# Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474] – ACM2

Part 1 – confidential information has been redacted

**Technology appraisal committee D [12th November 2025]**

**Chair:** Raju Reddy

**Evidence review group:** BMJ TAG

**Technical team:** Alice Bell, Nigel Gumbleton, Ross Dent

**Company:** Ipsen

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# Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

- ✓ Key issues & decision problem
- ❑ Modelling and cost-effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

RECAP

# Draft guidance

## Preliminary recommendations were that cabozantinib should not be used to treat advanced neuroendocrine tumours that have progressed after systemic treatment

Cabozantinib should not be used to treat unresectable or metastatic well differentiated extra-pancreatic neuroendocrine tumours (epNET) and pancreatic neuroendocrine tumours (pNET) that have progressed after at least 1 systemic treatment other than somatostatin analogues (SSAs)

Committee made this decision because:

- While clinical evidence suggests cabozantinib increases PFS it is not clear if it improves OS
- Evidence does not include everyone cabozantinib is licensed for in its MA
- Significant uncertainty in evidence because of how model predicts OS and includes other simultaneous and subsequent treatments
- Uncertainty in model meant it was not possible to determine a likely cost-effectiveness estimate
- Even so, all cost-effectiveness estimates are substantially above the range considered acceptable

MA: September 2025 (MHRA)

'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.'

Consultation responses received from company (Ipsen) and Neuroendocrine Cancer UK

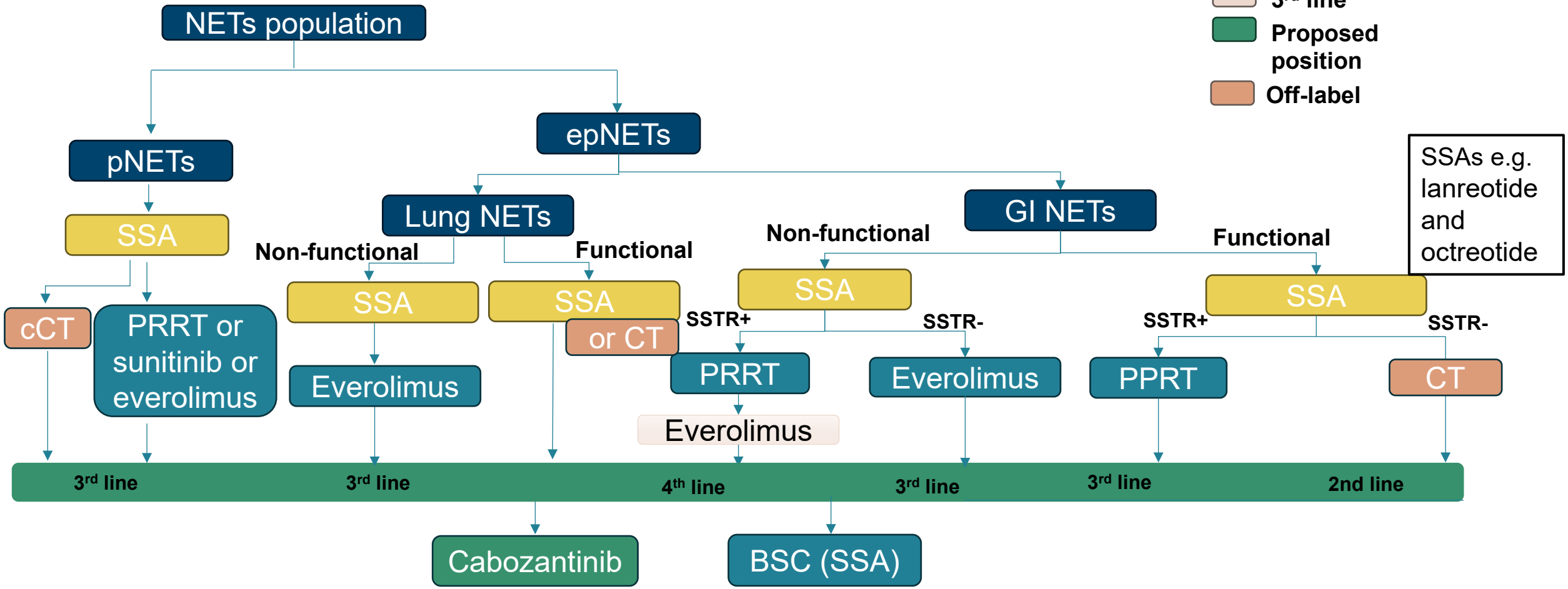


Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; MA, marketing authorisation; NETs, neuroendocrine tumours; OS, overall survival; PFS, progression free survival; pNETs, pancreatic neuroendocrine tumours

# Treatment pathway: pNETs and epNETs

The company positions cabozantinib as a later line alternative to BSC

RECAP




At ACM1 committee concluded:

- managing advanced NETs is highly complex, heterogeneous and individualised based on the specific characteristics of the person with the condition
- the company's positioning of cabozantinib as a later-line treatment and BSC was appropriate

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Abbreviations: BSC, best supportive care; cCT, cytotoxic chemotherapy; epNETs, extra-pancreatic neuroendocrine tumours; MA, marketing authorisation; NETs, neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor

# Equalities issues

RECAP

At ACM1 committee heard that:

- inequalities linked to age, disability, mobility, financial circumstances, or geographical distance from specialist NET centres
- differences arise from language and culture, which may limit understanding of treatment and side effect management
- literature suggests higher incidence of NETs and worse survival in people of Black family background: poorer outcomes for Black men, social determinants, support mechanisms, and access to health care may be contributing factors

**Committee concluded that differences in incidence and prevalence cannot be addressed in a technology appraisal. Because its recommendation does not restrict access to treatment for some people over others, the committee concluded that there were no potential equality issues**

## DG response

- No equalities issues raised in DG response

Are there any inequalities issues that have not yet been raised?



Abbreviations: DG, draft guidance; NETs, neuroendocrine tumours

# Responses to draft guidance

## Response from Neuroendocrine Cancer UK

Requests further discussion from committee on how different groups may benefit from this technology

**Complex group of cancers**

- At ACM1 variations in NETs were not clarified as well as they could have been – a fuller discussion about where the proposed medication may have most benefit was incomplete
- Negative outcome will disadvantage those with limited treatment options and therefore be an unequitable conclusion: specifically, those with non-pancreatic and/or functional NETs

**Further discussion of treatment benefit depending on: grading, functionality, SR-status, DPYD deficiencies**

- Primary site restrictions on licensed use of alternative options: treatment options differ depending on site
- Grading: some therapies are only licensed for Grade 1-2: those with Grade 3 are excluded
- Functionality: when life limiting factor is hormone excess syndrome not tumour alone. This group may not have the same alternative options as others
- SR status: NETs with negative status or positive status but not within the GI tract or pancreas - are currently precluded from radioligand therapy (Lutetium177) outside of a clinical trial.
- DPYD-deficiency will be precluded from Cap-Tem

**BSC costs**

- What's included in BSC costs?



Abbreviations: BSC, best supportive care; NETs, neuroendocrine tumours; DPYD, dihydropyrimidine dehydrogenase; HRQoL, health-related quality of life; NCUK, neuroendocrine cancer UK; ep/NETs, extra-pancreatic/neuroendocrine tumours; SR, somatostatin-receptor

# Resolved issues

| Key issues | Committee preferences at ACM1 | Company DG response | Resolved | ICER impact |
|---|---|---|---|---|
| **Positioning and comparators** | Appropriate positioning and BSC | BSC as the relevant comparator | Yes | Large |
| **Grouping approach for epNETs** | Lung and other epNETs grouped together as too much uncertainty and no clinical rationale for separating | pNETs and epNETs modelled as main subgroups. | Yes | Large |
| **Data cut-off** | August 2024 data used in decision making | Modelled OS informed by August 2024 data cut-off | Yes | Large |



Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue

# Key issues for committee discussion

| Key issues | Committee preferences at ACM1 | Company DG response | Resolved | ICER impact |
|---|---|---|---|---|
| Method for data crossover | RPSFTM more appropriate method with August 2024 DCO. Request results of TSE | IPCW most appropriate | No | Large |
| Modelling approach for PFS and OS | Preferred Weibull curves to extrapolate PFS and OS data from CABINET trial. See evidence of PFS and OS surrogacy | Weibull PFS, Log-logistic OS | Partially | PFS small, OS small |
| HR for OS | Assuming OS HR of 1 | OS HR of 1 not appropriate | No | Large |
| PF/PD utility values | Details of regression analysis of CABINET data, with additional analysis of raw data | Details for full utility analysis of CABINET | Partially | Small |
| Modelling concomitant SSA | Modelling concomitant SSAs from baseline until death | Included with constant discontinuation rate | Partially | Large |
| Subsequent treatments | no subsequent treatment to be modelled | Subsequent treatments modelled | Partially | Large |



Abbreviations: DCO, data cut-off; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; IPCW, inverse probability of censoring weights; RPSFTM, rank preserving structural failure time model; TSE, two-stage estimation

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# Key Issue: Method to adjust for crossover

**At ACM1**

- Committee prefer RPSFTM with August 2024 data cutoff
- Requested that company provide results of the TSE

| Tumour | CABINET Crossover | |
|---|---|---|
| DCO | **Original** | **August 2024** |
| **pNET** | [redacted] | [redacted] |
| **epNET** | [redacted] | [redacted] |

**Company DG response**

- Company preferred IPCW
- No evidence IPCW has more uncertainty or risk of bias than other approaches (RPSFTM+TSE also explored)

(1) TSE not provided. Not feasible - small sample size and small number of OS events

(2) Assumptions for IPCW satisfied - “no unmeasured confounders” and “positivity”

  - CEs determined choice of covariates, suggesting no important confounders missing from model

(3) IPCW weights were highly stable across cohorts and data cuts: no extreme values (Appendix 3 response)

(4) Latimer et al. state IPCW provide reliable estimates if sample sizes and proportion switching are moderate:

  - Although small sample sizes, <60% of control group eligible crossover so bias should not be extreme
  - NICE manual: committee may be able to make recommendations accepting higher degree of uncertainty

(5) RPSFTM results lack clinical plausibility→ implies placebo group would have higher OS if not crossed over

- Insufficient justification that RPSFTM is more appropriate, no reflection of substantial limitations of RPSFTM, especially when ITT HRs are close to or >1. Insufficient evidence for the common treatment effect assumption

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Abbreviations; DCO, data cut-off; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention-to-treat; NETs, neuroendocrine tumours; OS, overall survival; RPSFTM, rank preserving structural failure time model TSE, two-stage estimation

# Key Issue: Method to adjust for crossover

**EAG response**

(1)(2)(3) Agrees that TSE is unfeasible. Accepts 'positivity' assumption and IPCW stability of weights, 'no unmeasured cofounders' reasonable but untestable

(4) Diagnostic data not a concern but small no. of switchers relative to model complexity → structural uncertainty

(5) pNET data shows no benefit regardless of method, at odds with considering one method clinically implausible

+ SEE experts presented with data already adjusted for crossover for BSC, from 6-24 months, not reflective of last DCO → may be biased towards long-term values reflective of the crossover approach shown

- No approach to crossover analysis ideal → small numbers and high % crossing over, considerable uncertainty
- Adjustment has limited impact in pNET population. For epNETs, IPCW numerically favours cabozantinib (HR [redacted]), RPSFTM numerically favours placebo (HR [redacted])
- Considerable overlap in CIs for effect estimates with different choices of crossover, highlighting uncertainty
- IPCW is assumption-dependent and based on sparse switching data, leaving considerable uncertainty
- Prefers RPSFTM in base case (with HR capped at 1); provides scenario with IPCW for epNET cohort
- Limitations in RPSFTM no more concerning than IPCW but considers RPSFTM more conservative around the estimated treatment effect

| | Population | ITT (Unstratified)(95% CI) | ITT (Stratified) (95% CI) | IPCW (Stratified) (95% CI) | RPSFTM (Stratified) (95% CI) |
|---|---|---|---|---|---|
| Updated DCO | pNET | [redacted] | [redacted] | [redacted] | [redacted] |
| | epNET | [redacted] | [redacted] | [redacted] | [redacted] |

NICE

Which method is more appropriate to adjust for crossover?



Abbreviations; AFT, accelerated failure time; DCO, data cut-off; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention-to-treat; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

Small Impact

# Key Issue: Survival curves for modelling OS

**At ACM1**

- Choice of the PFS model for cabozantinib has a minor impact on results
- Company preferred log-logistic curve for epNETS
- Committee prefer:
  - OS and PFS Weibull curves for both pNETs and epNETs
  - August 2024 DCO

**Company DG response**

- Committee conclusion lacks justification
- Use of fixed HRs in combination with models that imply time-varying hazards (such as log-logistic) is common in oncology modelling, on the assumption that the resulting curves are clinically plausible
- No substantial differences between the AIC and BIC, suggesting similar goodness of fit to KM data in all curves
- Committee preferences are misaligned with clinician landmark estimates for cabozantinib - Clinicians asked to provide plausible estimate of OS, upper and lower limits at 5, 10 and 15 years for cabozantinib and BSC
- Loglogistic model for cabozantinib provides best statistical and visual fit → Fits to clinician estimates and with IPCW-adjusted HR for OS for BSC



Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PH, proportional hazard; pNETs, pancreatic neuroendocrine tumours; SSA, somatostatin analogue

Small Impact

# Key Issue: Survival curves for modelling OS

**EAG**

- HR should be derived for same parametric model used to estimate respective survival curves to maintain internal validity. Weibull curve can be expressed in AFT or PH (proportional hazards) form if adjusted
- Minimal difference in statistical fit according to AIC and BIC between the loglogistic and the Weibull curves
- EAG preferred Weibull extrapolation (more conservative approach). For pNETs, Weibull aligns best with SEE predictions for BSC, but company log-logistic approach aligns best with cabozantinib predictions
- Concerned clinical experts were not shown August 2024 DCO

**Clinician and committee/company survival estimates for OS in cabozantinib and BSC (epNETs)**

| Treatment | Category | Curve | OS% | | |
|---|---|---|---|---|---|
| | | | 5 | 10 | 15 |
| Cabozantinib | Clinician estimate | Lower plausible limit | 12.3% | 6.0% | 1.0% |
| | | Most likely | 21.1% | 10.5% | 3.5% |
| | | Upper plausible limit | 24.0% | 13.8% | 4.7% |
| | Extrapolation | Weibull | 10.4% | 0.5% | 0.0% |
| | | Loglogistic | 16.8% | 6.5% | 3.5% |
| BSC<br><br>CABINET data presented to CE from 6 to 24 months | Clinician estimate | Lower plausible limit | 5.8% | 2.0% | 0.5% |
| | | Most likely | 10.8% | 3.8% | 1.5% |
| | | Upper plausible limit | 15.5% | 6.8% | 2.3% |
| | Extrapolation | Weibull (RPSFTM) | 10.4% | 0.5% | 0.0% |
| | | Loglogistic (IPCW) | 9.4% | 2.6% | 1.2% |

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How should overall survival be modelled ?



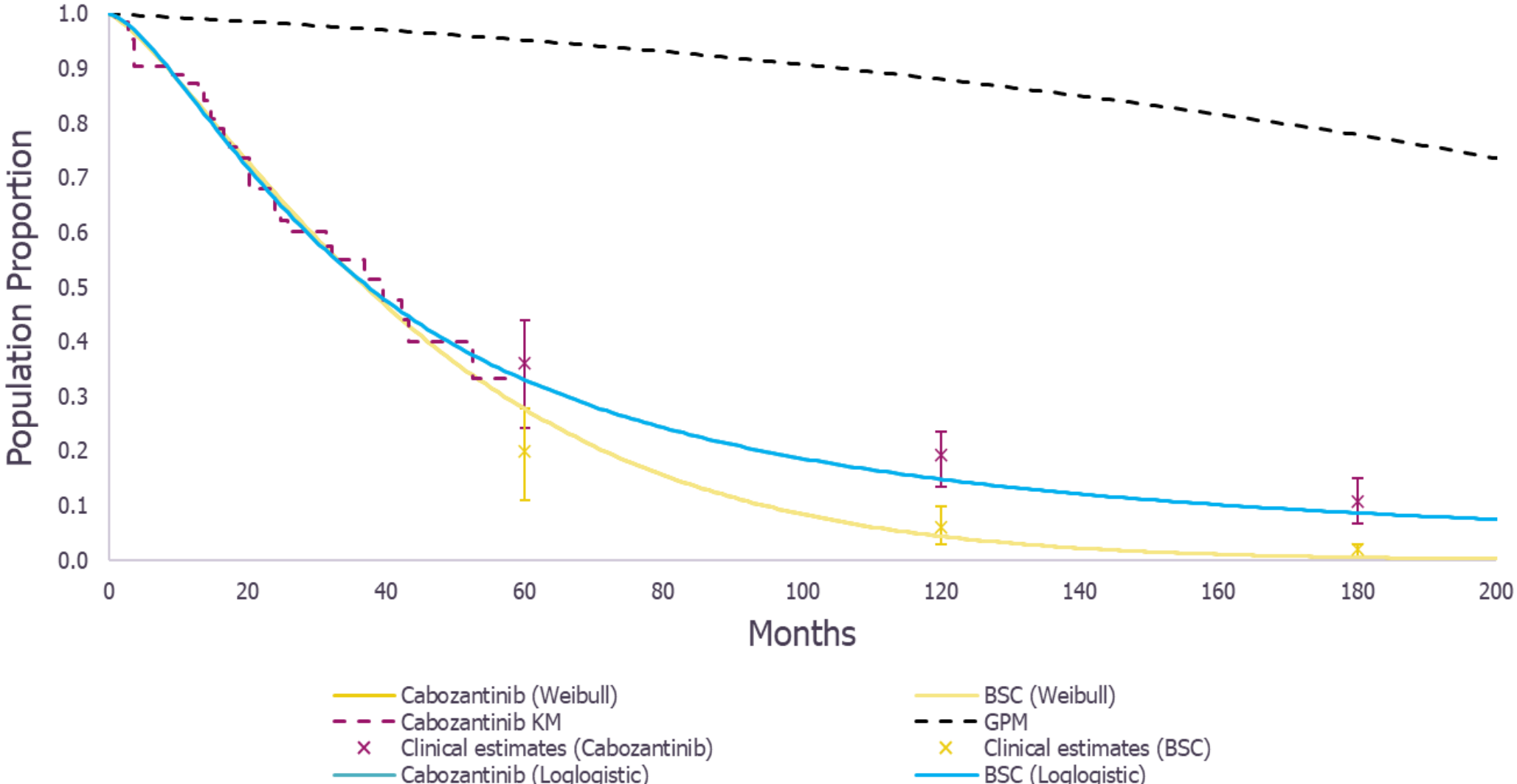
Abbreviations: AIC, Akaike Information Criterion; AFT, accelerated failure time; BIC, Bayesian Information Criterion; BSC, best supportive care; DCO, data cut off; HR, hazard ratio;; PH, proportional hazard; pNETs, pancreatic neuroendocrine tumours; SSA, somatostatin analogue

Small Impact

# pNETs Survival curves for modelling OS

**EAG**

- Because company and EAG use OS HR of 1, curves lie on top of each other and choice of curve has no impact on cost-effectiveness results




**Company versus committee-preferred OS extrapolations and clinician landmark estimates from the company – cabozantinib and BSC (pNETs)**

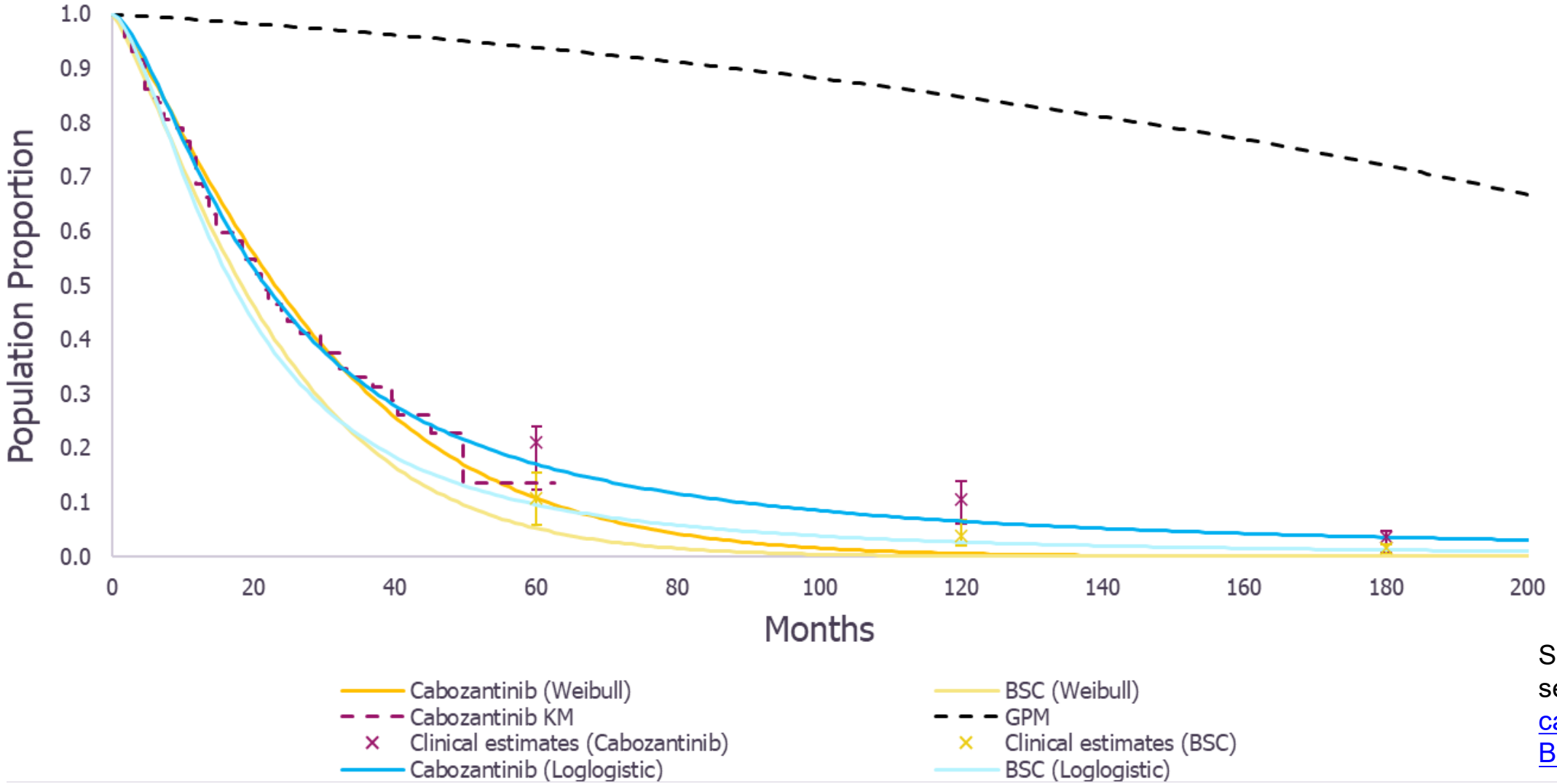
See slide for separate cabozantinib and BSC curves

Small Impact

# epNETS Survival curves for modelling OS

**EAG**

- In EAG base case using RPSFTM, choice of curve has no impact as OS HR capped at 1
- Choice of curve affects survival benefit if IPCW used as OS HR<1




**Company versus committee-preferred OS extrapolations and clinician landmark estimates – from the company–cabozantinib and BSC (epNETs) IPCW**

See slide for separate cabozantinib and BSC curves

Large impact

# Key Issue: OS Hazard Ratio

## At ACM1

- Committee concluded it would consider an overall-survival hazard ratio of 1 in its decision making, given results of preferred method of crossover adjustment (RPSFTM)
- Acknowledged the significant PFS survival benefit – (CABINET PFS results)
- Crossover in CABINET trial, uncertainty in OS extrapolation and lack of strong surrogacy validation could mean that PFS may not be a reliable surrogate for OS. Committee requested more evidence of surrogacy relationship

## Company DG response

- Modelling OS HR = 1 vs BSC lacks clinical plausibility and inappropriate for decision making. Clinical expert feedback and literature demonstrating OS and PFS association. Prefer HR [redacted] for epNETs and [redacted] for pNETs
- Experts estimate [better] survival with cabozantinib: no OS benefit in trial doesn't indicate no clinical benefit
- EAG and committee preferences for modelling of OS directly contradict clinical experts (SEE expert elicitation)
- Difficult to demonstrate OS benefit in NETs due to confounding with crossover, subsequent treatment variation, small sample size and long post-progression survival
- PFS is appropriate surrogate for OS: clinicians confirmed plausibility and evidence from literature:
  - observational cohort metastatic NETs - Kendall's tau of 0.31 (for SSAs) and 0.44 (for everolimus), $p<0.001$
  - literature review of 22 trials in NETs, significant association between median time to disease progression and median OS (coefficient: 0.595; $p=0.022$)
  - SLR of 20 trials in NENs: Spearman's rs = 0.587 (95% CI: 0.249–0.925).
  - TA449 everolimus and sunitinib: committee accepted clinical effectiveness despite non-significant OS results and high levels of crossover

Abbreviations: CI, confidence intervals; epNETs, extra-pancreatic neuroendocrine tumours; IPCW, inverse probability of censoring weights; HR, hazard ratio; pNETs, pancreatic neuroendocrine tumours; OS, overall survival; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

Large impact

# Key Issue: OS Hazard Ratio

EAG agrees potential for PFS to translate to OS benefits in this population but uncertainty remains

**EAG response**

- Reasonable to use SEE as limited evidence and generating robust evidence is difficult (TSD 26), EAG preference for a HR of 1 considers this evidence from company alongside evidence from CABINET trial
- Previous literature showed a degree of PFS and OS association but: lacked statistical power, were exploratory, included wider population (Imaoka 2017) or were not significant (Singh, 2014; Ter-Minassian 2017) → uncertainty in association remains
- HR of 1 chosen to assume that cabozantinib would not result in worse OS than BSC, this reflects CABINET August 2024 DCO → OS HR numerically favour BSC
- HR of 1 included in company base case for pNETs
- Agree plausibility of survival benefit given PFS benefit but CABINET not robust enough to determine magnitude
- Previous NICE appraisals show numerical advantage rather than disadvantage, so this is not sufficient evidence
    - RADIANT-3 and A6181111, numerically favour everolimus and sunitinib in comparison to BSC

| CABINET updated DCO | IPCW HR (95% CIs) | RPSFTM HR (95% CIs) |
|---|---|---|
| pNET | [redacted] | [redacted] |
| epNET | [redacted] | [redacted] |

| Study | HR (95% CIs) |
|---|---|
| RADIANT-3 (TA449 - everolimus) | 0.60 (0.09 to 3.95) |
| A6181111 (TA449 – sunitinib) | 0.34 (0.14 to 1.28) |
| NETTER-1 (TA539 – PRRT) | 0.49 (0.308 to 0.804) |

**NICE**

Is it appropriate to consider HR of 1 for OS?



Abbreviations: DCO, data cut-off; epNETs, extra-pancreatic neuroendocrine tumours; IPCW, inverse probability of censoring weights; HR, hazard ratio; OS, overall survival; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

# Key issue: Health-state utility values

Small Impact

## At ACM1

- Company: derived PF utility values from EORTC QLQ-30 data collected in CABINET, then applied relative decrement (from Swinburn et al) to CABINET PF data to inform the PD utility values
- At ACM1 EAG requested further details of regression analysis and additional analysis of the raw data

## Company (DG response)

- Provided full analysis of CABINET including justification for linear mixed model repeated measures structure, results of secondary analyses exploring treatment-specific utility values and all relevant prognostic factors
- Given remaining uncertainty in utility values from CABINET, optional eligibility into sub-study and limited observations for PD → revised base case aligns with EAG ACM1 preferences

## EAG

- At ACM1, insufficient info provided on CABINET data. Further detail provided with DG has solved most issues.
- Sufficient information provided to justify using the CABINET data to inform PF health state utility

| State | Company | | | EAG | | |
|---|---|---|---|---|---|---|
| | pNETs | epNETS | Source | pNETs | epNETS | Source |
| PF | [redacted] | [redacted] | **pNETs**: Swinburn et al. | [redacted] | [redacted] | CABINET |
| PD | [redacted] | [redacted] | **epNETs**: RADIANT-4 | [redacted] | [redacted] | Swinburn decrement (pNETs)/ RADIANT-4 decrement (epNETs) |

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What approach for estimating utility values is most appropriate?



Abbreviations:, epNETs, extra-pancreatic neuroendocrine tumours; EORTC, European Organisation for Research and Treatment of Cancer; PD, progressed disease; PF, progression-free PRRT, peptide receptor radionuclide therapy; pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours, QLQ; quality of life questionnaire

# Key Issue: Modelling concomitant treatment duration

Large impact

## At ACM1

- Committee: use of concomitant SSAs uncertain. Clinical experts broadly agreed concomitant SSAs don't stop with cabozantinib discontinuation. EAG's approach of modelling from baseline until death was more appropriate

## Company DG response

- Accept assuming concomitant SSAs stop on discontinuation of cabozantinib doesn't reflect clinical practice
- Clinical experts consulted by company stated that practice varies widely, SSA use can be determined by functional status but is not life-long and some discontinuation is anticipated
- Updates proportion of SSAs at baseline informed by estimates of functional status from clinical experts and overall proportion calculated by weighting based on proportion with functional disease in CABINET
- Same process used to derive proportion who discontinue concomitant SSAs prior to death (52.7% in epNETs, 56.2% in pNETs). These values used to derive constant discontinuation rates for concomitant SSAs (1.7% for cabozantinib and 2.4% for BSC (epNETs) and 1.1% for cabozantinib and BSC (pNETs)

## EAG

- Company elicited estimates have large variation, likely reflecting clinically meaningful heterogeneity (functional concomitant SSA use varies from 10%-100% and ratio of functional:non-functional varies from 2:1 to 1:1)
    - Heterogeneity makes pooled averages uncertain, but no alternative source
- Acknowledge expert elicitation highlights that assuming SSA use continues until death is an oversimplification
- EAG accepts company discontinuation rate but uses CABINET data for the proportion of concomitant SSAs

Abbreviations: SSA, somatostatin analogue; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours

Should a constant discontinuation rate be applied? Which approach to modelling proportion of concomitant SSA is more appropriate?

# Key Issue: Subsequent treatments

Large impact

**At ACM1**

- Where BSC is considered to be only available treatment, unclear why model included subsequent treatments

**Company DG response**

- Subsequent treatment costs should be modelled in line with CABINET (includes considerable proportion with subsequent treatment) → included in base case with EAG preference of cost applied when leaving PF state
- Scenario where subsequent treatments excluded, confounding impact of these treatments on treatment effect for OS must also be adjusted for. IPCW allows for adjustment for exposure to other subsequent treatments
- Exploratory IPCW analysis was conducted adjusting for all subsequent anticancer therapies in CABINET trial
  - favourable for cabozantinib with HRs of [redacted] (95% CI; [redacted]) [redacted](95% CI: [redacted]) versus BSC in pNETs and epNETs, respectively
- Scenario: no subsequent treatment costs, OS for BSC was derived by applying the IPCW-adjusted HRs above
  - The ICER for cabozantinib versus BSC was £15,958 in the epNETs group and £23,341 for pNETS group

**EAG**

- Company accepted EAG preferences for using the CABINET subsequent treatments in the model.
- Agrees that maintaining subsequent treatment costs in line with the trial maintains consistency with efficacy data.
- In original report EAG supported modelling of subsequent treatments from CABINET for comparison of cabozantinib with BSC, but did not include subsequent treatments in exploratory analysis comparing cabozantinib with other treatments.

**NICE** Do the committee agree with the company and EAG approach to subsequent treatments?



Abbreviations: BSC, best supportive care; IPCW, inverse probability of censoring weights; HR, hazard ratio; pNETs, pancreatic neuroendocrine tumours; OS, overall survival; pNETs, pancreatic neuroendocrine tumours

# Summary of company and EAG base case assumptions

| Assumptions | | Company base case: Updated after ACM1 | EAG base case |
|---|---|---|---|
| **Crossover adjustment** | | IPCW | RPSFTM |
| **OS HR** | | epNET < 1, pNET = 1 | epNET and pNET = 1 |
| **PFS** | **pNET** | Weibull | Weibull |
| | **epNET** | | |
| **OS** | **pNET** | Loglogistic | Weibull |
| | **epNET** | | |
| **Utilities** | **PF** | **pNETs:** Swinburn et al.; **epNETs:**RADIANT-4 | PFS from CABINET |
| | **PD** | **pNETs:** Swinburn et al.; **epNETs:**RADIANT-4 | Swinburn decrements for pNETs and RADIANT-4 decrements for epNETs |
| **Concomitant SSA use** | | Continue from baseline until death with constant discontinuation rate | Company approach but CABINET data for proportion of concomitant SSAs |
| **Resource use** | | From Casciano et al. (2013) | Aligning with TA449 and TA539, using Mujica-Mota et al. 2018 |
| **Adverse events** | | Maintain AEs applied per cycle | Apply AEs in first cycle |
| **AE's disutilities** | | -0.085 (hypertension), -0.370 (embolism) | Prefer -0.153 (hypertension), -0.330 (embolism) |

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Abbreviations: DCO, data cut-off; epNETs, extra-pancreatic neuroendocrine tumours; IPCW, inverse probability of censoring weights; NA, not applicable; OS, overall survival; PF, progression-free; PFS, progression-free survival; PD, progressed disease; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

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# Responses to draft guidance

## Other responses from company, Ipsen

| Summary | DG response | EAG comments summary |
|---|---|---|
| Additional benefits not captured by the QALYs | • Novel treatment for some with high unmet need due to limited treatment options<br>• Could simplify treatment pathway for some<br>• Impact on caregivers<br>• Burden of NETs on HRQoL not fully captured<br>• Should be taken into account when assessing uncertainty | For committee consideration |
| Description of target population as “later line” is overly simplistic | • Number and type of prior treatments differ according to individual patient characteristics (heterogeneity of NETs)<br>• For epNETs, limited treatment after progression on 1 or 2 systemic treatments.<br>• BSC only treatment option at earlier treatment lines for considerable proportion<br>• Description of company positioning as “later-line treatment” overly simplistic | • Agrees with committee positioning<br>• Population where BSC is comparator is people who are heavily pretreated and treatment with cabozantinib as a fourth (or more) line of systemic treatment for pNETs (excluding prior SSAs); or epNET treatment with cabozantinib as a third (or more) line of systemic treatment, excluding prior SSAs” |



Abbreviations: BSC, best supportive care; HRQoL, health-related quality of life; NCUK, neuroendocrine cancer UK; ep/NETs, extra-pancreatic/neuroendocrine tumours; SSA, somatostatin analogue.

# Responses to draft guidance

## Other responses from company, Ipsen

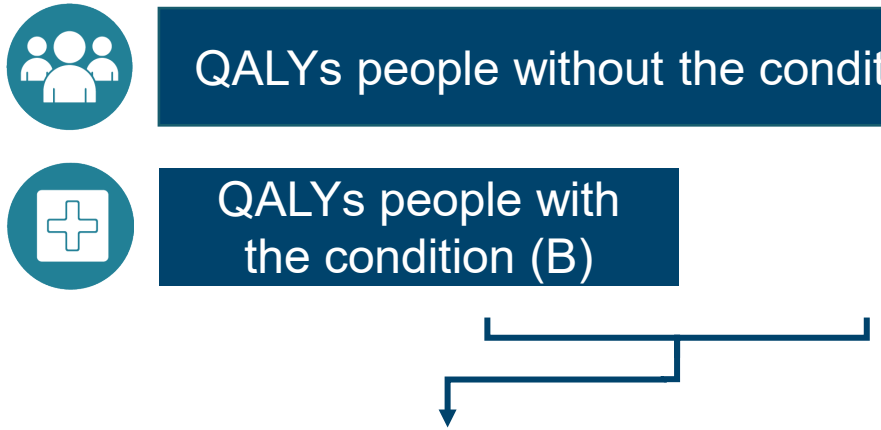
| Summary | DG response | EAG comments summary |
|---|---|---|
| Lung NETs | • Company agree overall epNETs group should be focus<br>• Lung NETs have higher unmet need, fragmented care pathway, poorer prognosis.<br>• Clinical expert opinion is split on biological distinctiveness for lung population versus epNETs. However, lung NETs face higher unmet need and fragmented UK care pathway leading to poorer prognosis<br>• Provided scenario analysis in lung NETs without relying on relative treatment effects from uncertain post-hoc analyses.<br>  • OS curves for cabozantinib derived from people with lung NETs (n=49).<br>  • BSC curves derived by applying company-preferred IPCW-adjusted HRs for overall epNETs cohort<br>• Analysis in lung NETs may be useful for committee consideration | • Emphasises difference in effect estimates between lung NET group and other epNETs<br>• Lung NETs: statistically significant benefit is observed for OS |



Abbreviations: ep/NETs, extra-pancreatic/neuroendocrine tumours; OS, overall survival.

# QALY weightings for severity (1/2)

**Severity modifier calculations and components:**




Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = ( A – B ) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

| QALY weight | Absolute shortfall | Proportional shortfall |
|---|---|---|
| 1 | Less than 12 | Less than 0.85 |
| X 1.2 | 12 to 18 | 0.85 to 0.95 |
| X 1.7 | At least 18 | At least 0.95 |



Abbreviations: QALY, quality-adjusted life year

# QALY weightings for severity (2/2)

| Population | QALE general population | Current treatment | Total QALE (living with NETs) | Absolute QALE shortfall | Proportional shortfall | Severity weighting |
|---|---|---|---|---|---|---|
| **Company base case: Updated after ACM1** | | | | | | |
| **pNETs** | 12.61 | BSC | [redacted] | [redacted] | [redacted] | 1.00 |
| **epNETs** | 11.61 | BSC | [redacted] | [redacted] | [redacted] | 1.20 |
| **EAG base case** | | | | | | |
| **pNETs** | 12.61 | BSC | [redacted] | [redacted] | [redacted] | 1.00 |
| **epNET(RPSFTM)** | 11.61 | BSC | [redacted] | [redacted] | [redacted] | 1.20 |
| **epNET (IPCW)** | 11.61 | BSC | [redacted] | [redacted] | [redacted] | 1.20 |

**EAG**

- EAG agrees with the company that a severity modifier of 1.2 is appropriate to use in their base case epNET analysis.

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off, epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progressed-free;pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours; RPSFTM, rank preserving structural failure time model; QALE, quality-adjusted life expectancy

Should a QALY weighting for severity be applied for any population?

# Cost-effectiveness results

All ICERs are reported in PART 2 slides due to confidential prices

NICE cost-effectiveness acceptability thresholds are determined by committee in part 2: these may range between £20,000/QALY to £30,000/QALY

**Company base case (for epNETS)**

- vs. BSC: under £30,000/QALY

**Company base case (for pNETS)**

- vs. BSC: over £30,000/QALY

**EAG base case**

- vs BSC (pNETs and epNETs): above £30,000/QALY

**EAG base case (IPCW scenario)**

- vs BSC (epNETs): under £30,000/QALY

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Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

# Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

- ❑ Key issues & decision problem
- ❑ Modelling and cost-effectiveness
- ❑ Other considerations
- ✓ Summary

NICE National Institute for Health and Care Excellence

# Key issues for committee discussion

| Key issues | Committee preferences at ACM1 | Company DG response | EAG response | Resolved | Impact |
|---|---|---|---|---|---|
| Data crossover | RPSFTM | IPCW | RPSFTM but no ideal method | No | Large |
| Modelling OS | Weibull for PFS and OS | Weibull PFS, Log-logistic OS | Weibull for PFS and OS | Partially | PFS small, OS small |
| HR for OS | OS HR of 1 | OS HR of 1 not appropriate | OS HR of 1. OS benefit plausible, no robust evidence for magnitude | No | Large |
| PF/PD utility values | Further analysis requested | pNETs: Swinburn et al. epNETs:RADIANT-4 | CABINET PFS with Swinburn (pNETs), RADIANT-4 (epNETs) decrements for PD | Partially | Small |
| Concomitant SSA | Modelling from baseline until death | Included with constant discontinuation rate | Company approach but CABINET data for proportion of concomitant SSAs | Partially | Large |
| Subsequent treatments | No subsequent treatment | Modelled with EAG preference | Accepted | Partially | Large |



Abbreviations: DCO, data cut-off; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; IPCW, inverse probability of censoring weights; RPSFTM, rank preserving structural failure time model; TSE, two-stage estimation

# Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

# Supplementary appendix

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# Background: Advanced neuroendocrine tumours

**Classification and epidemiology**

- Heterogenous group of rare tumours which typically present asymptomatically and can develop throughout the body
- Grouping based on location of primary tumour site → pancreas (pancreatic neuroendocrine tumours: pNETs) or any other location (extra-pancreatic neuroendocrine tumours: epNETs)
- Usually classified by primary tumour site, histological characteristics, stage and functional status
- ~3,600 estimated people eligible in England

**Causes**

- Family history of cancers (lung, stomach, pancreas, small intestine, colon and appendix)
- High BMI, diabetes, smoking and alcohol are potential risk factors

**Symptoms and prognosis**

- Depends on location of tumour and examples may include pain, tiredness, diarrhoea, nausea, rectal bleeding, shortness of breath and weight loss
- 5-year survival rates for stage 4 are less than 50% regardless of primary site, with the lowest being lung (12%), colon (18%), stomach (21%), rectum (22%) and pancreas (26%)



Abbreviations: BMI, body mass index

# Clinical perspectives

## Submissions from UKINETS and clinical experts

**Aim of treatment**

- The main aim is to control symptoms, delay tumour progression, improve overall and/or progression-free survival and quality of life

**Unmet need/current treatment options**

- Unmet need for NETs, particularly lung NETs → overall survival remains poor
- For epNETs, there are limited treatment options after progression on 1 or 2 lines of systemic therapy
- Unmet need for an additional treatment option to delay disease progression and improve outcomes for people with advanced NETs

**Cabozantinib**

- Improved progression-free survival in people with pNETs and epNETs which is clinically significant
- Common grade 3 or higher treatment-related adverse events include hypertension, fatigue, diarrhoea and thromboembolic events, but no toxicity signals of concern around use of cabozantinib

**Resource use issues**

- No anticipated additional infrastructure or staff costs required



Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours

# Patient perspectives

## Submissions from Insulinoma Support Network and Neuroendocrine Cancer UK

**Living with NETs**

- People and their families describe living with NETs as facing an uncertain and unpredictable future
- Lifelong medical appointments, invasive tests, and complex treatment regimens
- Symptoms can fluctuate daily → impacting on health and overall well-being

**Treating NETs**

- Often a delay in receiving an accurate diagnosis and timely access to treatment
- Not all therapies are suitable for individuals and not everyone will receive treatment in the same sequence
- Available therapies can cause mouth sores, digestive problems, diarrhoea & nausea

**Cabozantinib**

- Oral treatment, no need to travel to the hospital
- Meets an unmet need, especially for those with limited / no alternative treatment options beyond supportive care alone
- AEs with cabozantinib similar to other treatments or the disease itself → people previously treated with other TKIs (e.g., everolimus) have found cabozantinib more tolerable

*"The impact on daily living is profound, affecting relationships, employment, and social engagement."*

*"NHS care for metastatic insulinomas lacks consistent pathways, management varies widely between centres of excellence and local NHS hospitals and no national protocol exists, leading to delays, missed treatments, uncertainty and on occasions, death"*

Abbreviations: AEs, adverse events; NETs, neuroendocrine tumours; PFS, progression-free survival; TKI, tyrosine kinase inhibitors

# Cabozantinib (Cabometyx, Ipsen)

Technology details

| | |
|---|---|
| **Anticipated marketing authorisation** | '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.'<br><br>Authorisation received: September 2025 (MHRA IRP route) |
| **Mechanism of action** | • 3rd generation small molecule that inhibits the enzymatic activity of multiple tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer |
| **Administration** | • Oral: 60 mg tablet orally once daily |
| **Price** | • List price: £5,143 (30 x 60 mg tablets) per 30-day pack<br>• There is a simple patient access scheme (PAS) discount for cabozantinib |



Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; IRP: International Recognition Procedure; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; pNETs, pancreatic neuroendocrine tumours

# Key clinical trial: CABINET

| | CABINET |
|---|---|
| **Design** | Phase 3, multi-centre, double-blind, randomised, placebo-controlled trial |
| **Location** | US: 62 centres |
| **Population** | • Adults with pNETs or epNETs whose disease has progressed after prior systemic therapy, n=298 |
| **Intervention** | • Cabozantinib (60 mg once daily) |
| **Comparator** | • Placebo (60 mg once daily) |
| **Outcomes** | • **Primary**: PFS (assessed by blinded independent review committee [BIRC])<br>• **Secondary**: OS, ORR, safety and tolerability<br>• Exploratory: duration of response, disease control rate, HRQoL, and concordance between the investigator and BIRC response assessments |

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Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; HRQoL, health-related quality of life; pNETs, pancreatic neuroendocrine tumours; PFS, progression-free survival; ORR, objective response rate; OS, overall survival

# Baseline characteristics: CABINET

| Baseline | | pNET cohort | | epNET cohort | |
|---|---|---|---|---|---|
| | | CAB (n=64) | Placebo (n=31) | CAB (n=134) | Placebo(n=69) |
| **Functional status** | Functional | 11 (17%) | 5 (16%) | 41 (31%) | 25 (36%) |
| | Non-functional | 48 (75%) | 22 (71%) | 75 (56%) | 34 (49%) |
| **Prior systemic treatments** | SSA n (%) | 63 (98%) | 30 (97%) | 124 (93%) | 64 (93%) |
| | Mean (SD) | 2.7 (1.54) | 2.6 (1.74) | 1.9 (1.04) | 1.8 (1.07) |
| | ≥3 | 33 (52%) | 12 (39%) | 35 (26%) | 15 (22%) |
| **Types of prior systemic treatment** | Everolimus, n (%) | 51 (80%) | 25 (81%) | 96 (72%) | 44 (64%) |
| | PRRT, n (%) | 38 (59%) | 18 (58%) | 81 (60%) | 41 (59%) |
| | Sunitinib | 18 (28%) | 7 (23%) | 4 (3.0%) | 1 (1.4%) |
| | Anti-VEGFR TKI | 19 (30%) | 8 (26%) | 7 (5.2%) | 6 (8.7%) |
| | Other anti-VEGFR TKI | 1 (1.6%) | 1 (3.2%) | 3 (2.2%) | 5 (7.2%) |
| | Cytotoxic chemotherapy regimens | 44 (69%) | 18 (58%) | 51 (38%) | 23 (33%) |
| | Other | 6 (9.4%) | 3 (9.7%) | 10 (7.5%) | 2 (2.9%) |

**EAG**

- Baseline characteristics reasonable reflection of people in the NHS (heavily pretreated) rather than the potential use earlier in the treatment pathway allowed by the marketing authorisation
- Due to a lack of evidence, EAG experts would not want to use cabozantinib as an earlier treatment line than reflected in CABINET



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; PRRT, Peptide receptor radionuclide therapy; SD, standard deviation; SSA, somatostatin analogue; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

# Issue resolved at ACM1: Grouping approach for epNET

**Background**
- Company grouped GI NETs, lung NETs and other types of epNETs as epNETS
- Lung NETs have worse prognosis and fewer treatment options than other epNETs → grouping may be inappropriate

**Company:**
- Provided post-hoc analyses (PFS & OS) for lung NETs and epNETs (without lung NETs)
- CABINET included small lung NET population with some differences in baseline characteristics between cabozantinib and placebo → race, disease duration, grade 1 tumour and proportion with functional disease (see slide)

**EAG:**
- Lung NETs have fewer treatment options and grouping could mask treatment response
- Acknowledge uncertainties & differences in baseline characteristics, but an important subgroup
- Statistically significant improvements in PFS with cabozantinib (larger improvement for lung NETs)
- Results should be interpreted with caution due to imbalance in baseline characteristics → may bias towards cabozantinib (suggests slightly worse prognosis in placebo group)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; GI NETs, gastrointestinal neuroendocrine tumour; NETs, neuroendocrine tumours; OS, overall survival; PFS, progression-free survival;

# Issue as presented at ACM1: Modelling overall survival – original DCO

Company base case OS extrapolations for pNETs and epNETs using August 2023 DCO

pNETs: OS extrapolations (cabozantinib)

[redacted]

epNETs: OS extrapolations (cabozantinib)

[redacted]

# Issue: Modelling overall survival – updated DCO

pNETs: OS extrapolations (cabozantinib)

epNETs: OS extrapolations (cabozantinib)

Lung NETs: OS extrapolations (cabozantinib)

epNETs (w/o lung NET): OS extrapolations (cabozantinib)



Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; OS, overall survival; pNETs, pancreatic neuroendocrine tumours

# CABINET results: Overall survival

Company: first DCO, IPCW with lung NETS grouped into epNETS

| Stratified HR (95% CI) | ITT Analysis | RPSFTM | IPCW |
|---|---|---|---|
| **First DCO (cabozantinib vs placebo)** | | | |
| pNET | 0.95 (0.45 to 2.00) | [redacted] | 0.74 (0.36 to 1.52) |
| epNET | 0.86 (0.56 to 1.31) | [redacted] | 0.65 (0.39 to 1.07) |
| **Updated DCO (cabozantinib vs placebo)** | | | |
| pNET | [redacted] | [redacted] | [redacted] |
| epNET | [redacted] | [redacted] | [redacted] |

EAG prefer: updated DCO, RPSFTM and lung NETs separated

Method of crossover adjustment only matters if using updated DCO and lung NETs grouped as part of epNETs (HRs above or below 1 depending on method)

| epNETS separated | Lung NETs | | | epNETs (without lung) | | |
|---|---|---|---|---|---|---|
| | ITT | RPSFTM | IPCW | ITT | RPSFTM | IPCW |
| **Updated DCO (cabozantinib vs placebo)** | | | | | | |
| Unstratified HR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

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Abbreviations: CI, confidence intervals; DCO, data cut-off; epNETs, extra-pancreatic neuroendocrine tumours; IPCW, inverse probability of censoring weights; ITT, intent-to-treat; HR, hazard ratio; NETs, neuroendocrine tumours; OS, overall survival; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

# CABINET results: Progression-free survival

| PFS | pNETs | | epNETs | |
|---|---|---|---|---|
| | Cabozantinib (n=64) | Placebo (n=31) | Cabozantinib (n=134) | Placebo (n=69) |
| Number of events, n (%) | 32 (50) | 25 (81) | 71 (53) | 40 (58) |
| Median PFS (months) | 13.83 | 4.47 | 8.48 | 3.98 |
| HR (95% CI) | 0.23 (0.12 to 0.42) | | 0.38 (0.25 to 0.58) | |
| p value | <0.0001 | | <0.0001 | |

| PFS | Lung NETs | | epNETs (without lung) | |
|---|---|---|---|---|
| | Cabozantinib (n=33) | Placebo (n=16) | Cabozantinib (n=101) | Placebo (n=53) |
| Number of events, n (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median PFS (months) | [redacted] | [redacted] | [redacted] | [redacted] |
| Unstratified HR (95% CI) | [redacted] | | [redacted] | |

**EAG:** both lung NETs and epNETs (without lung) showed statistically significant improvements in PFS with cabozantinib, but a larger benefit was seen for the lung NETs group

Abbreviations: CI, confidence intervals; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; pNETs, pancreatic neuroendocrine tumours; PFS, progression-free survival

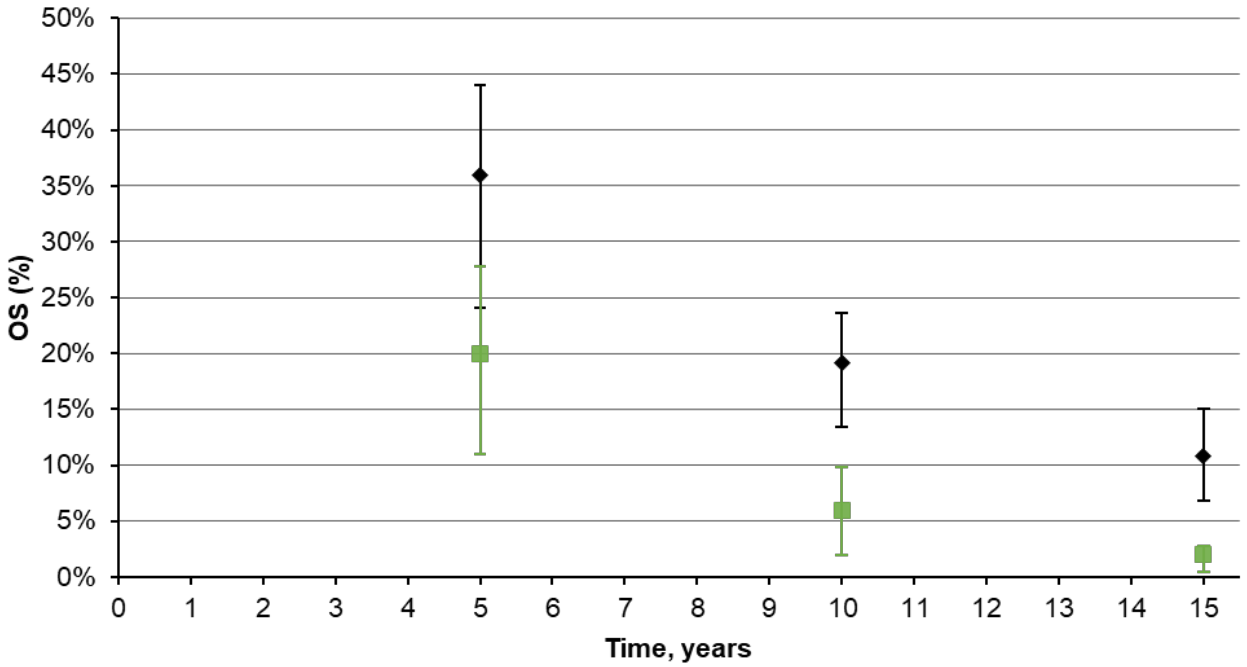


Main deck

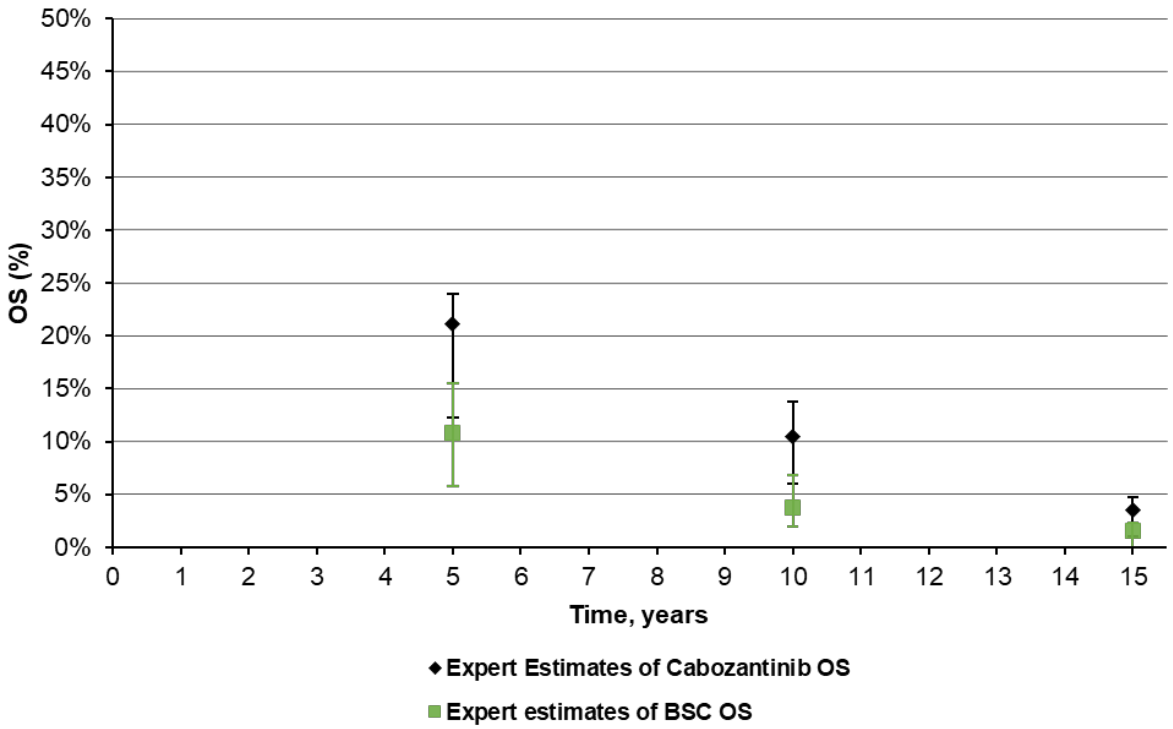
# SEE expert elicitation exercise results

**Figure 1. Clinician landmark estimates for OS for cabozantinib and BSC. (a) pNETs (b) epNETs**

(a)




(b)



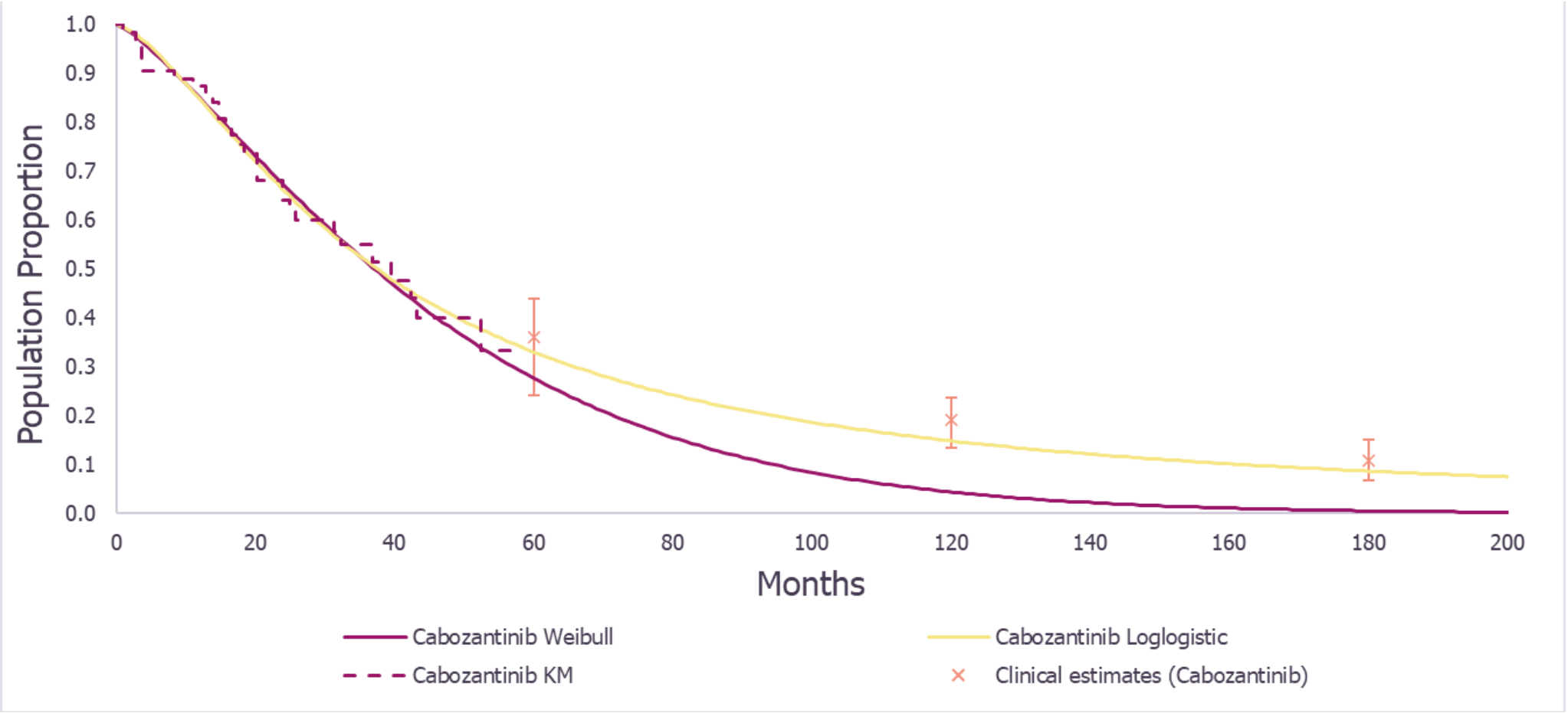

NICE



Abbreviations; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention-to-treat; NETs, neuroendocrine tumours; OS, overall survival; pNETs, pancreatic neuroendocrine tumours; RPSFTM, rank preserving structural failure time model

# pNETs Survival curves for modelling OS cabozantinib

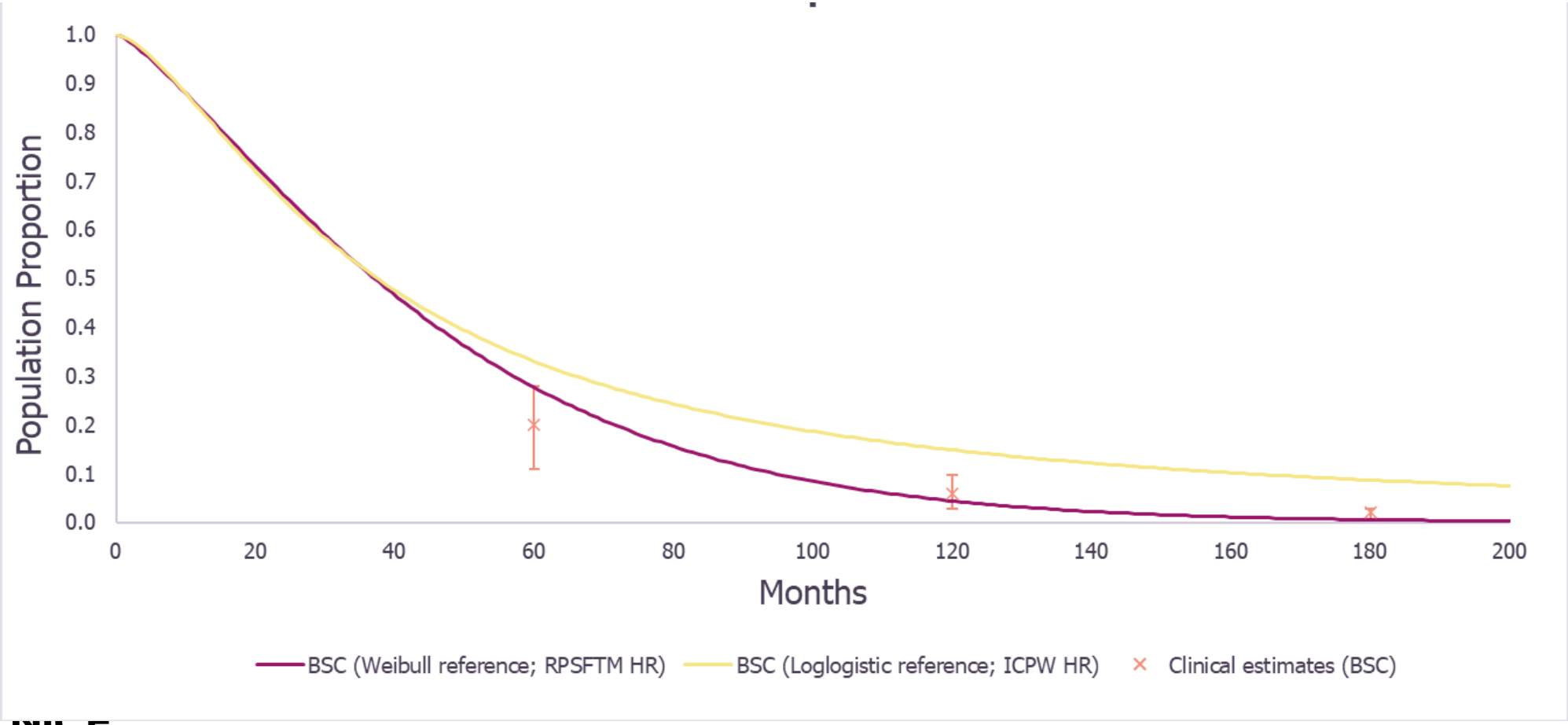
**Company versus committee-preferred OS extrapolations and clinician landmark estimates from the company – cabozantinib (pNETs)**




Main deck

# pNETs Survival curves for modelling OS BSC

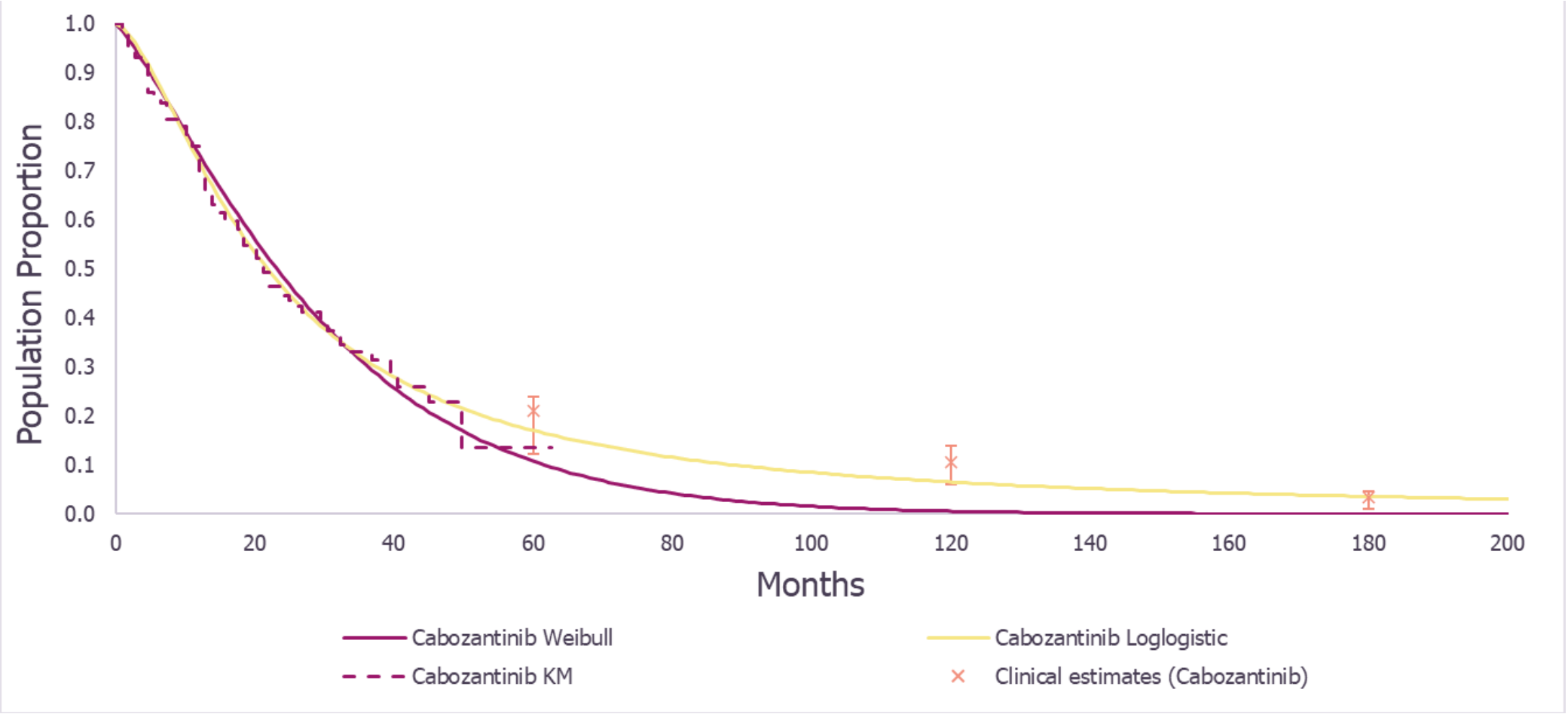
**Company versus committee-preferred OS extrapolations and clinician landmark estimates from the company –BSC (pNETs)**




Main deck

# epNETS Survival curves for modelling OS cabozantinib

**Company versus committee-preferred OS extrapolations and clinician landmark estimates – from the company– cabozantinib (epNETs) IPCW**

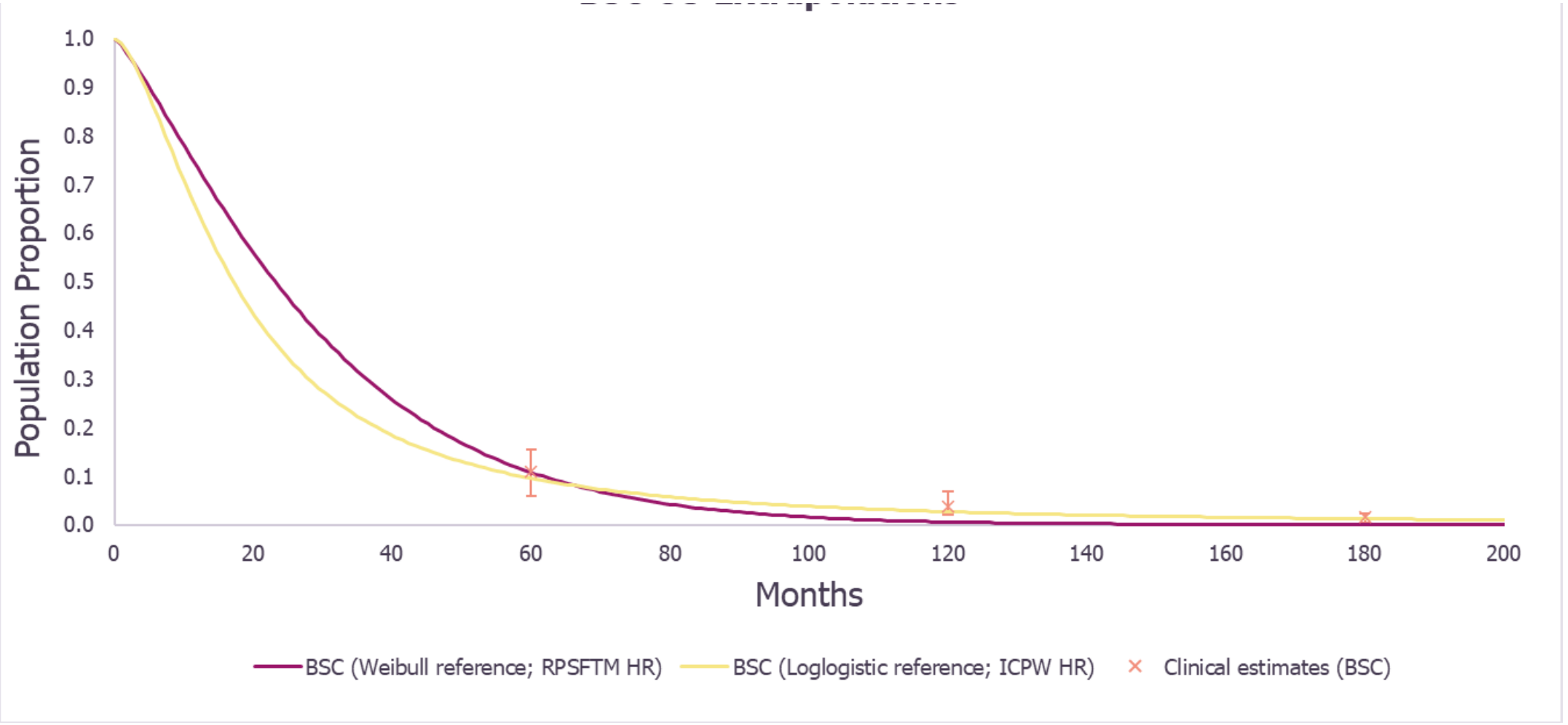



Main deck

Small Impact

# epNETS Survival curves for modelling OS BSC

**Company versus committee-preferred OS extrapolations and clinician landmark estimates – from the company–BSC (epNETs) IPCW**




Main deck

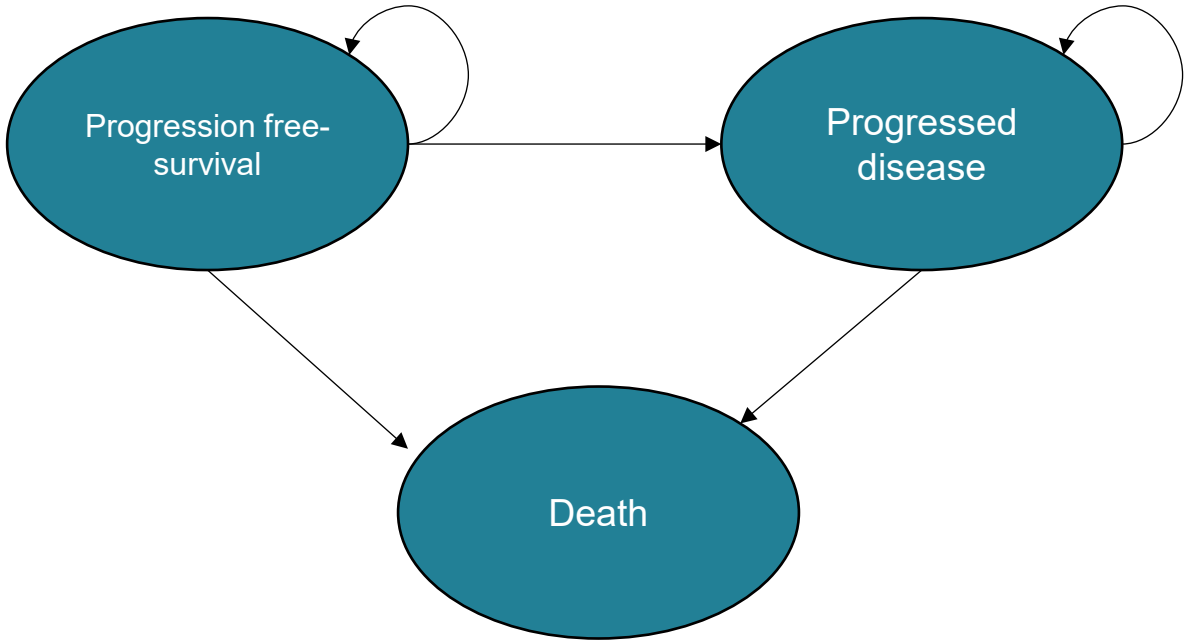
Large impact

# Modelling concomitant treatment duration: expert elicitation responses

| Clinician | Proportion of patients receiving concomitant SSA | | Proportion of patients who discontinue concomitant SSA before death | |
|---|---|---|---|---|
| | Functional vs non-functional | Weighted average | Functional vs non-functional | Weighted average |
| A | Functional: 20% Non-functional: 5% | 9.9% | Functional: 70% Non-functional: 70% | 70.0% |
| B | Functional: 100% Non-functional: 50% | 66.3% | Functional: 5% Non-functional: 50% | 35.4% |
| C | Functional: 25% Non-functional: 25% | 25% | - | - |
| D | Functional: 90% Non-functional: 50% | 63.0% | - | - |
| Pooled total | - | 41.0% | - | 52.7% |
| *Weighted averages calculated assuming 32.5% functional patients as per CABINET trial | | | | |

Abbreviations: BSC, best supportive care; PD, progressed disease; PSSRU, Personal Social Services Research Unit; SSA, somatostatin analogue; TTD, time to treatment discontinuation

# Company's model overview




**Company**

- Partition survival model in line with previous TA and clinical experts agreed with the proposed structure
- 3 – mutually exclusive states, people enter in PF with stable disease and remain until disease progression or death

**Affects QALYs by:**

- Delaying disease progression
- Increasing survival

**Affects costs by**:

- Higher total costs than current treatments

**EAG**

- Broadly agree with the model structure

Abbreviations: NETs, neuroendocrine tumours; PF, progression-free; QALYs; quality-adjusted life years; TA, technology appraisal

# How company incorporated evidence into model

| | Assumptions and evidence source |
|---|---|
| **Baseline characteristics** | • CABINET |
| **Time horizon** | • Lifetime (40 years) |
| **Cycle length** | • 4 weeks |
| **Treatment effect** | • CABINET |
| **Utilities** | • PF: Derived from CABINET (EORTC QLQ-C30)<br>• PD: A relative decrement applied to CABINET PF utility values calculated from Swinburn et al 2012 |
| **Resource use** | • Healthcare resource use (HCRU) SLR (Casciano et al. [2013]) |
| **Costs** | • PSSRU, BNF, National schedule of costs |
| **Perspective** | • NHS and PSS |

Abbreviations: BNF, British National Formulary; EORTC, European Organisation for Research and Treatment of Cancer; PF, progression-free; PD, progressed disease; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; SLR, systematic literature review; QLQ; quality of life questionnaire