Health Technology Appraisal

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6184]

(Renal cell carcinoma Pathways Pilot [ID6186])

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6184] (Renal cell carcinoma Pathways Pilot [ID6186])

Contents:

The following documents are made available to stakeholders:

1. **Company comments on the Pathways Model Report and Draft Guidance from Ipsen**

2. **Other stakeholder comments on the Model Report and Draft Guidance** from:
   a. Action Kidney Cancer
   b. Kidney Cancer UK
   c. Merck Serono
   d. MSD

3. **EAG Review of Responses to the Model Report and Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Renal cell carcinoma Pathways Pilot [ID6186]
Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6184]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments by the end of **21 December 2023**. Please submit via NICE Docs.

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		Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
	Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Ipsen Limited

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[Insert disclosure here]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[Insert name]

Document Pathways Model Report Or **Draft Guidance**	**Comment number**	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Overall Process	1	Ipsen is disappointed with the decision of NICE not to recommend cabozantinib in combination with nivolumab. This response highlights two areas of concern in addition to specific points in the Draft Guidance (DG) for cabozantinib with nivolumab for untreated advanced renal cell carcinoma and the DG for the renal cell carcinoma pathway model report. **1. The Pilot Pathway Process has presented significant challenges and this will be a deterrent to participation in such schemes for companies in the future**

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		• Ipsen acknowledges that the Pilot Pathway Process represents a new and untried method of evaluation by NICE as part of Phase 2 of its proportionate approach looking at streamlined ways of working. As such it is reasonable to expect there will be successes and failures as the process evolves. While recent public updates provided by NICE have demonstrated success in some pilots, the RCC pathway pilot has been beset with significant challenges which have caused processes to become protracted and at times unreasonable. Ipsen believes it is essential these shortcomings are acknowledged by NICE so that all relevant lessons can be learned and remedial solutions are implemented before taking this pathway process further forward. • In summary, the major process challenges experienced by Ipsen include: - Lack of transparency from NICE regarding access to key data in this pilot process. This includes the RWE and associated assumptions and not having had sight of the DSU report on model validation. NICE should adopt more reasonable processes regarding access to and requests for key data. These processes should enable more mutually fair and acceptable exchange of data between NICE, the EAG and the company to ensure the timely execution of the evaluation. - Level of complexity in the modelling using R; the difficulty in replicating the model results from a company perspective because of redaction and the challenges with the ability of a wide stakeholder group to understand and use such a model in practice, as well as practical limitations in presenting decision uncertainty. - Inconsistency and arbitrariness in the application of NICE methods and assumptions made, which seriously undermine the rigour and consistency of the wider evaluation and threaten the ability of the committee to appropriately consider uncertainty in their decision making. **We would ask the following of NICE:** • What if a company insisted on large amounts of data being marked CIC? • What if a company redacted or provided dummy data such that an EAG could not replicate the results the company obtained in their base case model submission? • What would NICE say if a company failed to present decision uncertainty in the form of PSA in a submission, in accordance with the new Methods of 2022? • What if a company presented a model that was so complex most stakeholders could not follow it, or perform a quality assessment? • What if a company mixed and matched different sources and methodologies such that it created multiple inconsistent assumptions and effectively an exponential set of uncertainties? **As a result of the above Ipsen would recommend:**

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		• The decision for cabozantinib with nivolumab should be balanced and consider all the variations and uncertainties that have surfaced in this pilot pathway appraisal and be cognisant of Section 6.2.28 (Structured decision making: value for money) of the NICE manual [PMG36] which states that "the committee should consider the likelihood of decision error and its consequences". Therefore, when considering the number of variables and assumptions that have been made in this pilot pathway appraisal, a pragmatic and balanced approach is required. • There should be no further development of the Pathways approach for NSCLC until there is a thorough review of this RCC pilot pathway process and the learnings from it before any further decision on the viability of its development is taken. - It is neither fair nor reasonable, in Ipsen's opinion, to expect companies to participate and fully contribute to the NSCLC pilot until all the issues in this appraisal are discussed and reviewed. **2. Clinical and Technical issues raised in the Draft Guidance** *Insufficient clinical expert representation to discuss the technology.* Section 1.3.17 of the NICE manual [PMG36] states clinical experts must be able to meet the several requirements including: • They have knowledge or experience of the condition, the technology being evaluated, or the way it is used in the NHS. • They are willing and able to discuss the condition and the technology at a committee meeting when members of the public and press are observing. Section 1.3.18 also states clinical experts must meet the following additional requirements: • They are in active clinical practice and have specialist expertise in the subject area of the evaluation. Although there were two clinical experts at the meeting, only one of them was a clinical oncologist who could reasonably have addressed the above points and met those criteria for the technology being assessed in having knowledge and experience of it. The meeting's excessive duration (over six hours for the public discussion) placed a large onus on this one expert as all the questions were directed to him. Whilst the NICE manual [PMG36] states under section 5.8.57 that for a subsequent meeting on production of draft guidance "The chair of the committee may invite 1 or more of the clinical experts to attend", which implies it is not mandatory, Ipsen would reasonably expect there to be two clinical experts which are practising renal oncologists with experience of IO/TKI therapies for the second committee meeting to ensure the place and need for cabozantinib in combination with nivolumab is properly discussed.

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		Finally, the company notes that the DG (page 3) states that an indirect comparison *"suggests that cabozantinib plus nivolumab works as well as nivolumab plus ipilimumab and pembrolizumab plus lenvatinib".* Given this acknowledgement by the committee, the company would like to emphasise the need for pragmatic decision making in order to provide patients with an alternative treatment option which would be welcomed by clinicians and patients.
Draft Guidance	2	**Decision uncertainty – Probabilistic sensitivity analysis (PSA)** According to the health technology evaluation (HTE) manual, Process and methods [PMG36], published by NICE, results of the cost-effectiveness model should be presented probabilistically for the base case and scenario analyses. Specifically, the manual puts an emphasis on the presentation of PSA results, mentioning that: • The committee's preferred cost-effectiveness estimate should be derived from a probabilistic analysis when possible unless the model is linear. If deterministic model results are used, this should be clearly justified, and the committee should take a view on if the deterministic or probabilistic estimates are most appropriate. • The computational methods used to implement an appropriate model structure may occasionally present challenges in doing probabilistic sensitivity analysis. Clearly specify and justify using model structures that limit the feasibility of probabilistic sensitivity analysis. Models should always be fit for purpose and should allow thorough consideration of the decision uncertainty associated with the model structure and input parameters. The choice of a 'preferred' model structure or programming platform should not result in the failure to adequately characterise uncertainty. At a recent NICE Industry Council meeting NICE expressed to the ABPI that *"not all topics were reporting probabilistic ICERs and net health benefits."* This implies NICE expect companies to present PSA results in their submissions. This is contradictory to the current pilot process and highlights mixed messages from NICE, which does little to help consistency and understanding of what is required for the NICE manual [PMG36]. To explore uncertainty, the EAG ran an extensive number of scenario analyses. Ipsen agrees that the scenario analyses conducted by the EAG provided useful insights into model behaviour and validation. However, the complexity of the selected model structure did not allow for uncertainty to be fully characterised and presented, as recommended by the NICE health technology evaluations: the manual, Process and methods [PMG36]. Specifically, results of the PSA (which provides stronger analytical support for decision making) to demonstrate how parameter uncertainty translates into joint uncertainty of incremental QALYs and costs for the base case and scenario analyses was not presented in the committee meeting. Consequently, the EAG probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves were not presented by the EAG, which prevents quantification and visualisation of the uncertainty around the decision.

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		According to the EAG, probabilistic results would be produced following the model's QC by the Decision Support Unit (DSU) (Page 15, EAG list price ICER report), and the base case analyses would be presented in a probabilistic manner to align with the NICE manual (Final EAG report, 24 August 2023). To accommodate this, the EAG built the cost-effectiveness model in R in order to reduce the computational burden and time required to perform the PSA, due to the complexity of the model structure (Page 294, Final EAG report, dated 24/08/23). However, in the EAG's review of the Company's response to technical engagement, PSA results were not presented, on the basis that probabilistic results using the lambda approximation method showed consistent results with the probabilistic analysis (Page 16, EAG Review of Company's Response to Technical Engagement, 13 October 2023). Ipsen would like to highlight that despite the point estimates of the probabilistic and deterministic analyses being similar, the lack of PSA results did not allow full quantification and visualisation of decision uncertainty, due to the limited feasibility imposed by the complexity of the model structure. Indeed, the decision to present deterministic results was justified by the EAG on the grounds of the PSA computational burden due to the complexity of the cost-effectiveness model structure used for this assessment, acknowledging that the run-time issues with the hybrid STM led to excessive run-time for probabilistic analyses (Page 57, EAG Review of Company's Response to Technical Engagement, 13 October 2023**). Specifically, the EAG mentions that given a PSA of 1000 iterations, the hybrid state transition model with four lines of treatment would require approximately 37.5 hours, only for one population, for the 4 treatment line pathways in that population, and only to compute the Markov trace. Ipsen suspects few people within NICE and the committee are aware of the computational power needed to execute this with the hybrid STM.** A run time of about a working week to run just one pathway PSA scenario clearly presents a wholly unrealistic situation to enable examination of different scenarios and assumptions to address NICE committee uncertainties that they would have and cannot fulfil what is recommended in the NICE manual [PMG36]. Consequently, the EAG concluded on three options for handling probabilistic results of the hybrid STM, including the use of a supercomputer, the estimation of time in health states using exponential approximation for the current decision problem, or foregoing a probabilistic analysis completely. The Draft Guidance highlights that the committee acknowledged multiple uncertainties in the evidence base. Although the committee considered the EAG's alternative partitioned survival model approach, it concluded that the complexity of the 4L STM model provides greater flexibility to explore uncertainties and alternative assumptions across different lines of treatment. The committee noted that these uncertainties would be present in the analysis but not visualised when using a simpler partitioned survival modelling approach. Despite the consistent use of partitioned survival models in previous RCC submissions, the committee also noted that it preferred the hybrid STM because a fundamental part of the pathway model approach is the ability to model multiple lines of treatment in as much detail as possible. **Although an extensive number of scenarios was conducted by the**

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		EAG, Ipsen would like to emphasise that the complexity of the 4L STM model did not allow to fully assess decision uncertainty. The DG describes in a number of areas uncertainty in the NICE committee's mind and one would have thought in this case that it would be reasonable to expect that the committee would demand a PSA to inform its decision making – Ipsen believes this would have facilitated a more efficient decision-making process, possibly avoiding a second committee meeting which is in line with NICE's desire to achieve efficiency. **Ipsen therefore finds it concerning that if in this pathway pilot appraisal, there remains a number of uncertainties in the committee's mind and assumptions that are not fully justified, PSA results have not been fully presented to characterise the decision uncertainty associated with the committee's preferred assumptions. As per the HTE manual, Process and methods [PMG36] (section 4.7.20), *"the choice of a 'preferred' model structure or programming platform should not result in the failure to adequately characterise uncertainty."***
Draft Guidance	3	**Committee preferred assumptions (Utilities) – Section 3.6, Page 9** In the DG it states that: *"The committee's preferred assumptions included: …applying utility values previously accepted in NICE technology appraisals to capture patient health-related quality of life as their disease progresses and they have multiple lines of treatment."* This statement means that all utility values that have been presented in all NICE TAs including TA858, TA650, TA581 should be taken into consideration and not just TA645 which has been used and has values of 0.753 for the pre-progression health state and 0.683 for the post-progression health state. Of note, these values were derived using an EQ-5D-5L to EQ-5D-3L crosswalk in order to align with NICE expectations although EQ-5D-3L utility values are readily available from CheckMate 9ER. Utilities based on a mapping algorithm would arguably increase uncertainty as opposed to using utilities directly derived from the trial. It has even been shown that using 5L instead of 3L may lead to different reimbursement decisions[1] and whether this carries over when mapping from 5L directly derived from a trial to 3L deserves consideration. Further, it was stated by the NICE technical team in ACM1 that previous utility values (that have been presented in RCC TAs for combination therapies) included a utility value of 0.79 for the pre-progression health state and 0.7 for the post-progression health state and were accepted. Considering how the committee were happy to consider redacted RWE data, which Ipsen and most other stakeholders cannot see, it is therefore unreasonable that some utilities from other appraisals are not considered, despite them being redacted, in the context of the utility values from 9ER which have a pre-progression value of [redacted] and a post-progression value of

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		[redacted]. Although these values from the 9ER trial may be high, they should not be dismissed as they are directly derived from the trial. Alternatively, the committee should consider if other (redacted) utility values from TA858, TA650, TA581 are plausible and have face validity. NICE committees have also mixed and matched utility values from different sources in appraisals where there has been concerns or uncertainty of the values presented using just one source. This has not been considered at all in the draft guidance. Ipsen's response to *Key Issue 5: Problems with the health-related quality of life data supplied by the company* is repeated again below for ease of reference: *"As mentioned previously in response to B1 of the EAG clarification questions, Ipsen would like to reiterate that it is unaware of any differences in their approach to collecting and analysing this data that would account for the difference in magnitude versus the TAs in advanced RCC**. The high utility values derived from the analysis of CheckMate9ER are, however, supported by other previously published studies assessing the cost-effectiveness of treatments with similar mechanisms of action**. For example, a recent cost-effectiveness analysis of treatment sequences for intermediate to poor risk aRCC patients reported a utility for first-line nivolumab with ipilimumab of 0.83, based on an analysis of EQ-5D-5L data from Checkmate 214[2]. Additionally, a cost-effectiveness analysis of pembrolizumab with axitinib (also in aRCC) used a mixed-effects regression of EQ-5D-3L data collected from KEYNOTE-426 to estimate utility values for different patient categories defined by days until death. The estimated utility value for patients at least one year prior to death was 0.824[3].* ***There is also precedence in the literature for maintaining a high post-progression utility value, which aligns with the results of the CheckMate9ER analysis**. For example, in a cost-effectiveness analysis comparing nivolumab to everolimus in aRCC, the utility values assigned to each health state were as follows: progression-free (complete response/partial response), 0.895; progression-free (stable disease), 0.846; and progressed disease, 0.817[4]. Another example, again with nivolumab, but in carcinoma of the head and neck, used utility values in the cost-effectiveness model of 0.805 for progression-free and 0.746 for progressed disease (comparator; 0.770 and 0.676 respectively)[5]. This is similar to the utilities derived from the larotrectinib study: 0.81 (PF) and 0.74 (PD)[6] .* ***One solution Ipsen would recommend and would be reasonable based on the discussion above is that the EAG applies the percentage drop in utility (from the PFS to PD health state) derived from their base case utilities, to the baseline utility derived from the 9ER study (i.e., PFS utility from 9ER) as this would be a logical option to consider in addition to the existing scenario analysis using the CheckMate 9ER derived utilities in the model.***
Draft Guidance	4	**Recommendation – Section 3.12 , Page 12**

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		"The committee concluded that cabozantinib plus nivolumab is an effective treatment for renal cell carcinoma. But the analyses either showed that cabozantinib plus nivolumab was not cost-effective, or did not reflect the committee's preferred assumptions, when compared with the most appropriate comparators in each risk group. So, cabozantinib plus nivolumab is not recommended for untreated advanced renal cell carcinoma in adults." Ipsen disagrees with this statement. There were analyses presented on a slide which included several key scenarios where cabozantinib was cost-effective versus lenvatinib with pembrolizumab and also ipilimumab with nivolumab. However, these were not discussed in depth and were brushed over in the interests of time it appeared. It is also surprising that there was a delay in NICE providing the slides from the committee meeting for this consultation to support stakeholders in responding to the draft guidance. The company had highlighted factual inaccuracies including the description of scenarios ahead of the committee meeting as did EAG during the meeting, but these have not been updated in the version which is now available but was delayed in being provided online.
Model Report	5	**On page 2, the report states:** *"the committee's preferred assumptions for the key issues were to….use the state transition model approach".* The EAG selected the hybrid STM with 4L as the base case model structure. This model structure and the granularity in modelling four subsequent lines of treatment deviates from precedence, **leading to inconsistencies in decision making for cabozantinib with nivolumab versus previous appraisals in aRCC**. Despite earlier assurances from the EAG that results between the models would be similar, there were **unexpected discrepancies in results between the STM and PartSA models**. Evidence and assumptions used to inform the modelling of 4L of treatment introduced further uncertainty inconsistencies within the appraisal of cabozantinib with nivolumab. The implementation of a STM with 4L of treatment informed by RWE, introduced certain challenges and potentially serves as a source of bias for the results of the cost-effectiveness analysis: • RWE limited sample size for 3L and 4L (please see below for comments on RWE) • TTD efficacy informed by PFS NMA
Model Report	6	**Treatment pathway – Section 1.4, page 4 – the triple combination of cabozantinib, nivolumab plus ipilimumab is not part of the scope of this appraisal**

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		"Treatment is decided based on risk status (see section 1.3). Cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus lenvatinib and avelumab plus axitinib are only available for intermediate- and poor-risk RCC" There is a factual inaccuracy in the DG. It implies that a triple combination of cabozantinib, nivolumab plus ipilimumab is part of the treatment pathway. This is not true. This triple combination is undergoing clinical trials at present and is not currently approved nor in routine practice. This should be corrected.
Model Report	7	**Clear and non-clear cell RCC – Section 1.10, page 9 – there is reason to believe that the cabozantinib with nivolumab combination will be effective in non-clear RCC** *"The committee concluded that, without evidence of a differential treatment effect, it was reasonable for the results of the model to be considered generalisable to both clear and non-clear cell RCC, even though trials mostly include clear cell RCC alone. The committee noted that further research on how clear and non-clear cell RCC respond to different treatments would be useful."* NICE should be reassured that there is in fact some evidence to suggest why the cabozantinib with nivolumab combination would be expected to be clinically effective in non-clear cell RCC. This was presented in Ipsen's response to *Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment,* which stated: *"The EAG notes that there are questions about the applicability of analyses to other RCC histologies. In RCC, trials are commonly restricted to patients with a clear cell histology. These patients make up the vast majority (circa. 75%) of RCC patients.* *It is worth noting that all histological epithelial subtypes of RCC (clear cell, papillary, chromophobe) can present with sarcomatoid differentiation, which is the most aggressive form of RCC. A high proportion of RCC patients with sarcomatoid features present with metastatic disease. These features are found in 5-8% of clear cell RCC and in the CheckMate 9ER trial 11.95% of the patients recruited had sarcomatoid features. This is similar to the IO/IO trial CheckMate 214 (ipilimumab with nivolumab) and the IO/TKI trial JAVELIN 101 (axitinib with avelumab) but higher than other IO/TKI combination trials such as CLEAR (6.8%). This helps increase the applicability of the CheckMate 9ER results to clinical practice.* ***Further, the EMA noted that in the application for approval of cabozantinib with nivolumab, non-clear cell RCC were not excluded from the sought indication, which was deemed acceptable by the EMA because cabozantinib had shown efficacy in non-clear cell RCC in a retrospective study[7].*** *As a final note, this highlights the difference in requirements between regulatory bodies and Health Technology Assessment (HTA) organisations. This key issue*

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		demonstrates both how the two may be at odds and the inability to resolve these concerns to the satisfaction of all parties and, thus some compromises may need to be made."
Model Report	8	**Real-world evidence – Section 1.12, page 10** *"The EAG only considered 1 out of 12 real-world datasets identified in the systematic review to be robust and relevant to the UK (Challapalli et al. 2022). The dataset owners gave the EAG access to unpublished patient level data."* It is unreasonable and unfair that Ipsen as the company with the intervention (in combination with nivolumab) being assessed in this pilot pathway does not have any access to these data. If Ipsen were submitting RWE as part of a standard technology appraisal and did not allow the EAG or NICE to have sight of these data, Ipsen would be charged by NICE with obstruction of processes. It is unreasonable and unfair that Ipsen should not have the ability to at least view these data under a confidentiality agreement. As a result, Ipsen cannot validate any of the results that are presented by the EAG, which of course would raise concerns by the NICE committee if this were the other way around because these data providing reference curves are the foundation of baseline risk in the model and thus have an impact on committee decision making. *"The committee also explained that the dataset provides a good indication of the likely treatment sequences that the pathway will rely on. See section 3.6 of the EAG's assessment report for more details on the real-world evidence."* A key issue is that Ipsen has no visibility or access to the treatment sequences from this real-world dataset and thus cannot replicate the EAG results. Again, this is unfair and unreasonable from Ipsen's perspective and would be heavily criticised by NICE and the EAG if this were the other way around.
Model Report	90	**Appropriateness – Section 1.14, page 12 – there is a failure in the DG to describe in detail what the limitations of the RWE are** *"It concluded that despite the limitations with real-world evidence, the UK real-world dataset reflected NHS practice. The committee further concluded that data used for baseline characteristics, natural history of RCC and treatment sequences were appropriate for the pathway model."* The DG does not describe what these limitations are in any detail, including how they impact on the cost-effectiveness analysis, so it is unclear what the committee considered they were. The company thinks that the limitations should have been described especially given the pre-existing lack of transparency surrounding the RWE.
Model Report	10	**Network meta-analyses – section 1.15, page 12**

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		"The trials from the systematic literature reviews (see section 1.8) were used to inform network meta-analyses for clinical outcomes to be used in the model. Network meta-analyses were done using the first-line networks for the all-risk group, favourable-risk, and intermediate- or poor-risk subgroups. The second and subsequent line network was used for a network meta-analysis only for the all-risk group. Networks were formed for overall survival, progression-free survival, overall response rate, stopping because of adverse events and the risk of treatment-emergent adverse events of grade 3 or higher. The committee concluded the networks were appropriate and considered all relevant outcomes and treatments in the pathway. See section 3.7 and appendix E of the EAG's assessment report for more details on the network meta-analyses." Ipsen disagrees with the inclusion of CABOSUN in the overall network as the trial includes only intermediate/poor risk patients. The treatment effect is higher in intermediate/poor risk populations and the survival outcomes are poorer. The results from CABOSUN are not comparable to other trials which include favourable risk patients. This leads to an overestimation of the treatment effect versus sunitinib in the overall population, as the EAG have acknowledged in their report. Additionally, the company would like to highlight the inconsistent methodologies applied in the indirect treatment comparison conducted by the EAG and their deviation from precedence in past appraisals including TA858. The company would like to re-iterate that the relative effects used in the economic model for the various comparators should be consistently derived using similar methods. Proportional hazards NMAs should be preferred throughout, because those methods align with past appraisals (e.g., TA858) and are intuitively interpretable ensuring appropriateness for decision-making purposes. • Further, the company would like to make the following comments regarding the structured expert elicitation (SEE): The populations considered by the FP NMAs and in the SEE are potentially inconsistent; the former utilised trial data, whilst the latter considered the average patient in England. Furthermore, the EAG did not take measures to ensure that clinical experts align on what they perceive the average patient in England to be. • Experts were not given the chance to interact with each other in order to exchange experiences, align on the population, nor were they offered the chance to see other experts' responses and update their opinion should they wish to. Hence, no measures were taken to promote high performance and reduce self-serving bias. Many questions were answered by less than five experts and by as little as two experts. It is unlikely that uncertainty can be appropriately estimated with such low sample sizes.

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Renal cell carcinoma Pathways Pilot [ID6186]
Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6184]

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Model Report	11	**First-line relative effects – Section 1.17, page 13 – the statement that the proportional hazards assumption is violated for all treatments is incorrect and misleading in the DG and is biased** *"The proportional hazards assumption was violated for all treatments in the pathway for each of the risk subgroups as the relative effect compared with sunitinib changed over time."* *"The committee considered this but noted that the proportional hazards assumption was not met for any treatment. The committee also considered that the flexible time-varying hazard ratios from a fractional polynomial approach provided a better, more plausible fit to observed short-term data. It concluded the fractional polynomial approach was preferred at first line."* It is incorrect to state that the proportional hazards assumption was violated for **all** treatments for each of the risk groups and the committee's conclusion that the PH assumption was not met for any treatment. Ipsen presented for cabozantinib with nivolumab in our response to the EAG Clarification Questions (Question A21) that there was no violation of the PH assumption for the All-risk and Intermediate/Poor risk populations so we disagree with the EAG conclusion that it does in Table 36 of the EAG report (dated 24/08/23). Table 36 also shows the committees conclusion that the PH assumption was not met for **any** treatments is incorrect and therefore there is a case for considering the PH assumption in the base case as has been done for previous combination therapy appraisals for RCC by NICE.

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<table>
<tr>
<td></td>
<td></td>
<td>
Table 36: Results of tests for proportional hazards in the all-risk group using Cox regression
<table>
<tr><th>Study</th><th>P value: PFS</th><th>Visual check: PFS</th><th>P value: OS</th><th>Visual check: OS</th></tr>
<tr><td>AXIS</td><td>0.59</td><td>Yes</td><td>0.75</td><td>Yes</td></tr>
<tr><td>BERAT</td><td>0.13</td><td>No</td><td>NA</td><td>NA</td></tr>
<tr><td>CABOSUN</td><td>0.90</td><td>Yes</td><td>0.92</td><td>Yes</td></tr>
<tr><td>CheckMate 025</td><td>0.00016</td><td>No</td><td>0.34</td><td>Yes</td></tr>
<tr><td>CheckMate 214</td><td>0.000025</td><td>No</td><td>0.59</td><td>Yes</td></tr>
<tr><td>CheckMate 9ER</td><td>0.084</td><td>No</td><td>0.08</td><td>No</td></tr>
<tr><td>CLEAR</td><td>0.0027</td><td>No</td><td>0.00014</td><td>No</td></tr>
<tr><td>COMPARZ</td><td>0.25</td><td>Yes</td><td>0.44</td><td>Yes</td></tr>
<tr><td>CROSS-J-RCC</td><td>0.19</td><td>No</td><td>0.56</td><td>NA</td></tr>
<tr><td>JAVELIN RENAL 101</td><td>0.33</td><td>No</td><td>0.87</td><td>Yes</td></tr>
<tr><td>METEOR</td><td>0.032</td><td>No</td><td>0.56</td><td>Yes</td></tr>
<tr><td>NCT01136733</td><td>0.92</td><td>Yes</td><td>0.70</td><td>Yes</td></tr>
<tr><td>RECORD-1</td><td>0.66</td><td>Yes</td><td>0.31</td><td>Yes</td></tr>
<tr><td>SWITCH</td><td>0.15</td><td>No</td><td>0.32</td><td>NA</td></tr>
<tr><td>SWITCH II</td><td>0.72</td><td>Yes</td><td>0.43</td><td>NA</td></tr>
<tr><td>TIVO-1</td><td>0.29</td><td>No</td><td>0.83</td><td>No</td></tr>
<tr><td>TIVO-3</td><td>0.039</td><td>No</td><td>0.54</td><td>Yes</td></tr>
</table>
Note: Yes is no clear evidence of violation of proportional hazards; No represents evidence of violation of proportional hazards. Lenvatinib arm dropped from analysis for three-arm NCT01136733 trial
</td>
</tr>
<tr>
<td>Model Report</td>
<td>12</td>
<td>
Second- and third-line relative effects – Section 1.18, page 14 – the use of the proportional hazards assumption for second- and third-line relative effects is inconsistent with what has been done for first-line therapies

“For second and third lines, the model used a proportional hazards approach using the second- and later-line network meta-analysis because of limitations in the data (see section 1.9 and section 1.15 for further details). For fourth-line treatment, a hazard ratio derived from pooled third- and fourth-line outcomes from the UK real-world evidence study was applied to generate a fourth-line curve. Because outcomes were worse at fourth line than third line, this approach effectively ‘down-weighted’ outcomes at later lines. A clinical expert explained that treatment efficacy is expected to diminish with each line (see section 1.5) and the committee considered that this down-weighting method reflected this. The committee concluded that, while it would have preferred to see a consistent approach applied across all lines, without an available alternative, the proportional hazards network meta-analyses were acceptable to use for subsequent lines.”

This assumption is contradictory in terms of arbitrarily mixing and matching according to what suits NICE without consideration of other views including Ipsen’s. There are limitations in the first line data, i.e., only one key trial informing each of the main comparators, as well as the second and third lines, so the proportional hazards assumption should be considered valid and not dismissed in favour of the
</td>
</tr>
</table>

Renal cell carcinoma Pathways Pilot [ID6186]
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		fractional polynomial for the first line setting only. The DG states the committee would have preferred to see a consistent approach applied across all lines but did not discuss what could have been an alternative which could reasonably have been expected rather than dismissing it. Overall, the dismissive approach to the proportional hazards assumption by the committee across the lines of therapy feels unreasonable and unfair to Ipsen and insufficiently pragmatic in its decision making.
Model Report	13	**Surrogacy between outcomes – Section 1.21, page 16 – the committee conclusion regarding the availability of data for TTP and TTNT are misleading.** *"**Unlike progression-free survival and overall survival outcomes, there was insufficient published trial data on time to progression, time to next treatment and time to stopping treatment to inform standalone networks for these outcomes.** The EAG did a targeted review to investigate the plausibility of surrogacy between progression-free survival, time to stopping treatment, and time to next treatment. Based on this review, the EAG applied hazard ratios from the progression-free survival network meta-analysis to the time to stopping treatment and time to next treatment reference curves. It did this to estimate time to stopping treatment and time to next treatment for other treatments. Ipsen considered that there were lots of assumptions involved in generating time to stopping treatment estimates and suggested a simplification in which time to stopping treatment is assumed to be equal to progression-free survival. The committee considered this but noted that, while simpler, assuming that time to stopping treatment was equal to progression-free survival was a strong assumption. **The committee considered the evidence and observed that there was moderate to high correlation between progression-free survival and both time to next treatment and time to stopping treatment for most comparators**. It noted that for nivolumab plus ipilimumab the relationship was less clear. The clinical expert explained that time to stopping treatment, time to progression and progression-free survival are not always similar, especially with immunotherapies. This is because some people may stop treatment because of adverse events but may still benefit from the treatment for some time. In these situations, time to stopping treatment will be somewhat shorter than progression-free survival or time to progression. The committee noted that if time to stopping treatment was assumed to be equal to progression-free survival, the off-treatment health states effectively disappeared from the model. It considered that setting time to stopping treatment and time to progression equal to progression-free survival would bias the results of the model. The committee concluded that it preferred to use available time to stopping treatment data and apply progression-free survival network meta-analyses to the time to stopping treatment and time to progression reference curves. See section 4.3.1.2 of the EAG's assessment report for further details."* The statements highlighted in **bold** above are contradictory. In the EAG report of the 24 trials included in the NMA there were only 3 trials that reported TTNT and 4 trials that reported TTP. Therefore, for the committee to state *"there was moderate*

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		to high correlation between progression-free survival and both time to next treatment and time to stopping treatment for most comparators" is incorrect and misleading to the reader of the DG.
Model Report	14	**Surrogacy between outcomes – Section 1.22, page 17 – the statement regarding tumour flare influencing outcomes is unsubstantiated for ipilimumab with nivolumab** *"A key assumption of the state transition model is that progression-free survival is an appropriate surrogate for overall survival. This is because the model is driven by multiple lines of progression-free survival to generate survival and quality-adjusted survival outcomes. So the model requires a surrogate relationship between progression-free survival at each line and overall survival to exist. The committee considered that the available evidence in the literature supported the assumption of surrogacy between progression-free survival and overall survival. But the mechanism of action of some treatments meant that the assumption was sometimes limited. For example, nivolumab plus ipilimumab was seen to have worse progression-free survival in CheckMate 214 than other combination treatments in their pivotal trials, but still has a sustained survival benefit. When considering the most recent publicly available data cut, nivolumab plus ipilimumab had a median progression-free survival of 12.3 months (Motzer et al. 2022) compared with 23.9 months for pembrolizumab plus lenvatinib (see the EAG's assessment report table 14). But, when considering overall survival, this translated to a median overall survival of 55.7 months for nivolumab plus ipilimumab compared with 53.7 months for pembrolizumab plus lenvatinib (see the EAG's assessment report table 13).* ***The EAG explained that this could be caused by tumour flare. This is when tumours increase in size in the initial stages of treatment, resulting in a progression event being recorded, before falling in size as the full treatment effect is realised."*** No evidence has been presented by the EAG for the impact of tumour flare on the outcome of treatment of ipilimumab with nivolumab. Ipsen wishes to see this evidence.
Model Report	15	**Surrogacy between outcomes – Section 1.22 , page 18 – the committee has not described what the strong assumptions in a partitioned survival model are over and above many of the strong assumptions that have been made for the state transition model in absence of evidence to inform the STM.** *"The committee acknowledged that a partitioned survival modelling approach has limitations compared with a state transition approach. These include reduced flexibility, limited ability to capture later-line costs and benefits, and the need to make other strong assumptions that could lead to additional uncertainty."* Ipsen believe there should be a more balanced view taken of all the evidence and assumptions that have been used for the STM versus the PSM modelling in this appraisal and a recognition that both have their strengths and weaknesses, and both have validity in terms of decision making.

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Model Report	16	**Surrogacy between outcomes – Section 1.22, page 18 – the statement in the DG that the EAG presented a scenario in which time to next treatment (TTNT) was used as a proxy for PFS for ipilimumab with nivolumab and that this was discussed at the committee meeting is misleading.** *"The EAG also presented a scenario in which time to next treatment was used as a proxy for progression-free survival for nivolumab plus ipilimumab. The EAG argued this might better reflect expected overall survival for nivolumab plus ipilimumab. The committee concluded that when there is evidence of poor surrogacy between progression-free survival and overall survival for a treatment in the model, alternative ways of driving health state occupancy should be explored."* There were many scenarios that the EAG conducted and were included on a slide for the committee meeting, and this included a scenario in which TTNT was used as a proxy for progression-free survival for nivolumab plus ipilimumab and demonstrated that cabozantinib with nivolumab was cost-effective. But this scenario, among several others, showed cabozantinib with nivolumab was cost-effective in the intermediate/poor risk group compared to lenvatinib with pembrolizumab and ipilimumab with nivolumab and were not properly discussed at the committee meeting. Instead, this slide was rushed through by the committee chair in the interests of time and stated that it was *"not permissive that a decision could be made"* by the committee which Ipsen disagrees with. If the TTNT analysis by the EAG had been properly discussed, the committee may have avoided the need for a second committee meeting or at least addressed the uncertainty regarding the cost-effective of cabozantinib with nivolumab compared to ipilimumab with nivolumab.
Model Report	17	**Sequencing subsequent treatments – Section 1.24, page 18/19 – Ipsen has no visibility or access to the assumptions made for subsequent treatments from the RWE because it is redacted which is unreasonable and unfair for the company in the evaluation of cabozantinib with nivolumab.** *"The model includes cost and outcomes for up to 3 lines of subsequent treatment. The model assumes that the type of subsequent treatment is independent of the risk group modelled at first line but is dependent on what treatment was had. Clinical advice and routine commissioning rules were used to determine the plausible sequence after each possible treatment at first, second and third line. Proportions of each treatment observed in the real-world evidence were used to capture subsequent treatments in the model. When a subsequent treatment was implausible, the proportion was set to 0 and the treatment's shares were reweighted across other plausible options. Clinical experts explained that the proportion of people moving on to each treatment at each line in the real-world evidence was plausible and the treatment rules applied were appropriate. Sequences are less certain at later lines, but the committee concluded that the proportions applied to later lines are appropriate. The data did not include pembrolizumab plus lenvatinib or cabozantinib plus nivolumab. Both treatments did not feature in the real-world*

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		dataset because they are not currently NHS standard care. The committee agreed that assumptions used to capture subsequent treatment in the model reflected expected clinical practice. See section 4.3.5.1 of the EAG's assessment report for full details on how clinical effectiveness was modelled for subsequent treatments." Ipsen and other stakeholders apart from the EAG and the NICE committee cannot see the assumptions made for the proportions of patients receiving subsequent treatment for the different lines of therapy from the RWE obtained by the EAG. Table 92 in the final EAG report is completely redacted. The proportions of patients receiving subsequent treatment at different lines could influence the cost-effectiveness results. Ipsen, therefore, believes it is unreasonable that it has no sight of the base case assumptions that have been made for treatments in second, third and fourth-line from the RWE.
Model Report	18	**Adverse events – Section 1.25, page 19 – additional events of hand-foot syndrome, diarrhoea and fatigue were reported in CheckMate 9ER. The company still disagrees with the committee conclusion that a naive comparison for adverse events is inappropriate** The DG states *"Three additional adverse events: hand-foot syndrome, diarrhoea and fatigue not seen in CheckMate 9ER were also included, informed by clinical advice and supported by a Cochrane review."* This statement is incorrect. The adverse events of hand-foot syndrome, diarrhoea and fatigue from CheckMate 9ER are presented in *Table 9: Summary of any-grade TRAEs in ≥ 20% of treated patients of either arm (with 30 days follow-up), mFU 44 months* of the company submission The DG states *"The committee explained that a naive comparison was not appropriate and preferred the network meta-analysis approach to model adverse events."* Ipsen disagrees with this conclusion as it is another example of inconsistency with prior appraisals in this therapy area. It would be helpful if NICE explicitly stated that they expect adverse events in health economic models to be sourced from an NMA where other comparators exist so that companies were clear on NICE committee expectations and avoid this situation occurring in future appraisals.
Model Report	19	**Source of utility values – Section 1.27, page 20 – Base case utility values chosen from TA645 fail to consider other values that are available and mapping variations** See response above to Committee preferred assumptions (Utilities) – Section 3.6, page 9, above.
Model Report	20	**Relative dose intensity – Section 1.29, page 22 – Lenvatinib dose titration is the wrong way round**

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		We fail to see how the DG has been written as follows in Section 1.29 of the DG Pathways where it describes that in clinical practice the lenvatinib dose in combination with pembrolizumab is increased from 10 mg once daily to a maximum of 20 mg once daily. • *"Clinical expert feedback was that **most healthcare professionals in the NHS employ a titration phase, in which the dose is gradually increased over a period of weeks if the person can tolerate the toxicity of their last dose (starting from 10 mg, then 14 mg and 18 mg, up to a maximum of 20 mg).** Lenvatinib is available in 4 mg and 10 mg tablets and has a flat pricing structure. So, as the dose increases the number of tablets needed to satisfy the dose changes, which has implications on the price. The model accounts for the expected proportion of people that tolerate each dose. The model assumes that:* - *100% of people start on 10 mg for 2 weeks* - *75% tolerated 10 mg so have 14 mg for the next 2 weeks* - *18% tolerated 14 mg, so have 18 mg for 2 weeks then 20 mg thereafter* • *the final proportions of people having each dose are 25% at 10 mg (1 tablet), 57% at 14 mg (2 tablets) and 18% at 20 mg (2 tablets)."* Upon further review of the cost-effectiveness model inputs sheet, the company identified that the model may not be able to differentiate between up and down titration meaning that the analysis does not fully account for the practical use of the comparators. This is the complete opposite of the summary of product characteristics and what was done in the CLEAR trial and by writing this NICE could be indirectly encouraging off-label use. The SmPC states a starting dose of 20 mg and titrating down to 14 mg, then 10 mg and then 8 mg once daily depending on toxicity. Such a different dosing regimen could result in very different outcomes, possibly worse than that recorded in the CLEAR trial as it may be that it is the high initial dose of lenvatinib that drives the regimens benefit. In addition, in an Intermediate/Poor risk population there would be a need to have an immediate response so it would make sense to use the lenvatinib dose that was studied in the trial. If there were real-world evidence outcomes for lenvatinib in combination with pembrolizumab being used that way then this statement in the DG might be plausible, but as noted in Section 1.14 of the DG Pathways, there are none in the real-world dataset that the EAG has used. If NICE wishes to apply this dosing regimen then it cannot assume the same outcomes and pragmatically in the absence of any data NICE should assume a worse outcome than that presented for the base case in the cost-effectiveness analysis.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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	Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Action Kidney Cancer

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Ipsen £5,000 Ask the expert video project Ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Document Pathways Model Report Or **Draft Guidance**	**Comment number**	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Draft guidance	1	The committee meeting and appraisal consultation document were extremely technical and very difficult for a lay person to understand, especially the methodology used to assess severity modifiers, statistical modelling of survival curves for comparisons of clinical effectiveness, and the economic modelling. The technical nature of the appraisal made it difficult for patients to contribute meaningfully to the appraisal committee meeting.

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Renal cell carcinoma Pathways Pilot [ID6186]
Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6184]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments by the end of **21 December 2023**. Please submit via NICE Docs.

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		The committee meeting was conducted in such a way that did not allow for inclusion of the patient voice. Uncertainty of clinical evidence might be mitigated through the inclusion of the patient experience of the disease in decision-making. NICE need to communicate with patients in a language they understand and give them the opportunity to describe their experience of living with the disease, something which was not carried out during the committee meeting for this appraisal. Patients need to understand in simple terms why treatments from which they might derive benefit are not available within NHS England and Wales.
Draft guidance	2	The committee is not willing to consider the cabozantinib/nivolumab combination for inclusion in the Cancer Drugs Fund (CDF) due to uncertainty about the clinical evidence and lack of data directly comparing cabozantinib/nivolumab with other standard treatments. Inclusion of the combination in the CDF for up to 3 years would enable collection of further clinical evidence and resolve the uncertainty regarding comparison with other combination treatments. At the same time, this would allow access to cabozantinib/nivolumab for patients looking for an effective and tolerable immunotherapy/VEGFR inhibitor treatment offering a potential long-term response.
Draft guidance	3	The committee considered the severity of the disease and the future health lost by people living with advanced renal cell carcinoma (RCC) having standard treatment and care. They concluded that a severity modifier was not recommended because the QALY shortfall thresholds were unlikely to be met when considering the most appropriate comparators (other combination therapies) for each IMDC risk group (poor, intermediate or favourable). Although we are not cognisant of the methodology used to assess whether a severity weighting applies to the QALY, we would like to understand why a severity modifier has not been applied to the QALY for cabozantinib/nivolumab for the treatment of patients with intermediate- or poor-risk untreated advanced RCC. These patients have a terminal disease, are at risk or their disease progressing, and their life shortened without treatment. We suggest that by allowing access to cabozantinib/nivolumab on the CDF additional clinical evidence could be collected such that the QALY threshold might be met for the application of a severity modifier.
Draft guidance	4	The cabozantinib/nivolumab combination is superior to sunitinib in all IMDC risk groups. The EAG noted that there may be differences in the combination's effectiveness compared to sunitinib between patients with favourable risk disease and those with intermediate- or poor-risk disease. Although the survival data were numerically better for the intermediate- and poor-risk patients compared to the favourable-risk patients, these differences were not conclusive. The overall survival data were not mature for patients with favourable-risk disease. The committee thought there was no compelling evidence that the efficacy of the combination was different between disease risk groups. The committee also concluded that analysing the data by disease risk status was necessary to compare the cabozantinib/nivolumab combination with the most appropriate comparators to reduce uncertainty. We suggest that inclusion of the combination in the CDF for the collection of further survival data and maturation of the overall survival data for favourable-risk patients, would address these concerns regarding the target patient population.

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Draft guidance	5	The cabozantinib/nivolumab combination showed superior efficacy in untreated advanced RCC and was granted priority review status by the FDA. Having priority review status, the cabozantinib/nivolumab combination was fast tracked for approval in several countries, including the USA, Canada, Europe, and Scotland, based on the phase 3 CheckMate-9ER trial data.
Draft guidance	6	Currently, English cancer survival rates trail behind other comparable European countries, including Denmark, Ireland, and Norway. If NHS England is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new treatments are made available to patients to allow them treatment options and the best care possible. If these drugs are not made available, it leaves UK patients at a disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe, North America, and even Scotland, where there is greater choice of effective treatment options.
Draft guidance	7	Current first line treatments have proven to shrink tumours and delay disease progression in some patients; however, these treatment options are not effective for everyone. The absence of a reliable biomarker makes treatment decisions difficult for individual patients. For this reason, choice in the first line, and access to new innovative treatments remains paramount to managing the progression of this disease. Undue restrictions in accessing the cabozantinib/nivolumab combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having a choice of treatment would enable patients and oncologists to better control this disease and individualise treatment plans according to specific disease/treatment history, co-morbidities and contraindications, thereby enabling the best possible quality of life for the patient.
Draft guidance	8	Some immunotherapies have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the cabozantinib/nivolumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC. Inclusion of the cabozantinib/nivolumab combination in the CDF would enable collection of further efficacy and tolerability data for the treatment of non-clear cell RCC to address this unmet need. https://pubmed.ncbi.nlm.nih.gov/35298296/

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Document Pathways Model Report Or **Draft Guidance**	**Comment number**	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Pathway	Example 1	We are concerned that this recommendation may imply that ……..
Draft guidance	1	We are concerned that this recommendation will affect many patients who urgently need more treatment options available to them to help extend their life and give them hope. Many patients are on their last line of treatment or their treatment has failed and their cancer is progressing and they are struggling psychologically. There is an unmet need for these patients and more treatment options are needed. Many patients have expressed to us how distressing it is to not have new treatment options and it is important that their voices are heard. Richard is a patient with stage

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		4 RCC and is on his last line of treatment and wrote this statement:' The prospect of my current treatment becoming ineffective and there being no other treatment available to replace it, is very scary. Having being on other treatments which have previously become ineffective, on those occasions it was frustrating, but it wasn't a disaster, as there was immediately another treatment option, which we could try. Knowing there isn't another treatment option makes you feel abandoned/lost, suddenly the support structure you had relied upon, potentially for years is going to be withdrawn, virtually overnight. The safety net of the treatments is to be replaced by what? Potentially nothing! The routine of scans and consultant appointments are potentially going to end just as abruptly as the treatments. The life you have known as a cancer patient under active treatment has ended, to be replaced by inevitable physical decline, the only treatment for which is palliative, primarily and pain management. If the cancer has spread to other areas of the body, or has grown to an extent whereby any treatment would be ineffectual, then that may warrant the end of any future treatment. But in my case, the tumours are still relatively small and haven't spread beyond the original site of my cancer, my right kidney bed. There are going to be instances whereby continued treatment would be in the patient's best interest, but the lack of an alternative treatment would prevent this. The situation is heart breaking enough, but the knowledge that there are new alternative drugs available, being used as first or second line treatments, but which cannot be used for a later line of treatment make the situation unnecessarily cruel. Surely it is better to make these drugs available for all stages of treatment and leave the decision/recommendations to the individual trusts/consultants based upon a patient by patient basis, that way any drug can be targeted at those cases whereby there is merit in trying the drug, accepting that as at any stage of treatment the drug may or may not have a benefit for each individual patient'. More treatment options are needed for patients with kidney cancer, at all stages of their disease. Having more effective treatment options can potentially extend patients lives and control their disease, which gives them reassurance and hope.
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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Document Pathways Model Report Or **Draft Guidance**	**Comment number**	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Draft Guidance	1	Section 3.2 – The following sentence on page 6 should be re-worded to avoid misinterpretation: *"For intermediate- or poor-risk cancer, cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus lenvatinib or avelumab plus axitinib (only available through the Cancer Drugs Fund) are also available."*

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		Avelumab plus axitinib has been recommended for use within the Cancer Drugs Fund (CDF) as an option for untreated advanced renal cell carcinoma in adults *across all risk groups* (TA645), which includes, but is not restricted to the intermediate/poor risk group. The above sentence implies that avelumab plus axitinib is recommended for use within the CDF only in the intermediate/poor risk group. Please update the Draft Guidance wording by removing avelumab plus axitinib from the sentence above and instead referencing it in the previous sentence to avoid confusion, please see below: *"Treatments for all risk groups include sunitinib, pazopanib or tivozanib* ***as well as avelumab plus axitinib recommended for use within the Cancer Drugs Fund****."*
Pathways Model Report	2	Section 1.4 – The following sentence on page 4 is incorrect: *"Treatment is decided based on risk status (see section 1.3). Cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus lenvatinib and avelumab plus axitinib are only available for intermediate- and poor-risk RCC."* Avelumab plus axitinib has been recommended for use within the CDF as an option for untreated advanced renal cell carcinoma in adults (TA645) *across all risk groups*. The NICE recommendation for avelumab plus axitinib is not restricted to intermediate/poor risk RCC. Please correct this in the Pathway Model report.
Pathways Model Report	3	General – Merck have overarching concerns with the development of the RCC Pathway model and thus the model's reliability in decision-making. Two key concerns with the RCC Pathway model include: • Complexity of the Pathway model, specifically the inclusion of four treatment lines and associated data requirements. We acknowledge the aim of the Pathway model is to consider the RCC treatment pathway in its entirety and thereby 'future-proof' the model for assessing upcoming RCC therapies. However, the NICE clinical expert stated that most people will have only one or two lines of therapy. On page 27 of the company submission, results of a UK real world evidence (RWE) study were reported showing that only 12% people receive 3L and 2.6% receive 4L treatment. There is a question regarding the value of attempting to model up to four lines of therapy when very few people make it to 3L and 4L treatment and when most QALYs are accrued in 1L and 2L treatment in the model. Merck's view is that the data limitations and assumptions associated with later lines of therapy, and the resulting uncertainty around this, outweigh the potential advantage of modelling the full treatment pathway in this way. Without more reliable data in later lines of therapy, there is a high likelihood that the uncertainty associated with this RCC Pathway model could disadvantage companies going through this route by limiting the reliability of model outputs

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		• The lack of stakeholder access to key data – in this case unpublished RWE used to inform baseline characteristics, natural history/underlying risk, treatment pathway and sequences in the model - raises concerns around transparency. At the very least, the submitting company should have access to this RWE to validate the data with clinical experts and to have the opportunity to re-create the EAG's analysis but it appears that is not the case in this Pathway pilot. As above, this is another way companies taking part in the Pathway approach may be disadvantaged by having limited/or no access to crucial data that impacts model outputs vs. companies going through the standard technology appraisal route that will have full oversight of the data going into their model

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Document **Pathways** Model Report Or **Draft Guidance**	Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Pathway	Example 1	We are concerned that this recommendation may imply that ……..
Model report	1	Figure 1: Please can the wording for TA858 be corrected, it currently reads that Pembrolizumab+Lenvatinib is used if nivolumab+ipilimumab is unsuitable. This is incorrect, Pembrolizumab+Lenvatinib should be used if nivolumab with ipilimumab would otherwise be offered https://www.nice.org.uk/guidance/ta858/chapter/1-Recommendations

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Committee Papers	2	Pg 242 of the PDF or pg 38 of "A Pathways Pilot Appraisal Assessment Report" Under the heading "1st line systemic treatment (untreated aRCC)" Again can the incorrect wording of the TA858 recommendation be corrected The incorrect wording is used twice in this section, once in paragraph 2 and again in paragraph 3
General	3	Regarding comments 1 and 2, we note that the wording of TA858 is inconsistently stated throughout, with some instances being correct and other instances not. Please may we ask NICE/The EAG ensure future documents and figures have the correct wording
Model report	4	Pg 12 section 1.14 the document incorrectly states TA858 was published in June 2023 when it was published in Jan 2023
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Treatments for renal cell carcinoma [ID6186]

A Pathways Pilot Appraisal

EAG Review of Responses to Appraisal Consultation Document

Produced by

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Declared competing interests of the authors None, however, Professor Larkin also provided clinical input to NICE during the scoping stages of the appraisal.

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Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Additional interests declared in January 2024:

Dawn Lee:

- Provided private consultancy services to Neuraxpharm, Ascenian Consulting and Market Research, unrelated to possible intervention, comparators, intervention or comparator companies in this RCC appraisal.
- Lumanity:
    - Was previously employed as the Chief Scientific Officer at Lumanity until September 2022. Work from December 2021 included projects and companies unrelated to possible intervention, comparators, intervention or comparator companies in this RCC appraisal.
    - A very small shareholder in Value Demonstration Group (who are the holding company for Lumanity),
- Fiecon Ltd:
    - A family member owns Fiecon. However, not a shareholder of Fiecon.
    - A member of Fiecon's strategic council from Nov 2023 (receiving financial income). Not specifically related to RCC.
    - Provides mentoring support (receiving financial income). Not specifically related to RCC.

- Provide consultancy services to Fiecon on several projects, including one topic for Eisai, unrelated to possible intervention, comparators, intervention or comparator companies in this RCC appraisal.

Darren Burns:

- Employed as an Analyst at Delta Hat Limited from September 2022. Principle Health Economist at Lumanity / Bresmed until September 2022.
- From December 2021, worked on projects and for companies unrelated to possible intervention, comparators, intervention or comparator companies in this RCC appraisal. Consultancy services (financial) for Pfizer on a technology unrelated to RCC, and Servier on Multilocular cystic renal cell carcinoma (MCRCC) which is not considered a possible comparator in this appraisal.
- Scottish Medicines Consortium on multiple projects.

All *CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all* [redacted] *is highlighted in yellow and underlined, all* [redacted] *is highlighted in green and underlined*

Table of contents

List of figures

List of tables

List of abbreviations

Acronym	Definition
1L / 2L / 3L / 4L	1st line / 2nd line / 3rd line / 4th line
ACD	Appraisal Committee Document
AE	Adverse event
AIC	Academic in confidence
ASCO	American Society of Clinical Oncology
Ave	Avelumab
Axi	Axitinib
BSC	Best supportive care
Cabo	Cabozantinib
CDF	Cancer Drugs Fund
DG	Draft guidance
EAG	External assessment group
eMIT	Electronic market information tool
EOL	End of life
FP	Fractional polynomials
HR	Hazard ratio
ICER	Incremental Cost Effectiveness Ratio
IO	Immuno-oncology
Ipi	Ipilimumab
KM	Kaplan Meier
Lenv	Lenvatinib
LY	Life year
MRU	Medical resource use
NICE	National Institute for Health and Care Excellence
Nivo	Nivolumab
NMA	Network meta-analysis
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
Pazo	Pazopanib
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1

Pem	Pembrolizumab
PFS	Progression free survival
PH	Proportional hazards
PPS	Post progression survival
PrePS	Pre-progression survival
PSA	Probabilistic sensitivity analysis
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
STM	State transition model
Suni	Sunitinib
TE	Technical engagement
Tivo	Tivozanib
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
TTD	Time to treatment discontinuation
TTP	Time to progression
TTNT	Time to next treatment
UK	United Kingdom

1. INTRODUCTION

This document provides the External Assessment Group's (EAG's) critique of stakeholder responses to the Pathways Model Report and Draft Guidance produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of treatments for renal cell carcinoma (RCC) [ID6186]. Responses were received from:

- Ipsen
- Action Kidney Cancer
- Kidney Cancer UK
- Merck Serono
- MSD

There was no update to the PAS for cabozantinib by Ipsen.

In addition, the following requests were made by NICE to the EAG:

- Include pembrolizumab + lenvatinib in the fractional polynomial network meta-analysis (FP NMA) using updated data from CLEAR published at ASCO.[1]
- Explore nivolumab + ipilimumab results; NICE enquired as to whether updated SACT data would be available to do this, unfortunately this was not the case.
- Identify any other literature or real-world evidence about relative effect of cabozantinib monotherapy at 1st line, given implausible results from CABOSUN with input from Ipsen.
- To inform the discussion about uncertainty in the relative effect of the subgroup estimates as the trial wasn't powered for subgroup analysis, include a scenario applying the NMA results for the all-risk NMA to the favourable risk reference curve.
- To inform the discussion about titration of lenvatinib present a scenario including 2 pills per person.
- Update relevant scenarios with new prices for sunitinib and everolimus (Table 1).

Table 1: Updated generic drug prices

Drug	Updated price eMIT Version Jul22 to Jun23	Previous eMIT price Version Jul22 to Dec22
Sunitinib 12.5mg x 28	£116.51	£215.86
Sunitinib 25mg x 28	£262.42	£537.62
Sunitinib 50mg x 28	£812.32	£1,388.77
Everolimus 2.5mg x 30	£403.03	£223.91

Everolimus 5mg x 30	£471.99	£747.55
Everolimus 10mg x 30	£536.65	£373.48

Abbreviation: eMIT, Electronic market information tool

New analyses were requested to be presented as follows:

- Pairwise
- Fully incremental
- Fully incremental excluding TKI monotherapies
- Severity presented as per the original three approaches presented to Committee

The updated EAG base case and additional scenarios are presented in Section 2. Review of the stakeholder responses is presented in Section 3, organised by theme.

2. UPDATED EAG BASE CASE ANALYSES

2.1. Model updates

The following updates were made to the Excel front end of the model to allow the new EAG base case to be run along with new scenario analyses:

- New switches were added to the Model Settings sheet to control the new scenarios in Cells V45 to V59.
- The updated prices for everolimus and sunitinib were included in the Resource use and costs sheet in Cells K42 – K45 and K29 – K31.
- The Resource use and cost sheet Cells AG69 - AH73 and BG19 – BG22 and BN19 - BO23 were updated for the two pills per dose scenario for lenvatinib as part of the pembrolizumab + lenvatinib combination.
- A new utility scenario was added to Utilities sheet > dd_util_scenarios (Cell H10), and the formulas in Cells K15-K27, K31-43, K47-59, 65-77, 81-93 and 97-109 were adjusted to accommodate the new scenario.
- New functionality was added to the Effectiveness settings sheet in Columns GH, GI, GW, HE, HF, HG and HH and Cells DY16 and ED16, to account for new effectiveness settings.

New files were created for the updated FP NMA. The R code was amended to allow for the all-risk NMA to be applied to the favourable risk population for Scenario 88 on lines 1063 to 1069 of the Model_Structure file and to update the handling of RDI in the PSA on lines 111 to 118 of the cost_processing file.

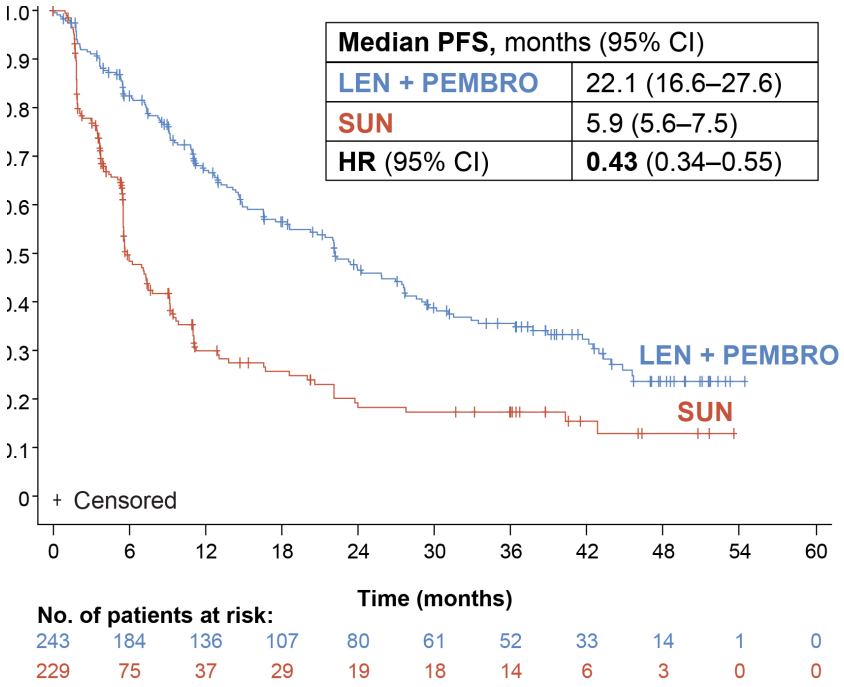
2.2. Updated FP NMA

The FP NMA was updated to include additional data provided by Eisai for PFS for the intermediate / poor risk subgroup for pembrolizumab + lenvatinib, which was presented at ASCO (Figure 1).[1] This data was not initially available to the EAG as it was only accessible via a paywall. The EAG requested information for additional endpoints such as TTNT. However, this data was not provided.

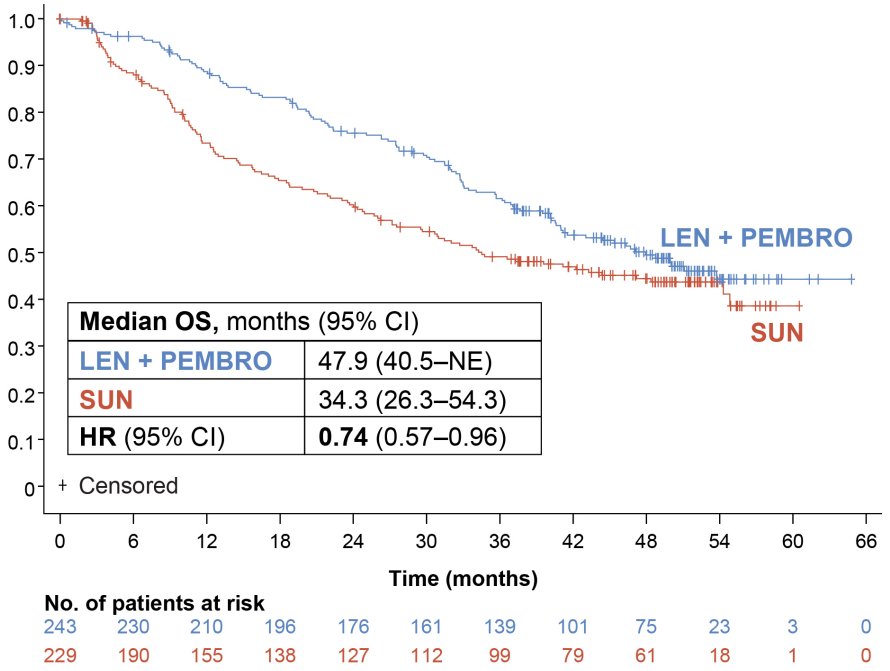
The NMA was re-run using this new data both using the original EAG base case analysis and scenario analyses, including data for TTNT as an alternate surrogate for OS within the economic model for nivolumab + ipilimumab.

Figure 1: CLEAR intermediate / poor risk subgroup

PFS



OS



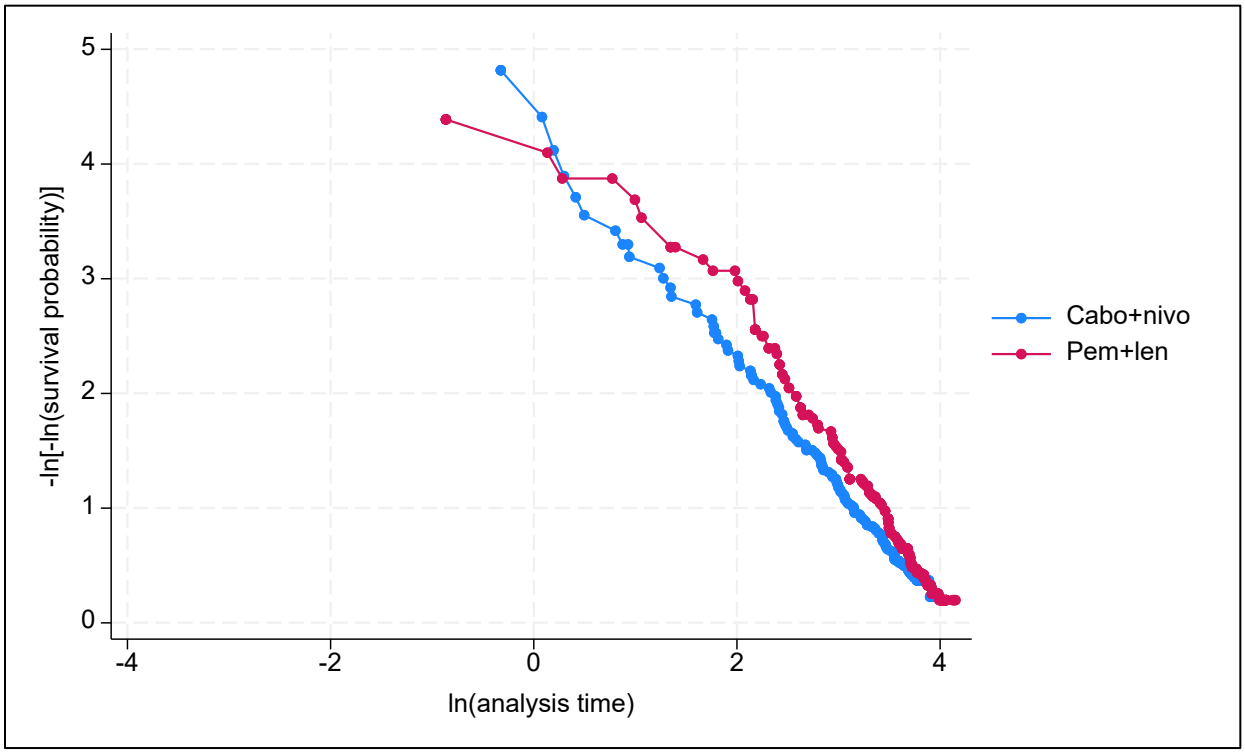
Figures pasted directly from ASCO presentation[1]

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression free survival

For OS, the original FP NMA used the same datacut presented at ASCO. Unfortunately, as detailed in the original EAG report, the model fitted failed to produce plausible results. This was due to issues caused by a lack of events in the sunitinib arm in the initial three months. Given this, the EAG have updated the PartSA scenario to use the hazard ratio between pembrolizumab + lenvatinib and cabozantinib + nivolumab (1.134 [0.800,1.619]) in the PartSA scenario analysis rather than the hazard ratio between pembrolizumab + lenvatinib and sunitinib. This assumes proportional hazards between pembrolizumab + lenvatinib and cabozantinib + nivolumab, which is considered more plausible due to the similar mechanism of action of the combinations. A naïve comparison of OS data in intermediate and poor risk patients from the arms of the relevant trials suggests that proportional hazards are broadly tenable although the need to make this assumption is not ideal.

The log cumulative hazard plot shows curves that cross very early on, then are broadly parallel until around 3 years, and then converge. A Grambsch-Therneau test yielded *p*=0.06, and a visual inspection of log-log plots (see Figure 2) did not provide conclusive evidence of violation of proportional hazards.

Figure 2: Log-log plot comparing cabo+nivo vs pem+lenv from key phase III trials

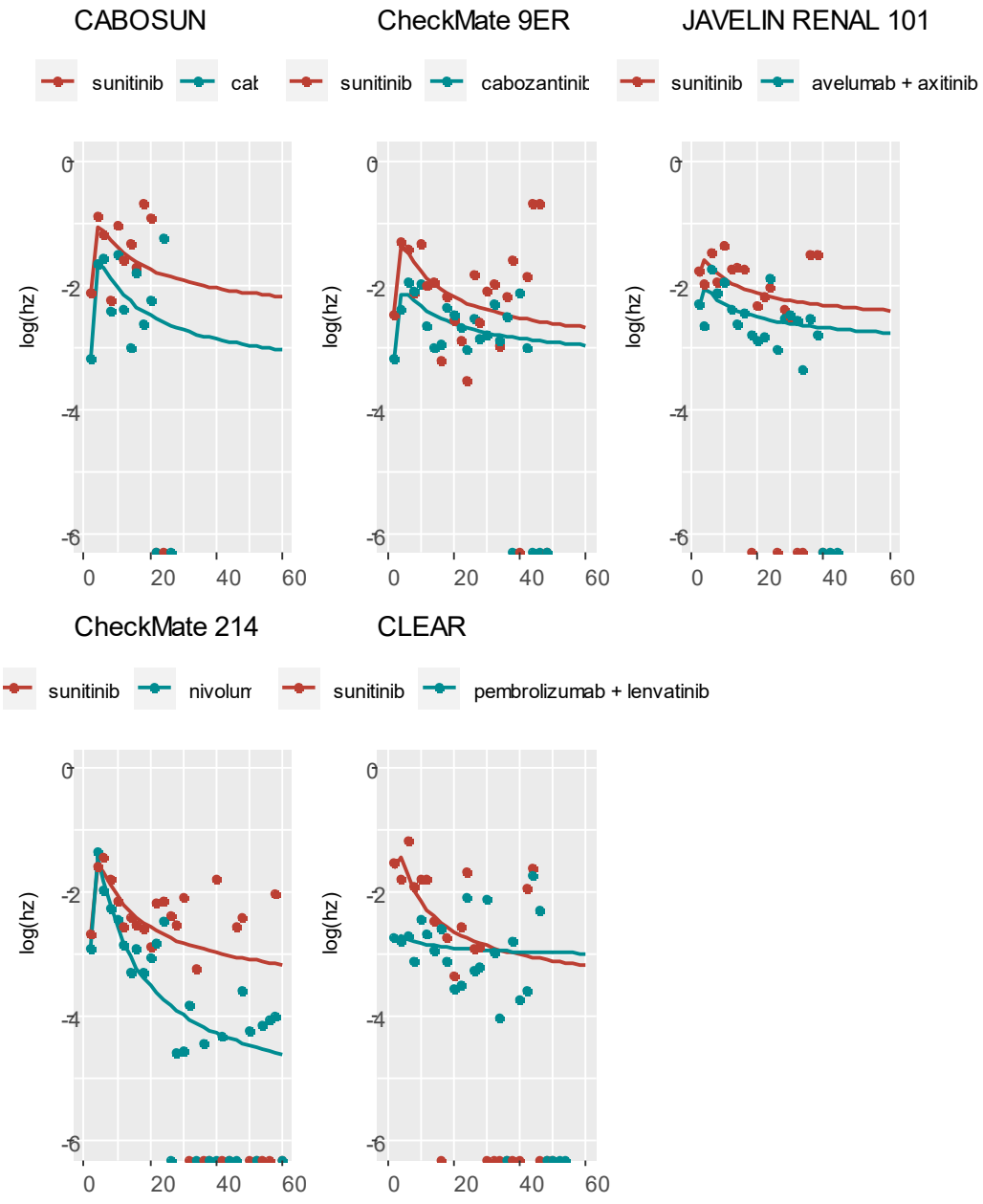


Abbreviation: ln, natural log

For the updated analysis incorporating new PFS data, candidate models within 5 AIC points included the model with exponents (-2, -0.5). This was selected as it had been identified in previous analyses (based on minimum DIC and expert elicitation). The updated log hazard plots are shown in Figure 44, and the hazard ratios and survival curves prior to application within the economic model in Figure 45.

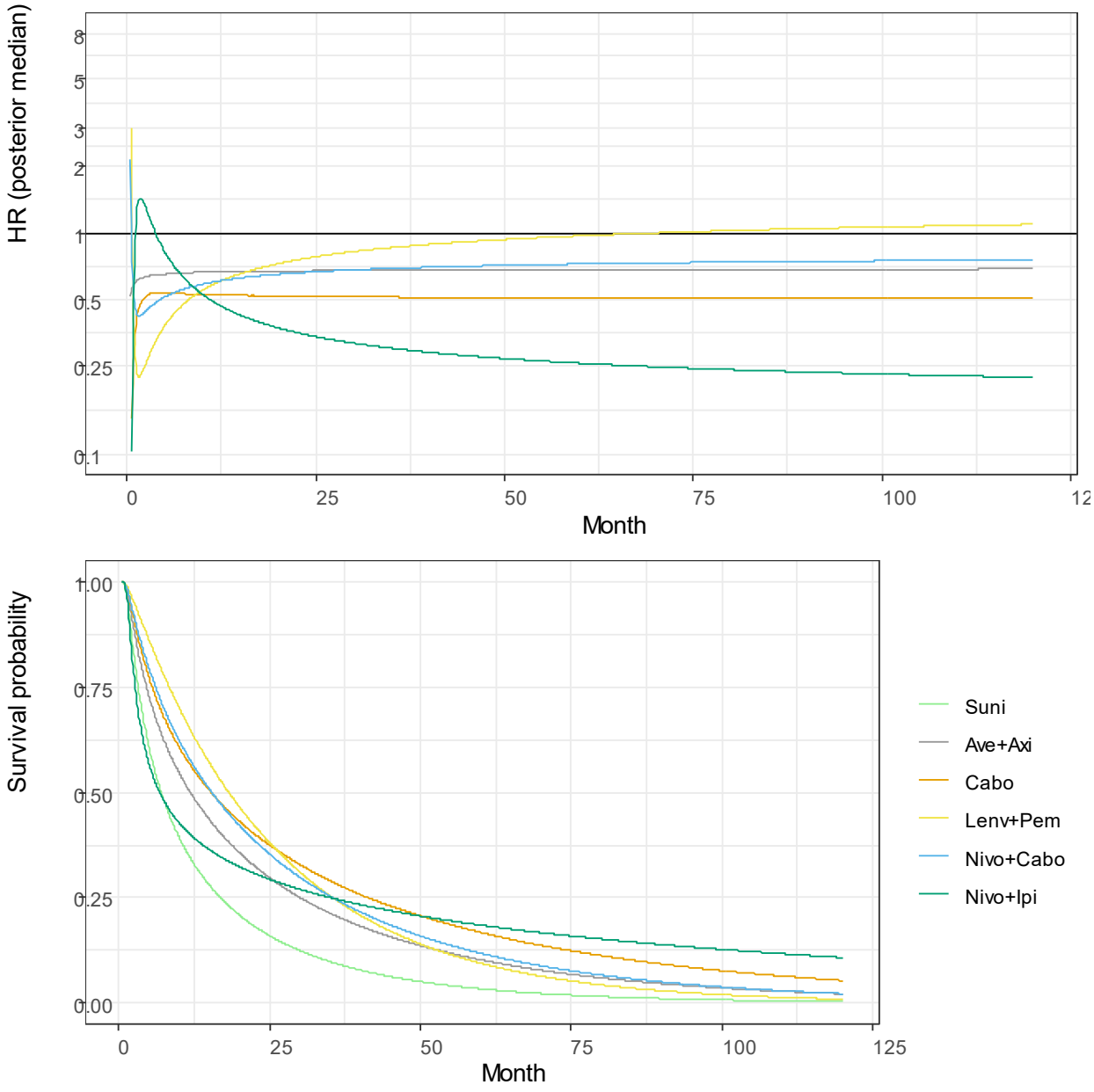
The plots show that the fitted model for pembrolizumab + lenvatinib does not follow the same trend as the fitted model for the other immune oncology combinations (initial increase in hazards followed by a longer-term decrease). This was unexpected based on the similar mechanism of action of many of the treatments. However, the PFS data for pembrolizumab plus lenvatinib within CLEAR do not clearly follow the expected pattern in the same way as they do for the other trials. There are a number of events observed between 40 and 45 months in the dataset for PFS (Figure 1). The hazard curve does not have the plateau shape of classic immune oncology, which is seen for the other treatments. The trend of the sunitinib arm looks similar across all fitted models (Figure 3).

Figure 3: Log hazard plots from NMA for PFS among untreated and intermediate/poor risk, with additional data from the CLEAR trial



Abbreviations: NMA, network meta-analysis; PFS, progression free survival

Figure 4: Hazard ratio and survival plots from NMA for PFS among untreated and intermediate/poor risk, with additional data from the CLEAR trial



Abbreviations: NMA, network meta-analysis; PFS, progression free survival

For the additional updated analysis also substituting TTNT for PFS in the CheckMate 214 trial, the set of models within 5 AIC points of the minimum did not include the model with exponents (-2, -0.5) that had been selected in previous analyses. Selection by the minimum DIC criterion from the candidate model set identified the model with exponents (-2, 0.5). These results are shown in Appendix D: Scenario analysis .

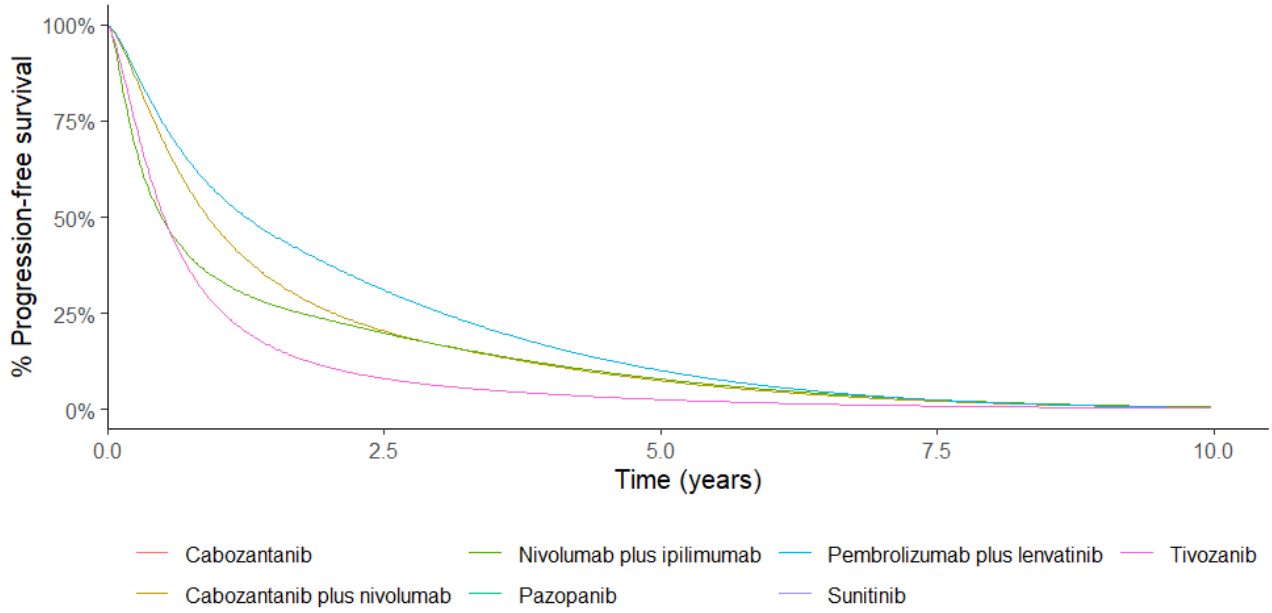
2.3. Updated EAG base case

The updated EAG base case includes the new sunitinib and everolimus prices (Table 1), the updated FP NMA for 1st line PFS for intermediate / poor risk patients, and an assumption of equal effectiveness for cabozantinib and sunitinib for 1st line PFS for intermediate / poor risk patients.

Figure 5 and Figure 6 show the final modelled OS and PFS with the updated FP NMA after all adjustments have been applied within the model accounting for the base case sequence of subsequent treatments.

Scenario analyses were conducted based upon Committee and stakeholder requests, along with a repeat of a select number of scenarios which had a major impact on the previous EAG base case. The updated company base case is also presented including previous company assumptions and the EAG updates to RDI as these were agreed by the company at the previous Committee meeting. It should be noted that the updated PartSA scenario analysis assumes proportional hazards for pembrolizumab + lenvatinib with nivolumab + cabozantinib, rather than assuming proportional hazards with sunitinib in the absence of a plausible FP NMA result. This was considered more clinically plausible due to the similar mechanism of action of the two treatments.

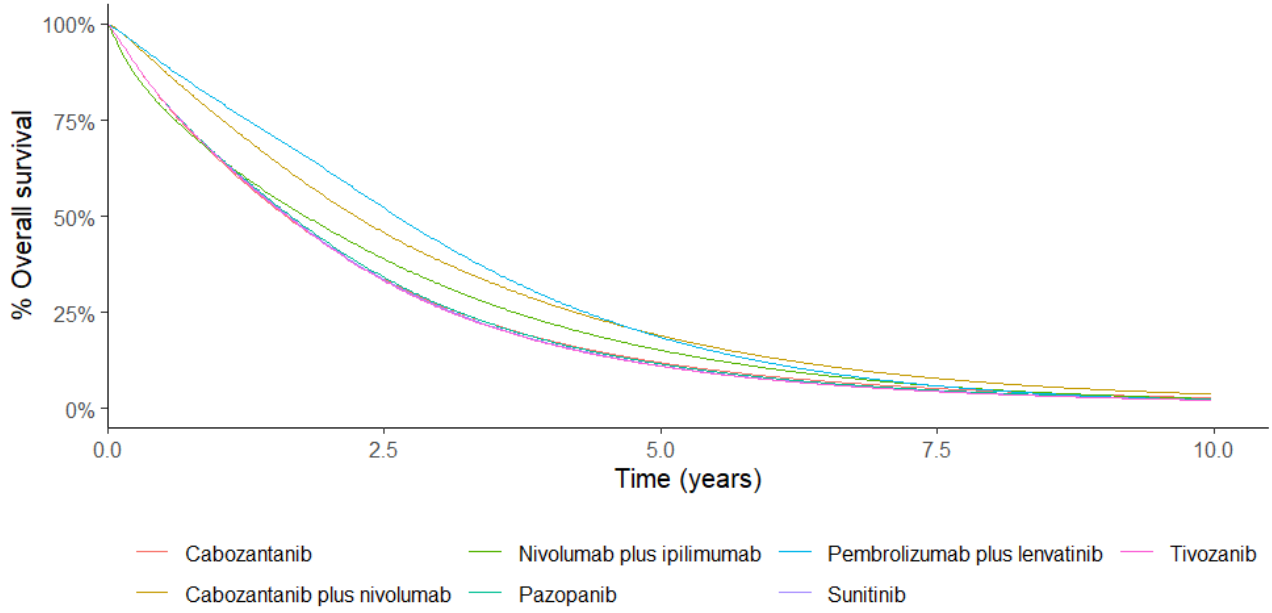
Figure 5: Updated final modelled PFS in the intermediate / poor risk population



Abbreviation: PFS, progression free survival

Note: suni, tivo and pazo all have equal PFS

Figure 6: Updated final modelled OS in the intermediate / poor risk population



Abbreviation: OS, overall survival

2.3.1. Deterministic

For the all-risk and favourable risk populations, the updated EAG base case provides the same conclusions as the EAG base case prior to the changes made in response to the ACD (Table 2). The price changes for sunitinib and everolimus led to a decrease in the price of treatment starting with sunitinib, and an increase in price for other sequences, due to the increase in the minimum price per mg for everolimus between eMIT versions. The price changes, however, had little impact on the conclusions. The ICERs remained considerably above NICE's willingness to pay threshold of £20,000 - £30,000.

For the intermediate / poor risk population, pembrolizumab + lenvatinib remained non-cost-effective in the Southwest quadrant, relative to cabozantinib + nivolumab, with a reduction in its effectiveness (from 2.23 QALYs to 2.02 QALYs) seen with the use of the data from the new NMA. This resulted in pembrolizumab + lenvatinib having an ICER of £396,657 relative to cabozantinib + nivolumab in the analysis excluding TKI monotherapies (Table 3).

The updates to the NMA also resulted in some change to the fits, and therefore QALY gains, predicted for nivolumab + ipilimumab (1.46 to 1.66 QALYs) and cabozantinib + nivolumab (2.00 to 1.97 QALYs). Cabozantinib + nivolumab remained more effective and more expensive than nivolumab + ipilimumab when PFS was used as a surrogate for OS for both treatments.

Table 2: Base-case results, list price (ordered in increasing cost)

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental	ICER cabo+nivo vs comparator	Severity modifier
Risk population: All risk									
Suni	£76,166	2.78	1.67	£0	0.00	0.00	£0	£268,351	1.0
Pazo	£80,399	2.84	1.70	£4,233	0.06	0.03	£154,645	£274,247	1.0
Tivo	£100,005	2.77	1.66				(dominated)	£223,361	1.0
Cabo+nivo	£225,144	3.71	2.22	£144,745	0.88	0.53	£274,247		-
Risk population: Favourable risk									
Suni	£80,328	3.67	2.20	£0	0.00	0.00	£0	£368,014	1.0
Pazo	£86,100	3.73	2.23	£5,772	0.06	0.03	£208,150	£378,083	1.0
Tivo	£116,790	3.66	2.19				(dominated)	£286,887	1.0
Cabo+nivo	£252,553	4.52	2.67	£166,454	0.78	0.44	£378,083		-
Risk population: Intermediate / poor risk									
Suni	£74,181	2.45	1.46	£0	0.00	0.00	£0	£251,374	1.2
Pazo	£77,793	2.50	1.49	£3,612	0.06	0.03	£133,449	£258,007	1.2
Tivo	£92,997	2.43	1.45				(dominated)	£212,280	1.2
Cabo	£121,724	2.57	1.49				(ext dominated)	£168,478	1.2
Nivo+ipi	£158,987	2.72	1.66				(ext dominated)	£139,508	1.0
Cabo+nivo	£201,953	3.30	1.97	£124,160	0.80	0.48	£258,007		-
Pem+lenv	£221,891	3.23	2.02	£19,938	-0.08	0.05	£396,657	SW quadrant £396,657	1.0

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year

Table 3: Base-case results, list price, fully incremental analysis excluding TKIs in the intermediate / poor risk population

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£158,987	2.72	1.66		-	-	-
Cabo+nivo	£201,953	3.30	1.97	£42,966	0.59	0.31	£139,508
Pem+lenv	£221,891	3.23	2.02	£19,938	-0.08	0.05	£396,657

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; TKI, tyrosine kinase inhibitor

2.3.2. Probabilistic

The mean predicted costs and QALYs per treatment regimen are broadly consistent with the deterministic analysis (Table 4), the probabilistic life years and QALYs predicted are generally a little higher than the deterministic. The ordering of the treatments in terms of effectiveness remains the same across the two analyses. The ICERs seen in the all-risk and favourable risk populations are generally somewhat higher in the probabilistic analysis.

When comparing the 3 IO regimens in the intermediate / poor risk population the confidence intervals for QALYs for all three of the IO combinations have considerable overlap (Table 5). The costs are similar between deterministic and probabilistic analysis for all 3 treatments. The ordering of the treatments in terms of effectiveness remains the same across the two analyses.

Table 4: Base-case results, list price (ordered in increasing cost, mean +/-95%CrI)

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER inc.	ICER cabo+nivo vs comparator	Severity modifier
Risk population: All risk									
Suni	£78,133 (£53,569, £109,534)	3.034 (2.438, 3.775)	1.847 (1.459, 2.315)	-	-	-	-	£289,570	1.2
Pazo	£82,117 (£57,651, £113,201)	3.069 (2.443, 3.871)	1.866 (1.451, 2.357)	£3984 (-£4,248, £12,851)	0.035 (-0.168, 0.255)	0.019 (-0.26, 0.289)	£208,795	£292,793	1.2
Tivo	£102,478 (£74,186, £137,191)	3.025 (2.419, 3.795)	1.852 (1.452, 2.323)	-	-	-	Dominated	£243,287	1.2
Cabo+nivo	£222,086 (£175,729, £264,057)	3.79 (3.073, 4.798)	2.344 (1.865, 2.942)	139970 (105856, 173311)	0.721 (0.113, 1.433)	0.478 (0.009, 0.958)	£292,793		-
Risk population: Favourable risk									
Suni	£81,172 (£53,054, £112,845)	3.939 (3.1, 4.906)	2.383 (1.832, 2.959)	-	-	-	-	£401,255	1.2
Pazo	£86,667 (£57,459, £119,049)	3.973 (3.136, 4.965)	2.397 (1.848, 2.979)	£5,494 (-£2,837, £14,809)	0.035 (-0.174, 0.253)	0.014 (-0.416, 0.431)	£384,361	£401,844	1.2
Tivo	£11,8249 (£82,959, £154,628)	3.928 (3.09, 4.921)	2.376 (1.82, 2.912)	-	-	-	Dominated	£308,246	1.2
Cabo+nivo	£251,229 (£177,994, £331,273)	4.656 (3.17, 6.562)	2.807 (1.89, 3.885)	£164,562 (£104,418, £234,516)	0.683 (-0.562, 2.19)	0.41 (-0.451, 1.369)	£401,844		-
Risk population: Intermediate / poor risk									
Suni	£75,820 (£50,019, £107,517)	2.699 (2.106, 3.449)	1.641 (1.275, 2.077)	-	-	-	-	£276,235	1.2

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER inc.	ICER cabo+nivo vs comparator	Severity modifier
Pazo	£79,207 (£52,807, £110,589)	2.734 (2.115, 3.497)	1.659 (1.293, 2.107)	£3,388 (-£5,640, £12,298)	0.035 (-0.166, 0.236)	0.019 (-0.197, 0.223)	£182,036	£280,341	1.2
Tivo	£94,860 (£65,931, £129,385)	2.683 (2.064, 3.496)	1.635 (1.253, 2.089)	-	-	-	Dominated	£230,501	1.2
Cabo	£123,051 (£90,323, £161,624)	2.760 (2.078, 3.704)	1.654 (1.255, 2.200)	-	-	-	Dominated	£175,443	1.2
Nivo+ipi	£154,537 (£117,209, £182,758)	2.849 (2.290, 3.537)	1.788 (1.429, 2.219)	-	-	-	Extendedly dominated	£148,909	1.0
Cabo+nivo	£198,891 (£157,371, £238,439)	3.381 (2.639, 4.436)	2.086 (1.590, 2.671)	-	-	-	Extendedly dominated	-	-
Pem+lenv	£218,520 (£186,447, £252,014)	3.411 (2.702, 4.343)	2.159 (1.643, 2.718)	£139,312 (£106,521, £170,038)	0.678 (0.112, 1.366)	0.499 (0.014, 1.022)	£278,910	SW quadrant £270,489	1.0

Abbreviations: CrI, Credibility Interval; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year

Table 5: Base-case results, list price, fully incremental analysis excluding TKIs in the intermediate / poor risk population (mean +/-95%CrI)

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£154,537 (£117,209, £182,758)	2.849 (2.290, 3.537)	1.788 (1.429, 2.219)				
Cabo+nivo	£198,891 (£157,371, £238,439)	3.381 (2.639, 4.436)	2.086 (1.590, 2.671)	£44,354	0.532	0.298	£148,909
Pem+lenv	£218,520 (£186,447, £252,014)	3.411 (2.702, 4.343)	2.159 (1.643, 2.718)	£19,629	0.030	0.073	£270,489

Abbreviations: CrI, Credibility Interval; Dom'd, dominated; Ext Dom'd, Extended Dominated; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; TKI, tyrosine kinase inhibitor

Figure 7: Cost-effectiveness acceptability curve (all risk population)

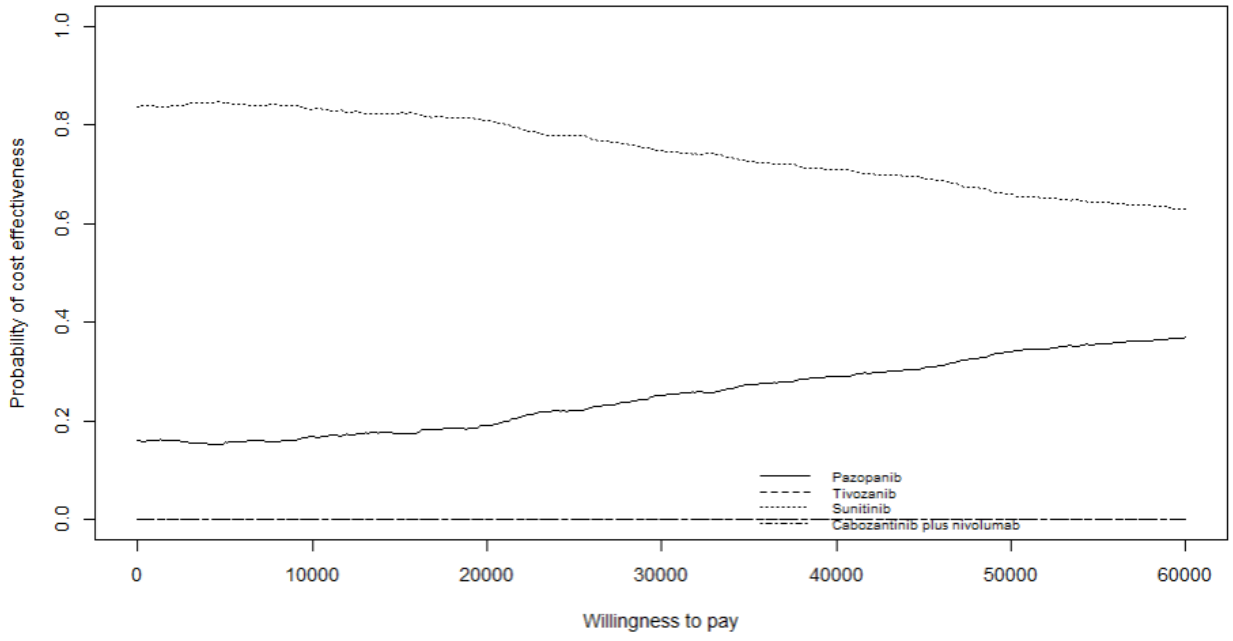


Figure 8: Cost-effectiveness acceptability curve (favourable risk population)

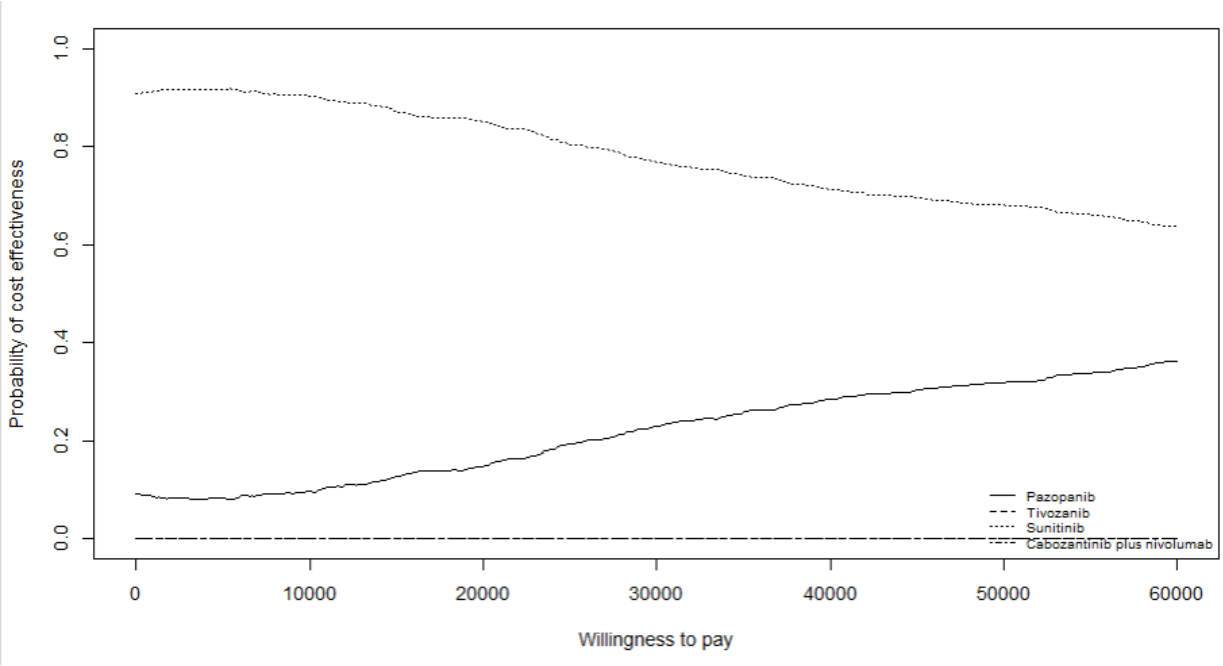
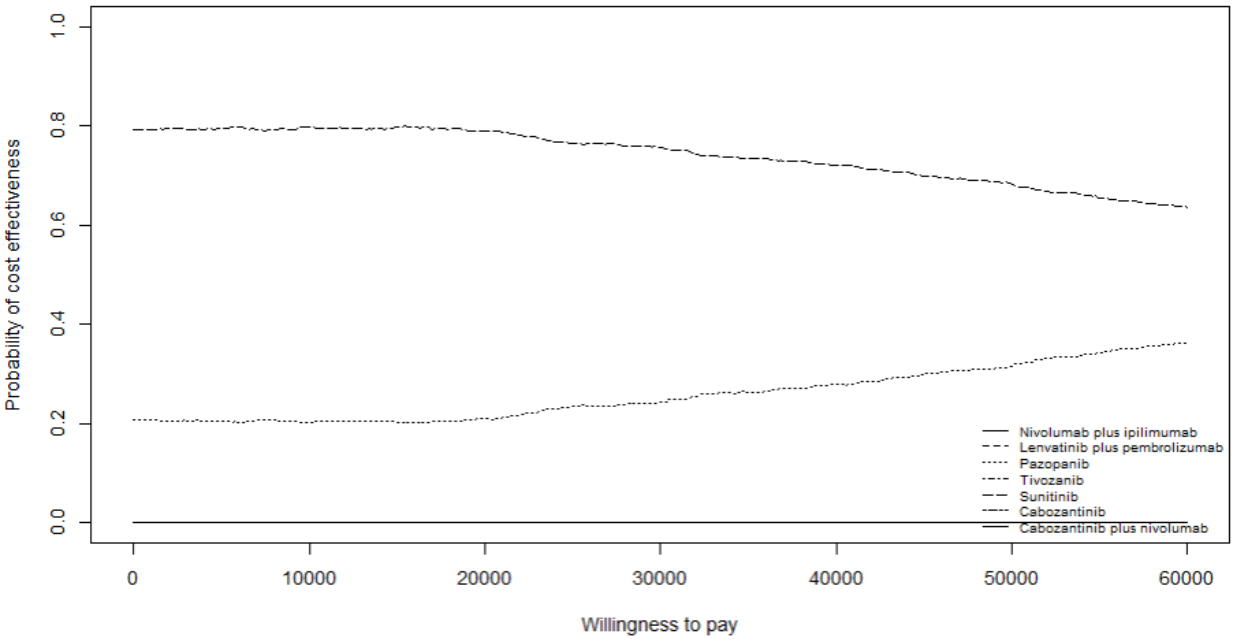


Figure 9: Cost-effectiveness acceptability curve (intermediate/poor risk population)



2.4. Updated scenario analysis

Updated scenario analyses using list prices for all treatments are presented in Table 4 to Table 6 with pairwise comparisons in Appendix C: Pairwise comparisons.

It remains the case that cabozantinib plus nivolumab is not cost-effective compared to TKI monotherapy in any of the populations.

The scenarios which impacted most on the cost-effectiveness were:

- Model structure: PartSA less favourable to cabo+nivo than state transition model structure vs TKI monotherapy and nivo+ipi and more favourable vs pem+lenv
- RDI: assuming 100% RDI for all drugs increases the ICER for cabo+nivo
- Use of TTNT data as a surrogate for PFS for nivo+ipi increases the predicted QALYs for nivo+ipi from 1.66 to 1.86 and also results in an increase in the cost of the combination due to increased duration of treatment

Using the company's alternative utility scenario resulted in a small decrease in the ICER relative to TKI monotherapy.

2.4.1. All risk

Table 6: Scenario analyses (All-risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised EAG base case				Pazo	£144,745	0.528	£274,247
Company base case		80	PH NMA, 2 lines, TTD = PFS, naïve AE NMA	Pazo	£174,969	0.839	£208,665
Company base case PartSA		85	PH NMA, 2 lines, TTD = PFS, naïve AE NMA, PartSA	Suni	£168,434	0.551	£305,902
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Suni	£144,679	0.319	£453,073
		3	State transition 2 lines	Pazo	£159,357	0.695	£229,389
Effectiveness							
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£150,302	0.656	£229,197
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Suni	£150,695	0.535	£281,611
Costs/RDI							
RDI	Applied	41	All RDI set to 100%	Pazo	£179,863	0.528	£340,786
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same	89	CheckMate 9ER for 1L PFS, remainder using same utility decrements (%) as EAG base case	Pazo	£144,745	0.574	£252,142

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	proportional decrease for 3L and 4L						

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

2.4.2. Favourable risk

Table 7: Scenario analyses (Favourable risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised EAG base case				Pazo	£166,454	0.440	£378,083
Company base case		80	PH NMA, 2 lines, TTD = PFS, naïve AE NMA	Pazo	£193,989	0.632	£307,096
Company base case PartSA		85	PH NMA, 2 lines, TTD = PFS, naïve AE NMA, PartSA	Suni	-	-	Dominated
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Suni	-	-	Dominated
		3	State transition 2 lines	Pazo	£181,551	0.612	£296,880
Effectiveness							
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£166,454	0.440	£378,083

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Preferred NMA	FP NMA 1L, PH NMA 2L	21	PH NMA throughout, PartSA	Suni	-	-	Dominated
Favourable risk	PH NMA favourable risk	88	Apply all risk NMA	Pazo	£187,392	0.599	£313,070
Costs/RDI							
RDI	Applied	41	All RDI set to 100%	Pazo	£211,010	0.440	£479,289
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	89	CheckMate 9ER for 1L PFS, remainder using same utility decrements (%) as EAG base case	Pazo	£166,454	0.487	£341,467

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

2.4.3. Intermediate / poor risk

Table 8: Scenario analyses (Intermediate / poor risk)SW

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER vs nivo+ipi	ICER vs pem+lenv
Revised EAG base case				Pazo	£124,160	0.481	£258,007	£139,508	SW £396,657
Company base case		80	PH NMA, 2 lines, TTD = PFS, naïve AE NMA	Pazo	£159,305	0.858	£185,581	£103,766	SW £367,535
Company base case PartSA		85	PH NMA, 2 lines, TTD = PFS, naïve AE NMA, PartSA	Suni	£152,719	0.722	£211,605	£178,836	Dominant
Model structure									
Overall structure	State transition 4 lines	1	PartSA 4 lines	Nivo+ipi	£37,726	0.024	£1,561,318	£1,561,318	Dominant
		3	State transition 2 lines	Pazo	£138,438	0.645	£214,682	£118,358	SW £743,493
Effectiveness									
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£137,015	0.676	£202,717	£122,554	SW £236,733
Preferred NMA	FP NMA 1L, PH NMA 2L	21	PH NMA throughout, PartSA	Nivo+ipi	£45,348	0.084	£540,524	£540,524	Dominant
	PFS	73	Using TTNT data as a proxy for	Pazo	£131,370	0.557	£235,771	£163,193	Dominant

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER vs nivo+ipi	ICER vs pem+lenv
Surrogate outcome for nivo+ipi			PFS for nivo+ipi						
	PFS	74	Using TTNT data as a proxy for PFS for nivo+ipi, PH NMA	Pazo	£137,015	0.676	£202,717	£73,795	SW £236,733
Costs/RDI									
RDI	Applied	41	All RDI set to 100%	Pazo	£152,390	0.481	£316,669	£203,855	SW £102,210
Lenv dosing within pem+lenv	TA858 & RDI data	87	2 pills	Pazo	£124,160	0.481	£258,007	£139,508	SW £655,233
Utilities									
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	89	CheckMate 9ER for 1L PFS, remainder using same utility decrements (%) as EAG base case	Pazo	£124,160	0.520	£238,998	£134,002	SW £275,555

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

3. EAG REVIEW OF STAKEHOLDER RESPONSES TO THE ACD

3.1. Importance of availability of a wide variety of treatment options

Both Action Kidney Cancer and Kidney Cancer UK highlighted the importance of the availability of a wide variety of treatment options, particularly for patients who are on their last line of treatment.

3.2. Favourable risk subgroup

Action Kidney Cancer made several additional comments in relation to the NICE appraisal process and the need for new treatment options. Those of specific relevance to the EAG review related to the favourable risk subgroup. Within the favourable risk subgroup, the EAG have now presented additional scenario analysis (Scenario 88) that considered the relative effectiveness of all treatments to be equal to that in the ITT population, whilst continuing to use the baseline risks associated with the subgroup. The incremental QALYs for cabozantinib plus nivolumab relative to pazopanib increased from 0.440 to 0.599, however, the cost of treatment also increased somewhat meaning the ICER remained non-cost-effective at list price.

Action Kidney Cancer highlighted that use of the CDF could provide an opportunity to collect further data whilst the OS data mature for favourable risk patients. PFS data for CheckMate 9ER are mature within the favourable risk subgroup. OS data, however, were not yet mature at the latest datacut (median only just met for sunitinib and not met for nivolumab + cabozantinib).[2] It is unclear whether data is still being collected to allow further follow-up. The EAG consider that collection of data via SACT would not be feasible given the long time required to collect mature data within this subgroup.

3.3. Non-clear cell RCC

Action Kidney Cancer noted that non-clear cell RCC is an area of significant unmet need. On this point, Ipsen reiterated information provided in the TE response. They said that while the EMA noted that in the application for approval of cabozantinib with nivolumab, participants with non-clear cell RCC were not excluded from the sought indication. This was deemed acceptable by the EMA because cabozantinib had shown efficacy in non-clear cell RCC in a retrospective study.[3] The study cited by the EMA (Martinez et al., 2019[4]) was an uncontrolled evaluation of cabozantinib monotherapy in people with non-clear cell RCC. It showed a benefit of treatment in a minority of participants with papillary, Xp11.2 translocation, chromophobe and collecting duct

RCC, and a smaller minority of people with unclassified RCC. While the EAG accept the conclusion of the EMA, it notes that the remit of the EMA is different to that of the EAG, and therefore conclusions about the clinical effectiveness of treatments across RCC populations may use different criteria.

Action Kidney Cancer highlighted evidence from a different uncontrolled, phase II trial showing that cabozantinib + nivolumab has also demonstrated some effectiveness for the treatment of non-clear cell RCC (Lee et al., 2022[5]). However, the EAG observe that this study shows the potential variation in treatment effect across non-clear cell subtypes. Notably, no participants with chromophobe RCC (out of seven participants) experienced a response with up to 13 months of treatment. The EAG also identified a further retrospective analysis of participants with non-clear cell RCC who were treated with nivolumab (monotherapy or in combination with ipilimumab or another targeted therapy before 2017) that showed potential variation in treatment response across RCC subtype.[6] Given the small sample sizes of people with each non-clear cell RCC subtype in these studies, it is not possible to draw firm conclusions about treatment efficacy from this evidence alone.

Therefore, within the remit of this appraisal, and based on the data supplied to the EAG by the company, the EAG was unable to appraise whether cabozantinib + nivolumab would be clinically and cost effective for people with non-clear cell RCC. The EAG agrees with Action Kidney Cancer that further data collection is required. There are a number of ongoing trials focussing on non-clear cell RCC, including SUNNIFORECAST (an RCT comparing nivolumab + ipilimumab with standard of care at 1st line) and a trial comparing sunitinib and cabozantinib at multiple lines.[7,8] At present, the EAG has concerns that the clinical and cost effectiveness of cabozantinib + nivolumab may vary in some non-clear cell subgroups.

3.4. Wording of indications / recommendations in the ACD

MSD flagged that Figure 1 in the ACD should say that “pembrolizumab + lenvatinib is used if nivolumab + ipilimumab would otherwise be offered”. The EAG agree and have checked that the EAG report (Figure 6) correctly states that pembrolizumab + lenvatinib is for patients “suitable” for nivolumab + ipilimumab as a shortening of the full NICE recommendation wording.

Merck Serono noted issues with the wording of the recommended population for avelumab + axitinib in the ACD. The EAG checked that the report correctly stated that avelumab + axitinib is available for both the intermediate/poor and favourable risk groups within the CDF.

Ipsen flagged issues with the wording that potentially indicated that the combination of nivolumab + ipilimumab + cabozantinib is in use. The EAG agree this combination is not relevant to the decision problem under consideration.

3.5. Inclusion of four treatment lines in the economic model

Both Ipsen and Merck Serono remarked on the complexity of the pathways model, and specifically on the inclusion of four treatment lines and associated data requirements as an issue. Merck Serono did, however, acknowledge the desire to 'future-proof' the model for assessing upcoming RCC therapies.

The EAG would note that it is possible for the user to define the number of lines to run in the pathway model. Also, scenario analysis demonstrated that running the model for four lines as opposed to two did relatively little to change modelled outputs. This remains the case with the EAG's updated base case (list price ICER in the all-risk population £274,247 with 4 lines and £229,389 with 2 lines for the state transition model and £453,073 for the PartSA). There is no indication that use of this model will "disadvantage companies". The EAG would also note that there are treatments currently being tested for later lines of treatment (such as belzutifan) making the inclusion of the functionality to consider later lines of treatment important.

3.6. Lack of stakeholder access to key data

Both Ipsen and Merck Serono noted issues with the lack of stakeholder access to key data. In particular, the unpublished RWE used to inform baseline characteristics, natural history/underlying risk, treatment pathway, and sequences in the model.

The EAG agree that full access to the data underlying the model would be ideal and would note that this applies equally to company data as well as the UK RWE. The EAG note the difficulties that heavy redacting of prior submissions caused in consideration of model inputs from trials outside of CheckMate 9ER. Also, that some data from CheckMate 9ER were not available to other stakeholders.

The EAG note that greater access to the UK RWE data will be possible once the data are published. The EAG also note that all stakeholders have full access to the curves fitted to the UK RWE in the survival analysis R file provided. To support validation, the EAG has provided results using the dummy treatment sequence data in this report (see Appendix A).

3.7. Probabilistic sensitivity analysis

Ipsen flagged a number of additional issues in relation to the pathways pilot process. The majority of these are outside of the remit of the EAG. However, some do fall within the EAG's remit, principally those issues relating to the PSA.

The EAG would note that PSA was presented in Appendix Q (see Section Q.2.6) and that results were generally consistent with the deterministic analysis. As the company correctly highlight, the NICE manual states that "the computational methods used to implement an appropriate model structure may occasionally present challenges in doing probabilistic sensitivity analysis." The EAG acknowledge that this is the case for the full state transition model, which represents the Committee preferred base case. PSA is possible in a reasonable run time for the PartSA, as would be expected. In the EAG's view, the benefits of being able to model the full UK treatment pathway and consequences of treatment sequences on effectiveness outweigh the benefits of being able to characterise uncertainty via probabilistic analysis.

The EAG do not consider it realistic that an updated PSA would have allowed the resolution of all the Committee's uncertainties – and hence allowed a recommendation at the first Committee meeting. The ACD states that: "the committee concluded that none of the analyses reflected its preferences so it could not make a recommendation", and highlights in particular the issues with the ITC comparing to pembrolizumab + lenvatinib, which required updated data. Presentation of PSA would not provide the Committee with the information to resolve this uncertainty.

The EAG further note that the purpose of the economic model is to characterise uncertainty. It is not there to either generate uncertainty, as implied by Ipsen's responses, or to replace Committee decision making. It should also be noted that the major uncertainties in this appraisal are not incorporated within the parameter uncertainty estimates. Rather, they are structural in nature.

3.8. Inconsistency and uncertainty

The EAG would disagree strongly with Ipsen's comment that the EAG model "mixed and matched different sources and methodologies such that it created multiple inconsistent assumptions and effectively an exponential set of uncertainties." The EAG instead considers that the pathways pilot has highlighted uncertainties which are present both within and between the range of appraisals for aRCC and in oncology generally, and which are often glossed over.

For example, the impact of subsequent treatments on effectiveness when treatments received in trials do not match those expected to be used in practice. This is very often the case, and was highlighted as a challenge in this appraisal. The Committee considered the model presented to them to be suitable to decision making. They were able to define a preferred Committee base case along with scenarios of key interest to explore the uncertainties inherent to an evidence base with numerous, although often-encountered, issues.

In conclusion, it is inaccurate to state that the EAG's approach created "an exponential set of uncertainties" as the thrust of the EAG's strategy has been to identify and characterise these uncertainties where they arise.

3.9. Utility data

Ipsen re-presented argumentation already put forth in their TE response and which the EAG has already responded to (Economic Key Issue 5 in TE response and page 321 of the EAG assessment report). This will therefore not be discussed further save to note that many of the additional sources provided by the company have limited validity when considering the need to apply them to this decision problem.

Ipsen also highlighted that the Committee preferred source of utility data may not reflect some other prior appraisals, data for which were redacted and not available for the EAG to use. Ipsen requested a scenario analysis that applies the percentage drop in utility – from the PFS to PD health state – derived from the EAG and Committee preferred base case utilities, to the baseline utility derived from the 9ER study (i.e., PFS utility from 9ER), given the fact that CheckMate 9ER data [redacted]. The EAG have presented the requested scenario in Section XX.

3.10. Impact of model structure (or lack thereof)

Ipsen continue to maintain that there are unexpected discrepancies in results between the STM and PartSA models. This is not the case, as demonstrated in the EAG's response to technical engagement (Section 5, Issue 7: Impact of model structure on results).

Where there are differences, these are expected and relate to two issues:

- PPS LYs are somewhat different between models. This is expected, given the PartSA model bases PPS on independent extrapolation of OS data and includes relative effects which come from trials where subsequent treatments may not align to UK practice

(including CheckMate 9ER). The STM, on the other hand, bases PPS on PFS for each subsequent line of treatment for each sequence, followed by PPS for the final line.

- PFS is a poor surrogate for OS for nivolumab + ipilimumab specifically. This was previously explored by the EAG in scenario analysis. TTNT was used in the scenario analysis as an alternative surrogate and was considered by the EAG to provide a more plausible estimate.

The EAG would also like to repeat that the STM provides an increased expectation of long-term survival due to the allowance for additional lines of active treatment. It is therefore, as well as being more realistic, generally more favourable to nivolumab + cabozantinib than the PartSA analysis.

Ipsen also flagged that a balanced view of the strengths and weaknesses of PartSA vs STM is required. The EAG would agree and considers that the initial report presents exactly this. However, to aid in any further discussion we have produced a table summarizing the pros and cons of the two approaches (Table 7).

Table 9: Pros and cons to PartSA vs STM approaches

	PartSA	STM
Surrogacy	OS and PFS are independent Con: can result in implausible extrapolations as curves can cross or PPS benefit where treatment is not expected to influence outcomes after progression	OS is dependent upon PFS Pro: better reflects real life disease processes Con: PFS may not be a good surrogate for nivo+ipi
Endpoints required	OS and PFS for disease process. TTD for costs (or assume equal to PFS). External data may be used to inform extrapolation. Pro: OS and PFS are widely available in clinical literature Con: Extrapolation of OS based only on trends observed at 1L. "Extrapolating within-trial trends without considering the underlying disease process may not produce appropriate extrapolations" and "may increase the uncertainty associated with the extrapolations"[9]	TTP, PrePS and PPS for disease process. PrePS can be calculated based upon PFS and TTP. TTD for costs (or assume equal to PFS). Data is required for all lines to be included within the model. External data may be used to inform extrapolation. Con: TTP is often not published. Splitting up transitions reduces the number of events available for extrapolation. In our case TTP data for the reference curve are mature, as are PPS data. The ideal methods for specification of survival analysis within a state transition framework are still an area of research (although the same could be said to some extent for PartSA).
Subsequent treatments	Unless OS is adjusted assumes that either the subsequent treatments in the underlying data sources are fully reflective of current practice or that any differences will not impact OS Con: available UK RWE indicate the trials are not reflective of current practice and 2L+ NMA shows type of subsequent treatment impacts outcomes considerably, there are also considerable differences in cost. OS could not be adjusted for differences in subsequent treatments using statistical methods such as those in TSD 16.	Allows subsequent treatments to be explicitly incorporated according to the proportion receiving each type of subsequent treatment Con: dependent upon the quality of data available for subsequent treatments. In our case data limitations did not allow a time-dependent approach to be taken from relative effectiveness for 2L+ treatments. The impact of the type of prior treatment on later lines was only able to be looked at in exploratory analysis.
Validation	As OS and PFS data are used directly fitted curves validate well against the observed KMs	Final OS projections using PFS and PPS require validation against OS data. In our case good validation was achieved vs the UK RWE; validation was less successful vs CheckMate 9ER due to considerable differences between subsequent treatments in the trial and those available in practice / within the 2L+ NMA

Abbreviations: 1L, 1st line; 2L, 2nd line; ipi, ipilimumab; nivo, nivolumab; KM, Kaplan Meier; OS, overall survival; PartSA, Partitioned survival analysis; PFS, progression free survival; PPS, post progression survival; PrePS, pre-progression survival; RWE, real world data; TTD, Time to treatment discontinuation; TTP, Time to progression; UK, United Kingdom

3.11. Inclusion of CABOSUN in the NMA

Ipsen disagrees with the inclusion of CABOSUN in the overall network as the trial includes only intermediate/poor risk patients. The EAG would reiterate that cabozantinib monotherapy is not included as a relevant comparator for decision making in the all-risk population at 1st line. As the CABOSUN trial forms a spoke of the network its inclusion has minimal, if any, impact on results in the all-risk network. Inclusion of CABOSUN does not magnify uncertainty (see Section 6.2.6 of the EAG's response to technical engagement).

An additional point raised by the EAG and the Appraisal Committee related to the credibility of the results from CABOSUN in providing a comparison of cabozantinib monotherapy vs sunitinib in the intermediate / poor risk population. To address these concerns, the EAG reviewed the results of the search for observational and real-world evidence conducted for the original report to identify any other real-world evidence of the effectiveness of cabozantinib monotherapy at 1st line. Four articles were retrieved (Table 8). Three were by the same author and drawn from the same dataset, and two (Loo Gan 2020, Loo Gan 2021) reported the same analysis in poster and article formats.

Table 10: Articles relevant to 1L cabo monotherapy

Article	Full reference	Study type
Loo Gan 2020	Gan C.L., Dudani S., Wells C., et al Cabozantinib real-world effectiveness in the first through fourth-line settings for the treatment of metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC). J. Clin. Oncol. 2020;38(6 Supplement):no pagination. doi:10.1200/JCO.2020.38.6_suppl.639	Retrospective analysis of 413 international patients
Loo Gan 2021	Gan C.L., Dudani S., Wells J.C., et al Cabozantinib real-world effectiveness in the first-through fourth-line settings for the treatment of metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Cancer Med. 2021;10(4):1212-1221. doi:10.1002/cam4.3717	Retrospective analysis of 413 international patients
Loo Gan 2023	Loo Gan C., Huang J., Pan E., et al Real-world Practice Patterns and Safety of Concurrent Radiotherapy and Cabozantinib in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur. Urol. Oncol. 2023;6(2):204-211. doi:10.1016/j.euo.2022.10.004	Retrospective analysis of 127 consecutive international patients
Pillai 2020	Pillai M., Powles T., Szabados B., et al A non-interventional retrospective study to describe early clinical experience with cabozantinib in patients with advanced renal cell carcinoma (aRCC) in the United Kingdom. J. Clin. Oncol. 2020;38(15):no pagination. doi:10.1200/JCO.2020.38.15_suppl.e17089	Non-interventional retrospective chart review of 100 UK patients

Unfortunately, all three analyses were non-comparative in nature, precluding use of these data in an analysis of relative treatment effects. The EAG conducted a naïve comparison of the UK RWE used in the model to compare PFS and OS for intermediate or poor risk patients who received cabozantinib and who received sunitinib. This drew on a total sample of 330 patients. Log-rank tests (see Figure 7 and Figure 8) did not suggest significant differences in the survivor functions for OS (p=0.18) or for PFS (p=0.32). This suggested that a reasonable assumption would be to set the effectiveness of cabozantinib equal to the effectiveness of sunitinib.

Figure 10: OS from RWE comparing cabo and suni

Figure 11: PFS from RWE comparing cabo and suni

Ipsen did not provide any comment on the issues with the CABOSUN trial and how the results should be interpreted (given that the PFS HR is more favourable for cabozantinib monotherapy than cabozantinib plus nivolumab).

Given the large number of issues with the CABOSUN trial and the trends shown in the available RWE, the EAG revised base case assumes equal effectiveness between sunitinib and cabozantinib in 1st line intermediate or poor risk patients.

3.12. Violation of proportional hazards

The EAG agree with Ipsen that the wording in the DG is incorrect in that the proportional hazards assumption was not violated for **all** treatments in the pathway. We would note, however (as described in Table 36 of the EAG report), that it was violated for a substantial number of treatments, including treatments of key relevance to the decision problem for nivolumab + cabozantinib. These included nivolumab + ipilimumab (CheckMate 214) and pembrolizumab + lenvatinib (CLEAR). Also, that the validity of proportional hazards for nivolumab + cabozantinib itself was questionable (CheckMate 9ER). Furthermore, even if proportional hazards were in evidence for individual treatments against their within-trial comparators, violation of proportional hazards in trials elsewhere in the network would mean that indirect comparisons of any treatment against those with within-trial violations of proportional hazards would also be susceptible to bias.

Ipsen reiterated concerns relating to the use of FP NMA as a base case for 1st line with PH NMA in 2nd line and beyond. The EAG notes this 'mismatch' but continue to believe that this was the most appropriate decision to manage plausibility of estimates and quantity of evidence (which were both greater for 1st line NMAs), and consistency across lines. The EAG further notes that treatments for 2nd line+ are not the focus of the decision problem for the appraisal of cabozantinib + nivolumab.

We continue to present the proportional hazards NMA within scenario analysis to allow the uncertainty around the NMA methodology used to be explored (Scenario 21). In the intermediate / poor risk population use of the PH NMA benefits the more effective treatments (pem + lenv, then cabo + nivo, then nivo + ipi, then TKI monotherapies) but not the extent of having a meaningful impact on results when list prices are used.

3.13. Issues with surrogacy of PFS for nivolumab + ipilimumab

Pseudo-progression or tumour flare was first identified as a potential issue for IO treatments during the ipilimumab trials in melanoma. Data for PD-1/PD-L1 plus ipilimumab in melanoma demonstrated that a larger number of patients (1/3 of progressed patients) within the trial experienced pseudo-progression than was seen with PD-1/PD-L1 monotherapy (2 – 10%).[10,11]

The paper by Atkins et al (2017)[12] provides a reasonable summary of the issue of pseudo-progression, and some of evidence available for this in advanced RCC. Trials of nivolumab monotherapy demonstrated that a number of patients treated beyond progression experienced subsequent tumor reduction or stabilisation in target lesion size. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma notes that for patients receiving IO treatment regimens in advanced RCC, *"pseudo-progression, defined as an initial flare of tumor size (suggestive of tumor progression) followed by a reduction in tumor mass, is considered an uncommon, but possible, event in solid tumors"*.[13]

No studies included in the review that reported the results from CheckMate 214 explicitly evaluated the presence of pseudo-progression in those receiving nivolumab + ipilimumab. During the timeframe of the appraisal, the EAG was unable to identify any such data in additional publications. While no evidence of pseudo-progression was identified following nivolumab + ipilimumab, given evidence for this in melanoma populations and the large difference between the KMs for TTNT and PFS observed in CheckMate 214, the EAG consider it plausible that pseudo-progression could be a reason for the discrepancy between PFS, TTNT and OS outcomes. However, the EAG also note that there are other reasons

which may explain the difference. For example, CheckMate 214 uses investigator assessed PFS whereas the majority of the other trials use an independent assessment.

The EAG would reiterate that using TTNT as a proxy for PFS is, however, also an imperfect way to estimate the effectiveness of nivolumab + ipilimumab. Using such an approach, patients who are too sick to receive a new active line of treatment (i.e. patients who go on to BSC) are only coded as having an event when they die within the Kaplan Meier. However, given the poor surrogacy between PFS and OS for nivolumab + ipilimumab it provides an additional point of evidence for consideration.

The EAG would also note that when TTNT is used as a proxy for PFS, the model extrapolation fits well to the observed survival for the UK RWE for nivolumab + ipilimumab (Figure 9). Use of PFS data within the updated NMA now also provides a reasonable prediction during the observed period (Figure 10) albeit more pessimistic in the long-run, although the underlying data for nivolumab plus ipilimumab have not changed the change created by the addition of pembrolizumab plus lenvatinib data has resulted in a less pessimistic fit.

Figure 12: Model fit to nivo+ipi OS when using suni reference curve from UK RWE and TTNT as a proxy for effectiveness (Scenario analysis 73)

Figure 13: Model fit to nivo+ipi OS when using suni reference curve from UK RWE and PFS as a proxy for effectiveness (basecase)

Abbreviation: KM, Kaplan Meier

3.14. Dosing of pembrolizumab + lenvatinib

Ipsen correctly identify that the economic model only looks at the proportion of patients on each dose level per time-period, not whether patients are specifically titrated up or down. Clinical advice to the EAG was that clinical practice varies in relation to the dosing of pembrolizumab + lenvatinib. Given that the model solely looks at the proportion using each number of tablets, the EAG do not consider that it is necessary to define clinical practice in respect of titrating up or down, but rather to approximate the mean number of tablets required to a reasonable degree of accuracy. The EAG present scenario analysis using an average of two tablets (in addition to the previous analysis, which assumed 25% have one tablet and the remainder have two tablets in the long run) in response to Committee requests for additional analyses (Scenario 87). The ICER increases in this scenario from £396,657 for pembrolizumab plus lenvatinib relative to cabozantinib plus nivolumab to £655,233.

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5. APPENDIX A: RESULTS USING RWE TREATMENT SEQUENCE DUMMY DATA FOR COMPANY VALIDATION

This Appendix replicates Section 2.3, Appendix B and Appendix C using the cPAS redacted model file which is available to the company. This provides the company with a full set of results that can be cross-checked to ensure the model is functioning as intended.

Deterministic results – redacted model

Table 11: Base case results, redacted PAS prices for comparators and RWE treatment sequence – redacted model

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental	ICER cabo + nivo vs comparator	Severity modifier
Risk population: All risk									
Suni	£47,482	2.41	1.48	£0.00	0.00	0.00	£0	£164,725	1.0
Pazo	£68,284	3.02	1.79	£20,802.75	0.60	0.31	£66,726	£247,445	1.2
Tivo	£90,595	2.91	1.75				(dominated)	£164,742	1.0
Cabo+nivo	£159,677	3.59	2.16	£91,392.91	0.57	0.37	£247,445		-
Risk population: Favourable risk									
Suni	£51,161	3.29	2.01	£0.00	0.00	0.00	£0	£200,753	1.0
Pazo	£73,776	3.92	2.33	£22,615.01	0.63	0.32	£71,579	£345,805	1.0
Tivo	£107,216	3.81	2.28				(dominated)	£192,286	1.0
Cabo+nivo	£171,070	4.39	2.61	£97,294.53	0.47	0.28	£345,805		-
Risk population: Intermediate / poor risk									
Suni	£45,851	2.09	1.28	£0	0.00	0.00	£0	£160,495	1.2
Pazo	£65,828	2.68	1.58	£19,977	0.59	0.31	£64,805	£251,730	1.2
Tivo	£83,703	2.58	1.53				(dominated)	£170,420	1.2
Cabo	£96,630	2.75	1.58				(dominated)	£154,786	1.2
Nivo+ipi	£144,228	2.89	1.75				(ext dominated)	£18,824	1.0
Cabo+nivo	£147,217	3.18	1.91				(ext dominated)		-
Pem+lenv	£211,372	3.54	2.19	£145,544	0.86	0.60	£240,786	SW quadrant £228,201	1.0

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year

Table 12: Base-case results, redacted comparator prices and RWE treatment sequence, fully incremental analysis excluding TKIs in the intermediate / poor risk population – redacted model

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£144,228	2.89	1.75		-	-	-
Cabo+nivo	£147,217	3.18	1.91	£2,989	0.29	0.16	£18,824
Pem+lenv	£211,372	3.54	2.19	£64,155	0.36	0.28	£228,201

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; TKI, tyrosine kinase inhibitor

Probabilistic results – redacted model

Table 13: Base case results, redacted PAS prices for comparators and RWE treatment sequence – redacted model, mean +/- 95%CrI

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental	ICER cabo + nivo vs comparator	Severity modifier
Risk population: All risk									
Suni	£45,496 (£32,241, £62,352)	2.582 (2.136, 3.141)	1.608 (1.290, 1.975)	-	-	-	-	£173,838	1.2
Pazo	£68,045 (£47,987, £93,653)	3.268 (2.589, 4.120)	1.989 (1.566, 2.507)	£22,549 (£14,108, £34,484)	0.686 (0.410, 1.086)	0.382 (0.056, 0.708)	£59,064	£344,193	1.2
Tivo	£91,681 (£68,465, £118,164)	3.192 (2.530, 4.025)	1.946 (1.509, 2.434)	-	-	-	Dominated	£215,893	1.2
Cabo+nivo	£156,573 (£126,384, £188,006)	3.603 (2.947, 4.468)	2.247 (1.782, 2.775)	£88,529 (£65,178, £112,294)	0.335 (-0.346, 0.963)	0.257 (-0.222, 0.735)	£344,193	-	-
Risk population: Favourable risk									
Suni	£48,938 (£34,314, £66,788)	3.480 (2.781, 4.262)	2.144 (1.675, 2.653)	-	-	-	-	£210,646	1.2
Pazo	£72,789 (£49,430, £101,856)	4.174 (3.278, 5.284)	2.512 (1.922, 3.156)	£23,851 (£14,207, £36,463)	0.694 (0.390, 1.118)	0.368 (-0.079, 0.864)	£64,834	£481,780	1.2
Tivo	£107,741 (£78,779, £139,909)	4.097 (3.209, 5.175)	2.473 (1.888, 3.106)	-	-	-	Dominated	£254,610	1.2
Cabo+nivo	£168,104 (£127,670, £210,262)	4.471 (3.082, 6.310)	2.710 (1.855, 3.708)	£95,315 (£62,606, £131,646)	0.297 (-0.971, 1.718)	0.198 (-0.601, 1.193)	£481,780	-	-
Risk population: Intermediate / poor risk									

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental	ICER cabo + nivo vs comparator	Severity modifier
Suni	£43,690 (£30,581, £58,825)	2.257 (1.814, 2.829)	1.404 (1.100, 1.741)	-	-	-	-	£168,332	1.2
Pazo	£65,380 (£44,184, £90,627)	2.932 (2.256, 3.811)	1.781 (1.378, 2.252)	£21,690 (£12,030, £33,815)	0.675 (0.388, 1.043)	0.377 (0.136, 0.65)	£57,534	£358,966	1.2
Tivo	£84,594 (£60,339, £112,362)	2.855 (2.219, 3.705)	1.738 (1.348, 2.215)	-	-	-	Dominated	£227,405	1.2
Cabo	£99,733 (£69,066, £141,959)	2.956 (2.202, 4.072)	1.768 (1.342, 2.354)	-	-	-	Dominated	£190,994	1.2
Nivo+ipi	£138,314 (£108,224, £161,718)	3.008 (2.423, 3.734)	1.880 (1.457, 2.341)	-	-	-	Extendedly Dominated	£47,719	1.0
Cabo+nivo	£144,036 (£114,526, £174,437)	3.196 (2.564, 4.078)	2.000 (1.563, 2.527)	-	-	-	Extendedly Dominated	-	-
Pem+lenv	£205,958 (£178,903, £233,274)	3.715 (3.075, 4.539)	2.330 (1.851, 2.881)	£140,578 (£110,452, £167,832)	0.783 (0.351, 1.221)	0.549 (0.125, 0.957)	£255,886	SW quadrant £187,496	1.0

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year

Table 14: Base-case results, redacted comparator prices and RWE treatment sequence, fully incremental analysis excluding TKIs in the intermediate / poor risk population – redacted model

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£138,314 (£108,224, £161,718)	3.008 (2.423, 3.734)	1.880 (1.457, 2.341)		-	-	-
Cabo+nivo	£144,036 (£114,526, £174,437)	3.196 (2.564, 4.078)	2.000 (1.563, 2.527)	£5,723	0.188	0.120	£47,719
Pem+lenv	£205,958 (£178,903, £233,274)	3.715 (3.075, 4.539)	2.330 (1.851, 2.881)	£61,922	0.519	0.330	£187,496

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year; TKI, tyrosine kinase inhibitor

Figure 14: Cost-effectiveness acceptability curve (redacted model, all risk population)

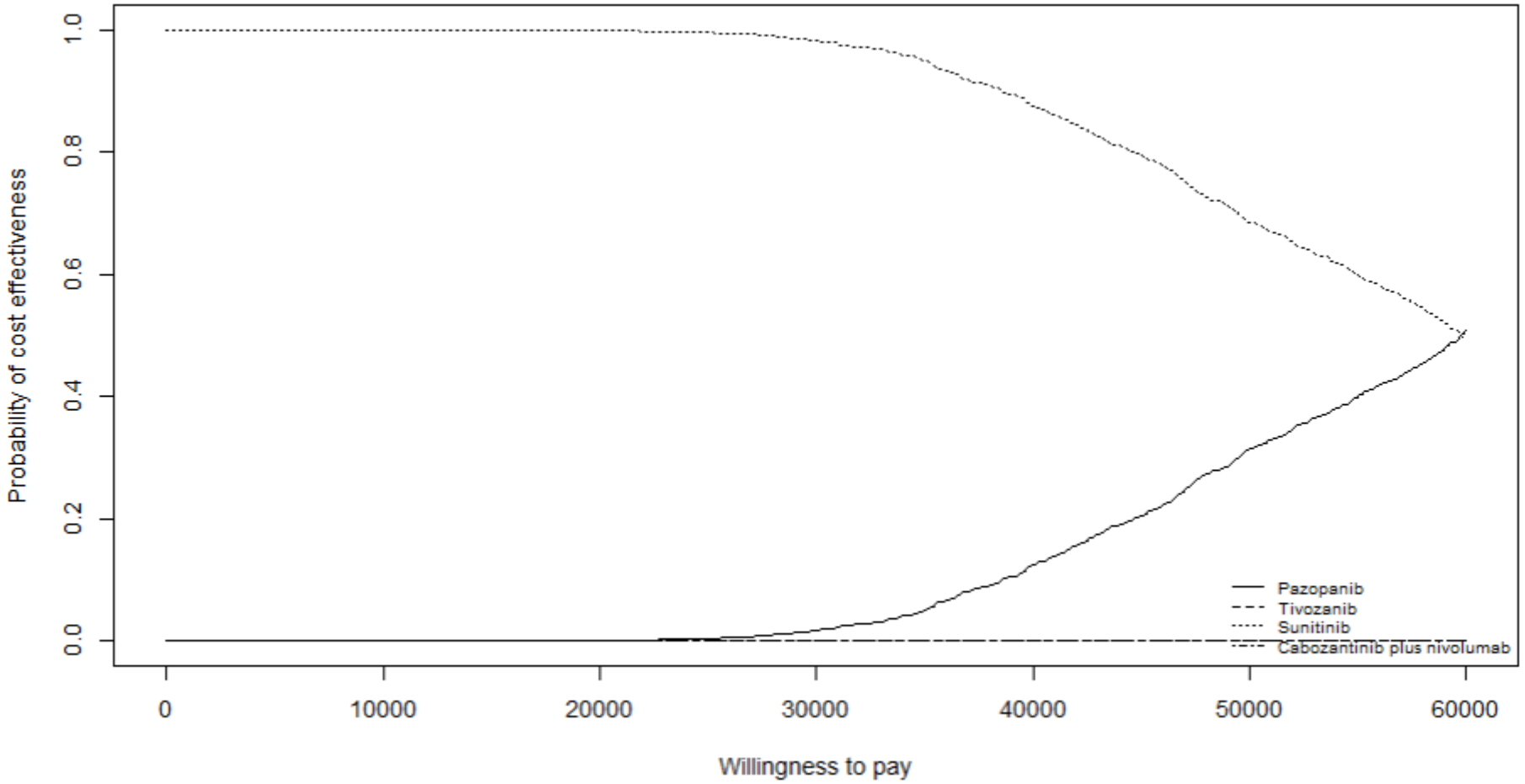


Figure 15: Cost-effectiveness acceptability curve (redacted model, favourable risk population)

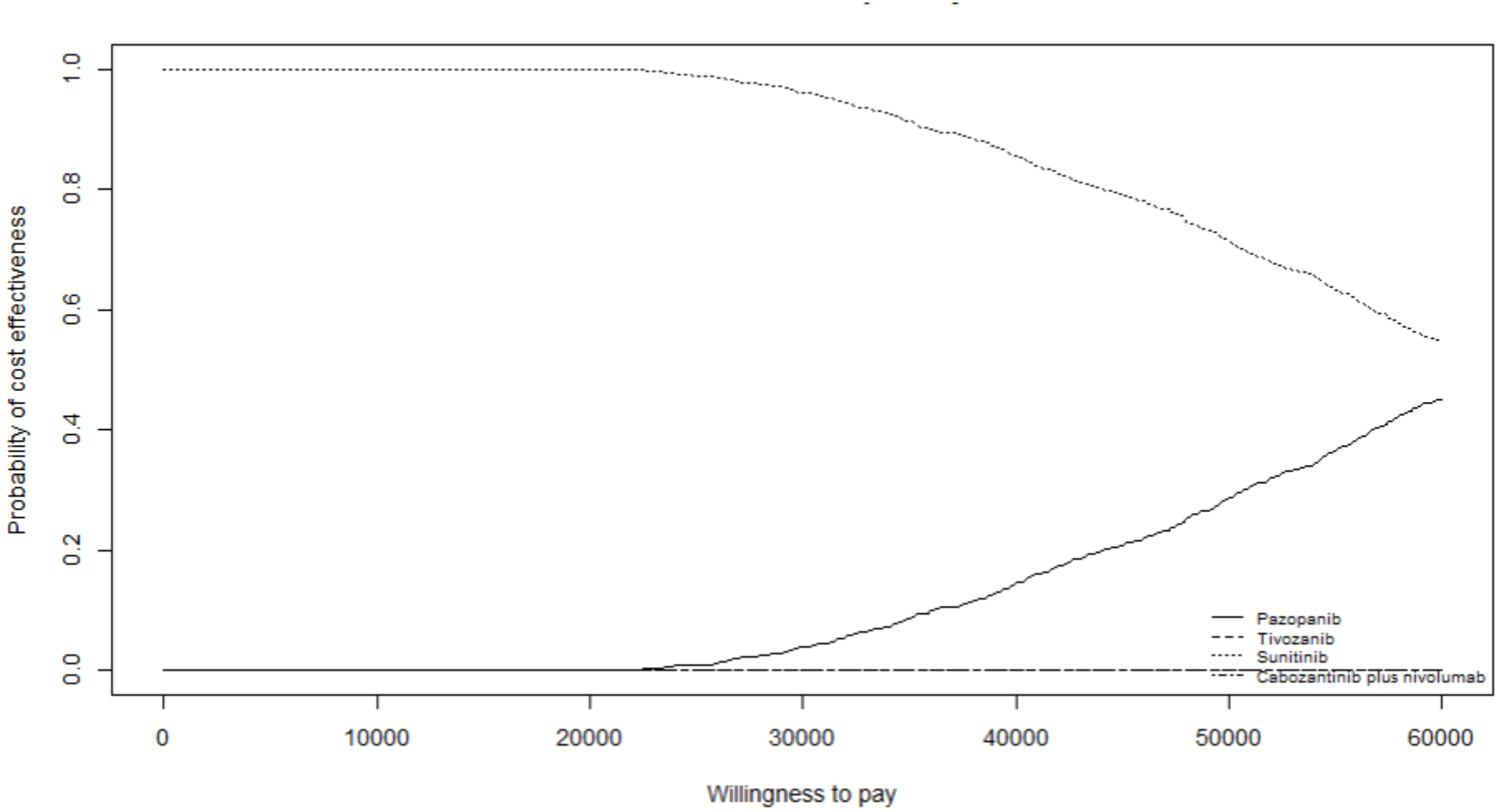
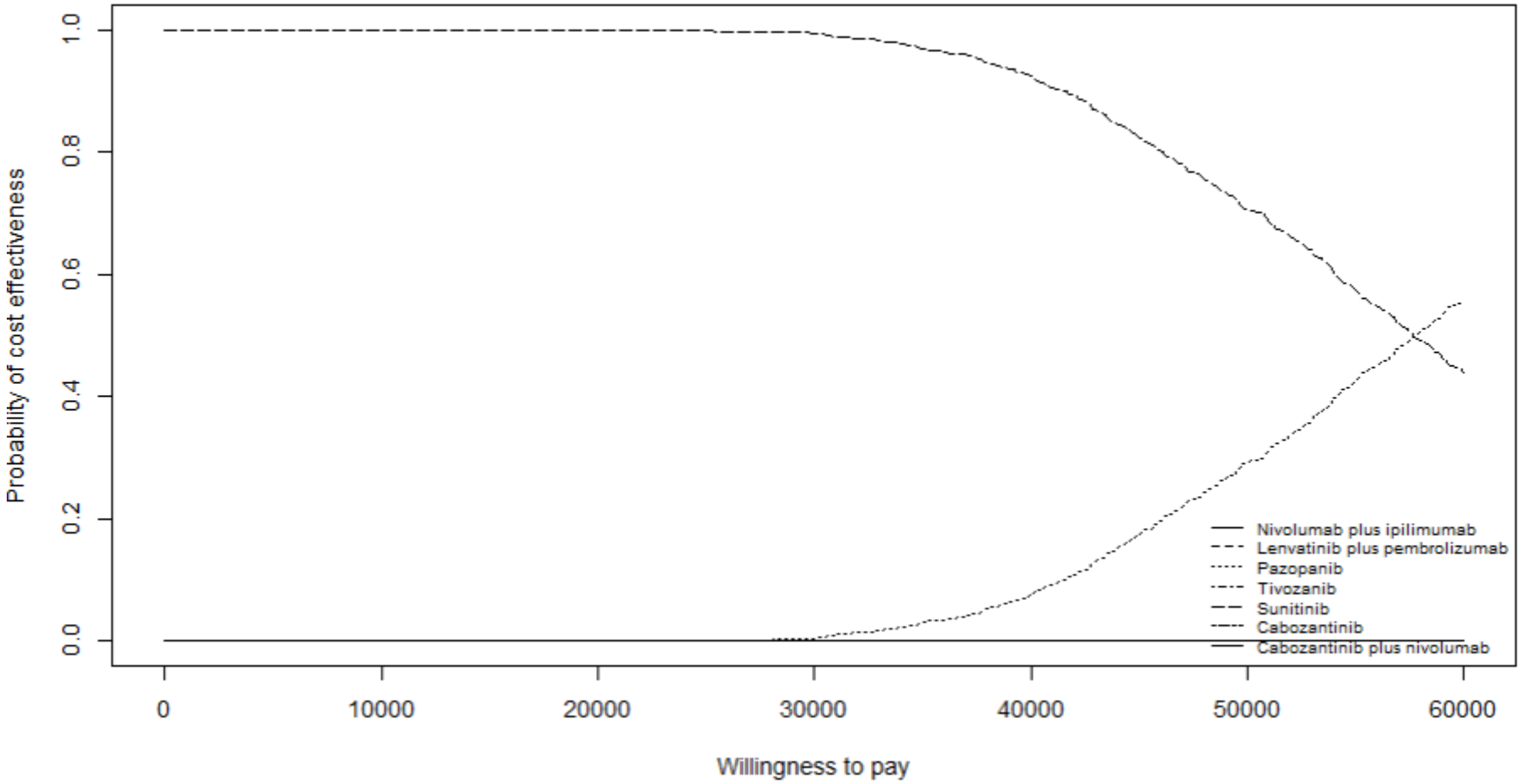


Figure 16: Cost-effectiveness acceptability curve (redacted model, intermediate/poor risk population)



Detailed results – redacted model

Table 15: Summary of LY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.109	0.115	-0.006	0.006	0%
1L: on treatment	1.945	1.144	0.801	0.801	57%
2L: off treatment	0.281	0.207	0.074	0.074	5%
2L: on treatment	0.798	0.692	0.106	0.106	8%
3L: off treatment	0.016	0.106	-0.091	0.091	6%
3L: on treatment	0.085	0.357	-0.272	0.272	19%
4L: off treatment	0.001	0.007	-0.007	0.007	0%
4L: on treatment	0.003	0.047	-0.044	0.044	3%
BSC	0.355	0.343	0.012	0.012	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.593**	**3.018**	**0.575**	**1.412**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 16: Summary of LY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.274	0.266	0.008	0.008	1%
1L: on treatment	2.582	1.828	0.753	0.753	56%
2L: off treatment	0.280	0.214	0.066	0.066	5%
2L: on treatment	0.797	0.718	0.079	0.079	6%
3L: off treatment	0.016	0.110	-0.094	0.094	7%
3L: on treatment	0.085	0.371	-0.286	0.286	21%
4L: off treatment	0.001	0.008	-0.007	0.007	1%
4L: on treatment	0.003	0.049	-0.045	0.045	3%
BSC	0.356	0.356	-0.001	0.001	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**4.394**	**3.921**	**0.473**	**1.339**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 17: Summary of LY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pem+lenv) – redacted model

Health state	LY cabo+nivo (X)	LY pem+lenv (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.076	0.084	-0.008	0.008	1%
1L: on treatment	1.572	2.068	-0.496	0.496	56%
2L: off treatment	0.280	0.216	0.064	0.064	7%
2L: on treatment	0.795	0.661	0.134	0.134	15%
3L: off treatment	0.016	0.032	-0.016	0.016	2%
3L: on treatment	0.085	0.144	-0.059	0.059	7%
4L: off treatment	0.001	0.006	-0.006	0.006	1%
4L: on treatment	0.003	0.037	-0.034	0.034	4%
BSC	0.354	0.289	0.065	0.065	7%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.182**	**3.537**	**-0.356**	**0.881**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 18: Summary of QALY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.074	0.079	-0.005	0.005	1%
1L: on treatment	1.316	0.790	0.526	0.526	67%
2L: off treatment	0.124	0.106	0.018	0.018	2%
2L: on treatment	0.429	0.411	0.018	0.018	2%
3L: off treatment	0.008	0.047	-0.039	0.039	5%
3L: on treatment	0.038	0.182	-0.143	0.143	18%
4L: off treatment	0.000	0.003	-0.003	0.003	0%
4L: on treatment	0.002	0.018	-0.016	0.016	2%
BSC	0.173	0.159	0.014	0.014	2%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.165**	**1.795**	**0.369**	**0.783**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 19: Summary of QALY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.177	0.175	0.002	0.002	0%
1L: on treatment	1.671	1.215	0.457	0.457	66%
2L: off treatment	0.122	0.108	0.015	0.015	2%
2L: on treatment	0.421	0.416	0.005	0.005	1%
3L: off treatment	0.008	0.048	-0.040	0.040	6%
3L: on treatment	0.038	0.184	-0.146	0.146	21%
4L: off treatment	0.000	0.003	-0.003	0.003	0%
4L: on treatment	0.002	0.018	-0.017	0.017	2%
BSC	0.170	0.161	0.009	0.009	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.609**	**2.328**	**0.281**	**0.693**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 20: Summary of QALY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pem+lenv) – redacted model

Health state	QALY cabo+nivo (X)	QALY pem+lenv (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.052	0.057	-0.005	0.005	1%
1L: on treatment	1.074	1.408	-0.334	0.334	66%
2L: off treatment	0.126	0.105	0.020	0.020	4%
2L: on treatment	0.433	0.380	0.053	0.053	10%
3L: off treatment	0.008	0.016	-0.007	0.007	1%
3L: on treatment	0.039	0.069	-0.030	0.030	6%
4L: off treatment	0.000	0.003	-0.003	0.003	1%
4L: on treatment	0.002	0.017	-0.015	0.015	3%
BSC	0.174	0.135	0.039	0.039	8%
Death	0.000	0.000	0.000	0.000	0%
Total	**1.908**	**2.189**	**-0.281**	**0.507**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 21: Summary of costs by health state – redacted model

	1L costs			Subsequent treatment			MRU			
Technologies	**Drug cost**	**Admin cost**	**AE cost**	**Drug cost**	**Admin cost**	**AE cost**	**1L**	**Subsequent treatment**	**EOL cost**	**Total cost**
Risk population: All risk										
Suni	£3,690	£275	£604	£19,468	£612	£435	£2,628	£11,715	£8,056	£47,482
Pazo	£6,481	£324	£512	£33,220	£1,011	£744	£2,628	£15,463	£7,901	£68,284
Tivo	£27,787	£336	£408	£34,525	£1,101	£689	£2,628	£15,195	£7,927	£90,595
Cabo+nivo	£98,595	£3,242	£1,127	£32,209	£226	£697	£4,088	£11,731	£7,762	£159,677
Risk population: Favourable risk										
Suni	£5,579	£320	£604	£19,789	£622	£442	£4,058	£11,908	£7,839	£51,161
Pazo	£9,859	£395	£512	£33,768	£1,028	£756	£4,058	£15,719	£7,682	£73,776
Tivo	£42,269	£413	£408	£35,094	£1,119	£700	£4,058	£15,446	£7,708	£107,216
Cabo+nivo	£109,390	£3,445	£1,127	£31,714	£223	£686	£5,354	£11,553	£7,579	£171,070
Risk population: Intermediate / poor risk										
Suni	£2,938	£258	£604	£19,228	£604	£429	£2,080	£11,570	£8,140	£45,851
Pazo	£5,137	£296	£512	£32,810	£999	£735	£2,080	£15,273	£7,988	£65,828
Tivo	£22,024	£305	£408	£34,099	£1,087	£680	£2,080	£15,007	£8,013	£83,703
Cabo	£14,499	£292	£732	£53,608	£1,313	£709	£2,080	£15,421	£7,977	£96,630
Nivo+ipil	£99,304	£4,025	£335	£16,718	£253	£681	£2,931	£12,043	£7,937	£144,228
Cabo+nivo	£86,725	£2,923	£1,127	£32,458	£228	£702	£3,368	£11,820	£7,866	£147,217
Pem+lenv	£168,700	£2,894	£1,062	£13,496	£253	£797	£4,281	£12,133	£7,757	£211,372

Abbreviations: admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Table 22: Summary of predicted resource use by category of cost (all risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Item	Cost cabo+nivo (X)	Cost pazo (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£98,595	£6,481	£92,114	£92,114	90%
Admin cost (1L)	£3,242	£324	£2,918	£2,918	3%
AE cost (1L)	£1,127	£512	£615	£615	1%
Drug acquisition cost (2L+)	£32,209	£33,220	£-1,011	£1,011	1%
Admin cost (2L+)	£226	£1,011	£-785	£785	1%
AE cost (2L+)	£697	£744	£-47	£47	0%
MRU 1L	£4,088	£2,628	£1,460	£1,460	1%
MRU 2L+	£11,731	£15,463	£-3,733	£3,733	4%
EOL	£7,762	£7,901	£-139	£139	0%
Total	**£159,677**	**£68,284**	**£91,393**	**£102,823**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 23: Summary of predicted resource use by category of cost (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo) – redacted model

Item	Cost cabo+nivo (X)	Cost pazo (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£109,390	£9,859	£99,531	£99,531	89%
Admin cost (1L)	£3,445	£395	£3,050	£3,050	3%
AE cost (1L)	£1,127	£512	£615	£615	1%
Drug acquisition cost (2L+)	£31,714	£33,768	£-2,053	£2,053	2%
Admin cost (2L+)	£223	£1,028	£-805	£805	1%
AE cost (2L+)	£686	£756	£-70	£70	0%
MRU 1L	£5,354	£4,058	£1,296	£1,296	1%
MRU 2L+	£11,553	£15,719	£-4,166	£4,166	4%
EOL	£7,579	£7,682	£-103	£103	0%
Total	**£171,070**	**£73,776**	**£97,295**	**£111,689**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

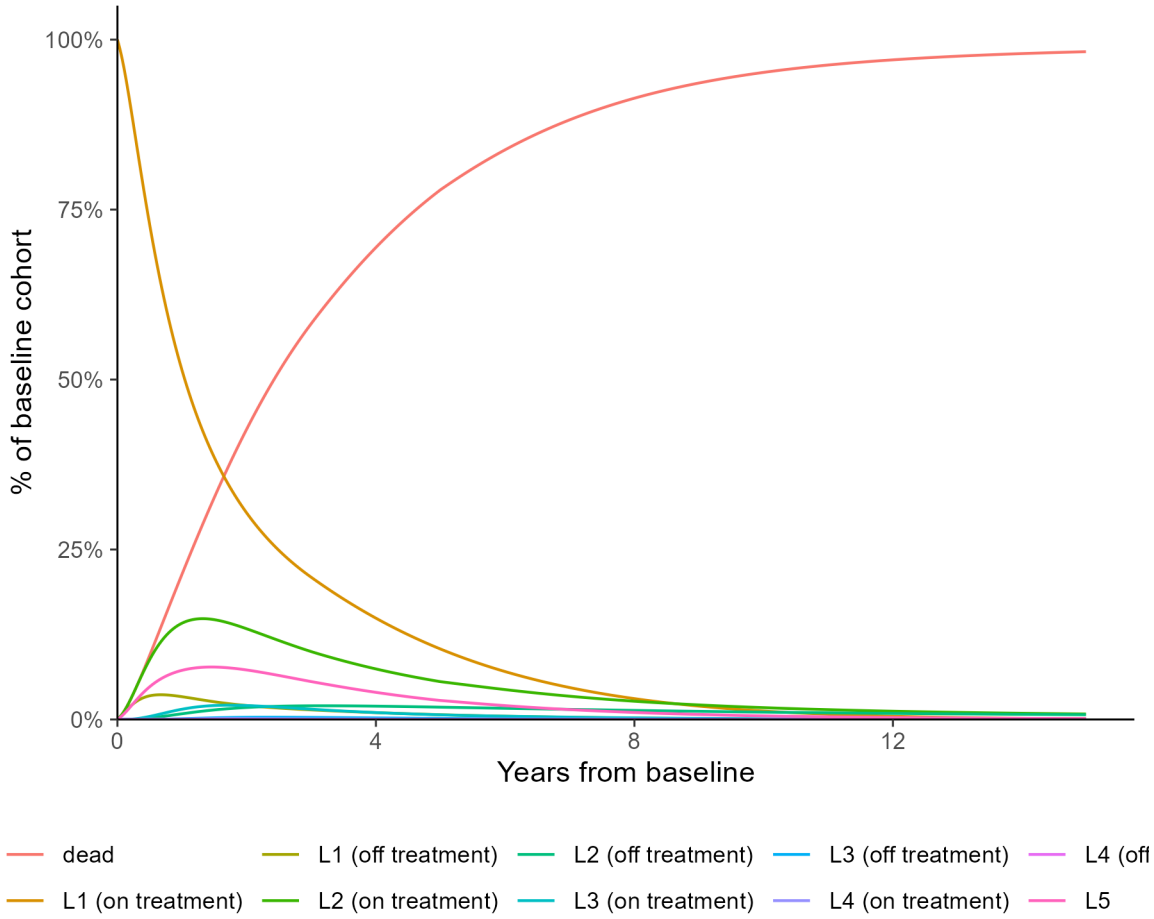
Table 24: Summary of predicted resource use by category of cost (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pem+lenv) – redacted model

Item	Cost cabo+nivo (X)	Cost pem+lenv (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£86,725	£168,700	£-81,975	£81,975	80%
Admin cost (1L)	£2,923	£2,894	£29	£29	0%
AE cost (1L)	£1,127	£1,062	£65	£65	0%
Drug acquisition cost (2L+)	£32,458	£13,496	£18,963	£18,963	19%
Admin cost (2L+)	£228	£253	£-25	£25	0%
AE cost (2L+)	£702	£797	£-95	£95	0%
MRU 1L	£3,368	£4,281	£-913	£913	1%
MRU 2L+	£11,820	£12,133	£-313	£313	0%
EOL	£7,866	£7,757	£109	£109	0%
Total	**£147,217**	**£211,372**	**£-64,155**	**£102,485**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

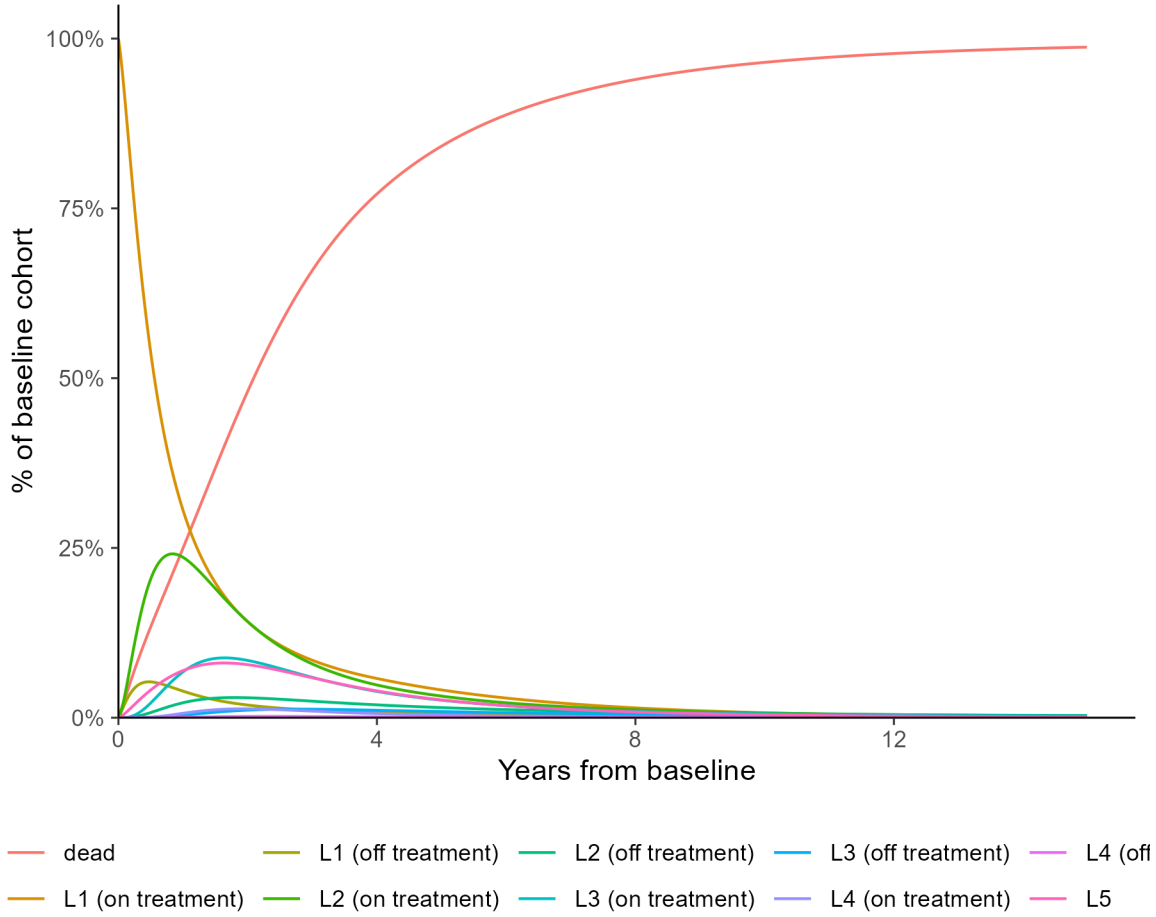
Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Figure 17: Markov trace: All risk, cabo+nivo – redacted model



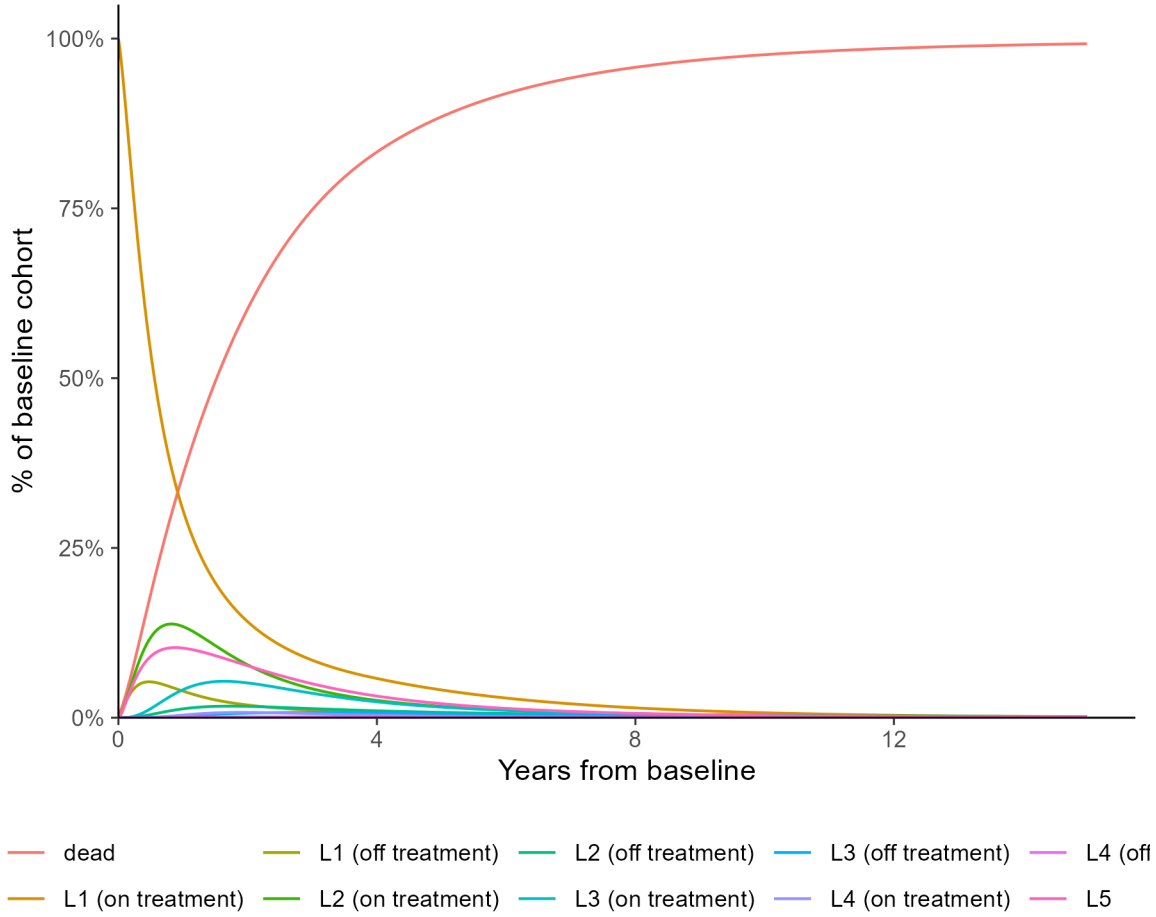
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 18: Markov trace: All risk, pazo – redacted model



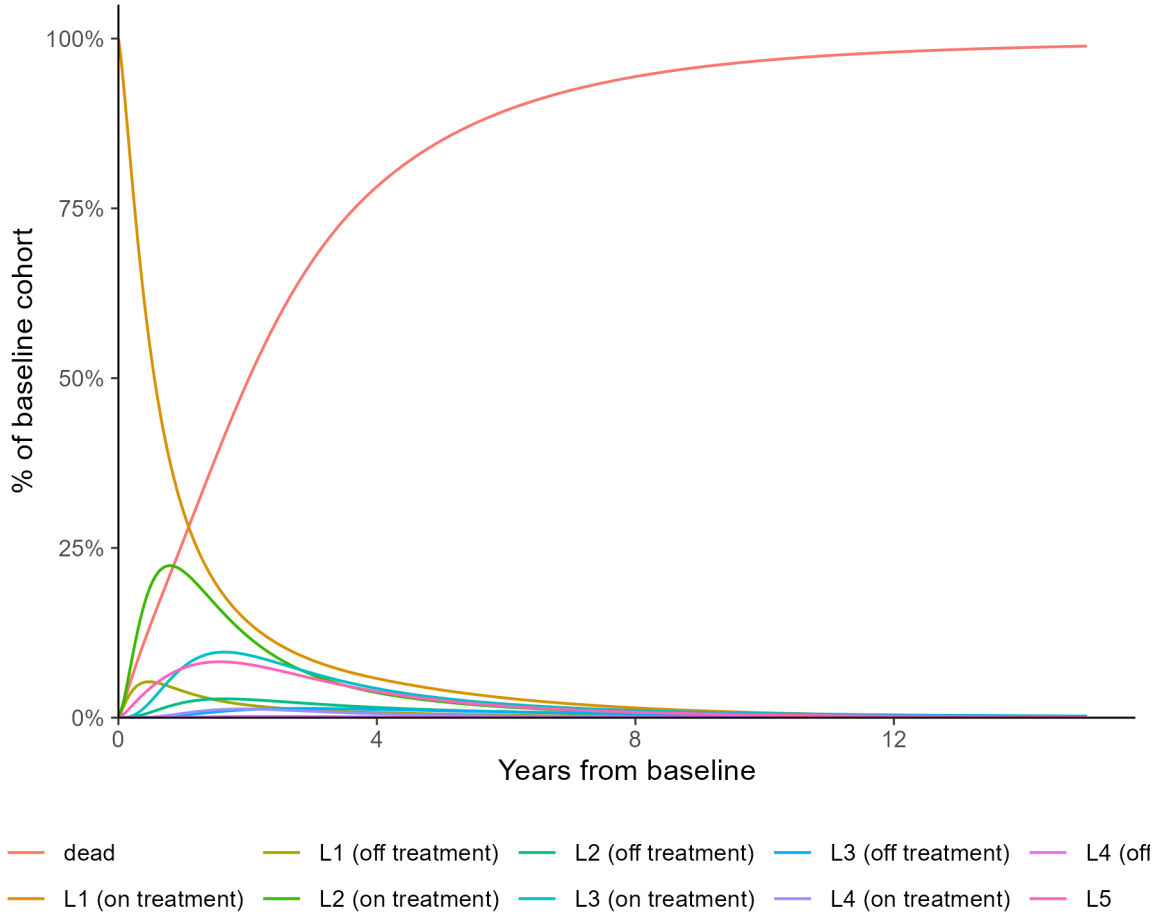
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 19: Markov trace: All risk, suni – redacted model



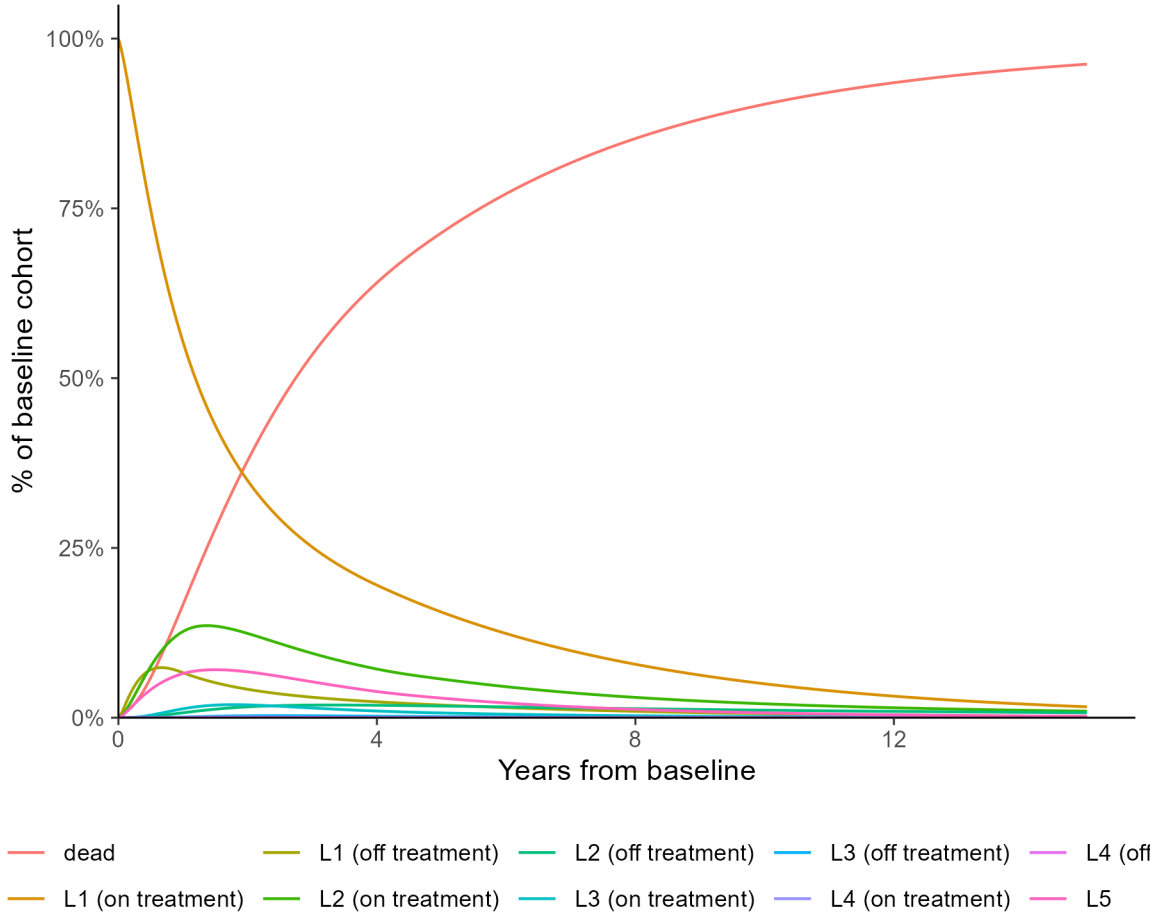
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 20: Markov trace: All risk, tivo – redacted model



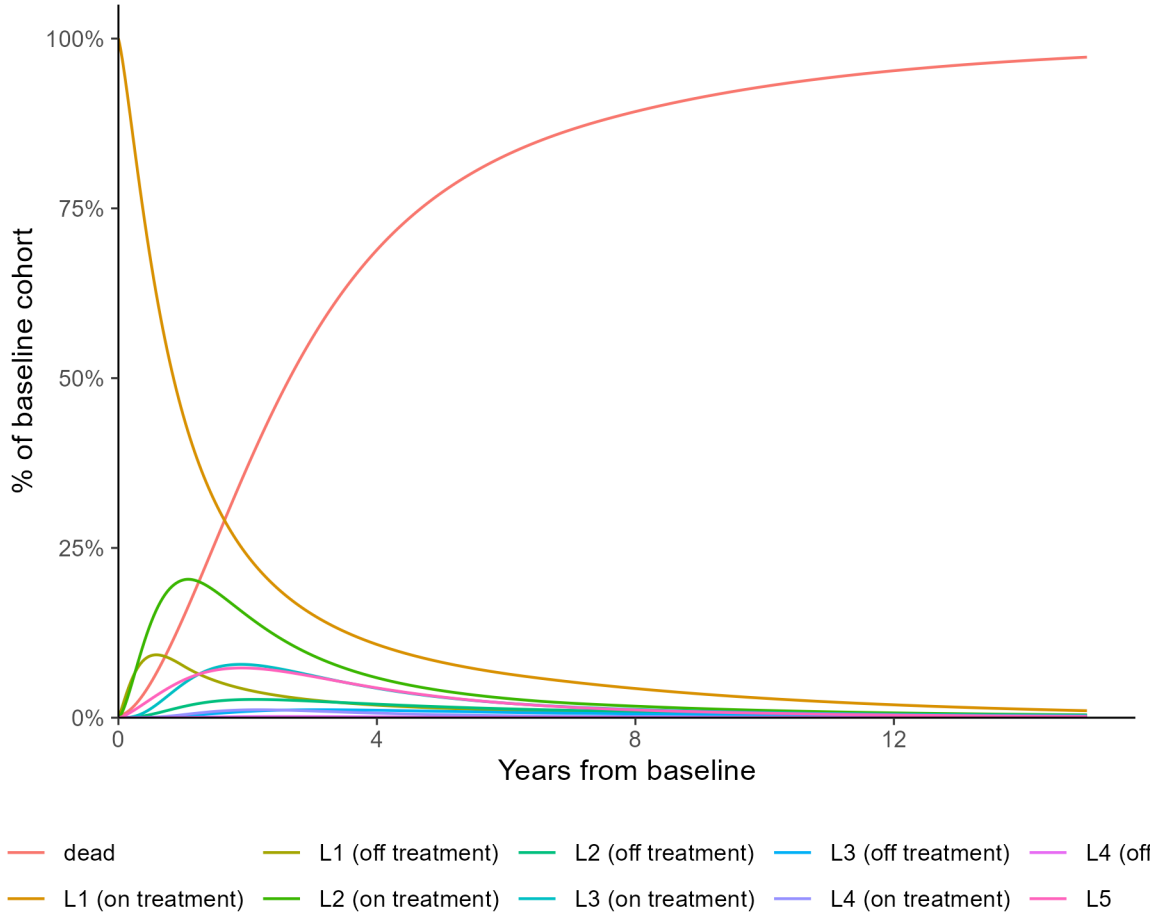
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 21: Markov trace: Favourable risk, cabo+nivo – redacted model



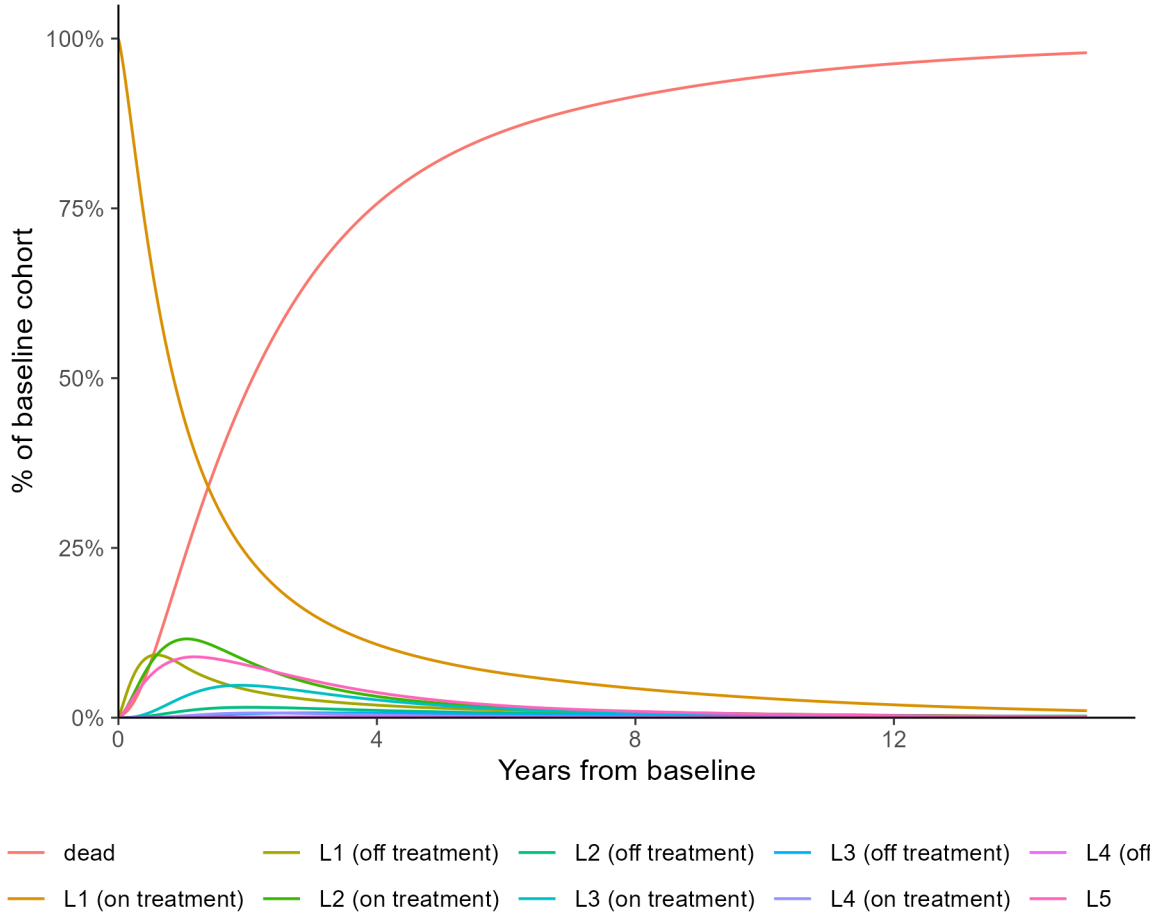
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 22: Markov trace: Favourable risk, pazo – redacted model



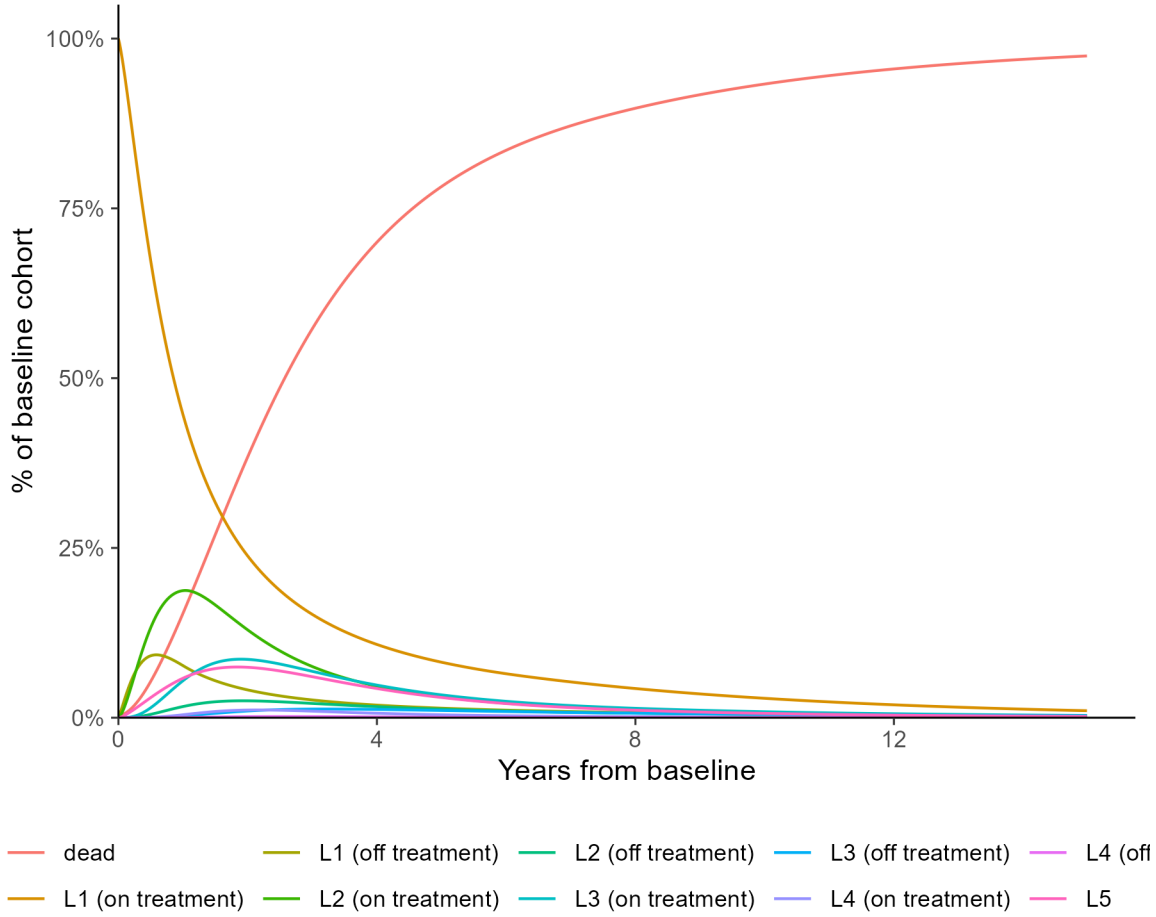
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 23: Markov trace: Favourable risk, suni – redacted model



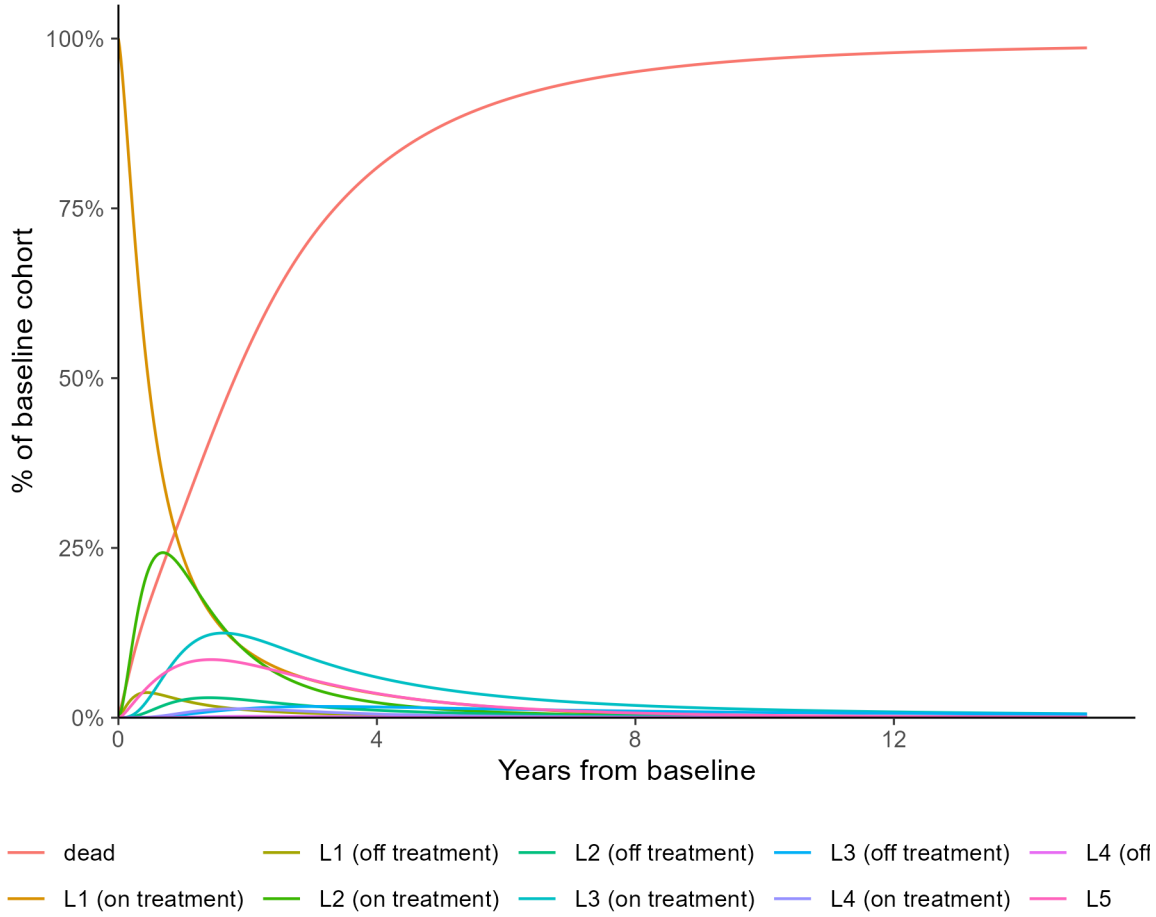
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 24: Markov trace: Favourable risk, tivo – redacted model



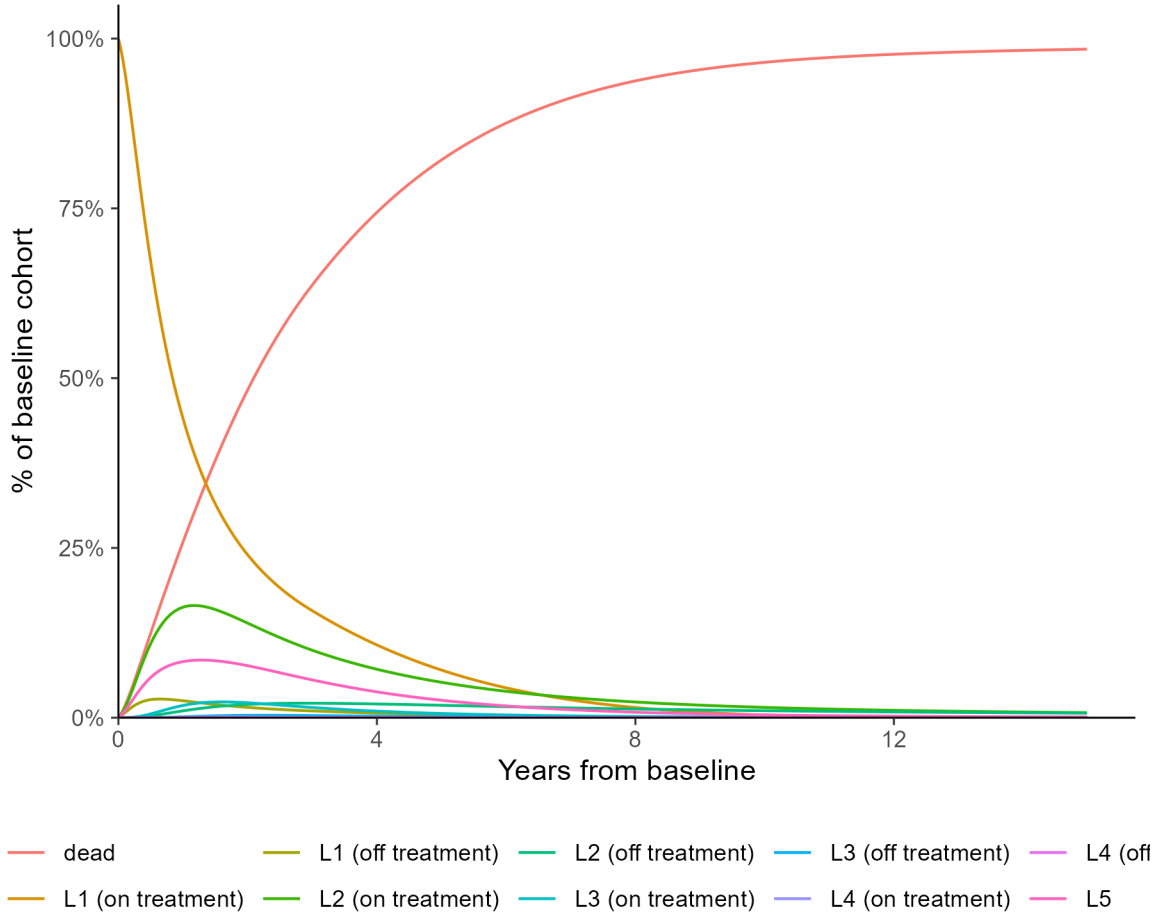
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 25: Markov trace: Intermediate / poor risk, cabo – redacted model



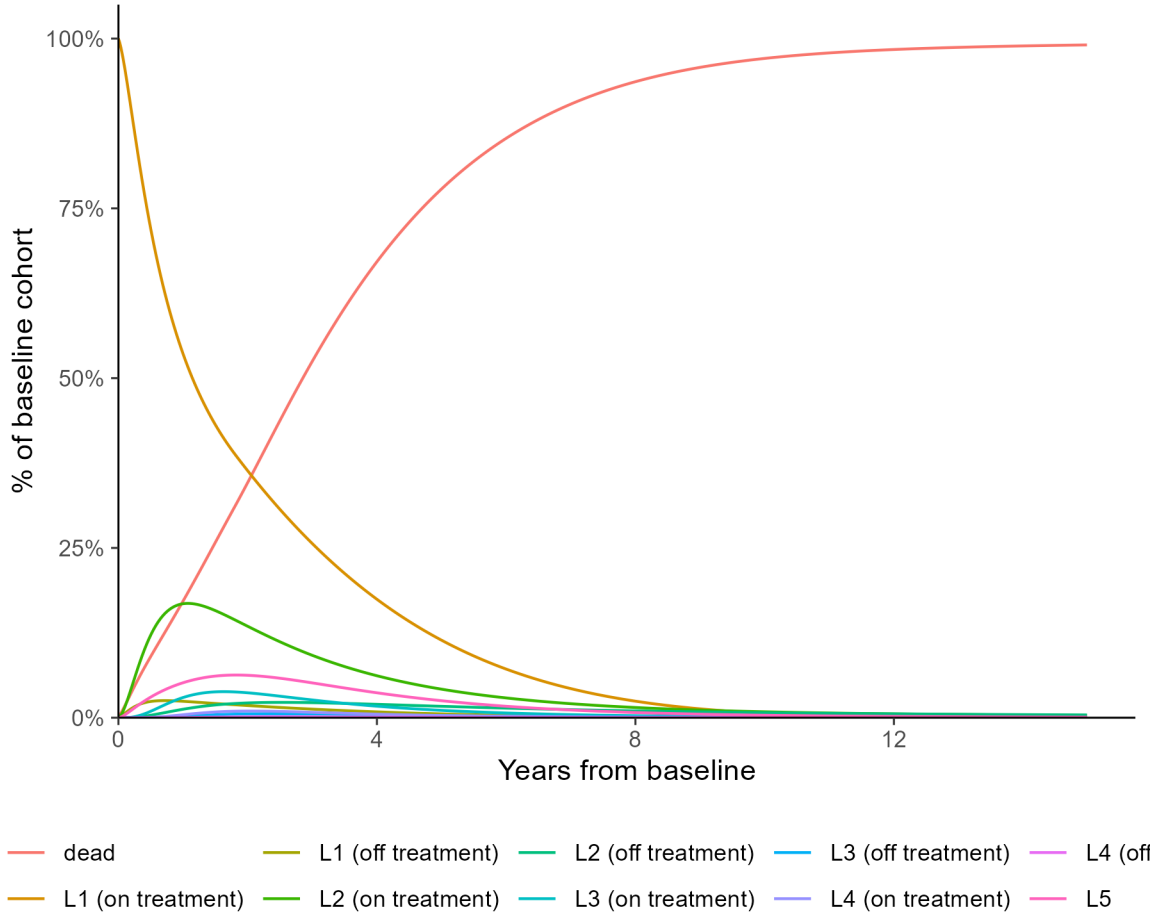
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 26: Markov trace: Intermediate / poor risk, cabo+nivo – redacted model



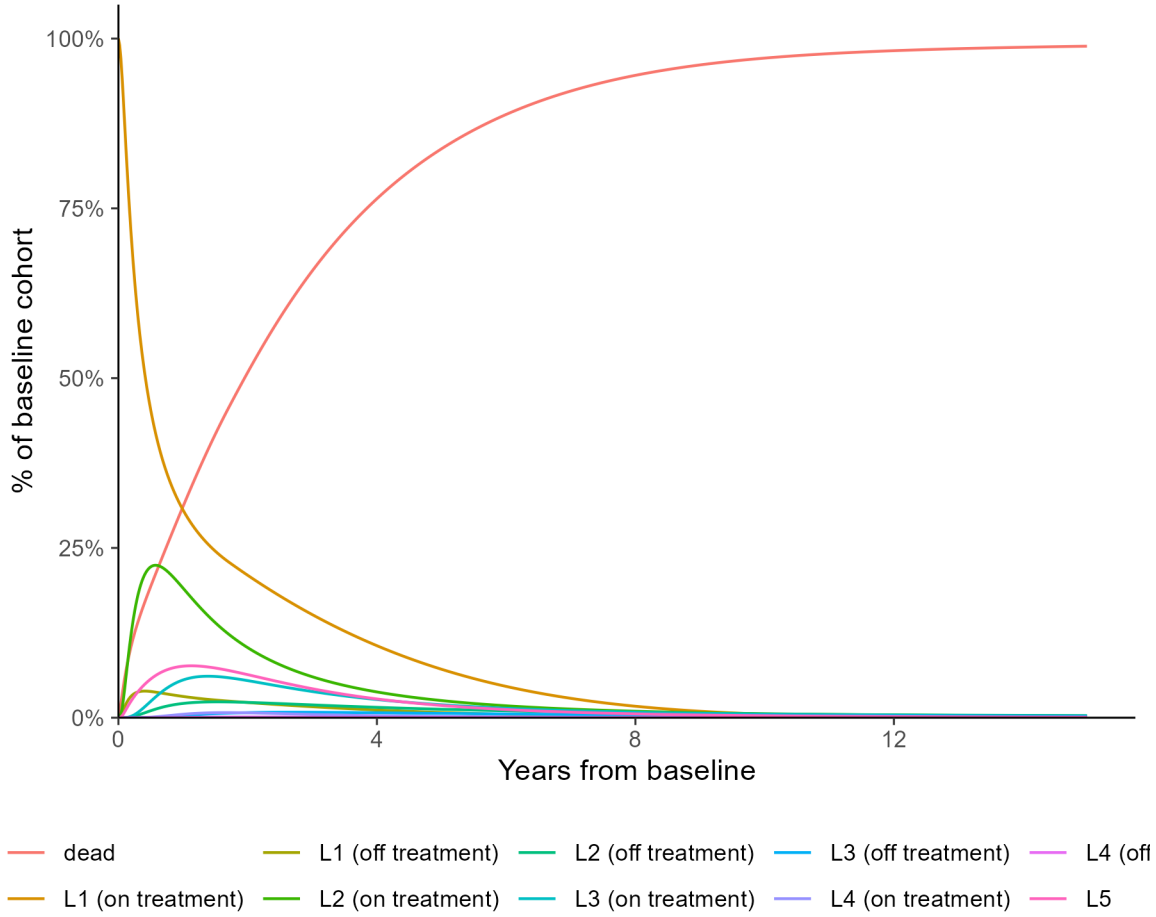
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 27: Markov trace: Intermediate / poor risk, pem+lenv – redacted model



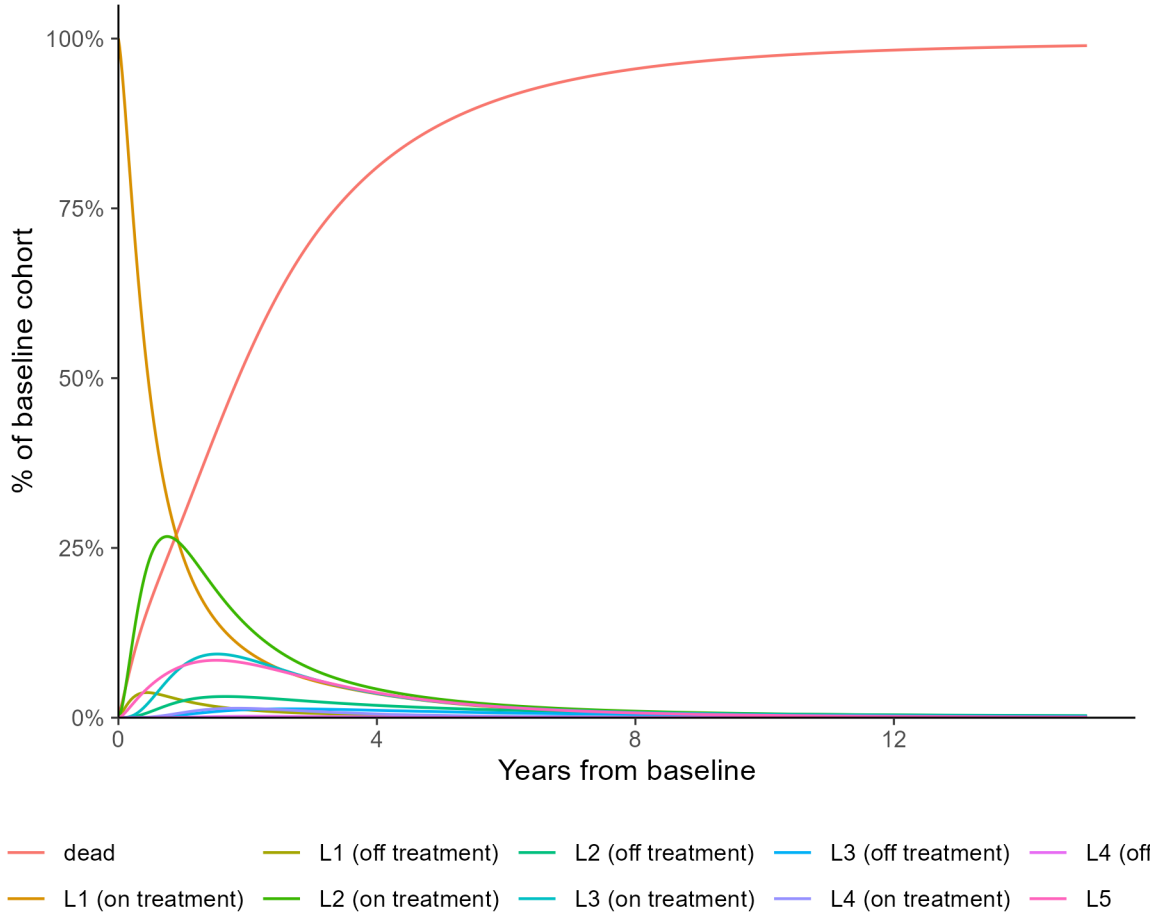
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 28: Markov trace: Intermediate / poor risk, nivo+ipi – redacted model



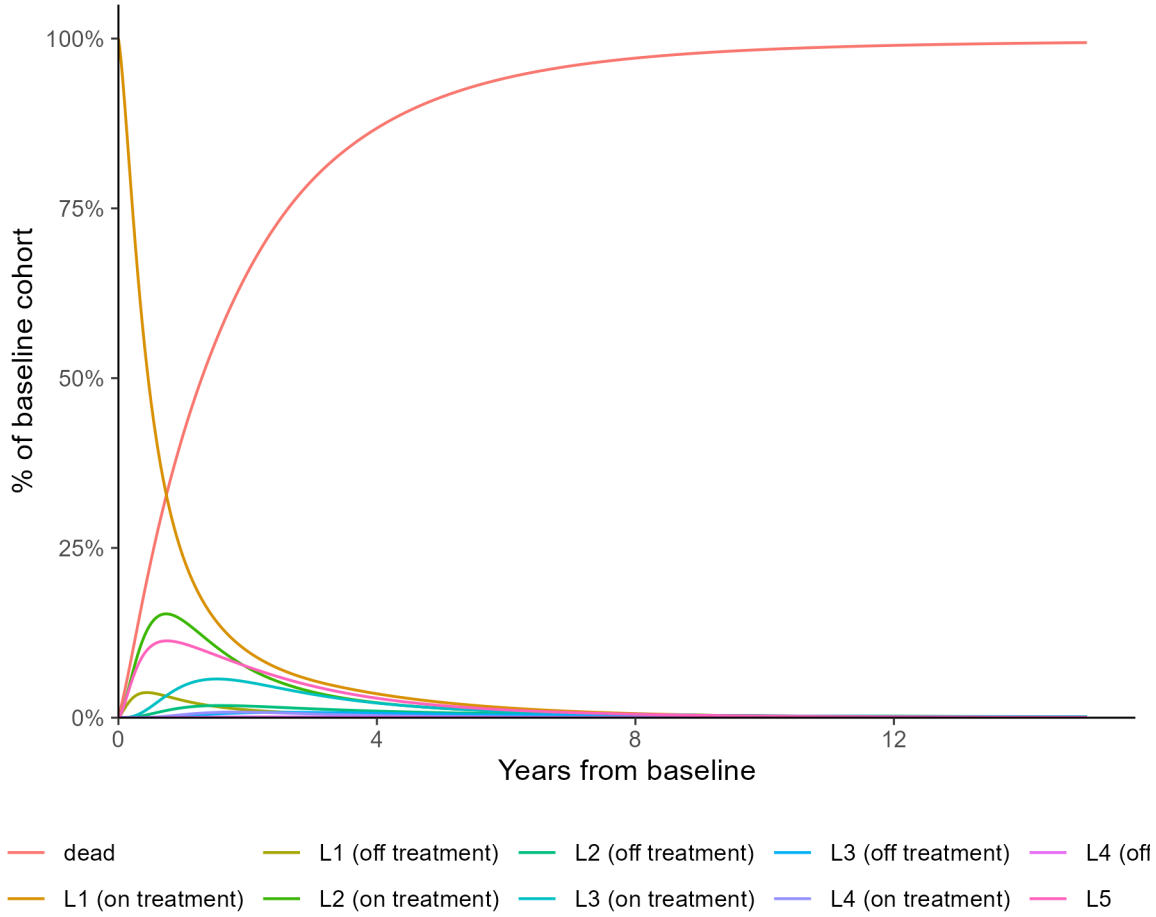
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 29: Markov trace: Intermediate / poor risk, pazo – redacted model



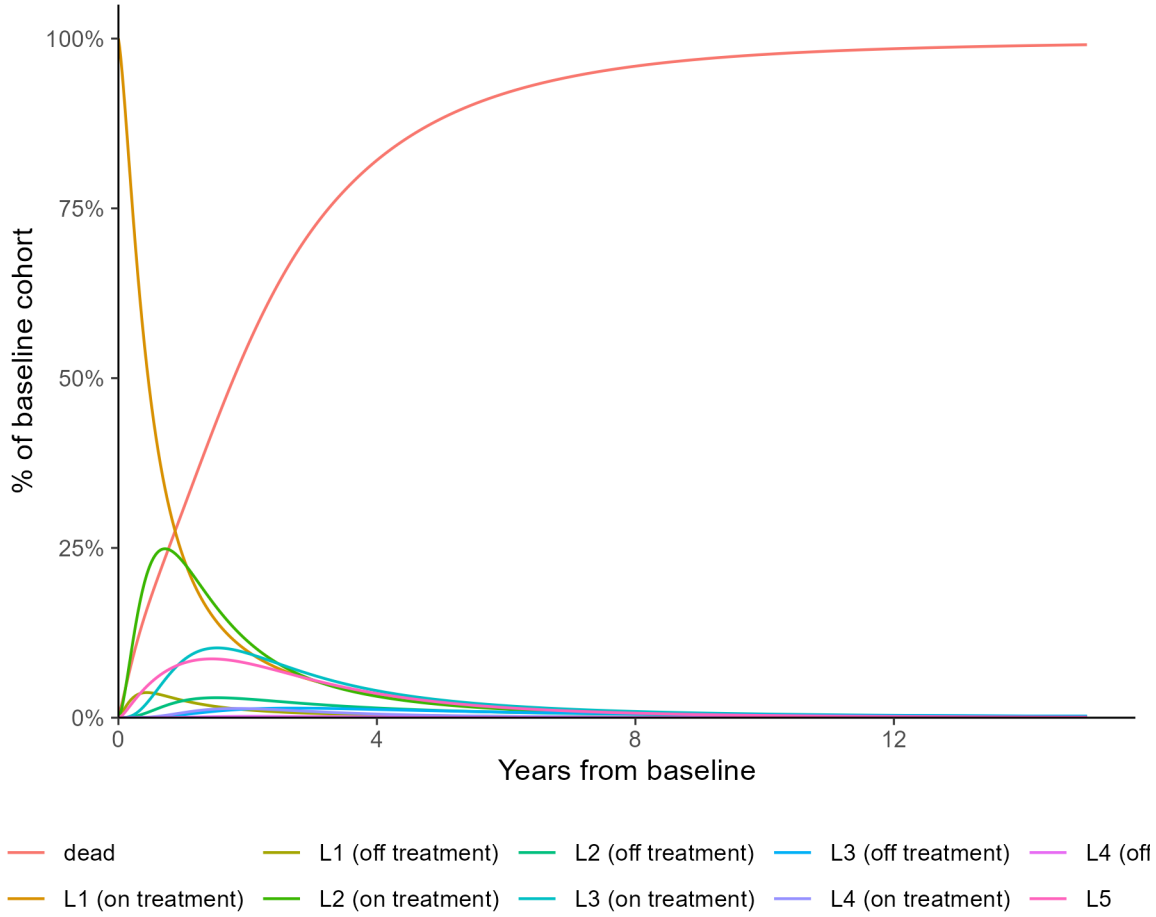
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 30: Markov trace: Intermediate / poor risk, suni – redacted model



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 31: Markov trace: Intermediate / poor risk, tivo – redacted model



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Pairwise comparisons – redacted model

Table 25: Base case pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,677	2.16	3.59	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,393	0.37	0.57	£247,445
Tivo	£90,595	1.75	2.91	£69,082	0.42	0.68	£164,742
Suni	£47,482	1.48	2.41	£112,196	0.68	1.18	£164,725
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.61	4.39	-	-	-	-
Pazo	£73,776	2.33	3.92	£97,295	0.28	0.47	£345,805
Tivo	£107,216	2.28	3.81	£63,854	0.33	0.58	£192,286
Suni	£51,161	2.01	3.29	£119,910	0.60	1.10	£200,753
Risk population: Intermediate / poor risk							
Cabo+nivo	£147,217	1.91	3.18	-	-	-	-
Nivo+ipi	£144,228	1.75	2.89	£2,989	0.16	0.29	£18,824
Pem+lenv	£211,372	2.19	3.54	£-64,155	-0.28	-0.36	SW quadrant £228,201
Pazo	£65,828	1.58	2.68	£81,389	0.32	0.50	£251,730
Tivo	£83,703	1.53	2.58	£63,514	0.37	0.61	£170,420
Suni	£45,851	1.28	2.09	£101,366	0.63	1.10	£160,495
Cabo	£96,630	1.58	2.75	£50,587	0.33	0.44	£154,786

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 26: Scenario analysis 1 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£150,422	2.16	3.35	-	-	-	-
Pazo	£66,441	1.83	2.90	£83,981	0.33	0.45	£257,368
Tivo	£92,446	1.84	2.90	£57,976	0.32	0.45	£182,284
Suni	£47,453	1.84	2.90	£102,968	0.32	0.45	£322,412
Risk population: Favourable risk							
Cabo+nivo	£162,118	2.70	4.41	-	-	-	-
Pazo	£71,605	2.91	4.90	£90,513	-0.21	-0.49	Cabo+nivo dominated
Tivo	£108,620	2.92	4.90	£53,498	-0.21	-0.49	Cabo+nivo dominated
Suni	£51,444	2.91	4.90	£110,674	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£138,084	1.91	2.95	-	-	-	-
Nivo+ipi	£139,620	1.88	2.92	£-1,536	0.03	0.03	Cabo+nivo dominant
Pem+lenv	£209,209	1.93	2.95	£-71,124	-0.02	-0.00	SW quadrant £3,463,069
Pazo	£64,599	1.47	2.28	£73,485	0.45	0.67	£164,306
Tivo	£86,228	1.47	2.28	£51,856	0.44	0.67	£118,130
Suni	£46,061	1.47	2.28	£92,023	0.44	0.67	£209,028
Cabo	£89,904	1.46	2.28	£48,180	0.45	0.67	£107,076

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 27: Scenario analysis 3 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£155,025	2.12	3.49	-	-	-	-
Pazo	£53,104	1.57	2.52	£101,921	0.56	0.97	£182,928
Tivo	£76,571	1.49	2.36	£78,455	0.63	1.13	£123,706
Suni	£38,682	1.34	2.11	£116,343	0.78	1.38	£149,292
Risk population: Favourable risk							
Cabo+nivo	£166,489	2.57	4.29	-	-	-	-
Pazo	£58,346	2.10	3.40	£108,143	0.47	0.89	£228,655
Tivo	£92,962	2.02	3.23	£73,527	0.55	1.06	£133,426
Suni	£42,217	1.87	2.98	£124,272	0.70	1.31	£178,023
Risk population: Intermediate / poor risk							
Cabo+nivo	£142,530	1.87	3.08	-	-	-	-
Nivo+ipi	£133,028	1.58	2.50	£9,502	0.29	0.58	£32,721
Pem+lenv	£204,101	2.10	3.33	£-61,572	-0.23	-0.25	SW quadrant £263,824
Pazo	£50,835	1.36	2.19	£91,695	0.51	0.89	£180,434
Tivo	£69,852	1.28	2.03	£72,677	0.58	1.05	£124,383
Suni	£37,160	1.14	1.79	£105,370	0.73	1.29	£144,774
Cabo	£68,225	1.21	1.91	£74,305	0.66	1.18	£113,253

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 28: Scenario analysis 11 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,979	2.29	3.83	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,695	0.50	0.81	£184,065
Tivo	£90,595	1.75	2.91	£69,385	0.55	0.92	£126,578
Suni	£47,482	1.48	2.41	£112,498	0.81	1.42	£138,898
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.61	4.39	-	-	-	-
Pazo	£73,776	2.33	3.92	£97,295	0.28	0.47	£345,805
Tivo	£107,216	2.28	3.81	£63,854	0.33	0.58	£192,286
Suni	£51,161	2.01	3.29	£119,910	0.60	1.10	£200,753
Risk population: Intermediate / poor risk							
Cabo+nivo	£150,794	2.10	3.53	-	-	-	-
Nivo+ipi	£156,175	1.93	3.26	£-5,381	0.17	0.27	Cabo+nivo dominant
Pem+lenv	£221,828	2.44	4.01	£-71,034	-0.33	-0.48	SW quadrant £214,392
Pazo	£65,828	1.58	2.68	£84,966	0.52	0.85	£163,295
Tivo	£83,703	1.53	2.58	£67,091	0.57	0.95	£117,767
Suni	£45,851	1.28	2.09	£104,944	0.83	1.44	£126,653
Cabo	£96,630	1.58	2.75	£54,164	0.52	0.78	£103,401

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 29: Scenario analysis 21 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£151,150	2.38	3.76	-	-	-	-
Pazo	£66,441	1.83	2.90	£84,709	0.54	0.86	£156,171
Tivo	£92,446	1.84	2.90	£58,704	0.53	0.86	£109,900
Suni	£47,453	1.84	2.90	£103,697	0.54	0.86	£193,653
Risk population: Favourable risk							
Cabo+nivo	£162,118	2.70	4.41	-	-	-	-
Pazo	£71,605	2.91	4.90	£90,513	-0.21	-0.49	Cabo+nivo dominated
Tivo	£108,620	2.92	4.90	£53,498	-0.21	-0.49	Cabo+nivo dominated
Suni	£51,444	2.91	4.90	£110,674	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£142,993	2.18	3.47	-	-	-	-
Nivo+ipi	£146,236	2.09	3.33	£-3,243	0.09	0.13	Cabo+nivo dominant
Pem+lenv	£218,367	2.20	3.47	£-75,374	-0.02	0.00	SW quadrant £3,809,611
Pazo	£64,599	1.47	2.28	£78,394	0.71	1.19	£109,826
Tivo	£86,228	1.47	2.28	£56,764	0.71	1.19	£80,457
Suni	£46,061	1.47	2.28	£96,932	0.71	1.19	£137,142
Cabo	£89,904	1.46	2.28	£53,088	0.72	1.19	£74,093

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 30: Scenario analysis 41 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£178,450	2.16	3.59	-	-	-	-
Pazo	£73,286	1.80	3.02	£105,164	0.37	0.57	£284,731
Tivo	£95,839	1.75	2.91	£82,612	0.42	0.68	£197,005
Suni	£50,611	1.48	2.41	£127,839	0.68	1.18	£187,693
Risk population: Favourable risk							
Cabo+nivo	£193,138	2.61	4.39	-	-	-	-
Pazo	£79,403	2.33	3.92	£113,735	0.28	0.47	£404,239
Tivo	£113,446	2.28	3.81	£79,692	0.33	0.58	£239,979
Suni	£54,780	2.01	3.29	£138,358	0.60	1.10	£231,639
Risk population: Intermediate / poor risk							
Cabo+nivo	£163,360	1.91	3.18	-	-	-	-
Nivo+ipi	£157,228	1.75	2.89	£6,132	0.16	0.29	£38,621
Pem+lenv	£230,113	2.19	3.54	£-66,752	-0.28	-0.36	SW quadrant £237,439
Pazo	£70,558	1.58	2.68	£92,803	0.32	0.50	£287,031
Tivo	£88,535	1.53	2.58	£74,825	0.37	0.61	£200,772
Suni	£48,772	1.28	2.09	£114,589	0.63	1.10	£181,430
Cabo	£101,350	1.58	2.75	£62,010	0.33	0.44	£189,739

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 31: Scenario analysis 73 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,677	2.16	3.59	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,393	0.37	0.57	£247,445
Tivo	£90,595	1.75	2.91	£69,082	0.42	0.68	£164,742
Suni	£47,482	1.48	2.41	£112,196	0.68	1.18	£164,725
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.61	4.39	-	-	-	-
Pazo	£73,776	2.33	3.92	£97,295	0.28	0.47	£345,805
Tivo	£107,216	2.28	3.81	£63,854	0.33	0.58	£192,286
Suni	£51,161	2.01	3.29	£119,910	0.60	1.10	£200,753
Risk population: Intermediate / poor risk							
Cabo+nivo	£151,198	1.98	3.30	-	-	-	-
Nivo+ipi	£163,152	1.95	3.21	£-11,954	0.03	0.10	Cabo+nivo dominant
Pem+lenv	£211,372	2.19	3.54	£-60,175	-0.21	-0.23	SW quadrant £293,239
Pazo	£65,828	1.58	2.68	£85,370	0.40	0.62	£213,827
Tivo	£83,703	1.53	2.58	£67,494	0.45	0.73	£150,450
Suni	£45,851	1.28	2.09	£105,347	0.71	1.22	£148,897
Cabo	£96,630	1.58	2.75	£54,567	0.40	0.56	£135,488

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 32: Scenario analysis 74 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,979	2.29	3.83	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,695	0.50	0.81	£184,065
Tivo	£90,595	1.75	2.91	£69,385	0.55	0.92	£126578
Suni	£47,482	1.48	2.41	£112,498	0.81	1.42	£138898
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.61	4.39	-	-	-	-
Pazo	£73,776	2.33	3.92	£97,295	0.28	0.47	£345,805
Tivo	£107,216	2.28	3.81	£63,854	0.33	0.58	£192,286
Suni	£51,161	2.01	3.29	£119,910	0.60	1.10	£200,753
Risk population: Intermediate / poor risk							
Cabo+nivo	£150,794	2.10	3.53	-	-	-	-
Nivo+ipi	£143,175	1.54	2.53	£7,619	0.57	1.00	£13,463
Pem+lenv	£221,828	2.44	4.01	£-71,034	-0.33	-0.48	SW quadrant £214,392
Pazo	£65,828	1.58	2.68	£84,966	0.52	0.85	£163,295
Tivo	£83,703	1.53	2.58	£67,091	0.57	0.95	£117,767
Suni	£45,851	1.28	2.09	£104,944	0.83	1.44	£126,653
Cabo	£96,630	1.58	2.75	£54,164	0.52	0.78	£103,401

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 33: Scenario analysis 80 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
Cabo+nivo	£168,862	2.26	3.72	-	-	-	-
Pazo	£59,099	1.56	2.51	£109,763	0.70	1.21	£156,498
Tivo	£84,646	1.48	2.35	£84,216	0.78	1.37	£108,115
Suni	£42,042	1.34	2.10	£126,820	0.92	1.62	£137,371
Risk population: Favourable risk							
Cabo+nivo	£183,022	2.50	4.15	-	-	-	-
Pazo	£64,711	2.01	3.25	£118,312	0.49	0.90	£240,758
Tivo	£101,661	1.93	3.08	£81,361	0.57	1.07	£142,496
Suni	£45,734	1.79	2.82	£137,288	0.72	1.33	£191,040
Risk population: Intermediate / poor risk							
Cabo+nivo	£158,088	2.08	3.43	-	-	-	-
Nivo+ipi	£142,501	1.58	2.50	£15,587	0.50	0.93	£30,916
Pem+lenv	£222,893	2.35	3.79	£-64,805	-0.27	-0.36	SW quadrant £238,399
Pazo	£56,538	1.36	2.19	£101,550	0.72	1.24	£140,445
Tivo	£76,958	1.28	2.03	£81,130	0.80	1.40	£101,456
Suni	£40,357	1.14	1.79	£117,731	0.94	1.64	£124,950
Cabo	£76,050	1.21	1.90	£82,038	0.87	1.53	£94,090

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 34: Scenario analysis 85 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
Cabo+nivo	£149,434	2.40	3.76	-	-	-	-
Pazo	£53,315	1.84	2.90	£96,119	0.55	0.86	£173,670
Tivo	£81,224	1.85	2.90	£68,210	0.55	0.86	£124,915
Suni	£39,502	1.85	2.90	£109,932	0.55	0.86	£199,723
Risk population: Favourable risk							
Cabo+nivo	£163,118	2.72	4.41	-	-	-	-
Pazo	£58,840	2.92	4.90	£104,279	-0.19	-0.49	Cabo+nivo dominated
Tivo	£97,977	2.92	4.90	£65,141	-0.20	-0.49	Cabo+nivo dominated
Suni	£43,705	2.92	4.90	£119,413	-0.20	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£139,730	2.20	3.47	-	-	-	-
Nivo+ipi	£138,562	1.89	2.92	£1,168	0.31	0.55	£3,803
Pem+lenv	£215,781	2.22	3.47	£-76,051	-0.02	-0.00	SW quadrant £3,719,115
Pazo	£51,134	1.48	2.28	£88,596	0.72	1.19	£122,234
Tivo	£73,996	1.48	2.28	£65,734	0.72	1.19	£91,630
Suni	£37,914	1.48	2.28	£101,816	0.72	1.19	£141,068
Cabo	£75,127	1.48	2.28	£64,603	0.72	1.19	£89,144

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 35: Scenario analysis 87 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,677	2.16	3.59	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,393	0.37	0.57	£247,445
Tivo	£90,595	1.75	2.91	£69,082	0.42	0.68	£164,742
Suni	£47,482	1.48	2.41	£112,196	0.68	1.18	£164,725
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.61	4.39	-	-	-	-
Pazo	£73,776	2.33	3.92	£97,295	0.28	0.47	£345,805
Tivo	£107,216	2.28	3.81	£63,854	0.33	0.58	£192,286
Suni	£51,161	2.01	3.29	£119,910	0.60	1.10	£200,753
Risk population: Intermediate / poor risk							
Cabo+nivo	£147,217	1.91	3.18	-	-	-	-
Nivo+ipi	£144,228	1.75	2.89	£2,989	0.16	0.29	£18,824
Pem+lenv	£224,949	2.19	3.54	£-77,732	-0.28	-0.36	SW quadrant £276,493
Pazo	£65,828	1.58	2.68	£81,389	0.32	0.50	£251,730
Tivo	£83,703	1.53	2.58	£63,514	0.37	0.61	£170,420
Suni	£45,851	1.28	2.09	£101,366	0.63	1.10	£160,495
Cabo	£96,630	1.58	2.75	£50,587	0.33	0.44	£154,786

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 36: Scenario analysis 88 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,677	2.16	3.59	-	-	-	-
Pazo	£68,284	1.80	3.02	£91,393	0.37	0.57	£247,445
Tivo	£90,595	1.75	2.91	£69,082	0.42	0.68	£164,742
Suni	£47,482	1.48	2.41	£112,196	0.68	1.18	£164,725
Risk population: Favourable risk							
Cabo+nivo	£183,175	2.77	4.61	-	-	-	-
Pazo	£73,776	2.33	3.92	£109,400	0.44	0.69	£248,222
Tivo	£107,216	2.28	3.81	£75,960	0.49	0.80	£154,560
Suni	£51,161	2.01	3.29	£132,015	0.76	1.32	£174,466
Risk population: Intermediate / poor risk							
Cabo+nivo	£147,217	1.91	3.18	-	-	-	-
Nivo+ipi	£144,228	1.75	2.89	£2,989	0.16	0.29	£18,824
Pem+lenv	£211,372	2.19	3.54	£-64,155	-0.28	-0.36	SW quadrant £228,201
Pazo	£65,828	1.58	2.68	£81,389	0.32	0.50	£251,730
Tivo	£83,703	1.53	2.58	£63,514	0.37	0.61	£170,420
Suni	£45,851	1.28	2.09	£101,366	0.63	1.10	£160,495
Cabo	£96,630	1.58	2.75	£50,587	0.33	0.44	£154,786

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 37: Scenario analysis 89 pairwise comparison table – redacted model

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£159,677	2.29	3.59	-	-	-	-
Pazo	£68,284	1.87	3.02	£91,393	0.42	0.57	£219,881
Tivo	£90,595	1.82	2.91	£69,082	0.47	0.68	£148,361
Suni	£47,482	1.56	2.41	£112,196	0.73	1.18	£154,240
Risk population: Favourable risk							
Cabo+nivo	£171,070	2.80	4.39	-	-	-	-
Pazo	£73,776	2.47	3.92	£97,295	0.33	0.47	£296,077
Tivo	£107,216	2.42	3.81	£63,854	0.38	0.58	£168,332
Suni	£51,161	2.15	3.29	£119,910	0.64	1.10	£186,034
Risk population: Intermediate / poor risk							
Cabo+nivo	£147,217	2.00	3.18	-	-	-	-
Nivo+ipi	£144,228	1.83	2.89	£2,989	0.17	0.29	£17,435
Pem+lenv	£211,372	2.31	3.54	£-64,155	-0.31	-0.36	SW quadrant £208,024
Pazo	£65,828	1.64	2.68	£81,389	0.36	0.50	£225,071
Tivo	£83,703	1.59	2.58	£63,514	0.41	0.61	£154,541
Suni	£45,851	1.33	2.09	£101,366	0.67	1.10	£151,320
Cabo	£96,630	1.64	2.75	£50,587	0.37	0.44	£138,551

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

6. APPENDIX B: EAG BASE CASE DETAILED RESULTS – LIST PRICE

Table 38: Summary of LY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.109	0.115	-0.006	0.006	0%
1L: on treatment	1.945	1.144	0.801	0.801	50%
2L: off treatment	0.288	0.158	0.130	0.130	8%
2L: on treatment	0.843	0.541	0.302	0.302	19%
3L: off treatment	0.026	0.109	-0.083	0.083	5%
3L: on treatment	0.142	0.365	-0.223	0.223	14%
4L: off treatment	0.001	0.009	-0.007	0.007	0%
4L: on treatment	0.007	0.054	-0.048	0.048	3%
BSC	0.353	0.341	0.011	0.011	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.715**	**2.837**	**0.878**	**1.611**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 39: Summary of LY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.274	0.266	0.008	0.008	1%
1L: on treatment	2.582	1.828	0.753	0.753	49%
2L: off treatment	0.288	0.164	0.124	0.124	8%
2L: on treatment	0.844	0.562	0.282	0.282	18%
3L: off treatment	0.026	0.113	-0.087	0.087	6%
3L: on treatment	0.142	0.379	-0.237	0.237	15%
4L: off treatment	0.001	0.009	-0.008	0.008	1%
4L: on treatment	0.007	0.056	-0.050	0.050	3%
BSC	0.353	0.355	-0.001	0.001	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**4.517**	**3.733**	**0.784**	**1.549**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 40: Summary of LY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.076	0.069	0.006	0.006	0%
1L: on treatment	1.572	0.887	0.685	0.685	46%
2L: off treatment	0.287	0.155	0.132	0.132	9%
2L: on treatment	0.840	0.530	0.310	0.310	21%
3L: off treatment	0.026	0.107	-0.081	0.081	5%
3L: on treatment	0.142	0.358	-0.216	0.216	14%
4L: off treatment	0.001	0.008	-0.007	0.007	0%
4L: on treatment	0.007	0.053	-0.046	0.046	3%
BSC	0.352	0.334	0.017	0.017	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.302**	**2.501**	**0.801**	**1.502**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 41: Summary of QALY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.074	0.079	-0.005	0.005	1%
1L: on treatment	1.315	0.790	0.525	0.525	59%
2L: off treatment	0.130	0.082	0.048	0.048	5%
2L: on treatment	0.455	0.322	0.134	0.134	15%
3L: off treatment	0.013	0.048	-0.035	0.035	4%
3L: on treatment	0.064	0.185	-0.121	0.121	14%
4L: off treatment	0.001	0.004	-0.003	0.003	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.166	0.164	0.003	0.003	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.223**	**1.695**	**0.528**	**0.892**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 42: Summary of QALY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.177	0.175	0.002	0.002	0%
1L: on treatment	1.670	1.214	0.456	0.456	56%
2L: off treatment	0.128	0.083	0.045	0.045	6%
2L: on treatment	0.448	0.326	0.122	0.122	15%
3L: off treatment	0.013	0.049	-0.036	0.036	4%
3L: on treatment	0.063	0.187	-0.125	0.125	15%
4L: off treatment	0.001	0.004	-0.004	0.004	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.164	0.166	-0.002	0.002	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.666**	**2.226**	**0.440**	**0.809**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 43: Summary of QALY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pazo)

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.052	0.048	0.004	0.004	0%
1L: on treatment	1.073	0.620	0.453	0.453	55%
2L: off treatment	0.131	0.081	0.050	0.050	6%
2L: on treatment	0.460	0.318	0.142	0.142	17%
3L: off treatment	0.014	0.048	-0.034	0.034	4%
3L: on treatment	0.065	0.183	-0.118	0.118	14%
4L: off treatment	0.001	0.004	-0.003	0.003	0%
4L: on treatment	0.003	0.020	-0.017	0.017	2%
BSC	0.168	0.162	0.006	0.006	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**1.967**	**1.485**	**0.481**	**0.828**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 44: Summary of costs by health state

	1L costs			Subsequent treatment			MRU			
Technologies	**Drug cost**	**Admin cost**	**AE cost**	**Drug cost**	**Admin cost**	**AE cost**	**1L**	**Subsequent treatment**	**EOL cost**	**Total cost**
Risk population: All risk										
Suni	£3,690	£275	£604	£45,047	£906	£692	£2,628	£14,362	£7,962	£76,166
Pazo	£6,481	£324	£512	£46,503	£893	£688	£2,628	£14,422	£7,949	£80,399
Tivo	£27,787	£336	£408	£44,922	£971	£660	£2,628	£14,328	£7,966	£100,005
Cabo+nivo	£158,898	£3,242	£1,127	£35,969	£271	£920	£4,088	£12,897	£7,732	£225,144
Risk population: Favourable risk										
Suni	£5,579	£320	£604	£45,797	£921	£704	£4,058	£14,602	£7,743	£80,328
Pazo	£9,859	£395	£512	£47,276	£908	£699	£4,058	£14,662	£7,730	£86,100
Tivo	£42,269	£413	£408	£45,670	£987	£671	£4,058	£14,567	£7,747	£116,790
Cabo+nivo	£185,764	£3,445	£1,127	£35,434	£267	£907	£5,354	£12,707	£7,549	£252,553
Risk population: Intermediate / poor risk										
Suni	£2,938	£258	£604	£44,491	£895	£684	£2,080	£14,185	£8,048	£74,181
Pazo	£5,137	£296	£512	£45,929	£882	£679	£2,080	£14,244	£8,035	£77,793
Tivo	£22,024	£305	£408	£44,367	£959	£652	£2,080	£14,151	£8,052	£92,997
Cabo	£48,330	£292	£732	£46,183	£1,073	£698	£2,080	£14,314	£8,024	£121,724
Nivo+ipi	£101,372	£4,025	£335	£30,114	£229	£634	£2,931	£11,366	£7,981	£158,987

	1L costs			Subsequent treatment			MRU			
Technologies	**Drug cost**	**Admin cost**	**AE cost**	**Drug cost**	**Admin cost**	**AE cost**	**1L**	**Subsequent treatment**	**EOL cost**	**Total cost**
Cabo+nivo	£136,260	£2,923	£1,127	£36,244	£273	£927	£3,368	£12,995	£7,836	£201,953
Pem+lenv	£166,122	£2,869	£1,062	£27,872	£219	£702	£4,106	£11,103	£7,835	£221,891

Abbreviations: 1L, 1st line; admin, administration; AE, adverse event; cabo, cabozantinib; EOL, end of life; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; MRU, medical resource use; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib; TKI, tyrosine kinase inhibitor

Table 45: Summary of predicted resource use by category of cost (all risk, cabo+nivo vs next best non-dominated comparator: pazo)

Item	Cost cabo+nivo (X)	Cost pazo (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£158,898	£6,481	£152,417	£152,417	89%
Admin cost (1L)	£3,242	£324	£2,918	£2,918	2%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition cost (2L+)	£35,969	£46,503	£-10,534	£10,534	6%
Admin cost (2L+)	£271	£893	£-622	£622	0%
AE cost (2L+)	£920	£688	£233	£233	0%
MRU 1L	£4,088	£2,628	£1,460	£1,460	1%
MRU 2L+	£12,897	£14,422	£-1,525	£1,525	1%
EOL	£7,732	£7,949	£-217	£217	0%
Total	**£225,144**	**£80,399**	**£144,745**	**£170,541**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Table 46: Summary of predicted resource use by category of cost (favourable risk, cabo+nivo vs next best non-dominated comparator: pazo)

Item	Cost cabo+nivo (X)	Cost pazo (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£185,764	£9,859	£175,905	£175,905	90%
Admin cost (1L)	£3,445	£395	£3,050	£3,050	2%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition cost (2L+)	£35,434	£47,276	£-11,842	£11,842	6%
Admin cost (2L+)	£267	£908	£-641	£641	0%
AE cost (2L+)	£907	£699	£208	£208	0%
MRU 1L	£5,354	£4,058	£1,296	£1,296	1%
MRU 2L+	£12,707	£14,662	£-1,956	£1,956	1%
EOL	£7,549	£7,730	£-181	£181	0%
Total	**£252,553**	**£86,100**	**£166,454**	**£195,693**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

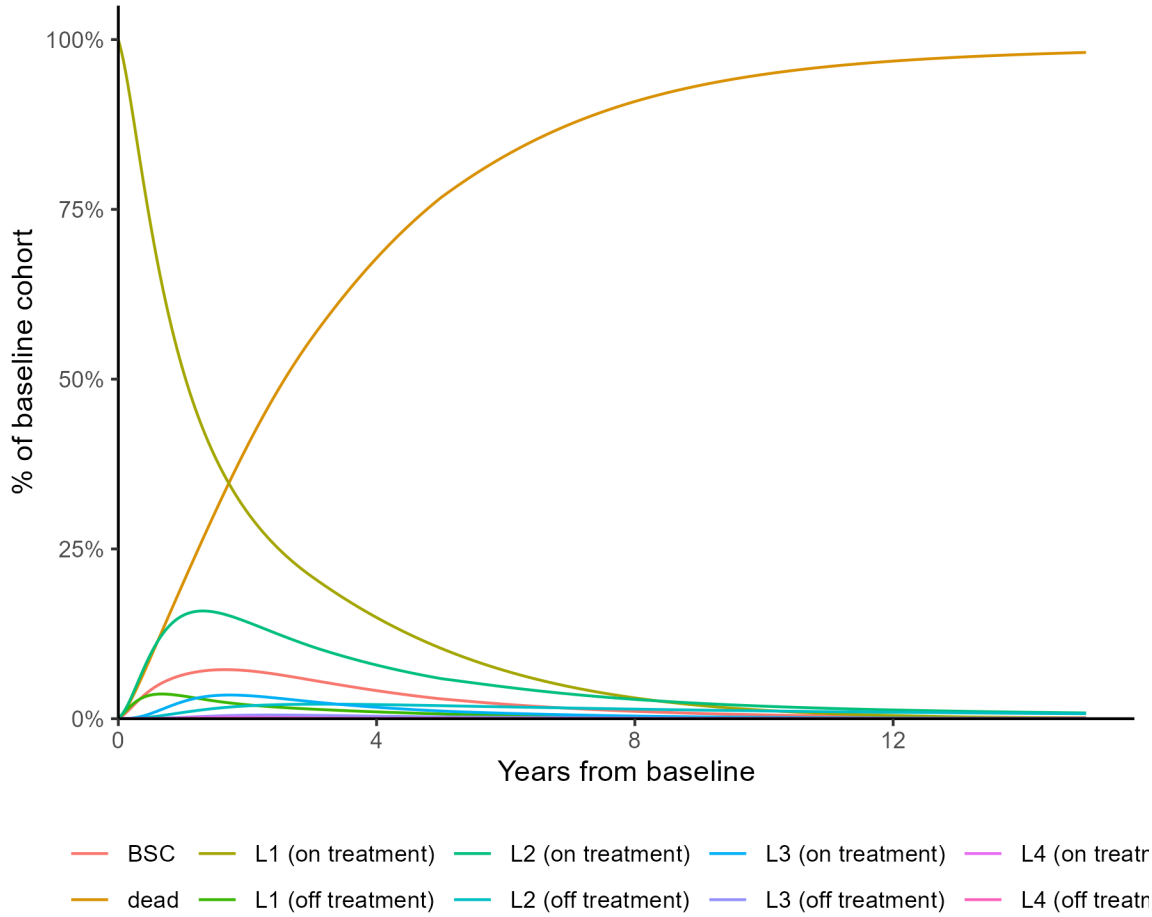
Table 47: Summary of predicted resource use by category of cost (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: pazo)

Item	Cost cabo+nivo (X)	Cost pazo (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£136,260	£5,137	£131,123	£131,123	89%
Admin cost (1L)	£2,923	£296	£2,627	£2,627	2%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition cost (2L+)	£36,244	£45,929	£-9,684	£9,684	7%
Admin cost (2L+)	£273	£882	£-609	£609	0%
AE cost (2L+)	£927	£679	£248	£248	0%
MRU 1L	£3,368	£2,080	£1,288	£1,288	1%
MRU 2L+	£12,995	£14,244	£-1,249	£1,249	1%
EOL	£7,836	£8,035	£-199	£199	0%
Total	**£201,953**	**£77,793**	**£124,160**	**£147,643**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

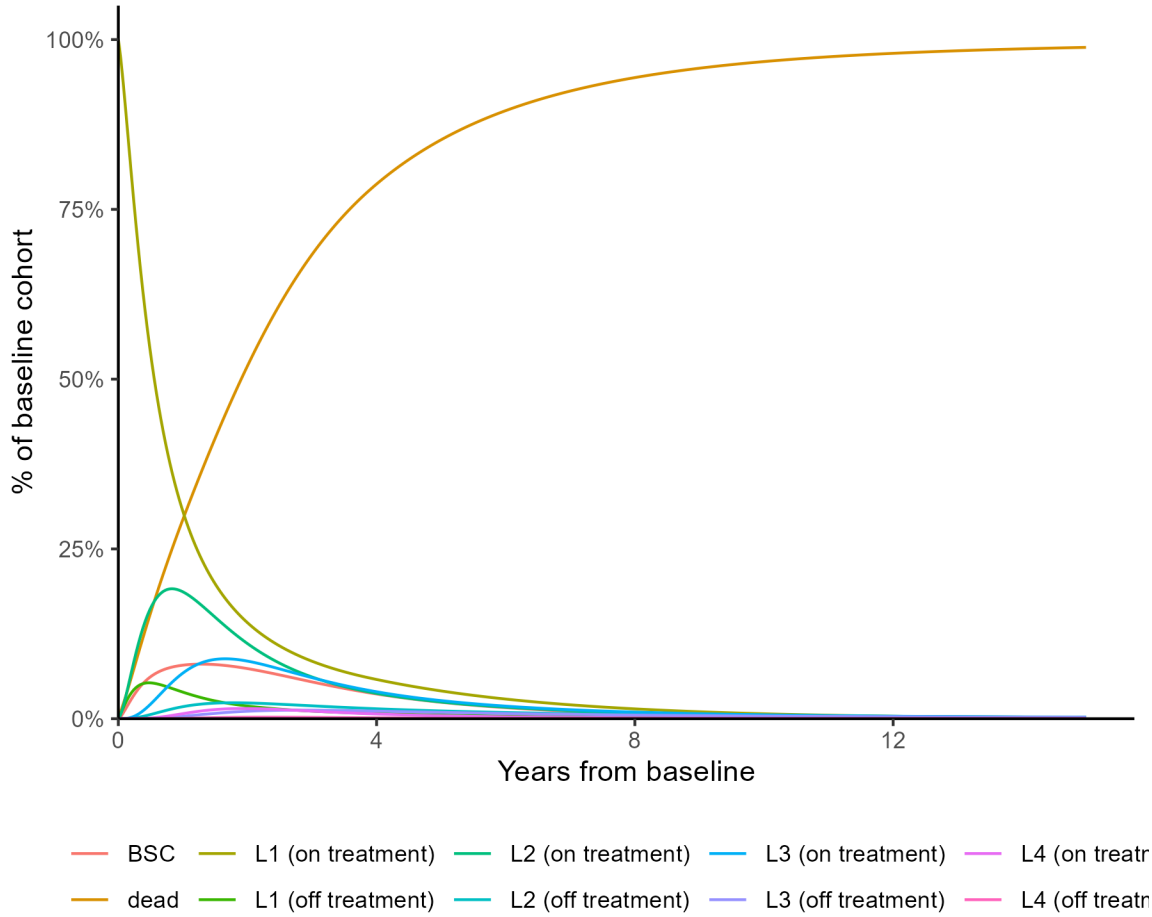
Note: Discrepancies in sums due to rounding errors; totals shown are calculated on unrounded numbers

Figure 32: Markov trace: All risk, cabo+nivo



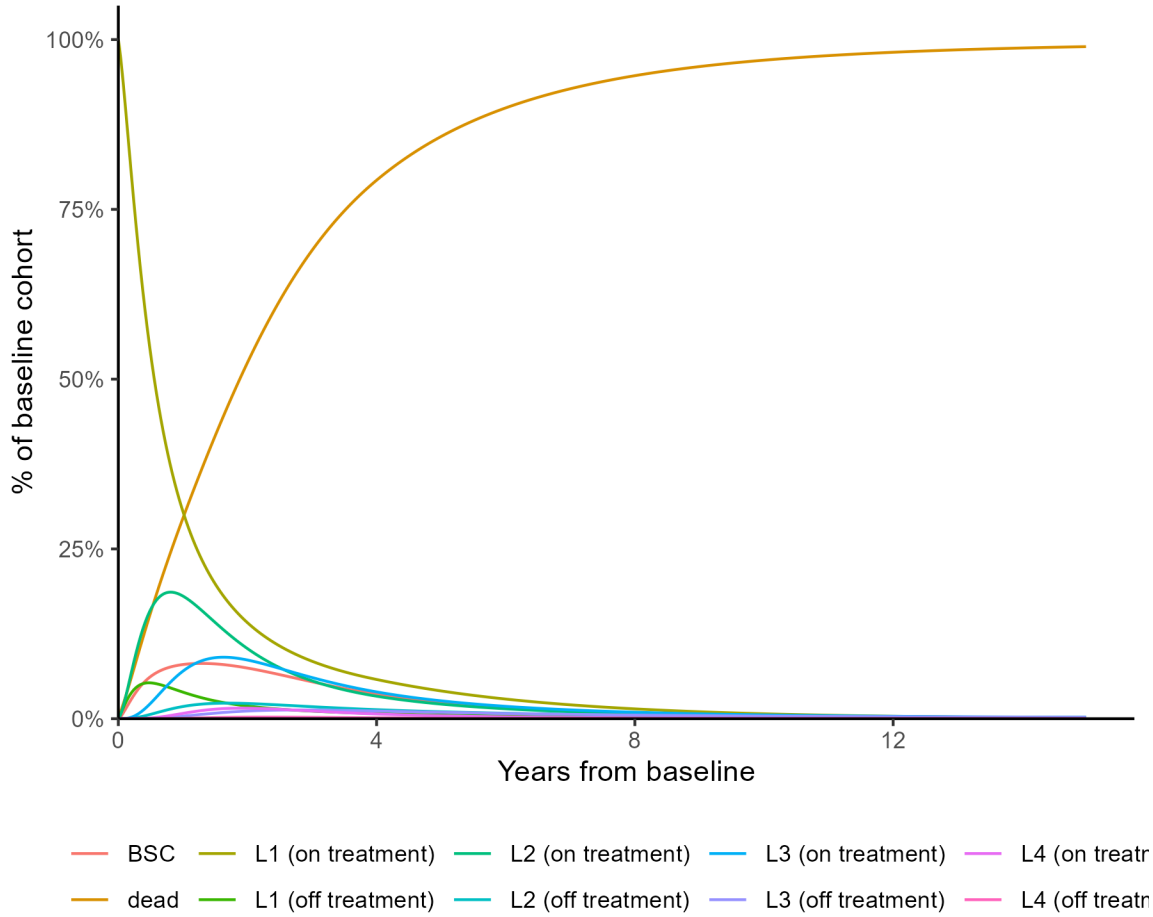
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 33: Markov trace: All risk, pazo



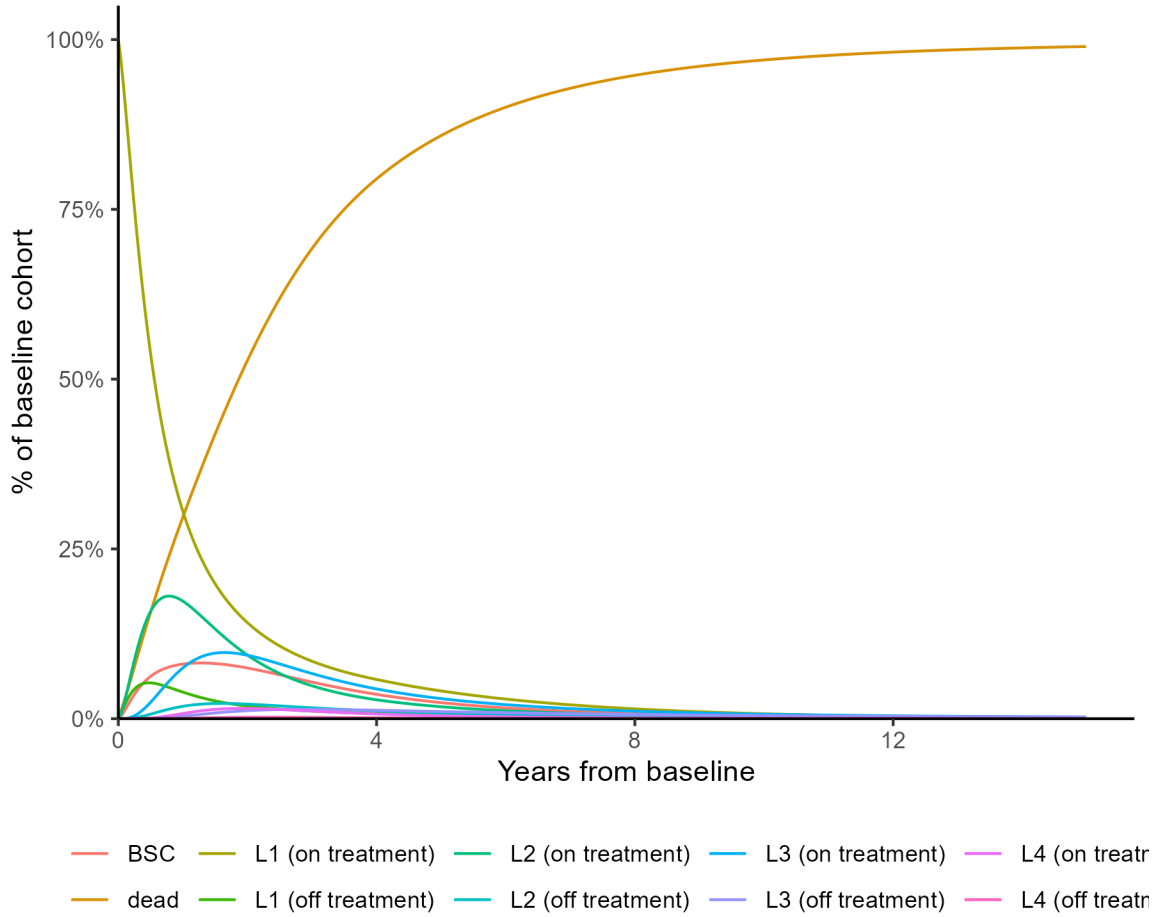
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 34: Markov trace: All risk, suni



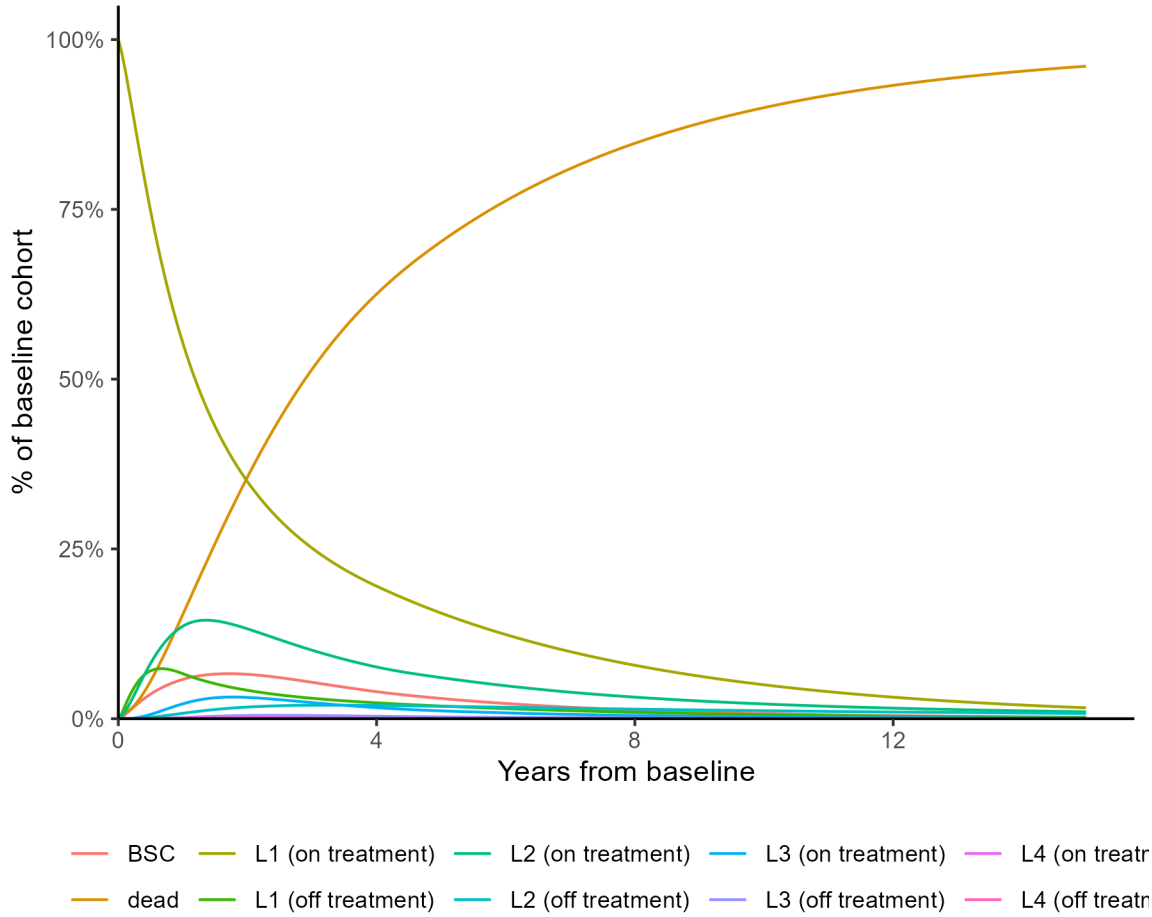
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 35: Markov trace: All risk, tivo



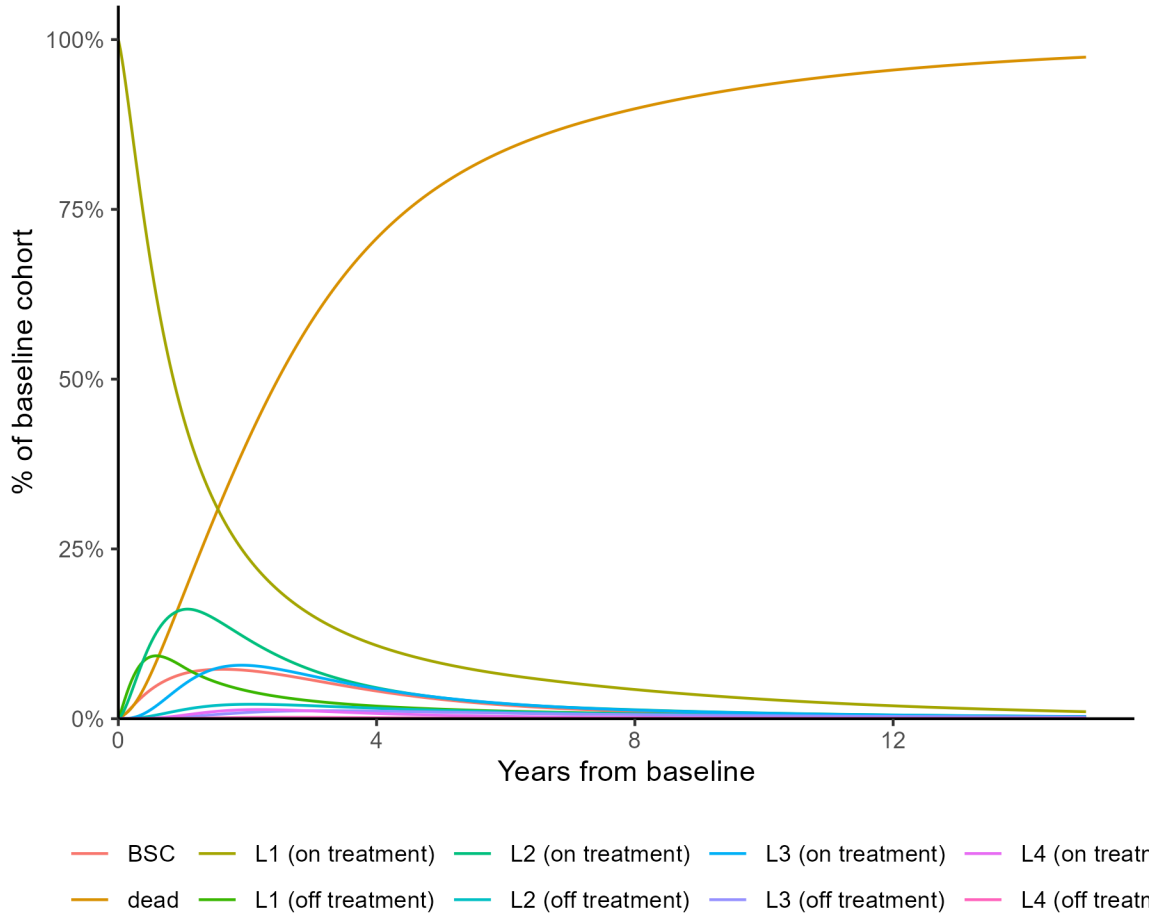
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 36: Markov trace: Favourable risk, cabo+nivo



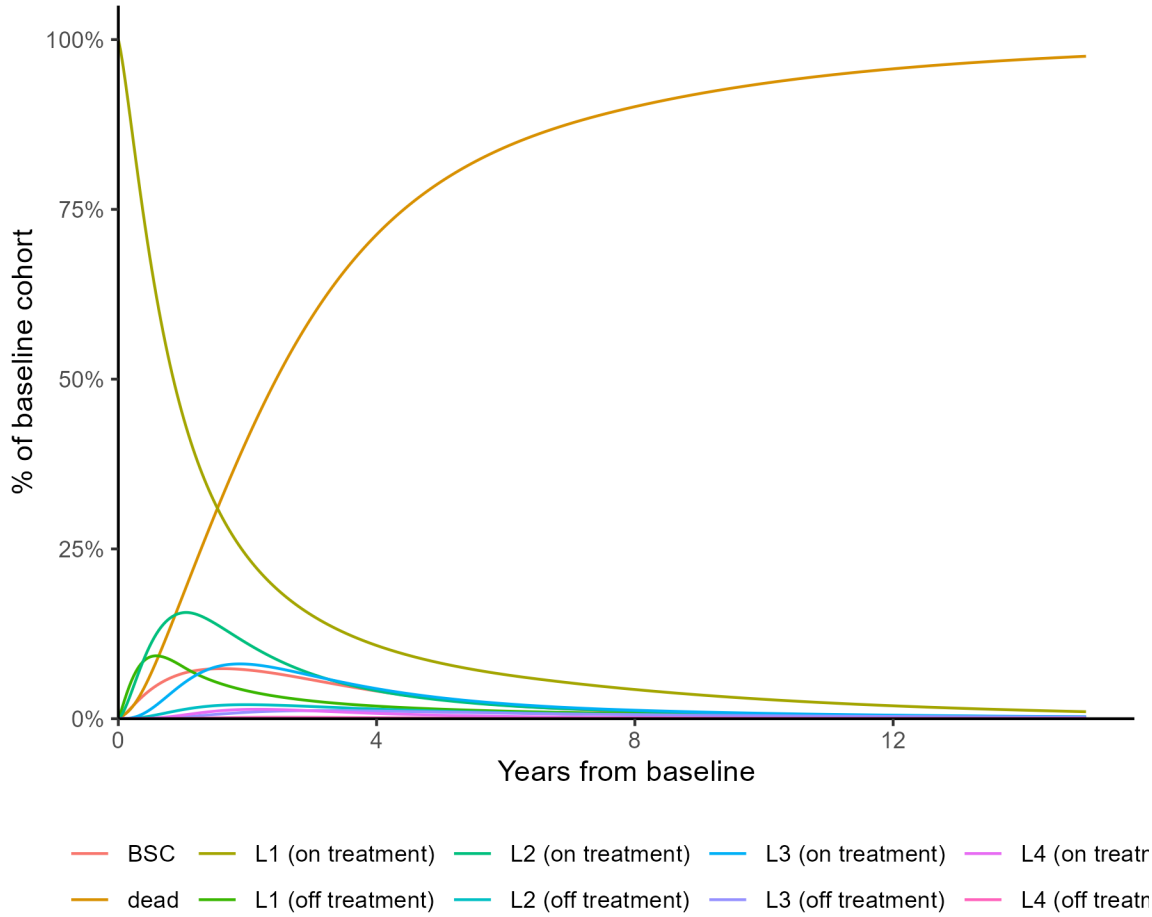
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 37: Markov trace: Favourable risk, pazo



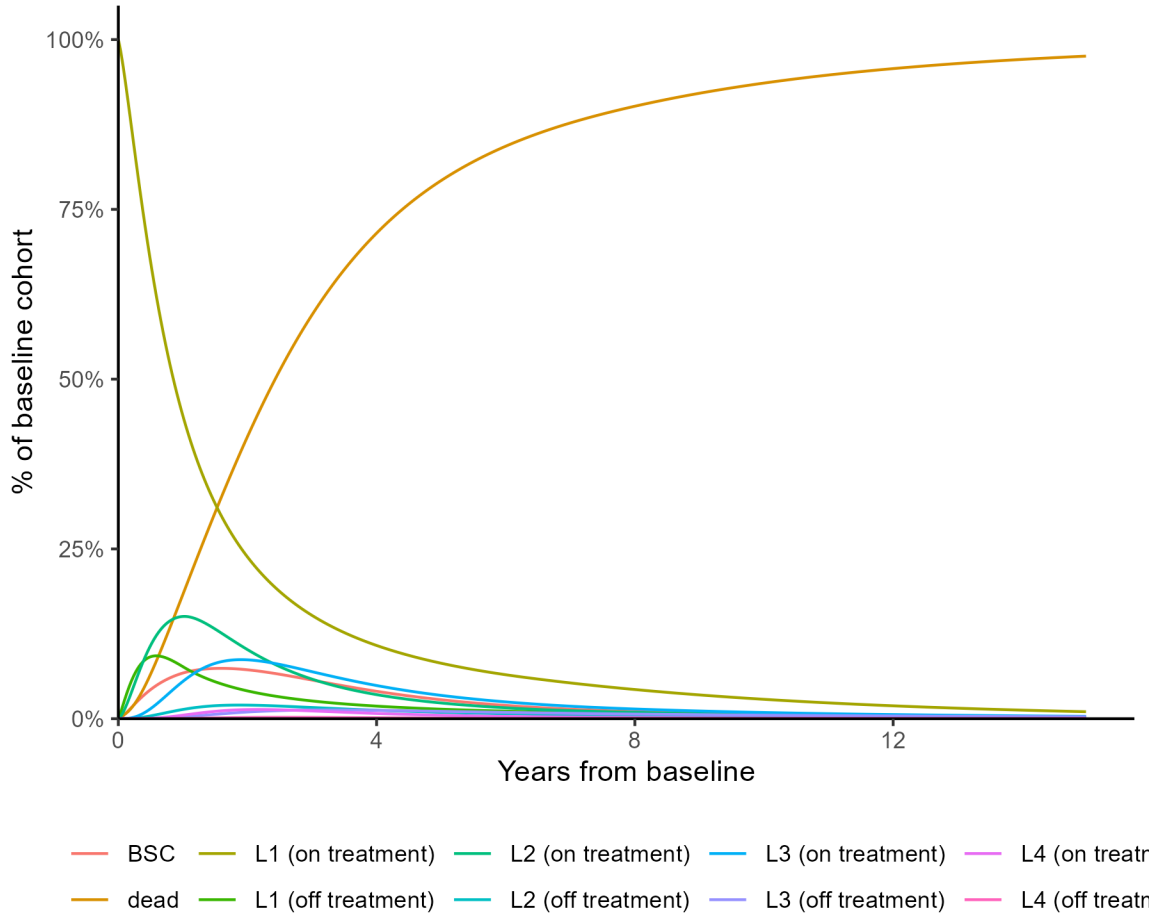
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 38: Markov trace: Favourable risk, suni



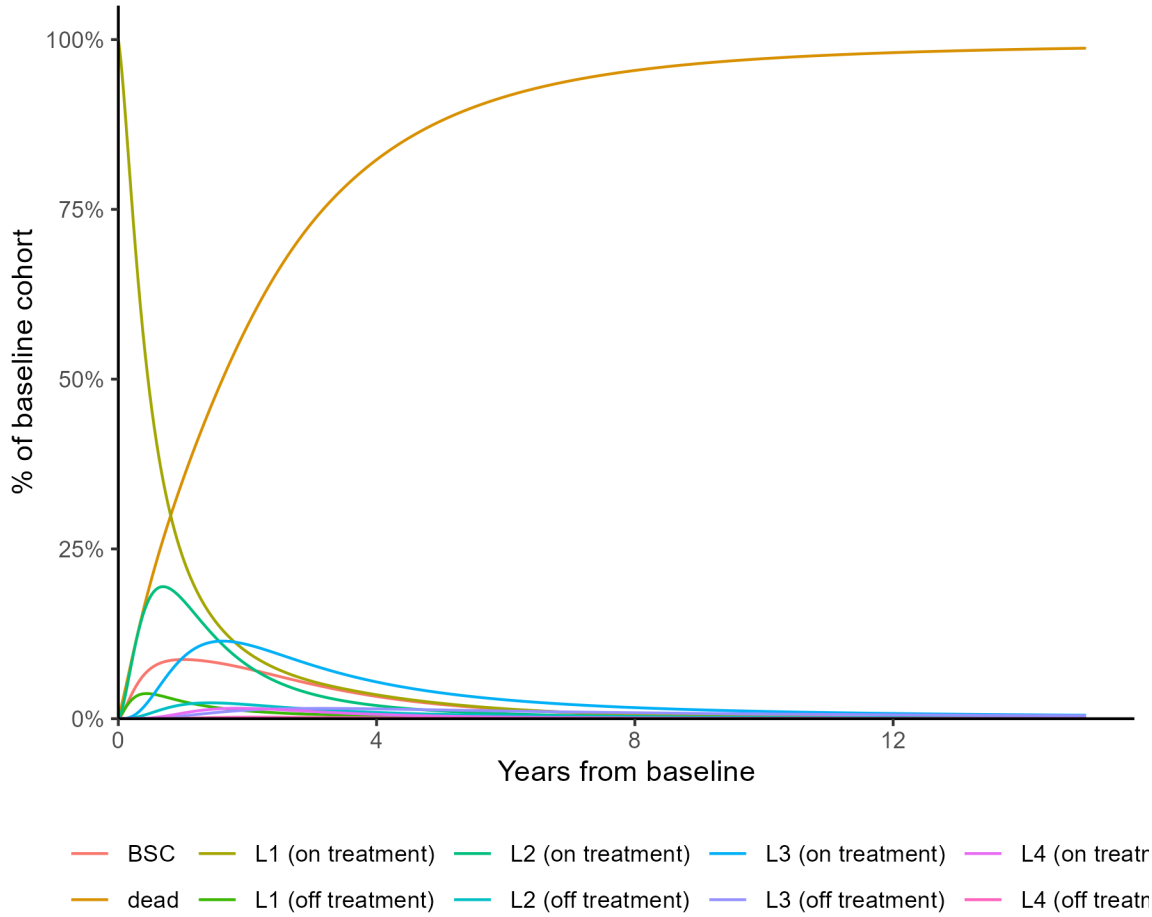
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 39: Markov trace: Favourable risk, tivo



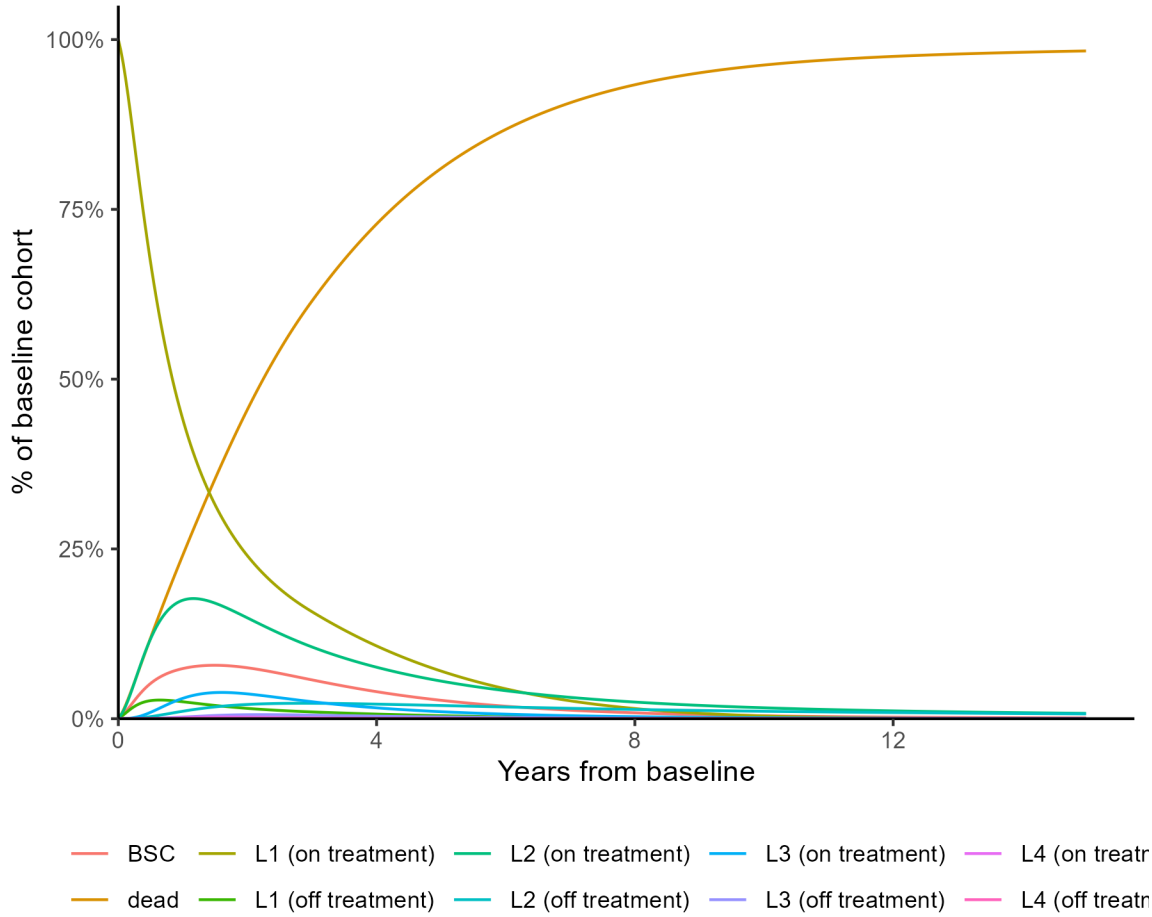
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 40: Markov trace: Intermediate / poor risk, cabo



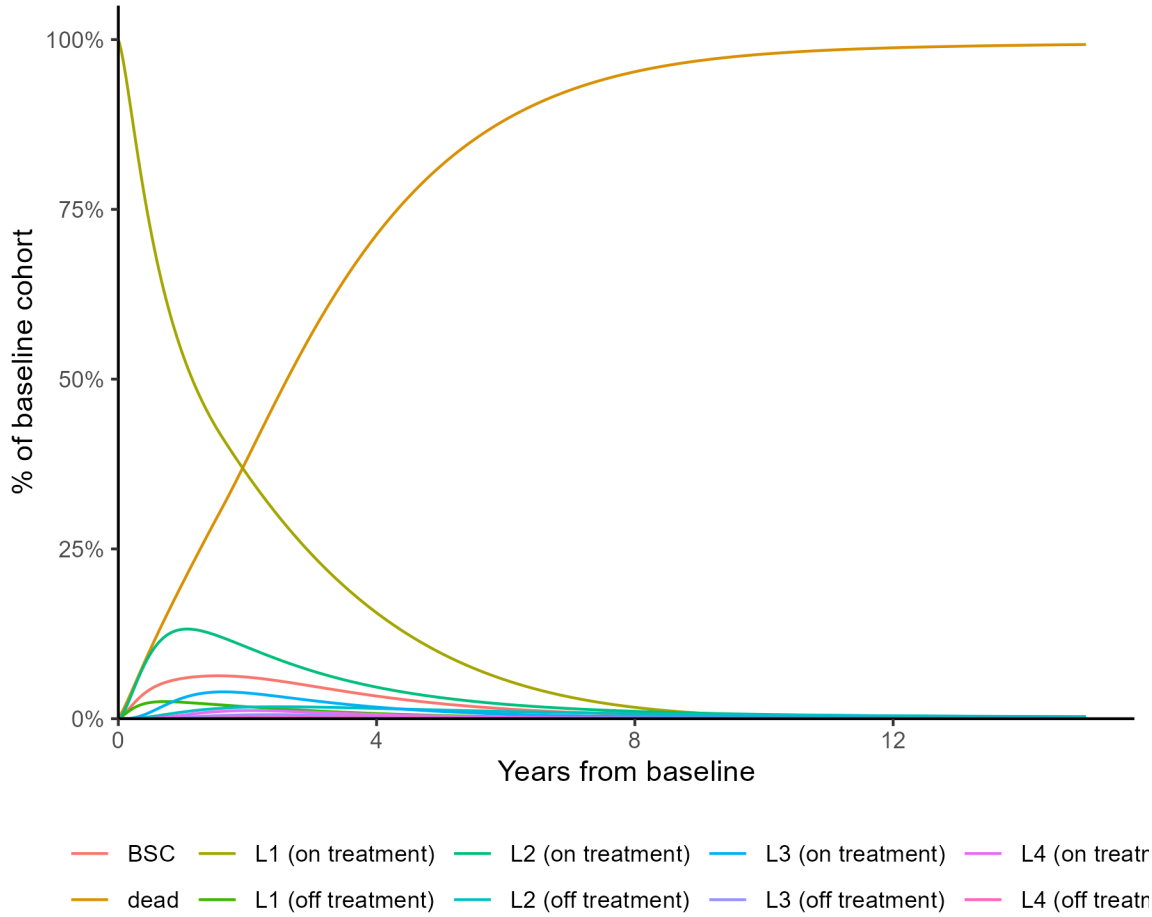
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 41: Markov trace: Intermediate / poor risk, cabo+nivo



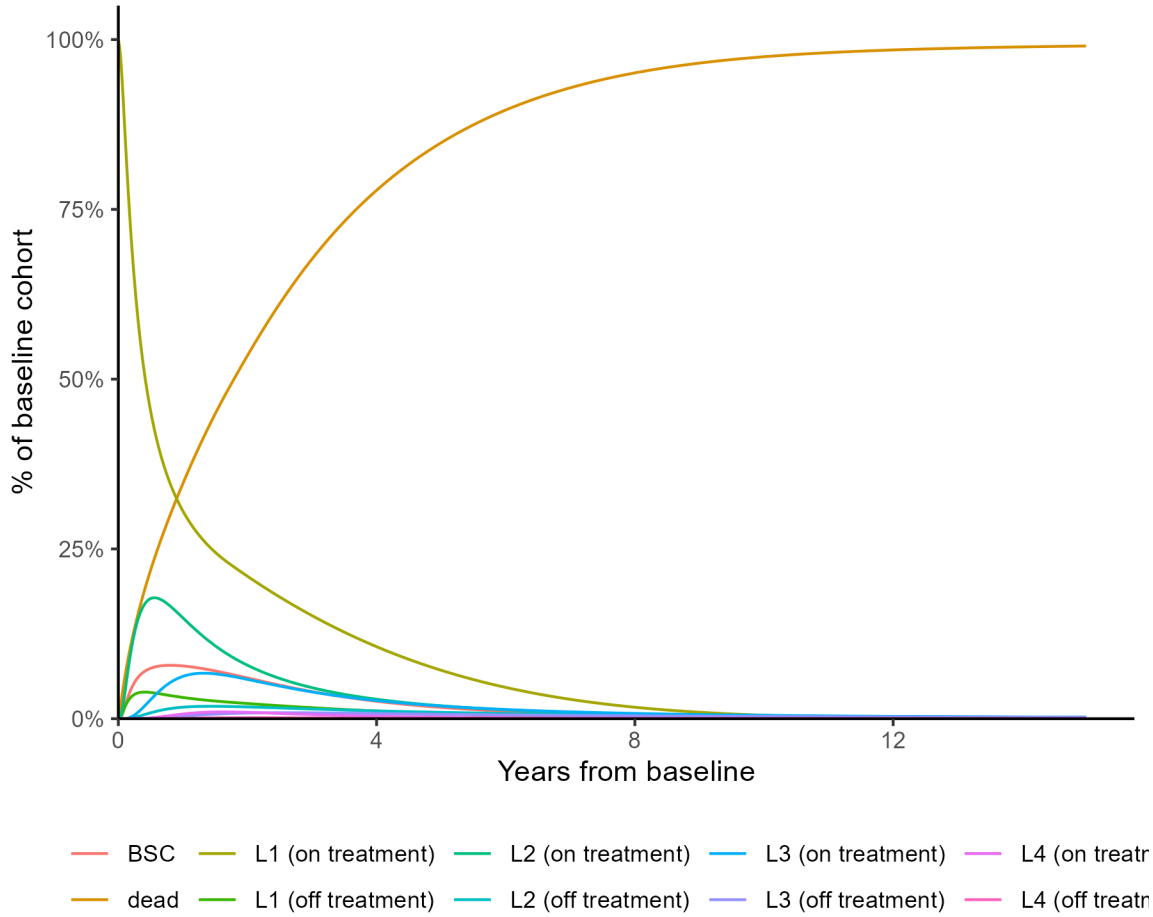
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 42: Markov trace: Intermediate / poor risk, pem+lenv



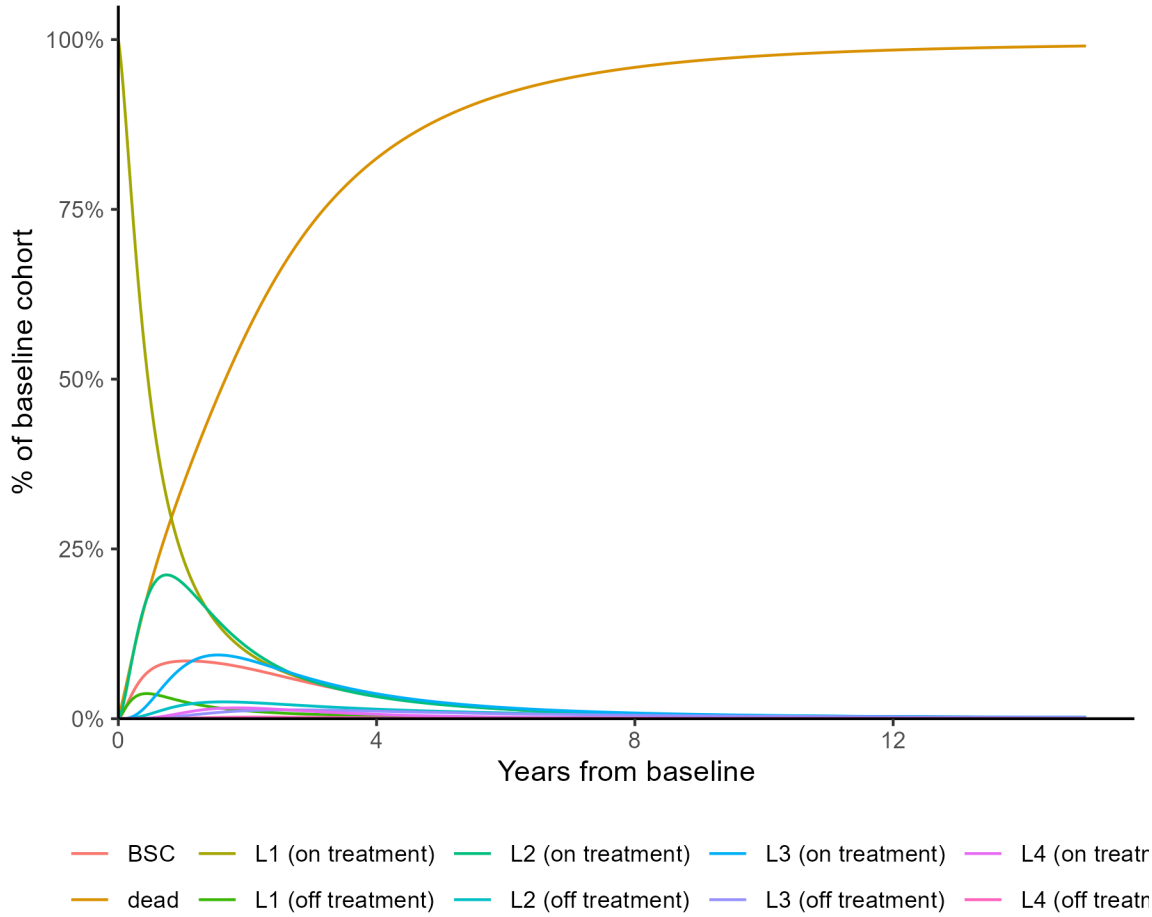
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 43: Markov trace: Intermediate / poor risk, nivo+ipi



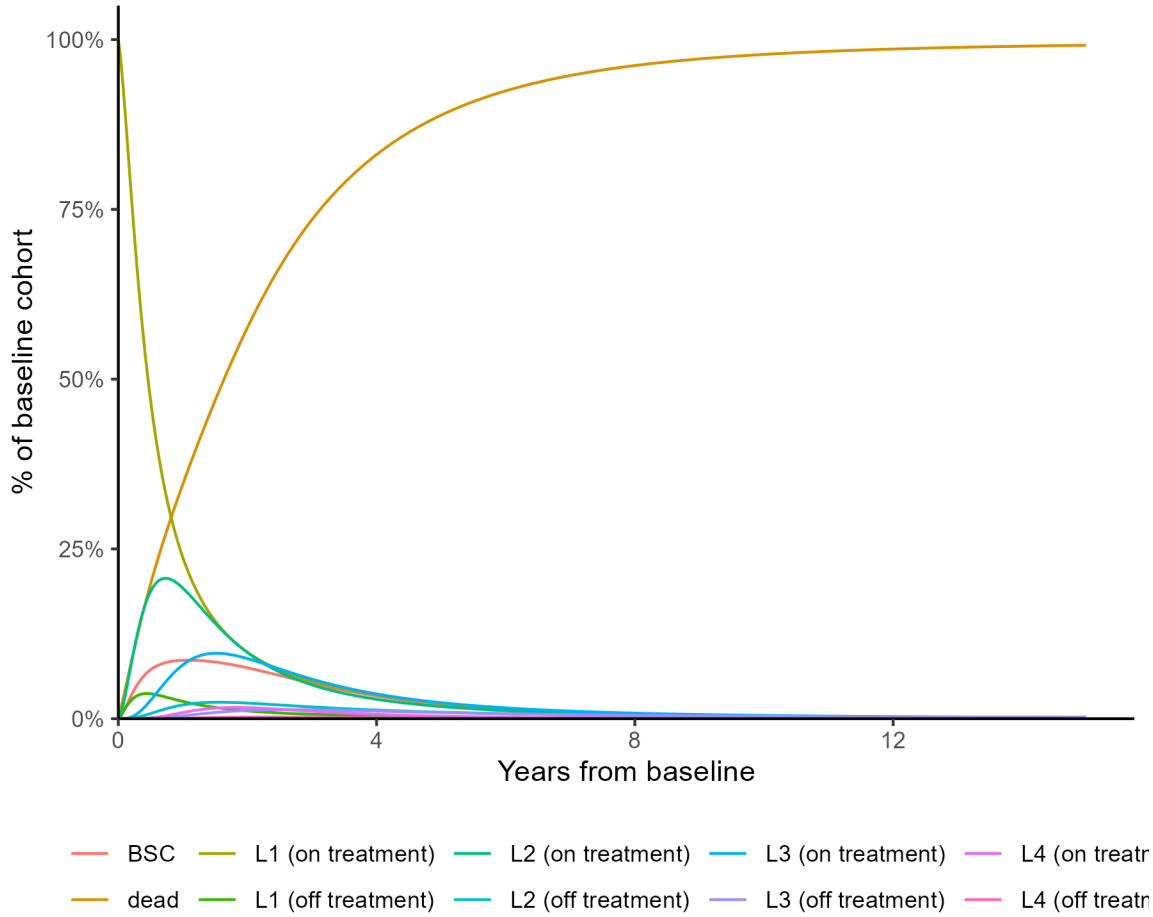
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 44: Markov trace: Intermediate / poor risk, pazo



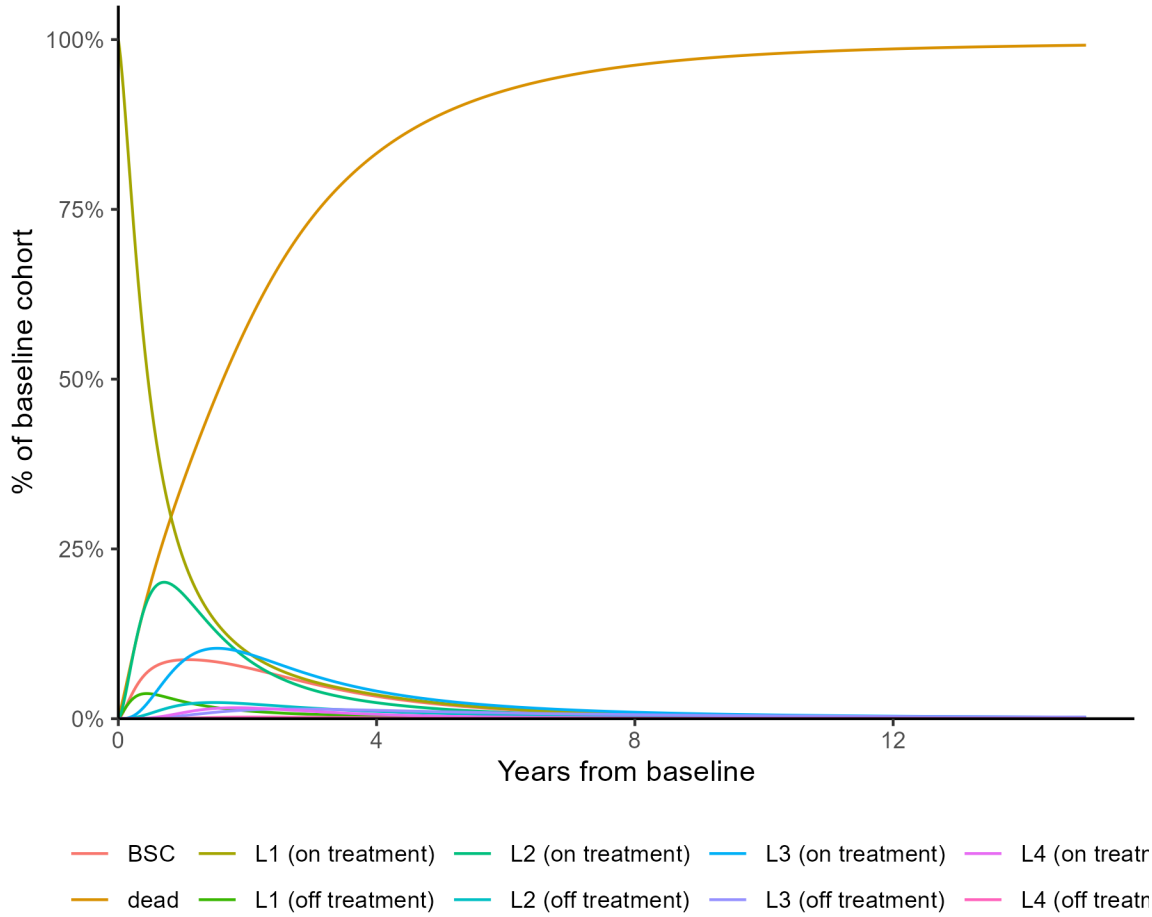
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 45: Markov trace: Intermediate / poor risk, suni



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

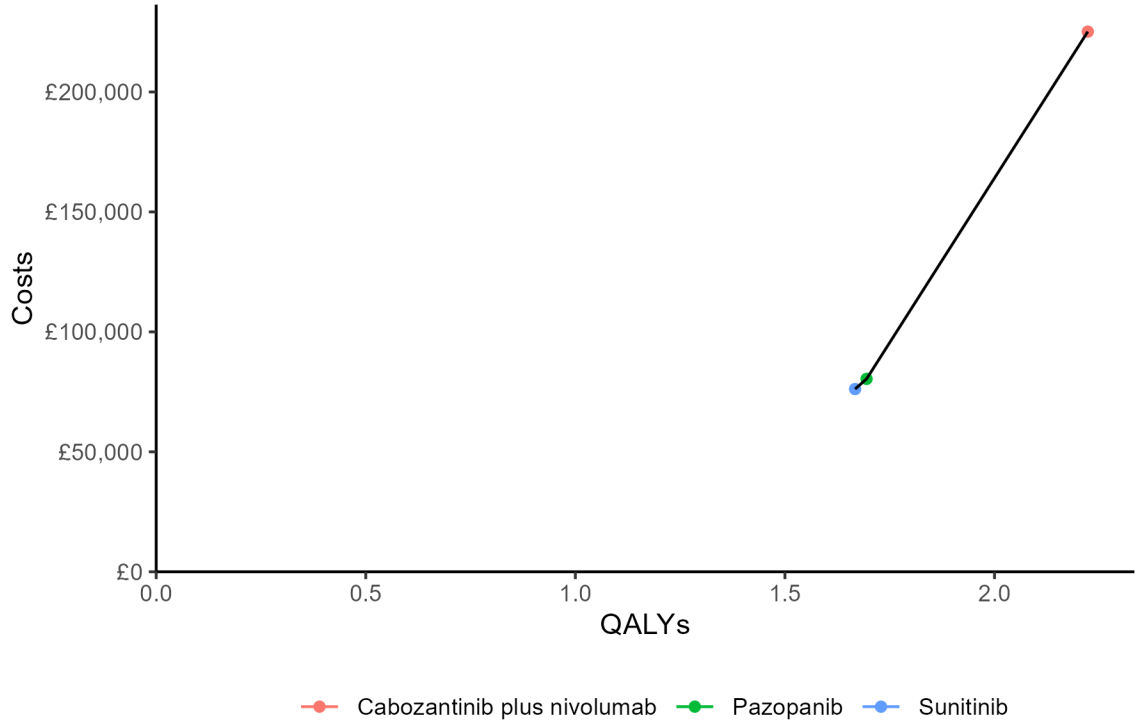
Figure 46: Markov trace: Intermediate / poor risk, tivo



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

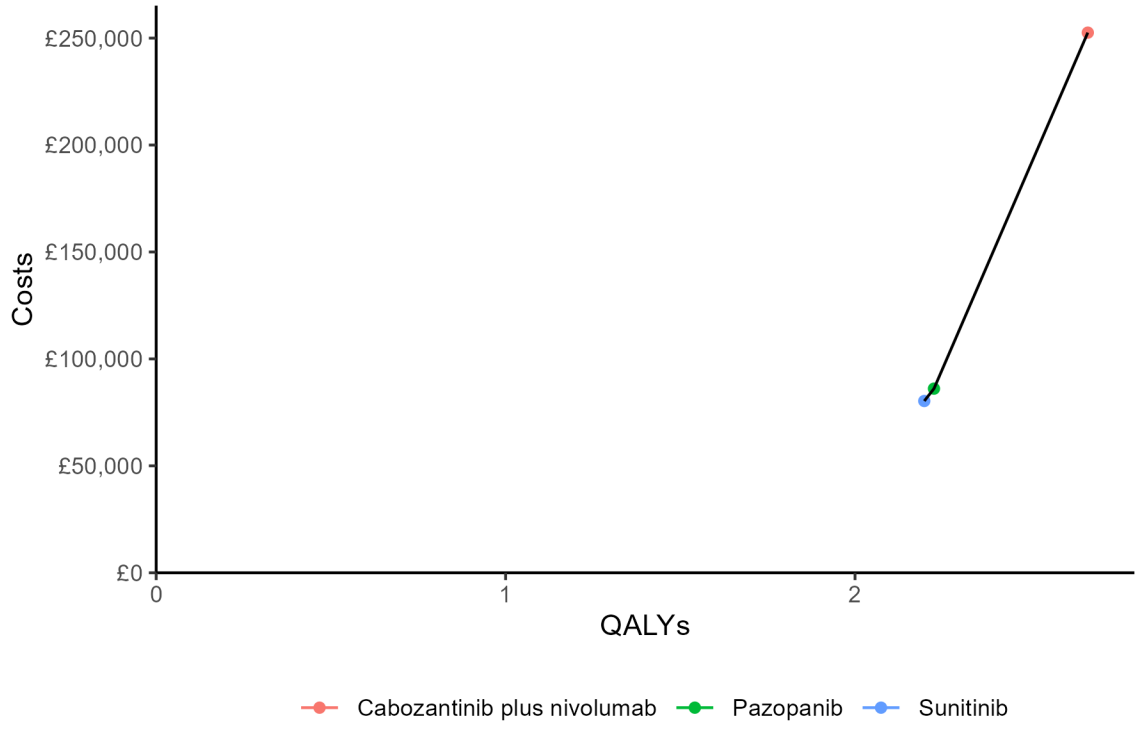
Cost-effectiveness acceptability frontiers are presented for all non-dominated treatments for each of the risk groups.

Figure 47: Cost-effectiveness acceptability frontier – all risk



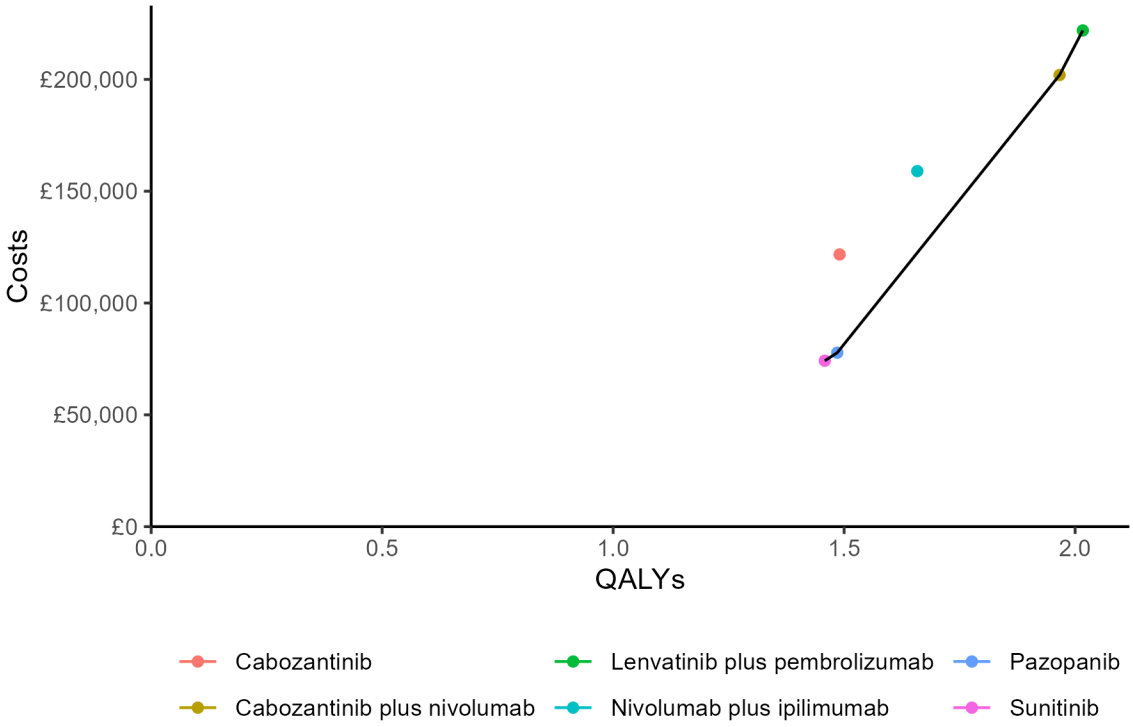
Abbreviations: QALYs, quality-adjusted life-years

Figure 48: Cost-effectiveness acceptability frontier – favourable risk



Abbreviations: QALYs, quality-adjusted life-years

Figure 49: Cost-effectiveness acceptability frontier – intermediate / poor risk



Abbreviations: QALYs, quality-adjusted life-years

7. APPENDIX C: PAIRWISE COMPARISONS – LIST PRICE

Table 48: Base case pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£225,144	2.22	3.71	-	-	-	-
Pazo	£80,399	1.69	2.84	£144,745	0.53	0.88	£274,247
Tivo	£100,005	1.66	2.76	£125,139	0.56	0.95	£223,361
Suni	£76,166	1.67	2.78	£148,977	0.56	0.93	£268,351
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.67	4.52	-	-	-	-
Pazo	£86,100	2.23	3.73	£166,454	0.44	0.78	£378,083
Tivo	£116,790	2.19	3.66	£135,763	0.47	0.86	£286,887
Suni	£80,328	2.20	3.68	£172,226	0.47	0.84	£368,014
Risk population: Intermediate / poor risk							
Cabo+nivo	£201,953	1.97	3.30	-	-	-	-
Nivo+ipi	£158,987	1.66	2.72	£42,966	0.31	0.59	£139,508
Pem+lenv	£221,891	2.02	3.22	£-19,938	-0.05	0.08	SW quadrant £396,657
Pazo	£77,793	1.49	2.50	£124,160	0.48	0.80	£258,007
Tivo	£92,997	1.45	2.43	£108,956	0.51	0.87	£212,280
Suni	£74,181	1.46	2.45	£127,772	0.51	0.86	£251,374
Cabo	£121,724	1.49	2.57	£80,229	0.48	0.73	£168,478

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 49: Scenario analysis 1 pairwise comparison table

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£213,276	2.15	3.35	-	-	-	-
Pazo	£72,099	1.83	2.90	£141,178	0.32	0.45	£440,975
Tivo	£95,457	1.84	2.90	£117,820	0.31	0.45	£377,102
Suni	£68,597	1.84	2.90	£144,679	0.32	0.45	£453,073
Risk population: Favourable risk							
Cabo+nivo	£240,996	2.70	4.41	-	-	-	-
Pazo	£77,144	2.91	4.90	£163,852	-0.21	-0.49	Cabo+nivo dominated
Tivo	£111,567	2.91	4.90	£129,428	-0.22	-0.49	Cabo+nivo dominated
Suni	£72,143	2.91	4.90	£168,853	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£190,204	1.91	2.95	-	-	-	-
Nivo+ipi	£152,478	1.88	2.92	£37,726	0.02	0.03	£1,561,318
Pem+lenv	£216,512	1.77	2.67	£-26,308	0.14	0.28	Cabo+nivo dominant
Pazo	£70,310	1.47	2.28	£119,894	0.44	0.67	£271,922
Tivo	£89,267	1.47	2.28	£100,936	0.43	0.67	£233,011
Suni	£67,404	1.47	2.28	£122,799	0.44	0.67	£279,035
Cabo	£112,281	1.46	2.28	£77,923	0.44	0.67	£175,185

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 50: Scenario analysis 3 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£217,399	2.15	3.54	-	-	-	-
Pazo	£58,041	1.46	2.32	£159,357	0.69	1.22	£229,389
Tivo	£76,437	1.40	2.19	£140,962	0.75	1.35	£186,721
Suni	£53,716	1.43	2.26	£163,683	0.72	1.28	£225,817
Risk population: Favourable risk							
Cabo+nivo	£244,923	2.60	4.35	-	-	-	-
Pazo	£63,371	1.99	3.20	£181,551	0.61	1.15	£296,880
Tivo	£92,832	1.93	3.06	£152,091	0.67	1.28	£226,112
Suni	£57,505	1.96	3.14	£187,418	0.64	1.21	£291,894
Risk population: Intermediate / poor risk							
Cabo+nivo	£194,149	1.90	3.13	-	-	-	-
Nivo+ipi	£144,686	1.48	2.32	£49,463	0.42	0.82	£118,358
Pem+lenv	£213,482	1.92	3.01	£-19,333	-0.03	0.12	SW quadrant £743,493
Pazo	£55,711	1.25	2.00	£138,438	0.64	1.14	£214,682
Tivo	£69,720	1.19	1.87	£124,430	0.70	1.26	£176,660
Suni	£52,008	1.22	1.94	£142,142	0.67	1.19	£210,687
Cabo	£95,024	1.15	1.81	£99,126	0.74	1.32	£133,140

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 51: Scenario analysis 11 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£230,701	2.35	3.95	-	-	-	-
Pazo	£80,399	1.69	2.84	£150,302	0.66	1.12	£229,197
Tivo	£100,005	1.66	2.76	£130,696	0.69	1.19	£189,899
Suni	£76,166	1.67	2.78	£154,535	0.68	1.17	£226,210
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.67	4.52	-	-	-	-
Pazo	£86,100	2.23	3.73	£166,454	0.44	0.78	£378,083
Tivo	£116,790	2.19	3.66	£135,763	0.47	0.86	£286,887
Suni	£80,328	2.20	3.68	£172,226	0.47	0.84	£368,014
Risk population: Intermediate / poor risk							
Cabo+nivo	£214,808	2.16	3.65	-	-	-	-
Nivo+ipi	£173,529	1.82	3.06	£41,279	0.34	0.59	£122,554
Pem+lenv	£231,811	2.23	3.63	£-17,004	-0.07	0.02	SW quadrant £236,733
Pazo	£77,793	1.49	2.50	£137,015	0.68	1.15	£202,717
Tivo	£92,997	1.45	2.43	£121,811	0.71	1.22	£172,066
Suni	£74,181	1.46	2.45	£140,627	0.70	1.20	£200,050
Cabo	£121,724	1.49	2.57	£93,084	0.67	1.08	£138,752

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 52: Scenario analysis 21 pairwise comparison table

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£219,292	2.37	3.76	-	-	-	-
Pazo	£72,099	1.83	2.90	£147,194	0.54	0.86	£274,647
Tivo	£95,457	1.84	2.90	£123,836	0.53	0.86	£234,438
Suni	£68,597	1.84	2.90	£150,695	0.54	0.86	£281,611
Risk population: Favourable risk							
Cabo+nivo	£240,996	2.70	4.41	-	-	-	-
Pazo	£77,144	2.91	4.90	£163,852	-0.21	-0.49	Cabo+nivo dominated
Tivo	£111,567	2.91	4.90	£129,428	-0.22	-0.49	Cabo+nivo dominated
Suni	£72,143	2.91	4.90	£168,853	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,537	2.17	3.47	-	-	-	-
Nivo+ipi	£159,189	2.09	3.33	£45,348	0.08	0.13	£540,524
Pem+lenv	£224,418	1.97	3.06	£-19,881	0.20	0.41	Cabo+nivo dominant
Pazo	£70,310	1.47	2.28	£134,227	0.71	1.19	£189,844
Tivo	£89,267	1.47	2.28	£115,270	0.70	1.19	£164,834
Suni	£67,404	1.47	2.28	£137,133	0.71	1.19	£194,181
Cabo	£112,281	1.46	2.28	£92,256	0.71	1.19	£129,769

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 53: Scenario analysis 41 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£270,061	2.22	3.71	-	-	-	-
Pazo	£90,198	1.69	2.84	£179,863	0.53	0.88	£340,786
Tivo	£109,390	1.66	2.76	£160,671	0.56	0.95	£286,783
Suni	£85,586	1.67	2.78	£184,475	0.56	0.93	£332,291
Risk population: Favourable risk							
Cabo+nivo	£307,615	2.67	4.52	-	-	-	-
Pazo	£96,605	2.23	3.73	£211,010	0.44	0.78	£479,289
Tivo	£127,231	2.19	3.66	£180,384	0.47	0.86	£381,178
Suni	£90,343	2.20	3.68	£217,272	0.47	0.84	£464,270
Risk population: Intermediate / poor risk							
Cabo+nivo	£239,651	1.97	3.30	-	-	-	-
Nivo+ipi	£176,866	1.66	2.72	£62,784	0.31	0.59	£203,855
Pem+lenv	£244,788	2.02	3.22	-£5,138	-0.05	0.08	SW quadrant £102,210
Pazo	£87,261	1.49	2.50	£152,390	0.48	0.80	£316,669
Tivo	£101,919	1.45	2.43	£137,732	0.51	0.87	£268,346
Suni	£83,315	1.46	2.45	£156,336	0.51	0.86	£307,570
Cabo	£133,567	1.49	2.57	£106,084	0.48	0.73	£222,771

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 54: Scenario analysis 73 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£225,144	2.22	3.71	-	-	-	-
Pazo	£80,399	1.69	2.84	£144,745	0.53	0.88	£274,247
Tivo	£100,005	1.66	2.76	£125,139	0.56	0.95	£223,361
Suni	£76,166	1.67	2.78	£148,977	0.56	0.93	£268,351
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.67	4.52	-	-	-	-
Pazo	£86,100	2.23	3.73	£166,454	0.44	0.78	£378,083
Tivo	£116,790	2.19	3.66	£135,763	0.47	0.86	£286,887
Suni	£80,328	2.20	3.68	£172,226	0.47	0.84	£368,014
Risk population: Intermediate / poor risk							
Cabo+nivo	£209,163	2.04	3.43	-	-	-	-
Nivo+ipi	£178,703	1.86	3.03	£30,460	0.19	0.40	£163,193
Pem+lenv	£221,891	2.02	3.22	£-12,728	0.03	0.20	Cabo+nivo dominant
Pazo	£77,793	1.49	2.50	£131,370	0.56	0.92	£235,771
Tivo	£92,997	1.45	2.43	£116,166	0.59	1.00	£197,149
Suni	£74,181	1.46	2.45	£134,982	0.58	0.98	£231,031
Cabo	£121,724	1.49	2.57	£87,439	0.55	0.86	£158,357

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 55: Scenario analysis 74 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£230,701	2.35	3.95	-	-	-	-
Pazo	£80,399	1.69	2.84	£150,302	0.66	1.12	£229,197
Tivo	£100,005	1.66	2.76	£130,696	0.69	1.19	£189,899
Suni	£76,166	1.67	2.78	£154,535	0.68	1.17	£226,210
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.67	4.52	-	-	-	-
Pazo	£86,100	2.23	3.73	£166,454	0.44	0.78	£378,083
Tivo	£116,790	2.19	3.66	£135,763	0.47	0.86	£286,887
Suni	£80,328	2.20	3.68	£172,226	0.47	0.84	£368,014
Risk population: Intermediate / poor risk							
Cabo+nivo	£214,808	2.16	3.65	-	-	-	-
Nivo+ipi	£102,694	0.64	0.80	£112,113	1.52	2.85	£73,795
Pem+lenv	£231,811	2.23	3.63	£-17,004	-0.07	0.02	SW quadrant £236,733
Pazo	£77,793	1.49	2.50	£137,015	0.68	1.15	£202,717
Tivo	£92,997	1.45	2.43	£121,811	0.71	1.22	£172,066
Suni	£74,181	1.46	2.45	£140,627	0.70	1.20	£200,050
Cabo	£121,724	1.49	2.57	£93,084	0.67	1.08	£138,752

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 56: Scenario analysis 80 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
Cabo+nivo	£240,767	2.29	3.77	-	-	-	-
Pazo	£65,798	1.45	2.32	£174,969	0.84	1.46	£208,665
Tivo	£84,878	1.39	2.18	£155,889	0.90	1.59	£173,362
Suni	£60,550	1.42	2.26	£180,217	0.87	1.52	£207,649
Risk population: Favourable risk							
Cabo+nivo	£265,584	2.53	4.21	-	-	-	-
Pazo	£71,596	1.90	3.05	£193,989	0.63	1.16	£307,096
Tivo	£101,905	1.84	2.91	£163,679	0.69	1.30	£235,863
Suni	£64,745	1.87	2.99	£200,839	0.66	1.22	£303,483
Risk population: Intermediate / poor risk							
Cabo+nivo	£222,455	2.11	3.48	-	-	-	-
Nivo+ipi	£157,041	1.48	2.32	£65,414	0.63	1.17	£103,766
Pem+lenv	£235,204	2.14	3.40	£-12,749	-0.03	0.08	SW quadrant £367,535
Pazo	£63,150	1.25	2.00	£159,305	0.86	1.48	£185,581
Tivo	£77,187	1.19	1.87	£145,269	0.92	1.61	£158,187
Suni	£58,623	1.22	1.94	£163,832	0.89	1.54	£184,611
Cabo	£104,119	1.15	1.81	£118,336	0.96	1.67	£123,371

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 57: Scenario analysis 85 pairwise comparison table

Technologies	Costs (£)	QALYs	lys	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
Cabo+nivo	£221,132	2.40	3.76	-	-	-	-
Pazo	£56,499	1.84	2.90	£164,633	0.55	0.86	£298,602
Tivo	£80,647	1.85	2.90	£140,485	0.54	0.86	£258,091
Suni	£52,697	1.85	2.90	£168,434	0.55	0.86	£305,902
Risk population: Favourable risk							
Cabo+nivo	£245,406	2.72	4.41	-	-	-	-
Pazo	£61,956	2.92	4.90	£183,450	-0.20	-0.49	Cabo+nivo dominated
Tivo	£97,412	2.92	4.90	£147,994	-0.20	-0.49	Cabo+nivo dominated
Suni	£56,623	2.92	4.90	£188,783	-0.20	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£203,953	2.20	3.47	-	-	-	-
Nivo+ipi	£149,366	1.89	2.92	£54,587	0.31	0.55	£178,836
Pem+lenv	£222,037	1.99	3.06	£-18,084	0.21	0.41	Cabo+nivo dominant
Pazo	£54,347	1.48	2.28	£149,605	0.72	1.19	£207,081
Tivo	£73,413	1.48	2.28	£130,540	0.72	1.19	£182,469
Suni	£51,234	1.48	2.28	£152,719	0.72	1.19	£211,605
Cabo	£103,762	1.47	2.28	£100,191	0.72	1.19	£138,432

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 58: Scenario analysis 87 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£225,144	2.22	3.71	-	-	-	-
Pazo	£80,399	1.69	2.84	£144,745	0.53	0.88	£274,247
Tivo	£100,005	1.66	2.76	£125,139	0.56	0.95	£223,361
Suni	£76,166	1.67	2.78	£148,977	0.56	0.93	£268,351
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.67	4.52	-	-	-	-
Pazo	£86,100	2.23	3.73	£166,454	0.44	0.78	£378,083
Tivo	£116,790	2.19	3.66	£135,763	0.47	0.86	£286,887
Suni	£80,328	2.20	3.68	£172,226	0.47	0.84	£368,014
Risk population: Intermediate / poor risk							
Cabo+nivo	£201,953	1.97	3.30	-	-	-	-
Nivo+ipi	£158,987	1.66	2.72	£42,966	0.31	0.59	£139,508
Pem+lenv	£234,889	2.02	3.22	£-32,936	-0.05	0.08	SW quadrant £655,233
Pazo	£77,793	1.49	2.50	£124,160	0.48	0.80	£258,007
Tivo	£92,997	1.45	2.43	£108,956	0.51	0.87	£212,280
Suni	£74,181	1.46	2.45	£127,772	0.51	0.86	£251,374
Cabo	£121,724	1.49	2.57	£80,229	0.48	0.73	£168,478

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 59: Scenario analysis 88 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£225,144	2.22	3.71	-	-	-	-
Pazo	£80,399	1.69	2.84	£144,745	0.53	0.88	£274,247
Tivo	£100,005	1.66	2.76	£125,139	0.56	0.95	£223,361
Suni	£76,166	1.67	2.78	£148,977	0.56	0.93	£268,351
Risk population: Favourable risk							
Cabo+nivo	£273,492	2.82	4.74	-	-	-	-
Pazo	£86,100	2.23	3.73	£187,392	0.60	1.00	£313,070
Tivo	£116,790	2.19	3.66	£156,701	0.63	1.08	£248,128
Suni	£80,328	2.20	3.68	£193,164	0.63	1.06	£308,424
Risk population: Intermediate / poor risk							
Cabo+nivo	£201,953	1.97	3.30	-	-	-	-
Nivo+ipi	£158,987	1.66	2.72	£42,966	0.31	0.59	£139,508
Pem+lenv	£221,891	2.02	3.22	£-19,938	-0.05	0.08	SW quadrant £396,657
Pazo	£77,793	1.49	2.50	£124,160	0.48	0.80	£258,007
Tivo	£92,997	1.45	2.43	£108,956	0.51	0.87	£212,280
Suni	£74,181	1.46	2.45	£127,772	0.51	0.86	£251,374
Cabo	£121,724	1.49	2.57	£80,229	0.48	0.73	£168,478

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

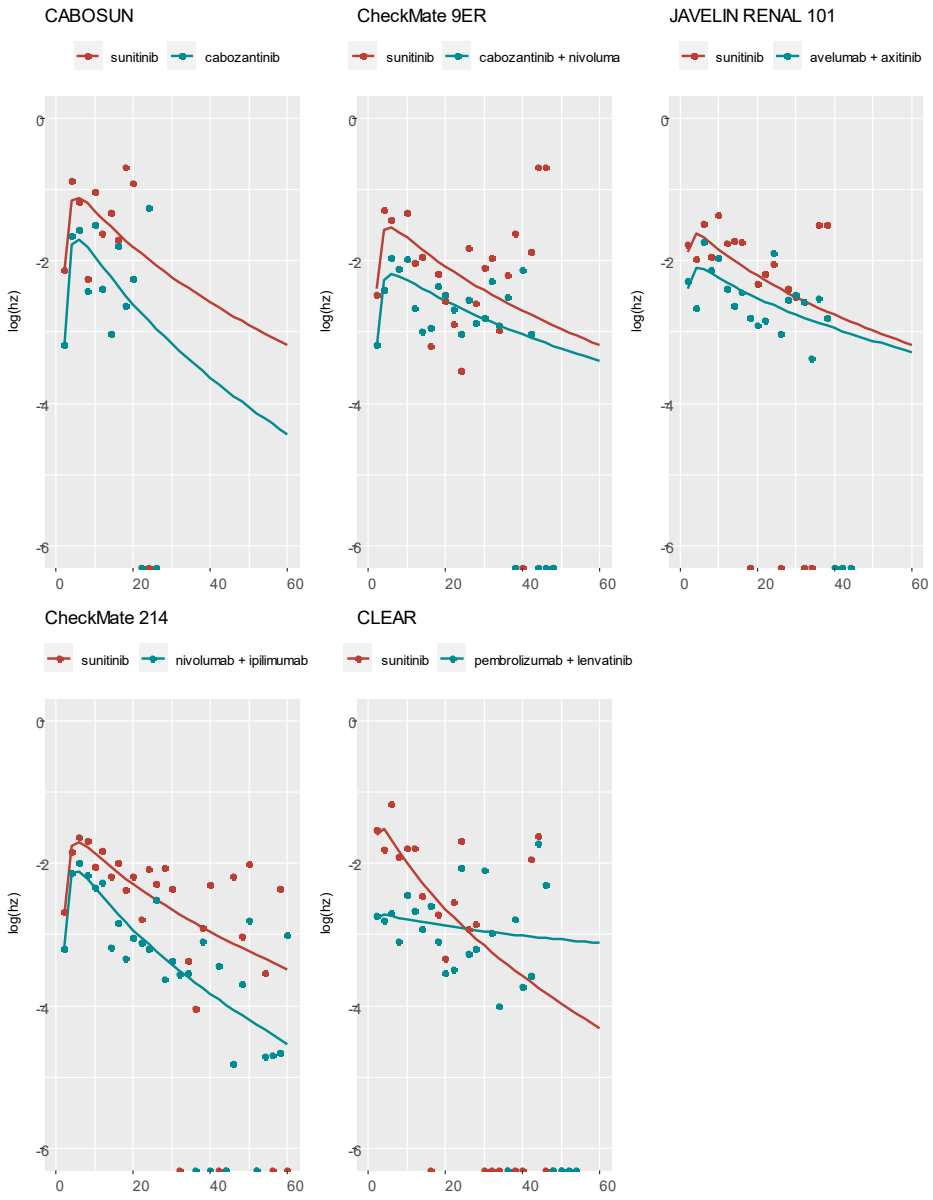
Table 60: Scenario analysis 89 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo+nivo vs comparator
Risk population: All risk							
Cabo+nivo	£225,144	2.34	3.71	-	-	-	-
Pazo	£80,399	1.77	2.84	£144,745	0.57	0.88	£252,142
Tivo	£100,005	1.74	2.76	£125,139	0.61	0.95	£206,321
Suni	£76,166	1.74	2.78	£148,977	0.60	0.93	£247,705
Risk population: Favourable risk							
Cabo+nivo	£252,553	2.85	4.52	-	-	-	-
Pazo	£86,100	2.37	3.73	£166,454	0.49	0.78	£341,467
Tivo	£116,790	2.33	3.66	£135,763	0.52	0.86	£260,864
Suni	£80,328	2.34	3.68	£172,226	0.52	0.84	£334,292
Risk population: Intermediate / poor risk							
Cabo+nivo	£201,953	2.06	3.30	-	-	-	-
Nivo+ipi	£158,987	1.74	2.72	£42,966	0.32	0.59	£134,002
Pem+lenv	£221,891	2.13	3.22	£-19,938	-0.07	0.08	SW quadrant £275,555
Pazo	£77,793	1.54	2.50	£124,160	0.52	0.80	£238,998
Tivo	£92,997	1.51	2.43	£108,956	0.55	0.87	£197,549
Suni	£74,181	1.51	2.45	£127,772	0.55	0.86	£233,771
Cabo	£121,724	1.55	2.57	£80,229	0.51	0.73	£155,944

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

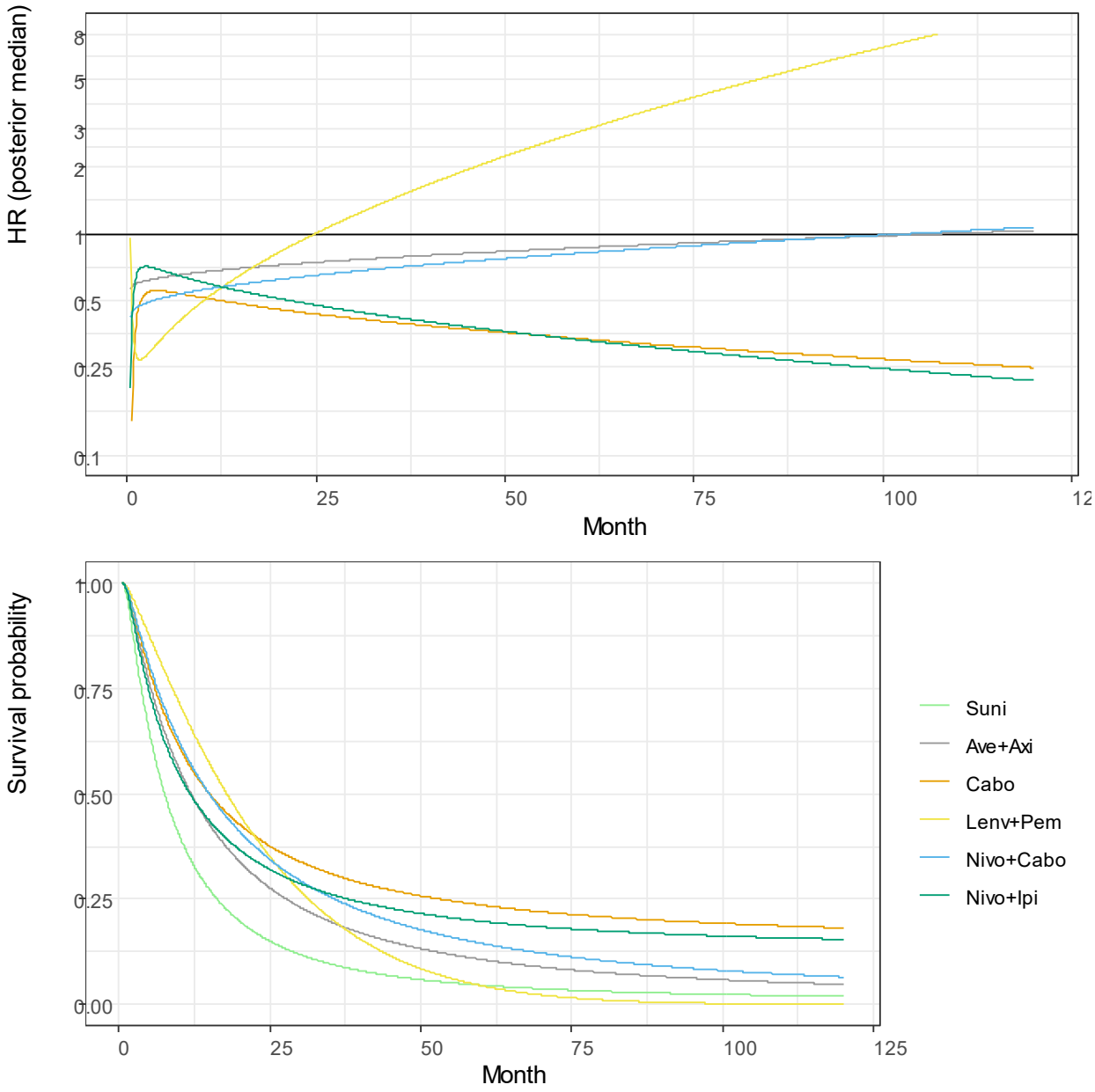
8. APPENDIX D: SCENARIO ANALYSIS USING TTNT FOR CM214

Figure 50: Log hazard plots from NMA for PFS among untreated and intermediate/poor risk, with additional data from the CLEAR trial, and substituting TTNT for PFS from the CheckMate 214 trial



Abbreviations: NMA, network meta-analysis; PFS, progression free survival; TTNT, time to next treatment

Figure 51: Hazard ratio and survival plots from NMA for PFS among untreated and intermediate/poor risk, with additional data from the CLEAR trial, and substituting TTNT for PFS from the CheckMate 214 trial



Abbreviations: NMA, network meta-analysis; PFS, progression free survival; TTNT, time to next treatment