Medicinrådet

Bilag til Medicinrådets vurdering af cabozantinib til behandling af inoperable eller metastatiske, veldifferentierede ekstra-pankreatiske (epNET) og pankreatiske (pNET) neuroendokrine tumorer

Patienter som har haft sygdomsprogression efter mindst én tidligere systemisk behandling, med undtagelse af somatostatinanaloger

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. cabozantinib
2. Amgros' forhandlingsnotat vedr. cabozantinib
3. Ansøgning vedr. cabozantinib

Ipsen's response to the Danish Medicines Council's draft assessment report for Cabometyx (cabozantinib) for the treatment of neuroendocrine tumours

Ipsen would like to thank the Danish Medicines Council (DMC) for the detailed and thorough draft assessment report of Cabometyx for the treatment of neuroendocrine tumours and appreciates the opportunity to provide a few clarifications.

1. **Danish Medicines Council states that the assessment of OS and PFS should be based on Kaplan–Meier curves, including median values and time-specific rates. However, such data have not been submitted by the applicant for IPCW-adjusted OS in the comparator arm.**

   Ipsen would like to clarify that the following has been communicated to the Danish Medicines Council:

   The IPCW adjustment has been implemented in accordance with NICE TSD 16 within the modelling framework by applying the IPCW-adjusted hazard ratio to the parametric survival function for the comparator arm (BSC), rather than directly modifying the observed Kaplan–Meier curves.

   The model is based on the observed KM data in combination with the selected parametric extrapolation (e.g. exponential or Weibull).

2. **The Danish Medicines Council assesses that there is currently no evidence that treatment with cabozantinib leads to an improvement in overall survival compared with placebo.**

   Ipsen agrees with Danish Medicines Council that there is currently no evidence that treatment with cabozantinib would lead to an improvement in overall survival (OS) However we would like to mention that:

   - The CABINET study was not powered to assess overall survival (OS); progression-free survival (PFS) was the primary endpoint, and the study demonstrated a statistically significant and clinically meaningful PFS benefit in both the epNET and pNET cohorts.
   - It is increasingly difficult to prove any OS-benefit in new treatment options in oncology. Most phase 3 studies have as a part of the protocol the option for placebo treated patients to cross over to active treatment

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if they progress. This is considered ethically correct in treatments that seem to have effect on progression free survival (PFS). This crossover makes it impossible to prove any OS-benefits in most studies and other endpoints, as PFS, is used. The low prevalence of NETs and their prolonged natural history make detecting OS benefits inherently challenging.[1]

3. **The applicant has not complied with the Danish Medicines Council's request to extrapolate overall survival (OS) separately for cabozantinib and the crossover-adjusted BSC arm**

Ipsen would also like to highlight that, in the CABINET trial, patients in the placebo arm were allowed to cross over to cabozantinib upon progression. To account for this, crossover has been adjusted for in the analyses by applying a crossover-adjusted hazard ratio to the cabozantinib arm to estimate the BSC arm.
Given the chosen method (IPCW) for crossover adjustment, Ipsen has not been able to extrapolate overall survival separately for cabozantinib and BSC while simultaneously accounting for crossover.

References

1: Fiteni F, Westeel V, Pivot X, et al. Endpoints in cancer clinical trials. Journal of visceral surgery 2014;151:17-22.

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22.05.2026

LSC/DBS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	27.05.2026
Leverandør	Ipsen
Lægemiddel	Cabometyx (cabozantinib)
Ansøgt indikation	Behandling af voksne patienter med inoperable eller metastatiske, veldifferentierede ekstra-pankreatiske (epNET) og pankreatiske (pNET) neuroendokrine tumorer, som har haft sygdomsprogression efter mindst én tidligere systemisk behandling, med undtagelse af somatostatinanaloger.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Cabometyx:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet rabat ift. AIP
Cabometyx	20 mg (28 stk.)	49.400,00	[redacted]	[redacted]
Cabometyx	40 mg (28 stk.)	49.400,00	[redacted]	[redacted]
Cabometyx	60 mg (28 stk.)	49.400,00	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Cabometyx, derløber frem til den 31.05.2026. [redacted]. Aftalen indeholder mulighed for forlængelse i op til 2 x 6 måneders samt mulighed for prisregulering.

Cabometyx blev anbefalet til ibrugtagning af KRIS (oktober 2016) til avanceret nyrecellekarcinom (RCC), primært som behandling efter tidligere VEGF-terapi. Leverandøren har et eksisterende salg på Cabometyx på [redacted]). Medicinrådet har tidligere vurderet Cabometyx indenfor tre andre terapiområder; metastatisk nyrekræft, hepatocellulært karcinom og nyrekarcinom. Ingen af disse indikationer er anbefalet af Medicinrådet. Patentet på Cabometyx forventes at udløbe i september 2029.

Konkurrencesituationen

Cabometyx er det første lægemiddel til neuroendokrine tumore (epNET) og (pNET) vurderet i Medicinrådet.

Tabel 2 viser de årlige lægemiddeludgifter til behandling med Cabometyx.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Cabometyx	40 mg (28 stk.)	40 mg dagligt, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Generelt tilskud til alle indikationer	Link til vurdering
England	Ikke anbefalet	Link til vurdering

Opsummering

Amgros har en aftale på Cabometyx der gælder frem til 31.05.2027.
[redacted]

Application for the assessment of Cabometyx® (cabozantinib) for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues

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

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Explanation	Abbreviation	Explanation
1L, 2L, 3L	First line, second line, third line	ICER	Incremental cost-effectiveness ratio
AE	Adverse event	IPCW	Inverse probability of censoring weights
AIC	Akaike Information Criterion	IPD	Individual patient data

BIC	Bayesian Information Criterion	JNHB	Joint Nordic Assessment / Join Nordic HTA Bodies
BOR	Best Overall Response	LYs	Life years
BSA	Body Surface Area	NEC	Neuroendocrine carcinoma
BSC	Best Supportive Care	NEN	Neuroendocrine neoplasm
CEAC	Effectiveness Acceptability Curve	NET	Neuroendocrine tumour
CNS	Central nervous system	OLS	Ordinary least squares
CR	Complete response	ORR	Objective response rate
CSR	Clinical Study Report	OS	Overall survival
CI	Confidence interval	PD	Progressed disease
DCO	Data cut-off	PF	Progression free
DCR	Disease Control Rate	PFS	Progression-free survival
DOR	Duration Of Response	PGIC	Patient's global impression of change
DTC	Differentiated Thyroid Carcinoma	PSM	Partitioned survival model
EMA	European Medicines Agency	QALYs	Quality adjusted life years
ENETS	European Neuroendocrine Tumor Society	QoL	Quality of life
EPAR	European Public Assessment Report	RAI	Radioactive iodine
GEP	Gastroenteropancreatic	RCC	Renal cell carcinoma
GI	Gastrointestinal	SAE	Serious adverse event
HCC	Hepatocellular Carcinoma	SE	Standard error
HR	Hazard Ratio	SSA	Somatostatin analogue
HRQoL	Health-related quality of life	TTO	Time trade off
HSUV	Health state utility values	VEGF	Vascular endothelial growth factor

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Cabometyx®
Generic name	Cabozantinib
Therapeutic indication as defined by EMA	Cabometyx® is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.
Marketing authorization holder in Denmark	Institut Produits Synthèse (IPSEN) AB
ATC code	L01EX07
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	The date of EC approval for the neuroendocrine tumour (NET) indication is July 23, 2025.
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	Not applicable since this application applies to a type 2 variation and label extension.
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Presented in Appendix L.
Other indications that have been evaluated by the DMC (yes/no)	Presented in Appendix L.
Joint Nordic assessment (JNHB)	The current treatment practices are similar across the Nordic countries. The product is not suitable for a joint Nordic assessment since Cabometyx® has a general reimbursement in Sweden.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Cabometyx® is available as 20 mg, 40 mg, and 60 mg in packs of 30 film-coated tablets.

2. Summary table

Summary	
Indication relevant for the assessment	Cabometyx® for the treatment of adult patients with unresectable or metastatic, well-differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.
Dosage regiment and administration	Cabometyx® is for oral use. The recommended dose for patients with NETs is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. If dose reduction is necessary, 40 mg or 20 mg daily is recommended.
Choice of comparator	No addition to best supportive care (BSC).
Prognosis with current treatment (comparator)	The ten-year overall survival reported for adult NET patients was 17.5% and 18.7%, for metastases at presentation or after initial diagnosis, respectively, versus 68.2% for non-metastatic cases (p<0.0001 for both comparisons)[1]. A Danish study from 2022 reported a 5-year survival rate of 65% and a 10-year OS of 38% [2].
Type of evidence for the clinical evaluation	Head-to-head pivotal trial CABINET (NCT03375320; Alliance A021602).
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS) – epNET: median OS was 21.95 months in the cabozantinib arm and 19.71 months in the placebo arm (HR: 0.86; 95% CI: 0.56, 1.31; p=0.4871). pNET: median OS was 40.08 months in the cabozantinib arm and 31.11 months in the placebo arm (stratified HR: 0.95; 95% CI: 0.45, 2.00; p=0.8852). Progression-free survival (PFS) – epNET: median PFS was 8.48 months (95% CI: 7.46, 12.45) in the cabozantinib arm and 3.98 months (95% CI: 3.02, 5.68) in the placebo arm, an estimated 4.5-month difference between treatment arms. pNET: 13.83 months (95% CI: 8.87, 16.95) in the cabozantinib arm and 4.47 months (95% CI: 3.02, 5.75) in the placebo arm, an estimated 9.36-month difference between treatment arms.
Most important serious adverse events for the intervention and comparator	epNET cohort: SAEs were reported for 44% of subjects (cabozantinib) and 40% (placebo). Frequently reported SAEs: hypertension (6.1% cabozantinib, 1.5% placebo), abdominal pain (5.3% cabozantinib, 6.0% placebo), diarrhoea (3.0% cabozantinib, 4.5% placebo), and vomiting (3.0% in both arms). pNET cohort: SAEs were reported for 46% of subjects (cabozantinib) and 23% (placebo). Frequently reported SAEs: vomiting (6.3% cabozantinib, 0% placebo), embolism, hypoxia, nausea, sepsis (each reported for 4.8% of subjects in the

Summary	
	cabozantinib arm and no subject in the placebo arm), and small intestinal obstruction (1.6% cabozantinib, 9.7% placebo).
Impact on health-related quality of life	Clinical documentation: Health-related quality of life (HRQoL) was assessed in a substudy of the CABINET trial (A021602-HO1) [3]. EORTC QLQ-C30 was the primary instrument in the assessment. pNET: baseline summary scores were 85.9 (cabozantinib) vs. 85.3 (placebo); at week 24, 85.5 vs. 81.3. epNET: baseline summary scores were 80.6 vs. 79.5; at week 24, 76.6 vs. 70.4 Health economic model: Progression-free (PF) utilities were derived from CABINET with Danish weights applied. A relative decrement was applied to PF to calculate the progressed disease (PD) state utilities based on an algorithm by Swinburn.
Type of economic analysis that is submitted	Cost-utility analysis using a partitioned survival model informed by PFS and OS data from CABINET. The outcomes of the model included incremental life years (LYs), incremental quality adjusted life years (QALYs), incremental costs, and an incremental cost-effectiveness ratio (ICER).
Data sources used to model the clinical effects	The pivotal trial CABINET (NCT03375320; Alliance A021602) [4-7]. This trial data was used to model the clinical effects.
Data sources used to model the health-related quality of life	EORTC QLQ-C30 mapped to EQ-5D-5L from the CABINET trial.
Life years gained (incremental)	pNET: 1.02; epNET: 0.88; Lung NET: 1.27
QALYs gained (incremental)	pNET: 0.89; epNET: 0.66; Lung NET: 0.77
Incremental costs	pNET: 627,772; epNET: 431,311; Lung NET: 334,005
ICER (DKK/QALY)	pNET: 704,039; epNET: 651,337; Lung NET: 431,217
Uncertainty associated with the ICER estimate	[redacted] HR for [redacted] in the [redacted] arm has the [redacted] effect on the model outcomes in all populations.
Number of eligible patients in Denmark	Estimated eligible patients: [redacted]; incidence: [redacted]; prevalence: [redacted]
Budget impact (in year 5)	pNET: [redacted]; epNET: [redacted]; Lung NET: [redacted]

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

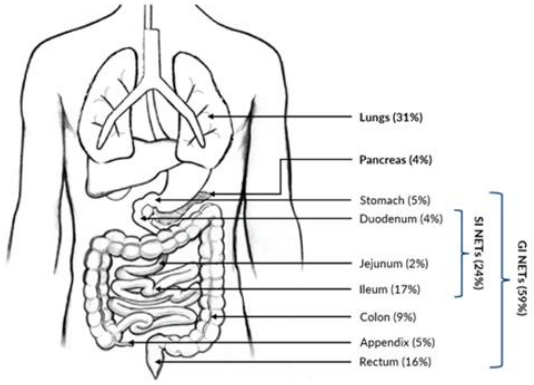
3.1 The medical condition

Neuroendocrine neoplasms (NENs) are a rare and heterogeneous group of cancers originating from neuroendocrine cells across various organs. NENs can be classified into well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) [8, 9]. NETs typically have a slower progression and lower risk of metastasis, though prognosis varies by subtype. In contrast, NECs are always high-grade, aggressive, and rapidly progressive. The majority of NENs are NETs, with NECs accounting for only 10-20% of all cases [9, 10].

NETs can be categorised into subtypes based on their site of origin, such as pancreatic (pNETs), lung, and gastrointestinal NETs (GI NETs) [8, 9, 11] (see Figure 1). While less common, NETs can also develop in other organs such as the breast, prostate, thymus, and skin [8]. pNETs and gastrointestinal NETs (GI) NETs are collectively called gastroenteropancreatic (GEP) NETs. Furthermore, epNETs (extra-pancreatic NETs) have recently been used in the literature to describe NETs occurring outside the pancreas. A family history of cancer is the most significant risk factor across NETs and NENs, affecting multiple organs [12].

NETs are classified as functional or non-functional. Functional NETs secrete bioactive proteins and hormones, such as serotonin, glucagon, insulin and gastrin, potentially leading to carcinoid syndrome (CS) and other hormone-related syndromes [13]. CS and NET-related symptoms include flushing and diarrhoea, and, in some cases, heart failure [13]. Symptom presentation varies by tumour location: bowel NETs may cause pain, diarrhoea, constipation, nausea, sickness and rectal bleeding; lung NETs may cause (bloody) cough, wheezing, shortness of breath, chest pain and tiredness [14]. These NET-symptoms can cause significant morbidity and reduced quality of life (QoL) [15, 16]. Symptoms often persist for years, with a median diagnostic delay of 9.2 years [17]. Localised and locally advanced NETs have a median survival of over 30 and 10 years, respectively. However, metastatic disease remains incurable and is associated with a poor prognosis, with a median survival ranging from 14 months to 60 months, depending on the location [18].

Figure 1 Proportion of NETs at each primary tumour location



Footnote: Please note that the percentages presented above do not add up to 100%; the locations of the remaining ~7% of tumours were not reported. Abbreviations: GI, gastrointestinal; NET, neuroendocrine tumour; SI, small intestine. Source: Bodei 2017 [11]

Although the mechanisms of NET progression are not fully defined, angiogenesis, particularly vascular endothelial growth factor (VEGF) signalling, plays a key role, contributing to high vascularisation in NETs [19, 20]. Overexpression of VEGF and its receptors is linked to tumour progression across NET types [20-22]. C-MET, mTOR, and RET signalling are also implicated, with c-MET overexpression tied to poor GEP NET survival and therapeutic relevance [21, 23, 24].

Diagnosing NETs requires a comprehensive evaluation of the primary tumour site, disease extent, and tumour grade. This involves a combination of diagnostic approaches, including endoscopic procedures, cross-sectional imaging such as CT and MRI, radionuclide imaging using somatostatin receptor (SSTR) scintigraphy or PET, biochemical analyses of blood and urine, and histopathologic assessment, with particular attention to the Ki-67 proliferation index and mitotic count [9, 25]. Diagnosis is confirmed through core biopsy, followed by World Health Organisation (WHO) grading and TNM staging. These assessments guide treatment decisions by providing crucial information about tumour location, proliferative activity, and SSTR expression [9]. Delayed diagnosis remains a common challenge, as symptoms are often vague or entirely absent, particularly in non-functional tumours. As a result, many NETs are discovered incidentally or at advanced stages.

NETs are classified through a multifaceted framework that considers site of origin, histological grade, TNM stage, and functional status [8]. Tumour grading is determined based on mitotic count, Ki-67 index, and SSTR expression, which together reflect tumour aggressiveness [26, 27]. NETs are categorised as G1 (low), G2 (intermediate), or G3 (high). In GEP NETs, both the mitotic rate and Ki-67 index are required for grading (see Table 1). Well-differentiated lung NETs include typical carcinoids (G1) with slow growth and atypical carcinoids (G2) with higher metastatic potential. Poorly differentiated lung carcinomas, by contrast, are not classified as NETs [9, 28, 29]**.** TNM staging defines the extent from stage I to IV by tumour size, nodal spread, and metastasis, with site-specific adaptations [30-33]. Functional status is determined by symptoms and hormone biomarkers [34].

Table 1 WHO 2019 classification for gastroenteropancreatic NENs

Morphology	Grade	Mitotic count (2 mm²)[a]	Ki-67 Index (%)[b]
Well-differentiated NETs	G1	<2	<3% of tumour cells divide
Well-differentiated NETs	G2	2–20	3–20% of tumour cells divide
Well-differentiated NETs	G3	>20	>20% of tumour cells divide
Poorly-differentiated NECs • Small-cell • Large-cell	G3	>20	>20% of tumour cells divide
Mixed neuroendocrine/nonendocrine neoplasm (MiNEN)			
Tumour-like lesions			

Abbreviations: HPF, high-power field; MiNEN, mixed neuroendocrine/nonendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; WHO, World Health Organization. [a] 10 HPF = 2 mm², at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density. [b] MIB1 antibody; percentage of 500–2000 tumour cells in areas of highest nuclear labelling. Source: Pavel 2020 [9]

Advanced or metastatic NETs, particularly those originating in the pancreas, lung, and specific other GI sites, carry a significant mortality burden. While extending OS and maintaining quality of life (QoL) are key treatment goals, no current therapies have demonstrated a statistically significant OS benefit [35-42]. A UK NCRAS registry analysis (NCRAS, White et al.) reported five-year OS rates in patients with Stage IV NETs were 26% for pancreatic NETs and 12% for lung NETs, though survival is relatively higher for GI NETs [43]. A retrospective study at Aarhus University Hospital in Denmark (2011-2021) analysed 174 patients with pNETs and pNECs, mostly pNETs grade 1-3; however, it included 14 patients with NECs grade 3. Patients undergoing surgical resection showed a 5- and 10-year survival rate of 95% and 87%, respectively. In contrast, the medically treated (MED) group had corresponding rates of 65% and 38%. However, direct comparisons are not possible, due to the MED group's higher age, greater co-morbidities, and more advanced disease [2]. Though poorly documented, available evidence suggests that advanced or metastatic NETs impose a high healthcare resource utilisation burden [44, 45].

3.2 Patient population

The relevant patient population is adult patients in Denmark with progressive pNET and epNET after systemic therapy. This aligns with that of the CABINET trial. Regarding epidemiology data for patients with pNET in Denmark, a study by Stensbøl et al. (2021) [46] reported an incidence of 0.42 (2010-2011) and 1.39 (2019-2020) per 100,000 people. Considering a population of 5,977,412 in 2024 in Denmark, this would correspond to 25 to 83 patients with pNET.

Regarding epNET patients in Denmark, according to a Danish clinical expert [47] a large group of epNET corresponds to small bowel NET. In a study by Stensbøl et al. (2021) [46] the small intestinal NET incidence reported per 100,000 people was 1.39 (2010-2011) and 1.84 (2019-2020). Considering a total population of 5,977,412 in 2024 in Denmark, this would correspond to 83 to 110 patients with small intestinal NET. For patients with lung NET, the Danish Lung Cancer Register Annual Report 2023 [48] states that from 2020 onwards, around 5,000 cases of lung cancer are newly diagnosed each year. It is reported that 1.5 to 2% of the patients have a carcinoid tumour, and 0.6 to 0.8% have a NET; this adds up to 2-3% out of 5,000 patients [48]. Thus, around 150 patients would correspond to lung NET. The incidence of all NETs was estimated by summing the previously described values across the three subgroups (see incidence in Table 2).

According to a clinical expert [redacted] and considering pNET and epNET patients that would be treated in 4L and lung NET patients in 2L, 3L and 4L, the number of patients eligible for treatment of Cabometyx® in Denmark is estimated to be [redacted] (see Table 3). This is based on approximately [redacted] total patients diagnosed with NET (prevalence) (see prevalence in Table 2), of whom [redacted] patients have locally advanced/metastasis/unresectable NETs. Of these, an estimated [redacted] patients would be eligible for treatment with Cabometyx® (Table 3): rounded values per patient population correspond to [redacted] patients with pNET, [redacted] patients with epNET, and of those with epNET, [redacted] patients with lung NET. The reason for the significant discrepancy between our assumptions and the total patient number is that many treatment options are used before Cabometyx®, which is considered in later treatment lines. In addition, even though there are many patients, not all of them will be eligible for active treatment.

Table 2 Incidence and prevalence in the past 5 years – all NETs

Year	2020	2021	2022	2023	2024
Incidence in Denmark*	340	340	340	340	340
Prevalence in Denmark**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note *Incidence was estimated based on data from Stensbøl et al. (2021) [46], The Danish Lung Cancer Register Annual Report 2023 [48], and input from Danish clinical expert [47]. Data from 2019-2020 was used for pNET and small bowel NET (large group of epNET) and assumed to remain constant for following years. **Prevalence data is based on clinical expert input [49] and was assumed to remain constant for the included years.

Table 3 Estimated number of patients eligible for treatment with Cabometyx® – all NETs

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

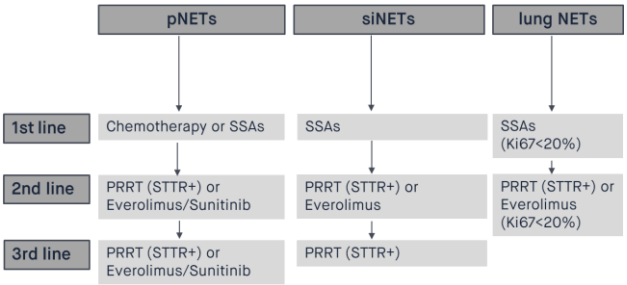
The Danish Neuroendocrine Tumour Society (Dansk Neuroendokrin Tumor Selskab, DANETS) recommends using the 2021 Nordic guideline [50-52]. Currently, the Danish Medicines Council (DMC) has no plans to prepare a new treatment guideline for NETs

after it recalled its last one in 2020. General guidelines for pNETs, GI NETs, and lung NETs are outlined below.

For advanced/progressed pNETs first-line treatment options include SSAs, chemotherapy, everolimus, or sunitinib (Figure 2). Chemotherapy is typically used first-line when Ki-67 expression >10%, whereas SSAs are preferred if Ki-67<10%. PRRT is administered as a second or third-line treatment in SSTR+ tumours. If the tumour is SSTR negative, everolimus or sunitinib is considered in the second- or third line. For GI NETs, particularly small intestinal NETs (siNETs), SSAs are the first-line treatment, followed by PRRT in SSTR+ tumours or everolimus in selected cases. Other GI NETs, including those of the appendix, colon, and rectum, are generally managed according to similar treatment guidelines. In GEP NETs stage G3, first-line treatment includes chemotherapy, everolimus, or sunitinib (if pancreatic) [51]. PRRT may be offered as a second or third-line treatment for SSTR+ tumours. Beyond third-line therapy, there are no specific recommendations; BSC is provided, according to a Danish clinical expert [47].

For lung NETs, the Nordic guidelines recommend SSAs as first-line treatment when Ki67 is <10%, and PRRT or everolimus as second-line options when Ki-67 is below 20% [52]. According to a Danish clinical expert [47], PRRT can be re-administered and is regarded as a pause in treatment rather than a distinct treatment line. Chemotherapy may be considered in selected cases. No specific guidelines are provided beyond the second line. Across treatment lines for pNETs, GEP NETs, and lung NETs, SSAs such as octreotide or lanreotide are used to manage symptoms and slow tumour progression. In general, SSAs serve both symptomatic and anti-proliferative roles in the treatment of NETs. For progressive tumours where surgery is not an option, prognosis remains poor. A Danish study from 2022 reported a 5-year survival rate of 65% and a 10-year OS of 38%, [2] (see section 3.1). There is a pressing need for new treatment options, particularly of later lines of therapy.

Figure 2 Simplified current treatment plan for advanced NETs in Denmark



The current treatment plan in Denmark is based on the 2021 Nordic guidelines [50, 52]. The first-line treatment for advanced/progressed pNETs depends on Ki-67: chemotherapy if >10%, SSAs if <10%. PRRT is used in later lines for SSTR+ tumours; otherwise, everolimus or sunitinib. siNETs typically start with SSAs, followed by PRRT (if SSTR+) or everolimus. Other GI NETs, such as appendix, colon, and rectal NETs are treated similarly as siNETs. In the cases where GEP NETs are stage G3, first-line treatment is chemotherapy, everolimus, or sunitinib (if pancreatic); PRRT is second/third-line if tumour is SSTR+. For lung NETs, SSAs are used first-line (Ki67<10%), with PRRT or everolimus as second-line (Ki-67< 20%).

3.4 The intervention

Cabometyx® (cabozantinib) is indicated for the treatment of adult patients with progressive, advanced or metastatic pNET and epNET after prior systemic therapy. Cabometyx® has the ATC-code L01EX07 and is part of the class of the pharmacotherapy group of antineoplastic agents. Cabometyx® treatment will not require any additional testing, compared to current treatments today. Cabometyx® is an orally administered, third-generation small-molecule inhibitor that targets multiple receptor tyrosine kinases (RTKs), including VEGFR2, RET, MET, and AXL [21, 23, 24, 53]. These RTKs are critical in tumour growth, angiogenesis, invasion, and metastasis. By inhibiting these key pathways, Cabometyx® exerts potent anti-tumour effects in NETs [54].

Table 4 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Cabometyx® is indicated for the treatment of adult patients with unresectable or metastatic, well-differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.
ATMP	N/A
Method of administration	Oral use
Dosing	60 mg daily
Dosing in the health economic model (including relative dose intensity)	60 mg daily, in 28-day cycles
Should the medicine be administered with other medicines?	Can be administered together with SSAs and painkillers.
Treatment duration / criteria for end of treatment	Until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	As most adverse reactions occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. It is recommended to monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin closely during treatment.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	20 mg, 40 mg, and 60 mg in packs of 30 tablets.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

In Denmark, Cabometyx® is expected to be offered to patients when other available treatment options have been exhausted. For pNET and epNET (excluding lung NETs), Cabometyx® will be an option in the fourth line of treatment in addition to BSC. Treatment options for lung NETs are more limited, and cabozantinib could be considered in the second line as an addition to BSC.

3.5 Choice of comparator(s)

Cabozantinib is indicated for the treatment of adult patients with unresectable or metastatic, well-differentiated epNET and pNET who have progressed following at least one prior systemic therapy other than somatostatin analogues. Treatment options for NET patients who have progressed are limited, and there are no guidelines or specific recommendations beyond the third line of treatment (see section 3.3). Consequently, when all treatment options are exhausted, patients are managed with BSC, according to a Danish clinical expert [47].

The lack of standardised later-line treatment options is also evident in the CABINET trial. In the pNET cohort, patients had received a median of [redacted] prior systemic anticancer therapies (range: [redacted] in the cabozantinib arm; [redacted] in the placebo arm), while those in the epNET cohort had received [redacted] (range: [redacted] in the cabozantinib arm; [redacted] in the placebo arm). These prior treatments included chemotherapy, everolimus, sunitinib, and PRRT. Despite multiple lines of therapy, patients had progressed and exhausted available treatment options. The range of FDA-approved therapies used in the CABINET population, before the start of the trial, mirrors those typically offered in Danish clinical practice. Consequently, when all other therapies are exhausted, the most suited comparator to cabozantinib is no addition to BSC this according to a clinical expert in Denmark [47]. External studies confirm that the effect of treatments used for populations similar to those in CABINET, in later lines for advanced, progressive NETs, is comparable or worse than the placebo arm in the CABINET trial [55-64]. Based on this, no addition to BSC is considered a clinically appropriate and relevant comparator to cabozantinib (see Table 5).

Table 5 Overview of comparator (best supportive care [BSC] alone)

Overview of comparator	
Generic name	Best supportive care (BSC)
ATC code	NA
Mechanism of action	NA

Overview of comparator	
Method of administration	NA
Dosing	NA
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	NA
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	NA

Patients in the CABINET trial were allowed to continue on SSAs if they had been stable for at least 2 months before enrolment. The number of patients on SSAs at baseline is presented in Table 6.

Table 6 Concurrent somatostatin analogue usage at baseline

	Extrapancreatic NET Cohort		Pancreatic NET Cohort		Source
	Cabozantinib	Placebo	Cabozantinib	Placebo	
Concurrent somatostatin analogue – no. (%)	92 (69)	48 (70)	35 (55)	17 (55)	[5]

3.6 Cost-effectiveness of the comparator(s)

The comparator to Cabometyx® in this assessment is BSC alone. BSC is often employed in the Danish clinical practice when all other treatments are exhausted. BSC includes symptomatic and anti-proliferative therapies and is not associated with any significant costs.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the base case scenario analysis, Cabometyx® + BSC is compared to BSC alone. The efficacy outcomes, comparing the intervention to the comparator, are presented in Table 7 and are based on the CABINET study trial.

Table 7 Efficacy outcome measures relevant for the application of the CABINET study

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) CABINET	Median follow-up for the pNET cohort was 13.8 months (95% CI: 10.1 to 19.7). Median follow-up for the epNET cohort was 10.2 months (95% CI: 8.2 to 13.8).	Time from randomisation to the earliest of PD or death due to any cause	BICR per RECIST 1.1
Overall survival (OS) CABINET	Median follow-up time for survival was 24.2 months for epNET cohort. Median survival follow-up was 23.1 months for pNET cohort.	Time from randomisation to death from any cause.	N/A
Objective response rate (ORR) CABINET	Radiographic tumour assessments (computed tomography or magnetic resonance imaging and chest X-ray) were performed every 12 weeks (±1 week) .	A confirmed response was defined as two consecutive scans showing complete or partial response, according to RECIST 1.1, as assessed by blinded independent central review.	Per RECIST 1.1

* Time point for data collection used in analysis (follow up time for time-to-event measures). Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group. Source: Chan et al. 2024 [5].

Validity of outcomes

According to EMA best clinical practice [65], PFS and OS are recognised as valid outcomes in anti-cancer trials and are relevant for assessing treatments in NETs. Both clinical outcomes were used as primary and secondary endpoints, respectively, in the

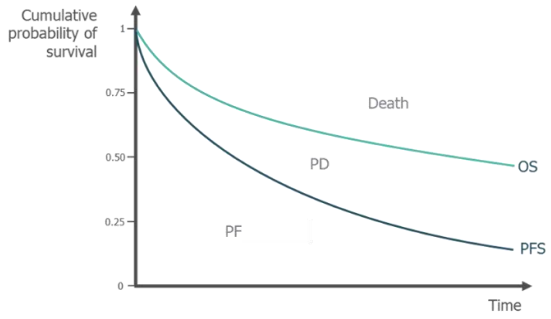
pivotal clinical trial CABINET [5]. PFS and OS have also been used in previous DMC submissions, including those for NETs [66].

4. Health economic analysis

4.1 Model structure

To assess the cost-effectiveness of Cabometyx®+ BSC in comparison to BSC alone, a Partitioned Survival Model (PSM) was used. The PSM consists of three health states: progression-free (PF), progressed disease (PD) and dead. The health states of the PSM were expected to align with the Danish clinical pathway of pNET and epNET, where individuals either remain responsive to treatment or experience disease relapse, ultimately leading to death. Patients progress through these states with no possibility of being completely cured. All patients enter the model in the PF state, and, for each subsequent cycle, they can either remain in the PF state, transition to the PD state or transition to the dead state. A patient in the PD health state can, for the subsequent cycle, either remain in the PD state or transition to the dead state. The dead health state is absorptive, and patients will stay in it until the end of the time horizon. The model structure is presented in Figure 3. CABINET is the primary source of efficacy for the health economic model. The proportions of patients in each health state were determined by the PFS and OS curves and calculated using the area under the curve.

Figure 3 Model structure



Abbreviations: OS, overall survival; PD, progressed disease; PFS, progression-free survival.

4.2 Model features

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with pNET or epNET. Patients with lung NET as a subgroup of epNET.	As presented in section 3.2.
Perspective	Limited societal perspective	According to DMC guidelines.

Model features	Description	Justification
Time horizon	Lifetime (approximately 40 years)	To capture all health benefits and costs in line with DMC guidelines. Based on CABINET and a mean age at diagnosis in Denmark of approximately 60 years. Mean age is tested in scenario analyses, based on feedback from a Danish clinical expert [47].
Cycle length	28 days	As per the treatment cycle of Cabometyx®.
Half-cycle correction	Yes	Events are, on average, assumed to take place mid-cycle.
Discount rate	3.5 %	According to DMC guidelines.
Intervention	Cabometyx® (cabozantinib) + BSC	The medicine being evaluated.
Comparator	BSC	Cabometyx® is anticipated to be the relevant treatment option when all other treatment options have been exhausted. The effect of the placebo arm in CABINET trial is assumed to be a good proxy for the effectiveness of no addition to BSC. This was validated with a Danish clinical expert [47]. For further justification, see section 3.5.
Outcomes	OS and PFS	PFS and OS are used to calculate patients' time in each model health state over time, derived directly from the PFS and OS projections.

5. Overview of literature

5.1 Literature used for the clinical assessment

Since the clinical assessment and health economic analysis are exclusively informed by the head-to-head study CABINET, the literature search for efficacy and safety studies was omitted. The relevant literature included in the assessment of efficacy and safety is presented in Table 9.

Table 9 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
Full paper - Chan JA, Geyer S, Zemla T, et al. Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors. N Engl J Med. 2025 Feb 13;392(7):653-665. [5] Conference abstract – Chan J, Geyer S, Ou F-S, et al. Alliance A021602: Phase III, double-blinded study of cabozantinib versus placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET). Abstract number: LBA53. ESMO Congress, Madrid, Spain, October 20–24, 2023. [7] Conference presentation – Chan JA GS, Zemla T, et al. Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET Trial/Alliance A021602). ESMO presentation. 2024. [67] ClinicalTrials.gov – Testing Cabozantinib in Patients With Advanced Pancreatic Neuroendocrine and Carcinoid Tumors (NCT03375320). 2025. [4] Data on file – Ipsen. [redacted]	CABINET	NCT03375320	Start: 26/10/18 Completion and data cut-off: 24/08/23	Cabozantinib vs. placebo for adult patients with locally advanced / unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed to at least one prior

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
Data on file – Ipsen. Survival Analysis Report CABINET trial. 2024. [69]				systemic therapy.

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

The CABINET trial assessed health-related quality of life (HRQoL) using the EORTC QLQ-C30, EORTC QLQ-GINET21 and Patients' Global Impression of Change (PGIC). Data from EORTC QLQ-C30 were mapped to 5Q-5D-3L and used to inform the progression-free health state. In the base case analysis, relative decrements were calculated from Swinburn et al. [70] and were applied to the progression-free utilities to inform the progressed disease health state. The effect of AEs on HRQoL was assumed to be captured by the HSUVs (health state utility values), as HRQoL was measured within the CABINET trial, thus disutilities were not included. All documentation for HRQoL is presented in section 10, and references in Table 10.

Table 10 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
Data on file – Ipsen. Cost-Effectiveness Model Report CABINET trial. 2024. [71] Data on file – Ipsen. Utility Analysis Report CABINET trial. 2024. [72]	**Progression-free** pNET: 0.819 epNET: 0.731 Lung NET: 0.552	Section 10

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Swinburn P, Wang J, Chandiwana D, Mansoor W, Lloyd A. Elicitation of health state utilities in neuroendocrine tumours. *J Med Econ*. 2012;15(4):681-687. doi:10.3111/13696998.2012.670175 [70] Data on file –Ipsen. Cost-Effectiveness Model Report CABINET trial. 2024. [71]	**Progressed disease** pNET: 0.650 epNET: 0.580 Lung NET: 0.438	Section 10

5.3 Literature used for inputs for the health economic model

The health economic model for pNET and epNET in Denmark is informed by the CABINET trial. Unit costs were sourced from publicly available Danish data. The literature used for input to the economic model is presented in Table 11.

Table 11 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
Data on file – Ipsen. [redacted] Data on file – Ipsen. Survival Analysis Report CABINET trial. 2024. [69]	Overall survival and progression-free survival	Head-to-head CABINET trial	Section 6.1.4

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available data	Medicines costs, monitoring and patient costs, management of adverse events costs.	Sourced from medicinpriser.dk [73], Catalogue for estimating unit costs (Værdisætning af Enhedsomkostninger [74]), Danish DRGs costs from Sundhedsdatastyrelsen [75], Takskort 29A [76], Rigshospitalets Labportal [77].	Section 11

6. Efficacy

6.1 Efficacy of cabozantinib compared to placebo for adult patients with locally advanced / unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed to at least one prior systemic therapy

6.1.1 Relevant studies

The application is based on the intent-to-treat (ITT) population in the head-to-head CABINET trial [5], which compares cabozantinib to placebo (proxy for BSC in this application). The ITT population includes all randomised patients within each cohort included in the study (pNET and epNET). The ITT populations were used to analyse patient baseline characteristics, disease characteristics, and efficacy endpoints. Patients were grouped based on their assigned treatment at randomisation. In addition, OS results adjusted for crossover are presented since these data are used in the health economic analysis.

CABINET was a Phase 3, US-based, academic, multicentre, randomised, double-blind, placebo-controlled study, which evaluated the efficacy, safety, and tolerability of cabozantinib in patients with progressive pNETs or epNETs, whose disease had progressed after prior FDA-approved therapy (excluding SSAs). Due to a significant improvement in PFS by investigator assessment (and consistent results using available BIRC results) for patients receiving treatment with cabozantinib compared with placebo in both the epNET and pNET cohorts, the trial was terminated earlier than planned and the study was unblinded to enable potential crossover for patients on the placebo treatment arms to receive open-label cabozantinib treatment. Investigators and study subjects were unblinded on 24 August 2023, which is the data cut-off (DCO) date for all results presented in this application. An overview of the CABINET study design is presented in Table 12.

The CABINET trial is described in detail in Appendix A.

Table 12 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 time
CABINET, NCT03375320 [5, 7, 67, 68, 78]	Phase 3, US-based, multicentre, randomised, double-blind, placebo-controlled study of cabozantinib versus placebo.	The trial began in July 2018. Patients continued the blinded trial regimen until the occurrence of disease progression, unacceptable toxic effects, or withdrawal of consent.	Adults with pNETs or epNETs whose disease has progressed after prior FDA-approved therapy (not including SSA).	Cabozantinib (oral administration), 60 mg once daily orally every 28 days.	Placebo	In the epNET cohort, the median follow-up times were 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm. In the pNET cohort, the median follow-up times were 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm. **Primary endpoint:** PFS, defined as the time from randomization to the earlier of progressive disease (PD) per RECIST 1.1 or death due to any cause, determined by BIRC **Secondary endpoints:** OS, defined as the time from randomization to death from any cause. ORR, defined as the proportion of subjects whose best response was either complete response (CR) or partial response (PR) Safety and tolerability of cabozantinib versus placebo **Additional endpoints:** DOR, defined as the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1. DCR, defined as the proportion of subjects with a best overall response (BOR) of CR, PR, or stable disease (SD) Concordance between the investigator and BIRC response assessments

6.1.2 Comparability of studies

Not applicable, as the application is based on the head-to-head study CABINET.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of patients included in the CABINET study (ITT populations [pNET and epNET]) are presented in Table 13.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CABINET (epNET)		CABINET (pNET)	
	Cabozantinib (N = 134)	**Placebo (N = 69)**	**Cabozantinib (N = 64)**	**Placebo (N = 31)**
Median age (range), years	66 (28-86)	66 (30-82)	59.5 (29-79)	64 (39-79)
Female sex, no. (%)	74 (55)	31 (45)	27 (42)	13 (42)
ECOG performance-status score, no. (%)				
0	49 (37)	32 (46)	35 (55)	15 (48)
1	84 (63)	36 (52)	28 (44)	16 (52)
2	1 (0.7)	1 (1.4)	1 (1.6)	0
Primary tumour site, no. (%)				
Pancreas	4 (3.0)	3 (4.3)	62 (97%)	30 (97%)
Lung	27 (20)	12 (17)	-	-
Stomach§	3 (2.2)	2 (2.9)	1 (1.6%)	0
Small bowel (including Duodenum, Jejunum, Ileum)	37 (28)	29 (42)	1 (1.6%)	0
Appendix	1 (0.7)	0		
Cecum§	3 (2.2)	0	0	1 (3.2%)
Non-cecum colon	2 (1.5)	0	-	-
Rectum	5 (3.7)	6 (8.7)	-	-
Thymus	6 (4.5)	4 (5.8)	-	-

	CABINET (epNET)		CABINET (pNET)	
	Cabozantinib (N = 134)	Placebo (N = 69)	Cabozantinib (N = 64)	Placebo (N = 31)
Unknown*	22 (16%)	2 (2.9%)	-	-
Other†	24 (18%)	11 (16%)	-	-
Tumor grade, no. (%)				
Grade 1	37 (28)	15 (22)	14 (22)	7 (23)
Grade 2	86 (64)	48 (70)	39 (61)	19 (61)
Grade 3	8 (6)	5 (7.2)	8 (13)	3 (9.7)
Unknown‡	3 (2.2)	1 (1.4)	3 (4.7)	2 (6.5)
Hormone syndrome present: functional tumor, no. (%)	41 (31)	25 (36)	11 (17)	5 (16)
Median no. (range) of previous systemic therapies not including somatostatin analogue A	2 (1-5)	2 (1-6)	3 (1-8)	2 (1-7)
Previous systemic therapy, no. (%)				
Somatostatin analogue	124 (93)	64 (93)	63 (98)	30 (97)
Lu-177 dotatate	80 (60)	41 (59)	38 (59)	18 (58)
Everolimus	96 (72)	44 (64)	51 (80)	25 (81)
Temozolomide with or without capecitabine	43 (32)	20 (29)	43 (67)	16 (52)
Cisplatin or carboplatin plus etoposide	11 (8.2)	8 (12)	1 (1.6)	2 (6.5)
Sunitinib	4 (3.0)	1 (1.4)	18 (28)	7 (23)

Notes: § 3 subjects with a diagnosis of epNET were misallocated during enrolment to the pNET cohort. *For epNET, exact primary tumour location could not be identified but a diagnosis of epNET was made. †Other includes small bowel, mesenteric, ampullary, midgut, hindgut, biliary tract, larynx, pre-sacral, kidney and ethmoid sinus. ‡ Eligible epNET subjects were required to meet only ONE of the following criteria: 1) well- or moderately differentiated NET; 2) low- or intermediate-grade NET; or 3) carcinoid or atypical carcinoid Tumor. Abbreviations: ECOG, Eastern Cooperative Oncology Group; epNET, extra pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

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

A Danish clinical expert assessed the study population in the CABINET study to reflect the characteristics of the relevant Danish patient population [47]. In the health economic (HE) model, patient baseline characteristics were based on the CABINET trial; however, inputs were varied in scenario analyses.

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population – pNET	Value in the health economic model	Value in the health economic model	Value in the health economic model
	All NETs [46, 47, 79]	[redacted]	[redacted]	[redacted]
Patient age, years (SE)	Range: 61-72	[redacted]	[redacted]	[redacted]
Female sex (%)	Range: 33-73%	[redacted]	[redacted]	[redacted]
Weight, kg (SE)	Not available	[redacted]	[redacted]	[redacted]
Body surface area, m^2 (SE)	Not available	[redacted]	[redacted]	[redacted]

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; SE, standard error.

6.1.4 Efficacy – results per CABINET

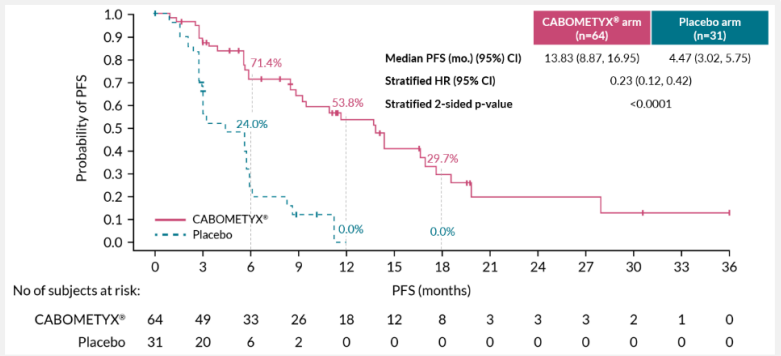
CABINET data have been published in the New England Journal of Medicine and presented at ESMO 2023 and 2024 [5, 7, 67]. There are slight differences in the data presented in the [redacted] and these publications, in particular for subgroup data, due to differences in the data cut-off dates and censoring rules applied. Since data from the CSR have been used to support the EMA regulatory submission for cabozantinib in the CABINET indication, these data are used to inform this application. A DCO of 24th August 2023 (the date of study unblinding) was used for efficacy and safety data.

Efficacy analyses in the CABINET trial were conducted according to the ITT principle. Results for PFS, OS and ORR are presented below. OS results adjusted for crossover using the inverse probability of censoring weights (IPCW) method are also presented below. Using the IPCW method to account for crossover to cabozantinib in the placebo arm, hazard ratios were generated for OS in the different subgroups of interest. Hazard ratios were estimated based on a Cox marginal structural model, which accounted for the same confounding baseline covariates as the weight estimation model. More details on the adjustment for crossover are presented in the section D.2.9 in Appendix D. All outcomes included in the application are presented in detail in Appendix B.

6.1.4.1 Progression-free survival (PFS)

For the final analysis and primary efficacy endpoint, PFS was assessed by BICR, which is presented in this section. There was a clinically meaningful and statistically significant improvement in BICR-assessed PFS per RECIST 1.1 for patients in the cabozantinib arm compared with the placebo arm, in both the pNET cohort and epNET cohort [redacted]. In the pNET cohort, PFS events had occurred for 50% of patients (n=32; median follow-up 23.2 months) in the cabozantinib arm and for 81% of patients (n=25; median follow-up 25.2 months) in the placebo arm by DCO. These results showed a statistically significant treatment effect, with a stratified hazard ratio (HR) of 0.23 (95% CI: 0.12, 0.42; stratified 2-sided p<0.0001) favouring the cabozantinib arm. Based on this HR, cabozantinib reduced the risk of disease progression or death by 77% compared with placebo [redacted]. The Kaplan-Meier (KM) estimate of median PFS using FDA-recommended censoring rules was 13.83 months (95% CI: 8.87, 16.95) in the cabozantinib arm compared with 4.47 months (95% CI: 3.02, 5.75) in the placebo arm, an estimated 9.36-month difference between treatment arms. The separation between the cabozantinib curve and placebo curve was maintained at landmarks of 6, 12 and 18 months. A KM plot of PFS is presented in Figure 4 showing the early and maintained separation of the treatment arms in favour of treatment with cabozantinib [redacted].

Figure 4 KM plot of PFS by BICR (pNET cohort; ITT population)

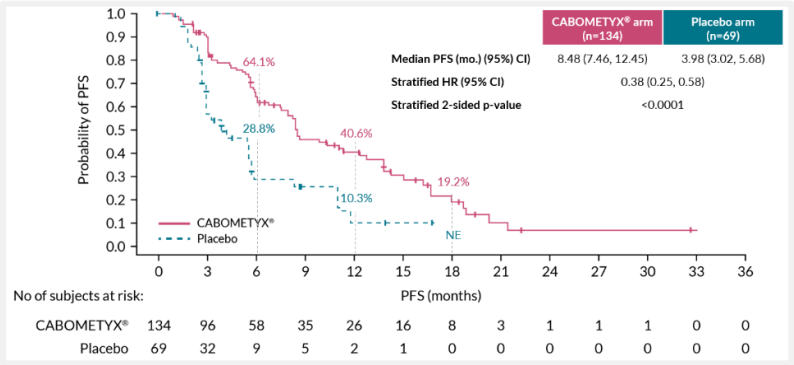


Footnotes: DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the CABOMETYX® or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria. Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; LR, log-rank test; pNET, pancreatic neuroendocrine tumour; OPEN, Oncology Patient Enrollment Network. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

In the epNET cohort, PFS events occurred for 53% of patients (n=71; median follow-up: 23.3 months) in the cabozantinib arm and for 58% of patients (n=40; median follow-up: 23.0 months) in the placebo arm by the DCO of 24th August 2023. These results showed a statistically significant treatment effect, with a stratified HR of 0.38 (95% CI: 0.25, 0.58; stratified 2-sided p<0.0001), favouring the cabozantinib arm. Based on this HR, cabozantinib reduced the risk of disease progression or death in patients with epNETs by 62% compared with placebo [redacted]. The KM estimate of median PFS using FDA-recommended censoring rules was 8.48 months (95% CI: 7.46, 12.45) in the cabozantinib arm compared with 3.98 months (95% CI: 3.02, 5.68) in the placebo arm, an estimated 4.5-month difference between treatment arms. The separation between the

cabozantinib curve and placebo curve was maintained at landmarks of 6, 12 and 18 months. A KM plot of BICR-assessed PFS is presented in Figure 5, showing the early and maintained separation of the treatment arms in favour of cabozantinib [redacted].

Figure 5 KM Plot of PFS by BICR (epNET cohort; ITT population)



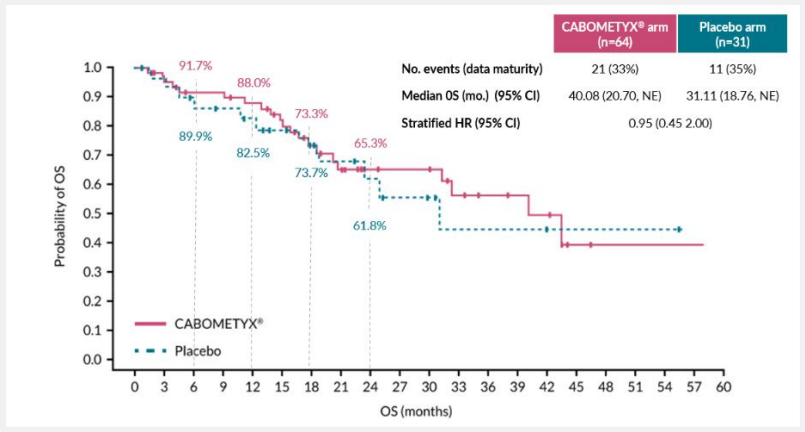
Footnotes: DCO: 24th August 2023. A bold pink or blue dash (– or |) indicates a censored observation. The grey dotted lines and associated percentages indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for epNET: 1. Concurrent SSA Use (Yes, No) and 2. Primary Site (Midgut/Unknown vs Non-midgut GI/Lung/Other). Stratification was per OPEN criteria. Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; LR, log-rank test; OPEN, Oncology Patient Enrollment Network. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

6.1.4.2 Overall survival (OS)

Interpretation of OS data is limited due to the crossover design of the CABINET trial and the immaturity of OS data at the time of clinical trial termination. 34% of patients (n=32) in the pNET cohort and 48% of patients (n=97) in the epNET cohort had died across the cabozantinib and placebo arms. OS results were also confounded by 39% of patients with pNETs in the placebo arm (n=12) and 29% of patients with epNETs in the placebo arm (n=20) crossing over to open-label cabozantinib treatment after progression. Despite these factors, a numerical benefit in OS was observed for cabozantinib vs placebo in the pNET cohort and epNET cohort. In both cohorts, OS HRs were <1, favouring the cabozantinib arm over the placebo arm [redacted].

In the pNET cohort, 33% of patients (n=21) in the cabozantinib arm and 35% of patients (n=11) in the placebo arm had died. A total of 39% of patients in the placebo arm (n=12) crossed over to receive cabozantinib; these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles [redacted]. The KM estimates of median OS were 40.08 months in the cabozantinib arm and 31.11 months in the placebo arm (stratified HR: 0.95; 95% CI: 0.45, 2.00; p=0.8852). KM estimates showed that, at most time-points, the proportion of patients estimated to be alive was greater in the cabozantinib arm compared with the placebo arm (Figure 6 KM plot of OS (pNET cohort; ITT population)) [68].

Figure 6 KM plot of OS (pNET cohort; ITT population)

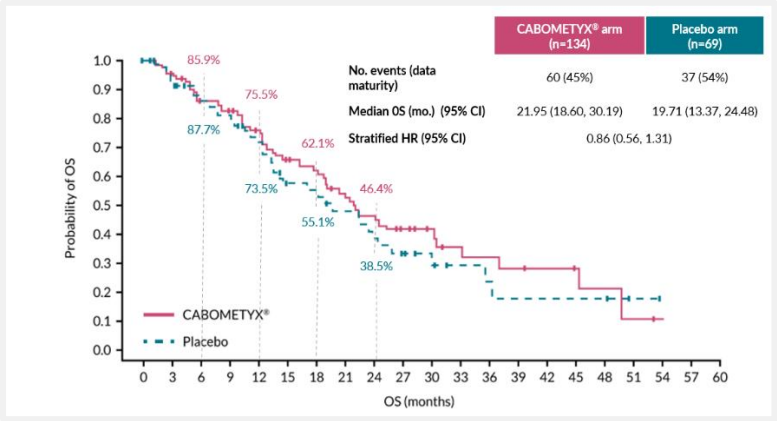


Footnotes: DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria. Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intent-to-treat; LR, log-rank test; OPEN, Oncology Patient Enrollment Network; OS, overall survival; pNET, pancreatic neuroendocrine tumour. Source: Ipsen Data on File, 2024 [redacted]

The IPCW-adjusted HRs of OS for cabozantinib versus placebo were stratified HR[redacted] ----- [redacted] and unstratified HR: [redacted]

In the epNET cohort, 45% of patients (n=60) in the cabozantinib arm and 54% of patients (n=37) in the placebo arm had died. In the placebo arm, 29% of patients (n=20) crossed over to receive cabozantinib; these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles [redacted]. The KM estimates of median OS were 21.95 months in the cabozantinib arm and 19.71 months in the placebo arm (HR: 0.86; 95% CI: 0.56, 1.31; p=0.4871). KM estimates showed that, at most time points, the proportion of patients estimated to be alive was greater in the cabozantinib arm than the placebo arm (Figure 7) [redacted]

Figure 7 KM plot of OS (epNET cohort; ITT population)



Footnotes: DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months.

Stratification factors for epNET: 1. Concurrent Somatostatin Analogue Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs Non-midgut GI/Lung/Other]. Stratification was per OPEN criteria. Abbreviations: CI, confidence interval; DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; LR, log-rank test; OPEN, Oncology Patient Enrollment Network; OS, overall survival. Source: Ipsen Data on File, 2024 [redacted]

The IPCW-adjusted HRs of OS for cabozantinib versus placebo were stratified HR: [redacted] and unstratified HR: [redacted]

6.1.4.3 Objective response rate (ORR)

The results of the secondary endpoint BICR-assessed objective response rate (ORR) per RECIST 1.1 are presented in Appendix B.1.

7. Comparative analyses of efficacy

Not applicable.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

The pivotal trial CABINET forms the basis of the comparative analysis. Thus, data from CABINET is presented in Table 15. As described in section 6.1.4, CABINET data have been published in the New England Journal of Medicine and presented at ESMO 2023 and 2024 [5, 7, 67]. There are slight differences in the data presented in the [redacted] and these publications, in particular for subgroup data, due to differences in the data cut-off dates and censoring rules applied. Since data from the CSR have been used to support the EMA regulatory submission for cabozantinib in the CABINET indication, these data are used to inform this application. A DCO of 24th August 2023 (the date of study unblinding) was used for efficacy and safety data. Data presented in Table 15 correspond to the ITT populations (epNET and pNET) and the DCO of 24th August 2023.

Table 15 Results from the comparative analysis of cabozantinib vs. placebo for adult patients with locally advanced / unresectable or metastatic, well differentiated extra-pancreatic (epNET)

and pancreatic (pNET) neuroendocrine tumours who have progressed to at least one prior systemic therapy

	epNET			pNET		
Outcome measure	**Cabozantinib (N=134)**	**Placebo (N=69)**	**Result (difference)**	**Cabozantinib (N=64)**	**Placebo (N=31)**	**Result (diff.)**
PFS by BICR, median, (95% CI) in months	8.38 (5.98, 11.07)	3.25 (2.99, 5.42)	5.13 HR: 0.41 (0.28, 0.60)	13.83 (8.87, 16.95)	4.47 (3.02, 5.75)	9.36 HR: 0.23 (0.12, 0.42)
OS, median, (95% CI) in months	21.95 (18.60, 30.19)	19.71 (13.37, 24.48)	2.24 HR: 0.86 (0.56–1.31)	40.08 (20.70, NE)	31.11 (18.76, NE)	8.97 HR: 0.95 (0.45, 2.00)
ORR by BICR	5.2% (2.1–10.5)	0.0% (0.0–5.2)	5.2% (95 % CI: 1.5–9.0)	19% (10.1–30.5)	0.0% (0.0–11.2)	18.8% (95 % CI: 9.2–28.3)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

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 CABINET trial, from the latest available data cut-off (23 August 2023), were used to model OS, PFS and TTD for Cabometyx® and BSC over the model time horizon. The method used for modelling the efficacy data was based on the DMC methods guide and the NICE Decision Support Unit [80, 81]. Standard survival models, including the exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, and the generalised gamma, were fitted to the CABINET trial data.

Model performance and selection of the base case were assessed through:

- **Visual comparison** with the Kaplan-Meier (KM) estimate (KM curves) and non-parametric hazards (kernel-smoothed hazards).
- **Goodness-of-fit** using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

- **Clinical plausibility** of the hazard function's shape and the estimated future event rates.

In CABINET, patients who were randomised to the BSC were allowed to crossover to cabozantinib upon progression. As such, the ITT analysis may overestimate the OS of BSC patients and underestimate the relative benefits (versus BSC) in OS for patients receiving cabozantinib. Thus, to estimate OS in the BSC arm, crossover-adjusted HRs were applied to the extrapolated cabozantinib arm. For a detailed description of the crossover adjustment, see Appendix D.2.9. Mortality estimates were constrained by age- and gender-specific general mortality rates from the current Danish life tables, as per DMC guidelines [80].

8.1.1 Extrapolation of efficacy data

The main assumptions and methods used for extrapolation of PFS, OS, and TTD are presented in Appendix D.

8.1.1.1 Extrapolation of progression-free survival

Table 16 Summary of assumptions associated with the extrapolation of progression-free survival

Method/approach	Description/assumption
Data input	Clinical data from CABINET NCT03375320 [68].
Model	The seven standard survival models were fitted to individual patient data from CABINET. Survival was assumed to follow one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	epNET Cabometyx®: Lognormal epNET BSC: Generalised gamma pNET Cabometyx®: Lognormal pNET BSC: Lognormal Lung NET Cabometyx®: Gamma Lung NET BSC: Lognormal
Function with best BIC fit	epNET Cabometyx®: Lognormal epNET BSC: Generalised gamma pNET Cabometyx®: Lognormal pNET BSC: Lognormal Lung NET Cabometyx®: Gamma Lung NET BSC: Lognormal
Function with best visual fit	epNET Cabometyx®: Gamma epNET BSC: Generalised gamma pNET Cabometyx®: Gamma

Method/approach	Description/assumption
	pNET BSC: Lognormal Lung NET Cabometyx®: Log-logistic Lung NET BSC: Generalised gamma
Function with best fit according to evaluation of smoothed hazard assumptions	epNET Cabometyx®: Weibull epNET BSC: Lognormal pNET Cabometyx® : Exponential pNET BSC: Gompertz Lung NET Cabometyx®: Weibull Lung NET BSC: Generalised gamma
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Lognormal in all populations and arms.
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable.
Assumptions of waning effect	No
Assumptions of cure point	No

In the figures below (Figure 8 through Figure 10) the observed PFS data for Cabometyx® and BSC are displayed next to all investigated extrapolation functions for the entire time horizon, for pNET, epNET, and lung NET.

Figure 8 epNET PFS Kaplan-Meier data and extrapolations of Cabometyx®

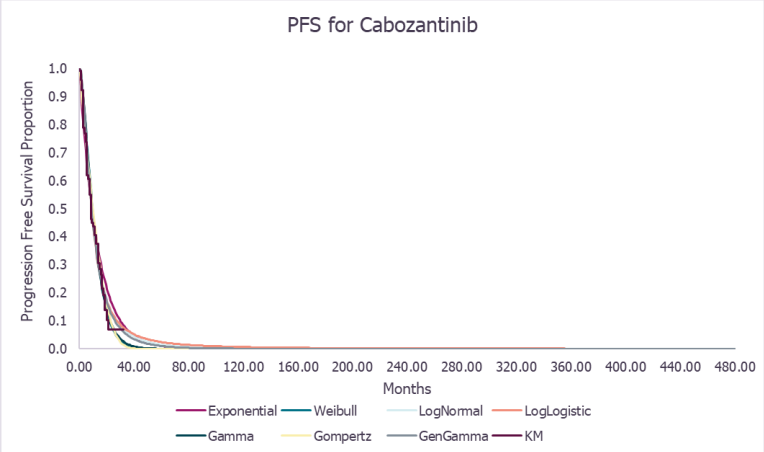


Figure 9 epNET PFS Kaplan-Meier data and extrapolations of BSC

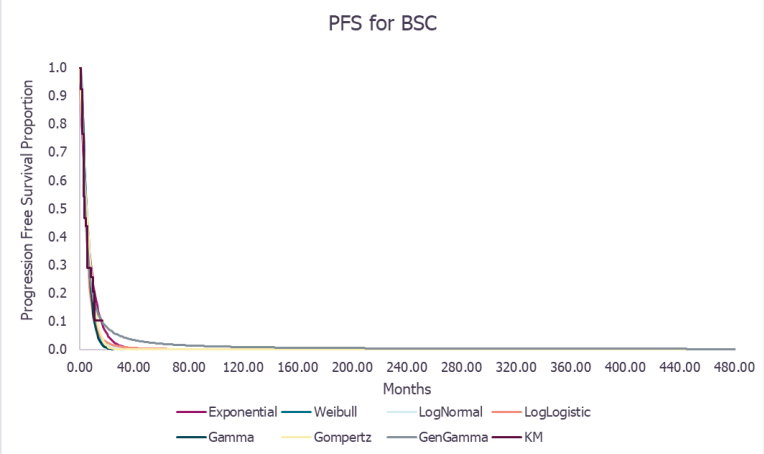


Figure 10 pNET PFS Kaplan-Meier data and extrapolations of Cabometyx®

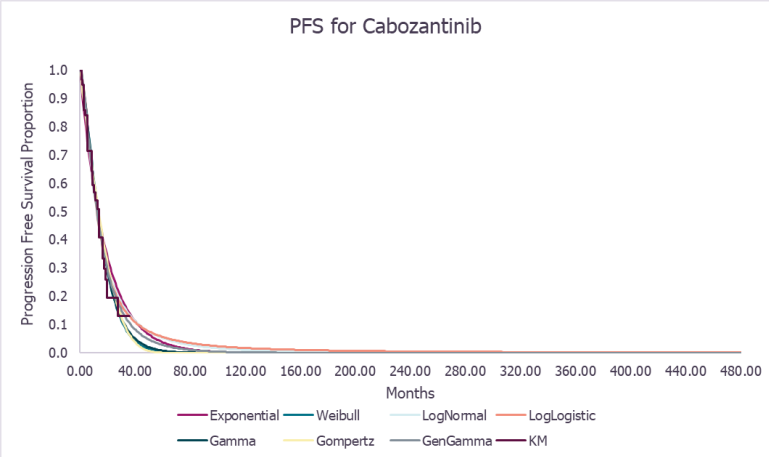


Figure 11 pNET PFS Kaplan-Meier data and extrapolations of BSC

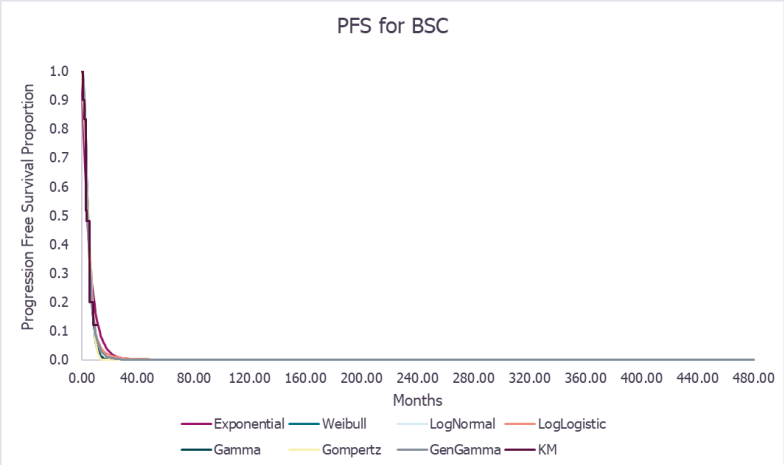


Figure 12 Lung NET Kaplan-Meier data and extrapolations of Cabometyx®

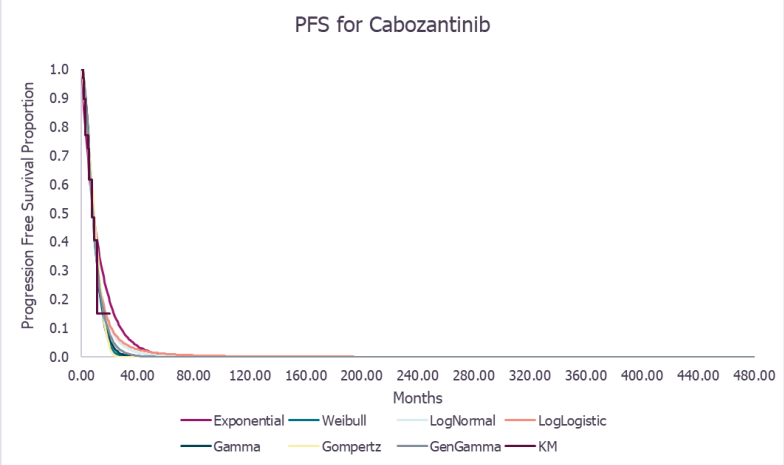
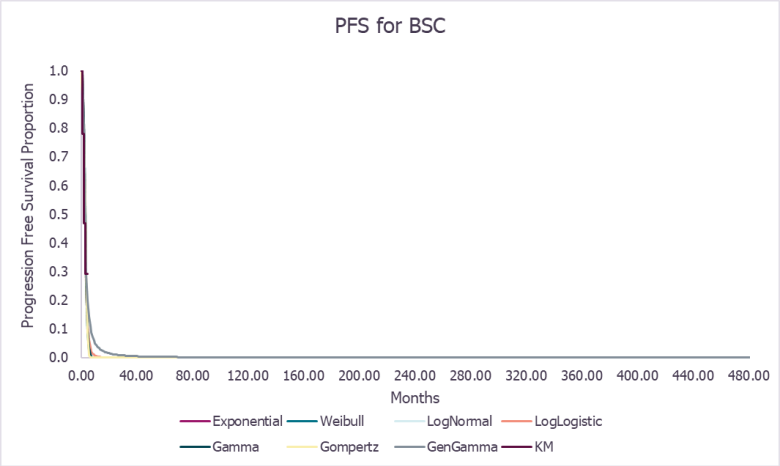


Figure 13 Lung NET Kaplan-Meier data and extrapolations of BSC



8.1.1.2 Extrapolation of overall survival

Table 17 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	Clinical data from CABINET NCT03375320 [68].
Model	The seven standard survival models were fitted to individual patient data from CABINET. Survival was assumed to follow one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma.
Assumption of proportional hazards between intervention and comparator	Yes (crossover adjusted). As a hazard ratio was applied to the BSC arm, the function with best fit is not presented below for this arm.

Method/approach	Description/assumption
Function with best AIC fit Cabometyx® arm	epNET Cabometyx®: Gamma pNET Cabometyx®: Exponential Lung NET Cabometyx®: Weibull
Function with best BIC fit Cabometyx® arm	epNET Cabometyx®: Gamma pNET Cabometyx®: Exponential Lung NET Cabometyx®: Exponential
Function with best visual fit Cabometyx® arm	epNET Cabometyx®: Generalised gamma pNET Cabometyx®: lognormal Lung NET Cabometyx®: log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	epNET Cabometyx®: Exponential pNET Cabometyx®: Exponential Lung NET Cabometyx®: Exponential
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	epNET Cabometyx®: Exponential pNET Cabometyx®: Exponential Lung NET Cabometyx®: Weibull
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Yes. The inverse probability of censoring weights (IPCW) method was used. Hazard ratios were applied to the extrapolated Cabometyx® arm, for epNET, pNET and lung NET separately, to estimate a comparator curve relative to the Cabometyx® arm.
Assumptions of waning effect	No
Assumptions of cure point	No /method

In the figures below, the observed OS data for Cabometyx® are displayed next to all investigated extrapolation functions for the entire time horizon, for pNET, epNET and lung NET.

Figure 14 pNET Kaplan-Meier data and extrapolations of Cabometyx®

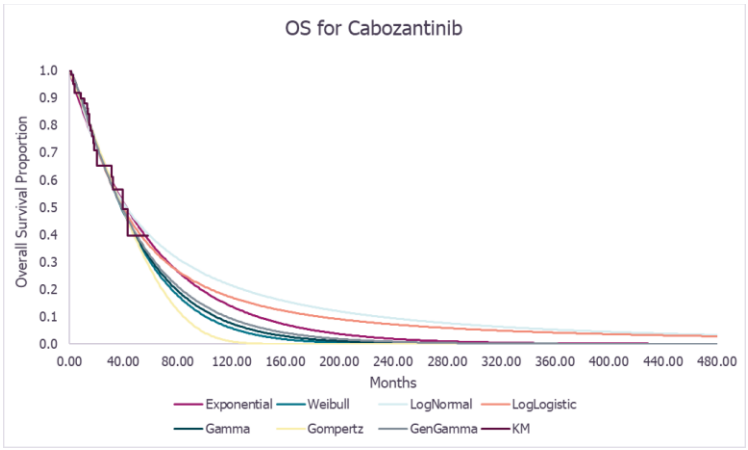


Figure 15 epNET Kaplan-Meier data and extrapolations of Cabometyx®

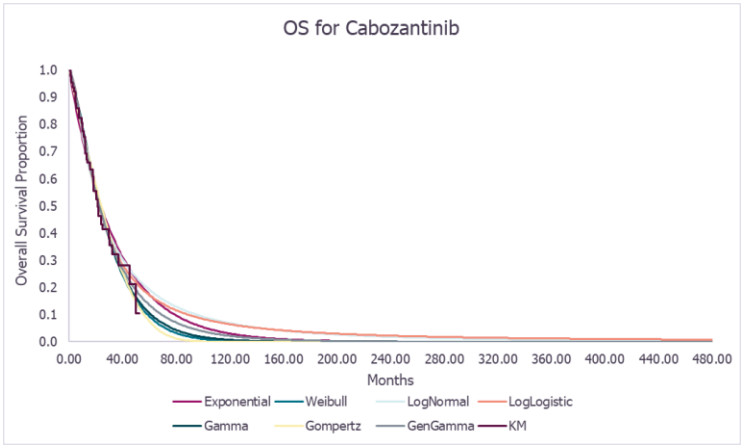
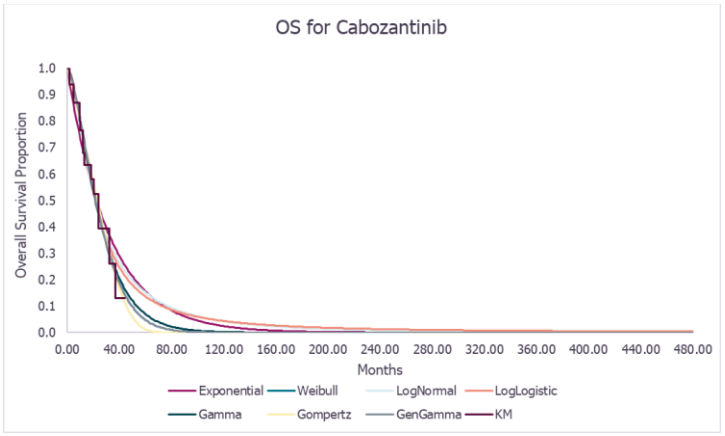


Figure 16 Lung NET Kaplan-Meier data and extrapolations of Cabometyx®



8.1.1.3 Extrapolation time to treatment discontinuation

Table 18 Summary of assumptions associated with extrapolation of time to treatment discontinuation

Method/approach	Description/assumption
Data input	Clinical data from CABINET NCT03375320 [68].
Model	The seven standard survival models were fitted to individual patient data from CABINET. Survival was assumed to follow one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	epNET Cabometyx®: Exponential epNET BSC: Log-logistic pNET Cabometyx®: Exponential pNET BSC: Gamma Lung NET Cabometyx®: Exponential Lung NET BSC: Gamma
Function with best BIC fit	epNET Cabometyx®: Exponential epNET BSC: Log-logistic pNET Cabometyx®: Exponential pNET BSC: Gamma Lung NET Cabometyx®: Exponential Lung NET BSC: Gamma
Function with best visual fit	epNET Cabometyx®: Gompertz epNET BSC: Log-logistic pNET Cabometyx®: Gamma pNET BSC: Log-logistic Lung NET Cabometyx®: Exponential Lung NET BSC: Gompertz
Function with best fit according to evaluation of smoothed hazard assumptions	epNET Cabometyx®: Generalised gamma epNET BSC: Lognormal pNET Cabometyx®: Weibull pNET BSC: Gompertz Lung NET Cabometyx®: Exponential Lung NET BSC: Gompertz
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A

Method/approach	Description/assumption
Selected parametric function in base case analysis	All Cabometyx® arms: Exponential All BSC arms: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	No

In the figures below the observed TTD data for Cabometyx® and BSC are displayed next to all investigated extrapolation functions for the entire time horizon, for pNET, epNET and lung NET.

Figure 17 pNET TTD Kaplan-Meier data and extrapolations of Cabometyx®

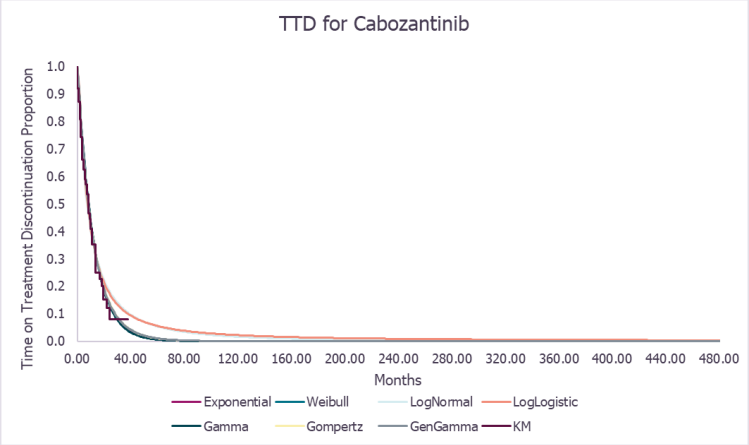


Figure 18 pNET TTD Kaplan-Meier data and extrapolations of BSC

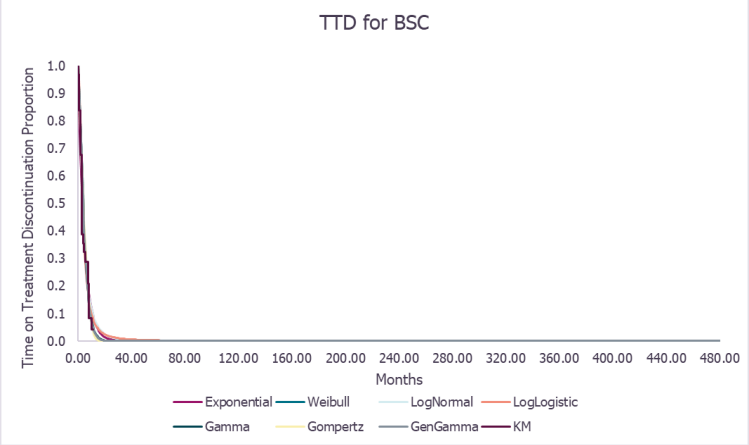


Figure 19 epNET TTD Kaplan-Meier data and extrapolations of Cabometyx®

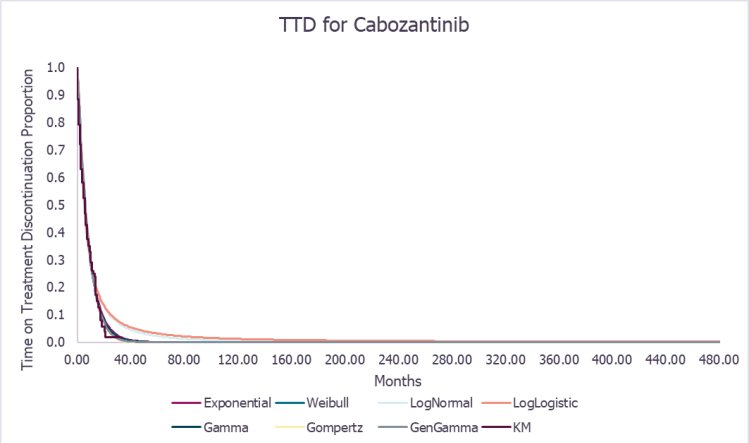


Figure 20 epNET TTD Kaplan-Meier data and extrapolations of BSC

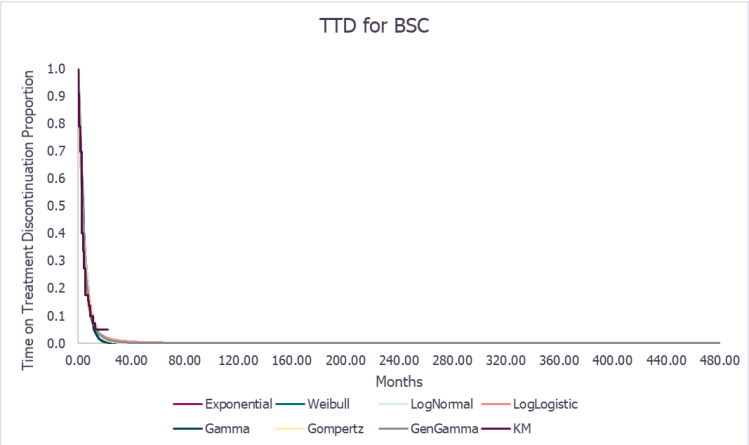


Figure 21 Lung NET TTD Kaplan-Meier data and extrapolations of Cabometyx®

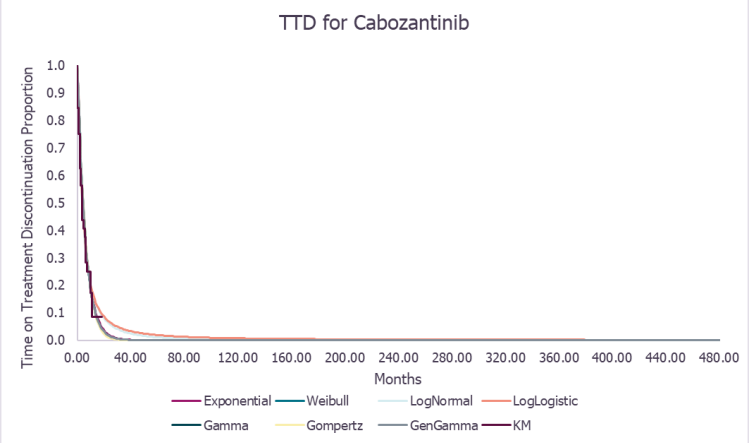
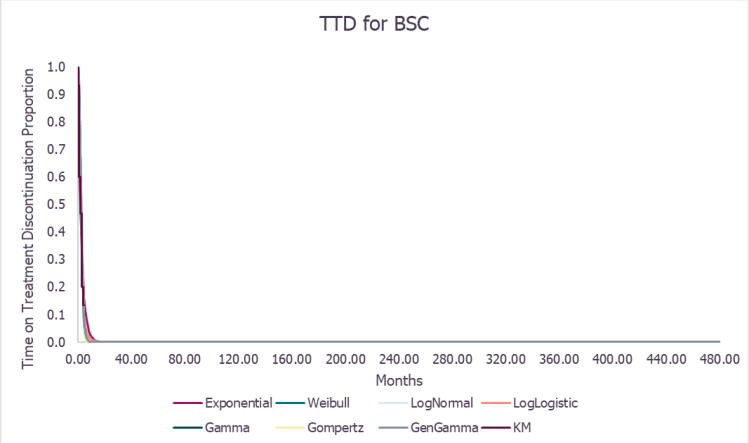


Figure 22 Lung NET TTD Kaplan-Meier data and extrapolations of BSC



8.1.2 Calculation of transition probabilities

N/A

Table 19 Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Modelling effects of subsequent treatments

Cabometyx® is expected to be the relevant treatment option when all other available treatments have been exhausted. Thus, there were no subsequent treatments included in the model.

8.3 Other assumptions regarding efficacy in the model

N/A

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

Table 20 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
pNET Cabometyx®	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	
pNET BSC	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	[redacted]
epNET Cabometyx®	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	
epNET BSC	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	
Lung NET Cabometyx®	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	
Lung NET BSC	[redacted]	[redacted]	[redacted]
months	[redacted]	[redacted]	

*In the CABINET trial, lung NET is reported as a part of epNET.

Table 21 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	PF [months]	PD [months]
pNET Cabometyx®	[redacted]	[redacted]	[redacted]

pNET BSC	[redacted]	[redacted]	[redacted]
epNET Cabometyx®	[redacted]	[redacted]	[redacted]
epNET BSC	[redacted]	[redacted]	[redacted]
Lung NET Cabometyx®	[redacted]	[redacted]	[redacted]
Lung NET BSC	[redacted]	[redacted]	[redacted]

9. Safety

9.1 Safety data from the clinical documentation

The safety data presented in this application is from the CABINET trial, the same head-to-head study used to document the efficacy of the intervention (cabozantinib) and the comparator (placebo). The safety population in the CABINET trial was defined as all patients who received ≥1 dose of any study medication. The safety population was used for exposure and safety analyses, and patients were grouped based on the actual treatments that they received [redacted].

An overview of safety events in both the pNET and epNET cohort in the CABINET trial is presented in Table 22. Data presented was sourced from the CABINET [redacted]. The median duration of exposure at DCO was longer in the cabozantinib arm compared with the placebo arm for both the pNET cohort (8.28 months vs 2.86 months) and the epNET cohort (5.37 months vs 2.79 months). Adverse events (AEs) were to be reported every cycle. For each AE, attribution to protocol treatment and severity grading (per CTCAE, version 5.0) were determined by the investigator from baseline through 30 days after the subject's last treatment date. AEs occurring more than 30 days after treatment discontinuation were recorded only if they were possibly, probably, or definitely related to study treatment [redacted].

In the epNET cohort, all subjects in both treatment arms had an AE (Table 22). Compared with the placebo arm, the cabozantinib arm had a higher proportion of subjects with AEs that were considered related to study treatment (referred to as adverse reactions in the table), serious, Grade 3/4, or leading to dose modification or reduction. Grade 5 events were similar between treatment arms. The available safety data for the different grades of AEs corresponded to the worst Grade 3 or 4 AE and to the worst Grade 5 AE. In order to report CTCAE grade ≥ 3 events, as required in Table 22, the above-mentioned events were summed.

In the pNET cohort, all subjects in both treatment arms had an AE (Table 22). Similar to the epNET cohort, the cabozantinib arm, compared with the placebo arm, had a higher proportion of subjects with AEs that were considered related to study treatment (referred to as adverse reactions in the table), serious, Grade 3/4, or leading to dose modification or reduction. In the pNET cohort, no Grade 5 events were reported,

although a single death did occur in a cabozantinib-treated subject due to tumour (per the patient status case report form) but was not entered in electronic data capture. For this cohort, in order to report CTCAE grade ≥ 3 events, as required in Table 22, worst Grade 3 or 4 AEs are reported.

Overall, there were no new safety findings from this study for cabozantinib compared to studies of cabozantinib in other indications [redacted]. In addition, among the 32 total crossover subjects (randomized to placebo and crossed over to open-label cabozantinib after disease progression), safety results were consistent with those from subjects who received cabozantinib only [redacted].

Table 22 Overview of safety events (DCO 24th August 2023)

	epNET			pNET		
	Cabozantinib (N=132) [68]	**Placebo (N=67) [68]**	**Difference, % (95 % CI)**	**Cabozantinib (N=63) [68]**	**Placebo (N=31) [68]**	**Difference, % (95 % CI)**
Number of adverse events, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	132 (100%)	67 (100%)	0.0% (0.0, 0.0)	63 (100%)	31 (100%)	0.0% (0.0, 0.0)
Number of serious adverse events, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	58 (44%)	27(40%)	3.6% (-10.8, 18.1)	29 (46%)	7 (23%)	23.5% (4.3, 42.6)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	98 (74.2%)	31 (46.3%)	28.0% (13.9, 42.1)	46 (73%)	14 (45%)	27.9% (7.2, 48.5)
Number of adverse reactions, n	N/A	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	130 (98%)	56 (84%)	14.9% (5.8, 24.0)	62 (98%)	26 (84%)	14.5% (1.2, 27.9)
Number and proportion of patients who had a dose reduction, n (%)	87 (66%)	7 (10%)	55.5% (44.6, 66.4)	43 (68%)	6 (19%)	48.9% (30.9, 66.9)

	epNET			pNET		
	Cabozantinib (N=132) [68]	**Placebo (N=67) [68]**	**Difference, % (95 % CI)**	**Cabozantinib (N=63) [68]**	**Placebo (N=31) [68]**	**Difference, % (95 % CI)**
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	111 (84%)	60 (90%)	-5.5% (-15.1, 4.2)	49 (78%)	29 (94%)	-15.8% (-29.2, -2.3)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	36 (27%)	13 (19%)	7.9% (-4.3, 20.0)	12 (19%)	3 (9.7%)	9.4% (-4.9, 23.6)
Subjects with a Grade 5 AE occurring within 30 days of the last dose of study drug, n (%)*	9 (6.8%)	5 (7.5%)	-0.6% (-8.3%, 7.0%)	0	0	0

Note: Subjects counted only once within each category but may be counted in multiple categories. *Death related to AE, according to the NCI CTCAE v5.0. Abbreviations: AE, adverse events; DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; SAE, serious adverse event. Source [redacted]

The serious adverse events (SAEs) reported with a frequency of ≥ 5% in the CABINET trial are reported for epNET and pNET cohorts in Table 23 and Table 24, respectively. A list of all SAEs observed in > 2 patients in the CABINET study are reported in Appendix E.

Table 23 Serious adverse events with frequency of ≥ 5% - epNET (DCO 24th August 2023)

Adverse events	Cabozantinib (N=132)		Placebo (N=67)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Hypertension, n (%)	8 (6.1%)	N/A	1 (1.5%)	N/A
Abdominal pain	7 (5.3%)	N/A	4 (6.0%)	N/A

Abbreviations: DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour. [redacted]

Table 24 Serious adverse events with frequency of ≥ 5% - pNET (DCO 24th August 2023)

Adverse events	Cabozantinib (N=63)		Placebo (N=31)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Vomiting	4 (6.3%)	N/A	0 (0%)	N/A
Small intestinal obstruction	1 (1.6%)	N/A	3 (9.7%)	N/A

Abbreviations: DCO, data cut-off; pNET, pancreatic neuroendocrine tumour. [redacted]

TEAEs Grade 3 or 4 TEAEs reported for > 4% of subjects in either treatment arm were included in the model and are presented in Table 25 to Table 27. The TEAEs in lung NET were assumed to be the same as for epNET. The per cycle probability of TEAEs was calculated based on the overall frequency of AEs and the mean trial follow-up. TEAEs for each epNET subgroup for cabozantinib and BSC were calculated using individual patient data (IPD) from the CABINET trial.

Table 25 Adverse events used in the health economic model - epNET

Adverse events	Cabozantinib	BSC	Source	Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		

Adverse events	Cabozantinib	BSC	Source	Justification
Fatigue	14.39%	8.96%	CABINET study CSR [68]	TEAEs Grade 3 or 4 TEAEs reported for > 4% of subjects in either treatment arm in the CABINET trial. Thus, only those AEs that are likely to occur with sufficient frequency and severity that they have an impact on costs and/or quality of life are captured.
Diarrhoea	10.61%	4.48%	CABINET study CSR [68]	
Hypertension	25.76%	5.97%	CABINET study CSR [68]	
Lymphocyte count decreased	9.09%	1.49%	CABINET study CSR [68]	
Blood alkaline phosphatase increased	4.55%	5.97%	CABINET study CSR [68]	
Blood bilirubin increased	2.27%	5.97%	CABINET study CSR [68]	
Dyspnoea	4.55%	4.48%	CABINET study CSR [68]	
Weight decrease	4.55%	0.00%	CABINET study CSR [68]	
Abdominal pain	8.33%	5.97%	CABINET study CSR [68]	
Syncope	3.79%	7.46%	CABINET study CSR [68]	

Note: At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events. Abbreviations: AEs, adverse events; BSC, best supportive care; CSR, clinical study report. [redacted]

Table 26 Adverse events used in the health economic model - pNET

Adverse events	Cabozantinib	BSC	Source	Justification
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**		
Fatigue	14.29%	6.45%	CABINET study CSR [68]	TEAEs Grade 3 or 4 TEAEs reported for > 4% of

Adverse events	Cabozantinib	BSC	Source	Justification
Diarrhoea	6.35%	0.00%	CABINET study CSR [68]	subjects in either treatment arm in the CABINET trial. Thus, only those AEs that are likely to occur with sufficient frequency and severity that they have an impact on costs and/or quality of life are captured.
Hypertension	22.22%	12.90%	CABINET study CSR [68]	
Stomatitis	6.35%	0.00%	CABINET study CSR [68]	
PPE syndrome	9.52%	0.00%	CABINET study CSR [68]	
Nausea	7.94%	3.23%	CABINET study CSR [68]	
Vomiting	6.35%	0.00%	CABINET study CSR [68]	
Lymphocyte count decreased	7.94%	0.00%	CABINET study CSR [68]	
Pain	4.76%	0.00%	CABINET study CSR [68]	
Blood bilirubin increased	4.76%	3.23%	CABINET study CSR [68]	
Blood pressure increased	4.76%	0.00%	CABINET study CSR [68]	
Hypoxia	4.76%	0.00%	CABINET study CSR [68]	
Embolism	6.35%	0.00%	CABINET study CSR [68]	
Pulmonary embolism	4.76%	0.00%	CABINET study CSR [68]	
Sepsis	4.76%	0.00%	CABINET study CSR [68]	

Note: At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events. Abbreviations: AEs, adverse events; BSC, best supportive care; CSR, clinical study report. [redacted].

Table 27 Adverse events used in the health economic model - Lung NET

Adverse events	Cabozantinib	BSC	Source	Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		
Fatigue	14.39%	8.96%	CABINET study CSR [68]	TEAEs Grade 3 or 4 TEAEs reported for > 4% of subjects in either treatment arm in the CABINET trial. Thus, only those AEs that are likely to occur with sufficient frequency and severity that they have an impact on costs and/or quality of life are captured.
Diarrhoea	10.61%	4.48%	CABINET study CSR [68]	
Hypertension	25.76%	5.97%	CABINET study CSR [68]	
Lymphocyte count decreased	9.09%	1.49%	CABINET study CSR [68]	
Blood alkaline phosphatase increased	4.55%	5.97%	CABINET study CSR [68]	
Blood bilirubin increased	2.27%	5.97%	CABINET study CSR [68]	
Dyspnoea	4.55%	4.48%	CABINET study CSR [68]	
Weight decrease	4.55%	0.00%	CABINET study CSR [68]	
Abdominal pain	8.33%	5.97%	CABINET study CSR [68]	
Syncope	3.79%	7.46%	CABINET study CSR [68]	

Note: At each level of subject summarization, a subject is counted once for the most severe event if the subject reported one or more events. Abbreviations: AEs, adverse events; BSC, best supportive care; CSR, clinical study report. [redacted]

9.2 Safety data from external literature applied in the health economic model (N/A)

Not applicable.

Table 28 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 adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A, not applicable.

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

HRQoL was measured in a substudy of the CABINET trial (A021602-HO1) [3] and included three QoL instruments (Table 29). EORTC QLQ-C30 results are presented below, and the EORTC QLQ-GINET21 and Patients' Global Impression of Change (PGIC) in Appendix F.

Table 29 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	QoL substudy of the CABINET trial (A021602-HO1) [3]	Data from EORTC QLQ-C30 were mapped to 5Q-5D-5L and used to calculate the health state utility values in the health economic analysis.
EORTC QLQ-GINET21	QoL substudy of the CABINET trial (A021602-HO1)[3]	It is a 21-item questionnaire addressing symptoms associated with GI-related NETs. Used as a supplement to the EORTC QLQ-C30 questionnaire.
Patients' Global Impression of Change (PGIC)	QoL substudy of the CABINET trial (A021602-HO1)[3]	It is a one-question questionnaire in which patients rate their overall status (self-reported scale)

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

10.1.1 Study design and measuring instrument EORTC QLQ-C30

The EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30) is widely used for assessing patient-reported outcomes in oncology. It consists of 30 items that evaluate various aspects of a cancer patient's experience, including functional status (across five domains), symptom burden (captured through eight symptom scales or items), overall health and quality of life, and the financial strain associated with cancer and its treatment. Items are rated on a four-point scale, ranging from "not at all" to "very much". The tool demonstrates strong reliability, with Cronbach's alpha exceeding 0.70 on seven of the nine multi-item scales and test-retest reliability scores of 0.78 or higher across all scales and one single-item measure [82]. The EORTC QLQ-C30 summary score ranges from 0 to 100, with higher scores indicating better HRQoL. The hypothesis was that cabozantinib would improve quality of life and decrease disease-related symptoms compared to placebo [82]. Out of the CABINET ITT population consisting of 298 subjects, 254 subjects (pNET=83, epNET=171) had at least one EORTC QLQ-C30 response during the course of the substudy and were included in the QoL analysis [3].

10.1.2 Data collection

Data were collected at baseline and every 12 weeks until disease progression or a new anticancer treatment was initiated. In some cases, data was collected outside the planned 12-week intervals; in such instances, an algorithm was used to define windows around each scheduled timepoint, allowing responses to be aligned with the intended assessment schedule. This approach prevented visits from being double-counted [72]. Missing items within a summary or scale score were handled according to each questionnaire's published scoring algorithms [82]. Any empty booklets (i.e., booklets with no missing items) were excluded before booklet selection [3]. All analyses were completed using all available data [82].

In line with the study protocol, patients were censored from QoL analyses upon disease progression or start of non-protocol anti-cancer therapy. Because of this, the majority of data were expected to be available for progression-free (PF) patients, while limited data were available for patients in the progressive disease (PD) health state. Crossover patients were not included in the QoL study [72]. Two cabozantinib patients and one placebo patient with non-pancreatic primary tumour site were misclassified into the pNET cohort. Additionally, four cabozantinib patients and one placebo patient with a pancreatic primary tumour site were misclassified into the epNET cohort. All these patients provided at least one response during the study; however, this does not necessarily imply the availability of responses at baseline. The utility analysis was based on corrected cohorts, excluding misclassified patients. Table 30 and Table 31 presents missing data and completion of the EORTC QLQ-C30 instrument in patients receiving cabozantinib and placebo, for the pNET and epNET cohorts.

HRQoL data cut is 24th August 2023 for EORTC QLQ-C30, with follow-up every 12 weeks up to week 60.

Table 30 Pattern of missing data and completion cabozantinib [83]

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	55	47	85.45	85.45
Week 12	52	38	73.08	69.09
Week 24	47	31	65.96	56.36
Week 36	34	26	76.47	47.27
Week 48	29	20	68.97	36.36
Week 60	25	15	60.00	27.27
		epNET		
Baseline	113	109	96.46	96.46
Week 12	109	79	72.48	69.91
Week 24	84	51	60.71	45.13
Week 36	65	32	49.23	28.32
Week 48	48	24	50.00	21.24
Week 60	42	18	42.86	15.93

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 31 Pattern of missing data and completion placebo [83]

Time	Number of patients “at risk ”* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients “at risk ” at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	28	26	92.86	92.86
Week 12	27	16	59.26	57.14
Week 24	15	6	40.00	21.43
Week 36	7	3	42.86	10.71
Week 48	4	1	25.00	3.57
Week 60	1	0	0.00	0.00
		epNET		
Baseline	58	57	98.28	98.28
Week 12	54	35	64.81	60.34
Week 24	30	10	33.33	17.24
Week 36	17	9	52.94	15.52
Week 48	16	5	31.25	8.62
Week 60	11	4	36.36	6.90

* Number of patients “at risk”: Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 32 Overview of responses by health states cabozantinib (pNET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	47	47
Progression-free (PF) - Post-baseline	130	39
Progressed disease (PD) - Post-baseline	14	8

Table 33 Overview of responses by health states placebo (pNET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	25	25
Progression-free (PF) - Post-baseline	24	15
Progressed disease (PD) - Post-baseline	31	10

Table 34 Overview of responses by health states cabozantinib (epNET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	102	102
Progression-free (PF) - Post-baseline	181	78
Progressed disease (PD) - Post-baseline	17	8

Table 35 Overview of responses by health states placebo (epNET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	56	56
Progression-free (PF) - Post-baseline	51	35
Progressed disease (PD) - Post-baseline	26	13

Table 36 Overview of responses by health states cabozantinib (lung NET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	24	24
Progression-free (PF) - Post-baseline	26	15
Progressed disease (PD) - Post-baseline	3	3

Table 37 Overview of responses by health states placebo (lung NET)

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Progression-free (PF) - Baseline	10	10
Progression-free (PF) - Post-baseline	5	5
Progressed disease (PD) - Post-baseline	2	1

10.1.3 HRQoL results

Table 38 presents the mean scores of the EORTC QLQ-C30 summary statistics at each study time point. Corresponding graphical representations, including 95% confidence intervals, are provided in Appendix F. In the pNET cohort, data were available until week 60 in the cabozantinib arm and until week 48 in the placebo arm. At baseline, mean scores were similar between the two treatment arms. A decline in HRQoL was observed in the placebo arm at week 36, otherwise, mean scores between the two groups remained comparable throughout the study period [83]. In the epNET cohort, mean scores at baseline were also comparable between the cabozantinib and placebo arms. Over the course of the study, a greater difference emerged, with the placebo group reporting higher mean scores, indicating an improvement in HRQoL, at later time points. It is noteworthy, that from week 24 and onward, questionnaire completion in the placebo arm dropped to 10 or fewer subjects, resulting in a smaller sample size compared to the cabozantinib arm [83].

Table 38 HRQoL EORTC QLQ-C30 summary statistics[83]

	Cabozantinib		BSC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value*
pNET					
Baseline	47	85.9 (1.9)	26	85.3 (2.2)	0.6 (-5.2, 6.4)
Week 12	38	83.3 (1.9)	15	83.5 (3.5)	-0.2 (-8.0, 7.6)
Week 24	30	85.5 (2.2)	6	81.3 (3.9)	4.1 (-4.6, 12.8)
Week 36	26	82.3 (2.7)	3	74.1 (11.8)	8.2 (-15.6, 32.0)
Week 48	20	83.9 (2.3)	1	84.9 (N/A)	-0.9 (N/A)
Week 60	15	82.7 (3.8)	0	N/A (N/A)	N/A (N/A)
epNET					
Baseline	104	80.6 (1.4)	57	79.5 (2.0)	1.1 (-3.7, 6.0)
Week 12	78	74.6 (2.0)	35	79.9 (2.7)	-5.3 (-11.8, 1.2)
Week 24	49	76.6 (2.0)	10	70.4 (5.6)	6.2 (-5.3, 17.8)
Week 36	31	75.4 (2.7)	9	79.3 (4.2)	-3.9 (-13.7, 5.9)
Week 48	24	78.3 (2.8)	5	80.6 (4.5)	-2.3 (-12.6, 8.0)

	Cabozantinib		BSC		Intervention vs. comparator
Week 60	17	75.1 (4.0)	4	86.0 (4.4)	-10.9 (-22.5, 0.7)

*Analysis of EORTC QLQ-C30 data was descriptive and not comparative. Thus, no p-values are available.

Abbreviations: N/A, not available.

Figure 23 illustrates the mean change from baseline in the pNET cohort. The results suggest that HRQoL remained relatively stable in the cabozantinib arm throughout the study period. In contrast, the placebo group displayed a more unstable trend, marked by a significant drop at week 36, where the mean score indicated a notable decline in health compared to baseline although there were few patients left [83].

Figure 23 Mean change from baseline EORTC QLQ-C30 pNET [83]

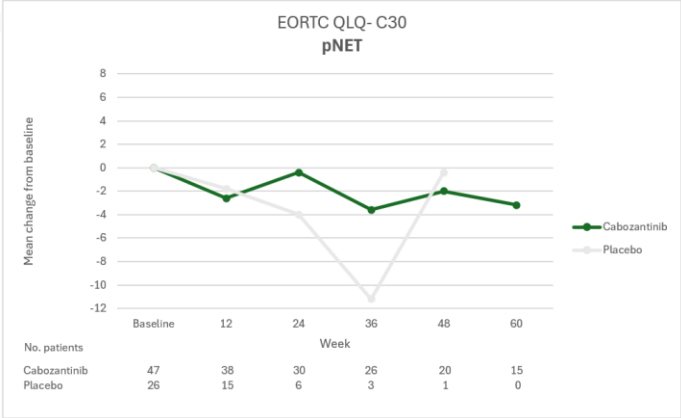
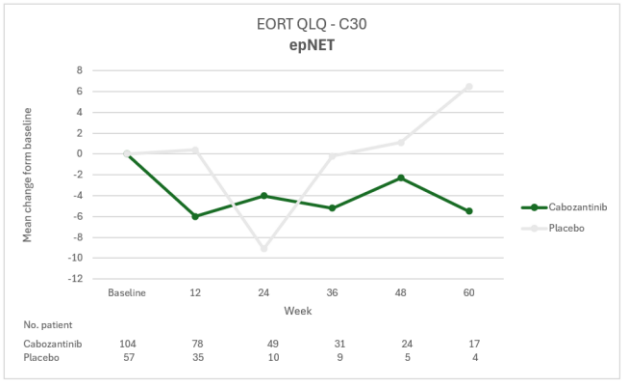


Figure 24 presents the mean change from baseline in the EORTC QLQ-C30 summary score in the epNET cohort. In the cabozantinib group, HRQoL decreased at week 12 and then remained relatively stable for the remainder of the study. In the placebo group, a similar but more significant drop occurred at week 24, followed by an improvement towards the study's end. As previously stated, fewer than 10 subjects completed the questionnaire in the placebo group after week 24 [83].

Figure 24 Mean change from baseline EORTC QLQ-C30 epNET [83]



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

10.2.1 HSUV calculation

In the CABINET trial, patient-level quality of life data were collected through the EORTC QLQ-C30 questionnaire. This data was mapped to EQ-5D-5L, through two mapping algorithms for each health state for the three populations separately. Linear mixed models for repeated measured (MMRMs) were fitted to derive the relationship between utility value and health state in pNET, epNET and lung NET separately. The regression coefficients used are presented in the table below.

Table 39 Summary of model regression coefficients: primary analysis

Model	Output	Intercept	PF State Indicator	Baseline Utility	Random Effect SD	
					Subject	Residual
pNET[a]	Estimate (95% CI)	0.433 (0.305, 0.561)	-0.017 (-0.061, 0.027)	0.474 (0.326, 0.621)	0.065	0.091
	SE	0.065	0.022	0.075	NA	NA
epNET[b]	Estimate (95% CI)	0.149 (-0.013, 0.312)	0.032 (-0.033, 0.097)	0.706 (0.518, 0.894)	0.151	0.122
	SE	0.083	0.033	0.096	NA	NA
Lung[c]	Estimate (95% CI)	-0.392 (-0.978, 0.194)	0.087 (-0.224, 0.398)	1.223 (0.547, 1.898)	0.100	0.272
	SE	0.299	0.159	0.345	NA	NA

Note: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup. Abbreviations: CI, confidence interval; epNET, extrapancreatic neuroendocrine tumours; pNET, pancreatic neuroendocrine tumours; PF, progression-free; SD, standard deviation; SE, standard error.

An alternative model specification included coefficients for treatment received (secondary analysis). The coefficients from the secondary analysis indicated minimal impact on expected utility when receiving cabozantinib compared with placebo across both pNETs and epNETs (coefficient: 0.001 and -0.025, respectively, with 95% CI including zero).

Table 40 Summary of model regression coefficients: secondary analysis

Model	Output	Intercept	Random Effect SD

			PF State Indicator	Baseline Utility	Treatment: cabozantinib	Subject	Residual
pNET[a]	Estimate (95% CI)	0.432 (0.301, 0.564)	-0.017 (-0.063, 0.029)	0.473 (0.324, 0.622)	0.001 (-0.055, 0.057)	0.067	0.091
	SE	0.067	0.023	0.076	0.029	NA	NA
epNET[b]	Estimate (95% CI)	0.160 (-0.006, 0.326)	0.036 (-0.030, 0.102)	0.709 (0.520, 0.898)	-0.025 (-0.098, 0.047)	0.152	0.122
	SE	0.085	0.034	0.096	0.037	NA	NA

Note: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup. Abbreviations: CI, confidence interval; epNET, extrapancreatic neuroendocrine tumours; pNET, pancreatic neuroendocrine tumours; PF, progression-free; SD, standard deviation; SE, standard error.

HSUVs were age-adjusted to the Danish general population according to guidelines.

10.2.1.1 Mapping

The mapping to EQ-5D-3L was done using a response-based algorithm proposed by Longworth et al. (2014) [84], with ordinary least squares (OLS) regression mapping as a sensitivity analysis. These approaches were selected based on the results from a previous SLR of mapping algorithms to EQ-5D-3L from the EORTC QLQ-C30 [85]. The PD health state utility results, however, were deemed clinically implausible; thus, a decrement based on Swinburn et al. was applied to the PF health state to generate PD values [86]. The algorithm by Longworth uses a UK tariff [87] (3L), thus the utility values generated were mapped through a linear model to the Danish EQ-5D-5L tariff [88]. The method of mapping is presented in detail in Appendix F.

10.2.2 Disutility calculation

Disutilities are not included in the model as HRQoL was measured within the pivotal trial, since the impact of AEs is assumed to be reflected in the HSUVs.

10.2.3 HSUV results

The HSUVs, mapped to EQ-5D-5L DK, are presented in Table 41.

Table 41 Health-state utility value results mapped to EQ-5D-5L Danish weights

Model	Health State	Value	SE	Instrument	Tariff	Comments
pNETs	PF	0.864	0.01	EQ-5D-5L	DK	

	PD	0.733	0.10	EQ-5D-5L	DK
epNETs	PF	0.796	0.02	EQ-5D-5L	DK
	PD	0.679	0.09	EQ-5D-5L	DK
GI NETs	PF	0.820	0.02	EQ-5D-5L	DK
	PD	0.699	0.09	EQ-5D-5L	DK
Lung NETs	PF	0.658	0.05	EQ-5D-5L	DK
	PD	0.570	0.07	EQ-5D-5L	DK
Other/Unknown NETs	PF	0.815	0.02	EQ-5D-5L	DK
	PD	0.695	0.09	EQ-5D-5L	DK

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

Not applicable.

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 42 Overview of health state utility values [and disutilities] N/A

	Results Mean (SD)	Instrument	Tariff (value set) used	Comments
N/A				

Table 43 Overview of literature-based health state utility values N/A

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

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Cabometyx® is the relevant intervention medicine for the indication addressed in this submission. Dose hold is included for Cabometyx® in the model to ensure acquisition costs are reflective of how treatments are received by patients in practice. Dose hold was calculated using the mean total dose [redacted] length and the mean dose [redacted], defined as the [redacted] between [redacted] and [redacted], for all patients who had a [redacted] due to any reason from CABINET [89, 90]. No medicine use is strictly associated with the comparator, as the analysis compares the addition of Cabometyx® to BSC vs BSC alone.

Table 44 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Cabometyx® (Cabozantinib)	60 mg	Dose hold: [redacted]	One tablet to be taken orally once daily.	N/A

11.2 Medicines– co-administration

SSAs are first-line treatment for metastatic or inoperable tumours, for tumours that are SSTR+. SSAs are primarily used for symptom control, but they also may have an antitumoral effect in small intestinal NETs and pNETs. SSAs are used as concomitant treatment in both treatment arms and were included in the health economic analysis in both arms. SSA usage is based on the CABINET trial and included in the model as follows:

- pNET: Cabometyx®, 54.69%; BSC, 54.84%.
- epNET: Cabometyx®, 68.66%; BSC, 69.67%
- Lung NET: Cabometyx®, 42.42%; BSC, 43.75%

In Denmark, two SSAs are available: lanreotide and octreotide. The usage is assumed to be equally distributed between these two medicines (50/50), according to a Danish clinical expert [47]. Patients eligible for treatment with SSAs remain on SSAs after disease progression. In the health economic analysis, this ongoing use is referred to as continuation of SSAs and was applied as a one-off cost.

11.3 Administration costs

Cabometyx® is administered orally and is assumed not to incur any additional costs.

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	Daily	0	N/A	N/A
Intramuscular injection	Once or twice daily	1,992.00	DRG 10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år.	DRG takster 2025. Sundhedsdata-styrelsen.
Deep subcutaneous injection	Once or twice daily	1,992.00	DRG 10MA98 MDC10 1-dagsgruppe, pat. Mindst 7 år.	DRG takster 2025. Sundhedsdata-styrelsen.

11.4 Disease management costs

Disease management costs were included in the analysis to include all relevant costs associated with the treatment of NETs. The included disease management costs were based on health state and type of NET. Resource use was validated with a Danish clinical expert [47].

Table 46 Disease management costs used in the model

Activity	Frequency (yearly)	Unit cost [DKK]	DRG code	Reference
CT scan	pNET PF: 1 epNET PF: 2 Lung NET PF: 2 PD state: 2, across all subgroups.	2,861.00	Diagnose: A (DC759)Kræft i endokrin kirtel UNS Procudure: P (UXCD55)CT-skanning af pancreas DRG 30PR06	DRG 2026
Hospitalisation	Once per year in the PD health state, in all subgroups.	31,472.00	Diagnose: A (DC759)Kræft i endokrin kirtel UNS DRG 10MA05 Varighed >= 12 timer (lang)	DRG 2026
Laboratory test	Once per year across all subgroups and health states.	Assumed to be included in a doctor's visit	N/A	N/A

Activity	Frequency (yearly)	Unit cost [DKK]	DRG code	Reference
Other imaging	Once per year across all subgroups and health states.	2,861.00	Diagnose: A (DC759)Kræft i endokrin kirtel UNS Procudure: P (UXCD55)CT-skanning af pancreas DRG 30PR06 Assumed similar as CT scan	DRG 2026
Ultrasound	Once per year across all subgroups and health states.	2,150.00	Diagnose: A (DC759)Kræft i endokrin kirtel UNS Procedure: P (BLNJ33) Ultralydbehandling DRG 10MA98	DRG 2026
Visit	PF state: 3; PD state: 4 across all subgroups	2,150.00	Diagnose: A (DC759)Kræft i endokrin kirtel UNS Procedure: P (DZ089)Kontrolundersøgelse efter behandling af kræft UNS DRG 10MA98	DRG 2026

11.5 Costs associated with management of adverse events

The frequency of the AEs applied in the model is presented in Table 25, Table 26, and Table 27 in Safety. The costs associated with the management of AEs were estimated using DRG tariffs to reflect the full scope of clinical management. Total AE-related costs were calculated as a cost per four-week model cycle.

Table 47 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Fatigue	DRG 23MA03	5,271
Diarrhoea	DRG 01MA11	4,977
Hypertension	DRG 05MA98	1,268
Stomatitis	DRG 03MA09	1,286
PPE syndrome	DRG 09MA98	1,578
Nausea	DRG 06MA11	4,977

	DRG code	Unit cost/DRG tariff
Vomiting	DRG 06MA11	4,977
Lymphocyte count decreased	DRG 23MA03	5,271
Pain	DRG 23MA03	5,271
Blood alkaline phosphatase increased	DRG 23MA03	5,271
Blood bilirubin increased	DRG 23MA03	5,271
Dyspnoea	DRG 04MA98	1,360
Weight decrease	DRG 10MA98	2,150
Abdominal pain	DRG 06MA98	1,729
Blood pressure increased	DRG 05MA98	1,268
Hypoxia	DRG 23MA03	5,737
Embolism	DRG 05MA98	34,499
Pulmonary embolism	DRG 04MA98	1360
Sepsis	DRG 18MA98	2416
Syncope	DRG 05MA98	1268

11.6 Subsequent treatment costs

Since Cabometyx® is expected to be considered once all other available treatment options have been exhausted, it is assumed that no other treatment options will be available upon disease progression. This was confirmed by a Danish clinical expert [47].

Table 48 Medicines of subsequent treatments – N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

The analysis includes cost for patient time during disease management and transportation costs incurred with each healthcare visit related to disease management (expect hospitalisation which was assumed as its own visits, as per DMC request (March 2026). To avoid double-counting, the model assumes that all disease management

activities occur during a single visit. The annual frequency of healthcare visits for disease management has been validated with a Danish clinical expert, and is expected to be the same for pNET, epNET, and lung NET [47]. Each visit is assumed to last three hours. The hourly cost associated with patient time is estimated at DKK 188, and the cost of a round-trip travel is DKK 140. Both values are sourced from Værdisætning af enhedsomkostninger [74].

Table 49 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Time spent for disease management	Visit Progression-free: 3 visits per year, 3 hours per visit Progressed disease: 4 visits per year, 3 hours per visit.

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 50 Base case overview

Feature	Description
Comparator	BSC
Type of model	Partitioned survival model
Time horizon	Approximately 40 years (lifetime)
Treatment line	epNET: Fourth and later lines pNET: Fourth and later lines Lung NET subgroup: Second and later lines
Measurement and valuation of health effects	Health-related quality of life was measured with EORTC QLQ-30 in CABINET and mapped to EQ-5D-3L using a Danish tariff, to estimate Danish health-state utility values. A utility decrement was added to the PF health state to estimate the PD health state.
Costs included	Medicine costs, Hospital costs, Costs of adverse events, Patient costs
Dosage of medicine	According to SmPC

Feature	Description
Average time on treatment	epNET Cabometyx®: 8.62 months pNET Cabometyx®: 12.51 months Lung NET Cabometyx®: 6.47 months epNET BSC: 5.19 months pNET BSC: 5.06 months Lung NET BSC: 3.01 months
Parametric function for PFS	Lognormal for both arms and all populations
Parametric function for OS	epNET Cabometyx®: Exponential pNET Cabometyx®: Exponential Lung NET Cabometyx®: Weibull epNET BSC: HR pNET BSC: HR Lung NET BSC: HR
Inclusion of waste	No
Average time in model health state (months)	**Progression-free** epNET Cabometyx®: 13.38 pNET Cabometyx®: 20.12 Lung NET Cabometyx®: 10.87 epNET BSC: 6.31 pNET BSC: 5.71 Lung NET BSC: 3.46 **Progressed disease** epNET Cabometyx®: 21.27 pNET Cabometyx®: 40.86 Lung NET Cabometyx®: 15.03 epNET BSC: 16.26 pNET BSC: 39.37 Lung NET BSC: 6.42

12.1.1 Base case results

Table 51 Base case results, discounted estimates pNET

	Cabometyx®	BSC	Difference
Medicine costs (DKK)	568,135	0	568,135
Medicine costs – co-administration (DKK)	83,010	34,268	48,742
Administration (DKK)	0	0	0
Disease management costs (DKK)	162,440	153,684	8,756
Costs associated with management of adverse events (DKK)	2,051	96	1,954

	Cabometyx®	BSC	Difference
Continuation of SSAs (DKK)	16,237	18,587	-2,350
Patient costs (DKK)	20,106	18,313	1,792
Palliative care costs (DKK)	N/A	N/A	N/A
Total costs (DKK)	**852,768**	**224,996**	**627,772**
Life years gained (progression-free)	1.55	0.44	1.12
Life years gained (progressed disease)	2.81	2.91	-0.10
Total life years	**4.38**	**3.36**	**1.02**
QALYs (progression-free)	1.34	0.38	0.97
QALYs (progressed disease)	2.07	2.14	-0.07
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**3.41**	**2.52**	**0.89**
Incremental costs per life year gained		**614,086**	
Incremental cost per QALY gained (ICER)		**704,039**	

Table 52 Base case results, discounted estimates epNET

	Cabometyx®	BSC	Difference
Medicine costs (DKK)	381,950	0	381,950
Medicine costs – co-administration (DKK)	72,520	44,458	28,062
Administration (DKK)	0	0	0
Disease management costs (DKK)	93,612	70,790	22,822
Costs associated with management of adverse events (DKK)	988	349	639
Continuation of SSAs (DKK)	11,486	16,710	-5,224
Patient costs (DKK)	11,693	8,631	3,062
Palliative care costs (DKK)	N/A	N/A	N/A

	Cabometyx®	BSC	Difference
Total costs	**572,249**	**140,938**	**431,311**
Life years gained (progression-free)	1.05	0.49	0.57
Life years gained (progressed disease)	1.59	1.28	0.31
Total life years	**2.64**	**1.76**	**0.88**
QALYs (progression-free)	0.84	0.39	0.45
QALYs (progressed disease)	1.08	0.87	0.21
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**1.92**	**1.25**	**0.66**
Incremental costs per life year gained		**490,686**	
Incremental cost per QALY gained (ICER)		**651,337**	

Table 53 Base case results, discounted estimates lung NET

	Cabometyx®	BSC	Difference
Medicine costs (DKK)	275,618	0	275,618
Medicine costs – co-administration (DKK)	33,779	16,269	17,509
Administration (DKK)	0	0	0
Disease management costs (DKK)	70,840	29,992	40,848
Costs associated with management of adverse events (DKK)	714	204	510
Continuation of SSAs (DKK)	13,425	19,110	-5,685
Patient costs (DKK)	8,891	3,687	5,204
Palliative care costs (DKK)	N/A	N/A	N/A
Total costs	**403,267**	**69,262**	**334,005**
Life years gained (progression-free)	0.86	0.25	0.61
Life years gained (progressed disease)	1.19	0.53	0.66
Total life years	**2.05**	**0.78**	**1.27**

	Cabometyx®	BSC	Difference
QALYs (progression-free)	0.56	0.16	0.40
QALYs (progressed disease)	0.68	0.30	0.38
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**1.24**	**0.47**	**0.77**
Incremental costs per life year gained		**263,842**	
Incremental cost per QALY gained (ICER)		**431,217**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The ten parameters with largest effects on the ICERs are presented in the tables below. The incremental costs, incremental QALYs, and ICER in the scenario analyses are presented as change from baseline. Tornado diagrams for change from base case for costs are QALYs are presented in Appendix K.

Table 54 One-way sensitivity analyses results, pNET

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			627,772	0.89	704,039
BSC , OS HR cabozantinib vs. placebo, Yes: IPCW, pNETs	95% CI (lower / upper)	To explore the uncertainty in the crossover-adjustment HR	97,018 / -162,145	1.19 / -2.04	-356,619/-1,111,285
Progression Free Utility, pNETs	95% CI (lower / upper)	According to DMC guidelines	0/0	-0.54 / 0.15	1,106,221/-102,419
Cabozantinib, Cost per pack	-+ 20%	According to DMC guidelines	-113,627/113,627	0/0	-127,431/127,431
Progressed Disease Utility, pNETs	95% CI (lower / upper)	According to DMC guidelines	0/0	0.03 / -0.02	-25,177/18,082

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Frequency per model cycle, Progressed disease, BSC, Hospitalisation, pNETs	-+ 20%	Important part of disease management	18,382/-18,382	0/0	20,615/-20,615
Frequency per model cycle, Progressed disease, Cabozantinib, Hospitalisation, pNETs	-+ 20%	Important part of disease management	-17,781/17,781	0/0	-19,941/19,941
% Of Lanreotide concomitant therapy usage Cabozantinib, pNETs	-+ 20%	SSAs are concomitant treatments	-9,646/9,646	0/0	-10,818/10,818
% Of Octreotide concomitant therapy usage Cabozantinib, pNETs	-+ 20%	SSAs are concomitant treatments	-6,956/6,956	0/0	-7,801/7,801
Frequency per model cycle, Progressed disease, BSC, Visit, pNETs	-+ 20%	Doctor's visit is an important part of disease management	5,023/-5,023	0/0	5,633/-5,633
Frequency per model cycle, Progressed disease, Cabozantinib, Visit, pNETs	-+ 20%	Doctor's visit is an important part of disease management	-4,859/4,859	0/0	-5,449/5,449

Table 55 One-way sensitivity analyses results, epNET

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			431,311	0.66	651,337
BSC , OS HR cabozantinib vs. placebo, Yes: IPCW, epNETs	95% CI (lower / upper)	To explore the uncertainty in the crossover-adjustment HR	43,128/-63,162	0.45 / -0.70	-226,554/-9,640,976

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Progression Free Utility, Full epNETs	95% CI (lower / upper)	According to DMC guidelines	0/0	-0.22 / 0.11	322,818/-93,080
Cabozantinib, Cost per pack	-+ 20 %	According to DMC guidelines	-76,390 /76,390	0/0	-115,359/115,359
Progressed Disease Utility, Full epNETs	95% CI (lower / upper)	According to DMC guidelines	0/0	-0.09 / 0.07	103,453/-63,272
Frequency per model cycle, Progressed disease, Cabozantinib, Hospitalisation, Full epNETs	-+ 20%	Important part of disease management	-10,012/10,012	0/0	-15,120/15,120
Frequency per model cycle, Progressed disease, BSC, Hospitalisation, Full epNETs	-+ 20%	Important part of disease management	8,037/-8,037	0/0	-12,726/12,726
% Of Lanreotide concomitant therapy usage Cabozantinib, Full epNETs	-+ 20%	SSAs are concomitant treatments	-8,427 /8,427	0/0	12,137/-12,137
% Of Octreotide concomitant therapy usage Cabozantinib, Full epNETs	-+ 20%	SSAs are concomitant treatments	-6,077 /6,077	0/0	-9,177/9,177
% Of Lanreotide concomitant therapy usage BSC, Full epNETs	-+ 20%	SSAs are concomitant treatments	5,166/ -5,166	0/0	7,802/-7,802
% Of Octreotide concomitant therapy usage BSC, Full epNETs	-+ 20%	SSAs are concomitant treatments	3,725/-3,725	0/0	5,626/-5,626

Table 56 One-way sensitivity analyses results, lung NET

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			334,005	0.77	431,217
BSC , OS HR cabozantinib vs. placebo, Yes: IPCW, Lung NETs	95% CI (lower / upper)	To explore the uncertainty in the crossover-adjustment HR	27,531/-40,275	0.20 / -0.35	-59,674/262,616
Progression Free Utility, Lung NETs	95% CI (lower / upper)	According to DMC guidelines	0/0	-0.17 / 0.14	119,453/-65,191
Progressed Disease Utility, Lung NETs	95% CI (lower / upper)	According to DMC guidelines	0/0	-0.15 / 0.14	103,464/-66,082
Cabozantinib, Cost per pack	-+ 20%	According to DMC guidelines	-55,124/55,124	0/0	-71,167/71,167
Frequency per model cycle, Progressed disease, Cabozantinib, Hospitalisation, Lung NETs	-+ 20%	Important part of disease management	-7,484/7,484	0/0	-9,662/9,662
Hospitalisation, Unit cost	-+ 20%	Important part of disease management	-4,145/4,145	0/0	-5,351/5,351
% Of patients who receive SSAs at progressed disease, BSC, Lung NETs	-+ 20%	SSAs are concomitant treatments	3,822/-3,822	0/0	-5,068/5,068
% Of Lanreotide concomitant therapy usage Cabozantinib, Lung NETs	-+ 20%	SSAs are concomitant treatments	-3,925/3,925	0/0	4,934/-4,934
Frequency per model cycle, Progressed disease, BSC, Hospitalisation, Lung NETs	-+ 20%	Important part of disease management	3,339/-3,339	0/0	4,311/-4,311

Scenario analyses were conducted to test the impact of alternative values for key parameters of the model and analysis. Parametric distributions with best and worst OS and PFS landmark rates were also tested. Scenario analyses for pNET, epNET and lung NET are presented in the tables below.

Table 57 Scenario analyses pNET

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
Base case			627,772 kr	-	0.89	-	704,039 kr	-
Discount rate (costs)	3.5%	0%	653,593 kr	4.11%	0.89	0.00%	732,997 kr	4.11%
		5%	618,791 kr	-1.43%	0.89	0.00%	693,967 kr	-1.43%
Discount rate (benefits)	3.5 %	0%	627,772 kr	0.00%	1.12	25.65%	560,296 kr	-20.42%
		5%	627,772 kr	0.00%	0.82	-8.17%	766,669 kr	8.90%
Time horizon	40	5	594,046 kr	-5.37%	0.42	-52.89%	1,414,138 kr	100.86%
		10	614,054 kr	-2.19%	0.70	-21.63%	878,742 kr	24.81%
		20	626,047 kr	-0.27%	0.87	-2.45%	719,721 kr	2.23%
Crossover adjusted	Yes	No	583,420 kr	-7.06%	0.34	-62.36%	1,738,151 kr	146.88%
Extrapolation of OS, Cabometyx®	Exponential	Lognormal (highest landmark)	649,838 kr	3.51%	1.17	31.23%	555,359 kr	-21.12%
Extrapolation of OS, Cabometyx®	Exponential	Gompertz (lowest landmark)	603,533 kr	-3.86%	0.57	-36.01%	1,057,777 kr	50.24%

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
Extrapolation of PFS, Cabometyx®	Lognormal	Log-logistic (highest landmark)	625,216 kr	-0.41%	0.90	0.99%	694,326 kr	-1.38%
Extrapolation of PFS, Cabometyx®	Lognormal	Weibull (lowest landmark)	638,002 kr	1.63%	0.86	-4.06%	745,757 kr	5.93%
Extrapolation of PFS, BSC	Lognormal	Exponential (highest landmark)	631,571 kr	0.61%	0.89	-0.37%	710,936 kr	0.98%
Extrapolation of PFS, BSC	Lognormal	Weibull (lowest landmark)	627,123 kr	-0.10%	0.89	0.19%	702,010 kr	-0.29%
Patient age	60.22	64	627,710 kr	-0.01%	0.89	-0.64%	708,510 kr	0.64%

Table 58 Scenario analyses epNET

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
Base case			431,311 kr	-	0.66	-	651,337 kr	-
Discount rate (costs)	3.5%	0%	441,539 kr	2.37%	0.66	0.00%	666,782 kr	2.37%

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
		5%	427,506 kr	-0.88%	0.66	0.00%	645,590 kr	-0.88%
Discount rate (benefits)	3.5 %	0%	431,311 kr	0.00%	0.75	13.45%	574,122 kr	-11.85%
		5%	431,311 kr	0.00%	0.63	-4.81%	684,236 kr	5.05%
Time horizon	40	5	416,234 kr	-3.50%	0.47	-29.12%	886,770 kr	36.15%
		10	428,633 kr	-0.62%	0.63	-5.08%	681,955 kr	4.70%
		20	431,254 kr	-0.01%	0.66	-0.11%	651,957 kr	0.10%
Crossover adjusted	Yes	No	411,496 kr	-4.59%	0.47	-28.83%	873,146 kr	34.05%
Extrapolation of OS, Cabometyx®	Exponential	Log-logistic (highest landmark)	442,632 kr	2.62%	0.81	22.34%	546,379 kr	-16.11%
Extrapolation of OS, Cabometyx®	Exponential	Gompertz (lowest landmark)	413,621 kr	-4.10%	0.46	-31.14%	907,119 kr	39.27%
Extrapolation of PFS, Cabometyx®	Lognormal	Log-logistic (highest landmark)	428,717 kr	-0.60%	0.67	1.14%	640,136 kr	-1.72%

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
Extrapolation of PFS, Cabometyx®	Lognormal	Weibull (lowest landmark)	435,229 kr	0.91%	0.65	-2.15%	671,721 kr	3.13%
Extrapolation of PFS, BSC	Lognormal	Exponential (highest landmark)	437,640 kr	1.47%	0.65	-1.53%	671,175 kr	3.05%
Extrapolation of PFS, BSC	Lognormal	Gamma	432,392 kr	0.25%	0.66	0.16%	651,915 kr	0.09%
Patient age	63.09	65	431,311 kr	0.00%	0.66	-0.13%	652,196 kr	0.13%

Table 59 Scenario analyses lung NET

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
Base case			334,005 kr	-	0.77	-	431,217 kr	-
Discount rate (costs)	3.5%	0%	338,928 kr	1.47%	0.77	0.00%	437,573 kr	1.47%
		5%	332,058 kr	-0.58%	0.77	0.00%	428,705 kr	-0.58%
Discount rate (benefits)	3.5 %	0%	334,005 kr	0.00%	0.81	5.20%	409,884 kr	-4.95%

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
		5%	334,005 kr	0.00%	0.76	-2.04%	440,197 kr	2.08%
Time horizon	40	5	332,018 kr	-0.59%	0.75	-2.85%	441,211 kr	2.32%
		10	334,003 kr	0.00%	0.77	-0.01%	431,255 kr	0.01%
		20	334,005 kr	0.00%	0.77	0.00%	431,217 kr	0.00%
Crossover adjusted	Yes	No	327,236 kr	-2.03%	0.73	-5.59%	447,491 kr	3.77%
Extrapolation of OS, Cabometyx®	Weibull	Log-logistic (highest landmark)	366,635 kr	9.77%	1.11	43.35%	330,192 kr	-23.43%
Extrapolation of OS, Cabometyx®	Weibull	Gompertz (lowest landmark)	333,877 kr	-0.04%	0.75	-3.35%	446,013 kr	3.43%
Extrapolation of PFS, Cabometyx®	Lognormal	Exponential (highest landmark)	325,074 kr	-2.67%	0.79	1.65%	412,857 kr	-4.26%
Extrapolation of PFS, Cabometyx®	Lognormal	Gompertz (lowest landmark)	331,747 kr	-0.68%	0.77	-0.88%	432,120 kr	0.21%
Extrapolation of PFS, BSC	Lognormal	Generalised gamma	339,203 kr	1.56%	0.77	-0.76%	441,271 kr	2.33%

	Base case	Scenario	Incremental costs (DKK)	% Δ from base case	Incremental QALYs	% Δ from base case	ICER (DKK)	% Δ from base case
		(highest landmark)						
Extrapolation of PFS, BSC	Lognormal	Log-logistic (lowest landmark)	333,913 kr	-0.03%	0.77	-0.02%	431,186 kr	-0.01%
Patient age	61.88	72	334,005 kr	0.00%	0.77	-0.01%	431,267 kr	0.01%

12.2.2 Probabilistic sensitivity analyses

A PSA of 1000 iterations was run for pNET, epNET and lung NET where all parameters associated with uncertainty were included, as well as parameters for all parametric distributions for the extrapolation of OS, PFS and TTD. Figure 25 presents the scatter plot from the PSA for pNET. The cloud of simulations illustrates a concentrated distribution of cost-effectiveness outcomes with most simulations clustered around the mean deterministic result, though some variability is observed with some iterations in the Northeast quadrant. Figure 26 presents the cost-effectiveness acceptability curve (CEAC) for pNET. The curve shows that at a WTP of approximately DKK 700,000, the probability of Cabometyx® to be cost-effective in comparison to BSC is approximately 50%. At a WTP of DKK 1,500,000 the probability is approximately 70%. Figure 27 illustrates the convergence of the estimated mean ICER as a function of the number of PSA simulations for pNET. At around 200 iterations, the mean estimated ICER appears to converge, suggesting that the number of PSA simulations is sufficient to produce stable cost-effectiveness results.

Figure 25 pNET PSA Scatter plot

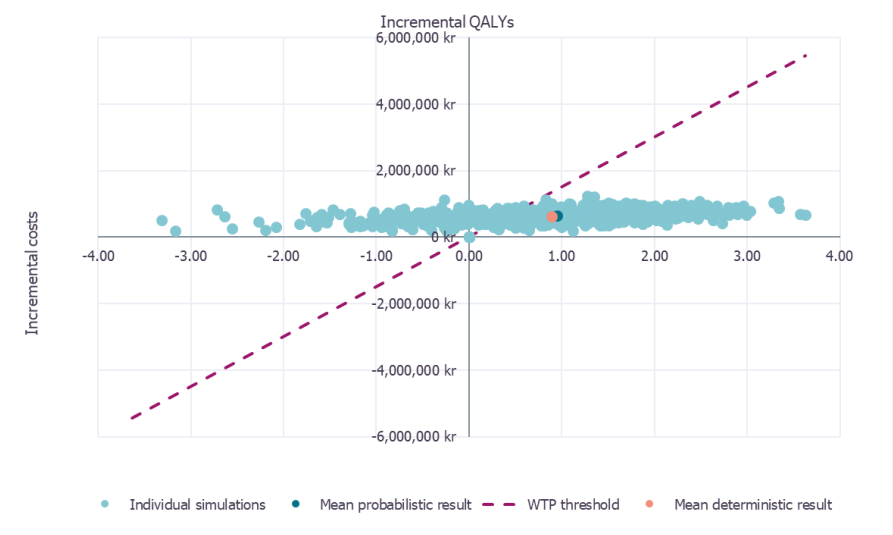


Figure 26 pNET PSA cost-effectiveness acceptability curve

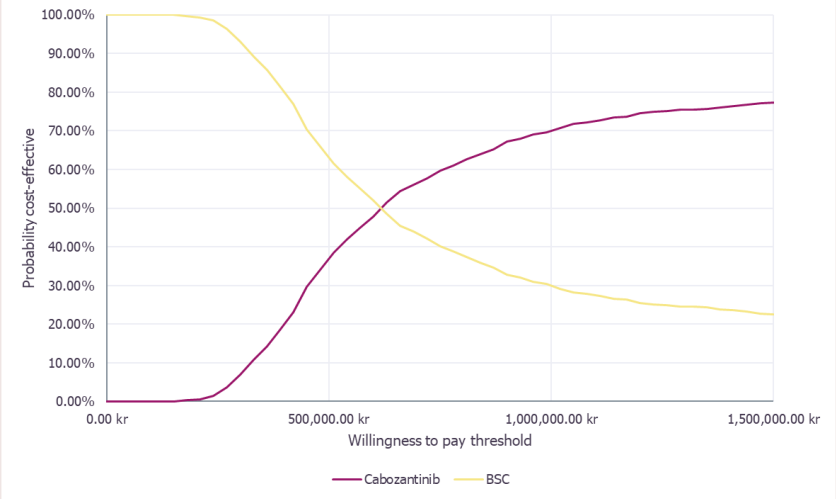


Figure 27 pNET PSA ICER convergence plot

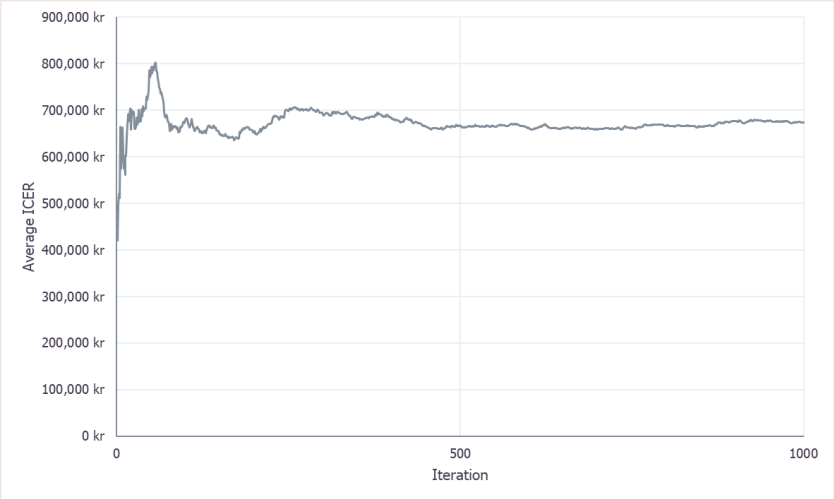


Figure 28 presents the scatter plot from the PSA for epNET. The cloud of simulations illustrates a concentrated distribution of cost-effectiveness outcomes with the majority of simulations clustered around the mean deterministic result in the Northeast quadrant, indicating that Cabometyx® is associated with higher costs and greater QALYs gained. Figure 29 presents the CEAC for epNET. The curve shows that at a WTP of approximately DKK 600,000 the probability of Cabometyx® being cost-effective in comparison to BSC is approximately 50%. At a WTP of approximately 1,500,000 the probability is estimated to 90%. Figure 30 illustrates the convergence of the estimated mean ICER as a function of the number of PSA simulations for epNET. At around 200 iterations, the mean estimated ICER appears to converge, suggesting that the number of PSA simulations is sufficient to produce stable cost-effectiveness results.

Figure 28 epNET PSA Scatter plot

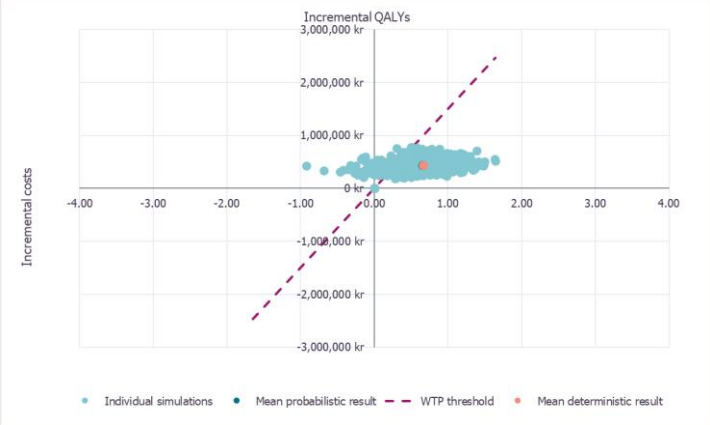


Figure 29 epNET PSA cost-effectiveness acceptability curve

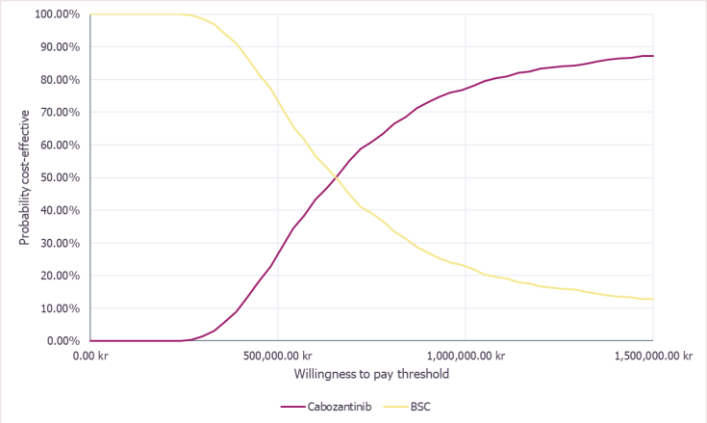


Figure 30 epNET PSA ICER convergence plot

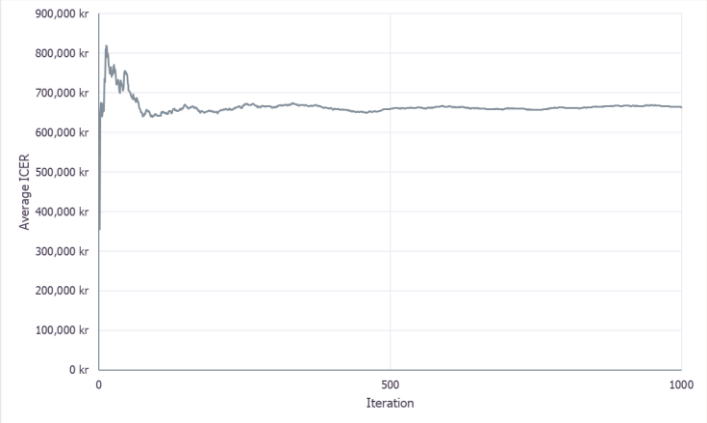


Figure 31 presents the scatter plot from the PSA for lung NET. The cloud of simulations illustrates a concentrated distribution of cost-effectiveness outcomes with the majority of simulations clustered around the mean deterministic result, indicating that Cabometyx® is associated with higher costs and greater QALYs gained. Figure 32 presents the CEAC for lung NET. The curve shows that at a WTP of approximately DKK 400,000 the

probability of Cabometyx® to be cost-effective in comparison to BSC is 50%. At a WTP of 1,000,000 the probability is almost 100%. Figure 33 illustrates the convergence of the estimated mean ICER as a function of the number of PSA simulations for lung NET. At around 200 iterations, the mean estimated ICER appears to converge, suggesting that the number of PSA simulations is sufficient to produce stable cost-effectiveness results.

Figure 31 lung NET PSA Scatter plot

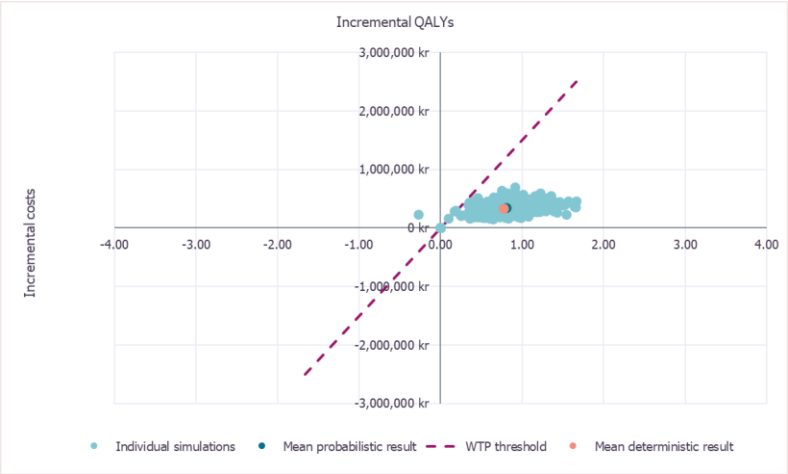


Figure 32 lung NET PSA cost-effectiveness acceptability curve

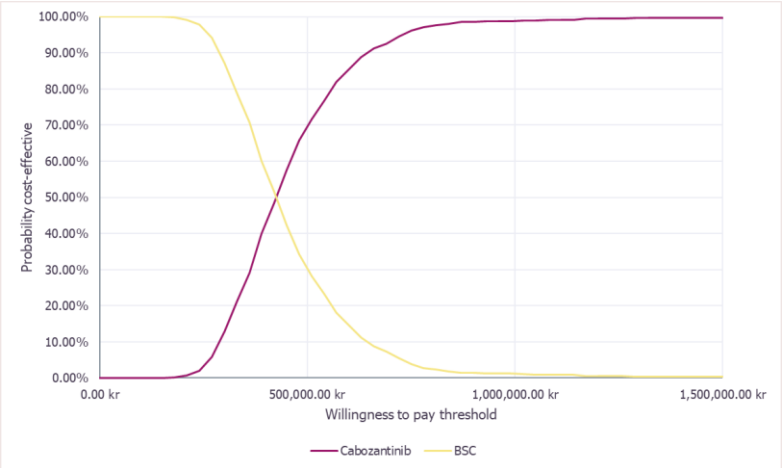
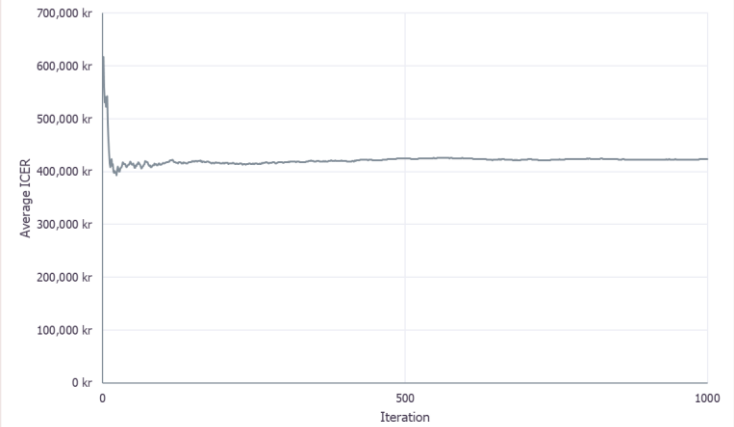


Figure 33 lung NET PSA ICER convergence plot



13. Budget impact analysis

Number of patients (including assumptions of market share)

In Denmark [redacted] with NETs are expected to become eligible for treatment with Cabometyx® annually. The medicine is expected to be used in fourth and later lines for pNET and epNET patients, and second and later lines for lung NET patients. Out of the expected eligible NET patients, [redacted] are expected to be diagnosed with epNET and [redacted] with pNET. From the [redacted] epNET patients, [redacted] are expected to be part of the lung NET subpopulation. In the budget impact the prevalence and incidence are expected to remain constant over the next 5 years. The market share is expected to develop from [redacted] in the first year, to [redacted] in the second, and reach peak at [redacted] from the third year, and remain on that level, in all patient populations. The presented patient numbers in Table 60, Table 61, and Table 62 have been rounded to the nearest whole number.

Table 60 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) - pNET

	2026	2027	2028	2029	2030
			Recommendation		
Cabometyx® + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Cabometyx® + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) – epNET

	2026	2027	2028	2029	2030
			Recommendation		
Cabometyx® + BSC					
BSC					
			Non-recommendation		
Cabometyx® + BSC					
BSC					

Table 62 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) – lung NET subpopulation

	2026	2027	2028	2029	2030
			Recommendation		
Cabometyx® + BSC					
BSC					
			Non-recommendation		
Cabometyx® + BSC					
BSC					

Budget impact

Table 63 Expected budget impact of recommending the medicine for the indication - pNET

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)					
The medicine under consideration is NOT recommended (DKK)					

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64 Expected budget impact of recommending the medicine for the indication - epNET

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65 Expected budget impact of recommending the medicine for the indication – lung NET

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

The main characteristics of the CABINET study trial are presented in Table 66.

Table 66 Main characteristics of studies included (CABINET study)

Trial name: CABINET	NCT number: NCT03375320
Objective	To determine whether Cabometyx® significantly improves PFS compared with placebo. Furthermore, to compare OS, ORR, safety, and tolerability between treatment groups.
Publications – title, author, journal, year	Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors. Chan JA., et., et al. N Engl J Med 2024 [5]. Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET Trial/Alliance A021602). Chan JA., et., et al. ESMO 2024 [91]. Alliance A021602: Phase III, double-blinded study of cabozantinib versus placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET). Abstract number: LBA53. Chan J, et al., ESMO Congress, Madrid, Spain, October 20–24, 2023 [7].

Study type and design	Phase 3, US-based, multicentre, randomised (2:1), double-blinded, placebo-controlled study. Due to significant improvement regarding PFS, the DSMB (Data and safety monitoring board) recommended termination of accrual and unblinding of the study to enable potential crossover for patients on the placebo treatment arms (i.e. to allow them to receive open-label Cabometyx® treatment), on the 28th of July 2023. The trial is completed.
	
	At the time of enrolment, patients were allocated to a cohort based on disease type: pNET vs epNET. Within each cohort, patients were then randomised in a 2:1 ratio to receive one of two treatments: Cabometyx® or placebo. Randomisation was stratified by the cohort-specific factors:
	• pNET cohort:
	  ○ Concurrent SSA use: Yes vs No
	  ○ Prior sunitinib therapy: Yes vs No
	• epNET cohort:
	  ○ Concurrent SSA use: Yes vs No
	  ○ Primary site: Midgut GI/Unknown primary site vs Non-midgut GI/Lung/Other

Sample size (n)	ITT population (n=298) were assigned to receive:

Trial name: CABINET	NCT number: NCT03375320
	• in the pNET cohort received either Cabometyx® (n=64) or placebo (n=31) and • in the epNET cohort received either Cabometyx® (n=134) or placebo (n= 69).
Main inclusion criteria	Disease characteristics: • Histological documentation: Well- or moderately differentiated pNETs or epNETs. • Stage: Locally advanced/unresectable or metastatic disease. • Grade: WHO tumour grades of 1 to 3. • Primary tumour site: NET of various origins (e.g. pancreatic, GI tract, lung, thymus, other, or unknown primary site). • Radiologic evaluation: Evidence of disease progression by RECIST 1.1 criteria within 12 months prior to study registration. • Functional status: Both functional (associated with symptoms or a clinical syndrome related to hormone secretion by the tumour) and non-functional tumours were allowed. • ECOG status: 0 to 2. Measurable disease: patients must have measurable disease per RECIST 1.1 by CT scan or MRI. Prior treatment: • Disease progression or unacceptable side-effect profile leading to discontinuation after at least one FDA-approved therapy (excluding SSAs). • Prior lines of therapy included the following: ○ pNET: everolimus, sunitinib, or 177Lu-dotatate. ○ epNET (excluding lung NET): everolimus or 177Lu-dotatate. ○ Lung NET: everolimus. Concomitant medications: Patients were allowed concurrent use of SSAs provided the dose was stable for at least two months prior to enrolment.
Main exclusion criteria	N/A
Intervention	Cabometyx® (cabozantinib) was administered orally at a daily dose of 60 mg (3* 20 mg-tablets) in each 28-day cycle to 198 patients. If a dose reduction was required due to toxicity, the dosage was reduced to 20 mg, but not below this level.
Comparator(s)	Placebo was administered orally once daily (3 tablets, matching same round, yellow film tablet as intervention tablets) to 100 patients.
Follow-up time	• For pNET follow-up time was 23.2 months (range 1.7-58.0) in the Cabometyx arm and 25.2 months (range 2.4-55.6) in the placebo arm.

Trial name: CABINET		NCT number: NCT03375320
	• For epNET follow-up time was 23.3 months (range 0.6-56.8) in the Cabometyx arm and 23.0 months (range 1.2-57.6) in the placebo arm.	
Is the study used in the health economic model?	Yes	
Primary, secondary, and exploratory endpoints	**Primary endpoint:** PFS measured by BICR per RECIST 1.1. **Secondary endpoints:** OS ORR measured per RECIST 1.1. Safety and tolerability measured by AEs per CTCAE and PRO-CTCAE. DoR measured per RECIST 1.1. DCR measured per RECIST 1.1. **Additional endpoints:** Concordance analysis, measured by proportion of cases whether there was agreement (PD or not PD) or non-agreement. HRQoL, measured by EORTC QLQ-C30, QLQ-GI.NET21, and PGIC.	
Method of analysis	The efficacy analyses were performed using the intention-to-treat (ITT) population. For PFS, a type 1 error spend of two-sided 0.002 had been pre-specified for each protocol-defined futility analysis and a two-sided spend of 0.046 had been pre-specified for the final primary analysis of PFS per RECIST 1.1. by BICR within each disease cohort, using the stratification factors as randomization. As the DSMB recommended early unblinding of the study at the trial IAs, the final PFS analysis was compared between the treatment arm at the two-sided significance level of 0.002. The HR for was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided [68]. OS at the final analysis was compared between treatment arms using the stratified log-rand test at a two-sided significance level of 0.046. A hierarchical approach was used to control for family-wise type-1 error rate for the final analysis of OS [68]. As OS data were immature at the DCO date of 24th of August 2023 and had not reached the prespecified number of events required for the final analysis, a nominal alpha of two-sided significance level 0.002 was used to compare the two treatment arms. Median OS was estimated for both treatment arms using the Kaplan-Meier method, along with 95% Cis and landmark OS values. For the analysis of OS, the duration of OS was calculated from randomization to the date of death or the last known alive date, with all deaths prior to the DCO date counted as events [68].	

Trial name: CABINET	NCT number: NCT03375320
	Point estimates of ORR with CIs were calculated using the Clopper Pearson method. The difference in ORR between the 2 treatment arms within each disease cohort and associated CIs were provided. The ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were performed. The DOR (the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1) was analysed using the Kaplan-Meier method for subjects with a response of CR or PR in the ITT population. The DCR estimate and 95% CI were determined similar to the methods used for ORR.
Subgroup analyses	• Two cohorts were included in the study: pNET and epNET. • All subgroup analyses presented below for the pNET cohort and epNET cohort were prespecified analyses, except for a post-hoc analysis of the epNET cohort by primary tumour site. This post-hoc analysis split the epNET cohort into the following primary tumour sites: GI NETs, lung/thymus NETs and other/unknown NETs. • The analyses of PFS and OS were repeated for the following subgroups: - Age (< 65 years, ≥ 65 years) - Sex (female, male) - Race (White, Other) - ECOG performance status (0, 1, 2) - Stratification factors for the epNET cohort at randomization - Concurrent somatostatin analog use (yes, no) - Primary site: Midgut (jejunum, ileum, appendix, cecum, ascending colon, hepatic flexure)/Unknown primary site vs Non-midgut GI (stomach, duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon, rectum)/Lung/Other known primary site not listed - Stratification factors for the pNET cohort at randomization - Concurrent somatostatin analog use (yes, no) - Prior sunitinib therapy (yes, no) - Number of prior systemic therapies (1, 2, ≥ 3) - Prior everolimus (yes, no) - Prior Lu-177 dotatate (yes, no) - Tumor grade (Grade 1, Grade 2, Grade 3, Unknown) - Histologic differentiation (well differentiated, moderately differentiated, poorly differentiated, not specified)

Trial name: CABINET		NCT number: NCT03375320
	- Histologic type (atypical, typical carcinoid; in epNET only).	
Other relevant information	No?	

Abbreviations: AE: adverse event; BICR: blinded independent central review; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; DoR: duration of response; EORTC: European Organisation for Research and Treatment of Cancer; epNET: extra-pancreatic neuroendocrine tumour; HRQoL: health-related quality of life; OS: overall survival; ORR: objective response rate; PD: progressive disease; PFS; progression-free survival; PGIC: Patient Global Impression of Change; pNET: pancreatic neuroendocrine tumour; QLQ: Quality of Life questionnaire; RECIST: Response Evaluation Criteria in Solid Tumours; ECOG: Eastern Cooperative Oncology Group.
Source: Chan et al. 2024 [5].

Appendix B. Efficacy results per study

Table 67 Results per study (CABINET) – pNET cohort (ITT population), DCO 24th August 2023

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median overall survival (OS)	Cabozantinib	64	40.08 (20.70–NE) months	8.97	N/A	N/A	HR: 0.95	0.45–2.00	0.8852	The distribution of OS was estimated using the Kaplan-Meier method. The median OS, along with 95% CIs, were estimated for the 2 treatment arms. Additionally, the 12-, 24-, and 36-month OS rates, along with the 95% CIs, were estimated. The stratified Cox regression was used to estimate the HR of OS, along with the 95% CI. Stratification factors for pNET: 1. Concurrent Somatostatin Analogue Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No).	[redacted]
	Placebo	31	31.11 (18.76–NE) months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										Stratification was per OPEN criteria.	
Median progression-free survival (PFS) by BICR	Cabozantinib	64	13.83 (8.87–16.95) months	9.36	5.10–13.62	N/A	HR: 0.23	0.12–0.42	<0.0001	The hazard ratio (HR) for PFS was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided. Results from an unstratified analysis was also provided. Kaplan-Meier methodology was used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves were produced. Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS for each treatment arm.	[redacted]
	Placebo	31	4.47 (3.02–5.75) months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median progression-free survival (PFS) by Investigator	Cabozantinib	64	10.97 (8.41–13.86) months	7.91	4.79–11.03	N/A	HR: 0.29	0.16–0.52	<0.0001	The hazard ratio (HR) for PFS was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided. Results from an unstratified analysis was also provided. Kaplan-Meier methodology was used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves were produced. Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS for each treatment arm.	[redacted]
	Placebo	31	3.06 (2.86–5.91) months								
Confirmed	Cabozantinib	64	19% (10.1–30.5)	18.8%	9.2–28.3	0.0115	N/A	N/A	N/A	Point estimates of ORR with CIs were calculated	[redacted]

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
objective response rate (ORR [CR+PR]) * by BIRC	Placebo	31	0.0% (0.0–11.2)							using the Clopper Pearson method. The difference in ORR between the 2 treatment arms within each disease cohort and associated CIs were provided. The ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were performed. Analyses for imaging assessments evaluated per BIRC and investigator were performed.	[redacted]

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Confirmed objective response rate (ORR [CR+PR]) * by Investigator	Cabozantinib	64	7.8% (2.6–17.3)	7.8%	1.2–14.4	0.1218	N/A	N/A	N/A	Point estimates of ORR with CIs were calculated using the Clopper Pearson method. The difference in ORR between the 2 treatment arms within each disease cohort and associated CIs were provided. The ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were performed. Analyses for imaging assessments evaluated per BIRC and	[redacted]
	Placebo	31	0.0% (0.0–11.2)								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										investigator were performed.	
Duration of response (DOR) by BIRC	Cabozantinib	12	Median: 11.20 (5.78–NE) months	N/A	N/A	N/A	N/A	N/A	N/A	The DOR (the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1) was analysed using the Kaplan-Meier method for subjects with a response of CR or PR in the ITT population.	[redacted]
	Placebo	0	Not evaluable†								
Duration of response (DOR) by Investigator	Cabozantinib	5	Median: 16.59 months (5.55–NE)	N/A	N/A	N/A	N/A	N/A	N/A	The DOR (the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1) was analysed using the Kaplan-Meier method for subjects with a response of CR or PR in the ITT population.	[redacted]
	Placebo	0	Not evaluable†								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Disease control rate (DCR) by BIRC	Cabozantinib		80% (67.8–88.7)	24.8%	4.7–44.9	N/A	OR: 3.27	1.28–8.34	N/A	The DCR was defined as the proportion of subjects with a BOR of CR, PR, or SD. The DCR estimate and 95% CI were determined similar to the methods used for ORR.	[redacted]
	Placebo		55% (36.0–72.7)								
Disease control rate (DCR) by Investigator	Cabozantinib		78% (66.0–87.5)	36.2%	16.1–56.3	N/A	OR: 4.90	1.94–12.37	N/A	The DCR was defined as the proportion of subjects with a BOR of CR, PR, or SD. The DCR estimate and 95% CI were determined similar to the methods used for ORR.	[redacted]
	Placebo		42% (24.5–60.9)								

Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour.

Note: *Confirmed ORR is defined as proportion of patients with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods. †No patients in the placebo arm had either a CR or PR as BOR, as such, KM estimates of DoR were not evaluable.

Table 68 Results per study (CABINET) – epNET cohort (ITT population), DCO 24th August 2023

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival (OS)	Cabozantinib	134	21.95 (18.60–30.19) months	2.24	-5.79 to 10.27	N/A	HR: 0.86	0.56–1.31	0.4871	The distribution of OS was estimated using the Kaplan-Meier method. The median OS, along with 95% CIs, were estimated for the 2 treatment arms. Additionally, the 12-, 24-, and 36-month OS rates, along with the 95% CIs, were estimated. The stratified Cox regression was used to estimate the HR of OS, along with the 95% CI. Stratification factors for epNET: 1. Concurrent Somatostatin Analogue Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs	[redacted]
	Placebo	69	19.71 (13.37–24.48) months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										Non-midgut GI/Lung/Other]. Stratification was per OPEN criteria.	
Median progression-free survival (PFS) by BICR	Cabozantinib	134	8.48 (7.46–12.45) months	4.50	1.67–7.33	N/A	HR: 0.38	0.25–0.58	< 0.0001	The hazard ratio (HR) for PFS was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided. Results from an unstratified analysis was also provided. Kaplan-Meier methodology was used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves were produced. Brookmeyer Crowley methodology was used to construct the 95% CI for	[redacted]
	Placebo	69	3.98 (3.02–5.68) months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										the median PFS for each treatment arm.	
Median progression-free survival (PFS) by Investigator	Cabozantinib	134	8.38 (5.98–11.07) months	5.13	2.31–7.95	N/A	HR: 0.41	0.28–0.60	<0.0001	The hazard ratio (HR) for PFS was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided. Results from an unstratified analysis was also provided. Kaplan-Meier methodology was used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves were produced. Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS for each treatment arm.	[redacted]
	Placebo	69	3.25 (2.99–5.42) months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Confirmed objective response rate (ORR [CR+PR]) * by BIRC	Cabozantinib	134	5.2% (2.1–10.5)	5.2%	1.5–9.0	0.0524	N/A	N/A	N/A	Point estimates of ORR with CIs were calculated using the Clopper Pearson method. The difference in ORR between the 2 treatment arms within each disease cohort and associated CIs were provided. The ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were performed. Analyses for imaging assessments evaluated per BIRC and	[redacted]
	Placebo	69	0.0% (0.0–5.2)								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										investigator were performed.	
Confirmed objective response rate (ORR [CR+PR]) * by Investigator	Cabozantinib	134	3.7% (1.2–8.5)	2.3%	-2.0 to 6.6	0.3652	OR: 2.71	0.30–24.41	N/A	Point estimates of ORR with CIs were calculated using the Clopper Pearson method. The difference in ORR between the 2 treatment arms within each disease cohort and associated CIs were provided. The ORR was compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) testing method primarily adjusting for the stratification factors. Sensitivity analyses using the unstratified 2-sample z-test and the Fisher's exact test were performed. Analyses for imaging assessments	[redacted]
	Placebo	69	1.4% (0.0–7.8)								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										evaluated per BIRC and investigator were performed.	
Duration of response (DOR) by BIRC	Cabozantinib	7	Median: 8.26 months (4.47–NE)	N/A	N/A	N/A	N/A	N/A	N/A	The DOR (the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1) was analysed using the Kaplan-Meier method for subjects with a response of CR or PR in the ITT population.	[redacted]
	Placebo	0	Not evaluable†								
Duration of response (DOR) by Investigator	Cabozantinib	5	Median: 10.74 months (5.32–NE)	N/A	N/A	N/A	N/A	N/A	N/A	The DOR (the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1) was analysed using the Kaplan-Meier method for subjects with a response of CR or PR in the ITT population.	[redacted]
	Placebo	1	5.59 months								

Results of CABINET (NCT03375320)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Disease control rate (DCR) by BIRC	Cabozantinib		70% (61.6–77.7)	16.5%	2.4–30.6	N/A	OR: 1.99	1.09–3.62	N/A	The DCR was defined as the proportion of subjects with a BOR of CR, PR, or SD. The DCR estimate and 95% CI were determined similar to the methods used for ORR.	[redacted]
	Placebo		54% (41.2–65.7)								
Disease control rate (DCR) by Investigator	Cabozantinib		65% (56.2–73.0)	24.3%	10.2–38.5	N/A	OR: 2.67	1.47–4.85	N/A	The DCR was defined as the proportion of subjects with a BOR of CR, PR, or SD. The DCR estimate and 95% CI were determined similar to the methods used for ORR.	[redacted]
	Placebo		41% (28.9–53.1)								

Abbreviations: Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Note: *Confirmed ORR is defined as proportion of patients with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods. †No patients in the placebo arm had either a CR or PR as BOR, as such, KM estimates of DoR were not evaluable.

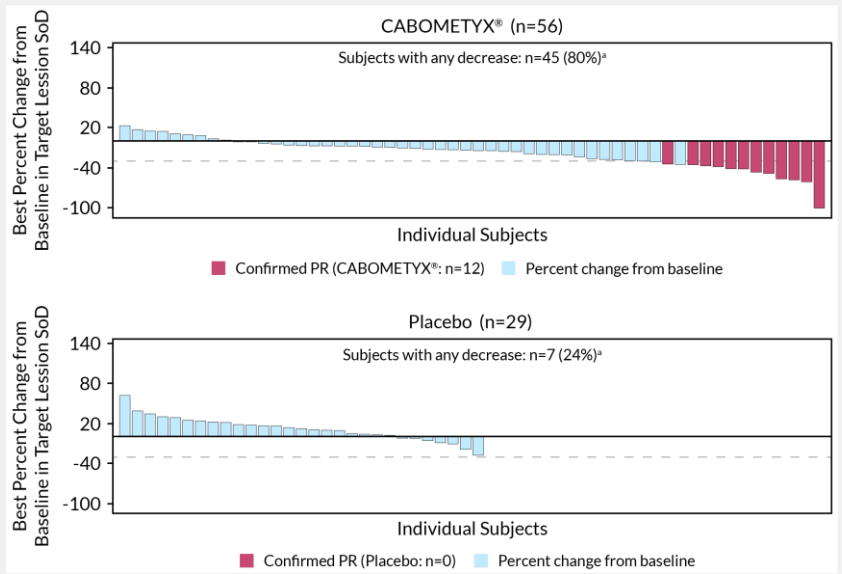
B.1 Objective response rate (ORR)

The secondary endpoint of BICR-assessed ORR per RECIST 1.1 showed a significant improvement with cabozantinib vs placebo (at a nominal significance level of 0.05) in the pNET cohort and a trend towards improvement with cabozantinib vs placebo in the epNET cohort [redacted].

In the pNET cohort, 19% of patients (n=12) in the cabozantinib arm had a confirmed PR, and no patients had a confirmed CR, giving a confirmed ORR of 19% (95% CI: 10.1%, 30.5%). In comparison, no patients in the placebo arm had either a CR or PR, giving an ORR of 0% (95% CI: 0%, 11.2%) (Table 69). These data yielded a confirmed ORR treatment difference of 18.8% (95% CI: 9.2%, 28.3%; with a p-value from the stratified Cochran–Mantel–Haenszel [CMH] test of 0.0115) (Table 69) [68]. The median time from randomisation to confirmed objective response was 5.78 months (range: 2.8–8.7) in the cabozantinib arm (n=12)[redacted].

The best percentage change in BICR-assessed tumour target lesion size from baseline is shown in Figure 34. The proportion of patients in the cabozantinib arm who had a post-baseline reduction in tumour target lesion size was higher than that observed in the placebo arm (80% vs 24%) [redacted].

Figure 34 Waterfall plot of best percentage change in tumour target lesion size from baseline by BICR (pNET cohort; ITT population)



Footnotes: DCO: 24th August 2023. The plot shows patients with at least one baseline and postbaseline assessment. Abbreviations: BICR, blinded independent central review; DCO, data cut-off; ITT, intent-to-treat; pNET, pancreatic neuroendocrine tumour; PR, partial response; SoD, sum of diameters. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

Table 69 ORR by BICR (pNET cohort; ITT population)

	Cabozantinib (n=64)	Placebo (n=31)

Subjects with measurable disease at baseline	64 (100%)	31 (100%)
Subjects with baseline and at least one post-baseline sum of diameters	56 (88%)	29 (94%)
Confirmed BOR[a]		
Confirmed CR	0	0
Confirmed PR	12 (19%)	0
Stable disease	39 (61 %)	17 (55%)
PD	5 (7.8%)	12 (39%)
Unable to evaluate	0	0
Missing	8 (13%)	2 (6.5%)
No qualifying post-baseline assessments on or before PFS censoring or event date[b]	8 (13%)	2 (6.5%)
Confirmed ORR (CR+PR), n(%)[c]	12 (19%)	0.0 (0.0%)
95% CI	(10.1%, 30.5%)	(0.0%, 11.2%)
Confirmed ORR treatment difference (95% CI)[d]	18.8% (9.2%, 28.3%)	
p-value from stratified CMH test	0.0115	

Footnotes: DCO: 24th August 2023.[a] Confirmed best overall response is derived based on RECIST 1.1. Only responses per the first radiographic documentation of disease progression, per RECIST 1.1 determined by BICR are considered. The protocol did not define a minimal interval between the initial response scan and confirmatory scan; for calculation purposes, a minimum of 28 days was used. [b] No qualifying post-baseline assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: AE (2 patients), other (death) (2 patients), withdrawal (2 patients), no study treatment given (1 patient), and first scheduled imaging time-point after the clinical cutoff date (1 patient). In the placebo arm: other (death) (1 patient) and withdrawal (1 patient). [c] Confirmed ORR is defined as proportion of patients with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods. [d] Using asymptotic confidence limits based on large number theorem. Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; DCO, data cut-off; ITT, intent-to-treat; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour; PR, partial response. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

In the epNET cohort, 5.2% of patients (n=7) in the cabozantinib arm had a confirmed partial response (PR), and no patients had a confirmed complete response (CR), giving a confirmed ORR of 5.2% (95% CI: 2.1%, 10.5%). In comparison, no patients in the placebo arm had either a CR or PR, giving an ORR of 0% (95% CI: 0%, 5.2%). These data yielded a confirmed ORR difference of 5.2% (95% CI: 1.5%, 9.0%; with a p-value from the stratified CMH test of 0.0524) (Table 70) [68]. The median time from randomisation to confirmed objective response was 5.5 months (range: 2.8–8.4 months) in the cabozantinib arm (n=7) [redacted].

The best percentage change in BICR-assessed tumour target lesion size from baseline is shown in Figure 35. The proportion of patients in the cabozantinib arm who had a post-baseline reduction in tumour size was higher than that observed in the placebo arm (68% vs 30%) [redacted].

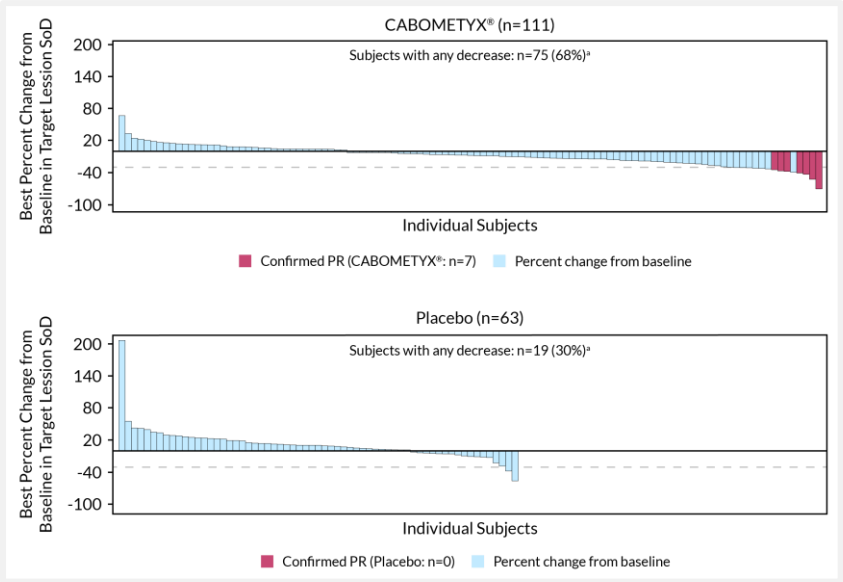
Table 70 ORR by BICR (epNET cohort; ITT population)

	Cabozantinib (n=134)	Placebo (n=69)
Subjects with measurable disease at baseline	133 (99%)	69 (100%)
Subjects with only non-target lesion at baseline	1 (0.7%)	0
Subjects with baseline and ≥1 post-baseline sum of diameters	111 (83 %)	63 (91 %)
Confirmed BOR[a]		
Confirmed CR	0	0
Confirmed PR	7 (5.2%)	0
Stable disease	87 (65%)	37 (54%)
PD	15 (11%)	24 (35%)
Unable to evaluate	0	1 (1.4%)
Missing	25 (19%)	7 (10%)
No qualifying post-baseline assessments on or before PFS censoring or event date[b]	23 (17%)	6 (8.7%)
SD or non-CR/non-PD not meeting minimum criteria (>42 days) from randomisation	2 (1.5%)	1 (1.4%)
Confirmed ORR (CR+PR), n(%)[c]	7 (5.2%)	0.0 (0.0%)
95% CI	(2.1%, 10.5%)	(0.0%, 5.2%)
Confirmed ORR treatment difference (95% CI)[d]	5.2% (1.5%, 9.0%)	
p-value from stratified CMH test	0.0524	

Footnotes: DCO: 24th August 2023.a Confirmed best overall response is derived based on RECIST 1.1. Only responses per the first radiographic documentation of disease progression, per RECIST 1.1 determined by BICR are considered. The protocol did not define a minimal interval between the initial response scan and confirmatory scan; for calculation purposes, a minimum of 28 days was used. b No qualifying post-baseline

assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: first scheduled imaging time-point after the clinical cutoff date (7 patients), AE (6 patients), death (4 patients), withdrawal (3 patients), no study treatment given (2 patients), and other complicating disease (1 patient). In the placebo arm: no study treatment given (2 patients), AE (1 patient), death (1 patient), first scheduled imaging time-point after the clinical cutoff date (1 patient), and other (death) (1 patient). c Confirmed ORR is defined as proportion of patients with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods. d Using asymptotic confidence limits based on large number theorem. Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour; ITT, intent-to-treat; ORR, objective response rate; PR, partial response. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

Figure 35 Waterfall plot of best percentage change in tumour target lesion size from baseline by BICR (epNET cohort; ITT population)



Footnotes: DCO: 24th August 2023. aThe plot shows patients with at least one baseline and postbaseline assessment. Abbreviations: BICR, blinded independent central review; DCO, data cut-off; epNET, extra-pancreatic neuroendocrine tumour; ITT, intent-to-treat; SoD, sum of diameters. Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

Appendix C. Comparative analysis of efficacy (N/A)

Table 71 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		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

Table 72 presents the selected parametric distributions chosen for the extrapolation of PFS, OS and TTD for pNET, epNET, and lung NET. In CABINET, patients randomised to placebo were allowed to crossover to cabozantinib upon progression. Thus, crossover-adjusted HRs were applied to the extrapolated Cabometyx® arm to estimate OS of BSC (see section D.2.9. for a detailed description).

Table 72 Extrapolations of PFS, OS and TTD

	Cabometyx	BSC
pNET		
OS	Exponential	Exponential (HR)
PFS	Lognormal	Lognormal
TTD	Exponential	Gamma
epNET		
OS	Exponential	Exponential (HR)
PFS	Lognormal	Lognormal
TTD	Exponential	Log-logistic
Lung NET		
OS	Weibull	Weibull (HR)
PFS	Lognormal	Lognormal
TTD	Exponential	Gamma

Parametric extrapolations were fitted independently for Cabometyx® and BSC for PFS, OS and TTD for pNET, epNET and lung NET. All standard parametric models (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic, and generalised gamma) were considered. Model fit was assessed visually, statistically, and clinically. The basis of model selection is presented in the following sections.

D.1 Extrapolation of progression-free survival

D.1.1 Data input

PFS was the primary endpoint of the CABINET trial [68]. PFS was extrapolated for each of the subgroups of interest (pNET, epNET and lung NET) using patient-level data from the trial's latest data cut-off (24 August 2023).

D.1.2 Model

All survival analyses within this application were performed following the framework of standardised survival models. Seven standard parametric distributions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalised gamma (see Table 73).

Table 73 Parametric survival functions used 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 hazards assumption was assessed to determine whether independent parametric models should be fitted for each treatment arm within the pNET, epNET and lung NET cohorts separately, or if a joint parametric model could be used. The proportional hazard assumption for PFS was evaluated using log cumulative hazard plots, Schoenfeld residual plots, and hypothesis tests for each treatment arm for both epNET and pNET.

The log-cumulative hazard plot for epNET (Figure 36) suggested a potential violation of the proportional hazard assumption, as the hazards for cabozantinib and BSC diverge and are not fully parallel. The potential violation of the proportional hazard assumption

was further supported by the Schoenfeld residual plot (Figure 39), which presents a fluctuating smoothed estimate of the log hazard ratio, with wide confidence intervals indicating uncertainty. In addition, the residuals indicated a non-random pattern, suggesting that PFS changes over time. However, the Schoenfeld tests (also displayed in Figure 39) had a p-value higher than 0.1, suggesting that the evidence may not be strong enough to reject the null hypothesis of proportional hazards. Despite that, parametric distributions for PFS for epNET were fitted separately for cabozantinib and BSC arms, so that the assumption of proportional hazards was not required.

The log-cumulative hazard plot for pNET (Figure 37) also suggested a violation of the proportional assumption, as the hazards for cabozantinib and BSC diverge and are not fully parallel. In addition, the Schoenfeld residual plot in Figure 40 did not show compelling evidence of proportional hazards violation, as it showed a varying estimate of the log hazard ratio with wide confidence intervals and residuals indicating a non-random pattern. However, as for the epNET cohort, the Schoenfeld test (Figure 40), had a p-value higher than 0.1, suggesting that the null hypothesis of proportional hazard may not hold. However, parametric distributions for PFS for pNET were fitted separately for Cabometyx® and BSC arms, and the assumptions of proportional hazards were not required.

The log-cumulative hazard plot for lung NET (Figure 38) also suggested a violation of the proportional assumption, as the hazards for Cabometyx ® and BSC are not fully parallel. However, the Schoenfeld residual plot (Figure 41) indicate that the hazard ratio between Cabometyx ® and BSC may be proportional, since the smooth curve of the Schoenfeld residuals is relatively flat. The p-value of the Schoenfeld test of 0.7021, indicates that the null hypothesis of the proportional hazard may not be rejected. The parametric distributions for PFS for lung NET were fitted separately for cabozantinib and BSC arms, and the assumption of proportional hazards was not required.

Figure 36 PFS epNET: log cumulative hazard plot (ITT Analysis)

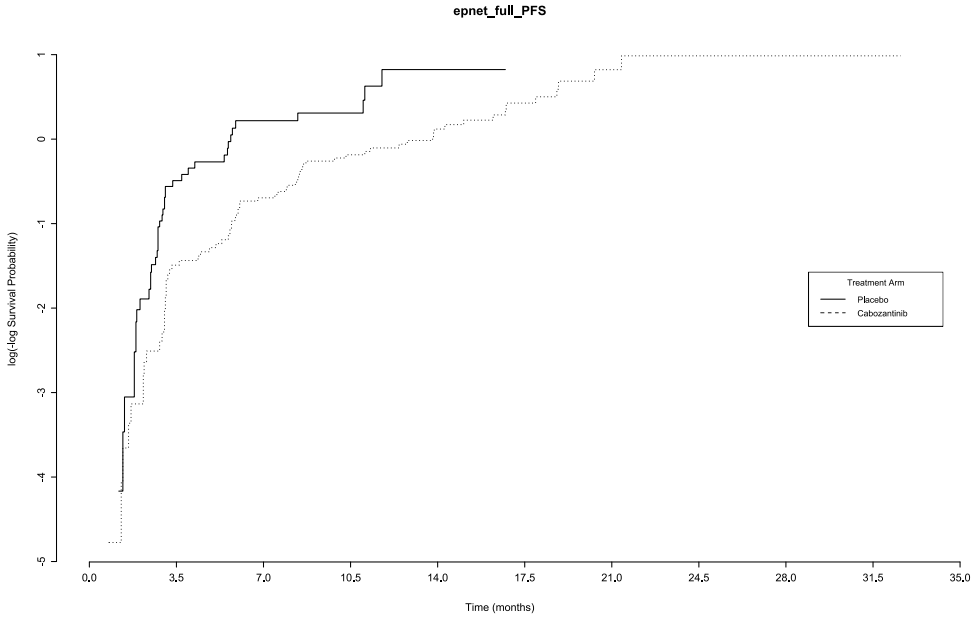


Figure 37 PFS pNET: log cumulative hazard plot (ITT Analysis)

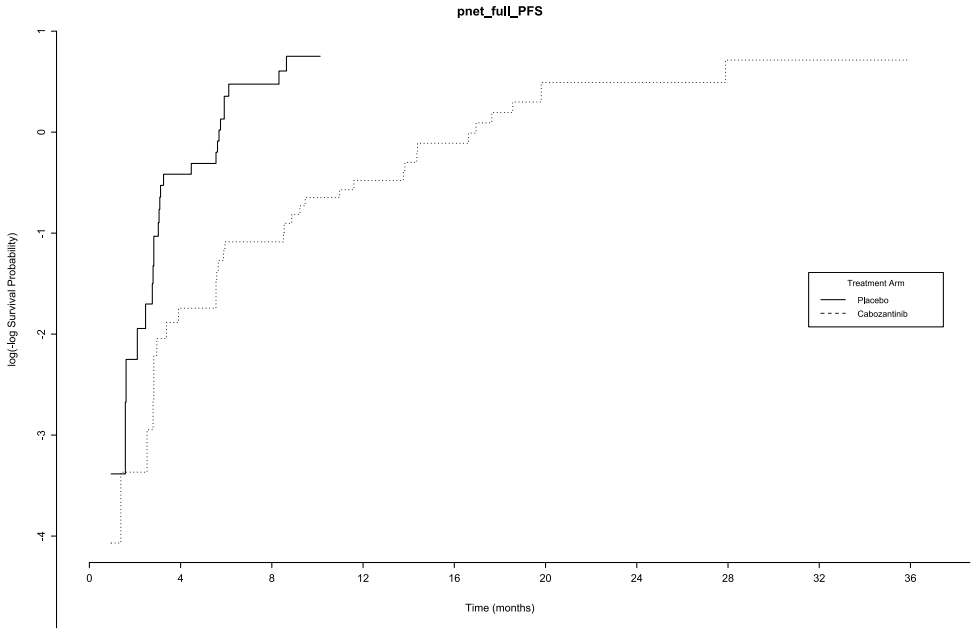


Figure 38 PFS lung NET: log cumulative hazard plot (ITT Analysis)

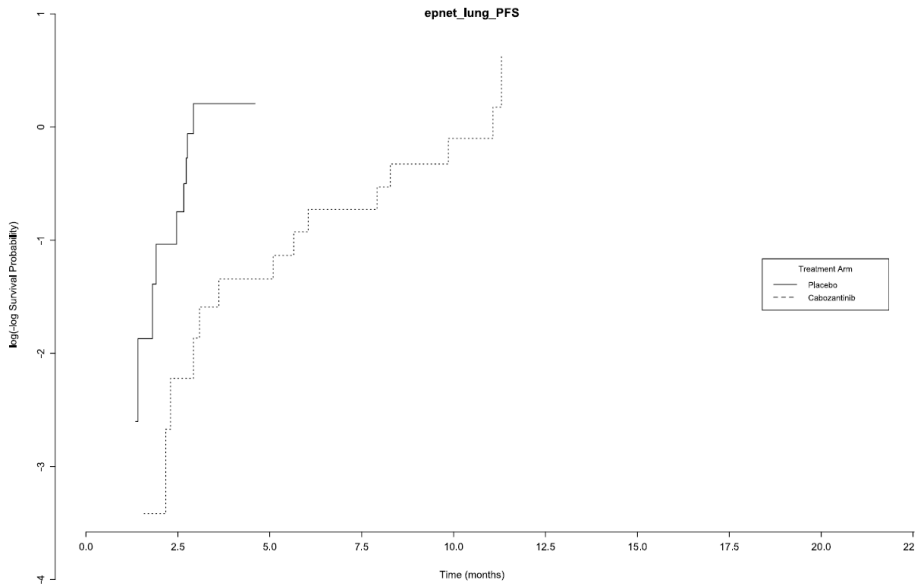


Figure 39 PFS epNET: Schoenfeld residual plot (ITT Analysis)

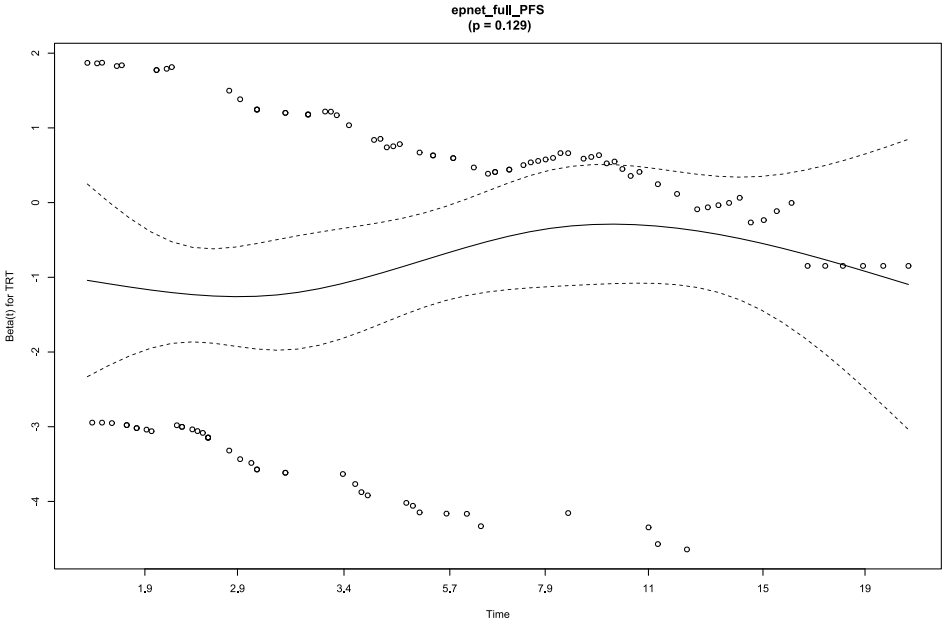


Figure 40 PFS pNET: Schoenfeld residual plot (ITT Analysis)

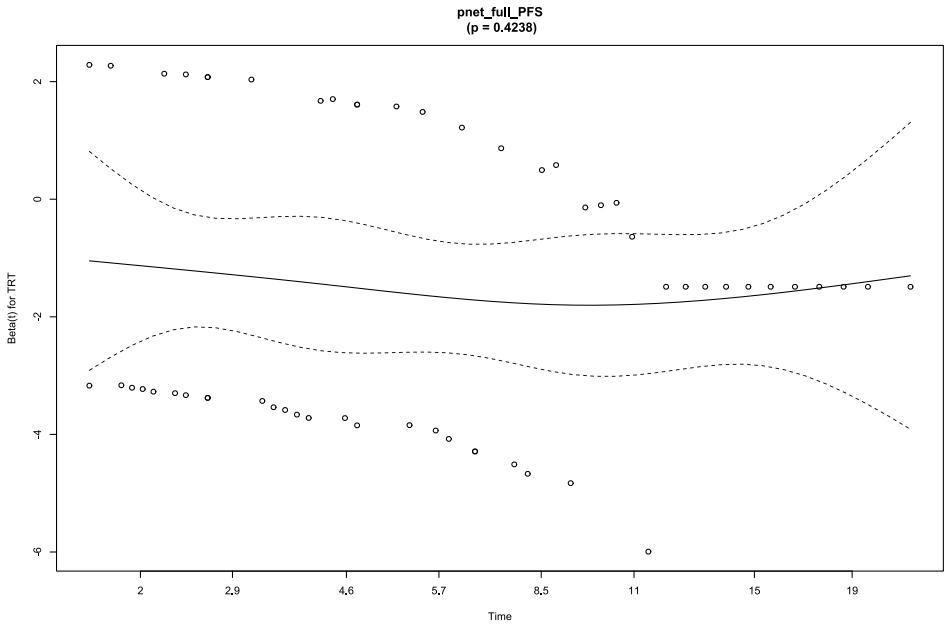
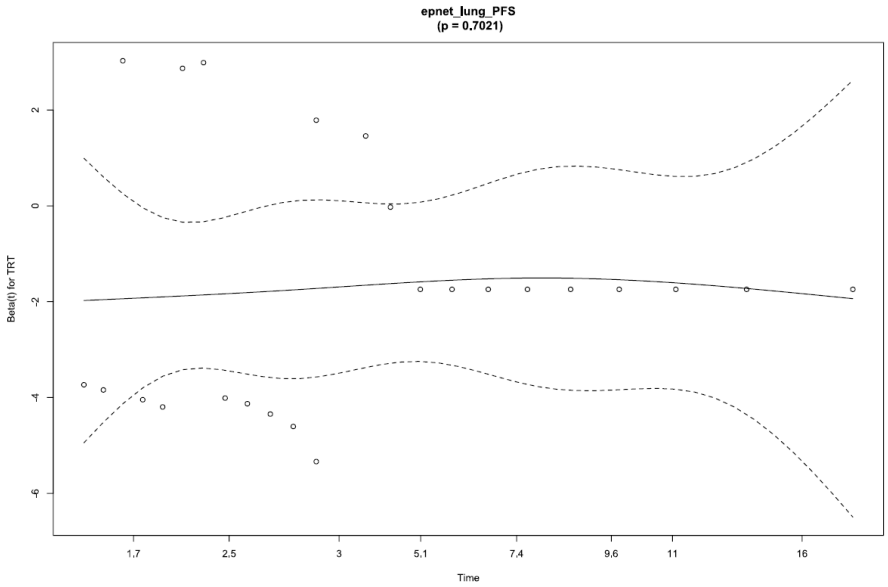


Figure 41 PFS lung NET: Schoenfeld residual plot (ITT Analysis)



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

Statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), for epNET, pNET and lung NET in both treatment arms. Lower values of AIC and BIC indicate better model performance while balancing goodness-of-fit and simplicity, penalizing excessive complexity to prevent overfitting. BIC applies a stronger penalty than AIC. To compare the different parametric distributions, delta values (ΔAIC and ΔBIC) were calculated as the difference between each model's AIC/BIC and the model with the lowest AIC/BIC observed. Models were ranked based on these deltas, and to provide an evaluation of model fit. Landmark PFS, estimated together with the estimated mean and median PFS, are presented for epNET, pNET and lung NET in this section.

Table 74 presents the statistical evaluation metrics for epNET in the Cabometyx® arm.

The statistically best-fitting distribution for epNET in the Cabometyx® arm was lognormal, which was the chosen parametric model for the base case for epNET in the Cabometyx® arm.

Table 74 Evaluation of statistical fit PFS epNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)
Exponential	509.111	512.008	15.54	12.64	40%	16%	6%	1%	0%	0%	0%	0%	9.20	13.09
Weibull	498.022	503.817	4.45	4.45	39%	8%	1%	0%	0%	0%	0%	0%	10.12	11.25
Lognormal	**493.572**	**499.367**	**0.00**	**0.00**	**36%**	**13%**	**6%**	**2%**	**0%**	**0%**	**0%**	**0%**	**9.20**	**12.95**
Log-logistic	495.671	501.466	2.10	2.10	36%	13%	6%	2%	1%	0%	0%	0%	9.20	14.22
Gamma	495.786	501.582	2.21	2.21	37%	8%	2%	0%	0%	0%	0%	0%	10.12	11.33

Gompertz	505.509	511.305	11.94	11.94	41%	8%	6%	0%	0%	0%	0%	0%	10.12	11.29
Generalised Gamma	495.441	504.134	1.87	4.77	36%	12%	5%	1%	0%	0%	0%	0%	9.20	12.44

Table 75 presents the statistical evaluation metrics for epNET in the BSC arm. The statistically best-fitting distributions in the BSC arm were generalised gamma, followed by lognormal. The lognormal distribution showed a similar statistical fit as generalised gamma, with a Δmin AIC at 4.64 and Δmin BIC at 2.41 [92], which supported that the lognormal distribution, which was the chosen parametric distribution had a good statistical fit.

Table 75 Evaluation of statistical PFS fit epNET BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)
Exponential	236.638	238.872	25.05	20.58	18%	3%	1%	0%	0%	0%	0%	0%	5.52	6.92
Weibull	229.402	233.870	17.81	15.58	9%	0%	0%	0%	0%	0%	0%	0%	5.52	5.90
Lognormal	216.229	220.698	4.64	2.41	9%	1%	0%	0%	0%	0%	0%	0%	4.60	5.88
Log-logistic	217.980	222.448	6.39	4.16	8%	2%	1%	0%	0%	0%	0%	0%	4.60	5.88
Gamma	224.705	229.173	13.12	10.88	7%	0%	0%	0%	0%	0%	0%	0%	5.52	5.74
Gompertz	237.250	241.718	25.66	23.43	13%	0%	0%	0%	0%	0%	0%	0%	5.52	6.19

Generalised Gamma	**211.590**	**218.292**	**0.00**	**0.00**	**15%**	**6%**	**4%**	**2%**	**1%**	**1%**	**0%**	**0%**	**4.60**	**10.00**

Table 76 presents the statistical evaluation metrics for pNET in the cabozantinib arm. The lognormal distribution had the best statistical fit according to both AIC and BIC, which supports the choice of lognormal for the base case.

Table 76 Evaluation of statistical fit PFS pNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)
Exponential	252.159	254.318	3.058	0.899	52%	27%	14%	4%	0%	0%	0%	0%	12.88	18.34
Weibull	249.950	254.268	0.849	0.849	54%	21%	6%	0%	0%	0%	0%	0%	13.80	15.60
Lognormal	**249.101**	**253.419**	**0.00**	**0.00**	**50%**	**24%**	**14%**	**5%**	**1%**	**0%**	**0%**	**0%**	**12.88**	**19.68**
Log-logistic	249.288	253.606	0.187	0.187	51%	23%	13%	6%	2%	1%	0%	0%	12.88	21.40
Gamma	249.308	253.626	0.21	0.21	49%	21%	7%	1%	0%	0%	0%	0%	12.88	15.82
Gompertz	252.528	256.846	3.427	3.427	54%	23%	6%	0%	0%	0%	0%	0%	13.80	15.62
Generalised Gamma	250.743	257.220	1.642	3.801	51%	23%	11%	3%	0%	0%	0%	0%	12.88	17.25

Table 77 presents the statistical evaluation metrics for pNET in the placebo arm. The lognormal distribution showed the best statistical fit according to both AIC and BIC, which supports the choice of lognormal for the base case.

Table 77 Evaluation of statistical fit PFS pNET BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)
Exponential	137.723	139.157	10.86	9.42	12%	1%	0%	0%	0%	0%	0%	0%	4.60	5.57
Weibull	129.241	132.109	2.37	2.37	2%	0%	0%	0%	0%	0%	0%	0%	5.51	5.09
Lognormal	**126.867**	**129.735**	**0.00**	**0.00**	**6%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**4.60**	**5.26**
Log-logistic	127.577	130.445	0.71	0.71	6%	1%	0%	0%	0%	0%	0%	0%	4.60	5.46
Gamma	127.744	130.612	0.88	0.88	3%	0%	0%	0%	0%	0%	0%	0%	4.60	5.09
Gompertz	133.394	136.262	6.53	6.53	2%	0%	0%	0%	0%	0%	0%	0%	5.52	5.03
Generalised Gamma	128.866	133.168	2.00	3.43	5%	0%	0%	0%	0%	0%	0%	0%	4.60	5.25

Table 78 presents the statistical evaluation metrics for lung NET in the Cabometyx® arm. Gamma showed the best statistical fit followed by lognormal, who had a similar statistical fit with Δmin AIC and Δmin BIC of 0.05 [92]. This supports that the lognormal, which was the chosen parametric distribution for the base case, had a good statistical fit.

Table 78 Evaluation of statistical fit PFS lung NET Cabometyx

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)
Exponential	107.177	108.674	4.84	3.35	38%	14%	5%	1%	0%	0%	0%	0%	9.20	12.26
Weibull	102.670	105.663	0.34	0.34	28%	1%	0%	0%	0%	0%	0%	0%	9.20	9.29
Lognormal	102.387	105.380	0.05	0.05	29%	7%	2%	0%	0%	0%	0%	0%	8.28	10.42
Log-logistic	103.242	106.235	0.91	0.91	29%	8%	3%	1%	0%	0%	0%	0%	8.28	11.33
Gamma	**102.333**	**105.326**	**0.00**	**0.00**	**27%**	**3%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**8.28**	**9.41**
Gompertz	104.698	107.691	2.37	2.37	33%	0%	0%	0%	0%	0%	0%	0%	9.20	9.39
Generalised Gamma	104.248	108.738	1.92	3.41	28%	4%	1%	0%	0%	0%	0%	0%	8.28	9.70

Table 79 presents the statistical evaluation metrics for lung NET in the placebo arm. The lognormal distribution showed the best statistical fit, which supported the choice of the lognormal distribution for the base case.

Table 79 Evaluation of statistical fit PFS lung NET BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median PFS (months)	Mean PFS (months)

Exponential	44.792	45.565	8.41	7.64	5%	0%	0%	0%	0%	0%	0%	0%	2.76	3.98
Weibull	38.514	40.059	2.13	2.13	0%	0%	0%	0%	0%	0%	0%	0%	3.68	2.92
Lognormal	**36.385**	**37.930**	**0.00**	**0.00**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**2.76**	**3.02**
Log-logistic	36.646	38.192	0.26	0.26	0%	0%	0%	0%	0%	0%	0%	0%	2.76	3.03
Gamma	37.116	38.661	0.73	0.73	0%	0%	0%	0%	0%	0%	0%	0%	3.68	2.95
Gompertz	41.408	42.954	5.02	5.02	0%	0%	0%	0%	0%	0%	0%	0%	3.68	2.85
Generalised Gamma	37.463	39.781	1.08	1.85	4%	1%	1%	0%	0%	0%	0%	0%	2.76	4.06

D.1.5 Evaluation of visual fit

The figures below show the parametric distributions together with the Kaplan-Meier estimate for pNET, epNET and lung NET separately for the Cabometyx® and BSC arm. The figures show that the selected parametric distribution for PFS (lognormal in all populations and treatment arms) has good visual fit to the Kaplan-Meier estimates.

Figure 42 PFS epNET PFS Cabometyx Fitted parametric distributions and Kaplan-Meier estimate

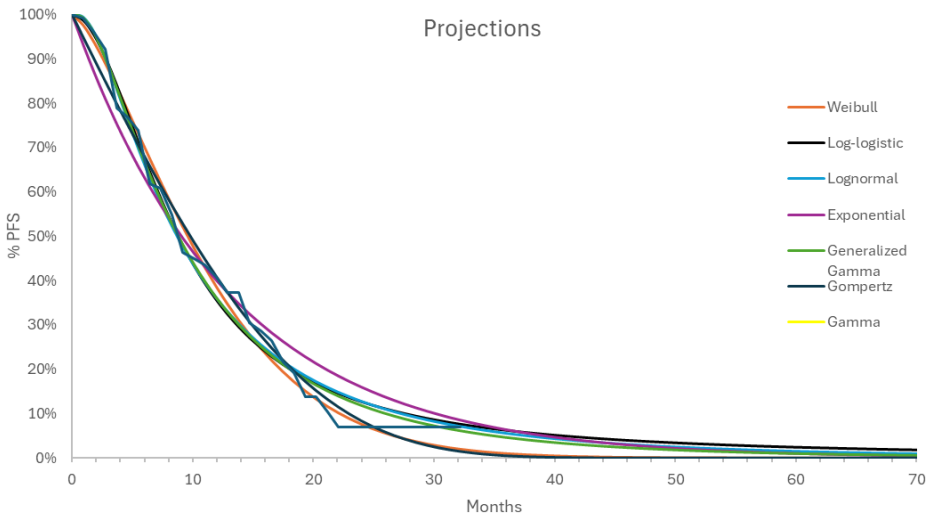


Figure 43 epNET BSC Fitted parametric distributions and Kaplan-Meier estimate

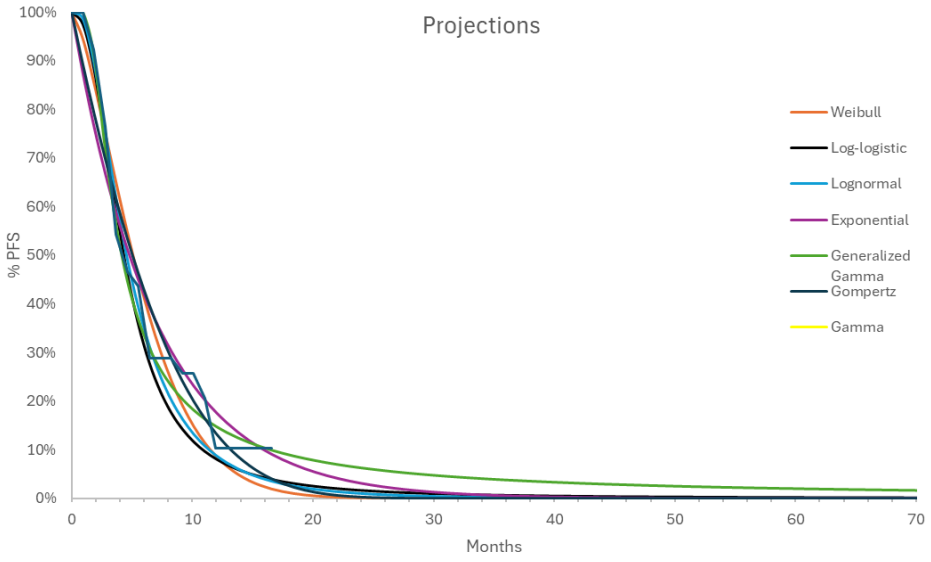


Figure 44 PFS pNET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

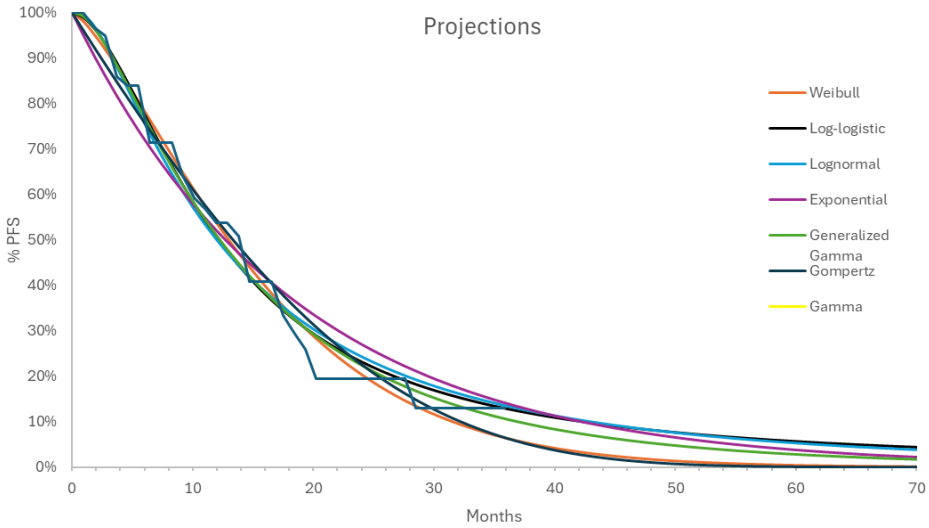


Figure 45 PFS pNET BSC Fitted parametric distributions and Kaplan-Meier estimate

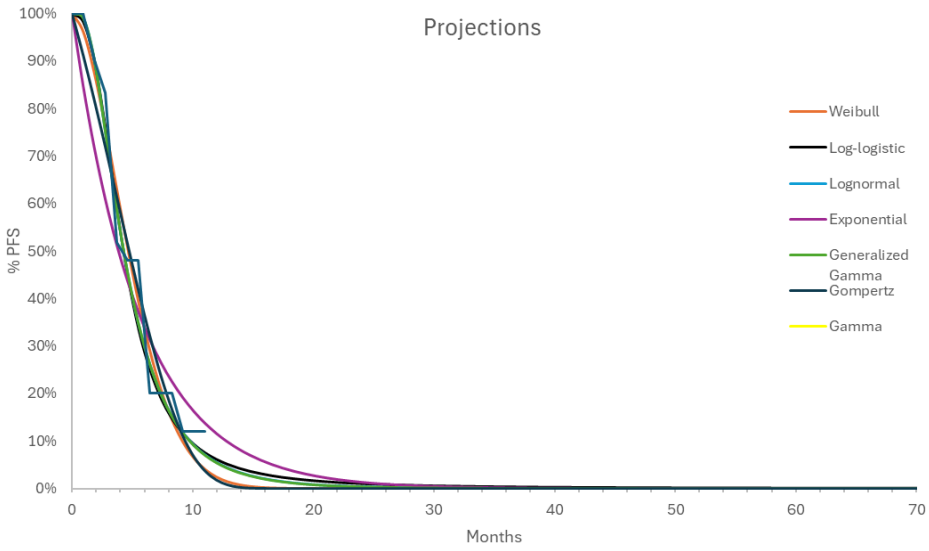


Figure 46 PFS lung NET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

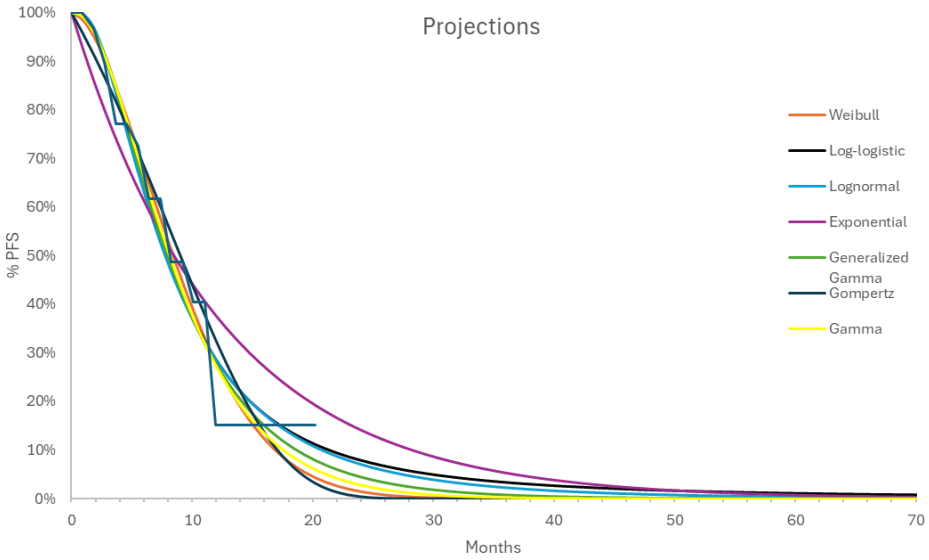
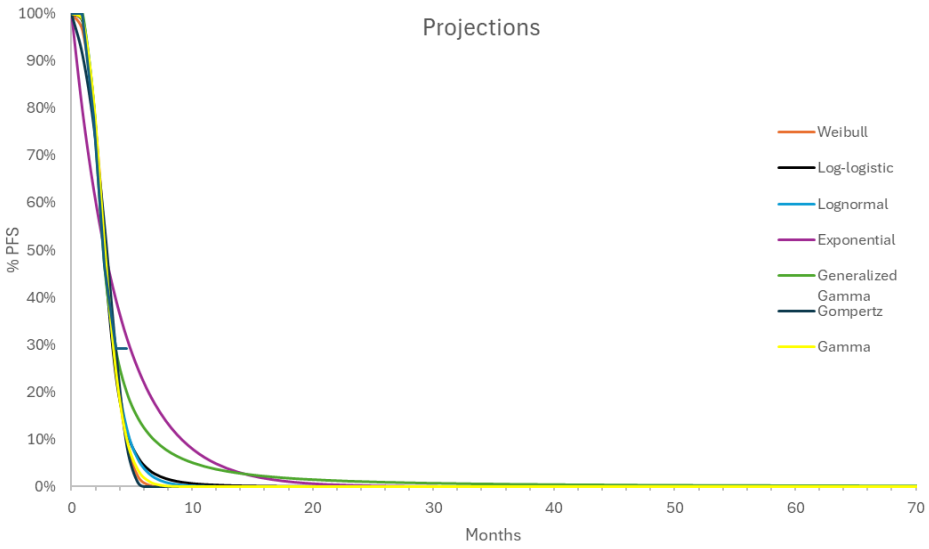


Figure 47 PFS lung NET BSC Fitted parametric distributions and Kaplan-Meier estimate



D.1.6 Evaluation of hazard functions

Figure 48, Figure 49 and Figure 50 show the smoothed hazard plots for epNET, pNET and lung NET for each treatment arm, respectively. An increasing trend indicates that the risk of a PFS event is increasing with time, while a decreasing trend suggests that the risk of a PFS event decreases with time.

For the extrapolation of Cabometyx®, the lognormal distribution was chosen for all subgroups. In all subgroups, the smoothed hazards showed an increasing trend, which can be captured by a parametric model such as the lognormal.

The smoothed hazard plot for BSC in the epNET cohort group shows a trend that initially increases and then, at approximately month five, starts to decrease. The lognormal distribution was deemed appropriate to capture such a trend accurately. The trend for BSC in the pNET cohort shows a steadily increase with time, and for BSC in the lung NET cohort, the trend initially increases and stabilises at approximately month three. The lognormal distribution is a non-monotonic distribution that could capture trends like this.

Figure 48 PFS epNET: Smoothed hazard plots (ITT Analysis)

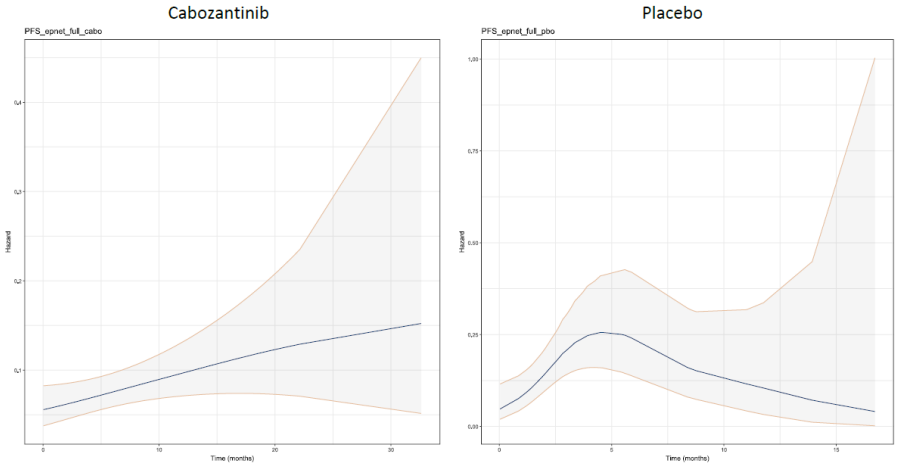


Figure 49 PFS pNET: Smoothed hazard plots (ITT Analysis)

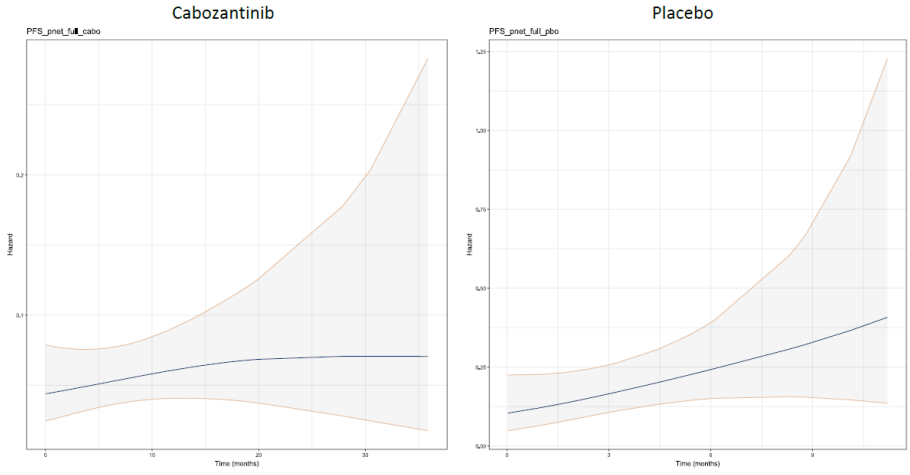
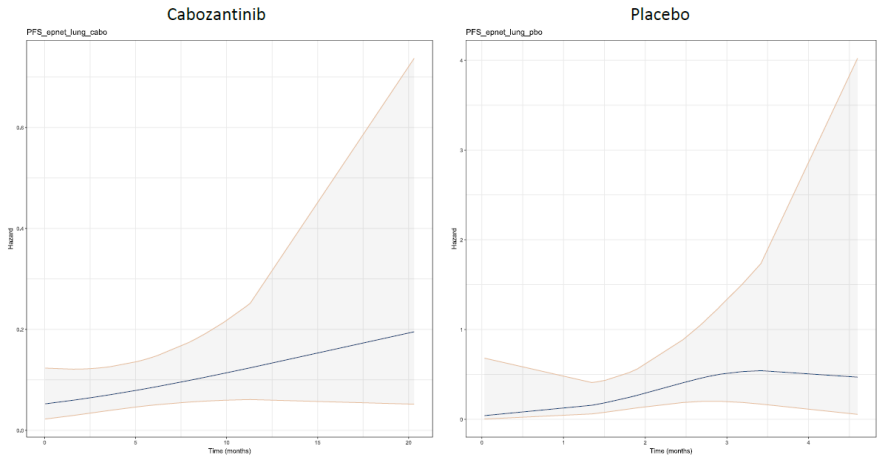


Figure 50 PFS lung NET: Smoothed hazard plots (ITT Analysis)



D.1.7 Validation and discussion of extrapolated curves

See section 8.1.1.

D.1.8 Adjustment of background mortality

In the model, PFS was capped by OS, meaning that PFS could not exceed OS. OS was capped by Danish general population mortality rates to ensure that modelled survival did not exceed that of the general population

D.1.9 Adjustment for treatment switching/cross-over

In the CABINET trial, cross-over was only permitted after confirmation of progressive disease by central radiology review. Thus, cross-over adjustment was not applicable for PFS.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of overall survival

D.2.1 Data input

OS for Cabometyx® was extrapolated using patient-level data from CABINET's latest data-cut off (24 August 2023).

D.2.2 Model

See D.1.2.

D.2.3 Proportional hazards

In the epNET cohort, the curves in the log cumulative hazard plot (Figure 51) are closely aligned and although roughly parallel, the figure showed some violation against the proportional hazard assumption with crossing lines at several time points, indicating that the effect may not be constant. However, in the CABINET trial patients, randomised to placebo were allowed to switch over to cabozantinib upon progression, which is not considered in the ITT analysis from which the log-cumulative hazards plots are estimated.

The Schoenfeld residual plot (Figure 52) supports the assumption of a proportional hazard since the smoothed curve of the Schoenfeld residuals is relatively flat over the time horizon. In addition, the p-value of 0.9472 indicates that there may not be enough evidence to reject the null hypothesis of proportional hazards. Thus, it was deemed appropriate to model BSC extrapolations by applying HRs obtained from the crossover-adjusted analyses.

Figure 51 OS epNET cohort: log cumulative hazard plot (ITT Analysis)

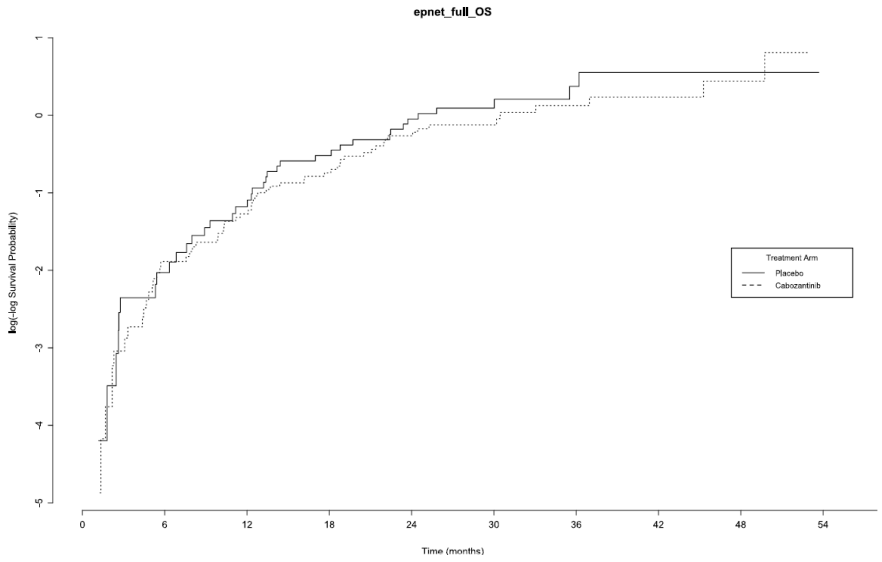
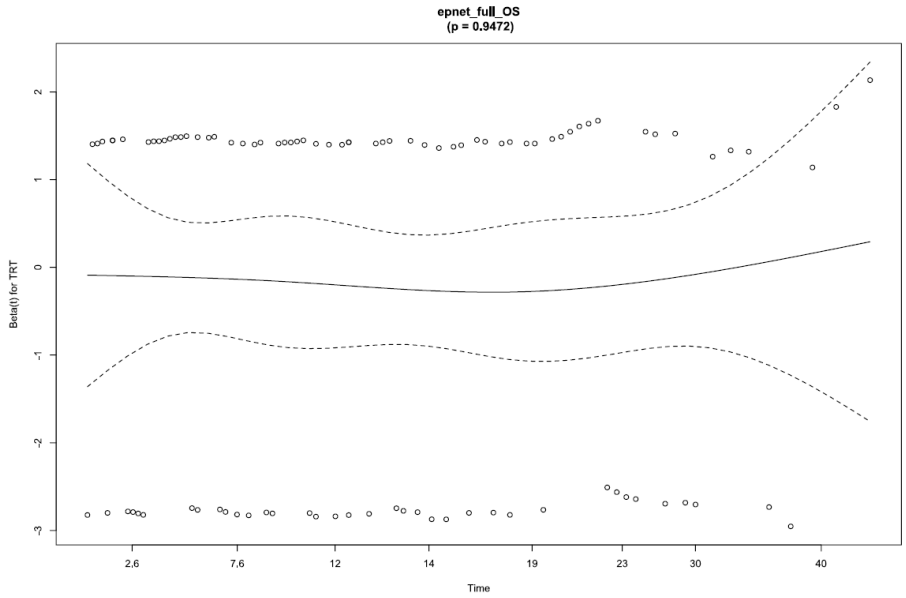


Figure 52 OS epNET cohort: Schoenfeld residual plot (ITT Analysis)



In the pNET cohort, the log cumulative hazard plot (Figure 53) showed some violation against the proportional hazard assumption with crossing lines at several time points, indicating that the effect may not be constant. However, the Schoenfeld test gave a p-value of 0.6717, indicating that there is not enough evidence to reject the null hypothesis of proportional hazards. Thus, it was deemed justified to model BSC extrapolations by applying HRs obtained from the crossover-adjusted analyses.

Figure 53 OS pNET cohort: log cumulative hazard plot (ITT Analysis)

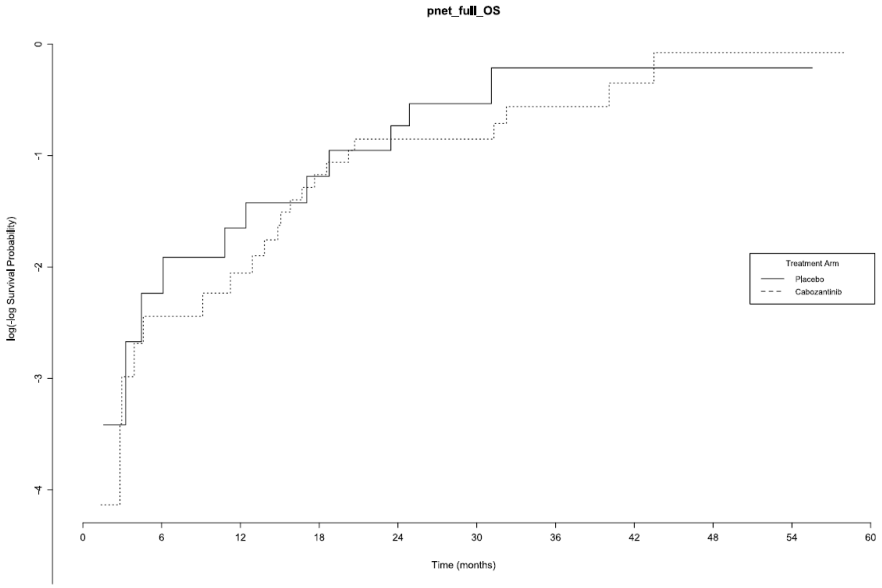
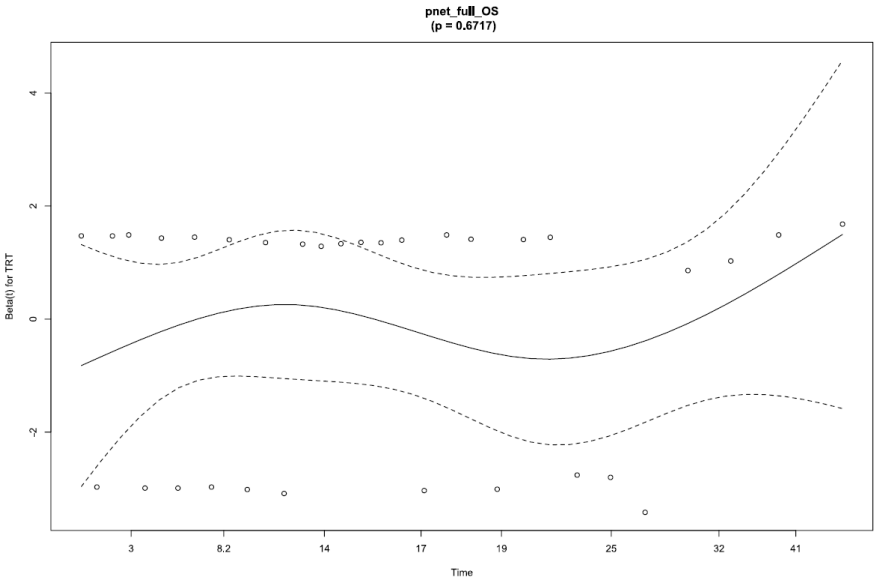


Figure 54 OS pNET cohort: Schoenfeld residual plot (ITT Analysis)



In the lung NET cohort, the log cumulative hazard plot shows a parallel trend after approximately 2.5 months, supporting the assumption of proportional hazards. In addition, the Schoenfeld test gave a p-value of 0.3218, suggesting that the null hypothesis of proportional hazard cannot be rejected. Thus, it was deemed appropriate to model BSC extrapolations by applying HRs obtained from the crossover-adjusted analyses.

Figure 55 OS lung NET subgroup: log cumulative hazard plot (ITT Analysis)

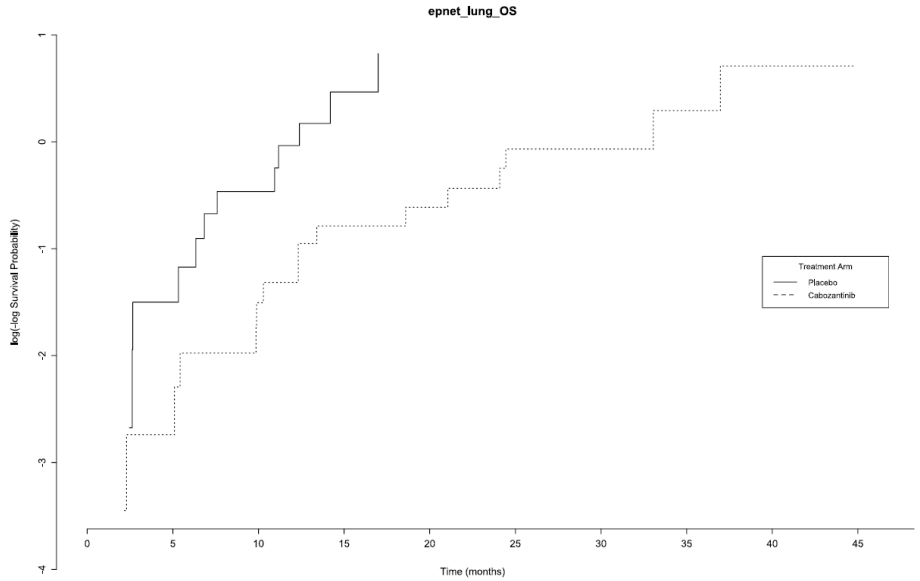
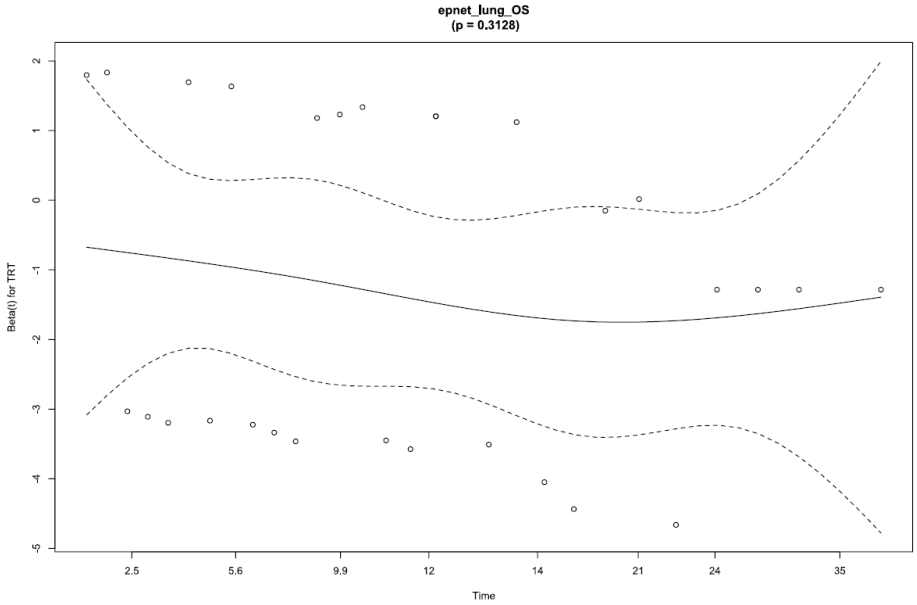


Figure 56 OS lung NET subgroup : Schoenfeld residual plot (ITT Analysis)



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

Table 80 presents the statistical evaluation metrics for epNET in the cabozantinib arm. The gamma distribution had the best statistical fit according to both AIC and BIC, however, the exponential distribution which was chosen for the extrapolation of Cabometyx® showed a similar statistical fit with Δmin AIC and Δmin BIC values below 5.

Table 80 Evaluation of statistical fit OS epNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median OS (months)	Mean OS (months)
Exponential	545.829	548.727	4.14	1.25	70%	50%	35%	17%	3%	1%	0%	0%	23.00	34.65
Weibull	542.227	548.023	0.54	0.54	74%	49%	29%	9%	0%	0%	0%	0%	23.00	28.87
Log-normal	542.631	548.426	0.95	0.95	71%	48%	34%	19%	7%	3%	1%	0%	22.08	41.33
Log-logistic	542.126	547.921	0.44	0.44	73%	47%	32%	17%	6%	3%	1%	1%	22.08	40.85
Gamma	**541.685**	**547.481**	**0.00**	**0.00**	**74%**	**48%**	**30%**	**11%**	**1%**	**0%**	**0%**	**0%**	**22.08**	**41.36**
Gompertz	545.056	550.852	3.37	3.37	74%	50%	31%	8%	0%	0%	0%	0%	23.92	28.01
Generalised Gamma	543.299	551.992	1.61	4.51	73%	48%	31%	14%	2%	0%	0%	0%	22.08	32.18

Table 81 presents the statistical evaluation metrics for pNET in the Cabometyx ® arm. The exponential distribution had the best fit according to AIC and BIC, supporting its selection for OS extrapolation

Table 81 Evaluation of statistical fit OS pNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median OS (months)	Mean OS (months)
Exponential	**216.355**	**218.513**	**0.00**	**0.00**	**82%**	**67%**	**55%**	**37%**	**14%**	**5%**	**0%**	**0%**	**41.40**	**60.98**
Weibull	217.104	221.422	0.75	2.91	85%	68%	53%	30%	6%	1%	0%	0%	37.72	48.57
Lognormal	217.706	222.024	1.35	3.51	83%	66%	55%	40%	21%	14%	5%	3%	41.40	82.22
Log-logistic	217.204	221.522	0.85	3.01	84%	67%	53%	36%	17%	10%	4%	3%	38.64	72.97
Gamma	217.062	221.380	0.71	2.87	85%	68%	53%	28%	8%	2%	0%	0%	37.72	50.90
Gompertz	217.598	221.916	1.24	3.40	84%	69%	54%	28%	1%	0%	0%	0%	38.64	43.55
Generalised Gamma	219.050	225.526	2.70	7.01	85%	67%	53%	32%	9%	3%	0%	0%	38.64	53.52

Table 82 presents the statistical evaluation metrics for lung NET in the Cabometyx® arm. The Weibull distribution showed the best statistical fit according to AIC, and the exponential distribution showed the best statistical fit according to BIC. The Weibull distribution also showed the best overall statistical fit with a lower Δmin BIC value than the exponential Δmin AIC value. This supports the choice of the Weibull distribution for the extrapolation of OS.

Table 82 Evaluation of statistical fit OS lung NET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median OS (months)	Mean OS (months)
Exponential	145.147	146.643	1.12	0.00	69%	48%	33%	16%	2%	0%	0%	0%	22.08	32.17
Weibull	**144.025**	**147.018**	**0.00**	**0.37**	**75%**	**45%**	**24%**	**5%**	**0%**	**0%**	**0%**	**0%**	**21.16**	**25.90**
Log-normal	145.144	148.138	1.12	1.49	71%	45%	30%	15%	4%	2%	0%	0%	21.16	35.38
Log-logistic	144.767	147.760	0.74	1.12	74%	45%	28%	14%	4%	2%	1%	0%	21.16	35.74
Gamma	144.087	147.080	0.06	0.44	74%	45%	25%	7%	0%	0%	0%	0%	21.16	26.96
Gompertz	144.666	147.659	0.64	1.02	75%	48%	23%	1%	0%	0%	0%	0%	22.08	24.80
Generalised Gamma	146.025	150.515	2.00	3.87	75%	45%	24%	5%	0%	0%	0%	0%	21.16	25.90

D.2.5 Evaluation of visual fit

The figures below show the parametric distributions together with the Kaplan-Meier estimate for pNET, epNET and lung NET separately for the Cabometyx®. The figures show that the selected parametric distribution for OS (exponential for pNET and epNET, and Weibull for lung NET has a good visual fit to the Kaplan-Meier estimates.

Figure 57 OS pNET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

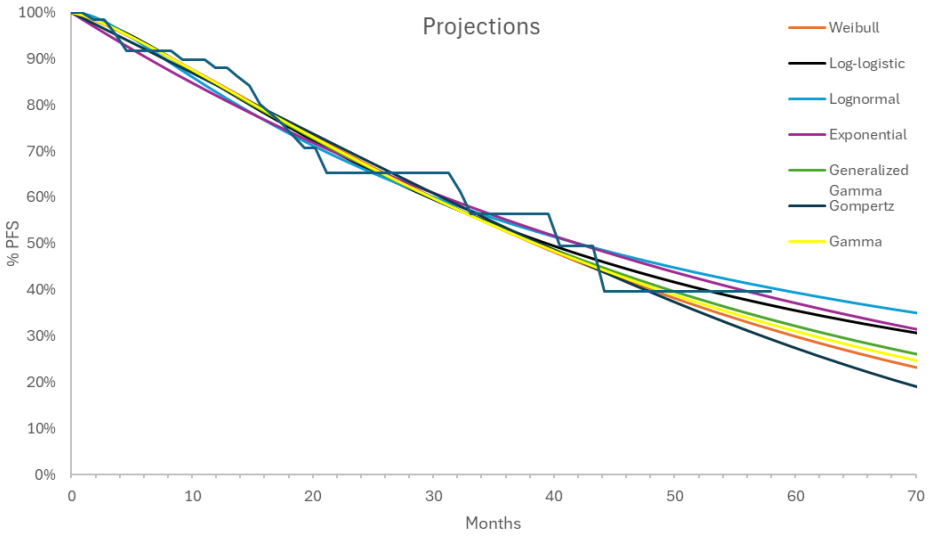


Figure 58 OS epNET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

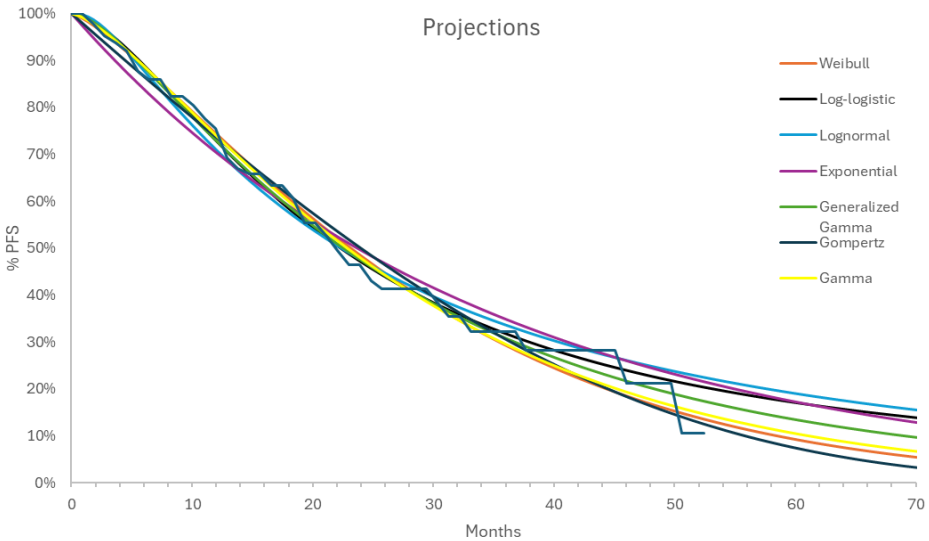
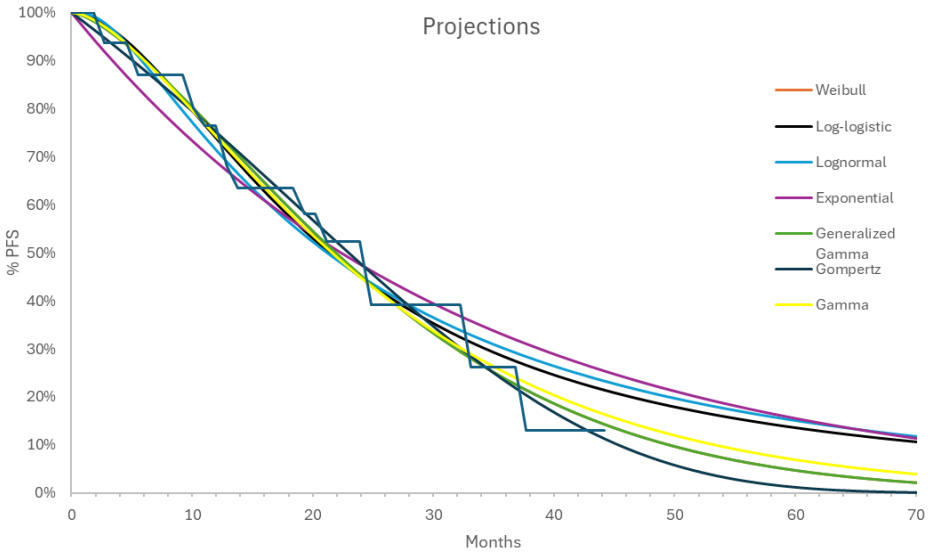


Figure 59 OS lung NET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

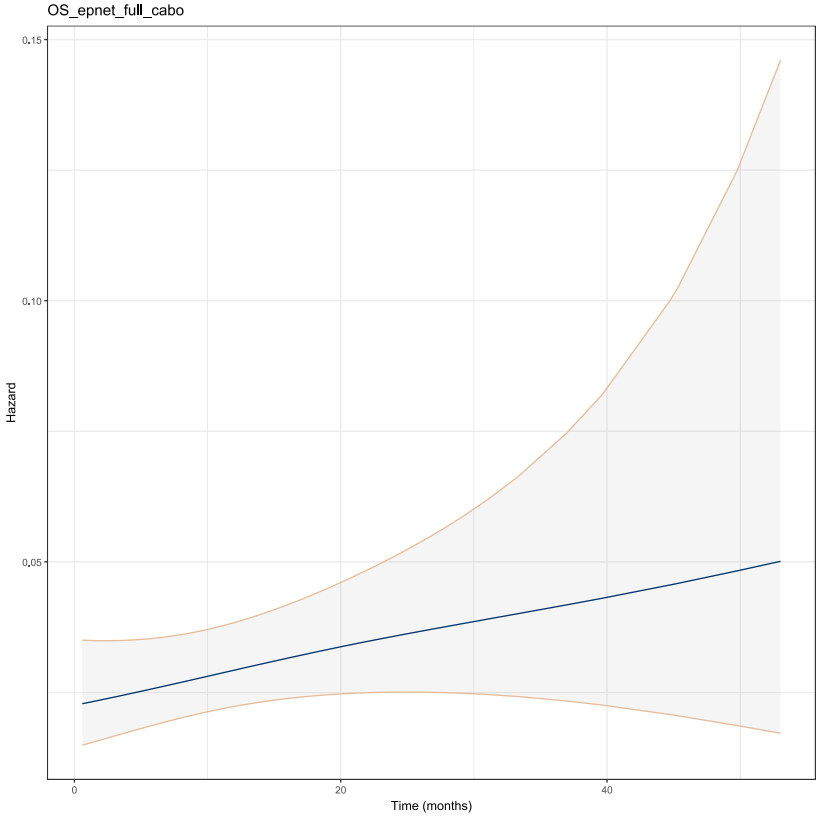


D.2.6 Evaluation of hazard functions

Figure 60, Figure 61 and Figure 62 presents the smoothed hazard for OS in the epNET, pNET and lung NET cohorts, respectively. All smoothed hazard plots show a slightly increasing trend over time. However, the changes in hazards are very small. This suggests the hazard is relatively stable, which supports using an exponential model for the extrapolation. Since the exponential model assumes a constant hazard and allows for a constant hazard ratio, it is a good choice for the crossover-adjusted analyses, which is based on the assumption of proportional hazards.

Figure 60 OS epNET Smoothed hazard plots (ITT Analysis)

epNET: Cabozantinib



epNET: Placebo

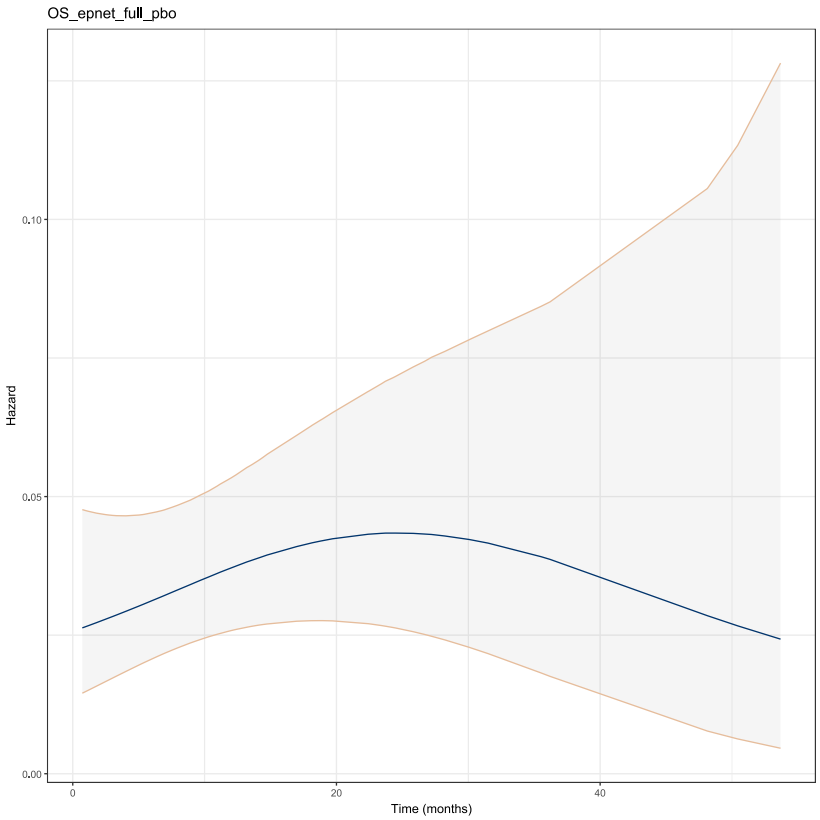
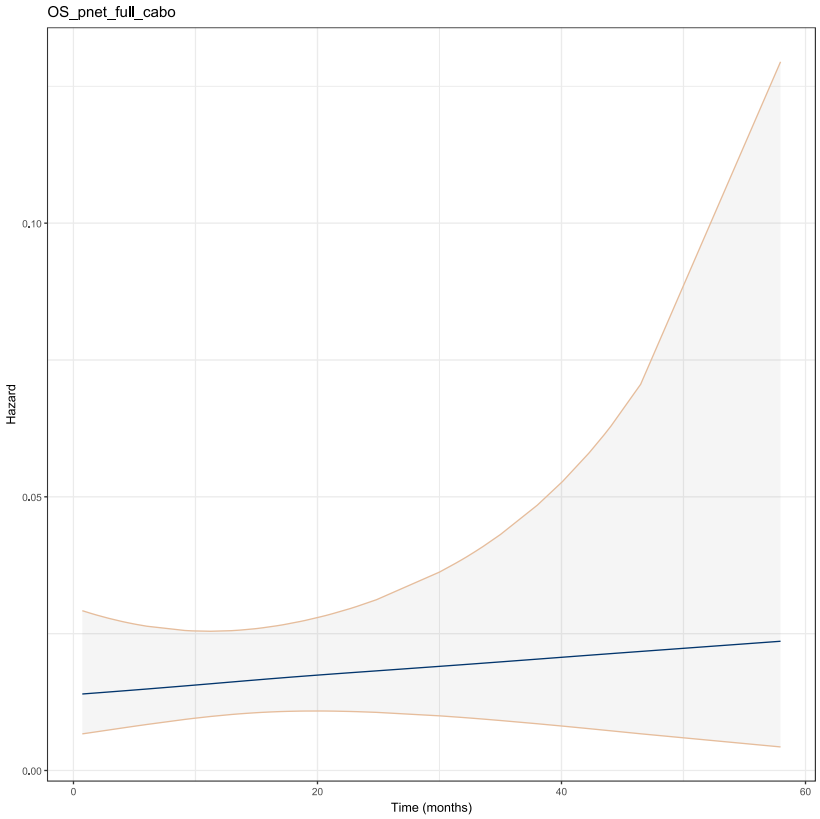


Figure 61 OS pNET Smoothed hazard plots (ITT Analysis)

pNET: Cabozantinib



pNET: Placebo

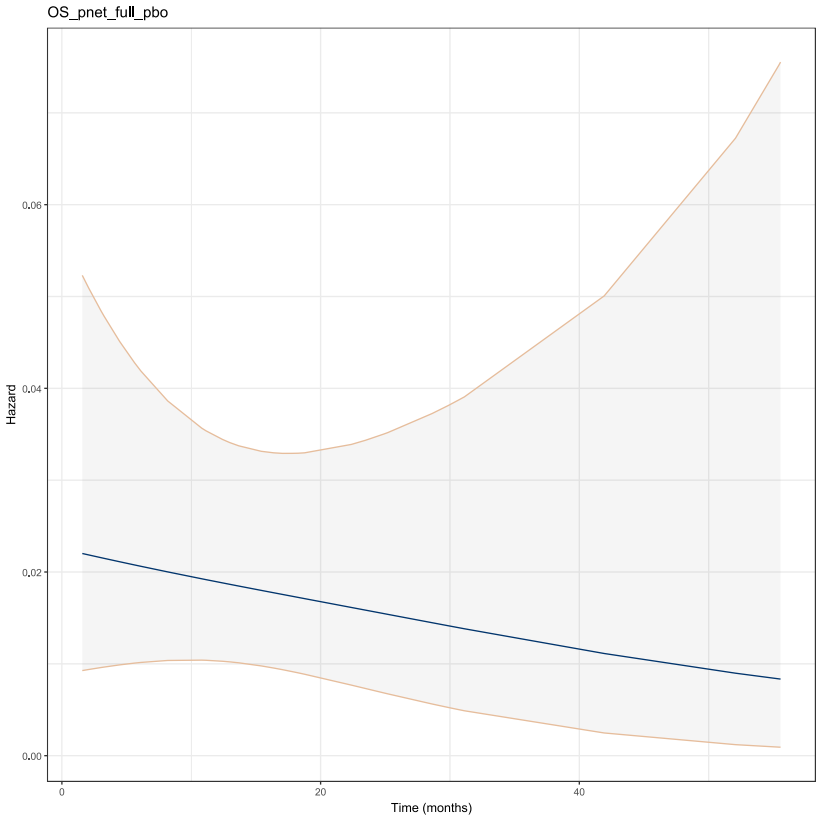
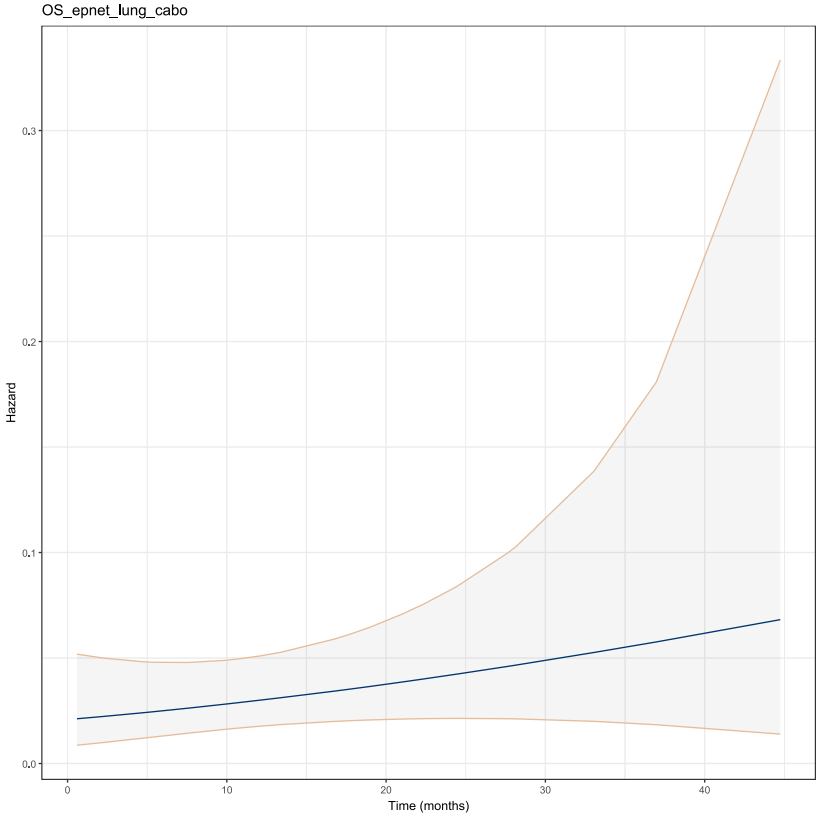
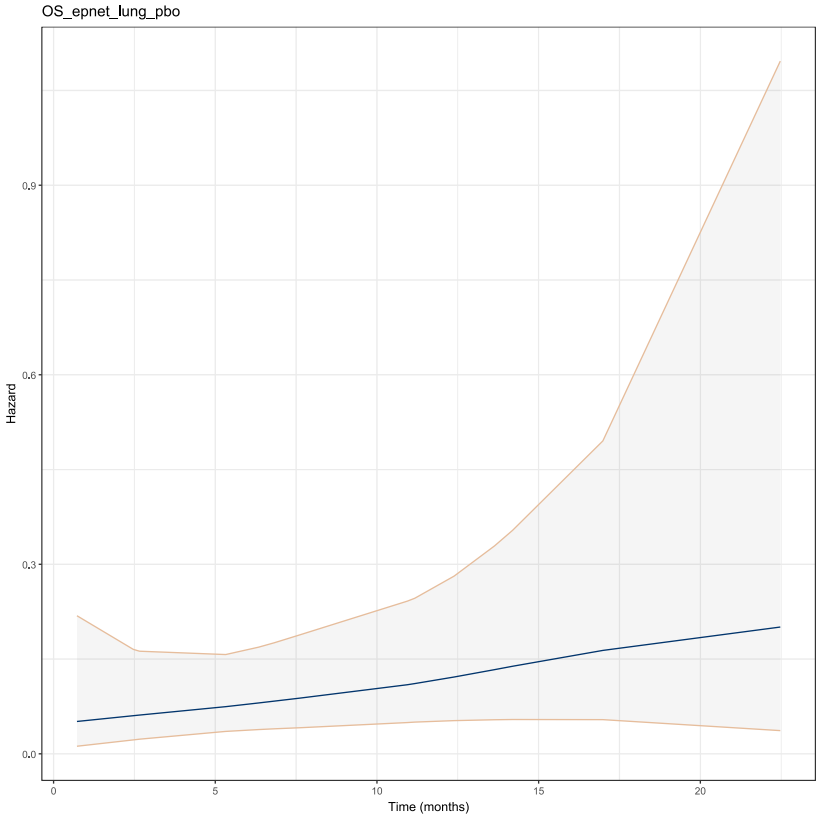


Figure 62 OS lung NET Smoothed hazard plots (ITT Analysis)

Lung NET:Cabozantinib



Lung NET: Placebo



D.2.7 Validation and discussion of extrapolated curves

See section 8.1.1.

D.2.8 Adjustment of background mortality

General mortality rates for the Danish population were applied.

D.2.9 Adjustment for treatment switching/cross-over

In CABINET, unblinded crossover from placebo to Cabometyx® was permitted after confirmation of progressed disease by central radiology review. As such, the intention-to-treat (ITT) analysis may overestimate OS for placebo patients and underestimate the relative benefits (versus placebo) in OS for patients randomised to Cabometyx®. The number and proportion of placebo patients who switched treatment are presented in Table 83.

Table 83 Crossover proportions

Population	Number of subjects randomised to cabozantinib	Number of subjects randomised to placebo	Number of placebo subjects who switched to cabozantinib	Proportion of placebo subjects who switched to cabozantinib
pNET	64	31	12	38.71%
epNET	134	69	20	29.00%
Lung NET	33	16	3	18.75%

Abbreviations: epNET, extra pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour

Source: Data on file – Ipsen. Survival Analysis Report CABINET trial. 2024. [69]

To account for the impact of patients switching from placebo to Cabometyx® after disease progression, crossover-adjusted analyses were required for OS. For the model base cases, inverse probability of censoring weights (IPCW) HRs were used to derive BSC OS to account for the crossover of BSC patients.

The IPCW approach artificially censors patients who switch at the time of switching. To mitigate the impacts of potential informative switching, the probability of switching is also estimated, conditional on prognostic baseline and time-dependent variables, and a weight is calculated for patients who have not switched based on the estimated switch probability. That is, patients who have similar characteristics to those artificially censored due to switching are weighted up to reduce the impact of informative switching. The estimated weights are time-dependent (i.e. they vary across the timepoints of observations for each patient) and can be highly variable. As such, “stabilised” weights were used. Time-dependent confounding variables included within the models were tumour size and ECOG status, both of which were reported for CABINET

based on 12-weekly assessments and were considered time-dependent characteristics of clinical relevance. In addition, the following baseline covariates were deemed prognostic factors for both switching and survival and were thus included in the model: age, tumour grade, functional status, number of prior therapies and prior usage of SSAs. For the full epNET cohort, primary tumour site was used as an additional baseline covariate.

The appropriateness of applying these HRs was assessed by evaluating the proportional hazards assumption using Schoenfeld residuals and log cumulative hazard plots to ensure that the effect of treatment on the hazard rate is consistent over time.

IPCW analyses can occasionally generate extreme weights, which can be mitigated by truncation. Therefore, both untruncated and truncated results (based on truncated weights) were generated. However, these results were very similar and thus extreme weights had not been generated. Therefore, the untruncated values were selected as most appropriate) as they are based on the full results from the weight estimation model and do not include any arbitrary truncation.

Stratified HRs were produced for the full cohorts (pNETs and epNETs). Due to the lung NET subgroup analysis employing different groups for tumour location compared to the stratification factor for the primary tumour site, using stratified Cox models was problematic. These models are intended to control for confounding by adjusting for strata-specific baseline hazards, which may not be relevant or meaningful in these non-stratified subgroups. Consequently, unstratified HRs were produced for the subgroups.

In Table 84 the IPCW HRs are presented for the three analyses. The IPCW HRs have been applied to each parametric extrapolation of Cabometyx® to estimate the survival probability in the placebo arm.

Table 84 OS HR (Cabometyx® vs. BSC)

Population	Measure	ITT analysis (95% CI)	IPCW (95% CI)
pNET	Stratified HR	0.95 (0.45, 2.00	[redacted]
epNET	Stratified HR	0.86 (0.56, 1.31)	[redacted]
Lung NET	Unstratified HR	0.28 (0.12, 0.62)	[redacted]

Abbreviations: BSC: best supportive care; CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; IPCW: inverse probability coefficient weighting; ITT: intention-to-treat; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour; somatostatin analogue.

Source: Ipsen Data on File, Survival analysis report.

D.2.10 Waning effect

Not applicable.

D.3 Extrapolation time-to-treatment discontinuation

D.3.1 Data input

TTD was extrapolated using patient level data from the CABINET trial (data cut off 23 August 2023).

D.3.2 Model

See D.1.2.

D.3.3 Proportional hazards

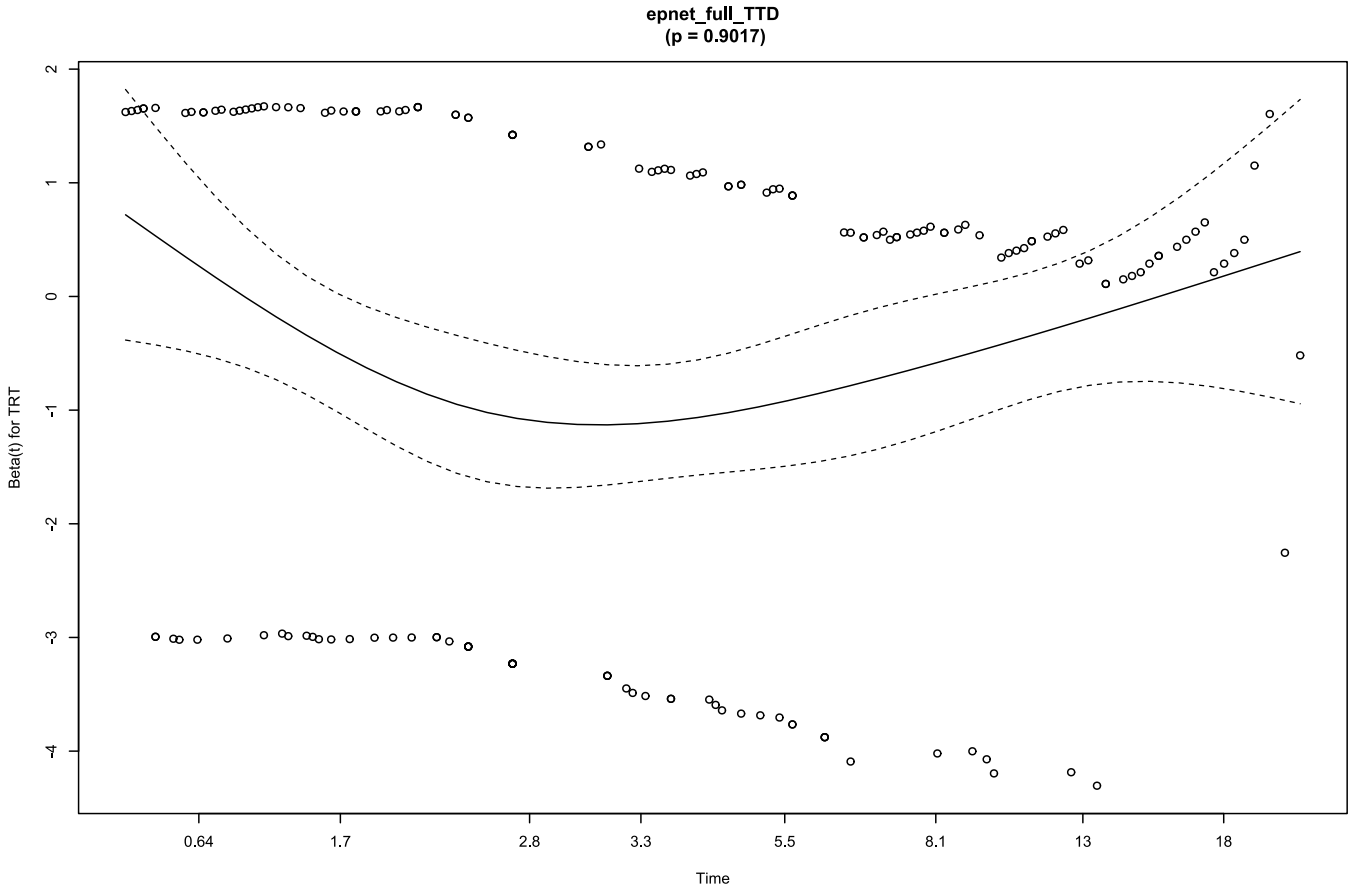
The proportional hazards assumption was assessed to determine whether independent parametric models should be fitted for TTD in each treatment arm for epNET, pNET and lung NET, or if a joint parametric model could be used. The proportional hazard assumption for PFS was evaluated with the log cumulative hazard plot and the Schoenfeld residual plot with a hypothesis test of the proportional hazards.

In Figure 63, Figure 64 and Figure 65 the Schoenfeld plots and log cumulative hazards plots are presented for each subgroup, respectively. The log cumulative hazard plots show similar trends in all subgroups, with the cumulative hazard plots closely aligned at the early time points, and then after approximately 2-4 months, the trends diverge to become roughly parallel. These trends show potential violations against the assumptions of proportional hazards, which is supported by the Schoenfeld plots, that all presents fluctuating trends. However, for epNET and pNET the Schoenfeld test of proportional hazards, indicates that there is not enough evidence to reject the null hypothesis of proportional hazards since the p-values are above 0.1. However, the p-value for the lung NET subgroup is 0.03, indicating that there is enough evidence to reject the null hypothesis.

In the analysis, the assumption of proportional hazards was not required since TTD were fitted independently for the Cabometyx® arm and BSC arm in all subgroups.

Figure 63 TTD epNET Schoenfeld plot and Log cumulative hazard plot

epNET: Schoenfeld plot



epNET: Log cumulative hazard plot

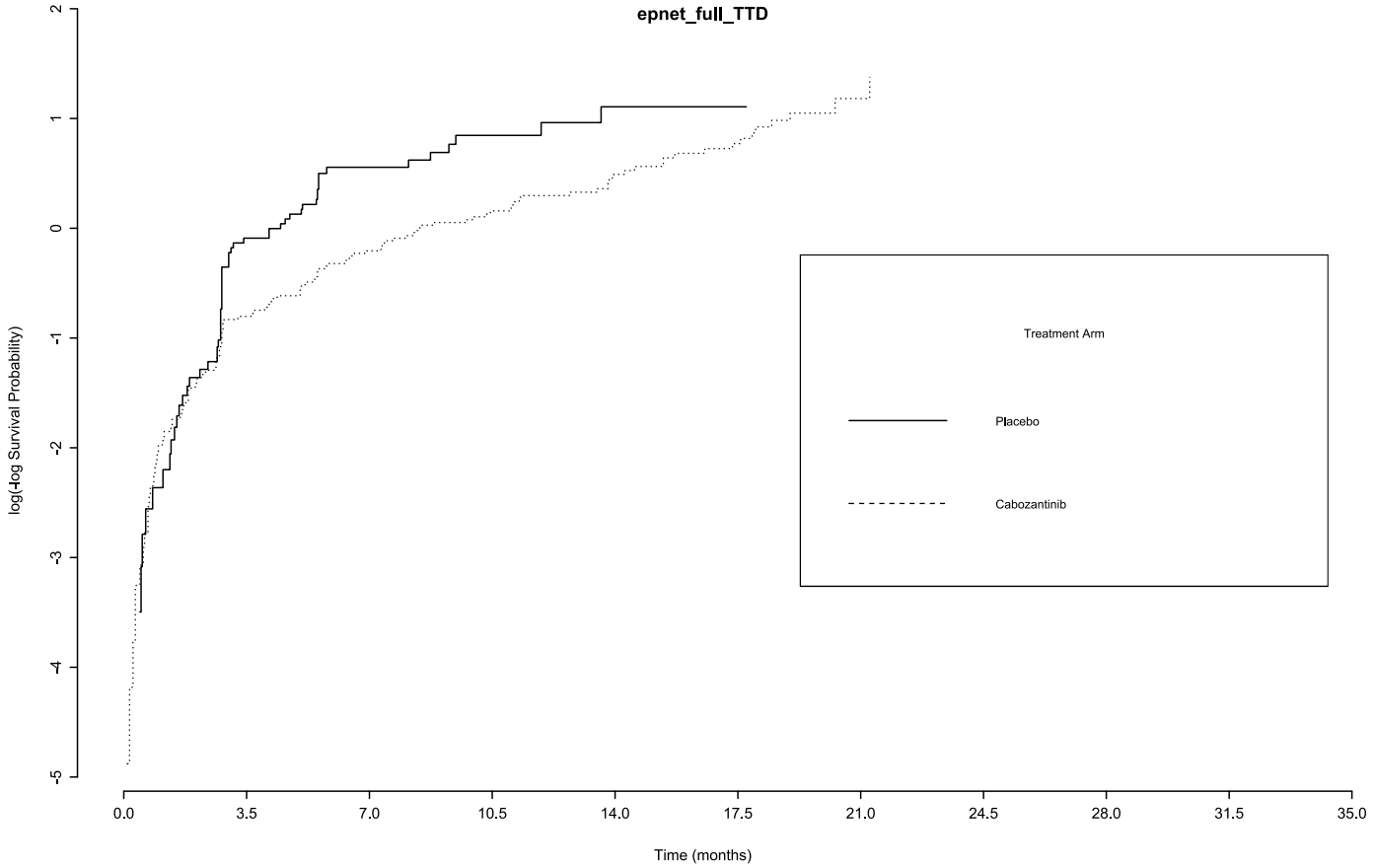
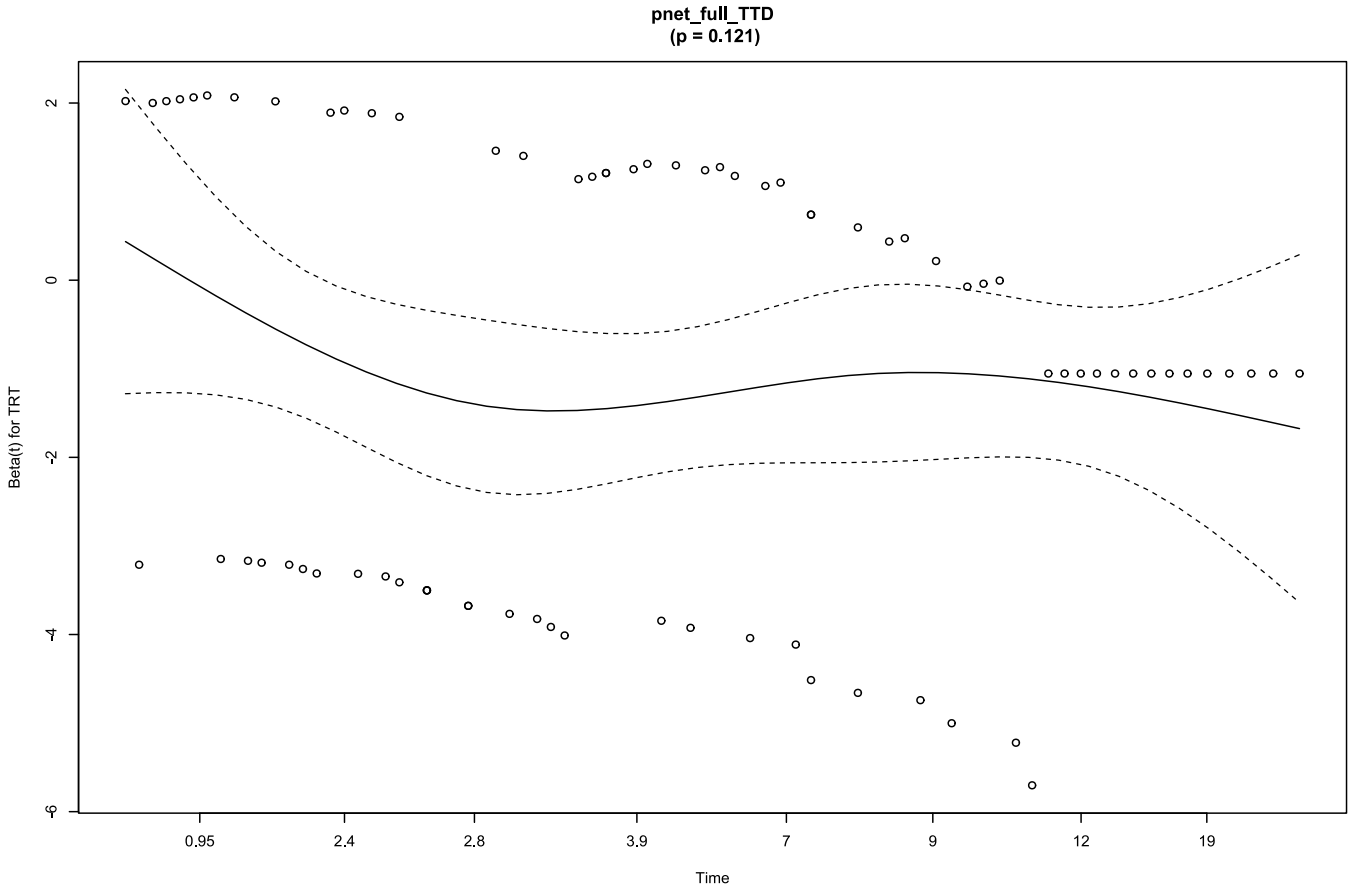


Figure 64 TTD pNET Schoenfeld plot and Log cumulative hazard plot

pNET: Schoenfeld plot



pNET: Log cumulative hazard plot

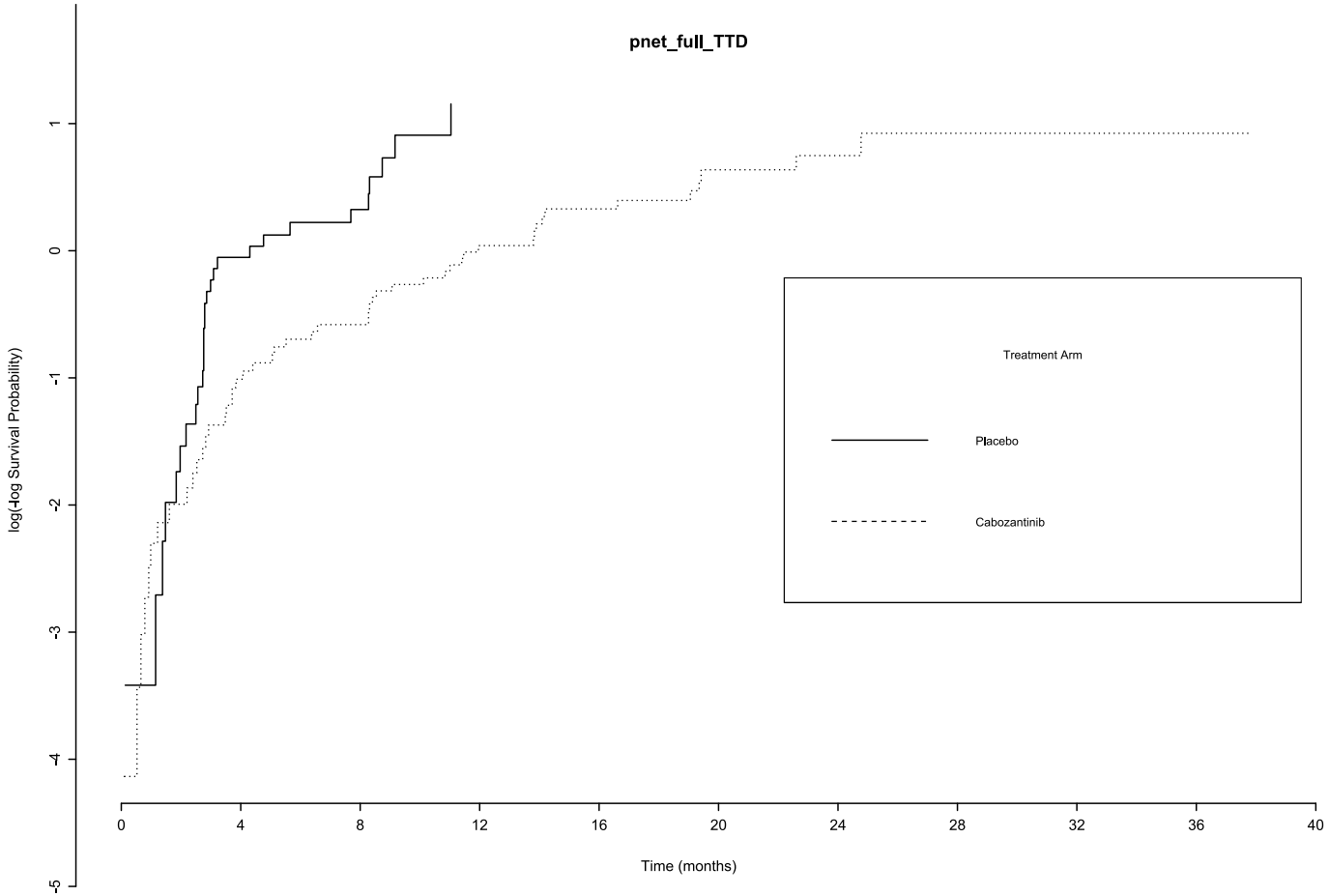
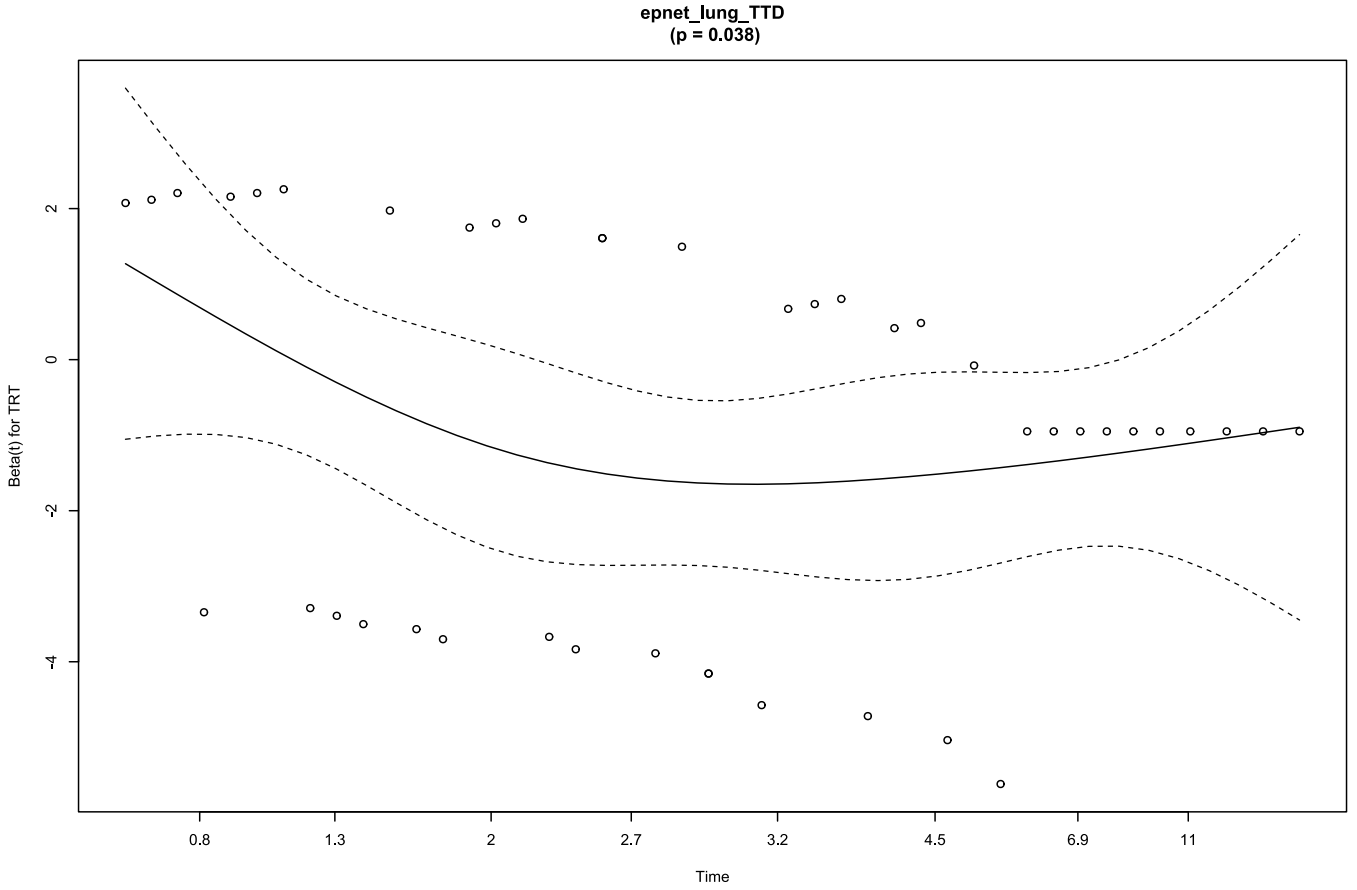
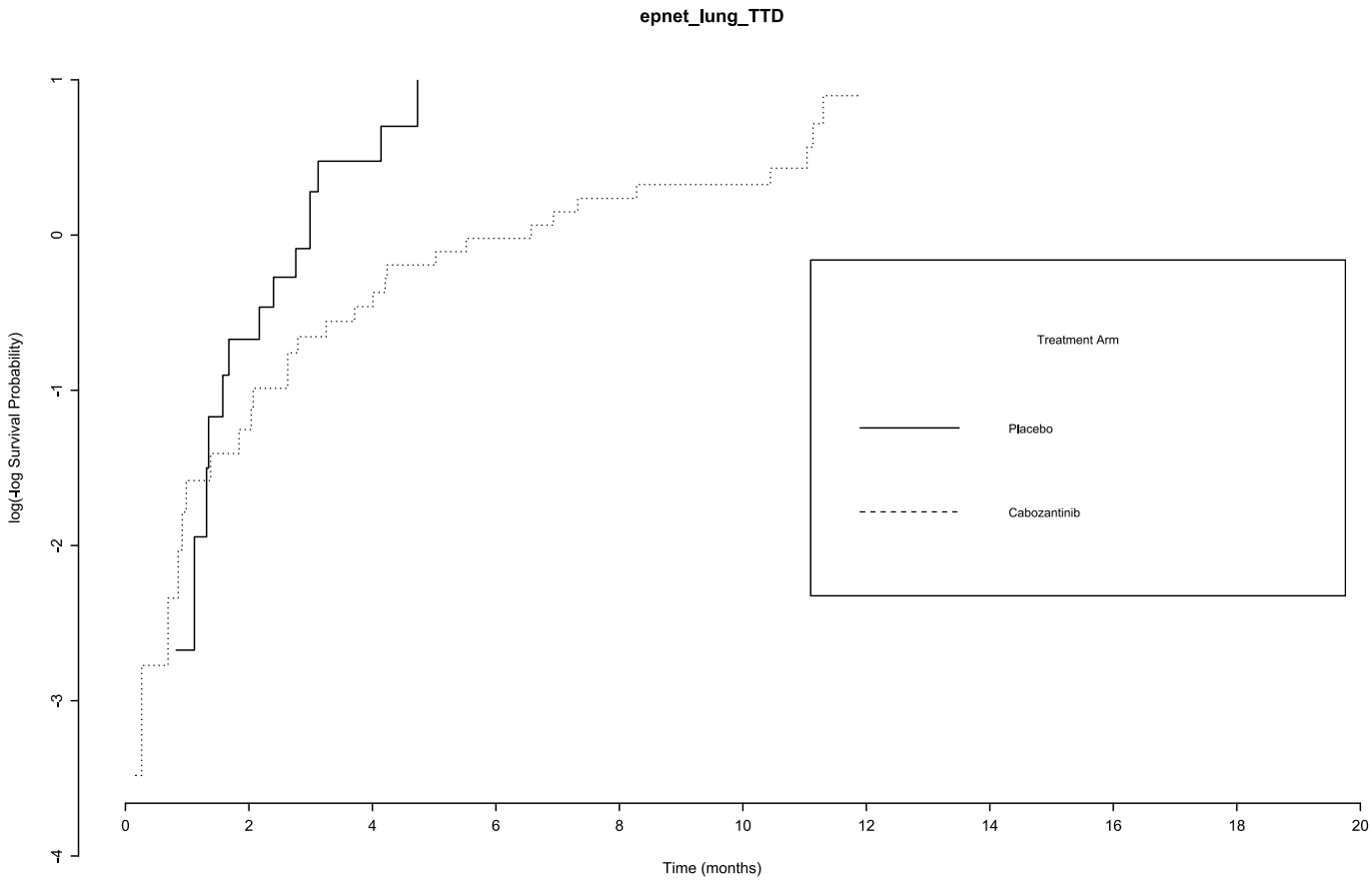

pnet_full_TTD
log(-log Survival Probability)
1
0
-1
-2
-3
-4
-5
0
4
8
12
16
20
24
28
32
36
40
Time (months)
Treatment Arm
Placebo
Cabozantinib

Figure 65 TTD lung NET Schoenfeld plot and Log cumulative hazard plot

Lung NET: Schoenfeld plot



Lung NET: Log cumulative hazard plot



D.3.4 Evaluation of statistical fit (AIC and BIC)

Table 85 presents the statistical evaluation metrics for Cabometyx® in the epNET cohort. The exponential distribution had the best statistical fit, which supports the choice of the exponential distribution for the base case analysis.

Table 85 Evaluation of statistical fit TTD epNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	**689.895**	**692.778**	**0.00**	**0.00**	**23%**	**5%**	**1%**	**0%**	**0%**	**0%**	**0%**	**0%**	**5.52**	**8.62**
Weibull	691.207	696.972	1.31	4.19	23%	4%	1%	0%	0%	0%	0%	0%	5.52	8.52
Lognormal	704.089	709.854	14.19	17.08	24%	10%	5%	2%	1%	0%	0%	0%	4.60	10.37
Log-logistic	703.960	709.726	14.07	16.95	24%	11%	6%	3%	1%	1%	0%	0%	4.60	10.70
Gamma	691.342	697.108	1.45	4.33	23%	5%	1%	0%	0%	0%	0%	0%	5.52	8.55
Gompertz	690.302	696.068	0.41	3.29	23%	4%	0%	0%	0%	0%	0%	0%	5.52	8.43
Generalised Gamma	692.983	701.631	3.09	8.85	23%	4%	1%	0%	0%	0%	0%	0%	8.47	5.52

Table 86 presents the statistical evaluation metrics for BSC in the epNET cohort. The log-logistic distribution had the best statistical fit according to AIC and BIC, which supports the choice of the log-logistic distribution for the base case analysis.

Table 86 Evaluation of statistical fit TTD epNET BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	309.946	312.151	11.89	9.68	8%	1%	0%	0%	0%	0%	0%	0%	2.76	5.13
Weibull	308.481	312.890	10.42	10.42	6%	0%	0%	0%	0%	0%	0%	0%	3.68	5.18
Lognormal	299.795	304.204	1.74	1.74	7%	1%	0%	0%	0%	0%	0%	0%	2.76	5.11
Log-logistic	**298.059**	**302.469**	**0.00**	**0.00**	**7%**	**2%**	**1%**	**0%**	**0%**	**0%**	**0%**	**0%**	**2.76**	**5.03**
Gamma	305.572	309.982	7.51	7.51	5%	0%	0%	0%	0%	0%	0%	0%	1.84	3.42
Gompertz	311.945	316.354	13.89	13.89	8%	1%	0%	0%	0%	0%	0%	0%	2.76	5.13
Generalised Gamma	301.752	308.366	3.69	5.90	7%	1%	0%	0%	0%	0%	0%	0%	2.76	5.11

Table 87 presents the statistical evaluation metrics for Cabometyx® in the pNET cohort. The exponential distribution showed the best statistical fit according to both AIC and BIC, which supports the choice of the exponential distribution for the analysis.

Table 87 Evaluation of statistical fit TTD pNET Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	**343.858**	**346.002**	**0.00**	**0.00**	**37%**	**14%**	**5%**	**1%**	**0%**	**0%**	**0%**	**0%**	**8.28**	**12.51**
Weibull	345.812	350.098	1.95	4.10	37%	13%	5%	1%	0%	0%	0%	0%	8.28	12.41
Lognormal	349.654	353.940	5.80	7.94	35%	18%	11%	6%	2%	1%	0%	0%	6.44	16.41
Log-logistic	347.332	351.618	3.47	5.62	35%	17%	11%	6%	2%	1%	0%	0%	7.36	16.43
Gamma	345.765	350.051	1.91	4.05	37%	13%	5%	1%	0%	0%	0%	0%	8.28	12.41
Gompertz	345.824	350.111	1.97	4.11	37%	14%	6%	1%	0%	0%	0%	0%	7.36	12.72
Generalised gamma	347.583	354.012	3.72	8.01	36%	14%	6%	1%	0%	0%	0%	0%	7.36	12.71

Table 88 presents the statistical evaluation metrics for BSC in the pNET cohort. Gamma showed the best statistical fit according to both AIC and BIC, which supports the choice of the gamma distribution for the analysis.

Table 88 Evaluation of statistical fit pNET TTD BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	149.778	151.212	3.18	1.75	8%	1%	0%	0%	0%	0%	0%	0%	2.76	4.83
Weibull	146.668	149.536	0.07	0.07	3%	0%	0%	0%	0%	0%	0%	0%	3.68	5.05
Lognormal	151.226	154.094	4.63	4.63	8%	2%	0%	0%	0%	0%	0%	0%	2.76	5.03
Log-logistic	147.582	150.450	0.99	0.99	7%	2%	1%	0%	0%	0%	0%	0%	2.76	5.06
Gamma	**146.595**	**149.463**	**0.00**	**0.00**	**4%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**3.68**	**5.06**
Gompertz	147.902	150.770	1.31	1.31	2%	0%	0%	0%	0%	0%	0%	0%	3.68	5.00
Generalised Gamma	148.552	152.854	1.96	3.39	4%	0%	0%	0%	0%	0%	0%	0%	3.68	5.05

Table 89 presents the statistical evaluation metrics for Cabometyx® in the lung NET subgroup. The exponential distribution had the best statistical fit according to both AIC and BIC, which supports the choice of the exponential distribution for the analysis.

Table 89 Evaluation of statistical fit lung NET TTD Cabometyx®

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	**163.921**	**165.417**	**0.00**	**0.00**	**14%**	**2%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**3.68**	**6.47**
Weibull	165.755	168.748	1.83	3.33	13%	1%	0%	0%	0%	0%	0%	0%	3.68	6.41
Lognormal	168.154	171.147	4.23	5.73	16%	6%	3%	1%	0%	0%	0%	0%	2.76	7.50
Log-logistic	168.050	171.043	4.13	5.63	16%	7%	4%	2%	1%	0%	0%	0%	3.68	7.71
Gamma	165.744	168.737	1.82	3.32	13%	1%	0%	0%	0%	0%	0%	0%	3.68	6.42
Gompertz	165.694	168.687	1.77	3.27	13%	1%	0%	0%	0%	0%	0%	0%	3.68	6.35
Generalised Gamma	167.743	172.233	3.82	6.82	13%	2%	0%	0%	0%	0%	0%	0%	3.68	6.43

Table 90 presents the statistical evaluation metrics for BSC in the lung NET subgroup. According to both AIC and BIC, gamma had the best statistical fit. This supports the assumption of the gamma distribution for the analysis.

Table 90 Evaluation of statistical fit lung NET TTD BSC

Distribution	AIC	BIC	Δmin AIC	Δmin BIC	1 yr	2 yrs	3 yrs	5 yrs	10 yrs	15 yrs	30 yrs	40 yrs	Median TTD (months)	Mean TTD (months)
Exponential	60.077	60.785	8.68	7.98	1%	0%	0%	0%	0%	0%	0%	0%	0.92	2.88
Weibull	51.833	53.249	0.44	0.44	0%	0%	0%	0%	0%	0%	0%	0%	1.84	3.02
Lognormal	51.497	52.913	0.10	0.10	0%	0%	0%	0%	0%	0%	0%	0%	1.84	3.03
Log-logistic	52.629	54.045	1.24	1.24	1%	0%	0%	0%	0%	0%	0%	0%	1.84	3.09
Gamma	**51.392**	**52.809**	**0.00**	**0.00**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0.92**	**2.64**
Gompertz	53.712	55.129	2.32	2.32	0%	0%	0%	0%	0%	0%	0%	0%	1.84	3.00
Generalised Gamma	53.359	55.483	1.97	2.67	0%	0%	0%	0%	0%	0%	0%	0%	1.84	3.01

D.3.5 Evaluation of visual fit

The figures below show the parametric distributions together with the Kaplan-Meier estimate for pNET, epNET and lung NET separately for the Cabometyx® and BSC arm. The figures show that the selected parametric distribution for TTD (pNET, Cabometyx®: Exponential; pNET, BSC: Gamma; epNET, Cabometyx®: Exponential; epNET, BSC: Log-logistic; lung NET, Cabometyx®: Exponential; lung NET, BSC: Gamma) have good visual fits.

Figure 66 TTD pNET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

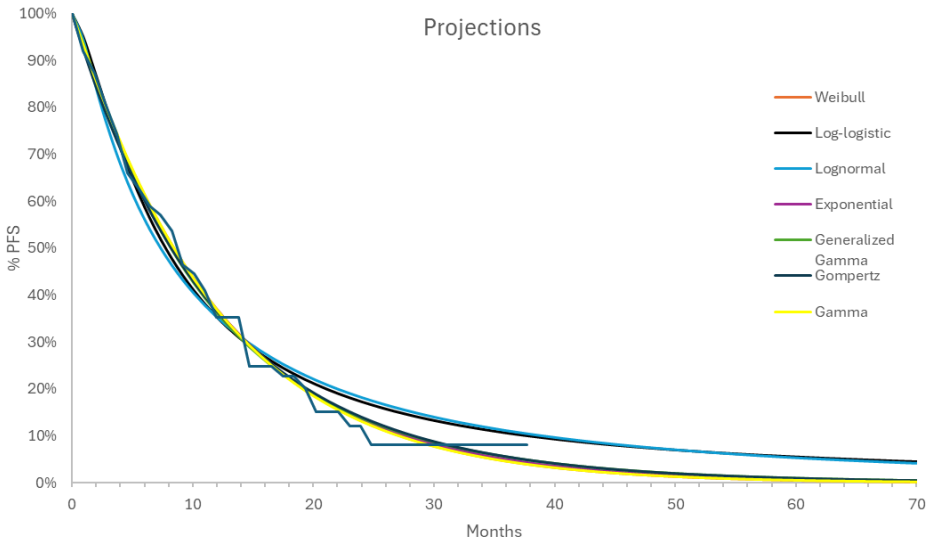


Figure 67 TTD pNET BSC Fitted parametric distributions and Kaplan-Meier estimate

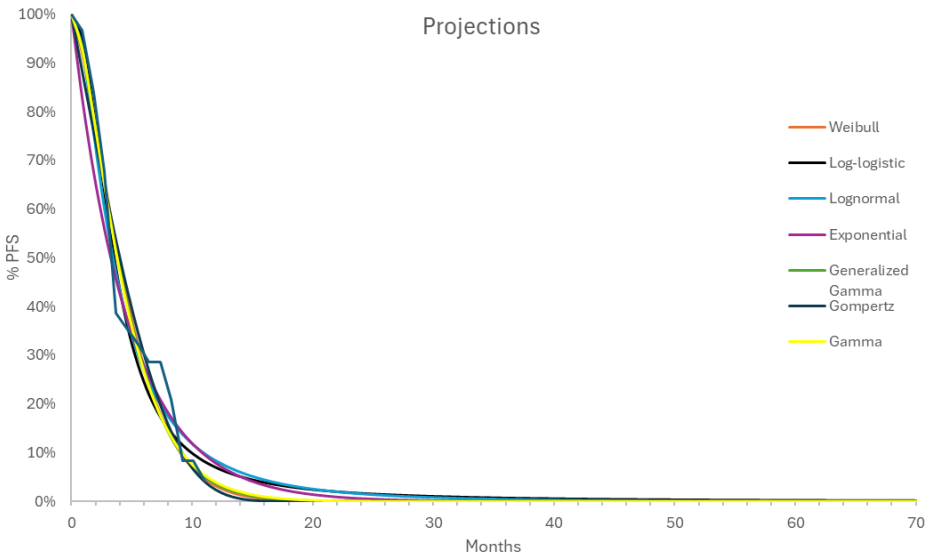


Figure 68 TTD epNET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

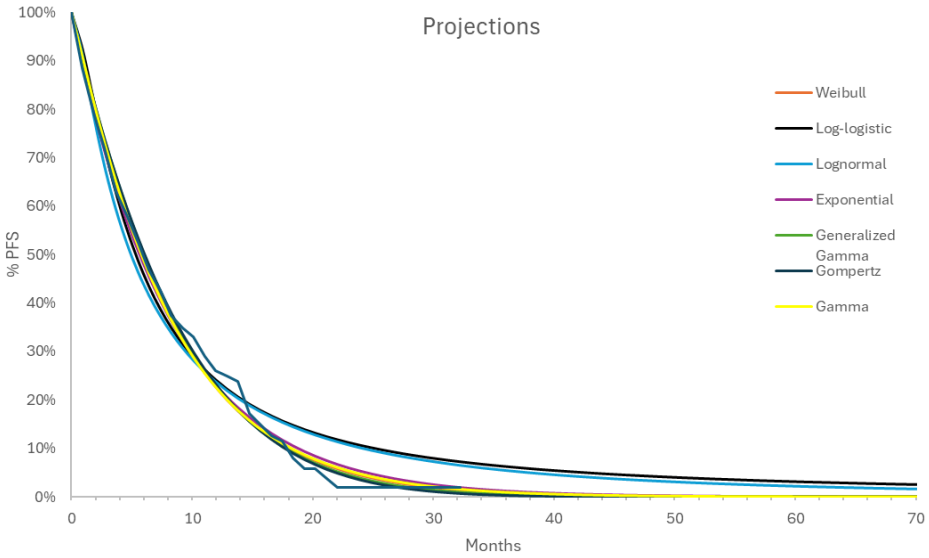


Figure 69 TTD epNET BSC Fitted parametric distributions and Kaplan-Meier estimate

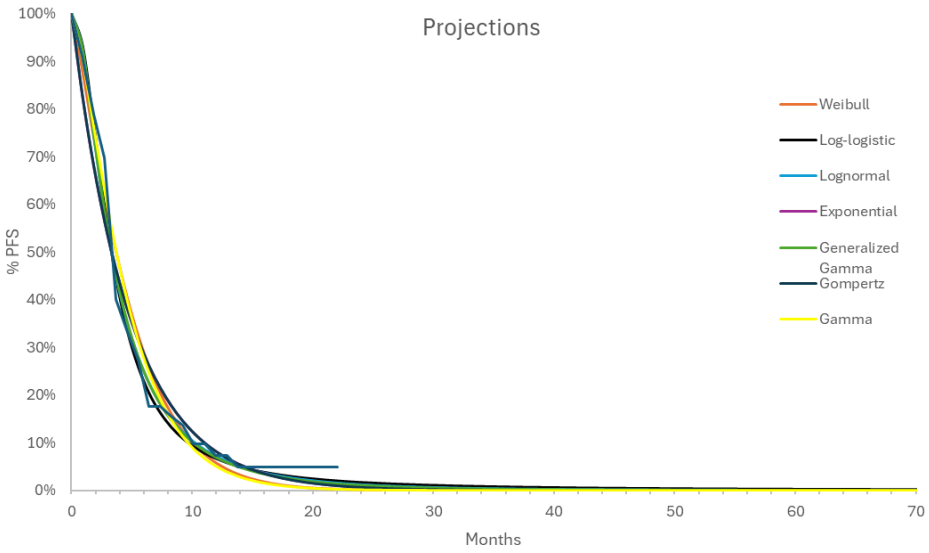


Figure 70 TTD lung NET Cabometyx® Fitted parametric distributions and Kaplan-Meier estimate

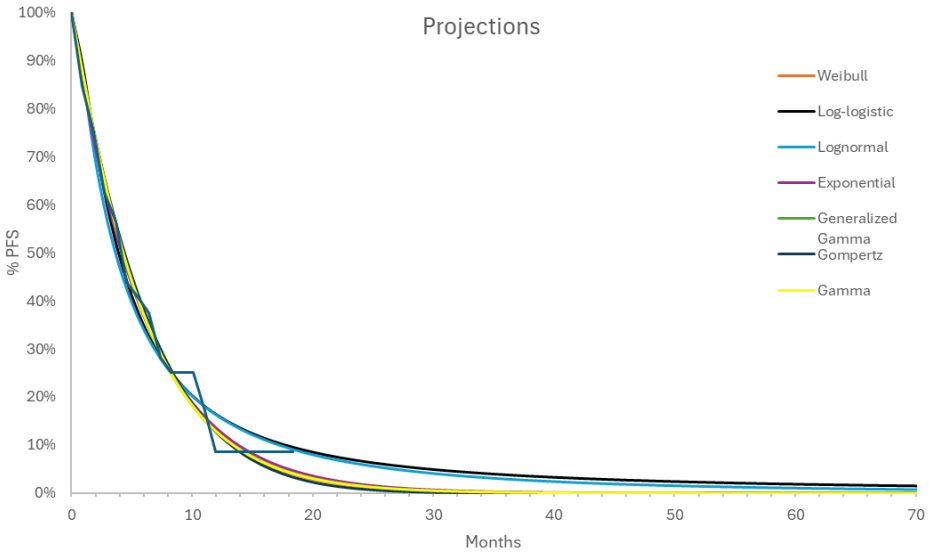
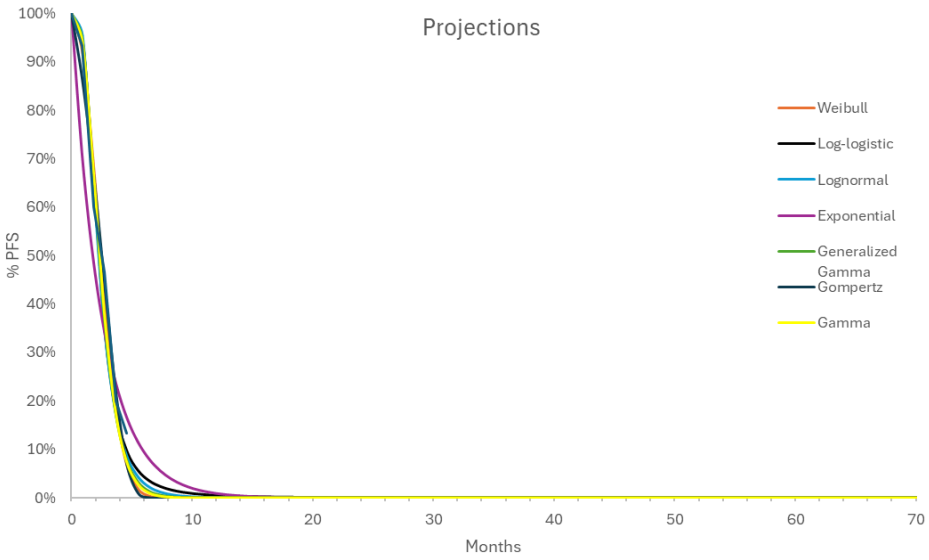


Figure 71 TTD lung NET BSC Fitted parametric distributions and Kaplan-Meier estimate



D.3.6 Evaluation of hazard functions

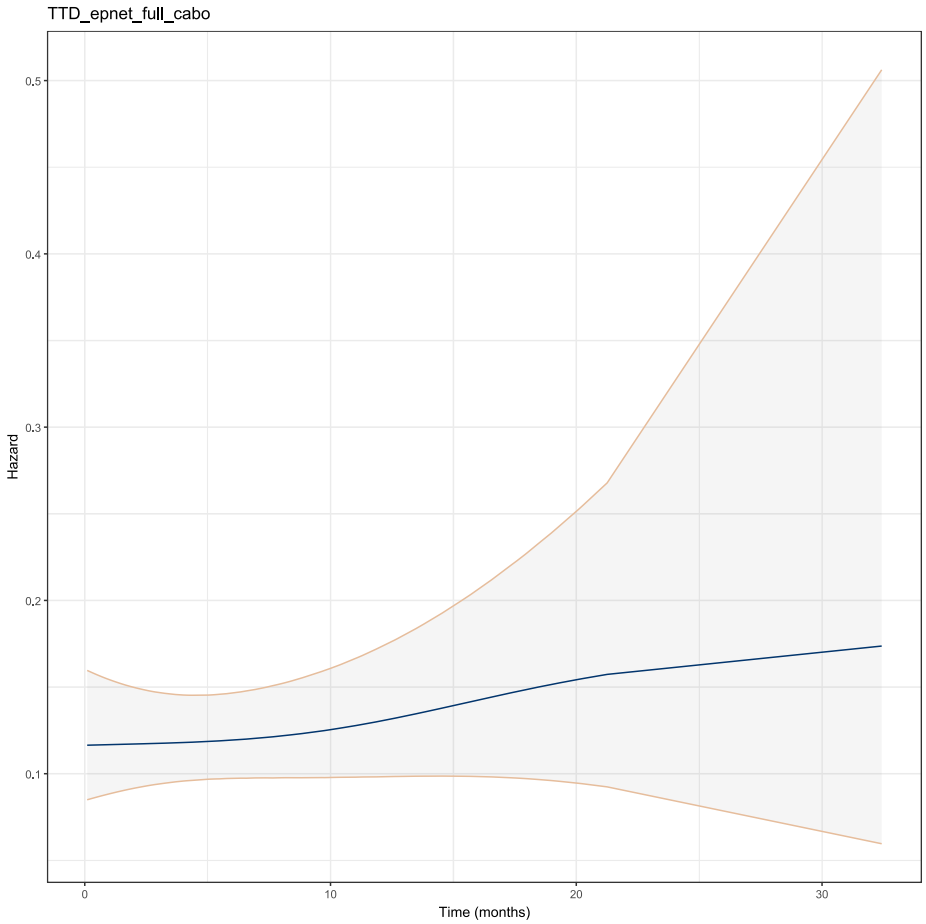
Figure 72 presents the smoothed hazard plots for epNET in the Cabometyx® and placebo arm. An increasing trend indicates that the risk of patients stopping treatment increases with time, while a decreasing trend indicates that the risk of patients stopping treatment decreases with time.

In the analysis, the exponential distribution was chosen for the extrapolation of the Cabometyx® arm. The smoothed hazard plot for the Cabometyx® arm shows a stable trend until approximately month 10. Following that, a slight increasing trend was observed; however, it was small, and therefore it was deemed appropriate to choose the exponential distribution. For the BSC arm, the log-logistic distribution was chosen for

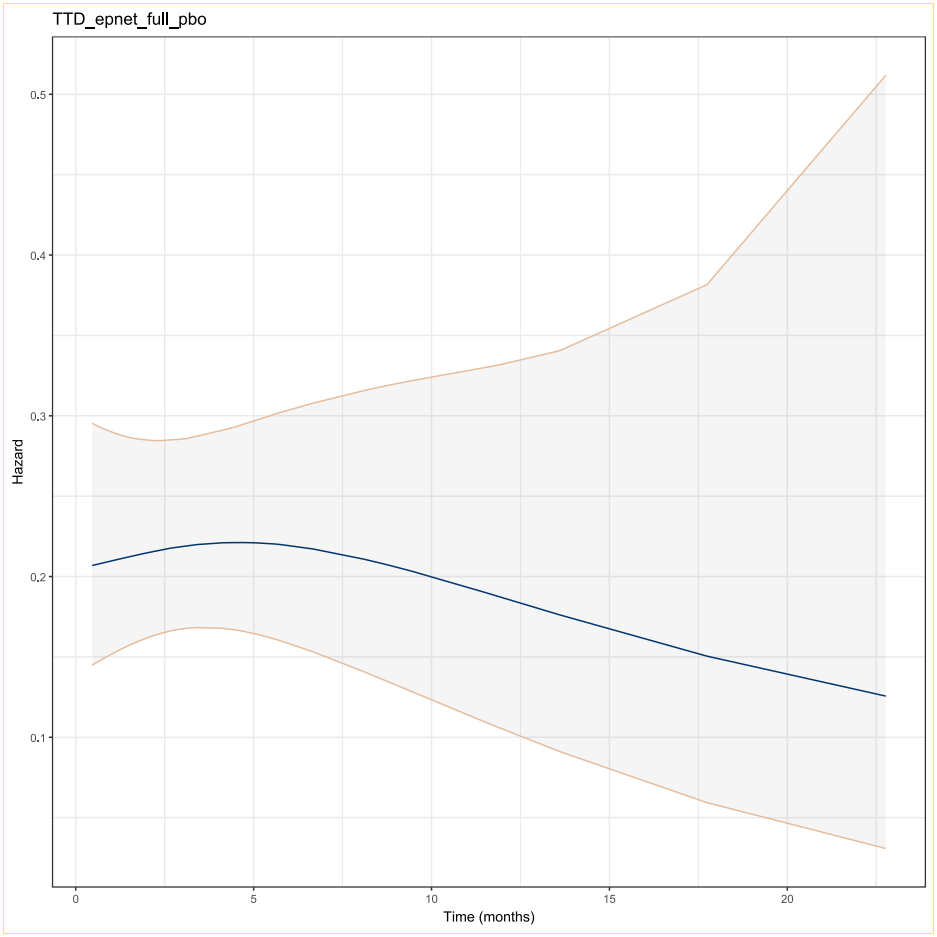
extrapolation. The log-logistic distribution has a non-monotonic hazard function, which makes it flexible and suitable for capturing a hazard rate that initially increases and then decreases, as observed in the smoothed hazard plot for BSC.

Figure 72 TTD epNET: Smoothed hazard plots (ITT)

epNET:Cabozantinib



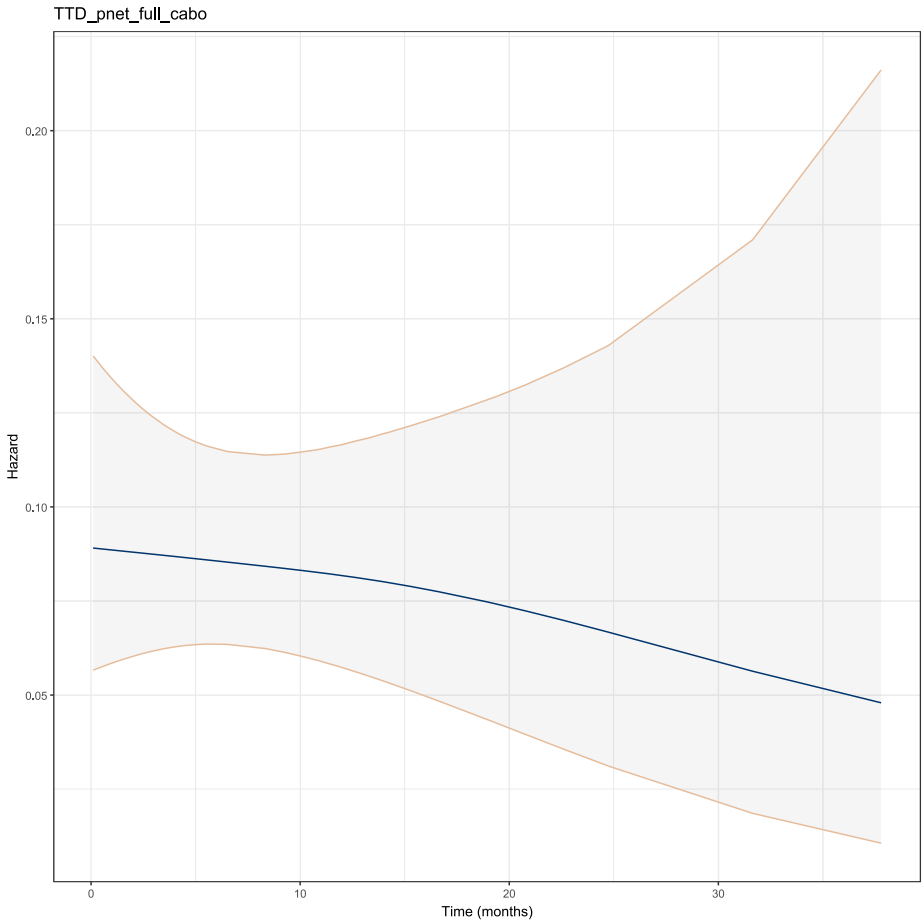
epNET: Placebo



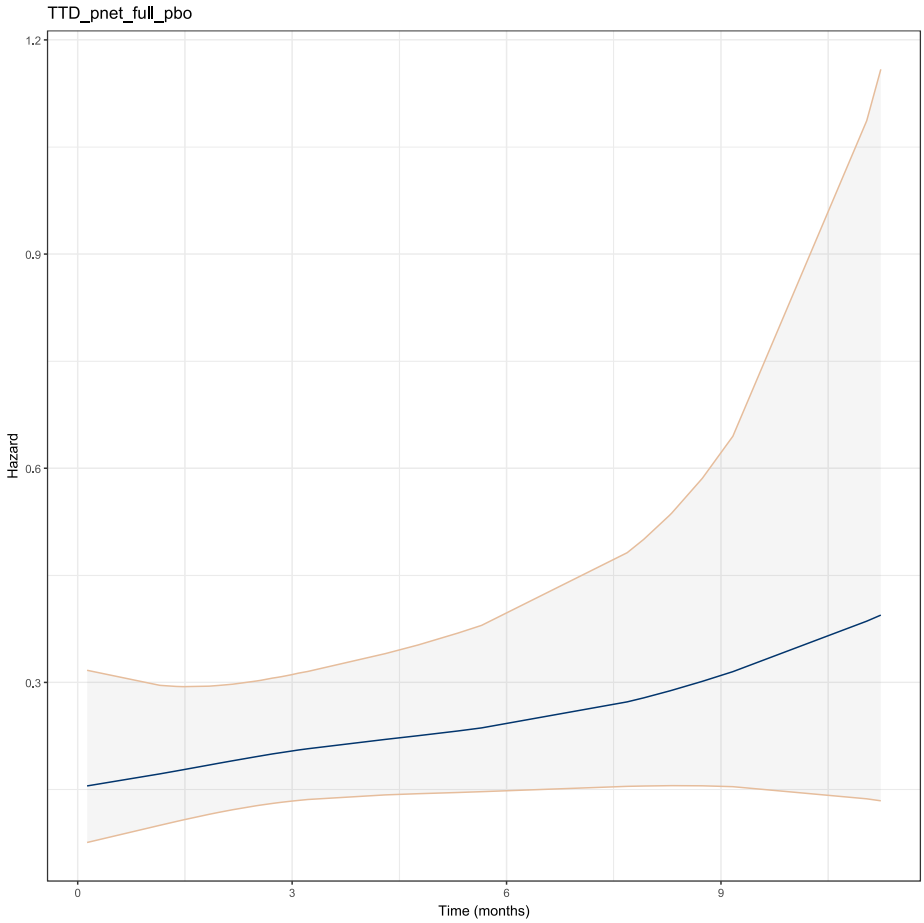
The smoothed hazard plot for Cabometyx® in the pNET cohorts shows a slightly decreasing trend; however, the magnitude of the decreasing trend is very small, and it was deemed appropriate to extrapolate with the exponential distribution. The smoothed hazard plot for the BSC arm showed a slightly increasing trend. The gamma distribution was considered appropriate for extrapolation because it can capture monotonically increasing hazard functions, aligning well with the observed pattern

Figure 73 TTD pNET: Smoothed hazard plots (ITT)

pNET Cabozantinib



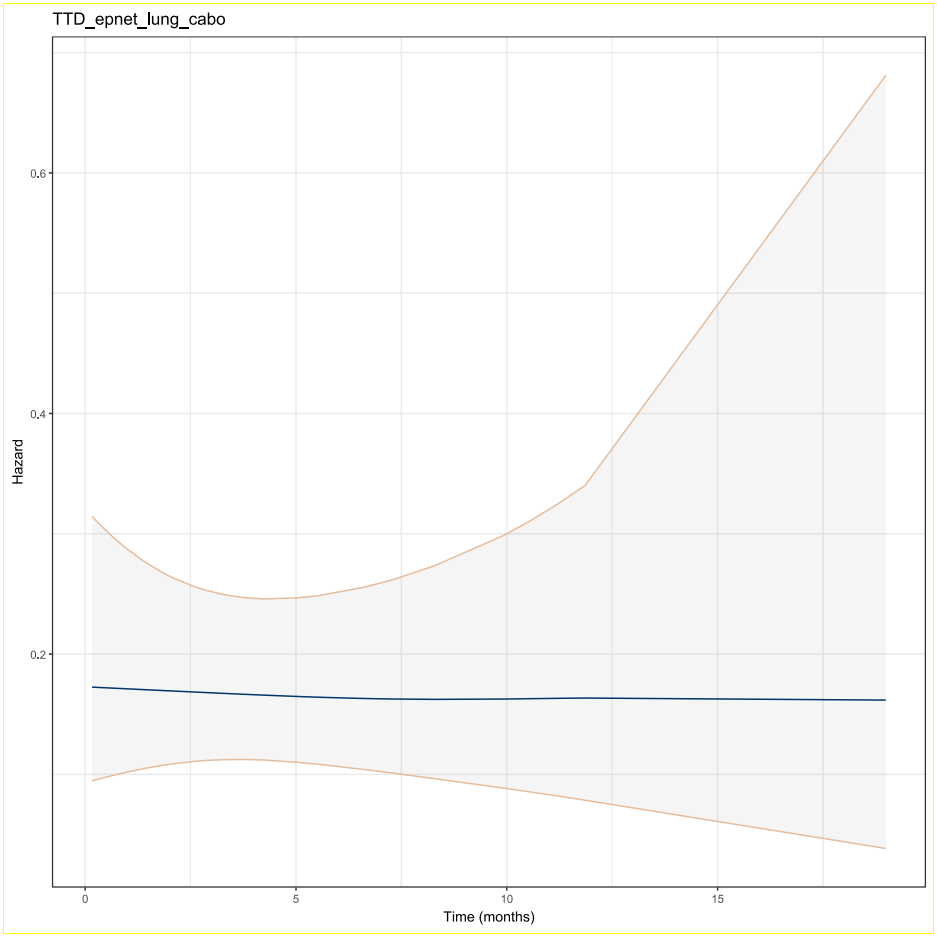
pNET: Placebo



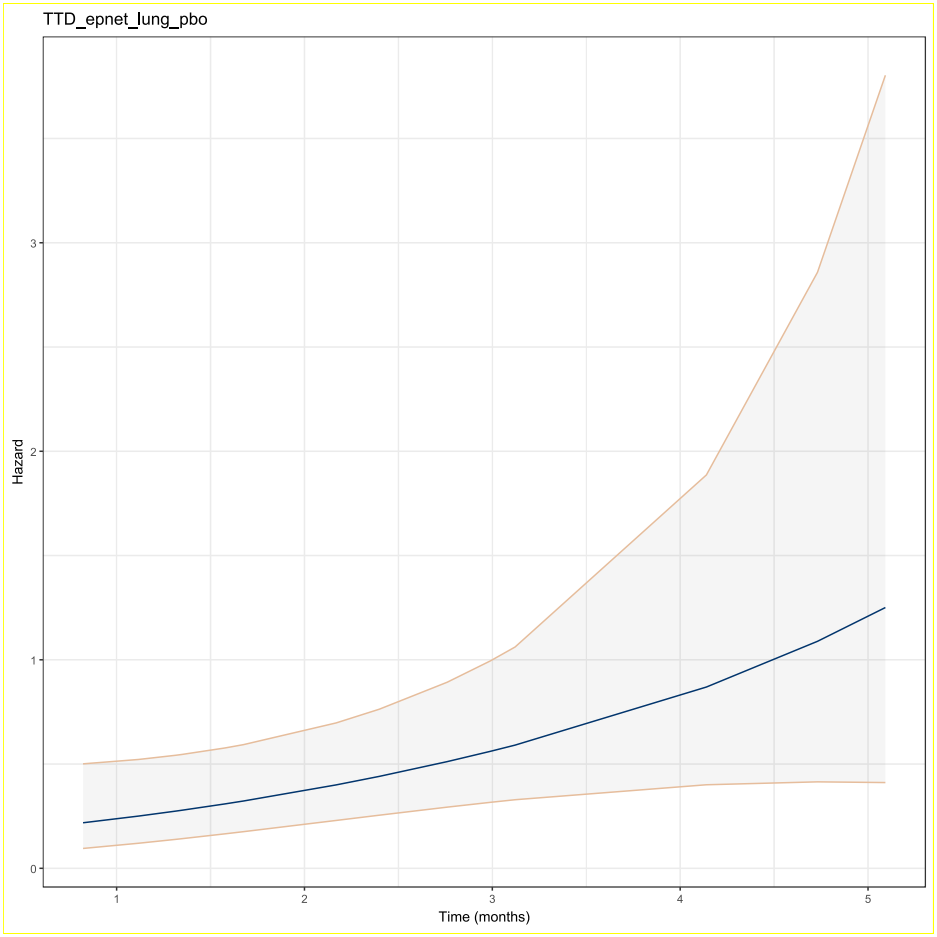
The smoothed hazard plot for Cabometyx® in the lung NET cohorts, shows a horizontal trend, making the exponential parametric distribution suitable for extrapolation. The smoothed hazard plot for BSC in the lung NET cohort, shows an increasing trend, and the gamma distribution was deemed appropriate to use as it can effectively model such a trend.

Figure 74 TTD lung NET: Smoothed hazard plots (ITT)

Lung NET: Cabozantinib



Lung NET: Placebo



D.3.7 Validation and discussion of extrapolated curves

See section 8.1.1.

D.3.8 Adjustment of background mortality

TTD was capped by OS, which in turn was capped by general population mortality in Denmark.

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

Appendix E. Serious adverse events

Table 91 Serious adverse events reported for > 2 subjects in any treatment arm (safety population) - epNET (DCO 24th August 2023)

Preferred Term	Cabozantinib (N=132)	Placebo (N=67)
Subjects with at least 1 SAE, n (%)	58 (44%)	27 (40%)
Hypertension	8 (6.1%)	1 (1.5%)
Abdominal pain	7 (5.3%)	4 (6.0%)
Diarrhoea	4 (3.0%)	3 (4.5%)
Vomiting	4 (3.0%)	2 (3.0%)
Anaemia	3 (2.3%)	0
Back pain	3 (2.3%)	1 (1.5%)
Blood bilirubin increased	3 (2.3%)	2 (3.0%)
Fatigue	3 (2.3%)	3 (4.5%)
Muscular weakness	3 (2.3%)	0
Nausea	3 (2.3%)	2 (3.0%)
Pulmonary embolism	3 (2.3%)	1 (1.5%)
Sepsis	3 (2.3%)	0
Syncope	3 (2.3%)	3 (4.5%)
Dyspnoea	2 (1.5%)	3 (4.5%)

Abbreviations: epNET, extra-pancreatic neuroendocrine tumor; SAE, serious adverse events.

Note: MedDRA 26.1 was used for coding.

[redacted]

Table 92 Serious adverse events reported for > 2 subjects in any treatment arm (safety population) - pNET (DCO 24th August 2023)

Preferred Term	Cabozantinib (N=63)	Placebo (N=31)
Subjects with at least 1 SAE, n (%)	29 (46%)	7 (23%)
Vomiting	4 (6.3%)	0
Embolism	3 (4.8%)	0
Hypoxia	3 (4.8%)	0
Nausea	3 (4.8%)	0
Sepsis	3 (4.8%)	0
Small intestinal obstruction	1 (1.6%)	3 (9.7%)

Abbreviations: pNET, pancreatic neuroendocrine tumor; SAE, serious adverse events.

Note: MedDRA 26.1 was used for coding.

Source: Ipsen Data on File, 2024 (CABINET CSR) [68].

Appendix F. Health-related quality of life

F.1 EORTC QLQ-C30

Figure 75 and Figure 76 presents the mean of the QLQ-C30 summary score in the two treatment arms, with corresponding 95% confidence intervals. In the pNET cohort (Figure 75), the confidence intervals at baseline were similar between the two treatments arms. However, they increase at later timepoints in the placebo cohort. A similar pattern is observed in the ep cohort (Figure 76), reflecting increased uncertainty in the placebo group at later stages of the study [83].

Figure 75 QLQ-C30: Summary Score pNET [83]

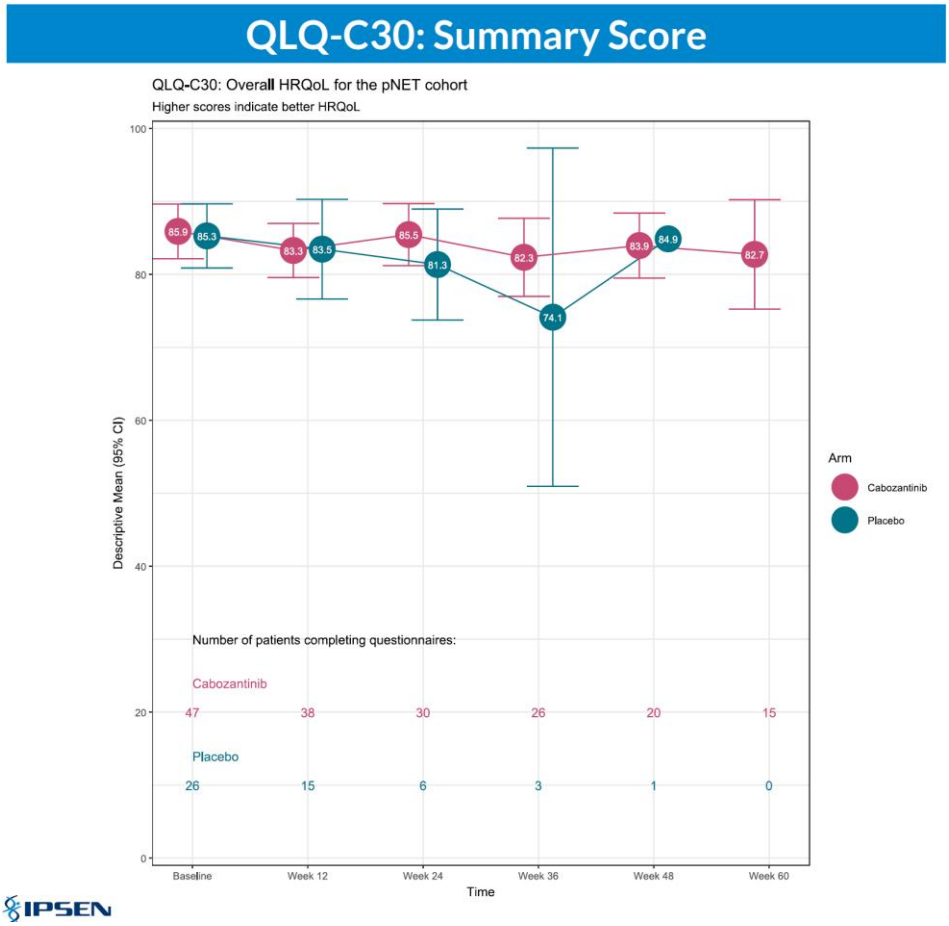
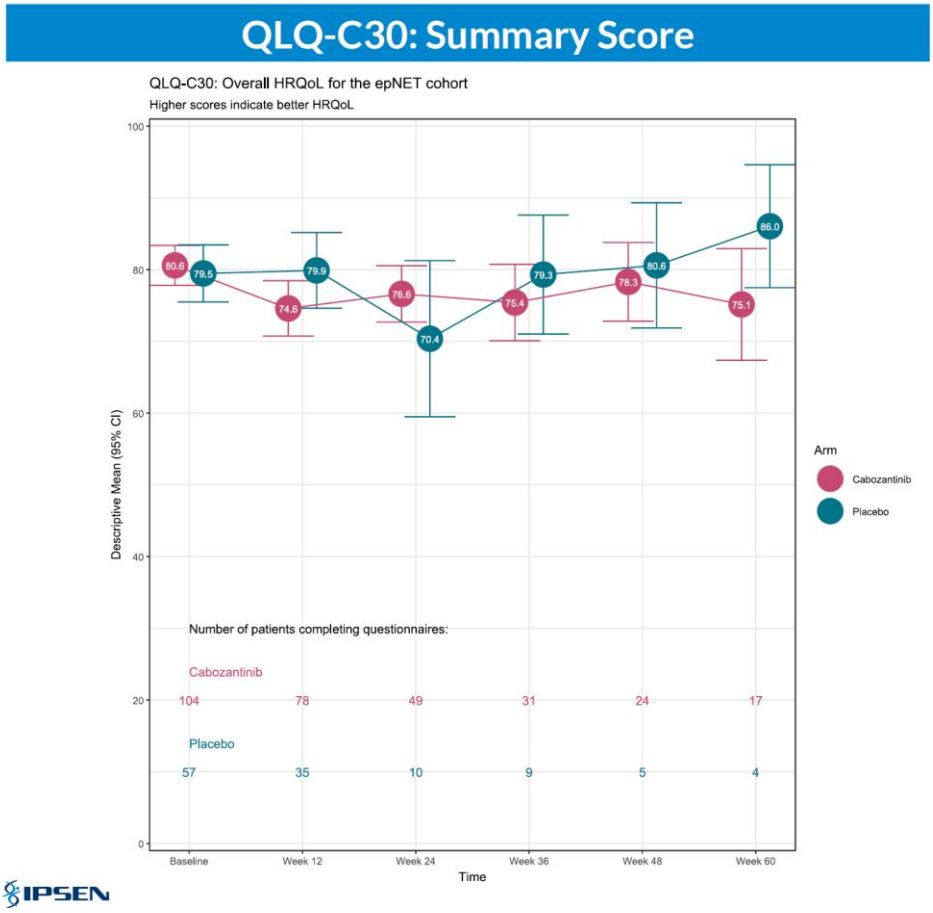


Figure 76 QLQ-C30: Summary Score epNET [83]



F.2 Presentation of health-related quality of life EORTC-QLQ-GINET21

F.2.1 Study design and measuring instrument EORTC QLQ-GINET21

EORTC QLW-GINET21 is a 21-item questionnaire that specifically assesses symptoms associated with GI-related NETs and has been validated in multinational studies [102]. It is designed to supplement the EORTC QLQ-C30 questionnaire. It covers the following symptom scales: endocrine, gastrointestinal, treatment-related side effects, social function, disease-related worries, bone/muscle pain, concern about weight loss, sexuality, and communication. Responses were collected at baseline and every 12 weeks, as previously described for EORTC QLQ-C30 (section 10.1.1). The hypothesis was that cabozantinib would improve quality of life and decrease disease-related symptoms as compared to placebo [100]. No method was identified to calculate an overall summary score for QLQ-GINET21, and therefore, this is not presented.

F.2.2 Data collection

Table 93 and Table 94 presents the missing data and completion rates in the cabozantinib and placebo arm, respectively. Available data decreased over time in both treatment arms and cohorts [83].

Table 93 Pattern of missing data and completion cabozantinib [83]

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	55	47	85.45	85.45
Week 12	52	38	73.08	69.09
Week 24	47	31	65.96	56.36
Week 36	34	26	76.47	47.27
Week 48	29	20	68.97	36.36
Week 60	25	15	60.00	27.27
		epNET		
Baseline	113	109	96.46	96.46

Time	Number of patients “at risk ”* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients “at risk ” at time point *t*** %	Proportion of responses among patients at randomisation*** %
Week 12	109	80	73.39	70.80
Week 24	84	52	61.90	46.02
Week 36	65	32	49.23	28.32
Week 48	48	24	50.00	21.24
Week 60	42	18	42.86	15.93

* Number of patients “at risk”: Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 94 Pattern of missing data and completion placebo [83]

Time	Number of patients “at risk ”* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients “at risk ” at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	28	25	89.29	89.29
Week 12	27	16	59.26	57.14
Week 24	15	6	40.00	21.43
Week 36	7	3	42.86	10.71
Week 48	4	1	25.00	3.57
Week 60	1	0	0.00	0.00
		epNET		

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Baseline	58	57	98.28	98.28
Week 12	54	35	64.81	60.34
Week 24	30	10	33.33	17.24
Week 36	17	9	52.94	15.52
Week 48	16	5	31.25	8.62
Week 60	11	4	36.36	6.90

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

F.2.3 HRQoL results

In the mean score in the nine domains of the EORTC QLQ-GINET 21 are presented. Lower scores indicate better health. In Figure 77 to Figure 94 mean scores with corresponding 95% confidence intervals are presented.

Overall, there were limited data available at later time points in the QoL study, particularly in the placebo cohorts, which made it difficult to compare the two treatment arms [83].

In the pNET cabozantinib, mean scores remained relatively stable over the study period in all domains except for "Treatment" where a more fluctuating trend was observed. In the pNET placebo cohort, greater variability were displayed across the domains [83].

In the epNET cohort, mean score were generally similar between the treatment groups and remained stable over the time period in the "Endocrine," "GI", "Treatment", and "Social Function domains". Similar to the pNET cohort, the limited data in the placebo makes it difficult to make comparisons between the treatment arms [83]. The mean score in the nine domains of the EORTC QLQ-GINET 21 are presented. Lower scores indicate better health. In Figure 77 to Figure 94 mean scores with corresponding 95% confidence intervals are presented.

Overall, there were limited data available at later time points in the QoL study, particularly in the placebo cohorts, which made it difficult to compare the two treatment arms [83].

In the pNET cabozantinib, mean scores remained relatively stable over the study period in all domains except for "Treatment" where a more fluctuating trend was observed. In the pNET placebo cohort, greater variability were displayed across the domains [83].

In the epNET cohort, mean score were generally similar between the treatment groups and remained stable over the time period in the "Endocrine," "GI", "Treatment", and "Social Function domains". Similar to the pNET cohort, the limited data in the placebo makes it difficult to make comparisons between the treatment arms [83].

Table 95 EORTC QLQ-GINET 21 [83]

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
			pNET Endocrine		
Baseline	47	7.3 (1.6)	25	6.7 (2.5)	0.7 (-5.1, 6.4)
Week 12	38	9.9 (2.7)	16	9.7 (3.8)	0.2 (-8.9, 9.4)
Week 24	31	7.9 (2.5)	6	7.4 (7.4)	0.5 (-14.8, 15.8)
Week 36	26	7.7 (2.2)	3	11.1 (6.4)	-3.4 (-16.7, 9.9)
Week 48	20	8.3 (2.8)	1	0.0 (NA)	NA
Week 60	15	6.7 (3.4)	0	NA	NA
			pNET GI		
Baseline	47	14.3 (2.1)	25	11.2 (2.2)	3.1 (-2.7, 9.0)
Week 12	38	17.0 (2.1)	16	10.8 (2.4)	6.2 (-0.1, 12.5)
Week 24	31	14.3 (2.0)	6	12.2 (2.0)	2.1 (-3.6, 7.7)
Week 36	26	18.7 (2.5)	3	20.0 (16.8)	-1.3 (-34.5, 32.0)

	Intervention		Comparator		Intervention vs. comparator
Week 48	20	15.7 (3.1)	1	6.7 (0.0)	9.0 (NA)
Week 60	15	15.6 (3.2)	0	NA	NA
pNET Treatment					
Baseline	47	6.4 (1.9)	25	1.6 (1.6)	4.8 (-0.1, 9.7)
Week 12	38	21.6 (2.9)	16	13.1 (4.6)	8.5 (-2.2, 19.2)
Week 24	31	14.9 (2.3)	6	2.8 (2.8)	12.1 (5.0, 19.2)
Week 36	26	21.4 (3.8)	3	11.1 (11.1)	10.3 (-12.8, 33.3)
Week 48	20	12.3 (2.4)	1	0.0 (NA)	12.3 (NA)
Week 60	15	17.8 (3.8)	0	NA	NA
pNET Social function					
Baseline	47	23.9 (2.9)	25	26.9 (3.8)	-3.0 (-12.4, 6.4)
Week 12	38	21.6 (3.1)	16	20.1 (4.2)	1.5 (-8.8, 11.8)
Week 24	31	20.4 (3.4)	6	20.4 (6.0)	0.1 (-13.5, 13.6)
Week 36	26	17.5 (3.4)	3	14.8 (9.8)	2.7 (-17.6, 23.1)
Week 48	20	14.4 (2.6)	1	11.1 (NA)	3.3 (NA)
Week 60	15	19.3 (4.0)	0	NA	NA
pNET Disease-related worries					

	Intervention		Comparator		Intervention vs. comparator
Baseline	47	31.8 (2.9)	25	33.1 (5.8)	-1.3 (-14.1, 11.5)
Week 12	38	27.5 (3.9)	16	33.3 (6.3)	-5.8 (-20.4, 8.7)
Week 24	31	26.3 (4.7)	6	35.2 (14.2)	-8.8 (-38.1, 20.4)
Week 36	26	30.3 (5.5)	3	11.1 (6.4)	19.2 (2.7, 35.7)
Week 48	20	22.8 (4.5)	1	0.0 (NA)	22.8 (NA)
Week 60	15	29.6 (5.3)	0	NA	NA
pNET Body image					
Baseline	47	17.0 (4.2)	25	20.0 (6.4)	-3.0 (-17.9, 12.0)
Week 12	38	14.9 (3.7)	16	14.6 (6.8)	0.3 (-14.8, 15.5)
Week 24	31	14.0 (4.6)	6	16.7 (7.5)	-2.7 (-19.8, 14.5)
Week 36	26	11.5 (3.7)	3	11.1 (11.1)	0.4 (-22.5, 23.4)
Week 48	20	10.0 (4.3)	1	0.0 (NA)	10.0 (NA)
Week 60	15	17.8 (4.4)	0	NA	NA
pNET Muscle/bone pain symptom					
Baseline	47	24.1 (4.0)	25	16.0 (4.8)	8.1 (-4.1, 20.3)
Week 12	38	21.9 (4.0)	16	25.0 (5.7)	-3.1 (-16.7, 10.6)
Week 24	31	28.0 (5.1)	6	33.3 (12.2)	-5.4 (-31.3, 20.5)

	Intervention		Comparator		Intervention vs. comparator
Week 36	26	25.3 (5.5)	3	44.4 (11.1)	-19.1 (-43.4, 5.2)
Week 48	20	26.7 (6.2)	1	0.0 (NA)	26.7 (NA)
Week 60	15	22.2 (6.2)	0	NA	NA
pNET Information/communication function					
Baseline	47	2.8 (2.2)	25	5.3 (4.2)	-2.5 (-11.8, 6.8)
Week 12	38	6.1 (3.0)	16	2.1 (2.1)	4.1 (-3.2, 11.3)
Week 24	31	3.2 (3.2)	6	0.0 (0.0)	3.2 (-3.1, 9.5)
Week 36	26	1.3 (1.3)	3	0.0 (0.0)	1.3 (-1.2, 3.8)
Week 48	20	3.3 (2.3)	1	0.0 (NA)	3.3 (NA)
Week 60	15	2.2 (2.2)	0	NA	NA
pNET Sexual function					
Baseline	47	18.8 (5.6)	25	30.8 (10.3)	-12.0 (-35.0, 11.0)
Week 12	38	15.1 (4.0)	16	30.3 (12.3)	-15.2 (-40.6, 10.1)
Week 24	31	11.9 (3.5)	6	6.7 (6.7)	5.2 (-9.5, 20.0)
Week 36	26	8.3 (4.1)	3	0.0 (0.0)	8.3 (0.3, 16.4)
Week 48	20	14.3 (4.6)	1	33.3 (NA)	-19.0 (NA)
Week 60	15	7.7 (5.5)	0	NA	NA
epNET Endocrine					
Baseline	109	15.2 (1.8)	57	14.0 (2.4)	1.1 (-4.7, 7.0)
Week 12	80	15.0 (2.0)	35	12.1 (3.1)	2.9 (-4.3, 10.2)

	Intervention		Comparator		Intervention vs. comparator
Week 24	52	13.7 (2.6)	10	13.3 (4.3)	0.3 (-9.6, 10.3)
Week 36	32	12.5 (2.7)	9	8.6 (3.6)	3.9 (-5.0, 12.7)
Week 48	24	13.4 (3.0)	5	13.3 (6.5)	0.1 (-13.9, 14.1)
Week 60	18	11.7 (3.4)	4	13.9 (5.3)	-2.2 (-14.6, 10.2)
		epNET GI			
Baseline	109	17.5 (1.6)	57	20.1 (2.6)	-2.6 (-8.5, 3.3)
Week 12	80	23.1 (1.9)	35	20.6 (3.5)	2.5 (-5.2, 10.3)
Week 24	52	23.8 (2.6)	10	22.7 (7.5)	1.2 (-14.3, 16.6)
Week 36	32	23.8 (3.1)	9	24.4 (10.2)	-0.7 (-21.7, 20.3)
Week 48	24	21.9 (3.2)	5	17.7 (6.8)	4.2 (-10.6, 19.0)
Week 60	18	21.5 (3.5)	4	26.7 (11.9)	-5.2 (-29.4, 19.0)
		epNET Treatment			
Baseline	109	9.1 (1.9)	57	6.3 (1.9)	2.8 (-2.6, 8.2)
Week 12	80	20.1 (1.9)	35	9.3 (2.1)	10.8 (5.2, 16.4)
Week 24	52	16.4 (2.1)	10	13.9 (4.3)	2.6 (-6.9, 12.0)
Week 36	32	14.9 (2.8)	9	9.0 (3.6)	5.9 (-3.2, 14.9)
Week 48	24	11.9 (1.8)	5	8.9 (4.2)	3.0 (-5.9, 11.9)

	Intervention		Comparator		Intervention vs. comparator
Week 60	18	10.8 (2.8)	4	11.1 (4.5)	-0.3 (-10.7, 10.1)
epNET Social function					
Baseline	109	27.9 (2.0)	57	32.2 (3.0)	-4.3 (-11.4, 2.8)
Week 12	80	32.5 (2.5)	35	24.4 (4.3)	8.1 (-1.6, 17.7)
Week 24	52	29.9 (3.1)	10	25.6 (3.7)	4.4 (-5.1, 13.8)
Week 36	32	27.6 (4.9)	9	21.0 (7.3)	6.6 (-10.6, 23.8)
Week 48	24	24.5 (3.9)	5	28.9 (7.5)	-4.4 (-21.0, 12.3)
Week 60	18	29.6 (5.7)	4	27.8 (10.6)	1.9 (-21.8, 25.5)
epNET Disease-related worries					
Baseline	109	38.2 (2.6)	57	45.6 (3.6)	-7.4 (-16.2, 1.4)
Week 12	80	40.8 (3.1)	35	33.8 (4.3)	7.0 (-3.4, 17.3)
Week 24	52	33.2 (3.7)	10	48.9 (9.7)	-15.7 (-36.0, 4.6)
Week 36	32	37.3 (5.2)	9	37.0 (6.4)	0.3 (-15.8, 16.4)
Week 48	24	30.3 (4.8)	5	48.9 (9.7)	-18.6 (-39.7, 2.6)
Week 60	18	35.8 (6.8)	4	55.6 (17.6)	-19.8 (-56.6, 17.1)
epNET Body image					
Baseline	109	15.0 (2.4)	57	20.0 (4.1)	-5.0 (-14.4, 4.4)

	Intervention		Comparator		Intervention vs. comparator
Week 12	80	19.5 (3.2)	35	6.7 (3.6)	12.8 (3.5, 22.2)
Week 24	52	28.8 (4.7)	10	10.0 (7.1)	18.8 (2.2, 35.5)
Week 36	32	32.3 (6.1)	9	14.8 (8.1)	17.5 (-2.3, 37.3)
Week 48	24	20.8 (5.6)	5	6.7 (6.7)	14.2 (-2.9, 31.2)
Week 60	18	16.7 (4.9)	4	8.3 (8.3)	8.3 (-10.6, 27.2)
epNET Muscle/bone pain symptom					
Baseline	109	30.6 (3.0)	57	35.1 (4.7)	-4.5 (-15.4, 6.4)
Week 12	80	33.8 (3.6)	35	25.7 (5.1)	8.0 (-4.3, 20.4)
Week 24	52	33.3 (4.3)	10	40.0 (6.7)	-6.7 (-22.2, 8.9)
Week 36	32	33.3 (5.0)	9	29.6 (11.7)	3.7 (-21.2, 28.6)
Week 48	24	22.2 (4.8)	5	20.0 (8.2)	2.2 (-16.3, 20.8)
Week 60	18	20.4 (4.8)	4	25.0 (16.0)	-4.6 (-37.3, 28.0)
epNET Information/communication function					
Baseline	109	4.6 (1.4)	57	2.3 (1.1)	2.2 (-1.3, 5.8)
Week 12	80	4.2 (1.5)	35	1.9 (1.3)	2.3 (-1.7, 6.2)
Week 24	52	3.2 (1.4)	10	16.7 (11.4)	-13.5 (-35.9, 9.0)
Week 36	32	7.3 (2.9)	9	0.0 (0.0)	7.3 (1.6, 13.0)
Week 48	24	4.2 (2.3)	5	6.7 (6.7)	-2.5 (-16.3, 11.3)

	Intervention		Comparator		Intervention vs. comparator
Week 60	18	0.0 (0.0)	4	0.0 (0.0)	0.0 (0.0, 0.0)
epNET Sexual function					
Baseline	109	26.3 (4.2)	57	29.1 (5.5)	-2.7 (-16.3, 10.8)
Week 12	80	29.0 (5.2)	35	25.3 (5.9)	3.6 (-11.7, 19.0)
Week 24	52	23.1 (5.1)	10	33.3 (14.1)	-10.3 (-39.6, 19.1)
Week 36	32	29.0 (7.6)	9	27.8 (18.1)	1.2 (-37.3, 39.7)
Week 48	24	13.0 (6.1)	5	26.7 (12.5)	-13.7 (-40.9, 13.5)
Week 60	18	12.1 (8.1)	4	25.0 (8.3)	-12.9 (-35.7, 9.9)

The result of the EORTC QLQ-GINET21 is reported in nine domains [83].

Figure 77 pNET QLQ-GINET21 Endocrine [83]

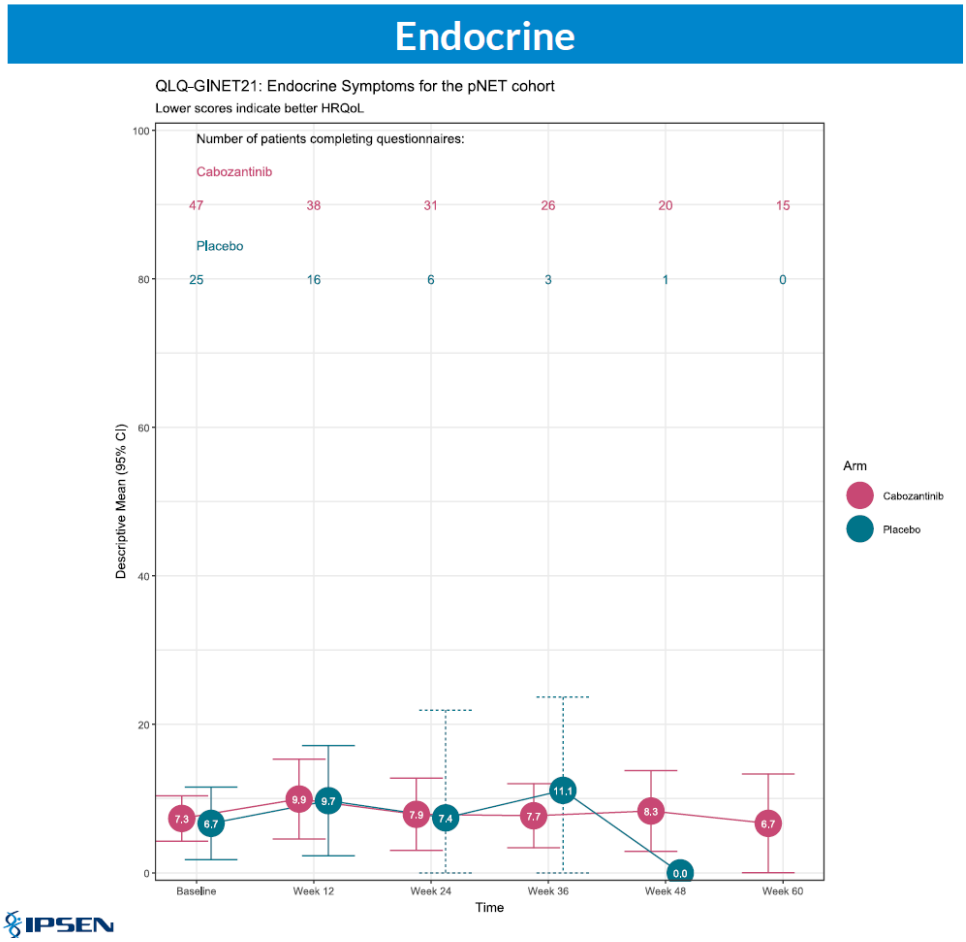


Figure 78 pNET QLQ-GINET21 GI [83]

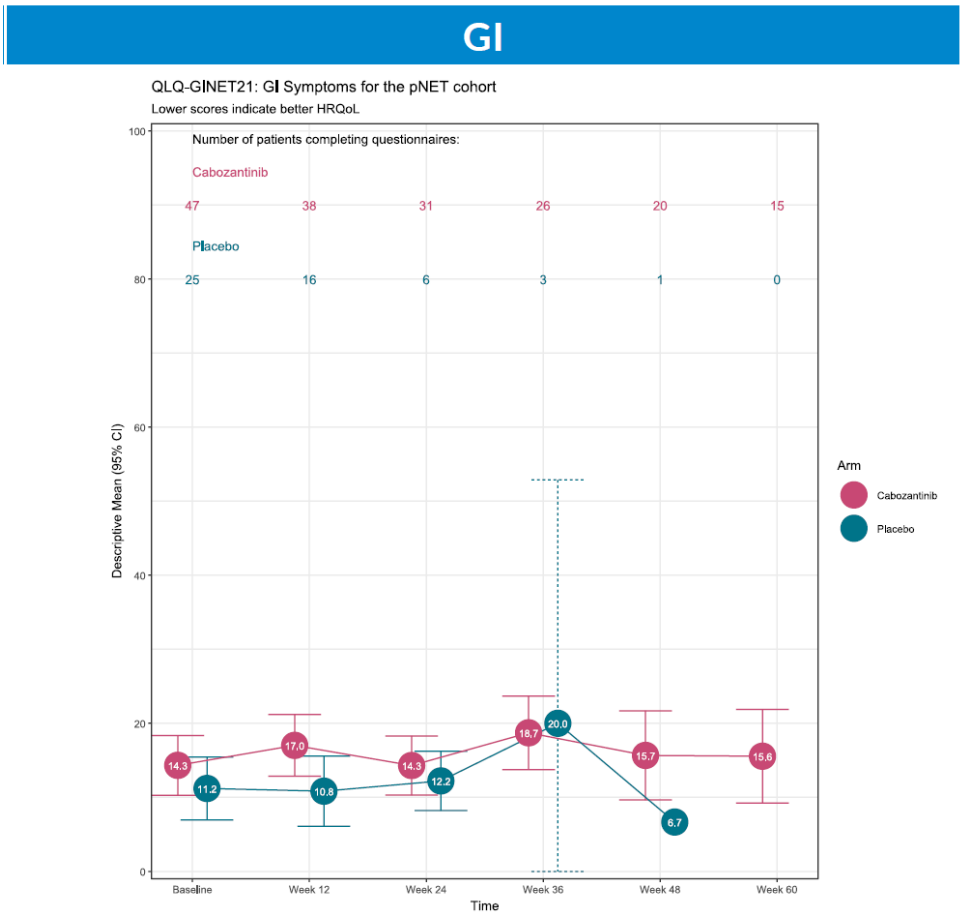


Figure 79 pNET QLQ-GINET21 Treatment [83]

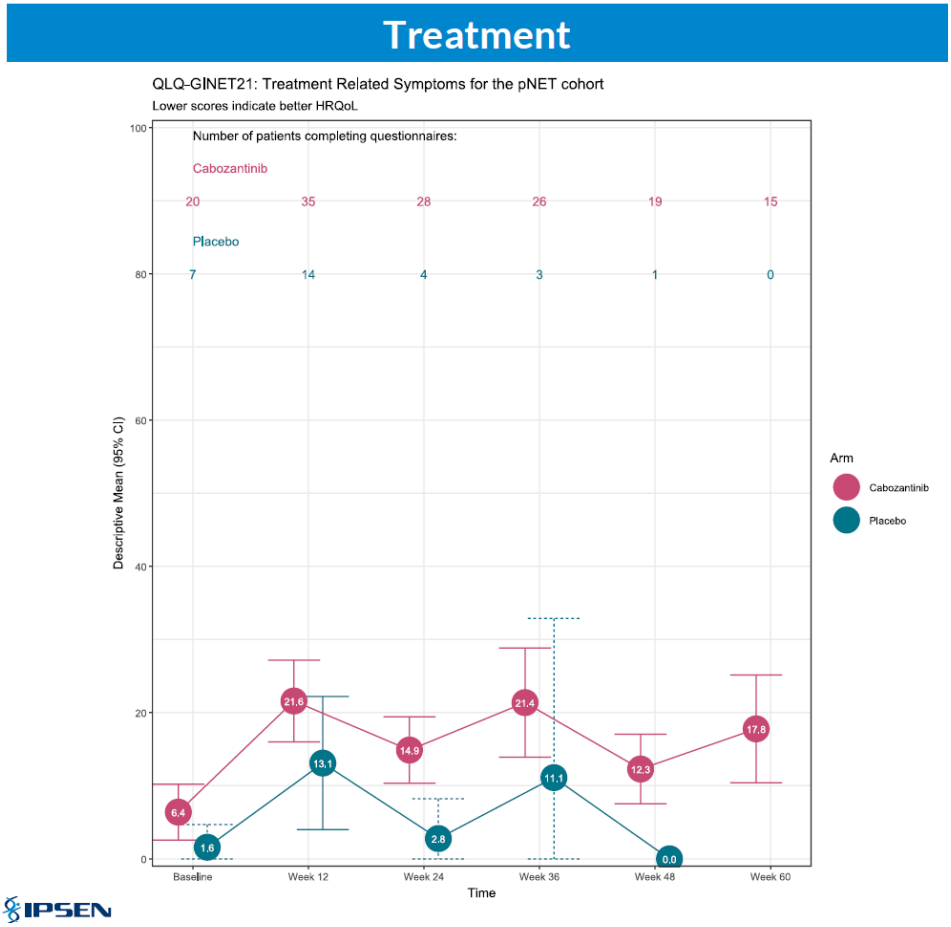


Figure 80 pNET QLQ-GINET21 Social Functioning [83]

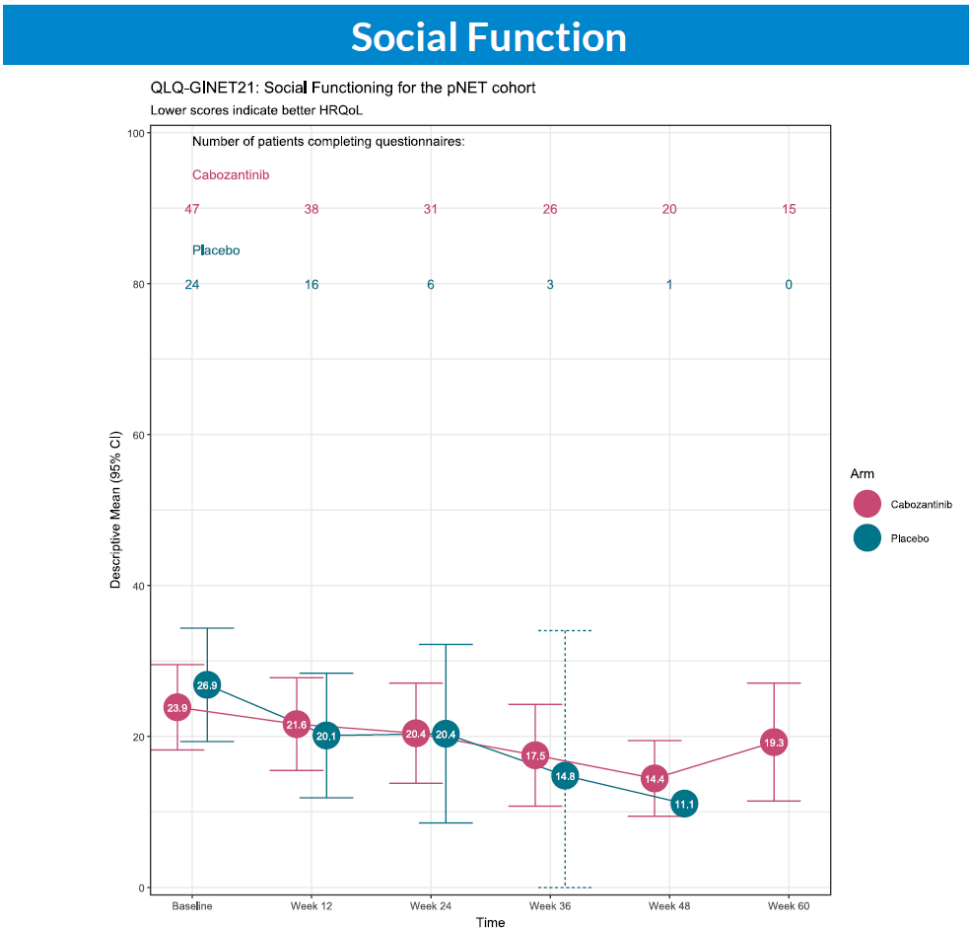


Figure 81 pNET QLQ-GINET21 Disease-Related Worries [83]

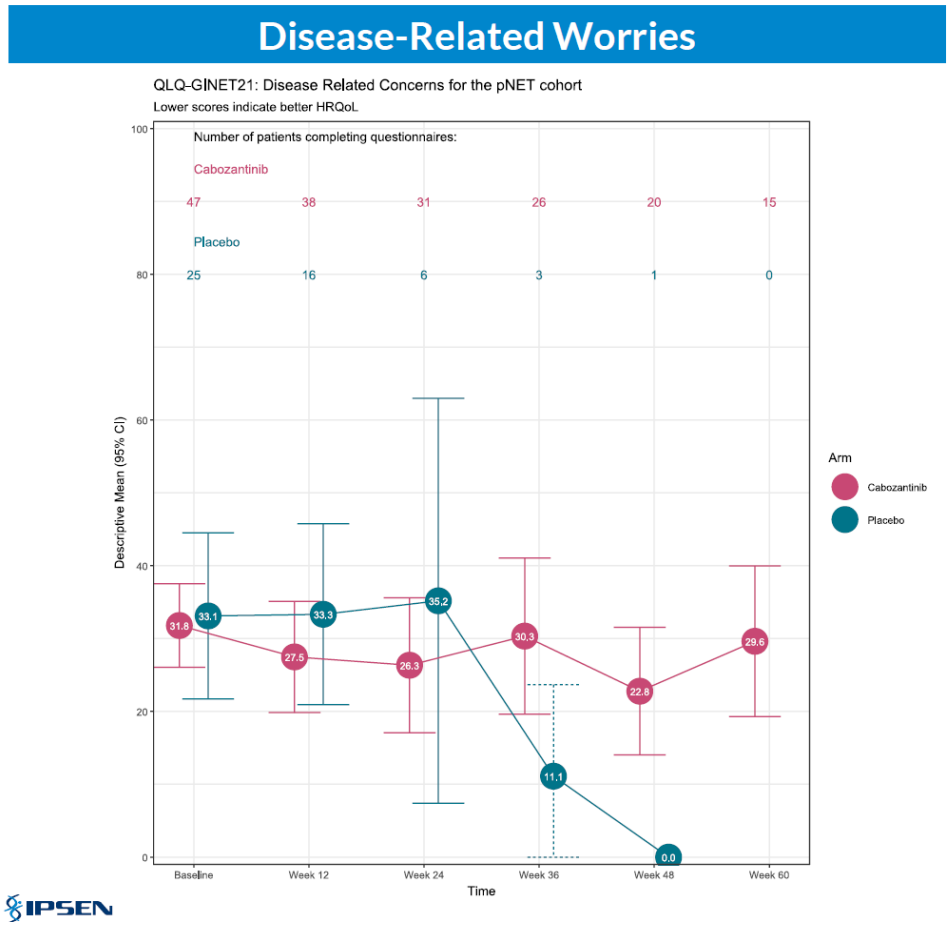


Figure 82 pNET QLQ-GINET21 Body Image [83]

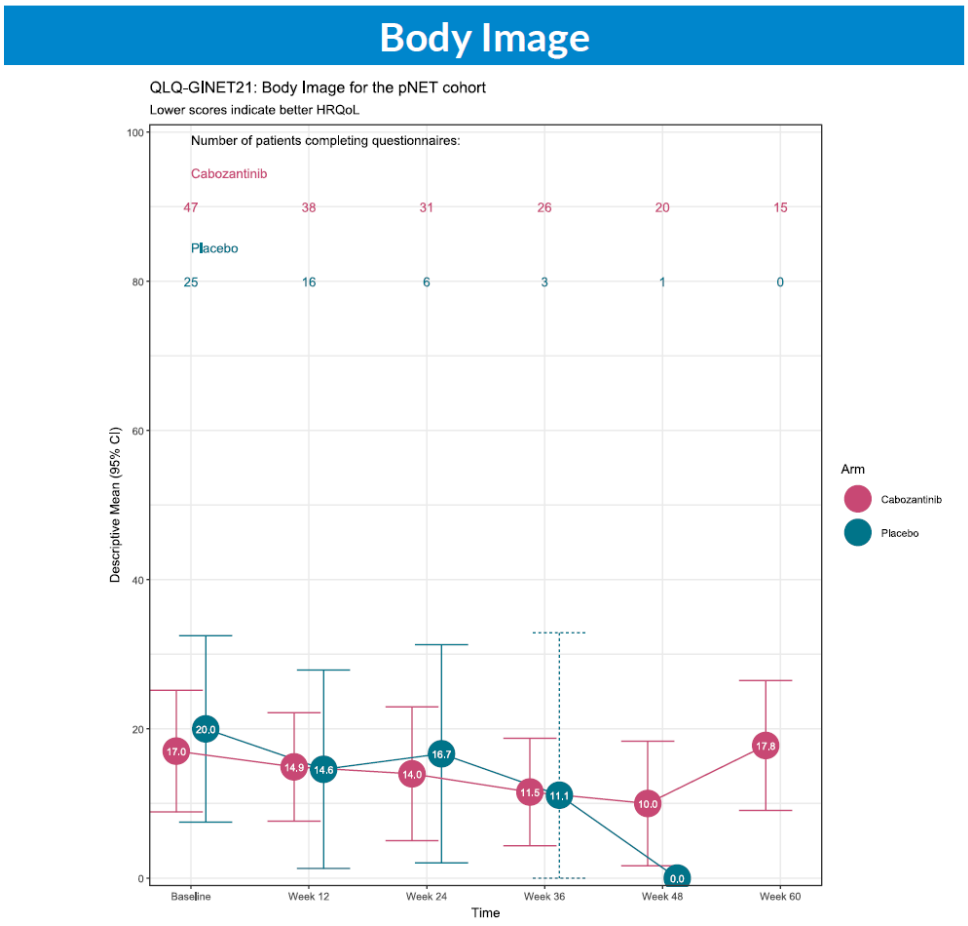


Figure 83 pNET QLQ-GINET21 Muscle/Bone Pain Symptom [83]

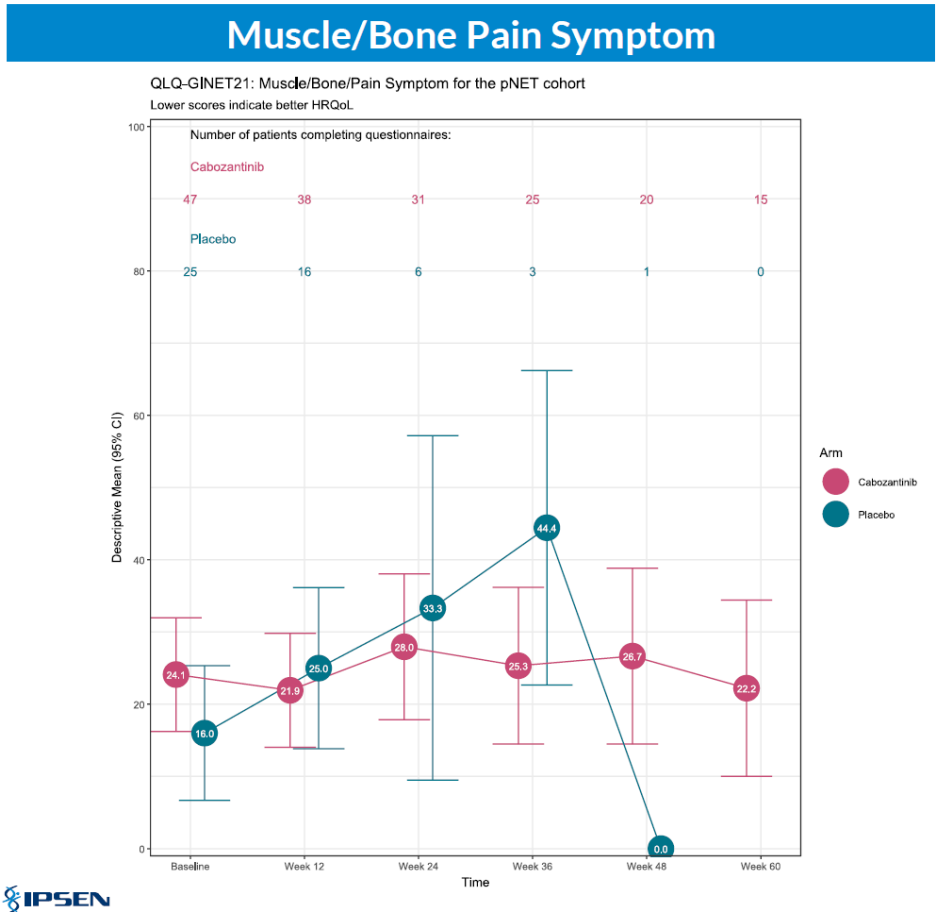


Figure 84 pNET QLQ-GINET 21 Information/Communication Function [83]

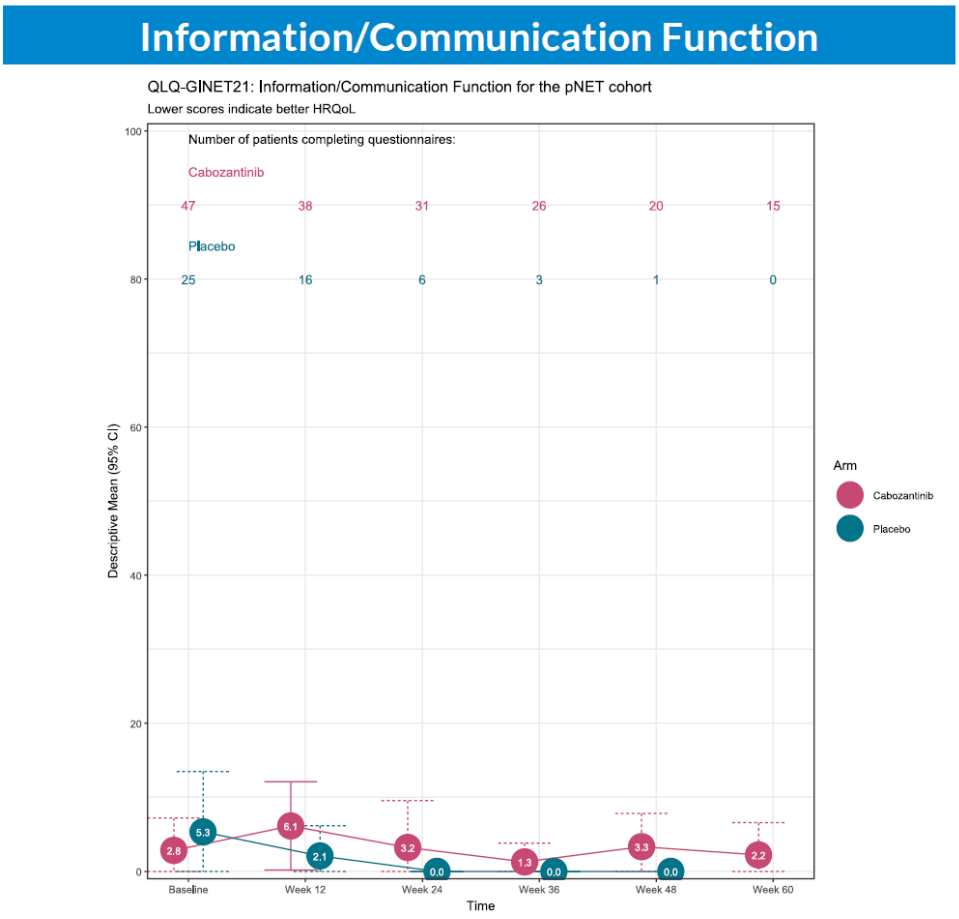


Figure 85 pNET QLQ-GINET21 Sexual Function [83]

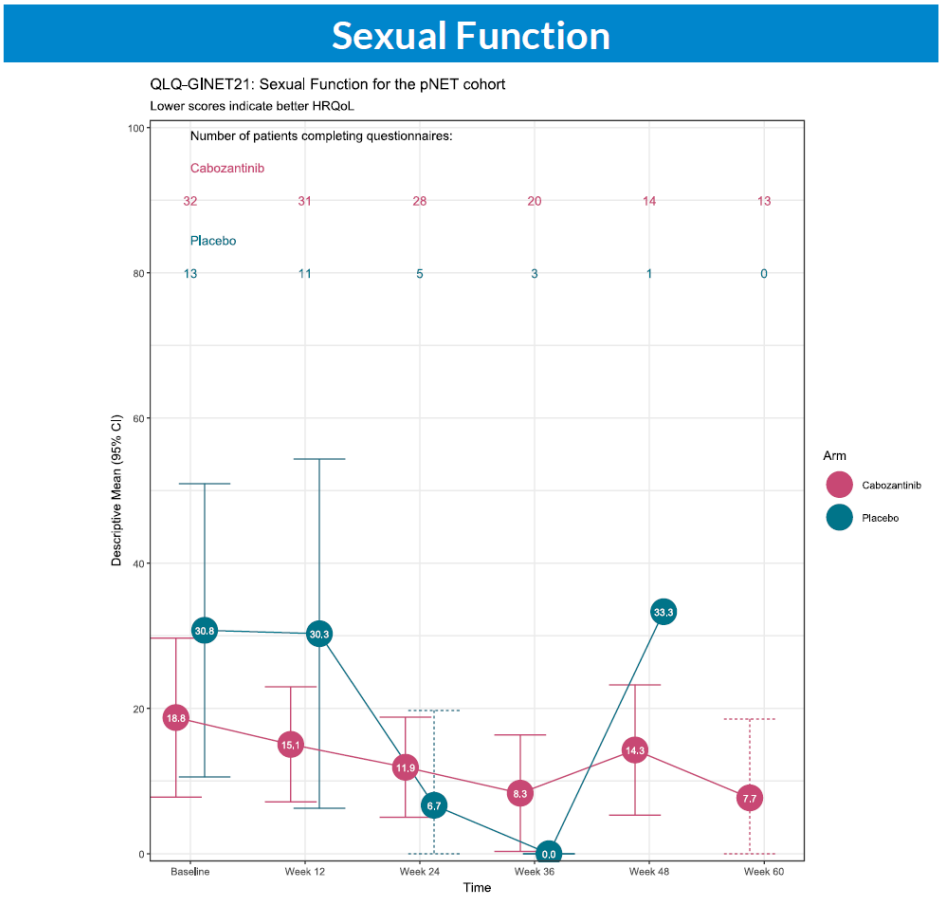


Figure 86 epNET QLQ-GINET21 Endocrine [83]

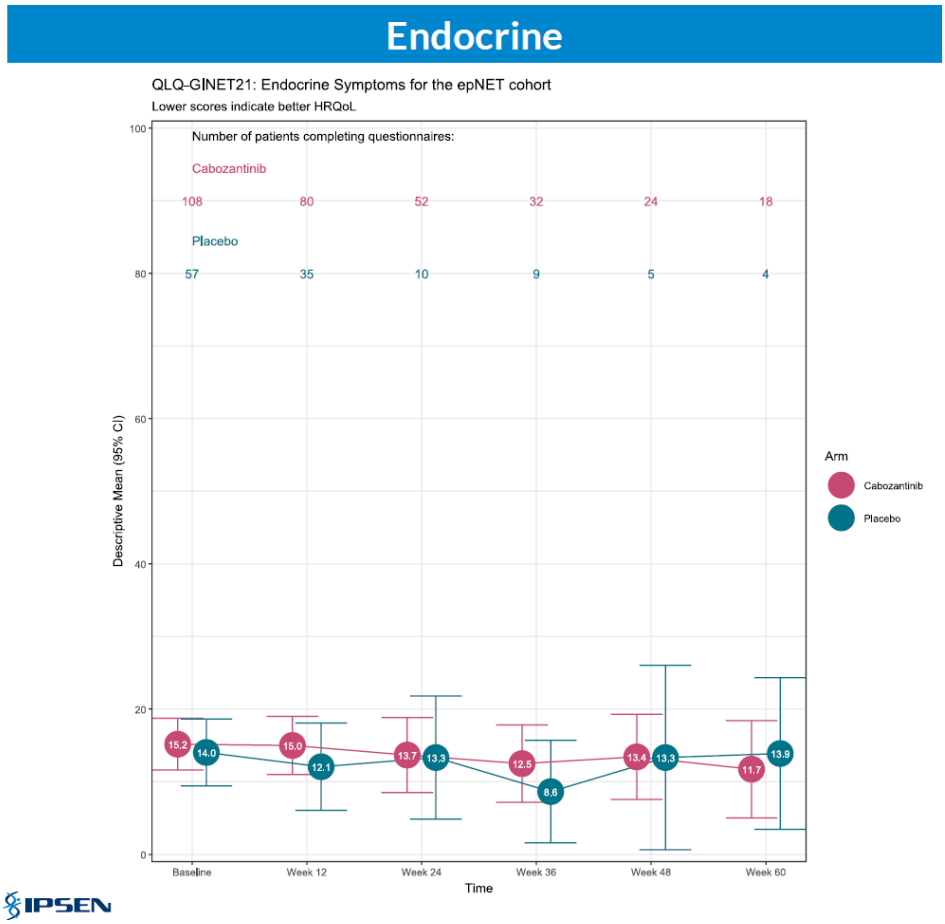


Figure 87 epNET QLQ-GINET21 GI [83]

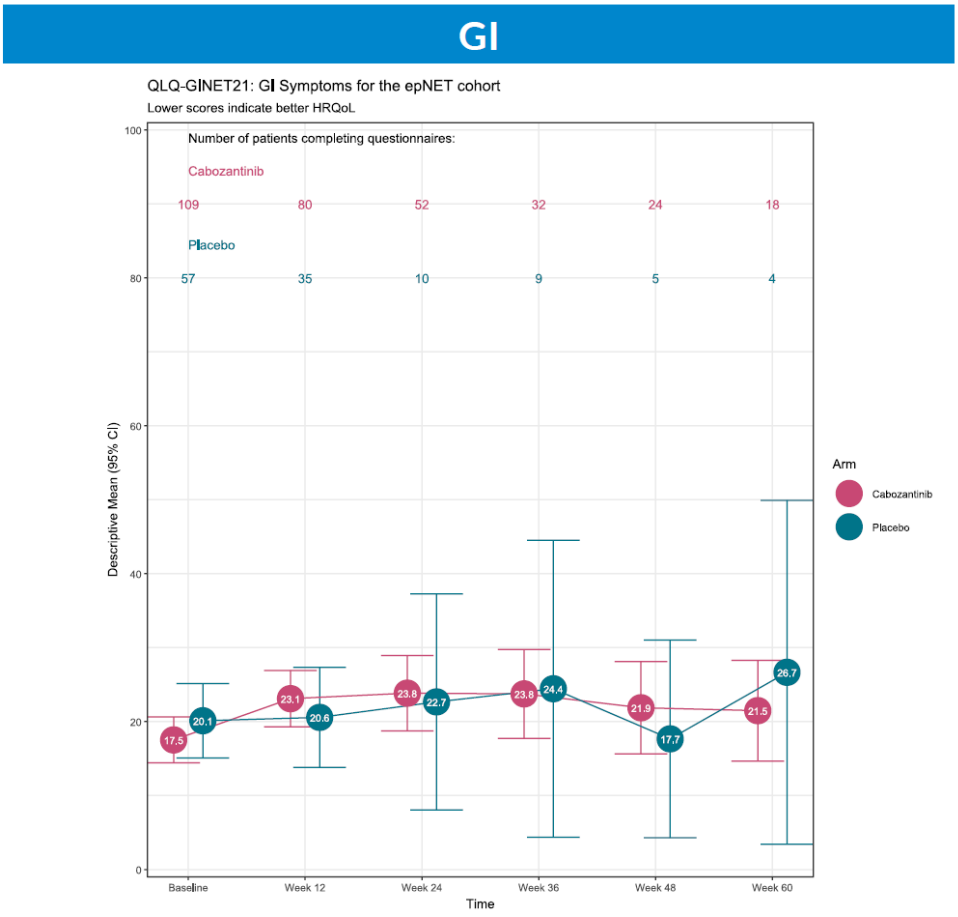


Figure 88 epNET QLQ-GINET Treatment [83]

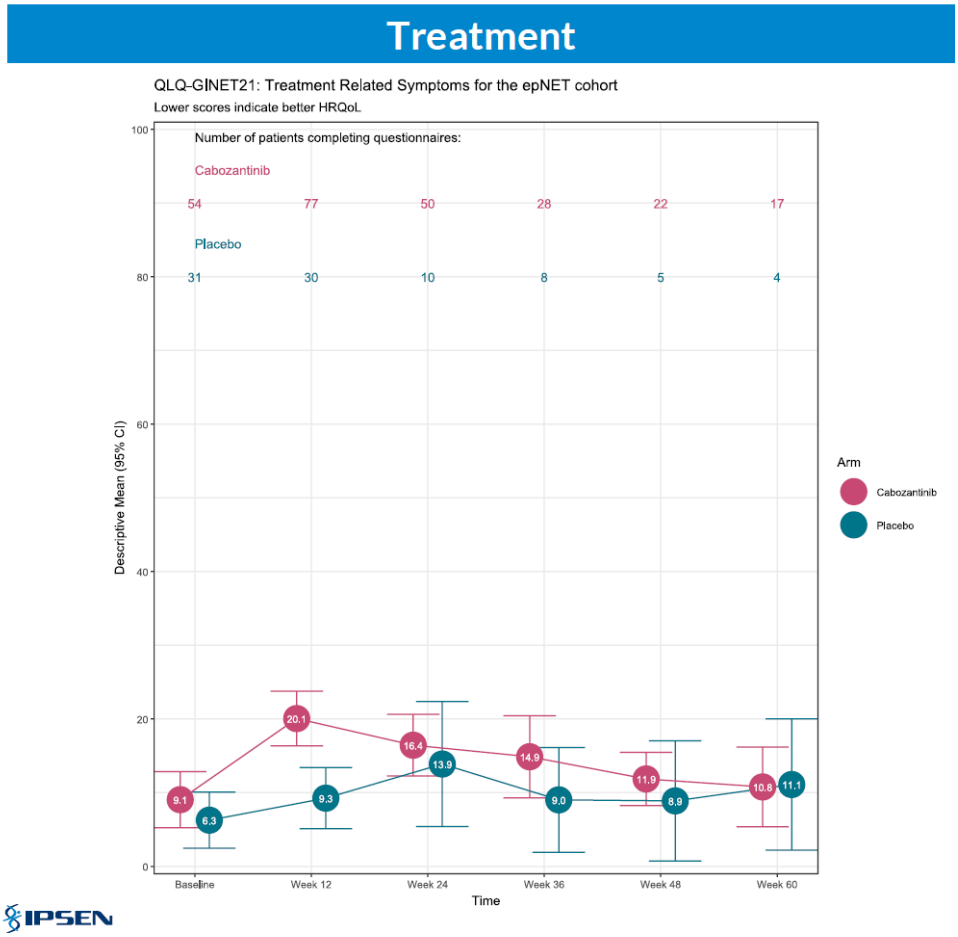


Figure 89 epNET QLQ-GINET Social Function [83]

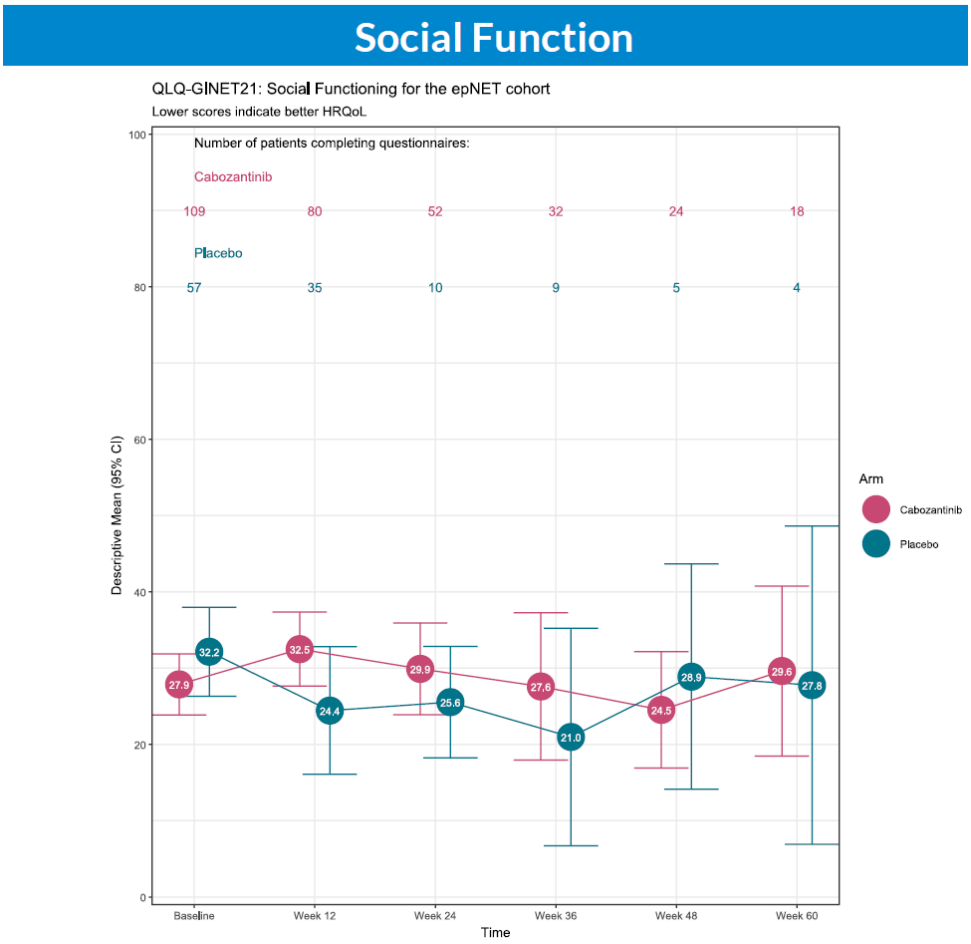


Figure 90 epNET Disease-Related Worries [83]

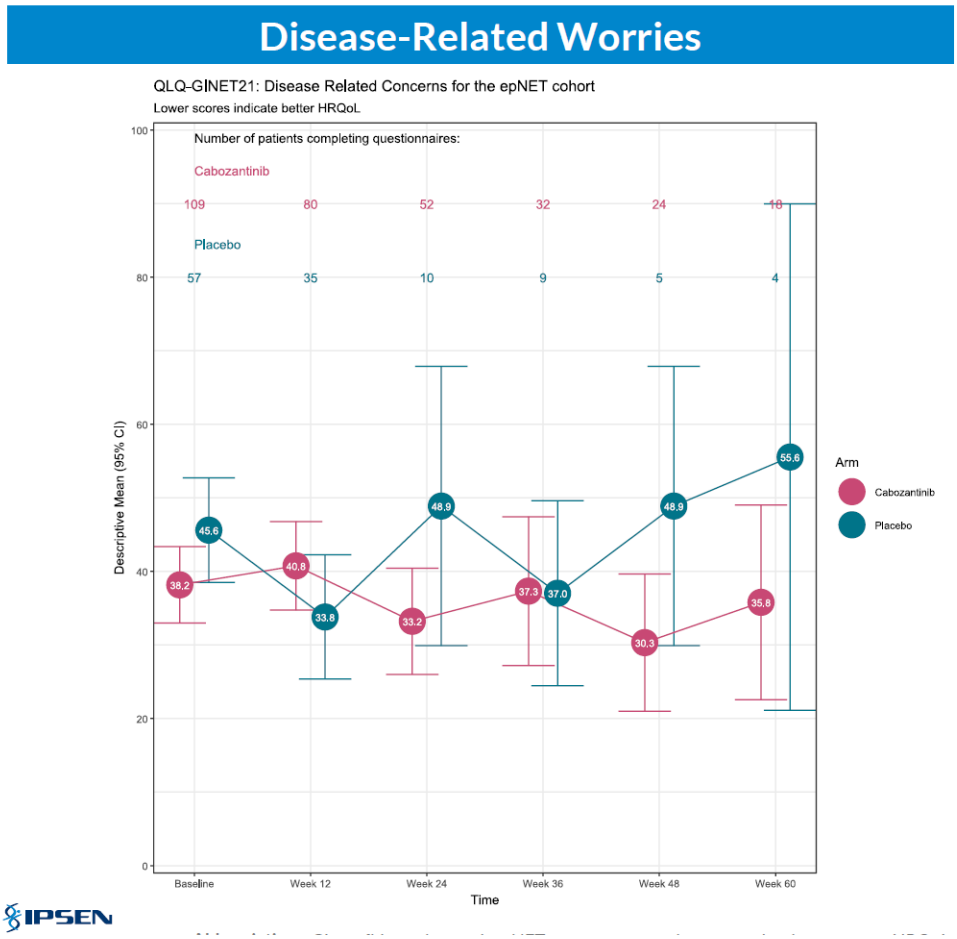


Figure 91 epNET QLQ-GINET Body Image [83]

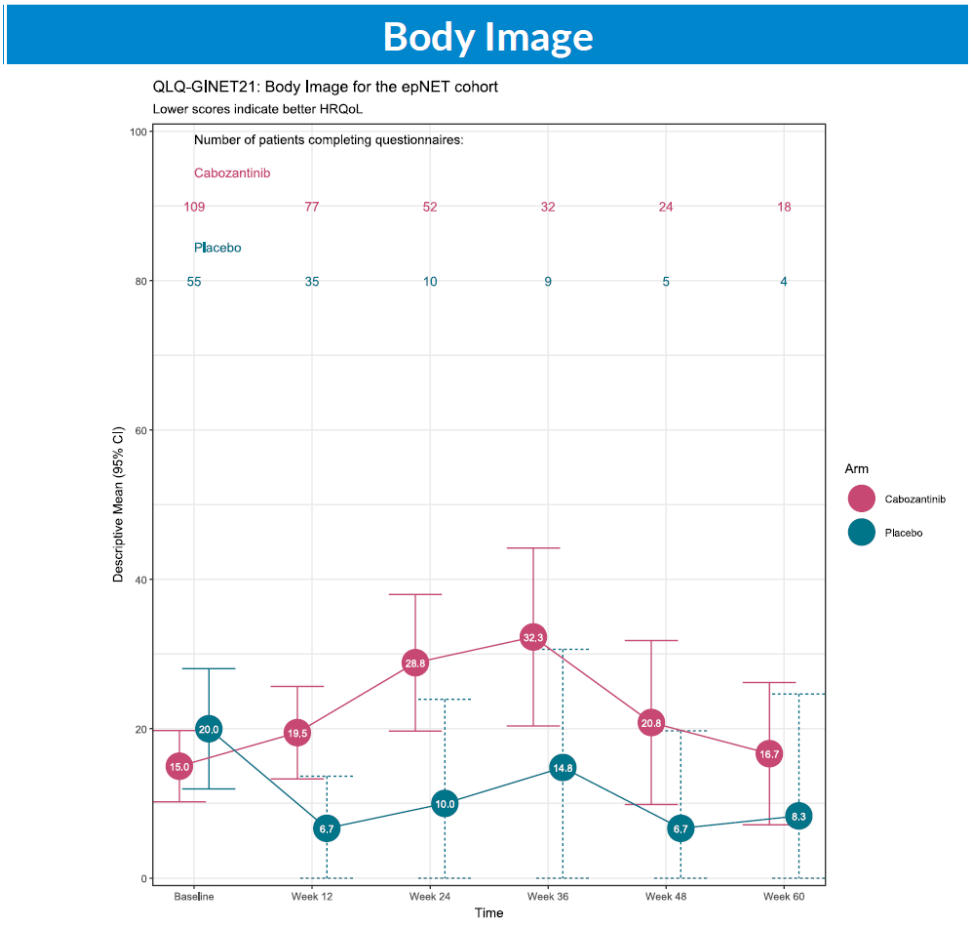


Figure 92 epNET QLQ-GINET Muscle/Bone Pain Symptom [83]

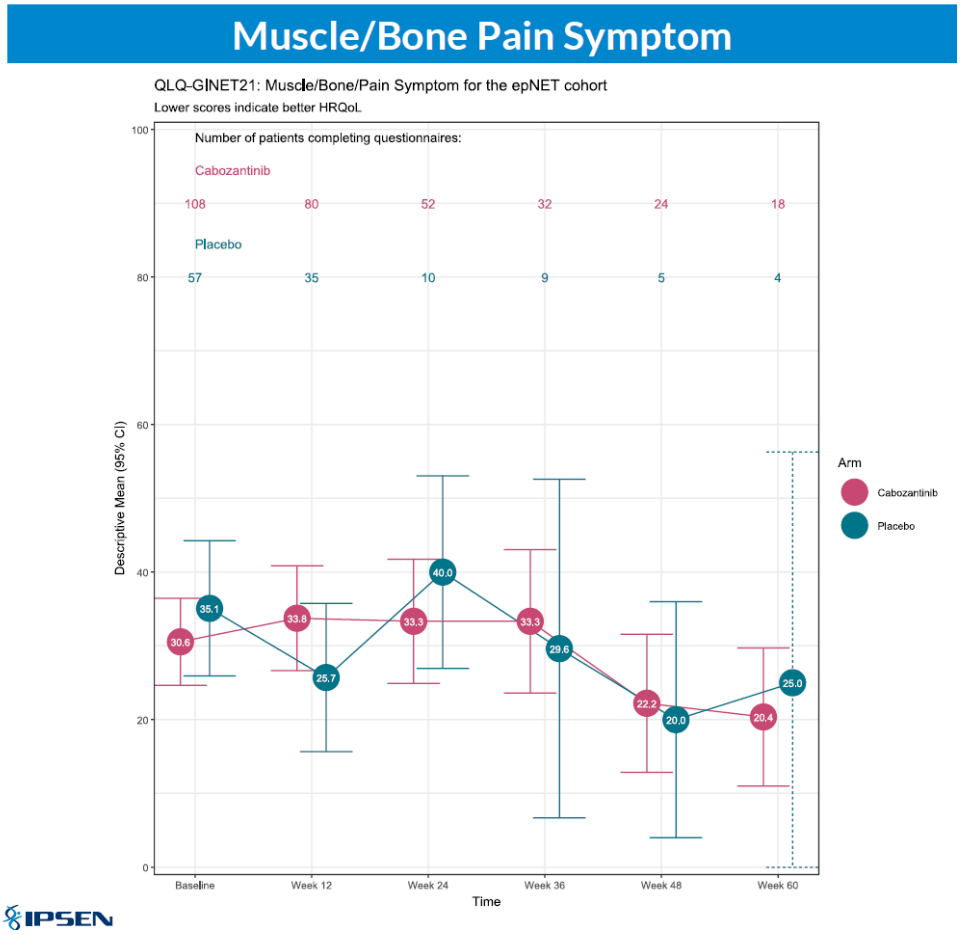


Figure 93 epNET QLQ-GINET21 Information/Communication Function [83]

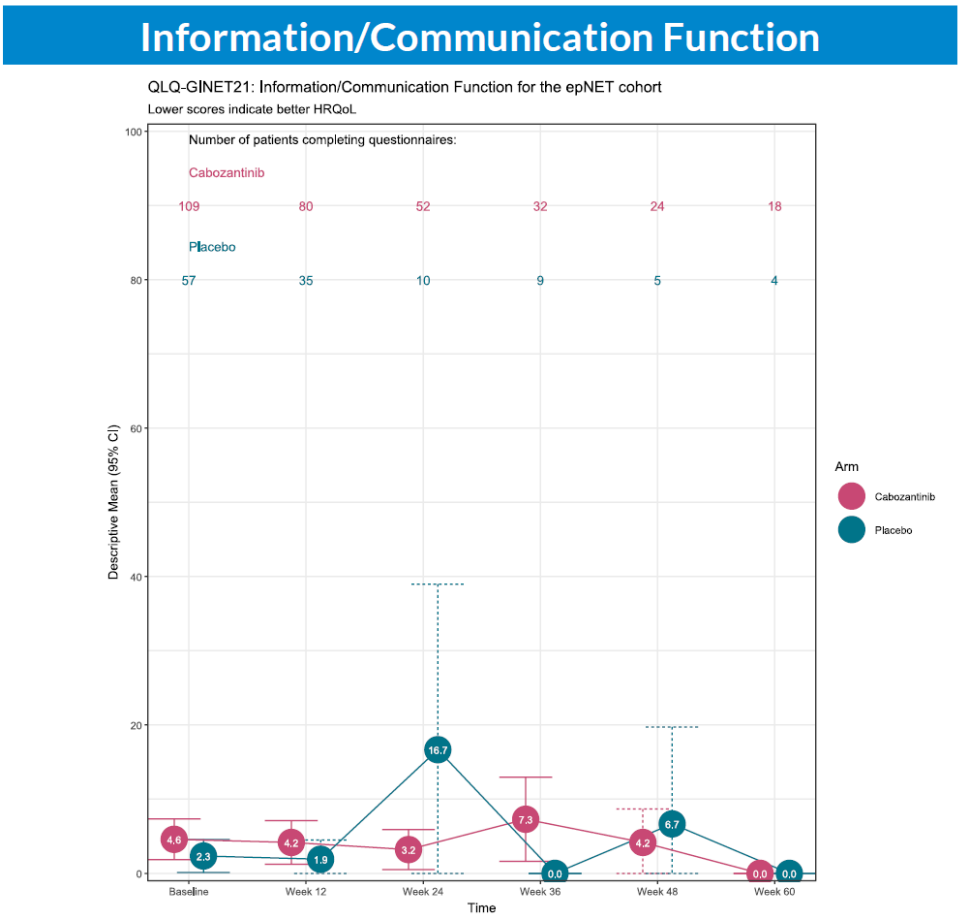
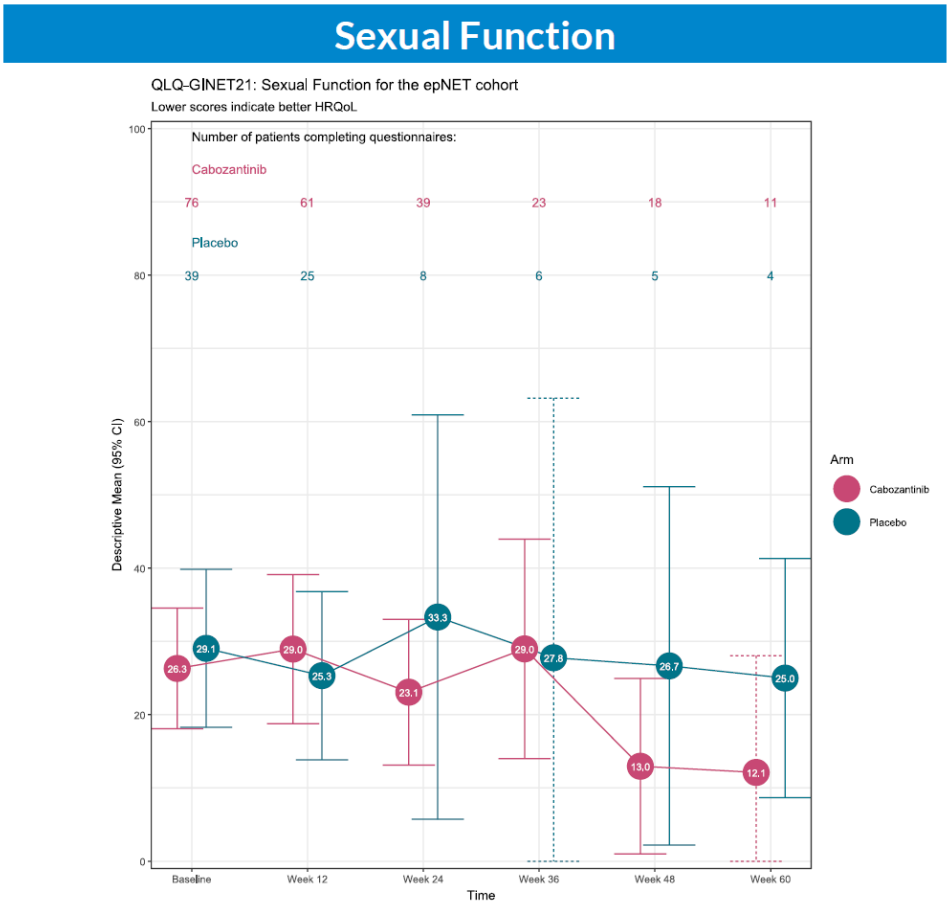


Figure 94 epNET QLQ-GINET21 Sexual Function [83]



F.3 Presentation of the health-related quality of life Patients' Global Impression of Change (PGIC)

F.3.1 Study design and measuring instrument Patients' Global Impression of Change

Perception of change was evaluated with a Patient Global Impression of Change item. Global Impression of Change Scale (also called the Subjective Significance Scale) has been used as an anchor for determination of minimally clinically significant differences in numerous oncology clinical trials [82]. The patient rates the change in his/her overall status in the levels: 1) Very much improved, 2) Much improved, 3) Minimally improved, 4) No change, 5) Minimally worse, 6) Much worse, 7) Very much worse. The responses are recorded as a numerical values, with a lower score indicating better HRQoL.

F.3.2 Data collection

Table 96 and Table 97 present the pattern of missing data and completion in the cabozantinib and placebo cohorts, respectively. Available data decreased over time in both treatment arms and cohorts. The available data was especially low in the placebo cohorts [83].

Table 96 Pattern of missing data and completion cabozantinib [83]

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	55	15	27.27	30.61
Week 12	52	38	73.08	77.55
Week 24	47	30	63.83	61.22
Week 36	34	26	76.47	53.06
Week 48	29	20	68.97	40.82
Week 60	25	14	56.00	28.57
		epNET		
Baseline	113	21	18.58	23.86
Week 12	109	76	69.72	86.36
Week 24	84	49	58.33	55.68
Week 36	65	32	49.23	36.36
Week 48	48	24	50.00	27.27
Week 60	42	18	42.86	20.45

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 97 Pattern of missing data and completion placebo [83]

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
		pNET		
Baseline	28	1	3.57	5.26
Week 12	27	15	55.56	78.95
Week 24	15	6	40.00	31.58
Week 36	7	3	42.86	15.79
Week 48	4	1	25.00	5.26
Week 60	1	0	0.00	0.00
		epNET		
Baseline	58	16	27.59	37.21
Week 12	54	32	59.26	74.42
Week 24	30	11	36.67	25.58
Week 36	17	6	35.29	13.95
Week 48	16	5	31.25	11.63
Week 60	11	4	36.36	9.30

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

F.3.3 HRQoL results

Summary statistics for the PGIC are presented in Table 98.

Data collection was designed to continue until disease progression or the initiation of a new anticancer treatment, ensuring that the majority of data would be available for

patients with PF. This trend is reflected in the results, where response rates decline over time. The number of respondents was higher in the cabozantinib arm compared to the placebo arm [83].

Among pNET cabozantinib subjects, the mean scores fell within the second and third response levels, much improved and minimally improved, at all time points. In contrast, the pNET placebo arm showed greater variability with responses[83].

In the epNET cohort, the mean score in the cabozantinib arm indicated an improvement in HRQoL over the study period. As in the pNET cohort, the mean score in the epNET placebo arm showed a larger variability in mean score over the study period [83].

Table 98 PGIC summary statistics [83]

	Cabozantinib		Placebo		Cabozantinib vs. placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
			pNET		
Baseline	15	3.9 (0.2)	1	4.0 (0.0)	-0.1 (-0.1, -0.1)
Week 12	38	3.3 (0.2)	15	4.0 (0.2)	-0.7 (-1.3, 0.0)
Week 24	30	3.3 (0.3)	6	3.3 (0.5)	-0.1 (-1.2, 1.0)
Week 36	26	3.0 (0.3)	3	3.3 (0.9)	-0.4 (-2.2, 1.4)
Week 48	20	2.8 (0.3)	1	5.0 (NA)	NA
Week 60	14	3.6 (0.4)	0	NA	NA
			epNET		
Baseline	21	4.0 (0.1)	16	3.9 (0.3)	0.1 (-0.5, 0.8)
Week 12	76	3.7 (0.2)	32	4.0 (0.2)	-0.4 (-0.8, 0.1)
Week 24	49	3.1 (0.2)	11	4.5 (0.3)	-1.3 (-2.1, -0.6)
Week 36	32	3.2 (0.2)	6	3.0 (0.5)	0.2 (-0.9, 1.3)
Week 48	24	2.8 (0.2)	5	3.6 (0.5)	-0.8 (-1.9, 0.3)
Week 60	18	3.0 (0.4)	4	2.8 (0.5)	0.3 (-0.9, 1.4)

In Figure 95, the result of the pNET cohort is presented as mean change from baseline. Notably, in the placebo group, only data from one patient was available at baseline, meaning that the mean change from baseline represents the mean change from one subject´s response. Overall, both treatment groups show fluctuations in the recorded data points, with no clear trend emerging.

Figure 95 PGIC pNET [83]

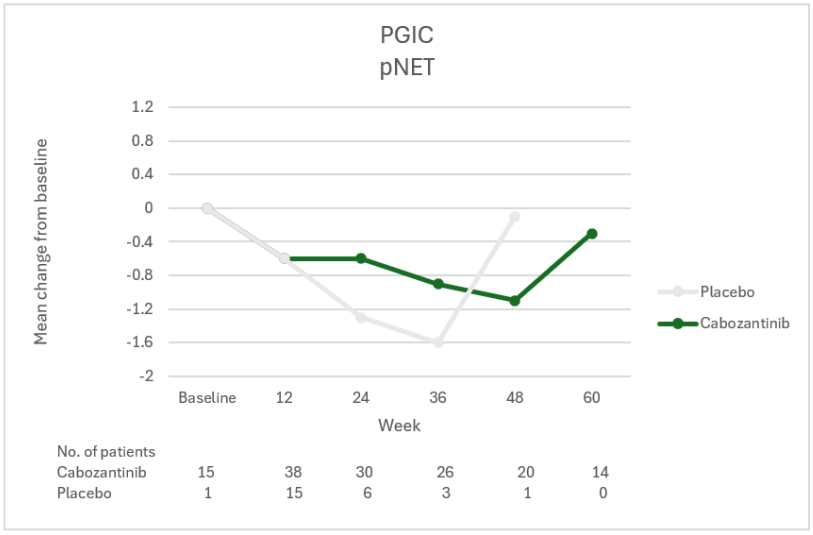


Figure 96 presents the results for the epNET cohort as mean change from baseline. The cabozantinib arm shows a slight downward trend, suggesting an improvement in patients' overall health, although the change is numerically small. In contrast, the placebo group shows greater variability between the measurement's points, lacking a clear trend.

Figure 96 PGIC epNET [83]

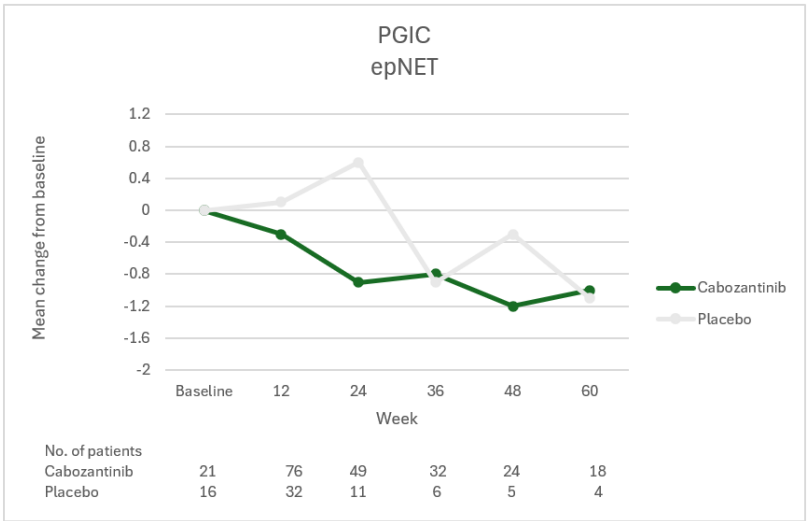


Figure 97 and Figure 98 presents the summary scores with corresponding confidence intervals for the pNET and epNET cohorts, respectively.

Figure 97 pNET PGIC Global Scores

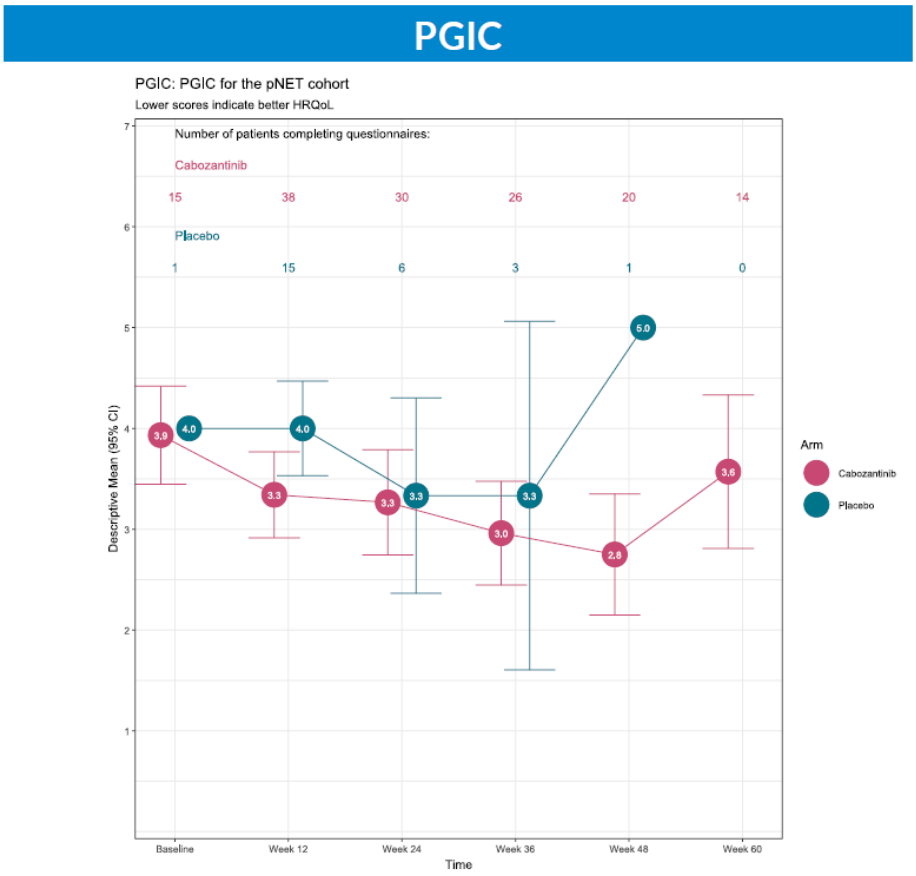
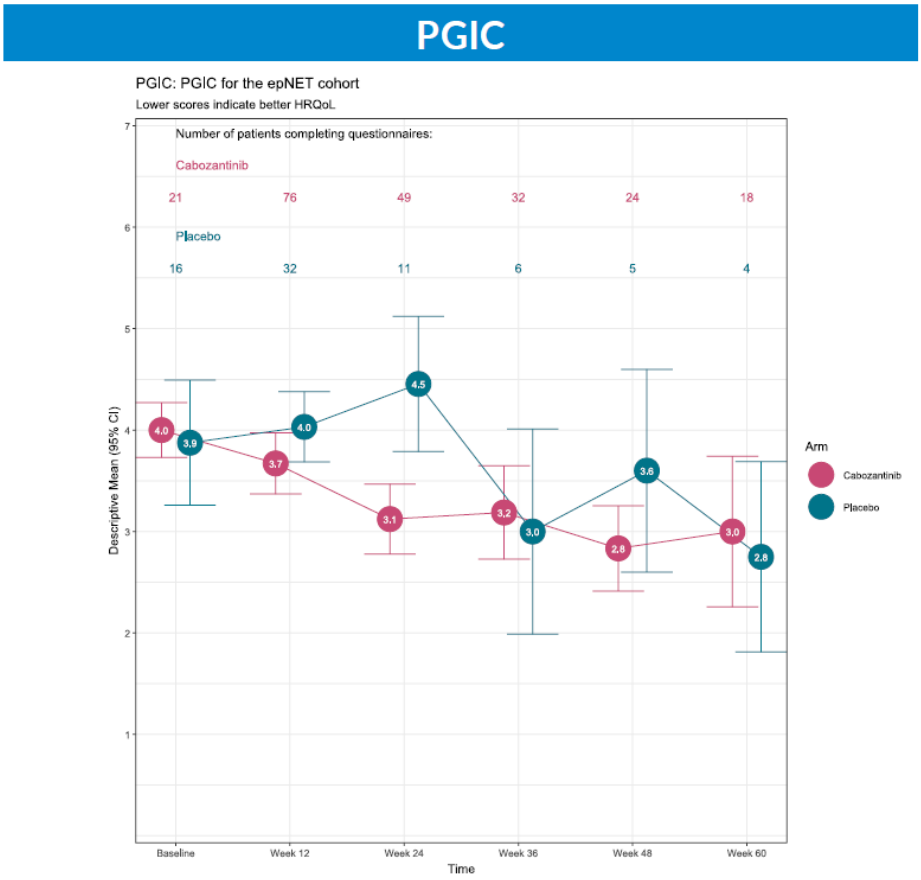


Figure 98 epNET PGIC Global Scores



F.4 Health state utility values (HSUVs) used in the health economic model

F.4.1 Mapping

F.4.1.1 Mapping EORTC QLQ-C30 to EQ-5D-3L UK weights

A previous systematic literature review (SLR) identified ten mapping algorithms for mapping the EORTC QLQ-C30 onto the EQ-5D-3L and assessed these with reference to external validity and generalisability [93]. Based on our search, no mapping algorithm exists from EORTC QLQ-C30 to EQ-5D-3L that is derived from a sample of NET patients.

A response mapping algorithm proposed by Longworth et al. (2014) [84] was deemed most appropriate for this task, as this algorithm has been applied previously in the NETs population (including in the Lutathera NICE submission [TA539]) [94]. It includes age as a covariate as recommended in NICE Technical Support Document (TSD) 22 [95]. The accuracy of the mapping process was assessed using both summary measures and diagnostic plots. This mapping algorithm uses a multinomial model to predict

probabilities of each EQ-5D-3L domain level from EORTC QLQ-C30 domain scores and then applies the UK tariff to produce an overall utility index [87, 96]. Four data sets were used for the mapping study; three contained the EORTC QLQ-C30 and EQ-5D, while one contained the FACT-G and EQ-5D. The three data sets containing EORTC QLQ-C30 were pooled into a single data set, one of which originated from a randomised trial (VISTA), and two of which originated from the Vancouver Cancer Clinic [84].

An ordinary least-squares (OLS) regression mapping algorithm was used as a sensitivity analysis to explore the effect of using a different mapping algorithm. This approach maps EORTC QLQ-C30 responses to an EQ-5D-3L utility value by applying regression coefficients from an OLS model. Due to the limitations involved in mapping, it is possible that responses may be mapped to a utility value greater than 1; in this instance, mapped values were truncated at 1.

Descriptive analyses were conducted to summarise the EQ-5D-based utility values. Summary statistics, including number of observations, mean, median, range, and standard deviation, were reported for each health state, by treatment status, and by cohort (including pNETs, epNETs, and subgroups of epNETs). These were generated at baseline and for all post-baseline values (pooling multiple visits together so there was only one post-baseline set of summary statistics for each health state). Particular consideration was given to the availability of data for the PD health state. Summary statistics, namely the number of observations and participants in each cohort highlighted this, and the arithmetic mean utility suggested that patients in the PD health state had a similar utility value to those in the PF health state.

Note that the values generated for the PD disease state are presented Table 99 were considered clinically non-feasible and were not applied in the health economic model. Instead, relative decrements calculated from Swinburn et al. (2012) [70] were applied to the CABINET PF utilities, which were used in the base case. Swinburn et al. (2012) [70] used a time trade-off (TTO) approach in which 22 articles were reviewed from targeted searches specifically in NETs. These were then supplemented by clinician and patient interviews and validation. It should be noted that these utility values were not specific to each subpopulation but to NETs as a whole. These calculated values are presented in Table 99.

In the article by Swinburn, stable disease had a utility value of 0.77, and disease progression was associated with a value of 0.61 [70]. The quotient of these values was used as the multiplier of the PF utility to estimate a PD utility with a decrement.

Table 99 Descriptive statistics of utility values

Population	Health state	Timepoint	Number of observations	Number of participants	Mean Utility (SD)	Median Utility (range)	Instrument and tariff
pNET[a]	PF	Baseline	72	72	0.807 (0.165)	0.865 (0.878)	EQ-5D UK weight

		Post-baseline	154	54	0.817 (0.142)	0.863 (0.774)	EQ-5D UK weight
	PD	Post-baseline	45	18	0.839 (0.107)	0.855 (0.488)	EQ-5D UK weight
epNET[b]	PF	Baseline	158	158	0.753 (0.190)	0.811 (0.986)	EQ-5D UK weight
		Post-baseline	232	113	0.745 (0.216)	0.791 (1.170)	EQ-5D UK weight
	PD	Post-baseline	43	21	0.778 (0.209)	0.840 (0.937)	EQ-5D UK weight
GI	PF	Baseline	73	73	0.792 (0.168)	0.829 (0.934)	EQ-5D UK weight
		Post-baseline	99	53	0.783 (0.172)	0.816 (0.858)	EQ-5D UK weight
	PD	Post-baseline	30	11	0.853 (0.081)	0.883 (0.273)	EQ-5D UK weight
Lung[c]	PF	Baseline	34	34	0.720 (0.182)	0.749 (0.765)	EQ-5D UK weight
		Post-baseline	31	20	0.553 (0.340)	0.647 (1.139)	EQ-5D UK weight
	PD	Post-baseline	5	4	0.475 (0.343)	0.517 (0.888)	EQ-5D UK weight
Unknown /Other	PF	Baseline	51	51	0.720 (0.216)	0.769 (0.977)	EQ-5D UK weight
		Post-baseline	102	40	0.767 (0.175)	0.799 (0.861)	EQ-5D UK weight
	PD	Post-baseline	8	6	0.682 (0.261)	0.754 (0.705)	EQ-5D UK weight

a Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; b Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup; c Includes patients with thymus primary tumour site. Abbreviations: epNET, extra-pancreatic neuroendocrine tumours; GI, gastrointestinal; pNET, pancreatic neuroendocrine tumours; PD, progressive disease; PF, progression-free; SD, standard deviation

F.4.1.2 Mapping EQ-5D-3L UK to EQ-5D-5L Danish weights

Based on an article by Torkilseng et al. 2025 [88] the previously estimated EQ-5D-3L index scores based on UK weights were converted to DK 5L weights. In this article, a simple linear model for mean utility scores is outlined and validated specifically for the

use of HTA assessments for the DMC. External validation using the algorithm to predict mean Danish EQ-5D-5L utilities was excellent, with the largest absolute prediction error being 0.020 [88]. The used algorithm is as follows

$$: \mu DK\_5L = 0.231 + \mu UK\_3L \times 0.773$$

where

- $\mu_(DK\_5L)$ is the mean EQ-5D-5L utility value on the Danish tariff,
- $\mu_(UK\_3L)$ is the mean EQ-5D-3L utility value on the UK tariff,
- 0.231 is an intercept coefficient,
- 0.773 is a slope coefficient. This can also be used to calculate the standard error.

The result of the mapping to EQ-5D-5L are presented in Table 94.

The results of this analysis are presented in Table 41 in Section 10.2.

Table 100 Summary of HSUV results EQ-5D

	Progression Free Utility / Progressed disease	Results	SE	Instrument	Tariff (value set) used	Comments
pNET[a]	PF	0.819	0.014	EQ-5D	UK	Ipsen data on file, calculated from CABINET IPD data (PF) [89]
	PD calculated with decrement	0.650	0.13	EQ-5D	UK	Swinburn et al. 2012[70] A relative decrement between PF and PD values were calculated which were then applied to the CABINET PF utility
epNET[b]	PF	0.731	0.018	EQ-5D	UK	Same as above
	PD calculated	0.580	0.12	EQ-5D	UK	Same as above
Lung[c]	PF	0.552	0.065	EQ-5D	UK	
	PD calculated	0.438	0.09	EQ-5D	UK	
	PD calculated	0.600	0.12	EQ-5D	UK	

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; NET: neuroendocrine tumour; PD: progressed disease; PF: progression-free; pNET: pancreatic neuroendocrine tumour; SE: standard error.

Appendix G. Probabilistic sensitivity analyses

In the tables below, the assumptions from the probabilistic sensitivity analysis are presented, including the inputs, point estimates, lower and upper values and probability distributions. Different populations are presented in separate tables.

Table 101 pNET Overview of parameters in the PSA

Variable	Input	Lower value	Upper value	Probability distribution
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Table 102 epNET Overview of parameters in the PSA

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Table 103 lung NET Overview of parameters in the PSA

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Appendix H. Literature searches for the clinical assessment (N/A)

H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable.

Table 104 Bibliographic databases included in the literature search (N/A)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 105 Other sources included in the literature search (N/A)

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Abbreviations:

Table 106 Conference material included in the literature search (N/A)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

H.1.1 Search strategies

Table 107 of search strategy table for [name of database] (N/A)

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A

No.	Query	Results
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

H.1.2 Systematic selection of studies

Table 108 Inclusion and exclusion criteria used for assessment of studies (N/A)

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 109 Overview of study design for studies included in the analyses (N/A)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded fulltext references

H.1.4 Quality assessment

H.1.5 Unpublished data

Appendix I. Literature searches for health-related quality of life (N/A)

I.1 Health-related quality-of-life search

Not applicable.

Table 110 Bibliographic databases included in the literature search (N/A)

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
Specific health economics databases[1]	N/A	N/A	N/A

Table 111 Other sources included in the literature search (N/A)

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
CEA Registry	N/A	N/A	N/A

Table 112 Conference material included in the literature search (N/A)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

I.1.1 Search strategies

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

N/A

Table 113 Search strategy for [name of database] (N/A)

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model (N/A)

J.1 External literature for input to the health economic model

Not applicable.

J.1.1 Example: Systematic search for […]

Table 51 Sources included in the search (N/A)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

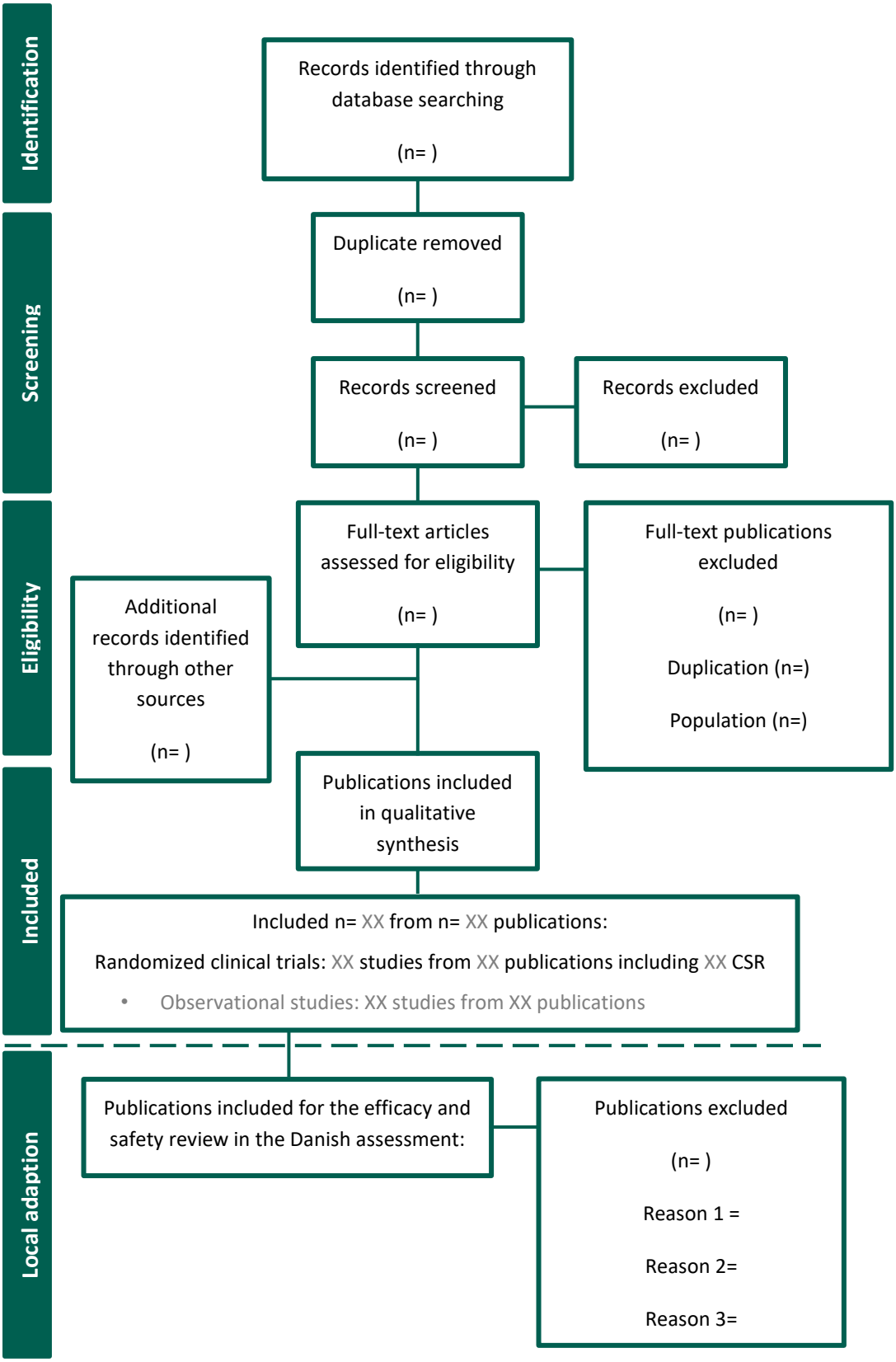
J.1.2 Example: Targeted literature search for [estimates]

Table 52 Sources included in the targeted literature search (N/A)

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Appendix K. Deterministic sensitivity analyses

Figure 99 pNET Tornado diagram costs

Figure 100 pNET Tornado diagram QALYs

Figure 101 epNET Tornado diagram costs

Figure 102 epNET Tornado diagram QALYs

Figure 103 Lung NET Tornado diagram costs

Figure 104 Lung NET Tornado diagram QALYs

Appendix L. Cabometyx® other therapeutic indications approved

Item	Description
Other therapeutic indications approved by EMA	**Renal cell carcinoma (RCC):** CABOMETYX is indicated as monotherapy for advanced renal cell carcinoma: ○ as first-line treatment of adult patients with intermediate or poor risk, ○ in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. **Hepatocellular carcinoma (HCC) :** CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. **Differentiated thyroid carcinoma (DTC):** CABOMETYX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.
Other indications that have been evaluated by the DMC (yes/no)	Yes, the following indications have been evaluated by the DMC: • Cabozantinib as a possible standard of care for adult patients with metastatic renal cell carcinoma (mRCC) who have not received prior therapy (1st line therapy). • Cabozantinib as a possible standard treatment for adult patients with hepatocellular carcinoma and liver function corresponding to Child-Pugh A, in performance status 0-1 in the following three populations: ○ Patients who have tolerated sorafenib and whose disease has progressed during treatment with sorafenib. ○ Patients who have previously been treated with but have not tolerated sorafenib. ○ Patients whose disease has previously progressed on two previous treatments, one of which is sorafenib. • Cabozantinib in combination with nivolumab as a first-line treatment of patients with advanced renal cell carcinoma.

Appendix M. Subsequent treatment

Table 114 lists the first anti-cancer treatment received by patients in the epNET cohort after discontinuing blinded study therapy. Twenty patients in the placebo group crossed over to receive cabozantinib on protocol after confirmation of progressive disease while receiving blinded therapy. Two patients in the cabozantinib group continued cabozantinib after stopping blinded therapy, and one patient in the placebo arm received cabozantinib off-protocol. Twenty-one patients in the cabozantinib group and seven patients in the placebo group were still receiving blinded therapy at the time of the study unblinding and data cutoff date. Additionally, two patients in the cabozantinib arm and two patients in the placebo arm never began blinded therapy.

Table 114 Subsequent Anti-cancer Therapy Received by Patients Enrolled in the epNET Cohort

	Cabozantinib (N=111)	Placebo (N=60)
	N (%)	N (%)
Crossover to cabozantinib	NA	20 (33)
Cytotoxic chemotherapy	15 (14)	6 (10)
Peptide receptor radionuclide therapy	13 (12)	3 (5)
Anti-VEGFR TKI	5 (5)	4 (7)
Everolimus	1 (1)	2 (3)
Radiation	4 (4)	0
Liver-directed therapy	3 (3)	4 (7)
Other	9 (8)	1 (2)
No additional therapy	61 (55)	20 (33)

Source: Chan et al. 2024 [5].

Table 115 lists the first anti-cancer treatment received by patients in the pNET cohort after discontinuing blinded study therapy. Twelve patients in the placebo group crossed over to receive cabozantinib on protocol after confirmation of progressive disease while receiving blinded therapy. Two patients in the cabozantinib group continued cabozantinib after stopping blinded therapy, and one patient in the placebo arm received cabozantinib off-protocol. Fourteen patients in the cabozantinib group and two patients in the placebo group were still receiving blinded therapy at the time of the study

unblinding and data cutoff date. Additionally, one patient in the cabozantinib arm never began blinded therapy.

Table 115 Subsequent Anti-cancer Therapy Received by Patients Enrolled in the pNET Cohort

	Cabozantinib (N=49)	Placebo (N=29)
	N (%)	N (%)
Crossover to cabozantinib	NA	12 (41)
Cytotoxic chemotherapy	10 (20)	0
Peptide receptor radionuclide therapy	6 (12)	2 (7)
Anti-VEGFR TKI	4 (8)	3 (10)
Liver-directed therapy	2 (4)	0
Radiation	1 (2)	0
Other	2 (4)	1 (3)
No additional therapy	24 (49)	11 (38)

Abbreviations: VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor.

Source: Chan et al. 2024 [5].

Appendix N. Supplementary analyses

N.1 Supplementary analyses lung NET

Figure 105 and Figure 106 present the Kaplan-Meier plots for OS for cabozantinib and placebo for the ITT population. The Kaplan-Meier plot for the IPCW-adjusted OS in the epNET lung subgroup for cabozantinib and placebo is presented in Figure 107.

Figure 105 Kaplan-Meier OS lung NET cabozantinib, ITT

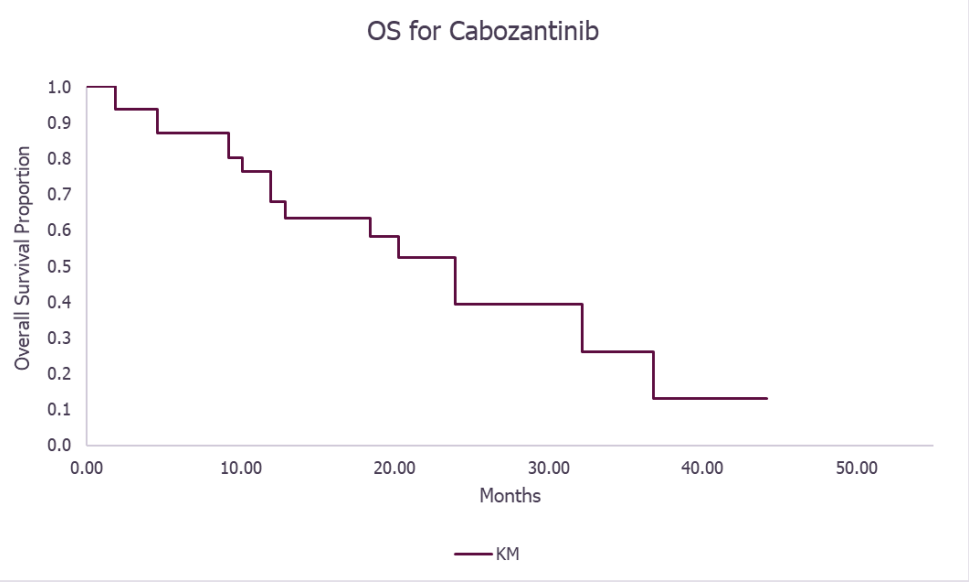


Figure 106 Kaplan-Meier OS lung NET placebo, ITT

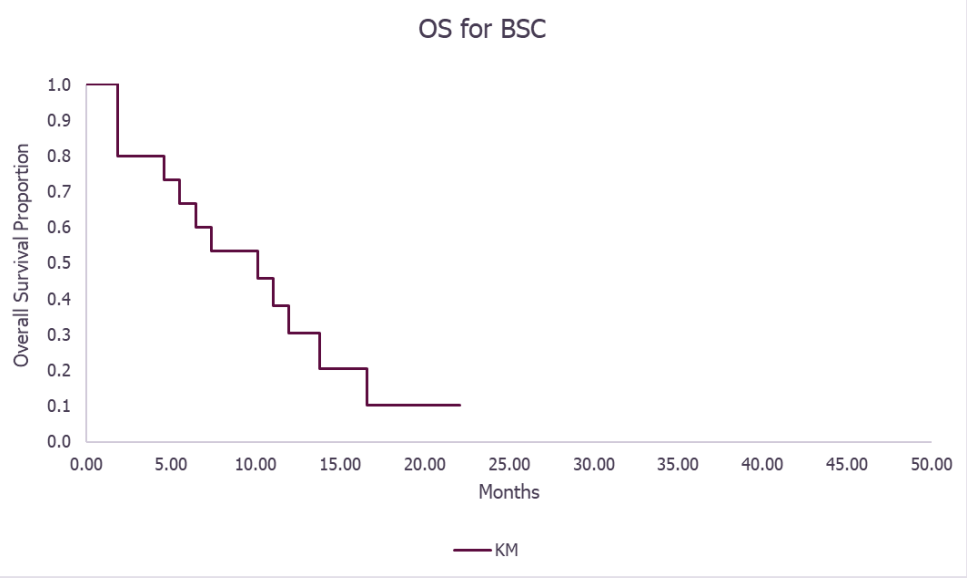
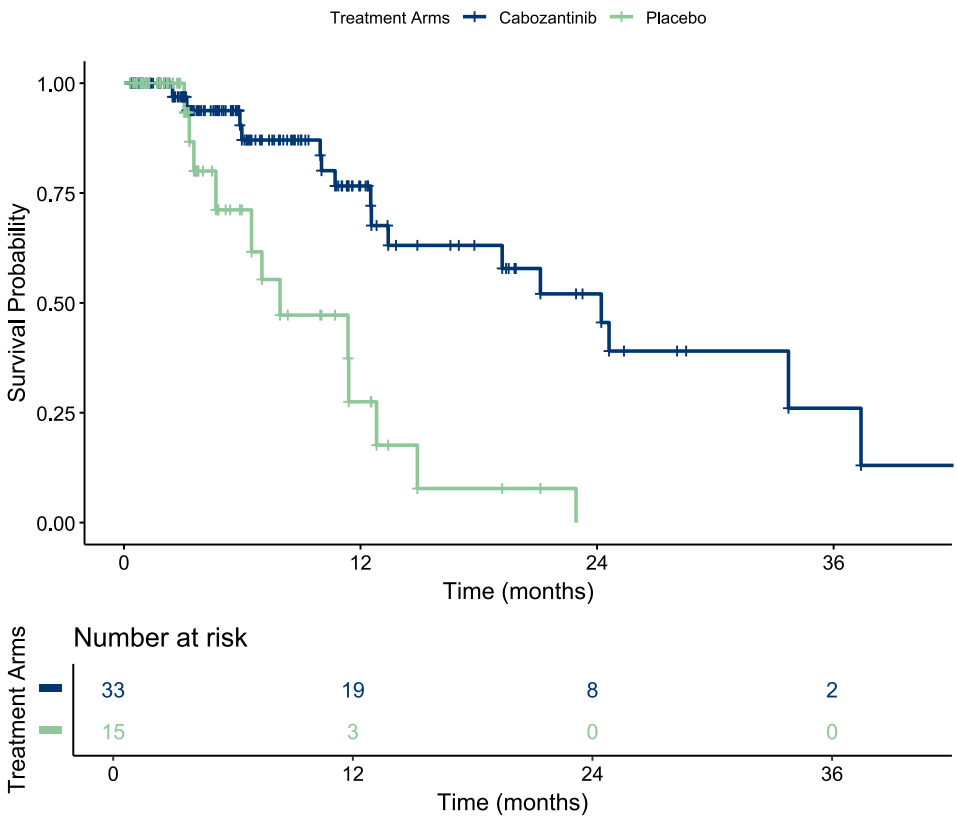


Figure 107 IPCW-adjusted OS in the epNET lung subgroup: KM plot



Footnotes: Patients have been centred upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.
Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier.

Figure 108 and Figure 109 present the Kaplan-Meier plots for PFS for cabozantinib and placebo.

Figure 108 Kaplan-Meier PFS lung NET cabozantinib, ITT

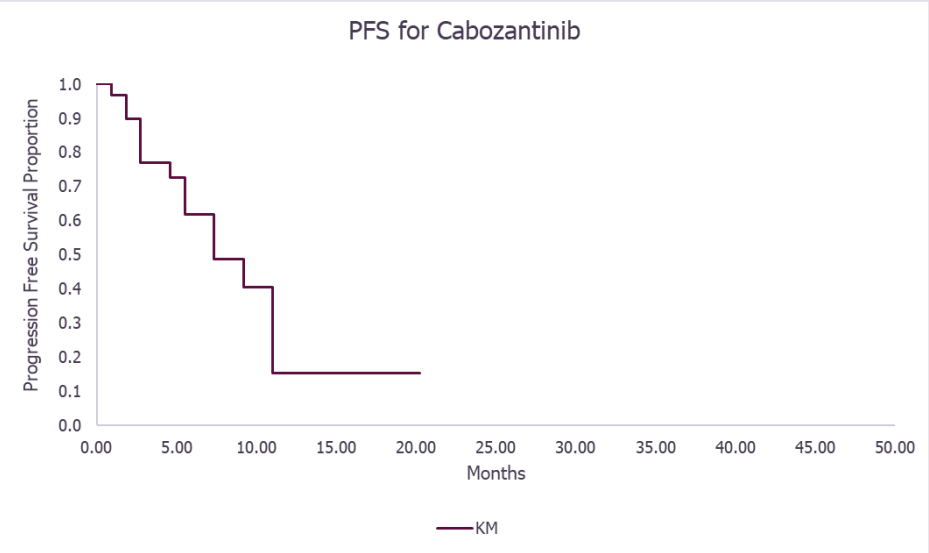


Figure 109 Kaplan-Meier PFS lung NET placebo, ITT

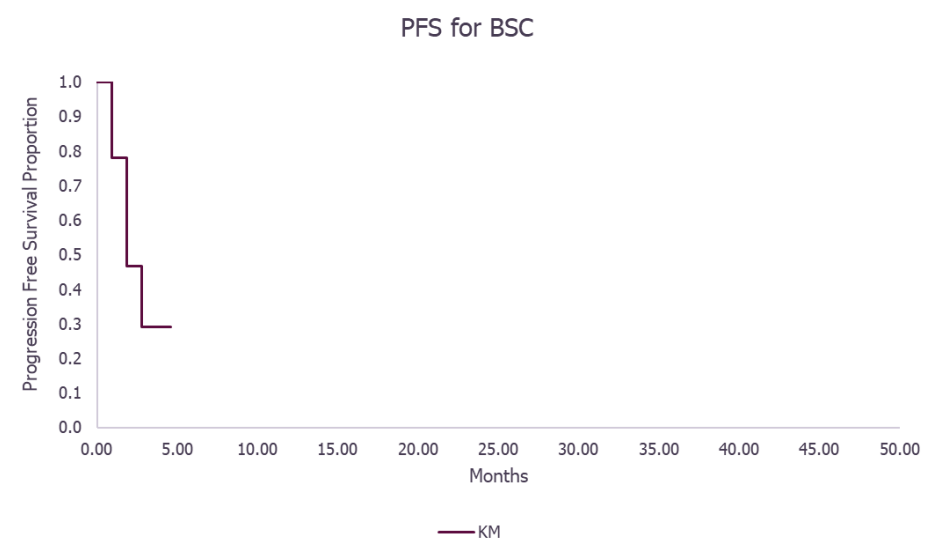


Table 116 presents the effect estimates for OS and Table 117 for PFS.

Table 116 Effect estimates OS lung NET, ITT

	Median (95% CI)	Events	6-month rate	12-month rate	18-month rate	HR (95% CI)
Cabozantinib	24.1 months (13.40, NE)	16	87.05%	76.45%	63.42%	0.28 (0.12, 0.62)

Placebo	10.9 months (6.34, NE)	13	73.33%	38.10%	10.16%	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimatable.

Table 117 Effect estimates PFS lung NET

	Median (95% CI)	Events	6-month rate	12-month rate	18-month rate	HR (95% CI)
Cabozantinib	8.28 (6.05, NE)	15	72.51%	15.19%	15.19%	0.18 (0.06, 0.51)
Placebo	2.73 (1.91, NE)	9	NE, no patients at risk	NE, no patients at risk	NE, no patients at risk	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimatable.

N.2 Supplementary analyses GI NET

In the following section, a supplementary analysis is presented for patients with epNET whose primary tumour was located in the gastrointestinal (GI) tract.

Figure 110 and Figure 111 present the Kaplan-Meier plot for OS for cabozantinib and placebo. The Kaplan-Meier plot for the IPCW-adjusted OS in the epNET GI tract subgroup for cabozantinib and placebo is presented in Figure 112.

Figure 110 Kaplan-Meier OS GI NET cabozantinib, ITT

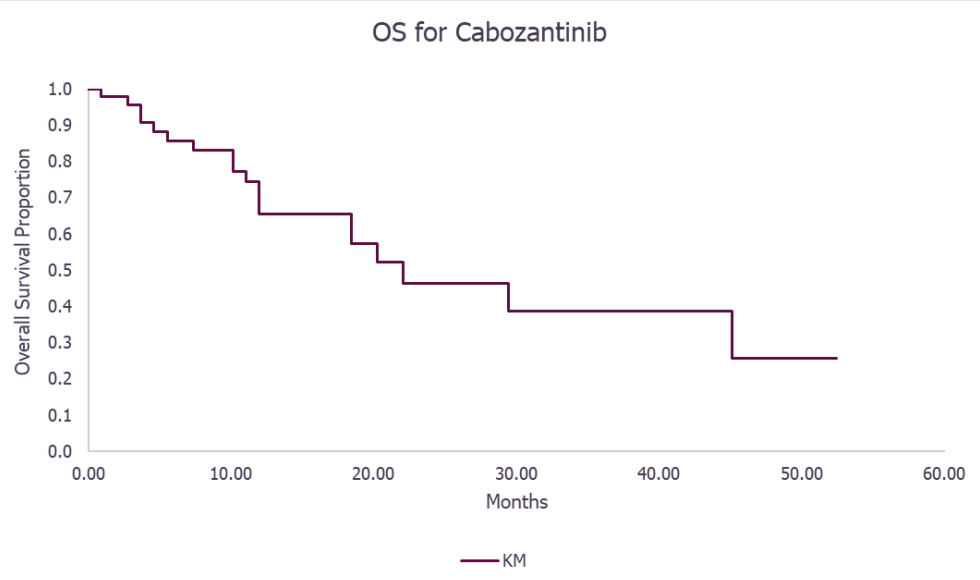


Figure 111 Kaplan-Meier OS GI NET placebo, ITT

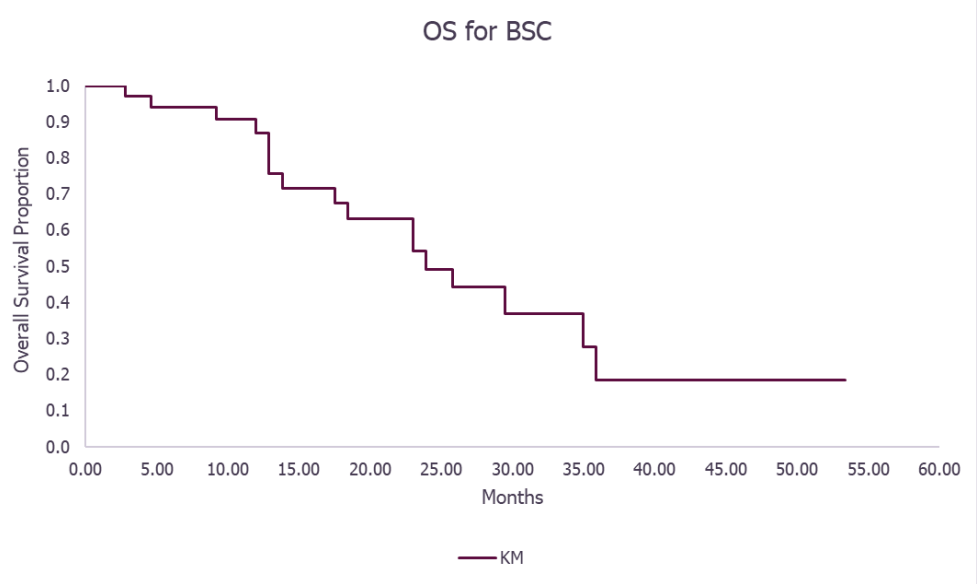
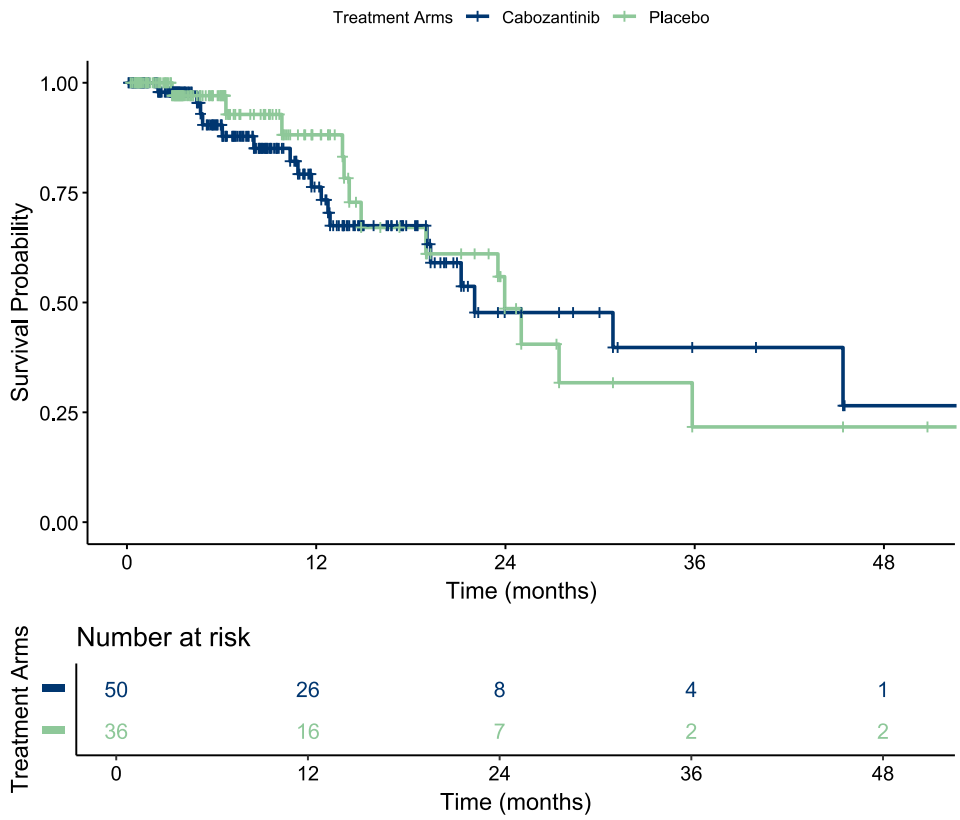


Figure 112 IPCW-adjusted OS in the epNET GI tract subgroup: KM plot



Footnotes: Patients have been centred upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of

artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; GI, gastrointestinal; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier.

Figure 113 and Figure 114 present the Kaplan-Meier plot for PFS for cabozantinib and placebo.

Figure 113 Kaplan-Meier PFS GI NET cabozantinib

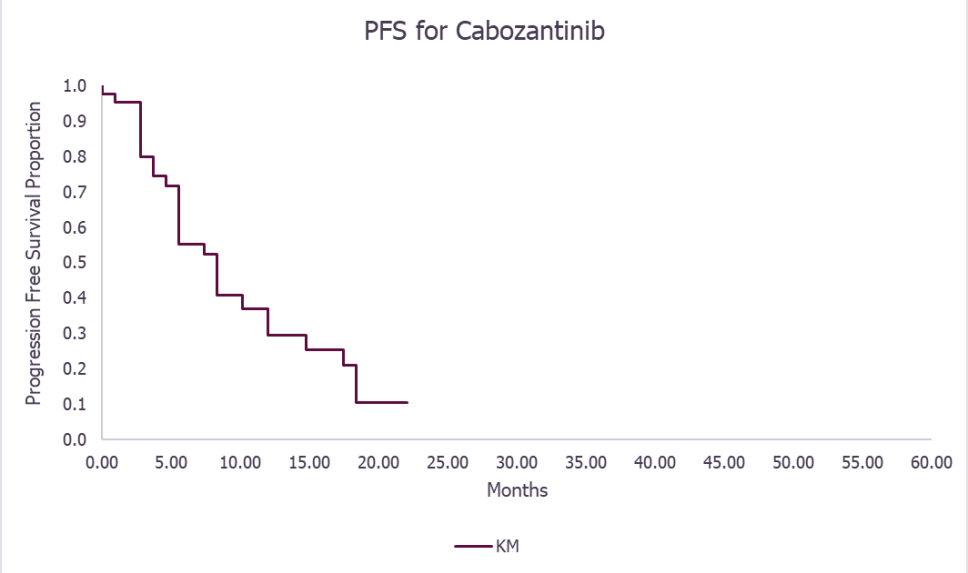


Figure 114 Kaplan-Meier PFS GI NET placebo

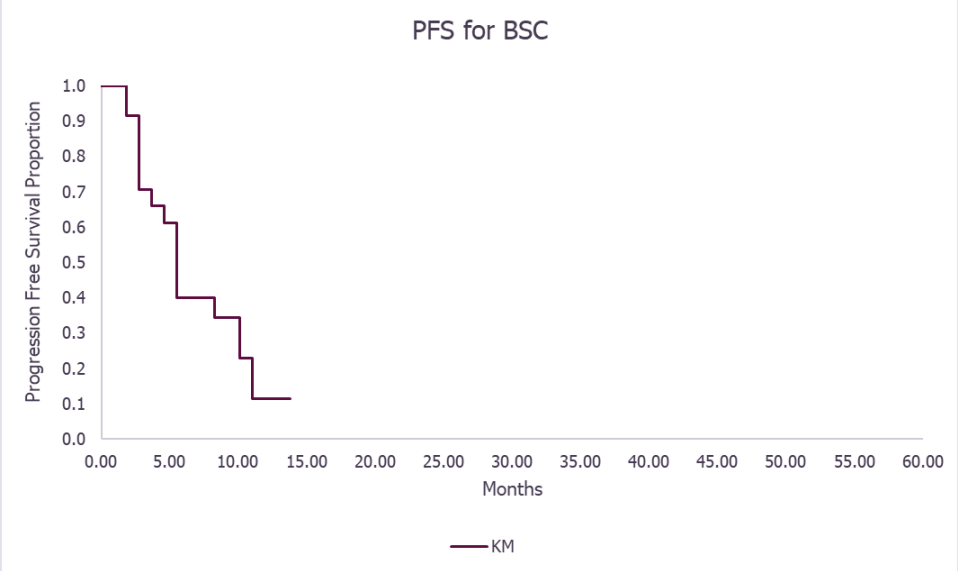


Table 118 presents the effect estimates for OS and Table 119 presents the effect estimates for PFS.

Table 118 Effect estimates OS GI NET, ITT

	Median (95% CI)	Events	6-month rate	12-month rate	18-month rate	HR (95% CI)
Cabozantinib	22.1 months (18.8, NE)	19	88.16%	74.39%	65.56%	1.10 (0.57, 2.13)
Placebo	24.5 (18.8, NE)	17	94.01%	90.65%	71.57%	

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 119 Effect estimates PFS GI NET

	Median (95% CI)	Events	6-month rate	12-month rate	18-month rate	HR (95% CI)
Cabozantinib	8.38 (5.72, 15)	29	71.78%	36.99%	25.36%	0.65 (0.35, 1.20)
Placebo	5.75 (5.42, NE)	18	61.03%	11.44%	NE, no patients at risk	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimatable.

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