411.61	1429.83	3.72	9.80	34%	18%	7%	1%	0%	0%	0%	0%	5.29	8.00

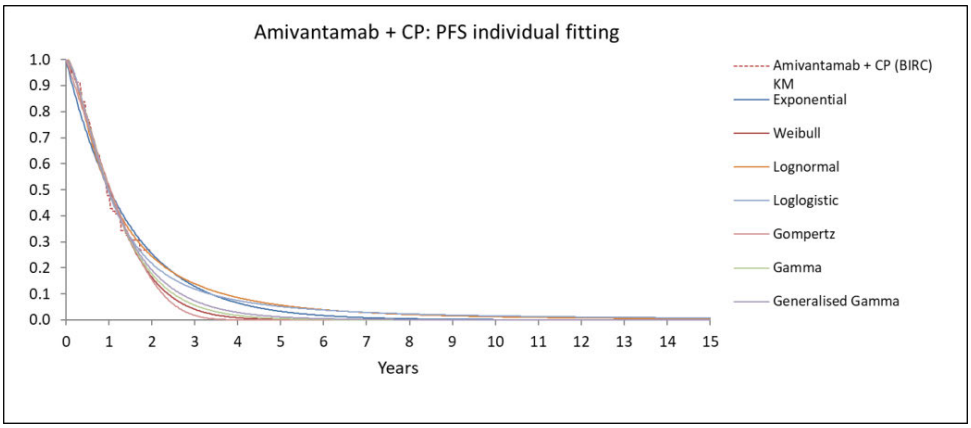
Abbreviations: BICR = blinded independent central review; CP = carboplatin + pemetrexed; PFS = progression-free survival

CP

D.1.5 Evaluation of visual fit

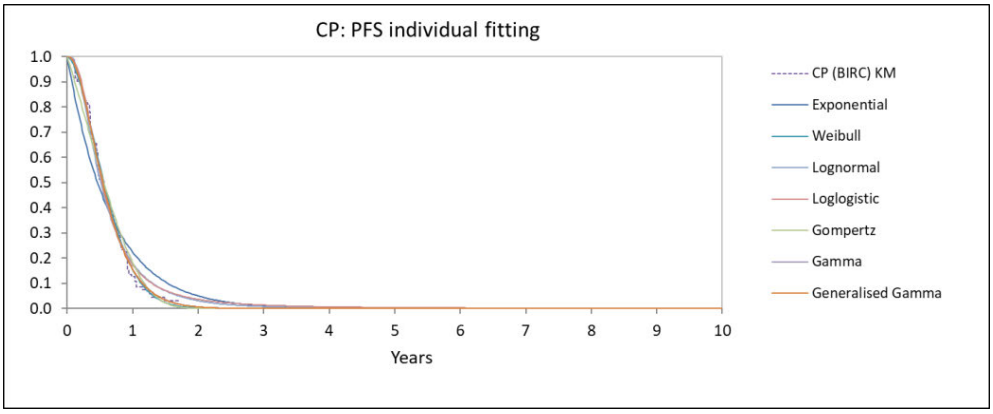
Figure 28 and Figure 29 show the observed time-to-event data with all the investigated extrapolation functions for amivantamab + CP and CP alone, respectively.

Figure 28. Long-term PFS projections of amivantamab + CP



Abbreviations: BICR = blinded independent central review; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 29. Long-term PFS projections of CP



Abbreviations: CP = carboplatin + pemetrexed; BICR = blinded independent central review; CP = carboplatin + pemetrexed; KM = Kaplan-Meier; PFS = progression-free survival

D.1.6 Evaluation of hazard functions

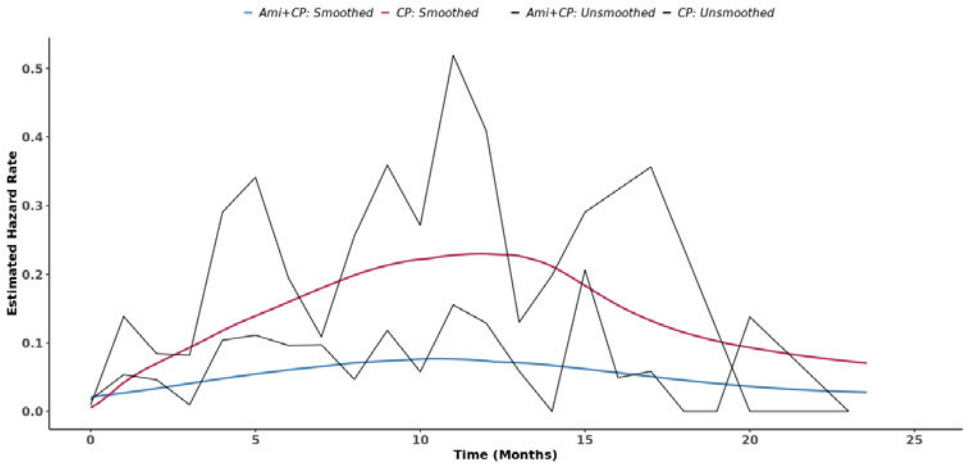
The smoothed hazards for amivantamab + CP and CP alone (Figure 30) are presented below. The smoothed hazard may be used to discern trends in the development of the hazard, such as whether it is increasing, decreasing, or levelling off over time. For example, an increasing hazard implies worsening survival rates over time, which is common in diseases like cancer, where risk increases with time. A decreasing hazard might suggest that survival chances improve after surviving an initial high-risk period (like

with some treatments or acute conditions). Constant hazard implies a steady risk, which may be appropriate for chronic conditions—the interpretation of the hazard at later times, when the number of patients still at risk is low, should be made cautiously. At 12 months, only 12 patients are at risk of progression in the CP arm.

The smoothed hazard for both arms in the trial shows an increase in the risk for progression or death up until 12 months, when it reaches a maximum. The individual plots (Figure 30 and Figure 31) emphasise this trend. The log-logistic, lognormal, and generalised gamma distributions may model an increasing and then decreasing hazard, and the log-logistic is a good fit for the amivantamab + CP arm, according to AIC.

However, the gamma distribution has the best statistical fit for the more mature CP arm. It models an increasing hazard with time, indicating that the decline in hazard may be associated with the low number of patients still at risk rather than an actual decline in the risk of progression.

Figure 30. Smoothed and unsmoothed hazard plot for amivantamab + CP and CP PFS (BICR)

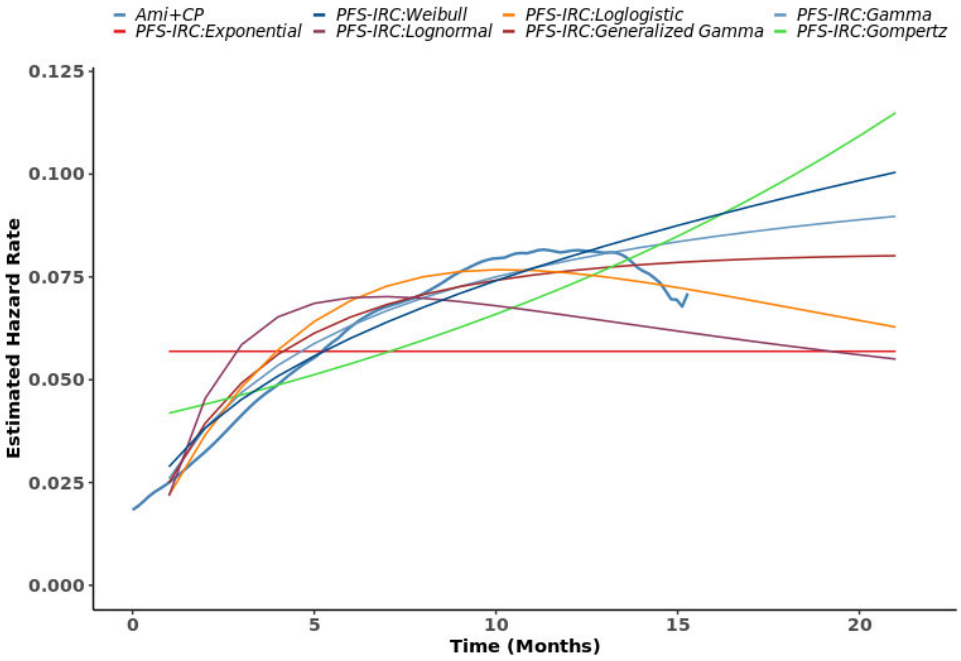


Abbreviations: CP = carboplatin + pemetrexed; BICR = blinded independent central review; PFS = progression-free survival

In Figure 31 and Figure 32 below, the smoothed hazards are overlayed with the fitted survival models. Visual comparison shows that the gamma and Weibull distributions are both good fits (also confirmed using AIC and BIC).

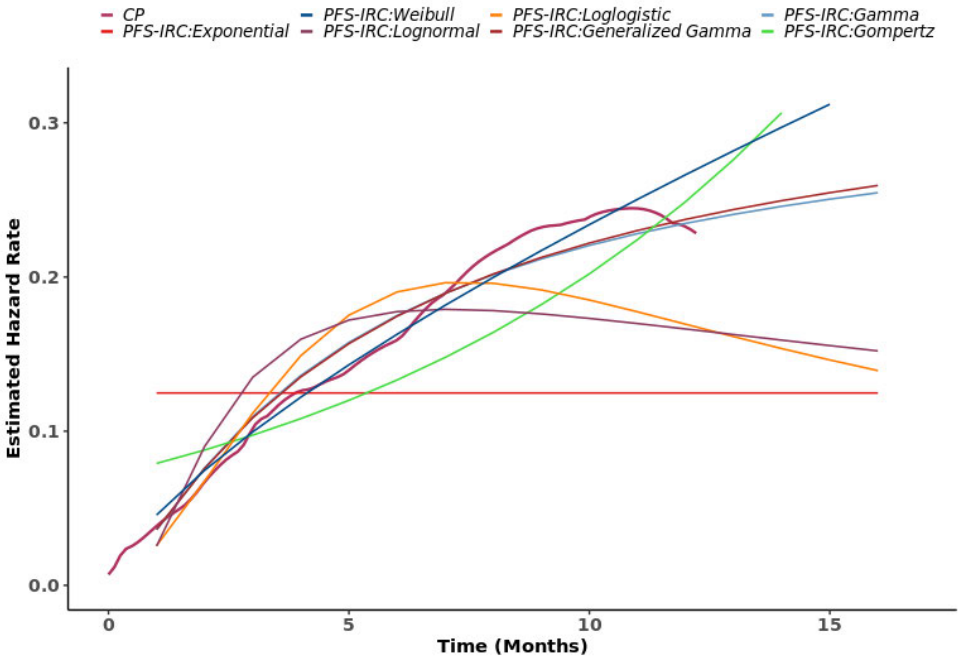
However, the gamma distribution captures the decline in the increase of hazard with time and maybe a more suitable choice for extrapolation beyond the trial duration.

Figure 31. Smoothed hazard plot with parametric extrapolations for amivantamab + CP PFS (BICR)



Abbreviations: BICR = blinded independent central review; PFS = progression-free survival

Figure 32. Smoothed hazard plot with parametric extrapolations for CP PFS (BICR)



Abbreviations: CP = carboplatin + pemetrexed BICR = blinded independent central review; PFS = progression-free survival.

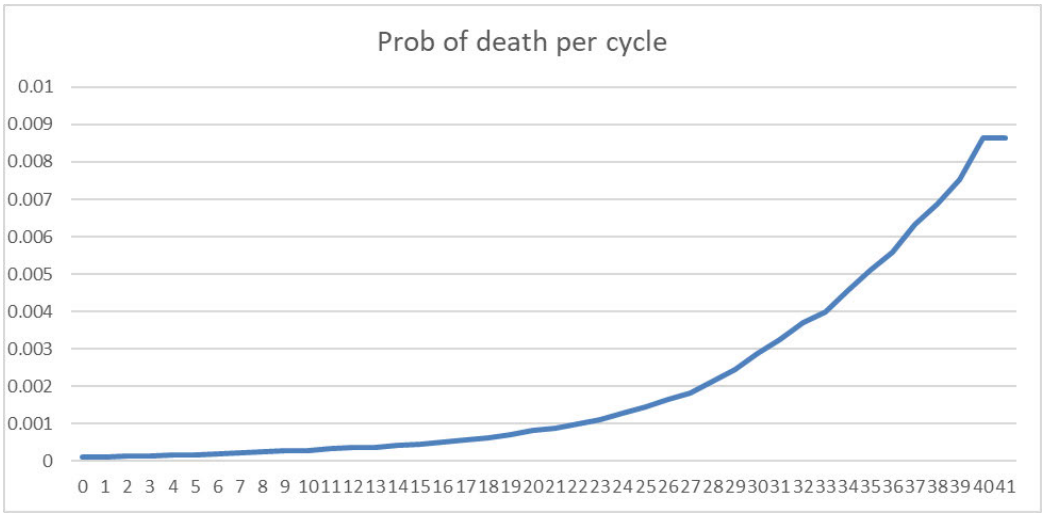
D.1.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the PFS curves was deemed acceptable to determine the distribution for PFS (gamma) given the maturity of the subject-level data from PAPILLON and reasonably similar extrapolations across distributions.

D.1.8 Adjustment of background mortality

The general mortality for the Danish population was used. The probability of death per cycle, as modelled, is shown in Figure 33 from 59 years of age.

Figure 33. General population risk of death (cycle-length probability)



D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of OS

D.2.1 Data input

OS was extrapolated from the subject-level data from the PAPILLON trial (Figure 13). The crossover to 2L amivantamab was adjusted using the IPCW method (see section D.2.9).

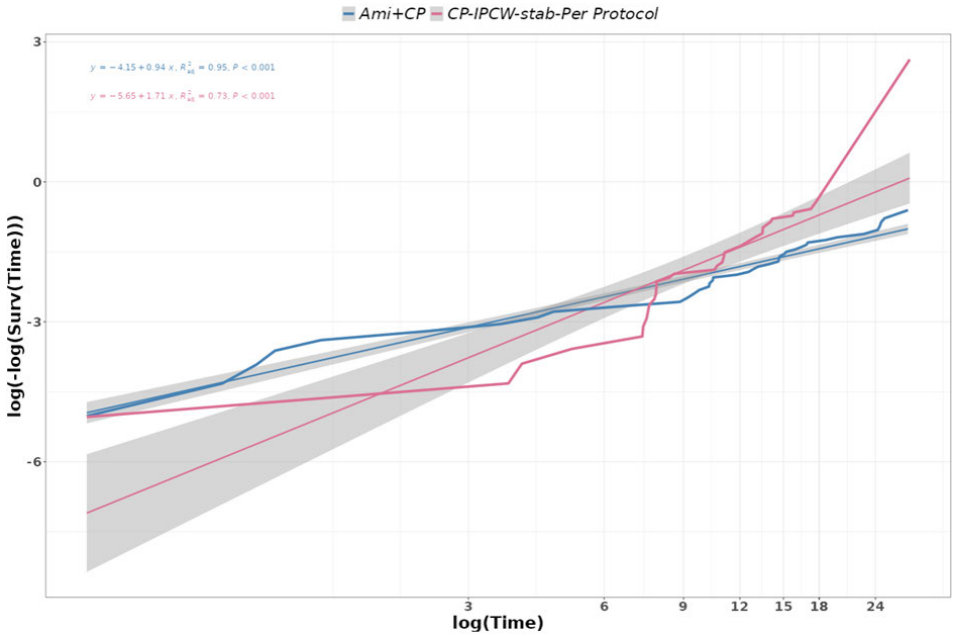
D.2.2 Model

See section D.1.2.

D.2.3 Proportional hazards

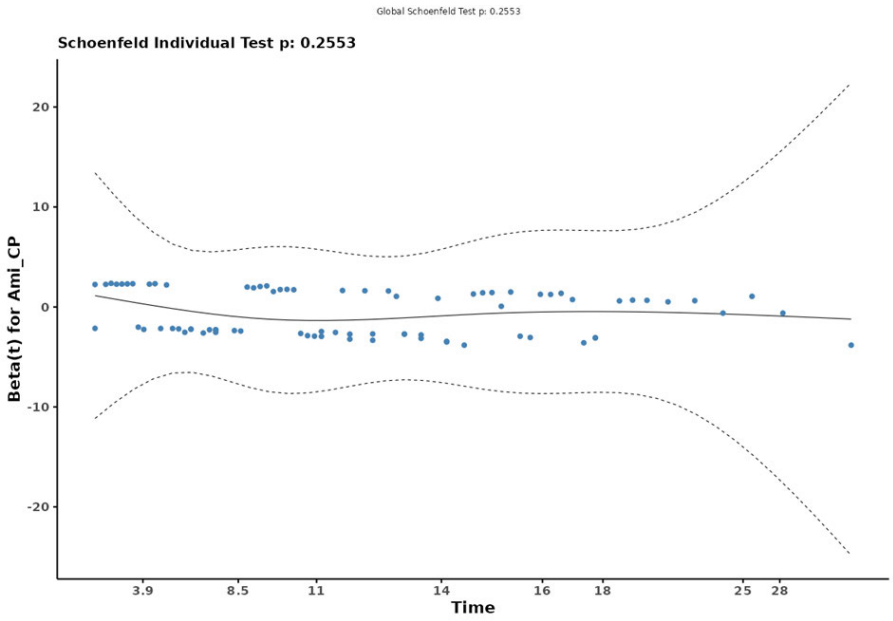
The PH assumption for OS was assessed graphically by the cumulative hazard plot (Figure 34) and the Schoenfeld residuals (Figure 35). For a discussion on the interpretation of the plots, see section D.1.3. For PFS, the log cumulative hazard plot indicates crossing hazards, i.e., a violation of the PH assumption. Thus, independent survival models were used for extrapolating OS.

Figure 34. Log cumulative hazard plot for amivantamab + CP and CP (IPCW, n=78) OS – October 2023



Abbreviations: CP = carboplatin + pemetrexed; OS = overall survival; IPCW = inverse probability of censoring weights

Figure 35. Schoenfeld plot and test for amivantamab + CP and CP (IPCW, n=78) OS – October 2023



Abbreviations: OS = overall survival; IPCW = inverse probability of censoring weights

D.2.4 Evaluation of statistical fit (AIC and BIC)

Statistical or goodness of fit was assessed by AIC and BIC, presented in Table 62, Table 63, and Table 64.

Table 62. Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for amivantamab+CP OS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median OS (months)	Mean OS (months)
Exponential	**418.43**	**421.46**	**1.32**	**0.00**	**83%**	**70%**	**58%**	**41%**	**17%**	**7%**	**3%**	**0%**	**46.69**	67.10
Weibull	**418.70**	**424.76**	**1.59**	**3.30**	**85%**	**69%**	**54%**	**32%**	**7%**	**1%**	**0%**	**0%**	**40.02**	50.55
Lognormal	424.07	430.13	6.96	8.67	83%	70%	61%	49%	32%	24%	19%	13%	57.49	125.53
Loglogistic	**419.92**	**425.98**	**2.81**	**4.52**	**85%**	**69%**	**57%**	**41%**	**22%**	**14%**	**10%**	**6%**	**45.08**	90.29
Gompertz	**417.11**	**423.17**	**0.00**	**1.71**	**86%**	**68%**	**47%**	**10%**	**0%**	**0%**	**0%**	**0%**	**34.50**	34.69
Gamma	**419.05**	**425.11**	**1.94**	**3.65**	**85%**	**69%**	**55%**	**35%**	**10%**	**3%**	**1%**	**0%**	**41.63**	55.58
Generalised Gamma	419.77	428.86	2.66	7.40	85%	68%	50%	15%	0%	0%	0%	0%	36.34	36.56

Table 63. Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for CP OS (IPCW)

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median OS (months)	Mean OS (months)
Exponential	376.72	379.76	22.42	19.37	76%	58%	45%	26%	7%	2%	0%	0%	31.28	45.0
Weibull	**356.00**	**362.09**	**1.70**	**1.70**	**79%**	**40%**	**13%**	**0%**	**0%**	**0%**	**0%**	**0%**	**21.16**	22.6
Lognormal	361.60	367.69	7.30	7.30	78%	49%	32%	15%	3%	1%	0%	0%	23.92	35.2
Loglogistic	**354.30**	**360.39**	**0.00**	**0.00**	**78%**	**42%**	**22%**	**8%**	**2%**	**1%**	**0%**	**0%**	**21.16**	28.6
Gompertz	362.68	368.77	8.38	8.38	80%	40%	4%	0%	0%	0%	0%	0%	21.62	21.1
Gamma	**355.70**	**361.78**	**1.40**	**1.39**	**79%**	**42%**	**19%**	**3%**	**0%**	**0%**	**0%**	**0%**	**21.62**	24.5
Generalised Gamma	357.53	366.66	3.23	6.27	79%	41%	16%	2%	0%	0%	0%	0%	21.39	23.6

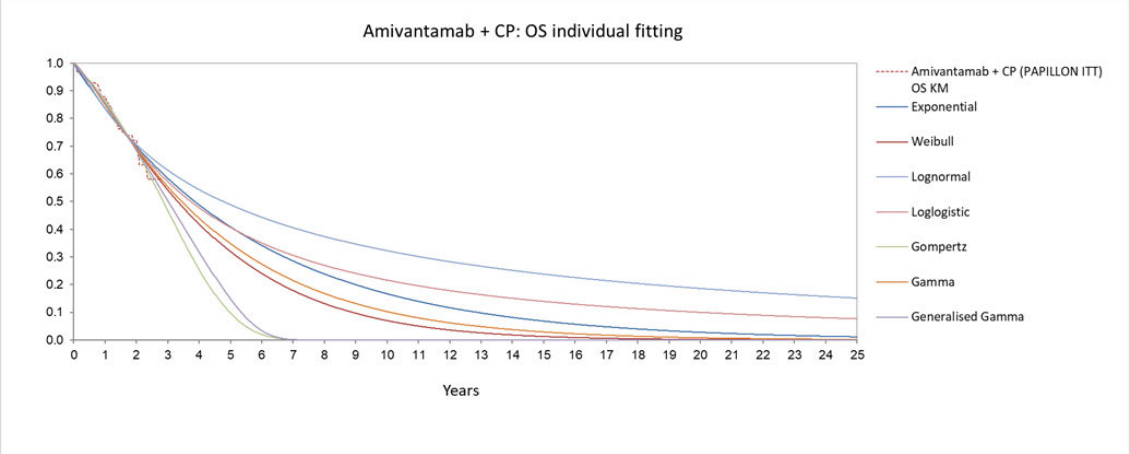
Table 64. Total (stratified) goodness-of-fit statistics and incremental difference in landmark survival rates, estimated median, and estimated mean survival for CP and amivantamab + CP OS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median OS (months)	Mean OS (months)
Exponential	795.15	801.22	20.93	14.85	7%	11%	14%	15%	10%	5%	2%	0%	15.41	22.11
Weibull	**774.70**	**786.85**	**0.48**	**0.48**	**5%**	**28%**	**41%**	**32%**	**7%**	**1%**	**0%**	**0%**	**18.86**	27.98
Lognormal	785.67	797.82	11.45	11.45	6%	21%	30%	34%	29%	23%	18%	13%	33.58	90.38
Loglogistic	**774.22**	**786.37**	**0.00**	**0.00**	**6%**	**28%**	**36%**	**33%**	**20%**	**13%**	**10%**	**6%**	**23.92**	61.73
Gompertz	779.79	791.94	5.57	5.57	6%	28%	43%	10%	0%	0%	0%	0%	12.88	13.62
Gamma	**774.75**	**786.89**	**0.53**	**0.52**	**6%**	**26%**	**36%**	**32%**	**10%**	**3%**	**1%**	**0%**	**20.01**	31.06
Generalised Gamma	777.30	795.52	3.08	9.15	6%	27%	34%	13%	0%	0%	0%	0%	14.95	12.97

D.2.5 Evaluation of visual fit

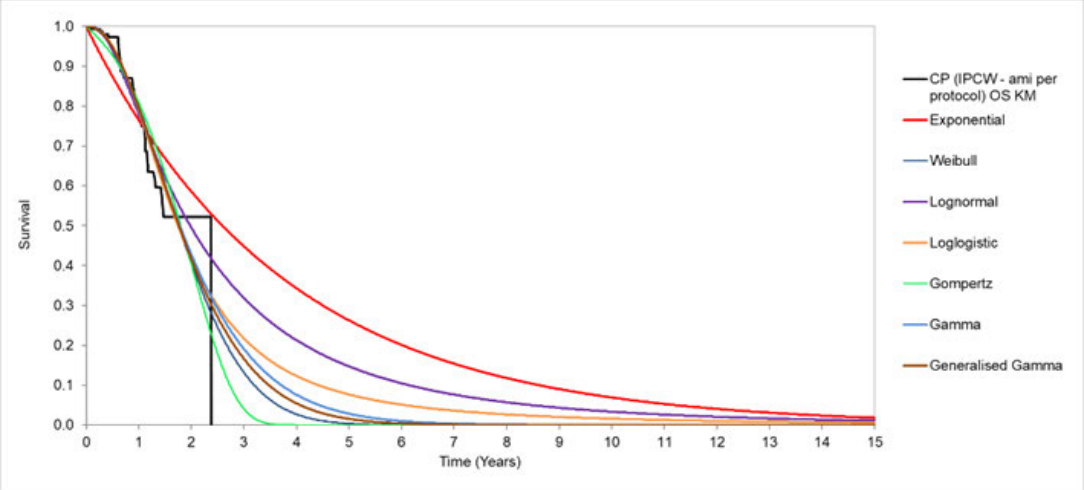
Figure 36, Figure 37 show the observed time-to-event data with all the investigated extrapolation functions for amivantamab + CP and CP alone, respectively. Several of the survival models demonstrate a good visual fit to the KM curves. However, the extrapolations show a wide variety of estimates of future survival rates, with the lognormal (amivantamab + CP) and exponential (CP) being the most optimistic, while Gompertz was the most pessimistic for both arms.

Figure 36. Long-term OS Projections of Amivantamab + CP – October 2023



Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; OS = overall survival.

Figure 37. Long-term OS Projections of CP Using IPCW, Amivantamab per protocol (n=78) – October 2023

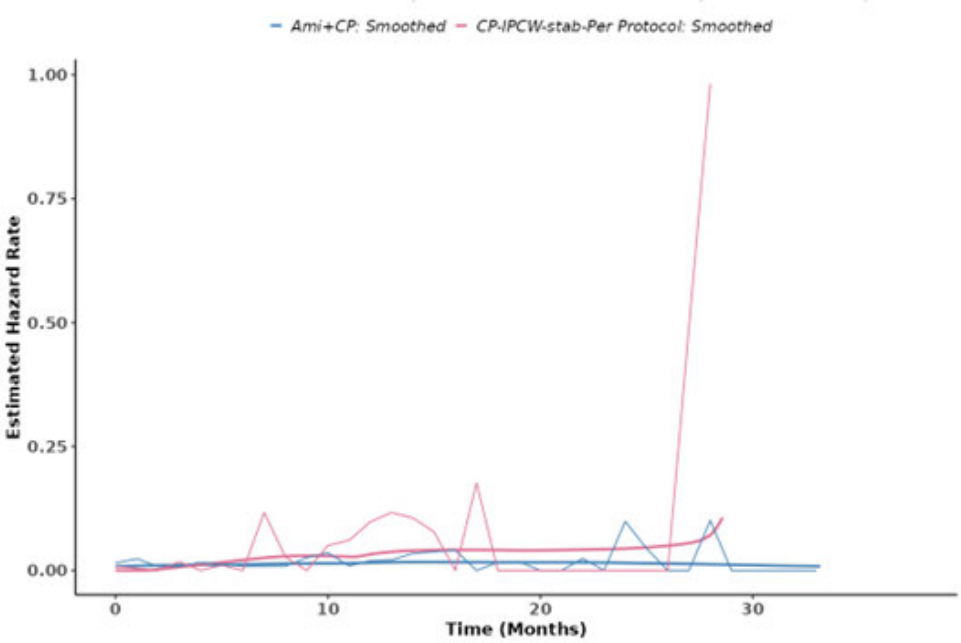


Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; OS = overall survival; IPCW = Inverse probability of censoring weight.

D.2.6 Evaluation of hazard functions

The smoothed hazards for amivantamab + CP and CP alone are presented below (Figure 30).

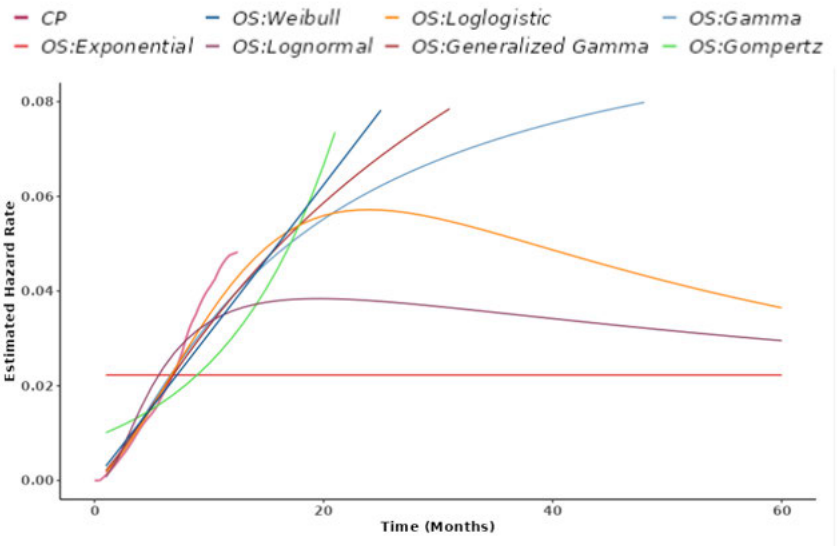
Figure 38. Smoothed and unsmoothed hazard plot for amivantamab + CP and CP (IPCW, n=78) OS – October 2023



Abbreviations: CP = carboplatin + pemetrexed; OS = overall survival; IPCW = inverse probability of censoring weights

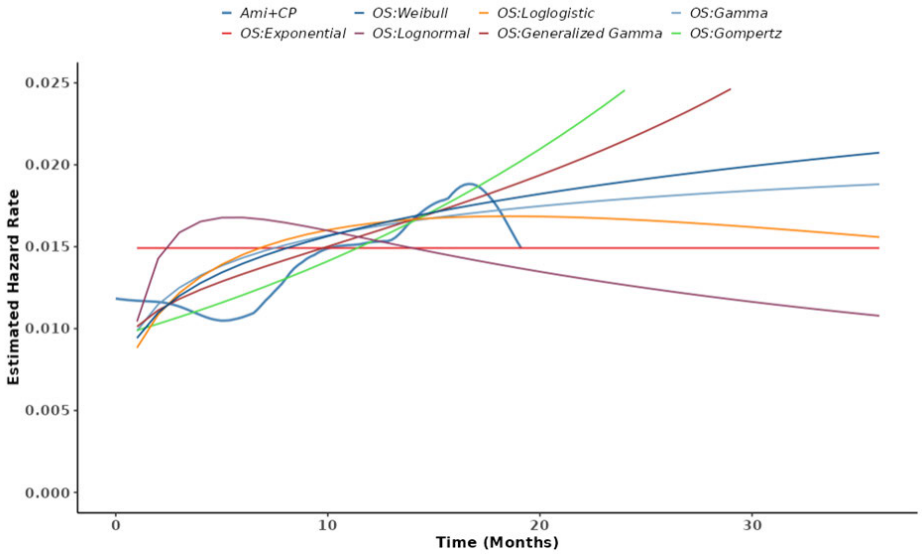
In Figure 39 and Figure 40 below, the smoothed hazards are overlayed with the fitted survival models. Visual comparison shows (similar to PFS) that the gamma and Weibull distributions are both good fits (also confirmed using AIC and BIC).

Figure 39. Smoothed hazard plot with parametric extrapolations for CP (IPCW, n=78) OS – October 2023



Abbreviations: CP = carboplatin + pemetrexed; OS = overall survival; IPCW = inverse probability of censoring weights Note: The KM data have been cut-off when the number of patients at risk of death dropped below 10

Figure 40. Smoothed hazard plot with parametric extrapolations for amivantamab + CP OS – October 2023



Abbreviations: CP = carboplatin + pemetrexed; OS = overall survival

D.2.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the OS curves was deemed acceptable to determine the distribution for OS (gamma) given the maturity of the patient-level data from PAPILLON. The predicted survival based on the gamma distribution was also validated by a Danish clinician as the most clinically plausible extrapolation for a Danish patient population [66].

D.2.8 Adjustment of background mortality

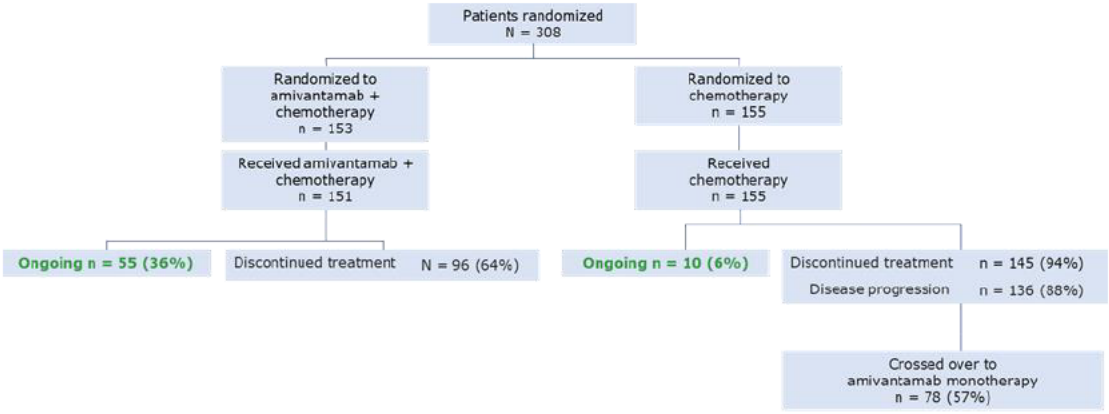
See section D.1.8

D.2.9 Adjustment for treatment switching/cross-over

PAPILLON (NCT04538664) [89] is an ongoing, phase 3, randomized, open-label, parallel, multicenter trial assessing the efficacy and safety of amivantamab vs CP alone in treatment-naive patients with locally advanced or metastatic NSCLC and EGFR exon20ins (median follow-up 20.9 months) [89, 90]. In total, 308 patients were randomized in a 1:1 treatment ratio to Arm A (amivantamab + CP, n=153) or Arm B (CP alone, n=155) [91]. The study design permitted patients in the CP arm with a blinded independent central review (BICR) - confirmed disease progression to switch to 2L amivantamab monotherapy [90].

Patients who switched were allowed to initiate treatment with amivantamab between 21 days up to 90 days after their last dose of chemotherapy, regardless of the time of progression [90]. Figure 41 summarizes the disposition of patients in the PAPILLON study [91]. [redacted] [91]. These patients are hereafter referred to as 'per-protocol AMI/amivantamab switchers'.

Figure 41. PAPILLON Patient Disposition (October 2023)



The exposure times (in months) to first and subsequent-line CP and amivantamab before death or administrative censoring are presented in a swim-lane plot (Figure 42). For each patient, the switch timepoint was defined as the time of the first amivantamab infusion in 2L treatment. Each line depicts the total available follow-up time for a single patient. The per-protocol amivantamab switchers were exposed to amivantamab [redacted] of their

[redacted]

An important preliminary step was conducting a feasibility assessment during which patient-level data from the PAPILLON trial were extensively reviewed to determine whether sufficient data were available and to validate the underlying assumptions of the IPCW, TSE, and RPSFT methods.

Evaluation of the Underlying Assumptions for the Adjustment Methods

D.2.9.1 IPCW

The IPCW method requires the absence of unmeasured confounders related to the baseline and time-varying patient characteristics and relies on correct model specification of treatment switching and outcome regression models. While the absence of unmeasured confounder assumption cannot be tested, a systematic approach was followed to identify relevant prognostic variables.

D.2.9.2 TSE

Per NICE DSU guidance [92], the TSE method necessitates the use of a disease-related secondary baseline to precede treatment switching. This is aligned with the PAPILLON study design, in which disease progression was a pre-requisite for treatment switching to 2L amivantamab, and time of progression can be used as a secondary baseline.

Similar to the IPCW method, the TSE method assumes no unmeasured confounding at secondary baseline in the comparison of post progression survival between switchers vs no switchers, and no time-dependent confounding after secondary baseline until treatment switching. All identified/measured confounders need to be included and correctly specified in the regression adjustment based on a well-fitting parametric accelerated failure time (AFT) model to the observed post-progression survival data. While the 'absence of unmeasured confounder' assumption cannot be tested, a systematic approach was followed to identify relevant prognostic variables.

D.2.9.3 RPSFT

The RPSFT model depends on the common treatment effect assumption, which implies that the survival benefit of 2L amivantamab monotherapy in patients who switched from 1L CP is similar to the survival benefit in patients who initiated amivantamab in 1L.

D.2.9.3.1 Prognostic Variables Considered for Treatment Switch Adjustments (IPCW and TSE)

The prognostic variables to be adjusted for in the IPCW and TSE analyses should be prognostic of both treatment switching and OS. Below, we describe how we identified the candidate prognostic variables that were considered in both the IPCW and TSE analyses.

An iterative process was followed to identify key prognostic factors to be accounted for in the OS adjustment analysis. First, an extensive list of factors was obtained using a systematic literature review and a Delphi panel including clinical experts (Janssen report: data on file). Afterwards, the final list of prognostic factors was obtained after an extensive medical review and determination of data availability. An advisory board was conducted to enable validation of the prognostic factors by clinical experts to ensure a wide range of the most clinically relevant factors were captured, and a final list was obtained:

- Age group (defined as ≥65 years vs. <65 years as defined in trial subgroups)
- Sex
- Asian race
- History of brain metastasis
- History of liver metastasis
- Eastern Cooperative Oncology Group (ECOG) performance status score
- History of smoking
- EQ-5D UK utility
- Time to progression (defined in months)
- Ongoing, serious treatment-emergent adverse events (TEAEs)
- Ongoing TEAE (febrile neutropenia)
- Prior major surgery
- Best overall response

Further descriptions of each variable are provided in Table 65.

Table 65. List of Prognostic Variables Considered in the IPCW and TSE Methods

Adjustment Variable	Assessment Time	Variable Type	Factor Levels
Age group	Secondary baseline/ time-variant	Binary	≥65 years vs. <65 years
Sex	Baseline	Binary	Male vs. female
Race (Asian vs Non-Asian)	Baseline	Binary	Non-Asiana vs. Asian
History of brain metastasis	Baseline	Binary	Yes vs. no
History of liver metastasis	Baseline	Binary	Yes vs. no
ECOG performance status	Secondary baseline/ time-variant	Binary	1+ vs. 0
History of smoking	Baseline	Binary	Yes vs. no

EQ-5D UK utility	Secondary baseline/ time-variant	Continuous	--
Time to progression (months)	Secondary baseline/ time-variant	Continuous	--
Ongoing serious TEAE	Secondary baseline/ time-variant	Binary	Yes vs. no
Prior major surgery	Baseline	Binary	Yes vs. no
Best overall response by BICR assessment in Period 01 of PAPILLON	Secondary baseline or latest timepoint available / time-variant	Binary	Responder vs. non-responder

Abbreviations: BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; TEAE = treatment-emergent adverse event; TSE = two-stage estimation a Four patients with unknown race were classified as 'non-Asian.'

D.2.9.4 Analysis Populations

Patients enrolled in the PAPILLON trial with treatment-naive, locally advanced or metastatic NSCLC characterized by EGFR exon20ins activating mutations were considered. A series of statistical analyses were conducted to adjust for treatment switching in PAPILLON. The analysis focused on the 'per-protocol amivantamab switchers' (n=78), who switched to 2L amivantamab as described in the study protocol.

D.2.9.5 Statistical Methods

The subsequent sections describe the statistical methods used to estimate OS while adjusting for treatment switching in the PAPILLON trial. Patient-level data from the October 2023 data cut of the PAPILLON trial were analysed using R version 4.0.4 (R Core Team, Vienna, Austria). The statistical analyses were conducted following current guidance from NICE DSU TSD 16 [92] and Sullivan et al [93].

The counterfactual OS (and PPS times for TSE) and censoring flags in the CP arm were derived after adjusting for treatment switching using the three methods, as detailed in the following sections. The Kaplan-Meier (KM) curves of the observed and counterfactual OS (and PPS for TSE) in the amivantamab + CP and CP arms were also compared.

D.2.9.5.1 Approach 1: IPCW Method

The IPCW method was implemented following three general steps:

- Creation of panel data
- Estimation of stabilized, time-dependent weights for the CP arm
- Estimation of an adjusted treatment effect on OS

The prognostic variables for covariate regression adjustment were selected according to the findings of the associated feasibility assessment.

The IPCW method considered all covariates outlined in Table 65, except for time to progression and best overall response; these covariates could not be included as baseline or time-varying covariates (TVCs). In contrast, these variables were available for TSE at a secondary baseline of time to progression. In addition, EQ-5D utility (defined as continuous variables), ECOG performance status, serious TEAEs (defined as yes vs. no), and a TEAE of febrile neutropenia (defined as yes vs. no) were tested as TVCs in the treatment switching model using the IPCW method.

Creation of Panel Data

For each patient, the follow-up time from randomization to treatment switching 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 these intervals were expected to provide the most reliable results that leverage all available information. Individual patient-level data from PAPILLON were then restructured to create panel data, with one record per patient per time interval. The baseline covariates were repeated across the time intervals for a given patient, and TVCs

were specific to each time interval. In the absence of TVC values specific to a particular time period, the last observation captured before was used.

Time-dependent outcome binary variables were then created for the treatment-switch status and death, with patients censored at the time of treatment switch if they crossed over (implemented in the panel data structure by omitting all observations after switching occurred).

Estimation of Time-dependent Weights (CP Arm)
After artificially censoring patients at the time of treatment switching, the follow-up information of patients who remained at risk of switching from 1L CP to 2L amivantamab was weighted such that the patients accounted not only for themselves but also for patients with similar characteristics (both baseline and time-varying) whose follow-up information was obscured due to informative censoring. This step involved the estimation of time-dependent weights for patients in the CP-arm only as follows:

CP patients who did not progress were not “at risk” for switching and were assigned a weight of 1.

For patients who progressed (and were “at risk” for switching), the probability of switching within each time period was estimated using the following two logistic regression models (including splines with three knots to ensure that time-dependent relationships were sufficiently flexible):

Model 1: was fitted to all progressed CP patients only and included all the above-mentioned time-varying and baseline covariates. A stepwise variable selection with a significance level of 0.25 was applied.

Model 2: was fitted to all CP patients, and stabilized weights for each timepoint were then calculated. The ratio of the probabilities comes from model 1 and model 2 in the numerator and the denominator, respectively.

As suggested by Latimer et al.[94], an additional analysis using non-stabilized weights was implemented, which are the inverse of the probabilities from model 1 (and thus leaving the model 1 probabilities out of the numerator).

Estimation of an Adjusted Treatment Effect on OS
An IPCW-adjusted HR for OS was estimated 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.

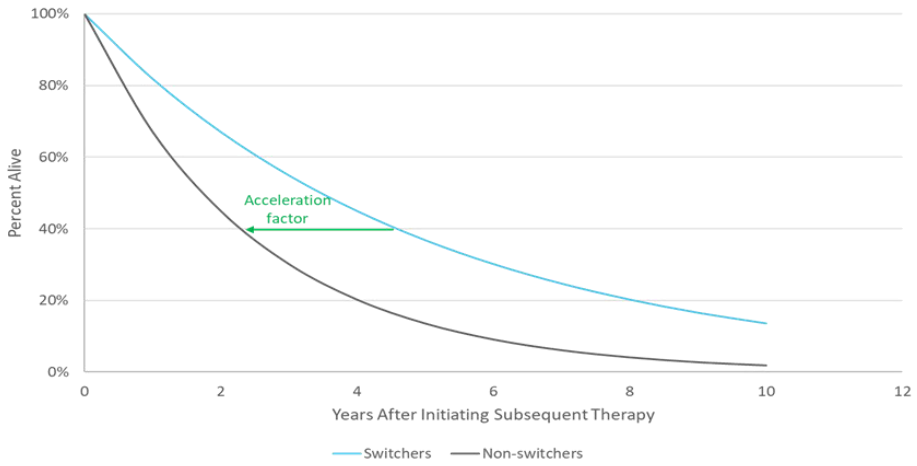
D.2.9.5.2 Approach 2: TSE Method

The TSE method[95, 96] involves two steps: first, a treatment effect specific to switching patients is estimated and the survival times of these patients are adjusted, subsequently allowing the treatment effect specific to experimental group patients to be estimated. In stage 1 of the TSE, a Weibull accelerated failure time model was fitted on the post-

progression survival, comparing the CP patients who switched to 2L amivantamab versus those who did not switch to 2L amivantamab, using data of progressive disease as a secondary baseline.[97] Prognostic factors available at secondary baseline were included as covariates in the AFT model to adjust for differences between the 2L amivantamab switchers versus 2L amivantamab non-switchers. Stepwise variable selection with a significance level of 25% was applied, keeping consistency with the approach for IPCW. Treatment switching to 2L was used as a TVC (using R-package FlexSurv).

A Weibull AFT model allowed estimation of an acceleration factor, denoted γ_B, which represents the treatment effect on PPS that is associated with 2L amivantamab (vs. no 2L amivantamab). In stage 2 of the TSE, the observed PPS survival for the patients who switched to 2L amivantamab was replaced by the counterfactual PPS estimated from the AFT model in stage 1. By adding the counterfactual PPS estimated in step 1 to the observed time to progression, the counterfactual OS of the switcher patients was obtained.

Figure 43. Illustrative Example of the Application of AFT



Abbreviations: AFT = accelerated failure time

The relative efficacy of amivantamab + CP vs. CP on adjusted/counterfactual OS was then estimated by fitting a Cox proportional hazards model with randomized treatment as a covariate. The conventional estimators of standard error (SE) 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 + CP compared with CP.

Variables Selected for the Treatment Switch Adjustment

The prognostic variables tested in the model selection process for the TSE and a description of the matched statistics of each variable are provided in Table 65.

It was not possible to include ongoing treatment-emergent febrile neutropenia (an adverse event) as a covariate because no events were observed at the time of progression. Due to limited counts, categories were collapsed for the ECOG performance status (1+ vs. 0) and best overall response (responder vs. non-responder), and these categorical variables were effectively redefined from multilevel to binary.

Re-censoring

Shrunken administrative censoring times based on the TSE (or RPSFT) model could be associated with patients' prognosis; in this case, counterfactual times would be prone to informative censoring bias. A process called 're-censoring' has been proposed as a potential solution to correct for this bias by breaking the dependence between the counterfactual censoring time and treatment received (2L amivantamab vs. other in this case).

Mathematically, the counterfactual survival times of all CP patients under consideration (including both those who switched from CP and those who did not) were re-censored at the minimum of the administrative censoring time, C_i, and adjusted administrative censoring time, where $D_i^* = \min(C_i, C_i\gamma_B^{-1})$. The counterfactual survival time was replaced by D_i^* if $D_i^* < T_i^{CF}$, and the censoring flag was updated accordingly.

Although re-censoring aims to correct for informative censoring bias, it can increase uncertainty and introduce another type of bias—in particular, missing information bias [95, 96]. Missing information bias can be particularly problematic for short-term survival data extrapolated from a control group affected by treatment switching, where re-censoring could result in a significant loss of long-term information (e.g., important change in the trend of the hazard is no longer captured) [95, 96]. NICE DSU TSD 16 [92], TSD 24, and Latimer et al., 2019 [95] caution that the loss of information due to re-censoring can be detrimental if the ultimate goal is long-term extrapolation in cost-effectiveness analyses.

Analyses were conducted both without (primary analysis) and with (sensitivity) re-censoring to investigate the range of possible results, consistent with the recommendations by the NICE DSU [92] and Sullivan et al. (2020) [93].

D.2.9.5.3 Approach 3: RPSFT Method

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

In the primary analysis, the RPSFT model was configured with 'treatment grouping' assuming a lagged treatment effect if a patient-initiated amivantamab.

The specific steps in the first stage of the RPSFT process were as follows, where T_E denotes a patient's time of death if the patient always received amivantamab + CP, and T_s denotes the same patient's time of death if the patient always received CP:

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.

For all patients in PAPILLON, the counterfactual survival times were calculated assuming that the patients were only randomized to the CP arm (T_s).

The observed OS time (T_E) using the following structural model: $T_s = T_E \times \exp(\varphi)$ were adjusted for patients randomized to the amivantamab + CP arm.

For patients randomized to the CP arm who never switched to 2L amivantamab, T_s was observed directly.

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

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 + CP and CP 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).[98] 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 step of RPSFT, the counterfactual OS distribution (i.e., KM curves) with CP 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 switched and 2) retaining the observed OS for those who did not switch. The counterfactual survival with CP was compared with the observed OS with amivantamab + CP 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 ITT analysis by adjusting the conventional estimate of the SE.

Like the TSE method, counterfactual censoring times based on the RPSFT method may be prone to informative censoring bias, when only survival times for the 2L amivantamab switchers are shrunken. Re-censoring could possibly address this bias. However, re-censoring may introduce missing information bias and increase uncertainty. As stated previously, a simulation study by Latimer et al., 2019[95] found that the RPSFT model with re-censoring generally resulted in increased bias and uncertainty (empirical SE, and root mean square error) compared to no re-censoring.

Due to the increased missing information bias caused by the additional re-censoring and high treatment effectiveness in this data cut, where a significant proportion of the death

events of CP patients occurred in relatively later time points, RPSFT results without re-censoring are presented in the primary analyses.

D.2.9.6 Results

D.2.9.6.1 IPCW Method

The fitted multivariate logistic regression models 1 and 2 that were used to predict the probability of switching from CP to 2L amivantamab as per the protocol are summarized in Table 66 and [redacted] respectively. In logistic regression model 1, ECOG and EQ-5D Utility as TVCs were statistically significant at the 25% threshold.

Table 66. Multivariate logistic regression model 1 to predict treatment switch, including baseline and time-varying covariates

Variable	Estimate	SE	p-value
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPCW = inverse probability of censoring weight; SE = standard error; TVC = time-varying covariate

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted] presents the KM curves of the observed OS for amivantamab + CP (in black) and CP (in green), and the counterfactual OS for CP estimating OS for CP patients in the absence of switching to 2L amivantamab (in blue). The unadjusted median OS for amivantamab+CP was not reached and the median unadjusted OS for CP [redacted] and the adjusted median OS for CP was [redacted].

[redacted]

[redacted]

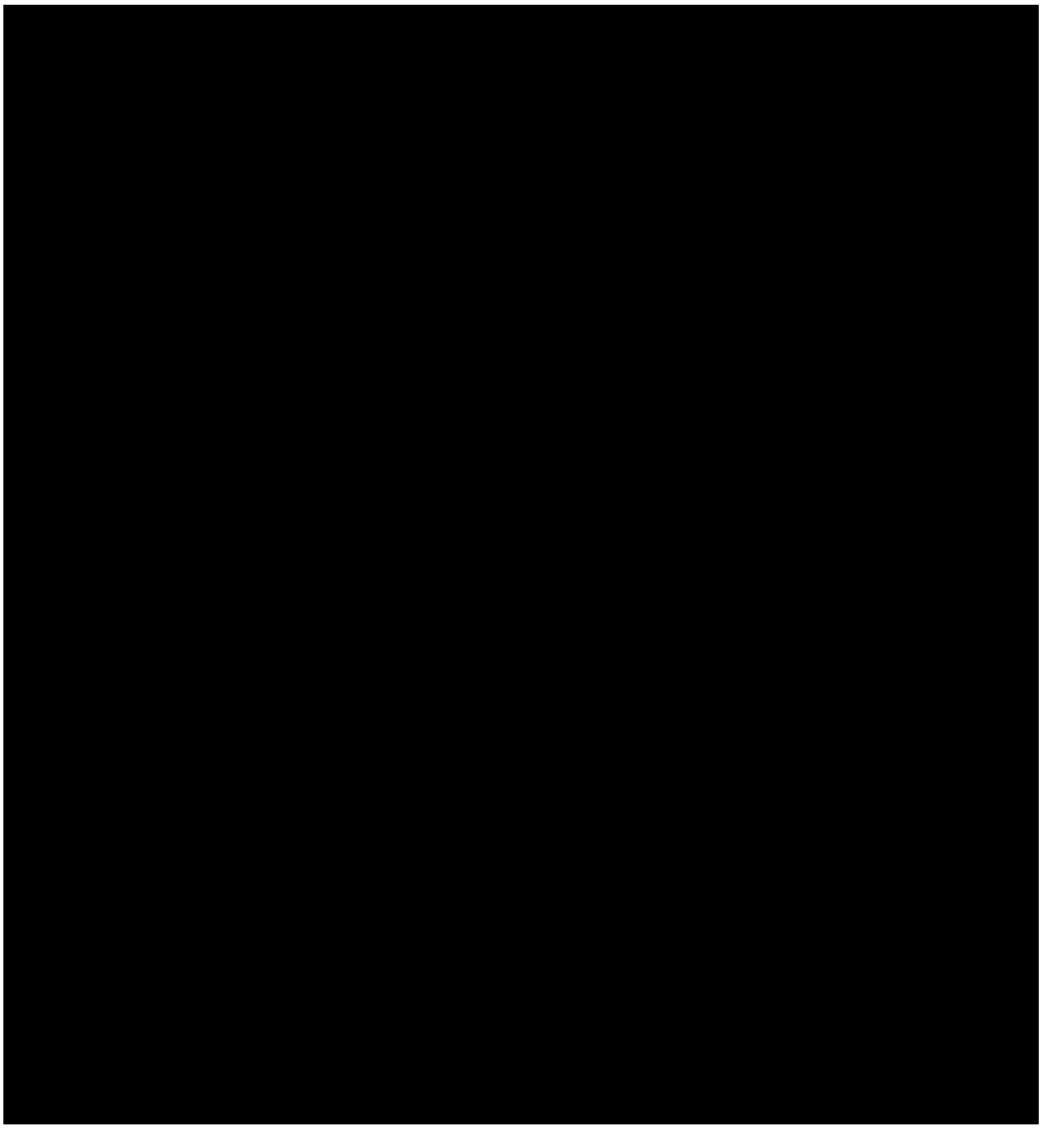
D.2.9.6.2 TSE Method

Stage 1: Fit AFT Model for PPS (BICR)

Multivariate Weibull AFT model

The final multivariate regression model developed via a stepwise variable selection approach retained seven of the 13 candidate covariates in addition to the treatment-switch status as detailed in [redacted] reports the estimates for each of the variables from the final Weibull model in the order they entered the model in the stepwise procedure (e.g., treatment switch in step 1, ECOG in step 2, etc.).

The estimate for the 2L AMI treatment is [redacted] indicating that patients who switched to 2L AMI had about twice as long survival post progression compared to non-switchers. Risk factors associated with worse PPS were ECOG1 status, age 65+, non-asian ethnicity, short time to progression and lack of response in first line and liver or brain metastasis. The risk factors associated with worse survival post progression are in line with expectations; thus, increasing face validity of the analysis. The inverse of the treatment effect estimate ([redacted] P=<0.001) provides the shrinkage factor to be applied in the second stage to the observed PPS to estimate the counterfactual outcome when these patients would not have switched to 2L AMI.



Stage 2: Estimate Counterfactual Survival

The counterfactual survival times were estimated by shrinking the survival times using the estimated acceleration factor, which represents the estimate of treatment effect on PPS from the parametric Weibull survival model. [redacted] presents the KM curves of the observed and counterfactual PPS for the progressed patients from the CP-arm, with time 0 representing the date of progression as secondary baseline.

Figure 46 presents the KM curves of the observed OS for amivantamab + CP (in black) and CP (in green), and the counterfactual OS for CP estimating OS for CP patients in the absence of switching to 2L amivantamab (in blue). The unadjusted median OS for amivantamab+CP was not reached and the unadjusted median OS for CP was [redacted] the adjusted median OS for CP without recensoring was [redacted] and the adjusted median OS for CP with resensoring was [redacted]

According to the TSE method, the OS with amivantamab + CP was superior to that with CP in the absence of cross-over, with an HR [bootstrapped 95% CI] of

D.2.9.6.3 RPSFT Model

The optimal φ value (denoted $\varphi_{\mathbf{optimal}}$) to balance counterfactual survival between the two arms was found via g-estimation, where a grid of potential values between -1 and 1 were tested; $\varphi_{\mathbf{optimal}} = -0.28$ resulted in a chi-square test statistic with the maximum p-value of approximately 1 (Figure 47). The negative $\varphi_{\mathbf{optimal}}$ indicates that time on amivantamab + CP extends survival time compared to CP alone. The implied shrinkage factor is $\exp(-0.28) = 0.76$, which quantifies the relative decrease in survival if a patient had received CP instead of amivantamab + CP (this is applied to the entire follow-up of amivantamab + CP and the post 2L-amivantamab survival).

The observed and counterfactual KM curves of amivantamab + CP (in black) and CP (in green) and the counterfactual OS for CP estimating OS for CP patients in the absence of switching to 2L amivantamab (in blue). are presented in Figure 48. The unadjusted median OS for amivantamab+CP was not reached and the unadjusted median OS for CP was), the adjusted median OS for CP without recencoring was) and the adjusted median OS for CP with rescensoring was not reached (

The adjusted HR on OS for amivantamab + CP vs. CP in the absence of treatment switching was The adjustment on HR using RPFSTM with re-censoring was very similar to the primary analysis without re-censoring, with the adjusted The RPFSTM retained the p-value from the ITT analysis by design, with the CI widened compared to the original ITT-based CI.

D.2.9.6.4 Comparison of results versus results based on the first data-cut for PAPILLON

The findings presented in this scientific report are based on the most recent data available for the PAPILLON study (median follow-up of [redacted]), which was requested by the EMA during the regulatory approval process and included in both SmPC and the EPAR [99]. Similar analyses were conducted on the initial data cut for PAPILLON, which had a median follow-up of [redacted] (compared to [redacted] at the October 2023 data cut) [100].

Table 69 provides an overview of the results obtained using the May 2023 and October 2023 data-cuts. The table shows the OS HRs utilising the ITT analysis as well as the three crossover methods described in this report.

[redacted]

D.2.9.7 Discussion

To adjust OS for treatment switching from CP to 2L amivantamab in the PAPILLON trial, statistical analyses were conducted using the IPCW model, TSE, and RPSFT methods. The results of the three approaches were generally consistent, with adjusted HRs for OS comparing amivantamab + CP vs. CP of [redacted] using the IPCW method, [redacted] using the TSE method, and [redacted] using the RPSFT model. The findings from these adjusted analyses illustrate that the ITT-based comparison of amivantamab + CP vs CP (HR of [redacted]) underestimates the true treatment effect and survival benefit for amivantamab + CP when treatment switching from CP to 2L amivantamab is not adjusted for.

All three statistical methods for treatment switching adjustment rely on different sets of assumptions, but provide similar treatment effect estimates. Firstly, the IPCW and TSE

methods rely on the 'no unmeasured confounders' assumption and can provide unbiased estimates of the relative treatment effect if all baseline and time-varying factors prognostic for both switching to amivantamab 2L and survival are adjusted for. Although this assumption cannot be verified directly, prognostic variables were systematically identified in consultation with clinical experts to ensure that the most important and clinically relevant prognostic factors were included, thus also minimizing the risk of bias. Secondly, the RPSFT model is subject to the viability of the common treatment effect assumption; the validity of this assumption is difficult to validate. The counterfactual results (without re-censoring for TSE and RPSFT) were comparable between all methods, suggesting that these methods share the strength of producing consistent and reliable counterfactual results.

Consistent with current guidance from NICE TSD16 and TSD24, the RPSFT and TSE analyses were conducted with and without re-censoring, and the impact of re-censoring varied by method. Re-censoring led to substantially shorter follow-up for the CP arm, and a higher loss of information due to additional censoring of death events leading to substantially increased uncertainty (e.g. re-censoring led to a maximum survival time of ~16 months for the TSE and ~24 months for the RPSFT, compared with a maximum survival time of ~33 months observed in the OS from CP arm of PAPILLON). In order to minimize additional uncertainty in terms of long-term survival extrapolations, estimates based on the analyses of counterfactual survival data without re-censoring are recommended for input into the associated cost-effectiveness model to mitigate potential bias [95].

[redacted]

[redacted]

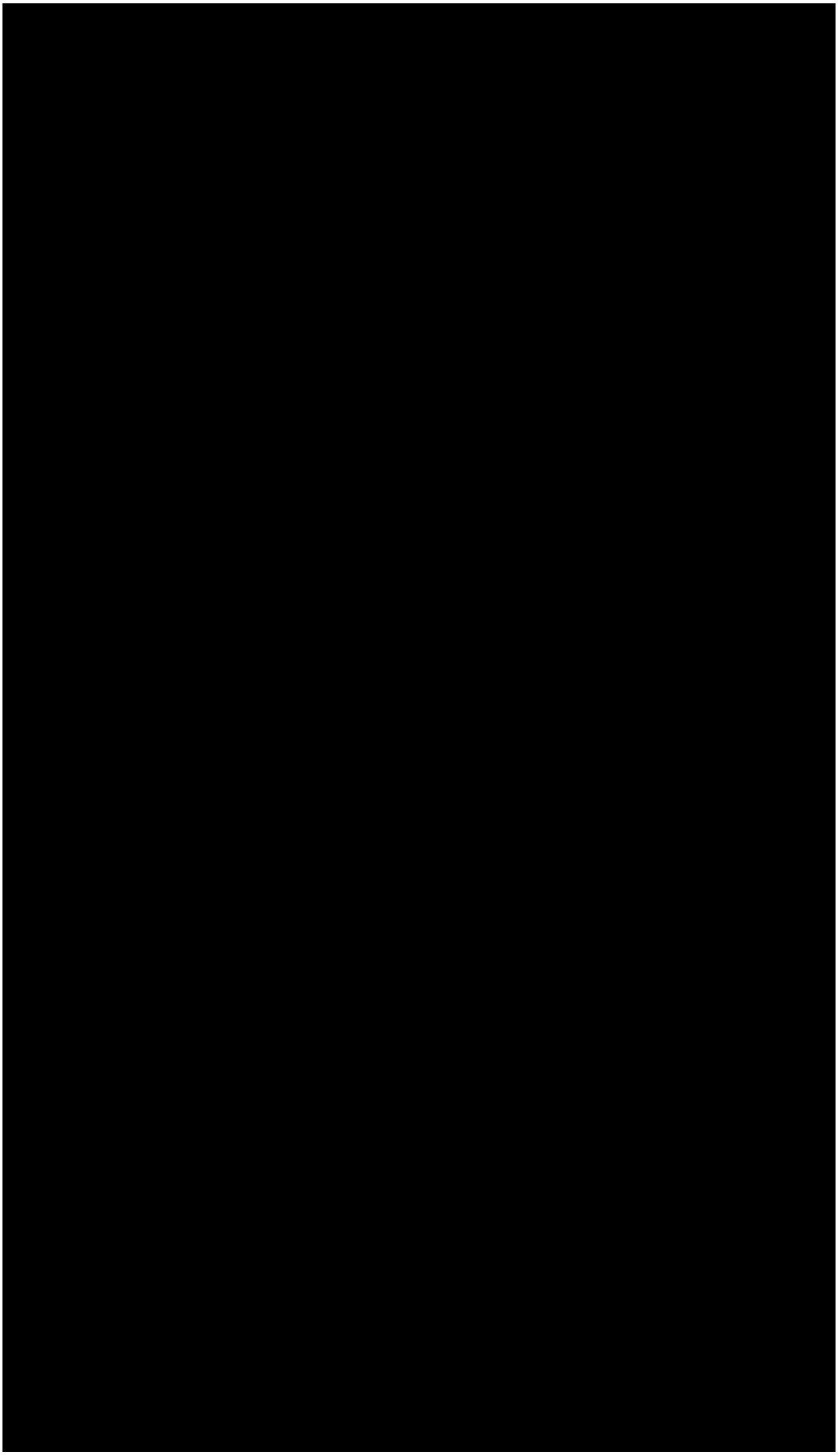
[redacted]

[redacted]

D.2.9.8.1 Baseline patient characteristics for both patients who switched and patients who did not switch treatment

A summary of the comparisons of the time-varying patient characteristics at progression is presented in [redacted]. In the TSE analysis, the imbalances in prognostic factors in the CP subgroups (switchers vs. non-switchers) at progression were adjusted using covariate regression adjustment.

[redacted]



[redacted]

[redacted]

[redacted]

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

Appendix E. Extrapolation of TTDD

E.1.1 Data input

TTDD was extrapolated based on subject-level data from the PAPILLON. TTDD was not used in the base case analysis (treatment was based on PFS), TTDD is included as a scenario analysis.

E.1.2 Model

See section D.1.2.

E.1.3 Proportional hazards

The PH assumption was not considered as the scenario using TTDD used three separate and independently fitted distributions for amivantamab and CP in the amivantamab + CP arm and CP in the CP alone arm.

E.1.4 Evaluation of statistical fit (AIC and BIC)

The goodness-of-fit statistics for the three treatments in the trial are presented below in Table 72, Table 73, and Table 74 for CP alone, CP in amivantamab + CP and amivantamab in amivantamab + CP. Given the maturity of the survival data (see [redacted]), the overall best-fitting distribution was chosen for the scenario. The overall best-fitting distribution based on AIC was the Weibull distribution.

Table 72. Goodness-of-fit of survival distributions for TTDD - CP

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median TTDD (months)	Mean TTDD (months)
Exponential	849.4762	849.4762	63.99097	63.99097	27%	0%	1%	0%	0%	0%	0%	0%	6.67	9.46
Weibull	787.6145	787.6145	2.1293	2.1293	21%	4%	1%	0%	0%	0%	0%	0%	8.05	8.64
Lognormal	797.6945	797.6945	12.20928	12.20928	22%	4%	0%	0%	0%	0%	0%	0%	7.36	9.26
Loglogistic	787.982	787.982	2.496806	2.496806	21%	0%	0%	0%	0%	0%	0%	0%	7.59	9.55
Gompertz	811.0732	811.0732	25.58799	25.58799	20%	1%	0%	0%	0%	0%	0%	0%	8.05	8.53
Gamma	785.4852	785.4852	0	0	20%	0%	0%	0%	0%	0%	0%	0%	7.82	8.71
Generalised Gamma	787.23	787.23	1.74356	1.74356	0%	0%	0%	0%	0%	0%	0%	0%	7.82	8.68

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Table 73. Goodness-of-fit of survival distributions for TTDD – CP in amivantamab + CP

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median TTDD (months)	Mean TTDD (months)
Exponential	694.90	697.93	6.09	3.06	49%	25%	12%	3%	0%	0%	0%	0%	12.19	17.39
Weibull	688.81	694.87	0.00	0.00	50%	18%	6%	0%	0%	0%	0%	0%	12.19	14.90
Lognormal	700.00	706.06	11.19	11.19	49%	27%	17%	8%	2%	1%	1%	0%	11.96	23.38
Loglogistic	692.52	698.58	3.71	3.71	49%	24%	14%	7%	2%	1%	1%	0%	11.96	23.09
Gompertz	690.21	696.28	1.40	1.41	51%	16%	2%	0%	0%	0%	0%	0%	12.65	13.99
Gamma	689.38	695.44	0.57	0.57	49%	20%	7%	1%	0%	0%	0%	0%	12.19	15.50
Generalised Gamma	690.69	699.78	1.88	4.91	50%	17%	4%	0%	0%	0%	0%	0%	12.42	14.61

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

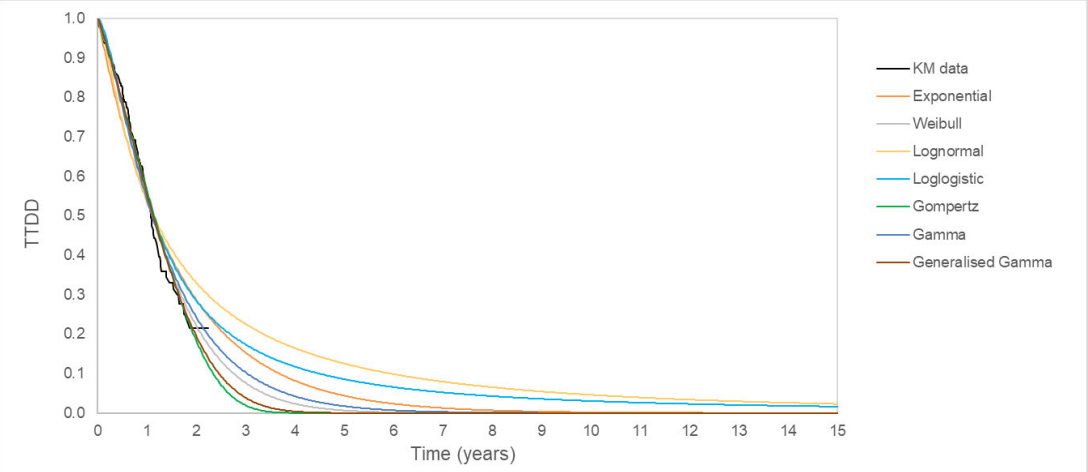
Table 74. Goodness-of-fit of survival distributions for TTDD – amivantamab in amivantamab + CP

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1-year	2-years	3-years	5-years	10-years	15-years	20-years	30-years	Median TTDD (months)	Mean TTDD (months)
Exponential	682.1	697.93	7.2	3.06	53%	28%	15%	4%	0%	0%	0%	0%	13.34	19.30
Weibull	676.36	694.87	1.46	0	54%	22%	8%	1%	0%	0%	0%	0%	13.34	16.28
Lognormal	698.74	706.06	23.84	11.19	53%	33%	22%	13%	5%	2%	1%	1%	13.80	30.62
Loglogistic	683.04	698.58	8.14	3.71	54%	28%	17%	9%	3%	2%	1%	1%	13.57	26.37
Gompertz	674.9	696.28	0	1.41	56%	18%	2%	0%	0%	0%	0%	0%	13.80	14.91
Gamma	678.14	695.44	3.24	0.57	53%	24%	10%	2%	0%	0%	0%	0%	13.34	17.24
Generalised Gamma	676.67	699.78	1.77	4.91	55%	19%	4%	0%	0%	0%	0%	0%	13.57	15.26

E.1.5 Evaluation of visual fit

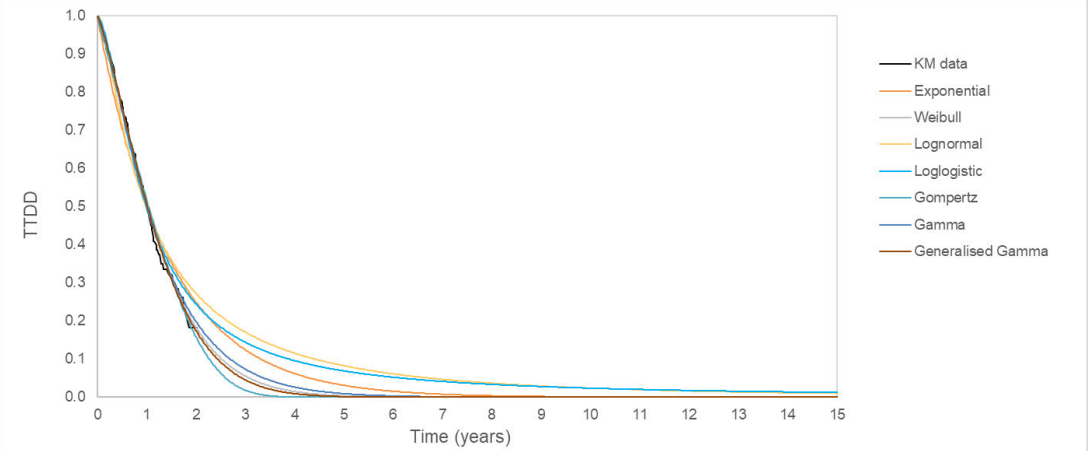
The long-term TTDD extrapolations for amivantamab alone and CP alone are presented in Figure 51 and Figure 52.

Figure 51. Long-term TTDD Projections of amivantamab alone for amivantamab + CP



Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; TTDD = time to treatment discontinuation or death.

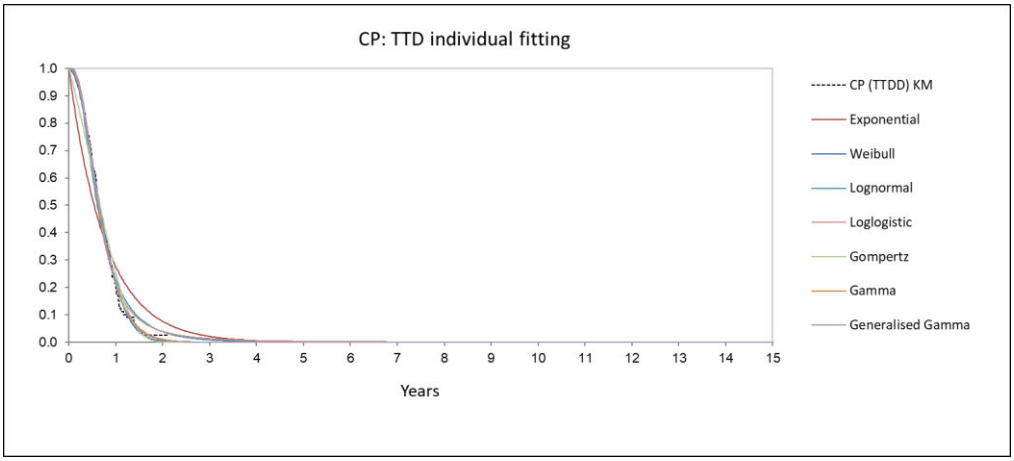
Figure 52. Long-term TTDD Projections of CP alone for amivantamab + CP



Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; TTDD = time to treatment discontinuation or death.

The long-term TTDD extrapolations for CP are presented in Figure 53.

Figure 53. Long-term TTDD Projections of CP

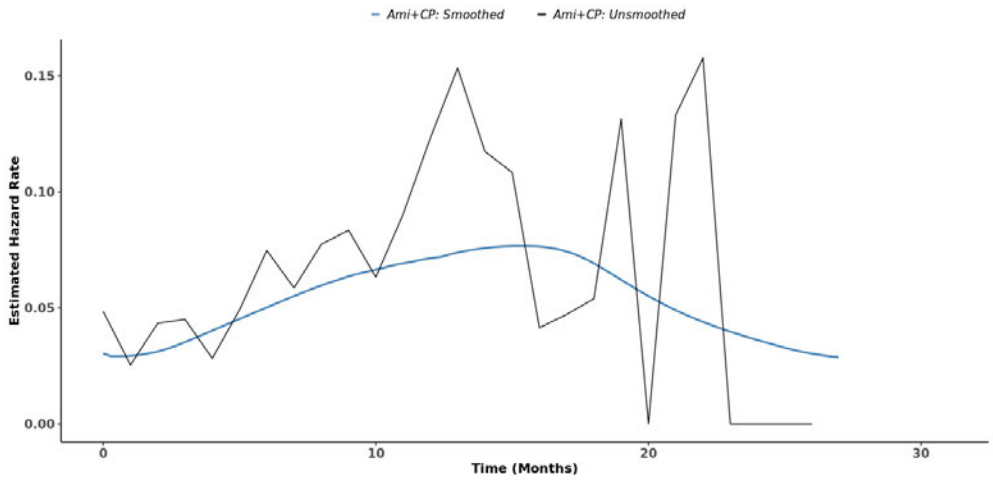


Abbreviations: CP = carboplatin + pemetrexed; KM = Kaplan-Meier; TTDD = time to treatment discontinuation or death.

E.1.6 Evaluation of hazard functions

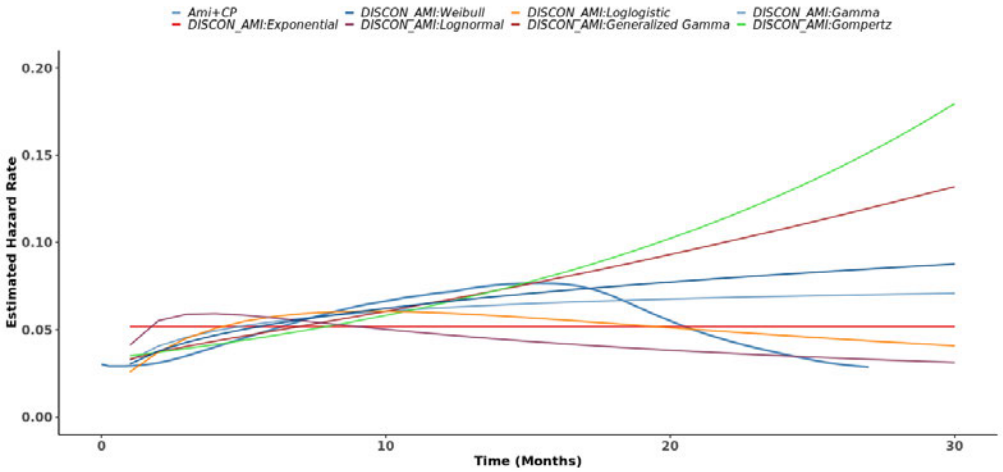
E.1.6.1Amivantamab + CP – Amivantamab alone

Figure 54. Smoothed and unsmoothed hazard plot for amivantamab + CP (amivantamab alone) TTDD



Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death.

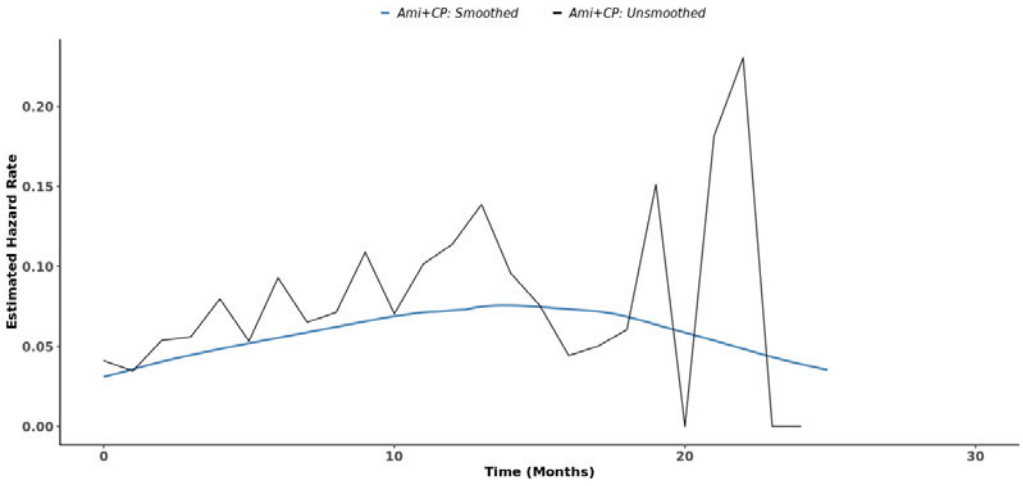
Figure 55. Smoothed hazard plot with parametric extrapolations for amivantamab + CP (amivantamab alone) TTDD



Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death.

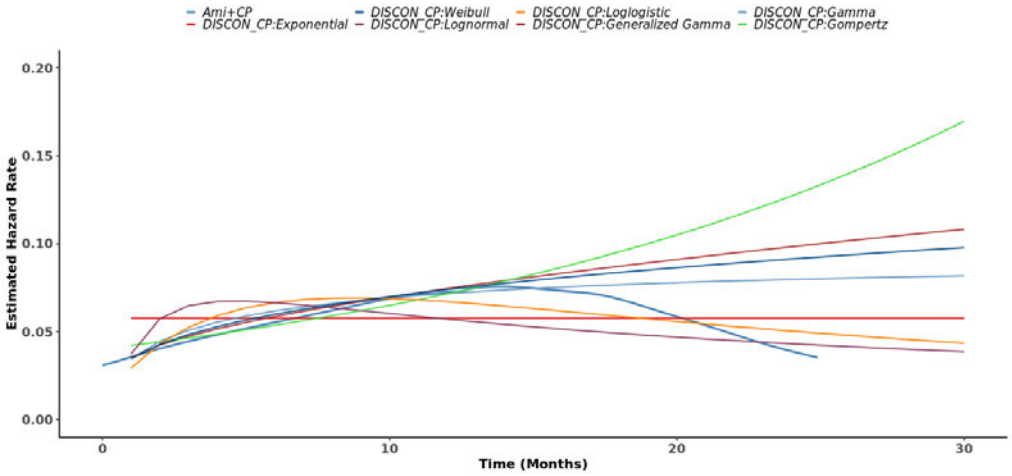
E.1.6.2 Amivantamab + CP – CP alone

Figure 56. Smoothed and unsmoothed hazard plot for amivantamab + CP (CP alone) TTDD



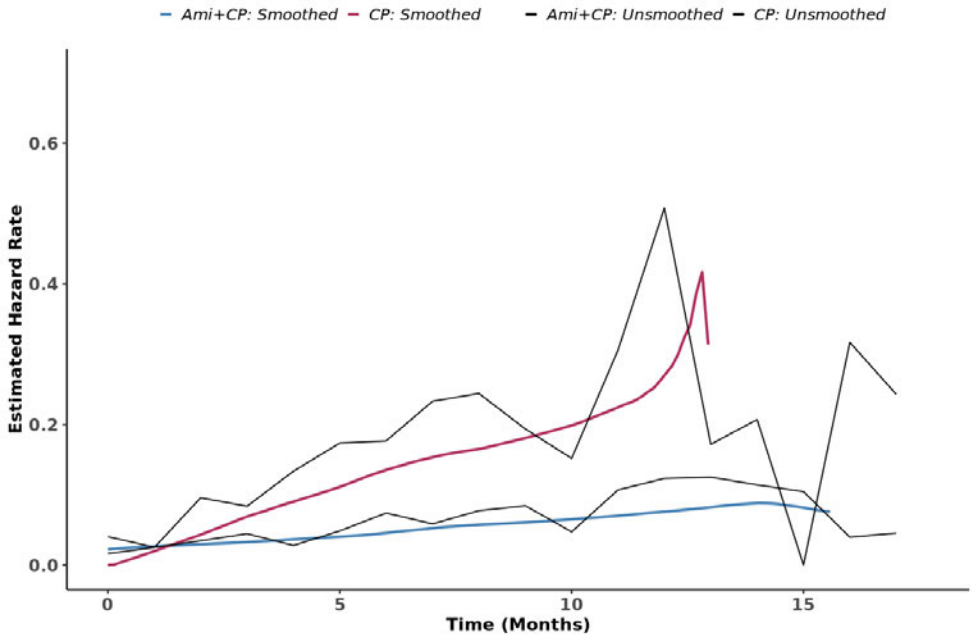
Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 57. Smoothed hazard plot with parametric extrapolations for amivantamab + CP (CP alone) TTDD



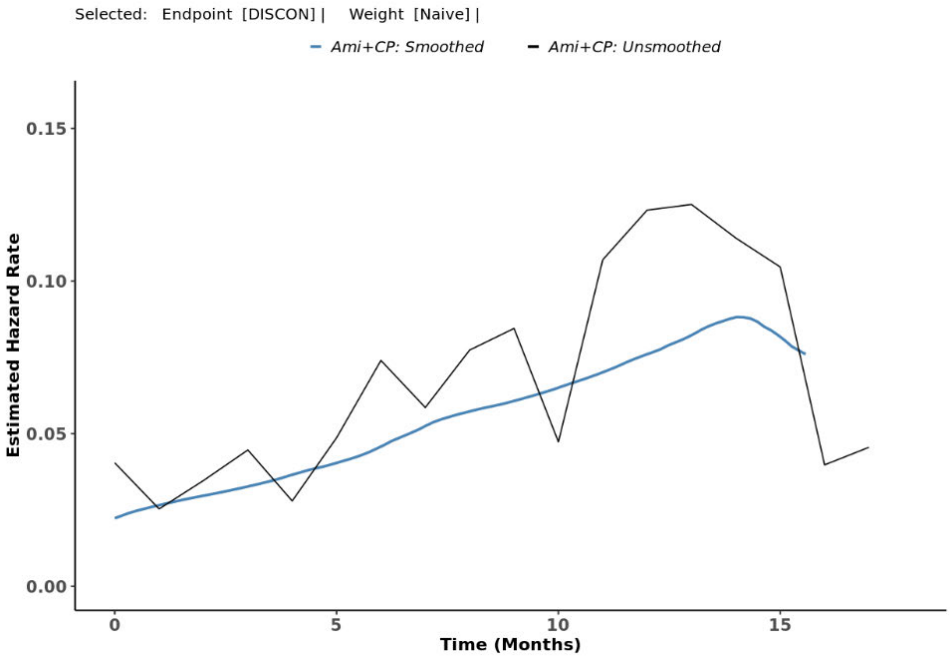
Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 58. Smoothed and unsmoothed hazard plot for amivantamab + CP and CP TTDD



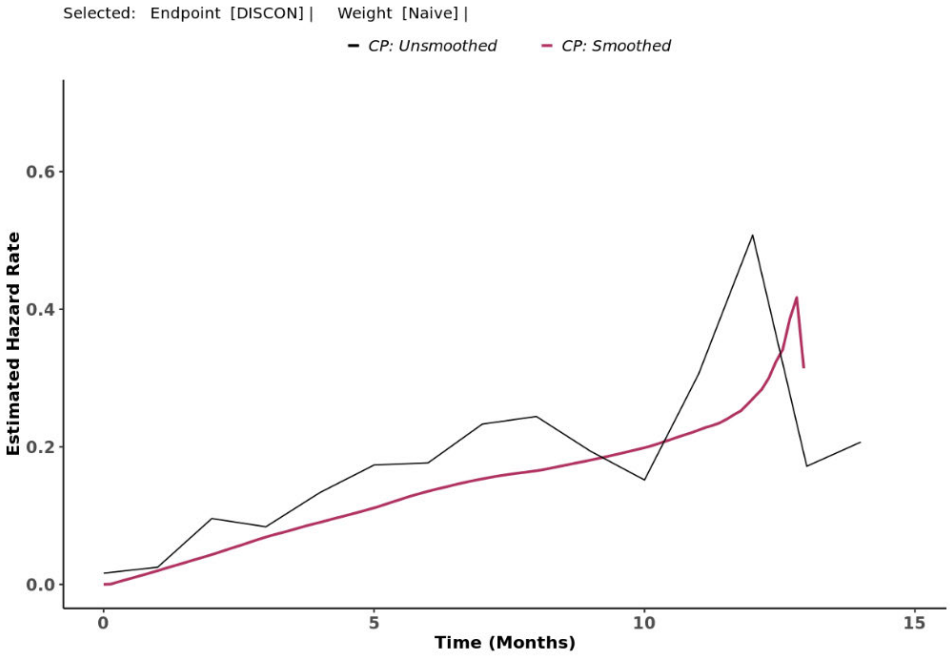
Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 59. Smoothed and unsmoothed hazard plot for amivantamab + CP TTDD



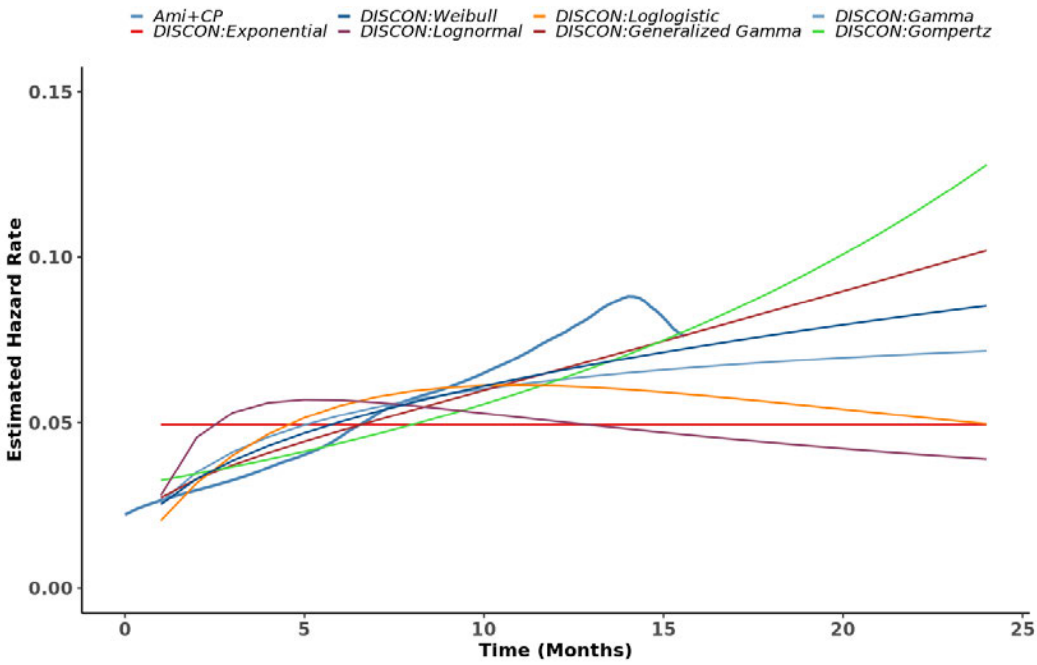
Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 60. Smoothed and unsmoothed hazard plot for CP TTDD



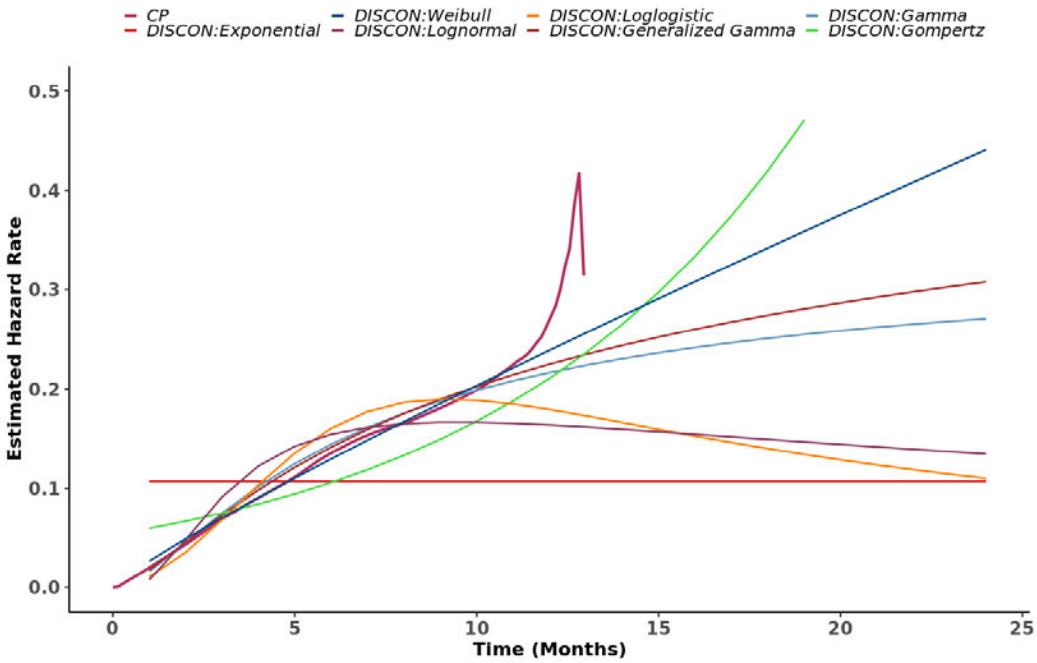
Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 61. Smoothed hazard plot with parametric extrapolations for amivantamab + CP TTDD



Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

Figure 62. Smoothed hazard plot with parametric extrapolations for CP TTDD



Abbreviations: CP = carboplatin + pemetrexed; TTDD = time to treatment discontinuation or death

E.1.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the TTDD curves was deemed acceptable to determine the distributions for TTDD (Weibull) given the maturity of the patient-level data from PAPILLON and reasonably similar extrapolations across distributions.

E.1.8 Adjustment of background mortality

See section D.1.8.

E.1.9 Adjustment for treatment switching/cross-over

Not applicable.

E.1.10 Waning effect

Not applicable.

E.1.11 Cure-point

Not applicable.

Appendix F. Serious adverse events

Table 75 lists all the treatment emergent serious AEs as recorded in the study.

Table 75. Number of Subjects with Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set

Category	CP alone	Amivantamab + CP
Analysis set: Safety population	N= 155	N= 151
Subjects with 1 or more SAEs	48 (31.0%)	56 (37.1%)
Infections and infestations	10 (6.5%)	18 (11.9%)
Pneumonia	4 (2.6%)	6 (4.0%)
COVID-19	1 (0.6%)	3 (2.0%)
Cellulitis	1 (0.6%)	2 (1.3%)
Rash pustular	0	2 (1.3%)
Skin infection	0	2 (1.3%)
COVID- 19 pneumonia	0	1 (0.7%)
Infection	0	1 (0.7%)
Pneumonia viral	0	1 (0.7%)
Postoperative wound infection	1 (0.6%)	1 (0.7%)
Sepsis	1 (0.6%)	1 (0.7%)
Appendicitis	1 (0.6%)	0
Enterocolitis infectious	1 (0.6%)	0
Gastrointestinal disorders	4 (2.6%)	10 (6.6%)

Vomiting	1 (0.6%)	3 (2.0%)
Diarrhoea	1 (0.6%)	2 (1.3%)
Abdominal pain	0	1 (0.7%)
Cheilitis	0	1 (0.7%)
Duodenitis	0	1 (0.7%)
Enterocolitis	0	1 (0.7%)
Lower gastrointestinal haemorrhage	0	1 (0.7%)
Ascites	1 (0.6%)	0
Gastrointestinal haemorrhage	1 (0.6%)	0
Respiratory, thoracic and mediastinal disorders	14 (9.0%)	8 (5.3%)
Pneumonitis	0	4 (2.6%)
Pulmonary embolism	4 (2.6%)	4 (2.6%)
Dyspnoea	5 (3.2%)	1 (0.7%)
Haemoptysis	1 (0.6%)	1 (0.7%)
Pleural effusion	5 (3.2%)	1 (0.7%)
Hypoxia	1 (0.6%)	0
Metabolism and nutrition disorders	5 (3.2%)	6 (4.0%)
Hypokalaemia	1 (0.6%)	3 (2.0%)
Decreased appetite	0	1 (0.7%)
Dehydration	0	1 (0.7%)
Hypomagnesaemia	0	1 (0.7%)

Hyponatraemia	1 (0.6%)	1 (0.7%)
Hypophagia	1 (0.6%)	1 (0.7%)
Hyperglycaemia	1 (0.6%)	0
Malnutrition	1 (0.6%)	0
Blood and lymphatic system disorders	11 (7.1%)	5 (3.3%)
Thrombocytopenia	5 (3.2%)	3 (2.0%)
Neutropenia	0	2 (1.3%)
Anaemia	6 (3.9%)	1 (0.7%)
Febrile neutropenia	3 (1.9%)	1 (0.7%)
Leukopenia	0	1 (0.7%)
Myelosuppression	1 (0.6%)	0
Skin and subcutaneous tissue disorders	0	5 (3.3%)
Dermatitis acneiform	0	2 (1.3%)
Rash	0	2 (1.3%)
Rash maculo-papular	0	1 (0.7%)
Nervous system disorders	5 (3.2%)	4 (2.6%)
Cerebrovascular accident	0	1 (0.7%)
Encepha1opathy	0	1 (0.7%)
Myoclonic epilepsy	0	1 (0.7%)
Transient ischaemic attack	0	1 (0.7%)
Depressed level of consciousness	1 (0.6%)	0

Dysarthria	1 (0.6%)	0
Headache	1 (0.6%)	0
Lacunar infarction	1 (0.6%)	0
Syncope	1 (0.6%)	0
Vertebrobasilar insufficiency	1 (0.6%)	0
General disorders and administration site conditions	6 (3.9%)	3 (2.0%)
Asthenia	1 (0.6%)	2 (1.3%)
Death	1 (0.6%)	1 (0.7%)
Fatigue	1 (0.6%)	0
General physical health deterioration	1 (0.6%)	0
Influenza like illness	1 (0.6%)	0
Pain	1 (0.6%)	0
Investigations	2 (1.3%)	3 (2.0%)
Alanine ammino transferase increased	1 (0.6%)	1 (0.7%)
Blood creatinine increased	1 (0.6%)	1 (0.7%)
C-reactive protein increased	0	1 (0.7%)
Aspartate aminotransferase increased	1 (0.6%)	0
Injury, poisoning and procedural complications	2 (1.3%)	2 (1.3%)
Infusion related reaction	0	1 (0.7%)

Lumbar vertebral fracture	0	1 (0.7%)
Femur fracture	1 (0.6%)	0
Incisional hernia	1(0.6%	0
Musculoskeletal and connective tissue disorders	4 (2.6%)	2 (1.3%)
Back pain	0	1 (0.7%)
Myalgia	0	1 (0.7%)
Arthralgia	1 (0.6%)	0
Bone pain	1 (0.6%)	0
Pain in extremity	1 (0.6%)	0
Pathological fracture	1 (0.6%)	0
Reproductive system and breast disorders	0	2 (1.3%)
Endometrial thickening	0	1 (0.7%)
Ovarian mass	0	1 (0.7%)
Cardiac disorders	2 (1.3%)	1 (0.7%)
Cardio-respiratory arrest	0	1 (0.7%)
Acute myocardial infarction	1 (0.6%)	0
Pericardial effusion	1 (0.6%)	0
Hepatobiliary disorders	1 (0.6%)	1 (0.7%)
Biliary obstruction	0	1 (0.7%)
Cholecystitis acute	0	1 (0.7%)
Jaundice cholestatic	1 (0.6%)	0

Immune system disorders	0	1 (0.7%)
Contrast media reaction	0	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.6%)	1 (0.7%)
Prostate cancer	0	1 (0.7%)
Cancer pain	1 (0.6%)	0
Renal and urinary disorders	0	1 (0.7%)
Acute kidney injury	0	1 (0.7%)
Ear and labyrinth disorders	1 (0.6%)	0
Hypoacusis	1 (0.6%)	0

SAE = serious adverse event. Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0

Appendix G. Health-related quality of life N/A

Appendix H. Probabilistic sensitivity analyses

Table 76. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Age (mean)	58.925	58.265	60.935	Normal
Proportion of female	0.64	0.52	0.63	Beta
Body weight (mean)	66.954	64.187	67.413	Normal
Body surface area (mean)	1.713	1.688	1.734	Normal
Proportion of patients <80 kg	0.87	0.80	0.88	Beta
Individual curve fitting for PFS				
Amivantamab + CP – Gamma Shape	0.5164	-	-	Multi-normal (Cholesky decomposition)
Amivantamab + CP – Gamma Rate	-2.1811	-	-	Multi-normal (Cholesky decomposition)
CP – Gamma Rate	0.909	-	-	Multi-normal (Cholesky decomposition)
CP – Gamma Shape	-1.103	-	-	Multi-normal (Cholesky decomposition)
Individual curve fitting for OS				
Amivantamab + CP – Gamma Shape	0.211	-	-	

Amivantamab + CP – Gamma Rate	-3.805	-	-	Multi-normal (Cholesky decomposition)
CP – Gamma Rate	0.967	-	-	Multi-normal (Cholesky decomposition)
CP – Gamma Shape	-2.226	-	-	Multi-normal (Cholesky decomposition)
Adverse event incidence (%) amivantamab + CP				
Anemia	0.11	0.09	0.13	Beta
Paronychia	0.07	0.05	0.08	Beta
Hypokalaemia	0.07	0.07	0.10	Beta
Asthenia	0.06	0.04	0.06	Beta
Neutropenia	0.35	0.27	0.40	Beta
Leukopenia	0.11	0.09	0.14	Beta
Rash	0.13	0.09	0.14	Beta
Adverse event incidence (%) Pemetrexed + carboplatin - CP				
Anemia	0.13	0.10	0.15	Beta
Paronychia	0.00	0.00	0.00	Beta
Hypokalaemia	0.01	0.01	0.02	Beta
Asthenia	0.03	0.02	0.03	Beta
Neutropenia	0.23	0.18	0.27	Beta
Leukopenia	0.03	0.03	0.04	Beta

Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.11	0.08	0.12	Beta
Adverse event incidence (%) Pemetrexed + cisplatin - CP				
Anemia	0.13	0.10	0.15	Beta
Paronychia	0.00	0.00	0.00	Beta
Hypokalaemia	0.01	0.01	0.02	Beta
Asthenia	0.03	0.02	0.03	Beta
Neutropenia	0.25	0.18	0.27	Beta
Leukopenia	0.03	0.03	0.04	Beta
Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.11	0.08	0.12	Beta
Adverse event incidence (%) Osimertinib - EGFR TKIs				
Anemia	0.00	0.00	0.00	Beta
Paronychia	0.00	0.00	0.00	Beta
Hypokalaemia	0.00	0.00	0.00	Beta
Asthenia	0.00	0.00	0.00	Beta
Neutropenia	0.00	0.00	0.00	Beta
Leukopenia	0.00	0.00	0.00	Beta
Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.00	0.00	0.00	Beta

Adverse event incidence (%) Pembrolizumab + CP - CP + IO				
Anemia	0.00	0.00	0.00	Beta
Paronychia	0.00	0.00	0.00	Beta
Hypokalaemia	0.00	0.00	0.00	Beta
Asthenia	0.00	0.00	0.00	Beta
Neutropenia	0.00	0.00	0.00	Beta
Leukopenia	0.00	0.00	0.00	Beta
Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.00	0.00	0.00	Beta
AE duration (days) - Literature				
Anemia	20.411	15.984	23.777	Normal
Paronychia	49.018	31.177	46.377	Normal
Hypokalaemia	16.449	16.670	24.797	Normal
Asthenia	15.830	13.311	19.800	Normal
Neutropenia	15.703	12.911	19.206	Normal
Leukopenia	10.618	9.966	14.826	Normal
Rash	31.656	21.661	32.222	Normal
Thrombocytopenia	9.381	9.254	13.765	Normal
HSUV				
PFS	0.89	0.88	0.89	Beta
PD	0.85	0.78	0.87	Beta

Anemia	-0.06	-0.04	-0.12	Beta
Paronychia	-0.02	-0.01	-0.08	Beta
Hypokalaemia	-0.05	-0.02	-0.10	Beta
Asthenia	-0.09	-0.05	-0.09	Beta
Neutropenia	-0.13	-0.05	-0.13	Beta
Leukopenia	-0.09	-0.05	-0.13	Beta
Rash	-0.02	-0.02	-0.05	Beta
Thrombocytopenia	-0.10	-0.09	-0.13	Beta
Caregiver's disutility due to progression	-0.01	-0.01	-0.01	Beta
Costs				
Drug monitoring costs - frequency per week required				
Pemetrexed -Full blood count	0.239	0.240	0.358	Normal
Pemetrexed -Liver function	0.284	0.240	0.358	Normal
Pemetrexed -Renal function	0.322	0.240	0.358	Normal
% patients receiving subsequent lines of treatments by 1L treatments - 2L				
Amivantamab + CP	0.49	0.44	0.66	Beta
CP	0.54	0.44	0.66	Beta
EGFR TKIs	0.47	0.44	0.66	Beta
IO alone	0.51	0.44	0.66	Beta

CP + IO	0.55	0.44	0.66	Beta
% patients receiving subsequent lines of treatments by 1L treatments - 3L+				
Amivantamab + CP	0.24	0.22	0.33	Beta
CP	0.24	0.22	0.33	Beta
EGFR TKIs	0.26	0.22	0.33	Beta
IO alone	0.26	0.22	0.33	Beta
CP + IO	0.28	0.22	0.33	Beta
Distribution of 2L treatments by 1L treatment **Amivantamab + CP as 1L**				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.87	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.04	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.09	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
CP as 1L				

Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.80	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.11	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.09	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
IO alone as 1L				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.80	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.11	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.09	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
IO + CP as 1L				

Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.75	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.12	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.14	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
Other treatments as 1L				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.81	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.10	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.09	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
Median PFS for treatment duration calculation 2L treatments				

Platinum based chemotherapy	5.68	4.07	6.03	Gamma
Non-platinum Chemo	4.39	3.50	5.18	Gamma
Amivantamab	6.69	5.51	8.16	Gamma
Mobocertinib	7.19	5.94	8.80	Gamma
TKI	2.38	2.03	3.01	Gamma
TKI combination	2.25	2.03	3.01	Gamma
IO	2.59	1.87	2.77	Gamma
IO combination	2.46	1.87	2.77	Gamma
VEGFi w/wo combination	5.55	4.07	6.03	Gamma
Distribution of 3L+ treatments by 1L treatment **Amivantamab + CP as 1L**				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.72	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.17	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.11	-	-	Dirichlet

VEGFi w/wo combination	0.00	-	-	Dirichlet
CP as 1L				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.83	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.09	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet
IO combination	0.08	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
All other treatments as 1L				
Platinum based chemotherapy	0.00	-	-	Dirichlet
Non-platinum Chemo	0.79	-	-	Dirichlet
Amivantamab	0.00	-	-	Dirichlet
Mobocertinib	0.00	-	-	Dirichlet
TKI	0.10	-	-	Dirichlet
TKI combination	0.00	-	-	Dirichlet
IO	0.00	-	-	Dirichlet

IO combination	0.11	-	-	Dirichlet
VEGFi w/wo combination	0.00	-	-	Dirichlet
Median PFS for treatment duration calculation 3L treatments				
Platinum based chemotherapy	2.32	2.32	2.12	3.13
Non-platinum Chemo	2.31	2.31	2.03	3.01
Amivantamab	4.15	4.15	3.42	5.06
Mobocertinib	3.53	3.53	3.42	5.06
TKI	2.90	2.90	2.36	3.50
TKI combination	2.66	2.66	2.36	3.50
IO	4.59	4.59	3.42	5.06
IO combination	4.69	4.69	3.42	5.06
VEGFi w/wo combination	3.86	3.86	3.42	5.06
Adverse event incidence subsq tx (%) Platinum based chemotherapy				
Anemia	0.12	0.10	0.14	Beta
Diarrhea	0.11	0.09	0.13	Beta
Fatigue	0.01	0.01	0.01	Beta
Febrile neutropenia	0.00	0.00	0.00	Beta
Neutropenia	0.14	0.10	0.14	Beta

Neutrophil count decreased	0.00	0.00	0.00	Beta
Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.08	0.06	0.09	Beta
Adverse event incidence subsq tx (%) Non-platinum Chemo				
Anemia	0.04	0.03	0.05	Beta
Diarrhea	0.24	0.20	0.29	Beta
Fatigue	0.04	0.03	0.04	Beta
Febrile neutropenia	0.10	0.08	0.11	Beta
Neutropenia	0.14	0.12	0.18	Beta
Neutrophil count decreased	0.12	0.09	0.13	Beta
Rash	0.04	0.03	0.05	Beta
Thrombocytopenia	0.24	0.20	0.29	Beta
Adverse event incidence subsq tx (%) Amivantamab				
Anemia	0.01	0.01	0.02	Beta
Diarrhea	0.14	0.11	0.16	Beta
Fatigue	0.01	0.01	0.01	Beta
Febrile neutropenia	0.00	0.00	0.00	Beta
Neutropenia	0.03	0.02	0.03	Beta
Neutrophil count decreased	0.00	0.00	0.00	Beta
Rash	0.01	0.01	0.01	Beta

Thrombocytopenia	0.01	0.01	0.01	Beta
Adverse event incidence subsq tx (%) TKI				
Anemia	0.00	0.00	0.00	Beta
Diarrhea	0.62	0.55	0.83	Beta
Fatigue	0.01	0.01	0.02	Beta
Febrile neutropenia	0.00	0.00	0.00	Beta
Neutropenia	0.00	0.00	0.00	Beta
Neutrophil count decreased	0.00	0.00	0.00	Beta
Rash	0.05	0.05	0.07	Beta
Thrombocytopenia	0.00	0.00	0.00	Beta
Adverse event incidence subsq tx (%) IO combination				
Anemia	0.13	0.10	0.14	Beta
Diarrhea	0.14	0.13	0.19	Beta
Fatigue	0.02	0.01	0.02	Beta
Febrile neutropenia	0.00	0.00	0.00	Beta
Neutropenia	0.12	0.10	0.14	Beta
Neutrophil count decreased	0.00	0.00	0.00	Beta
Rash	0.00	0.00	0.00	Beta
Thrombocytopenia	0.08	0.06	0.09	Beta

Resource use calculation PROGRESSION FREE				
Oncology outpatient visit	1.96	1.63	2.41	Gamma
Clinical nurse specialist	1.68	1.63	2.41	Gamma
GP surgery visit	0.00	0.00	0.00	Gamma
Therapist visit	0.00	0.00	0.00	Gamma
GP home visit	0.00	0.00	0.00	Gamma
Community nurse home visit	0.00	0.00	0.00	Gamma
Chest radiography	0.00	0.00	0.00	Gamma
CT scan (chest)	0.85	0.81	1.21	Gamma
Electrocardiogram	0.00	0.00	0.00	Gamma
Resource use calculation PROGRESSED DISEASE				
Oncology outpatient visit	3.84	3.25	4.82	Gamma
Clinical nurse specialist	3.66	3.25	4.82	Gamma
GP surgery visit	0.00	0.00	0.00	Gamma
Therapist visit	1.07	0.81	1.21	Gamma
GP home visit	0.00	0.00	0.00	Gamma
Community nurse home visit	0.00	0.00	0.00	Gamma
Chest radiography	0.00	0.00	0.00	Gamma
CT scan (chest)	2.08	1.63	2.41	Gamma

Electrocardiogram	1.29	1.22	1.81	Gamma
Patient time cost				
Hourly rate (DKK)	181.03	165.17	244.67	Gamma
Hours per drug administration	3.42	3.25	4.82	Gamma
Travel cost				
Round trip (DKK)	107.48	80.22	118.83	Gamma

Appendix I. Literature searches for the clinical assessment N/A

The clinical assessment was informed by the head-to-head study PAPILLON used in this application. Therefore, this appendix is not applicable.

Appendix J. Literature searches for health-related quality of life N/A

The health-related quality of life data was informed by the head-to-head study PAPILLON used in this application. Therefore, this appendix is not applicable.

Appendix K. Literature searches for input to the health economic model N/A

Inputs for the health economic model were sourced via targeted search in publicly available sources. Therefore, this appendix is not applicable.

Appendix L. Pattern of missing data and completion

Below in Table 77 and Table 78, the pattern of missing data and completion for the HRQoL data are presented for amivantamab + CP and CP alone.

Table 77. Pattern of missing data and completion for the HRQoL data for amivantamab + CP EQ-5D

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	**151**	4 (3%)	**151**	147 (97%)
3	**151**	14 (9%)	**141**	137 (97%)
5	**151**	18 (12%)	**138**	133 (96%)
7	**151**	23 (15%)	**131**	128 (98%)
9	**151**	40 (26%)	**118**	111(94%)
11	**151**	52 (34%)	**105**	99(94%)
13	**151**	70 (46%)	**89**	81(91%)
15	**151**	86 (57%)	**71**	65 (92%)
17	**151**	100 (66%)	**54**	51 (94%)
19	**151**	114 (75%)	**43**	37 (86%)
21	**151**	121 (80%)	**35**	30 (86%)
23	**151**	126 (83%)	**26**	25 (96%)
25	**151**	135 (89%)	**17**	16 (94%)
27	**151**	139 (92%)	**14**	12 (86%)

Table 78. Pattern of missing data and completion for the HRQoL data for CP EQ-5D

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	155	4 (3%)	155	151 (97%)
3	155	10 (6%)	151	141 (93%)
5	155	16 (10%)	138	135 (98%)
7	155	37 (24%)	119	114 (96%)
9	155	59 (38%)	100	92 (92%)
11	155	88 (57%)	71	63 (89%)
13	155	103 (66%)	52	48 (92%)
15	155	115 (74%)	37	36 (97%)
17	155	132 (85%)	21	19 (90%)
19	155	139 (90%)	13	12 (92%)
21	155	143 (92%)	9	8 (89%)
23	155	144(93%)	7	7 (100%)
25	155	147 (95%)	4	4 (100%)
27	155	148 (95%)	3	3 (100%)

Table 79. Pattern of missing data and completion for the HRQoL data for amivantamab + CP EORTC-QLQ-30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	151	4 (3%)	151	147 (97%)
3	151	14 (9%)	141	137 (97%)
5	151	17 (11%)	138	134 (97%)
7	151	23 (15%)	131	128 (98%)
9	151	40 (26%)	118	111 (94%)
11	151	52 (34%)	105	99 (94%)
13	151	69 (46%)	89	82 (92%)
15	151	86 (57%)	71	65 (92%)
17	151	100 (66%)	54	51 (94%)
19	151	114 (75%)	43	37 (86%)
21	151	121 (80%)	35	30 (86%)
23	151	126 (83%)	26	25 (96%)
25	151	135 (89%)	17	16 (94%)
27	151	139 (92%)	14	12 (86%)

Table 80. Pattern of missing data and completion for the HRQoL data for CP EORTC-QLQ-30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	155	4 (3%)	155	151 (97%)
3	155	9 (6%)	151	142 (94%)
5	155	16 (10%)	138	135 (98%)
7	155	37 (24%)	119	114 (96%)
9	155	59 (38%)	100	92 (92%)
11	155	88 (57%)	71	63 (89%)
13	155	103 (66%)	52	48 (92%)
15	155	115 (74%)	37	36 (97%)
17	155	132 (85%)	21	19 (90%)
19	155	139 (90%)	13	12 (92%)
21	155	143 (92%)	9	8 (89%)
23	155	144 (93%)	7	7 (100%)
25	155	147 (95%)	4	4 (100%)
27	155	148 (95%)	3	3 (100%)

Appendix M. Dose details and model costs

Below are listed the dosing details for amivantamab and amivantamab + CP and the relevant weekly costs in the model, by treatment arm.

Table 81. Dosing Details for Amivantamab + CP

Component	Dose	Treatment Duration	Dosing Frequency Per Week in Cycle 1 (with % skipped)	Dosing Frequency Per Week in Cycle 2 (with % skipped)	Dosing Frequency Per Week in Cycle 3–4 (with % skipped)	Dosing Frequency Per Week in Subsequent Cycles (with % skipped)	Average Dose Per Admin	Dose skipping %	Dose reduction (amivantamab)/ RDI	Units (Vials/Caps) Per Admin*
Amivantamab	1,400 mg	< 80 kg patients: 4 weeks (up to C2D1)	1.00 (0.85)	0.33 (0.28)	0.00 (0.00)	0.00 (0.00)	1,400 mg	14.51%	93.70%	3.75
Amivantamab	1,750 mg	≥ 80 kg patients: 4 weeks (up to C2D1)	1.00 (0.88)	0.33 (0.29)	0.00 (0.00)	0.00 (0.00)	1,750 mg	11.87%	93.45%	4.67
Amivantamab	1,750 mg	< 80 kg patients: C3D1 until progression	0.00 (0.00)	0.00 (0.00)	0.33 (0.28)	0.33 (0.28)	1,750 mg	14.51%	93.70%	4.69
Amivantamab	2,100 mg	≥ 80 kg patients: C3D1 until progression	0.00 (0.00)	0.00 (0.00)	0.33 (0.29)	0.33 (0.29)	2,100 mg	11.87%	93.45%	5.61
Pemetrexed	500 mg/m^2	Until progression	0.33 (0.29)	0.33 (0.29)	0.33 (0.29)	0.33 (0.29)	855 mg	12.87%	94.93%	2.0

Carboplatin	AUC 5	4 cycles		0.33 (0.32)	0.33 (0.32)	0.33 (0.32)	0.00 (0.00)	550 mg*	3.89%	97.96%	1.0

* No vial sharing (i.e. drug wastage) is assumed*An average dose per administration of 550 mg is assumed for carboplatin. Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; CP = carboplatin + pemetrexed; D = day; RDI = relative dose intensity

Table 82. Dosing Details for CP

Component	Induction Period (Weeks)	Dose	Treatment Duration	Dosing Frequency Per Week of Induction (with % skipped)	Dosing Frequency Per Week of Maintenance	Average Dose Per Admin	Dose skipping %	RDI	Units (Vials/Caps) Per Admin*
Pemetrexed	12	500 mg/m^2	Until progression	0.33 (0.30)	0.33 (0.30)	855 mg	10.32%	96.87%	2.0
Carboplatin	12	AUC 5	4 cycles	0.33 (0.33)	0.00 (0.00)	550 mg*	1.64%	99.09%	1.0

* No vial sharing (i.e. drug wastage) is assumed. *An average dose per administration of 550 mg is assumed for carboplatin. Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; CP = carboplatin + pemetrexed; D = day; RDI = relative dose intensity

Table 83. Medicine costs used in the model – cost per week, amivantamab + CP

Medicine	Dose	Treatment duration	Relative dose intensity	Frequency	Vial sharing	Units (vials/caps) per admin*	Cost per avg. dose required (DKK)	Cost per week in cycle 1 (DKK)**	Cost per week in cycle 2 (DKK)**	Cost per week in cycle 3-4 (DKK)**	Cost per week in subsequent cycles (DKK)**
Medicine	Dose	Treatment duration	Relative dose intensity		Vial sharing	Units (vials/caps) per admin*	Cost per avg. dose required (DKK)	Cost per week in cycle 1 (DKK)**	Cost per week in cycle 2 (DKK)**	Cost per week in cycle 3-4 (DKK)**	Cost per week in subsequent cycles (DKK)**
Amivantamab	1,400 mg	< 80 kg patients: 4 weeks (up to C2D1)	93.70%		No	3.75	35,917.41	30,693.31	10,231.10	0.00	0.00
Amivantamab	1,750 mg	≥ 80 kg patients: 4 weeks (up to C2D1)	93.45%		No	4.67	44,773.95	38,487.95	12,829.32	0.00	0.00
Amivantamab	1,750 mg	< 80 kg patients: C3D1 until progression	93.70%		No	4.69	44,896.76	0.00	0.00	12,788.88	12,788.88

Amivantamab	2,100 mg	≥ 80 kg patients: C3D1 until progression	93.45%		No	5.61	53,728.74	0.00	0.00	15,395.18	15,395.18
Pemetrexed	500 mg/m^2	Until progression	94.93%		No	2.00	1,104.98	320.93	320.93	320.93	320.93
Carboplatin	AUC 5†	4 cycles	97.96%		No	2.00	452.00	144.81	144.81	144.81	0.00
Total Amivantamab + CP				See Table 81				**32,536.85**	**11,156.11**	**13,726.11**	**13,581.30**
Total Amivantamab				See Table 81				**32,071.11**	**10,690.37**	**13,260.37**	**13,260.37**
Total CP				See Table 82				**465.74**	**465.74**	**465.74**	**320.93**

* No vial sharing (i.e. drug wastage) is assumed

**Weekly costs are adjusted for dose skipping

† An average dose per administration of 550 mg is assumed for carboplatin

Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; CP = carboplatin + pemetrexed; D = day; RDI = relative dose intensity

Table 84. Medicine costs used in the model – cost per week, CP alone

Medicine	Dose	Treatment duration	Relative dose intensity	Frequency	Vial sharing	Units (vials/caps) per admin	Cost per avg. dose required (DKK)	Cost per week of induction (DKK)*	Cost per week of maintenace (DKK)*
CP Total				See Table 82				**478.53**	**330.33**
Pemetrexed	500 mg/m2	Until progression	96.87%		No	2.0	1,104.98	330.33	330.33
Carboplatin	AUC 5†	4 cycles	99.09%		No	2.0	452.00	148.20	0.00

* No vial sharing (i.e. drug wastage) is assumed

**Weekly costs are adjusted for dose skipping

† An average dose per administration of 550 mg is assumed for carboplatin

Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; CP = carboplatin + pemetrexed; D = day; RDI = relative dose intensity

Table 85. Subsequent treatments dosing details by treatment category

Treatment Category	Component	Induction Period (Weeks)	Dose	Treatment Duration	Dosing Frequency per Week	Average Dose Per Admin	Proportion of full dose administered (ami)/RDI	Dose skipping
Non-platinum chemotherapy	Docetaxel	12	75 mg/m2	12 weeks	0.33	128 mg	100.0%	0.00%
TKI	Osimertinib	1§	80 mg	Until progression	7.00	80 mg	100.0%	0.00%
IO combination*	Pembrolizumab	12	200 mg	Until progression	0.33	200 mg	100.0%	0.00%
	Pemetrexed	12	500 mg/m2	Until progression	0.33	855 mg	96.9%	10.32%
	Cisplatin	12	75 mg/m2	5 cycles	0.33	128 mg	99.1%	1.64%
	Carboplatin	12	AUC 5	4 cycles	0.33	550 mg†	99.1%	1.64%

* Treatment regimen is costed based on the assumption that 50% receive carboplatin and 50% cisplatin, combined with other treatment components. §1-week induction period included to model different administration costs for the first cycle; there is no induction period with regards to dosing requirements. Abbreviations: AUC 5 = area under the concentration-time curve 5 mg/mL per minute; C = cycle; D = day; IO = immuno-oncology drug; TKI = tyrosine kinase inhibitor

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