

## **Single Technology Appraisal**

# **Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]**

## **Committee Papers**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer  
[ID3743]**

**Contents:**

The following documents are made available to consultees and commentators:

- 1. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
- 2. Comments on the Appraisal Consultation Document from Eli Lilly**
- 3. Consultee and commentator comments on the Appraisal Consultation Document from:**
  - a. Roche
- 4. Evidence Review Group critique of company comments on the ACD**

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

**Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer**

**Single Technology Appraisal**

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**Type of stakeholder:**

**Consultees** – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators** – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public** – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Eli Lilly and Company Limited (Lilly)	<p>Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for seliperatinib for previously treated rearranged during transfection (<i>RET</i>) fusion-positive advanced non-small cell lung cancer (NSCLC) [ID3743].</p> <p>We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend seliperatinib for this patient group, as advanced non-squamous <i>RET</i> fusion-positive NSCLC, previously treated with immunotherapy and/or platinum-based chemotherapy, is a disease with considerable unmet need and poor outcomes with current therapies. We understand the Committee’s concerns, and hope that the Committee will consider the additional evidence provided within this response document sufficient to make seliperatinib available for this patient group.</p> <p>To address the Committee’s concerns regarding uncertainty resulting from the generation of the pseudo-control arm for LIBRETTO-001, Lilly present further analyses in which the pseudo-control arm has been generated without an adjustment for <i>RET</i> status, whilst maintaining an adjustment for other available relevant prognostic factors using propensity score matching. This approach aligns with feedback from clinical experts that the effect of <i>RET</i> fusion on treatment effectiveness for people with advanced NSCLC is unknown,<sup>1</sup> and that previous OS estimations for the docetaxel arm were clinically implausible. In addition, to offer further value for money to the NHS, Lilly have increased the Patient Access Scheme (PAS) discount from █████ to █████ (80mg 60 x capsule pack: █████; 40mg 60Xcapsule pack: █████). Crucially, while Lilly acknowledges the uncertainties caused by immature survival data from LIBRETTO-001, further data collection from LIBRETTO-001 would resolve these uncertainties while under the Cancer Drug’s Fund (CDF).</p> <p>Lilly therefore welcomes the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will recommend seliperatinib as a treatment option for patients with pre-treated advanced non-squamous <i>RET</i> fusion-positive NSCLC.</p>	Comments noted. Please see responses to individual comments below.
2	Consultee (company)	Eli Lilly and Company	<p><b>Uncertainty resulting from generation of the pseudo-control arm for LIBRETTO-001</b></p> <p>Lilly would first like to address the concerns of the Appraisal Committee that patient survival in the pseudo-</p>	Comments noted. See FAD

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		Limited (Lilly)	<p>control arm is overestimated, and the implications that this has on the validity of subsequent clinical and economic analyses. As outlined in Section B.1.3.1 of the Company’s original submission, patients that exhibit <i>RET</i> fusions tend to be younger, female, have a better tumour performance status and more frequently have a non-smoking status, when compared with advanced NSCLC patients whose tumour does not exhibit a <i>RET</i> fusion.<sup>2,4</sup> These social and clinical factors are known to be prognostic. However, evidence for the independent prognostic effect of <i>RET</i> fusion, in people with advanced NSCLC, is currently inconclusive, as confirmed by expert clinicians during the Appraisal Committee discussion.<sup>1</sup></p> <p>Considering this uncertainty, Lilly deemed it appropriate in their original submission to take the conservative approach of adjusting survival outcomes in the pseudo-comparator arm to account for an independent prognostic effect of the presence of a <i>RET</i> fusion. To Lilly’s knowledge, the best currently available dataset that provides an insight into survival outcomes of <i>RET</i> fusion-positive NSCLC patients is the Flatiron Clinico-Genomic Database (CGDB). Data from <i>RET</i> fusion-positive and -negative patients from this dataset were used to calculate a time acceleration factor for <i>RET</i> fusion-positive status. This adjustment appeared to artificially increase overall survival (OS) in the pseudo-control arm, thus overestimating length of survival, as informed by expert clinician opinion, in advanced <i>RET</i> fusion-positive NSCLC patients treated with docetaxel monotherapy.<sup>1</sup></p> <p>Since the development of the original submission, Lilly has identified the analysis reported by Hess et al. (2021), who assessed tumour response outcomes in 5,807 NSCLC patients (<i>RET</i> positive: 46; <i>RET</i> negative: 5,761) in the United States using data from the Flatiron CGDB.<sup>5</sup> In unadjusted analyses, Hess et al. (2021) found that there was no significant difference in progression free survival (PFS) by <i>RET</i> fusion status (p=0.06), but that OS did differ significantly (hazard ratio [HR]: 1.91; 95% CI: 1.22–3.0; p=0.005). However, after adjusting for baseline covariates, there was no statistically significant difference identified for either PFS (HR: 1.24; 95% CI: 0.86–1.78; p=0.25) or OS (HR: 1.52; 95% CI: 0.95–2.43; p=0.08) in patients treated with standard therapy prior to the availability of selective <i>RET</i> inhibitors.<sup>5</sup> While Lilly acknowledges that the study is limited due to the small sample size of the <i>RET</i> fusion-positive population and potential unmeasured confounding,<sup>5</sup> the lack of statistically significant difference in adjusted survival outcomes by <i>RET</i> status suggests that the adjustment for <i>RET</i> in the original submission was not necessary to calculate a clinically plausible estimate of OS in the pseudo-comparator arm, given these recent findings.</p> <p>Given the above analysis and feedback from expert clinicians on probable survival times for <i>RET</i> fusion-positive patients treated with docetaxel, Lilly therefore considers it appropriate to remove the <i>RET</i> adjustment step from the process used to generate the pseudo-control arm (further details on the revised methodology is provided below). This avoids the artificial inflation of OS caused by Flatiron CGDB adjustment, providing a more clinically plausible reflection of OS in <i>RET</i> fusion-positive patients treated with docetaxel monotherapy. As outlined below, differences in prognostic baseline characteristics between</p>	<p>sections 3.7 and 3.19. The committee concluded based on the limited data available, it was appropriate to remove the adjustment for <i>RET</i> status from the simulated pseudo-control arm, but that significant uncertainty remained from this. The committee agreed that this uncertainty would not be fully resolved by data collection in the Cancer Drugs Fund.</p>

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			<p>the LIBRETTO-001 selpercatinib arm and the pseudo-control arm continued to be adjusted for in the Company's approach.</p> <p><b>Revised approach to the generation of the pseudo-control arm for LIBRETTO-001</b></p> <p>As described in the Company's response to Key Issue 6 at Technical Engagement, the pseudo-control arm was simulated for the LIBRETTO-001 trial using individualised patient data (IPD) from the docetaxel plus placebo arm of the REVEL RCT, which included patients with advanced non-squamous NSCLC who had progressed after a first line platinum-based chemotherapy regimen.<sup>6</sup> The IPD from the REVEL trial were adjusted for prognostic factors through matching with IPD from the LIBRETTO-001 trial, using propensity scores with a logistic regression model.<sup>7</sup> The covariates that were used as adjustment factors during propensity score matching remain the same from the Company's Technical Engagement responses and are listed in Table 3 in the Technical Engagement response document. This adjustment was necessary to account for any differences in characteristics between trial populations, and to generate a reliable treatment effect estimate for the two treatments.</p> <p><b>Error! Reference source not found.</b> provides a summary of the baseline patient characteristics of the LIBRETTO-001 and REVEL trial populations, alongside data showing the impact of matching using propensity scores. The matching process can be seen to have aligned key population characteristics between the selpercatinib and pseudo-control arm.</p> <p><b>Table 1 and analyses not reproduced here – see company's response to consultation p. 3-6.</b></p> <p>Lilly considers that the updated NMA method, which does not adjust the pseudo-control arm for the effect of <i>RET</i> status, provides more robust PFS and OS estimates for docetaxel and will ultimately lead to a more plausible measure of the treatment effect of selpercatinib in the economic analysis.</p> <p><b>NMA meta-regression and model selection</b></p> <p>Consistent with the Company's submission at Technical Engagement, a meta-regression was explored to relate the size of the treatment effects obtained from the meta-analysis to certain numerical characteristics of the included trials. The study-covariates explored align with those explored at Technical Engagement, and the same models were selected for OS, PFS and objective response rate (ORR) (i.e. a fixed effects [FE] hierarchical exchangeable model without age adjustment was used for OS and PFS, while a FE hierarchical exchangeable model with adjustment for the proportion of Asian patients was used for ORR). Further information is available in the Company's response to Key Issue 6 at Technical Engagement.</p> <p><b>NMA results</b></p> <p>Updated results from the NMA, generated using the amended approach to adjusting the pseudo-control</p>	



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			<p>arm and using a FE hierarchical exchangeable model for OS and PFS are presented.</p> <p><b><u>Analyses and results for ORR, PFS, and OS not reproduced here - see p. 6-8 company's response to consultation on the ACD.</u></b></p>	
3	Consultee (company)	Eli Lilly and Company Limited (Lilly)	<p><b>Uncertainty in the OS and PFS survival extrapolations</b></p> <p>Lilly would like to address the concerns of the Committee regarding the uncertainty in OS and PFS survival extrapolations. As discussed during the Committee meeting, the increase in OS in the simulated control arm was because of the adjustment processes for <i>RET</i> fusion status used in its generation. Given the revisions to the generation of the pseudo-control arm to produce more clinically plausible survival estimates for <i>RET</i> fusion-positive NSCLC patients treated with docetaxel monotherapy (see Comment 2), it was necessary to review an updated set of survival extrapolations for selpercatinib and docetaxel monotherapy for PFS and OS.</p> <p>PFS and OS functions for the other relevant comparator (nintedanib plus docetaxel) were constructed through the application of the HR generated in the revised NMA to the reference (docetaxel) arm extrapolation.</p> <p><b><u>Analyses and results for the OS and PFS survival extrapolations not reproduced here - see page 11-13 of the company's response to consultation on the ACD.</u></b></p> <p><b>Scenario analyses</b></p> <p>Scenario analyses for PFS included using the unstratified Gompertz, Gamma, stratified Weibull and Spline/Knot=1 survival functions. Scenario analyses for OS included applying the unstratified exponential, Weibull, stratified Weibull and stratified Gamma survival functions. Results from the scenario analyses are presented in Table 16, Appendix B.</p> <p><b><u>Results from the scenario analyses not reproduced here. See Error! Reference source not found.6, Error! Reference source not found. in the company's response to consultation on the ACD.</u></b></p>	<p>Comments noted. See FAD sections 3.9, 3.10 and 3.19. The committee concluded long-term survival with selpercatinib remained uncertain, but it agreed it was appropriate to consider the company's survival estimates for selpercatinib in its decision making. It also agreed that further data collection in the ongoing LIBRETTO 001 trial may reduce the uncertainties.. The committee agreed that the company's revised survival</p>



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				<p>extrapolations for the simulated control arm were clinically plausible and therefore appropriate for its decision making. However, the committee also agreed that the other extrapolations were equally plausible and because of this the survival estimates were highly uncertain. The committee noted that these uncertainties would not be fully resolved by data collection in the Cancer Drugs Fund.</p>
4	Consultee (company)	Eli Lilly and Company Limited (Lilly)	<p><b>The economic model should use time to discontinuation (TTD) when calculating the cost of selpercatinib</b></p> <p>Lilly understands the Committee’s rationale for suggesting that TTD extrapolations, based on LIBRETTO-001 data, be used to inform time on treatment for selpercatinib in the cost-effectiveness analysis, instead of PFS. Namely, as described in the ACD, clinicians may deem that patients can derive further benefit from continued treatment with selpercatinib following progression. This may be because an initially large tumour</p>	<p>Comments noted. See FAD section 3.11. The committee concluded that TTD should be</p>

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			<p>may have substantially decreased in size with selpercatinib treatment, and so 'progressed disease' is less severe than the patient's original disease status, or alternatively because a secondary tumour in the body has progressed, but there is still a positive effect of treatment on the first tumour.</p> <p>Lilly would like to clarify the approach taken to model time on treatment for selpercatinib during the technical engagement stage. To account for the fact that patients may continue treatment following progression (as discussed above), the mean time from progression to treatment discontinuation was sourced directly from LIBRETTO-001 and applied to the PFS curve.</p> <p><b><u>Analyses and results for mean time from progression to treatment discontinuation not reproduced here - see p. 14-15 company's response to consultation.</u></b></p> <p>Since use of TTD extrapolations based on LIBRETTO-001 data are observed to over-estimate time on treatment relative to progression, Lilly have maintained the approach to time on treatment adopted during Technical Engagement. In addition, to assist the Committee's decision-making, sensitivity analyses have also been conducted in which time to discontinuation following progression is varied through the 95% confidence intervals to the mean.</p> <p><b><u>Appendix B not reproduced here – see Appendix B, company's response to consultation on the ACD.</u></b></p>	<p>used when calculating the cost of selpercatinib.</p>
5	Consultee (company)	Eli Lilly and Company Limited (Lilly)	<p><b>Revised base-case cost-effectiveness results</b></p> <p>Lilly has updated the results from the economic model to incorporate the change in pseudo-control arm generation (see Comment 2) and the revised PAS (see Comment 1). As deemed acceptable by the Committee, Lilly have retained the progressed disease (PD) utility value that was applied at Technical Engagement (0.628). As such, utility values for progression free and PF health states were █████ and 0.628, respectively (please see the Company's response to Key Issue 9 of the Technical Engagement Response for further details). Lilly has also retained the approach for time-on-treatment adopted during Technical Engagement, applying the mean time from progression to treatment discontinuation from LIBRETTO-001 (please see the Company's Comment 4 above for further details).</p> <p>A summary of the results for the revised company base case analysis for RET fusion-positive NSCLC, using LIBRETTO-001 data from the 16th December 2019 data cut, is presented in Appendix B.</p> <p><b><u>Appendix B not reproduced here – see Appendix B, company's response to consultation on the ACD.</u></b></p>	<p>Comments noted. See FAD sections 3.14, 3.18 and 3.19. The committee concluded that the most plausible ICER for selpercatinib compared with docetaxel would be closer to the ERG's ICER of £76,210 per QALY gained, as this ICER incorporated its</p>

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				<p>preferred assumption. It was therefore outside the range normally considered a cost-effective use of NHS resources, even considering the end of life criteria. The committee concluded it could not recommend selpercatinib for routine use. The company proposed a confidential commercial arrangement for use within the Cancer Drugs Fund. The committee was satisfied that when the commercial access agreement was applied, selpercatinib had plausible potential to be</p>

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				cost effective. It concluded that selpercatinib met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
6	Consultee (company)	Eli Lilly and Company Limited (Lilly)	<p><b>Evidence is not sufficiently robust to determine if selpercatinib meets the criteria to be an end-of-life treatment</b></p> <p>Lilly is in agreement with the Appraisal Committee’s conclusion that NICE’s end-of-life Criterion 1 (the treatment is indicated for patients with a short life expectancy, normally less than 24 months) is met for pre-treated patients with advanced non-squamous <i>RET</i> fusion-positive NSCLC in England and Wales.</p> <p>To address the concerns of the Committee that uncertainty around the OS estimate for docetaxel monotherapy meant that it is unclear whether treatment with selpercatinib met Criterion 2 (treatment offers an extension to life, normally of at least an additional 3 months), Lilly has revised its approach to generating the pseudo-control arm (please see Lilly’s Comment 2). These updates produced a median OS for docetaxel monotherapy (██████████) that more closely aligns with clinical expectation and the published literature.<sup>1,9</sup> Two key consequences of this are as follows. Application of the NMA-derived HR for nintedanib plus docetaxel to docetaxel in the model gives rise to a more clinically plausible estimate of OS for nintedanib plus docetaxel. Secondly, a more reliable estimate of the difference in survival likely to be achieved by patients treated with selpercatinib, compared to docetaxel or nintedanib plus docetaxel, can be obtained from the model.</p> <p><b><u>Revised base case survival outcomes for PFS and OS not reproduced here – see p. 16 company’s response to consultation on the ACD.</u></b></p> <p>Lilly believes that:</p> <ul style="list-style-type: none"> <li>• Uncertainty in the OS estimate for docetaxel monotherapy has been addressed through revisions to the method for generating the pseudo-control arm, providing a reliable measure of effect from the economic model that aligns with clinician estimates and clinical practice</li> <li>• Pre-treated advanced non-squamous <i>RET</i> fusion-positive NSCLC patients receiving docetaxel</li> </ul>	Comments noted. See FAD sections 3.16 and 3.17. The committee accepted that there was uncertainty in how the simulated control arm was generated. But it agreed that the updated OS results for docetaxel were plausible and concluded that the short life expectancy criterion was met. A wide range of survival extrapolations

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			monotherapy or nintedanib plus docetaxel in the second line or beyond in England and Wales have a life expectancy <24 months and are highly likely to experience an extension to life >3 months if they were to receive selpercatinib monotherapy <ul style="list-style-type: none"> <li>Lilly’s revisions confirm that selpercatinib monotherapy meets Criterion 1 and Criterion 2 of NICE’s end-of-life criteria, when used in pre-treated advanced non-squamous RET fusion-positive NSCLC patients.</li> </ul>	could be made from the results for the simulated control and selpercatinib treatment arms, so the committee agreed that there was uncertainty about the extent of the additional survival gain from selpercatinib compared with the simulated control arm. However, it concluded that it was likely that people having selpercatinib would benefit from an extension to life of more than 3 months.
7	Commentator	Roche Products Limited	As per the ACD papers Section 3.10, page 12, in reference to the use of TTD to model treatment costs, <i>“The company stated that this approach overestimated TTD, and therefore costs, because the data was immature.”</i>  Roche note there is an inconsistency in the company approach with LIBRETTO-001 clinical trial data used to inform the OS and PFS endpoints in the cost-effectiveness model but stating that TTD is too immature to model treatment costs. A consistent approach to modelling endpoints should be used across OS, PFS	Comments noted. See FAD section 3.11. The committee concluded that TTD should be

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			and TTD where appropriate. Therefore, Roche agree with the committee's preference of using TTD to inform the treatment costs for this appraisal.	used when calculating the cost of selpercatinib.
8	Commentator	Roche Products Limited	As per the ACD papers Section 3.11, page 13, NHS England provided a cost per test for use in the economic model which was accepted by the company. This cost per test remains confidential. Given the expected upcoming roll-out of widespread NGS testing, it is Roche's view that if a cost of testing is to be included in the economic model for this appraisal, the cost of testing attributed to selpercatinib should represent a percentage of overall testing costs. This percentage should represent the short term additional uptake in testing over and above what the expected testing roll-out would have been.	Comments noted. See FAD section 3.12. The committee concluded that incorporating the cost of genetic testing for RET fusions was appropriate.

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>• 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;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Eli Lilly and Company Limited (Lilly)</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p><b>Name of commentator person completing form:</b></p>	<p>Hamish Lunagaria, Health Economics Adviser &amp; New Product Planning</p>
<p><b>Comment number</b></p>	<p><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>



Do not paste other tables into this table, because your comments could get lost – type directly into this table.	
1	<p>Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for selpercatinib for previously treated rearranged during transfection (<i>RET</i>) fusion-positive advanced non-small cell lung cancer (NSCLC) [ID3743].</p> <p>We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend selpercatinib for this patient group, as advanced non-squamous <i>RET</i> fusion-positive NSCLC, previously treated with immunotherapy and/or platinum-based chemotherapy, is a disease with considerable unmet need and poor outcomes with current therapies. We understand the Committee’s concerns, and hope that the Committee will consider the additional evidence provided within this response document sufficient to make selpercatinib available for this patient group.</p> <p>To address the Committee’s concerns regarding uncertainty resulting from the generation of the pseudo-control arm for LIBRETTO-001, Lilly present further analyses in which the pseudo-control arm has been generated without an adjustment for <i>RET</i> status, whilst maintaining an adjustment for other available relevant prognostic factors using propensity score matching. This approach aligns with feedback from clinical experts that the effect of <i>RET</i> fusion on treatment effectiveness for people with advanced NSCLC is unknown,<sup>1</sup> and that previous OS estimations for the docetaxel arm were clinically implausible. In addition, to offer further value for money to the NHS, Lilly have increased the Patient Access Scheme (PAS) discount from [REDACTED] to [REDACTED] (80mg 60Xcapsule pack: [REDACTED]; 40mg 60Xcapsule pack: [REDACTED]). Crucially, while Lilly acknowledges the uncertainties caused by immature survival data from LIBRETTO-001, further data collection from LIBRETTO-001 would resolve these uncertainties while under the Cancer Drug’s Fund (CDF).</p> <p>Lilly therefore welcomes the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will recommend selpercatinib as a treatment option for patients with pre-treated advanced non-squamous <i>RET</i> fusion-positive NSCLC.</p>
2	<p><b>Uncertainty resulting from generation of the pseudo-control arm for LIBRETTO-001</b></p> <p>Lilly would first like to address the concerns of the Appraisal Committee that patient survival in the pseudo-control arm is overestimated, and the implications that this has on the validity of subsequent clinical and economic analyses. As outlined in Section B.1.3.1 of the Company’s original submission, patients that exhibit <i>RET</i> fusions tend to be younger, female, have a better tumour performance status and more frequently have a non-smoking status, when compared with advanced NSCLC patients whose tumour does not exhibit a <i>RET</i> fusion.<sup>2-4</sup> These social and clinical factors are known to be prognostic. However, evidence for the independent prognostic effect of <i>RET</i> fusion, in people with advanced NSCLC, is currently inconclusive, as confirmed by expert clinicians during the Appraisal Committee discussion.<sup>1</sup></p> <p>Considering this uncertainty, Lilly deemed it appropriate in their original submission to take the conservative approach of adjusting survival outcomes in the pseudo-comparator arm to account for an independent prognostic effect of the presence of a <i>RET</i> fusion. To Lilly’s knowledge, the best currently available dataset that provides an insight into survival outcomes of <i>RET</i> fusion-positive NSCLC patients is the Flatiron Clinico-Genomic Database (CGDB). Data from <i>RET</i> fusion-positive and -negative patients from this dataset were used to calculate a time acceleration factor for <i>RET</i> fusion-positive status.</p>

This adjustment appeared to artificially increase overall survival (OS) in the pseudo-control arm, thus overestimating length of survival, as informed by expert clinician opinion, in advanced *RET* fusion-positive NSCLC patients treated with docetaxel monotherapy.<sup>1</sup>

Since the development of the original submission, Lilly has identified the analysis reported by Hess et al. (2021), who assessed tumour response outcomes in 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761) in the United States using data from the Flatiron CGDB.<sup>5</sup> In unadjusted analyses, Hess et al. (2021) found that there was no significant difference in progression free survival (PFS) by *RET* fusion status ( $p=0.06$ ), but that OS did differ significantly (hazard ratio [HR]: 1.91; 95% CI: 1.22–3.0;  $p=0.005$ ). However, after adjusting for baseline covariates, there was no statistically significant difference identified for either PFS (HR: 1.24; 95% CI: 0.86–1.78;  $p=0.25$ ) or OS (HR: 1.52; 95% CI: 0.95–2.43;  $p=0.08$ ) in patients treated with standard therapy prior to the availability of selective *RET* inhibitors.<sup>5</sup> While Lilly acknowledges that the study is limited due to the small sample size of the *RET* fusion-positive population and potential unmeasured confounding,<sup>5</sup> the lack of statistically significant difference in adjusted survival outcomes by *RET* status suggests that the adjustment for *RET* in the original submission was not necessary to calculate a clinically plausible estimate of OS in the pseudo-comparator arm, given these recent findings.

Given the above analysis and feedback from expert clinicians on probable survival times for *RET* fusion-positive patients treated with docetaxel, Lilly therefore considers it appropriate to remove the *RET* adjustment step from the process used to generate the pseudo-control arm (further details on the revised methodology is provided below). This avoids the artificial inflation of OS caused by Flatiron CGDB adjustment, providing a more clinically plausible reflection of OS in *RET* fusion-positive patients treated with docetaxel monotherapy. As outlined below, differences in prognostic baseline characteristics between the LIBRETTO-001 selpercatinib arm and the pseudo-control arm continued to be adjusted for in the Company's approach.

#### **Revised approach to the generation of the pseudo-control arm for LIBRETTO-001**

As described in the Company's response to Key Issue 6 at Technical Engagement, the pseudo-control arm was simulated for the LIBRETTO-001 trial using individualised patient data (IPD) from the docetaxel plus placebo arm of the REVEL RCT, which included patients with advanced non-squamous NSCLC who had progressed after a first line platinum-based chemotherapy regimen.<sup>6</sup> The IPD from the REVEL trial were adjusted for prognostic factors through matching with IPD from the LIBRETTO-001 trial, using propensity scores with a logistic regression model.<sup>7</sup> The covariates that were used as adjustment factors during propensity score matching remain the same from the Company's Technical Engagement responses and are listed in Table 3 in the Technical Engagement response document. This adjustment was necessary to account for any differences in characteristics between trial populations, and to generate a reliable treatment effect estimate for the two treatments.

Table 1 provides a summary of the baseline patient characteristics of the LIBRETTO-001 and REVEL trial populations, alongside data showing the impact of matching using propensity scores. The matching process can be seen to have aligned key population characteristics between the selpercatinib and pseudo-control arm.

**Table 1. Summary of patient characteristics of the REVEL and LIBRETTO-001 pre-treated NSCLC trial populations, before and after propensity score matching**

Characteristic	Baseline characteristics		After propensity score matching <sup>a</sup>	
	LIBRETTO-001, IAS (selpercatinib) (N=174) <sup>b</sup>	REVEL (docetaxel + placebo) (N=447) <sup>c</sup>	Docetaxel + placebo arm (N=174)	Difference
Age (mean, years)	████	████	████	████
Female, %	██	██	██	██
Race: White, %	██	██	██	██
Race: Asian, %	██	██	██	██
Race: Other, %	█	█	█	██
Never smoked, %	██	██	██	█
Histology: Non-squamous	████	████	████	█
Stage III, %	█	█	█	█
Stage IV, %	██	██	██	██
ECOG ≥ 1, %	██	██	██	██
Time since diagnosis to start of trial (median months)	██	██	██	██

**Notes:** <sup>a</sup> The analysis followed greedy match as the matching algorithm. <sup>b</sup> The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the need to exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on covariates required for the matching process. <sup>c</sup> A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to generate the pseudo-control arm.

**Abbreviations:** ECOG: Eastern Cooperative Oncology Group; IAS: Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.

Non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process, to obtain significance tests for the treatment effect and estimate log HRs and standard errors for selpercatinib versus the pseudo-control arm (Table 2). The HRs were then introduced into the network meta-analyses (NMA) of second line treatments, described previously in the Company submission.

**Table 2. Estimated treatment effects for selpercatinib versus docetaxel (pseudo-control arm) in pre-treated advanced non-squamous NSCLC patients**

Endpoint	HR (95% CrI)	P value
PFS	██████████	██████
OS	██████████	██████

**Abbreviations:** CrI: credible interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

The Kaplan-Meier outputs for PFS and OS, following propensity score matching, are presented in Figure 1 and Figure 2, respectively.

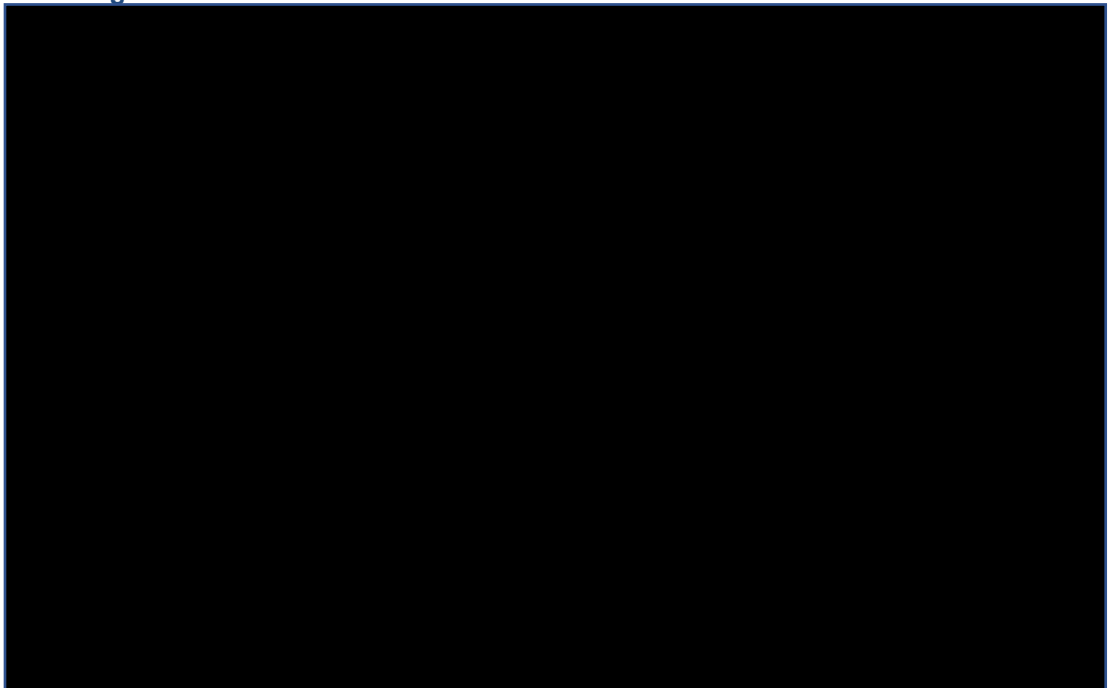
**Figure 1. Revised Kaplan-Meier chart for PFS for selpercatinib and docetaxel pseudo-control arm in pre-treated advanced NSCLC patients following propensity score matching**



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 2. Revised Kaplan-Meier chart for OS for selpercatinib and docetaxel pseudo-control arm in pre-treated advanced NSCLC patients following propensity score matching**



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

The impact of the Company's revised adjustment approach produced a median OS of [REDACTED] in the pseudo-control arm. Clinical experts estimated survival to be slightly more than 9–10 months during Committee consultation, because patients with *RET* fusion-positive advanced NSCLC tend to be younger and non-smokers.<sup>1</sup> Consequently, median OS in the pseudo-control arm, using the Company's revised approach, more closely aligns with the estimates given by clinical experts, when compared to the median OS produced when the pseudo-control arm was adjusted for *RET* status ([REDACTED]) in Company's submission at Technical Engagement. In addition, the revised approach more closely aligns with the median OS reported in pretreated adenocarcinoma patients without a *RET* fusion receiving docetaxel monotherapy (7.9 months).<sup>9</sup> The median PFS produced by the revised adjustment process ([REDACTED]) also closely aligns with the median PFS reported in pretreated adenocarcinoma patients without a *RET* fusion receiving docetaxel monotherapy (2.7 months).<sup>9</sup>

Given the above, Lilly considers that the updated NMA method, which does not adjust the pseudo-control arm for the effect of *RET* status, provides more robust PFS and OS estimates for docetaxel and will ultimately lead to a more plausible measure of the treatment effect of selpercatinib in the economic analysis.

#### **NMA meta-regression and model selection**

Consistent with the Company's submission at Technical Engagement, a meta-regression was explored to relate the size of the treatment effects obtained from the meta-analysis to certain numerical characteristics of the included trials. The study-covariates explored align with those explored at Technical Engagement, and the same models were selected for OS, PFS and objective response rate (ORR) (i.e. a fixed effects [FE] hierarchical exchangeable model without age adjustment was used for OS and PFS, while a FE hierarchical exchangeable model with adjustment for the proportion of Asian patients was used for ORR). Further information is available in the Company's response to Key Issue 6 at Technical Engagement.

#### **NMA results**

Updated results from the NMA, generated using the amended approach to adjusting the pseudo-control arm and using a FE hierarchical exchangeable model for OS and PFS are presented in the following section. ORR results are reported using a FE hierarchical exchangeable model, adjusted for the proportion of Asian patients, and remain unchanged since Technical Engagement, but are reported below for completeness. The results of the revised NMA have also been incorporated into the cost-effectiveness results presented in this ACD response (See Comment 5). Treatment effects are presented versus the common comparator in the network, docetaxel plus placebo.

#### **ORR by RECIST v1.1 (primary endpoint)**

The relative treatment effects using the FE hierarchical exchangeable model, adjusted for the proportion of Asian patients, for interventions of interest for ORR versus docetaxel plus placebo are presented in Table 3, and the forest plot is presented in Figure 3. Relative to nintedanib plus docetaxel, selpercatinib demonstrated higher odds of inducing a tumour response compared to docetaxel plus placebo (ORR: [REDACTED]; 95% CrI: [REDACTED]).

**Table 3. Relative treatment effects expressed as odds ratios versus docetaxel plus placebo (with 95% CrI) for ORR in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

Treatment	Median OR (95% CrI) versus docetaxel + placebo
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	██████████
Nintedanib + docetaxel	██████████

**Footnotes:** <sup>a</sup> Fixed effects hierarchical exchangeable model adjusted for the proportion of Asian patients.  
**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 3. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for ORR in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable model adjusted for the proportion of Asian patients)**



**Abbreviations:** CrI: Credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

#### **PFS (secondary endpoint)**

The relative treatment effects for interventions of interest for PFS versus docetaxel plus placebo are presented in Table 4, using the FE hierarchical exchangeable model. The forest plot is presented in Figure 4. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of disease progression compared to docetaxel plus placebo (HR: █████; 95% CrI: █████).

**Table 4. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for PFS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

Treatment	Median HR (95% CrI) versus docetaxel + placebo
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	██████████
Nintedanib + docetaxel	██████████

**Abbreviations:** CrI: credible interval; HR: hazard ratio; NSCLC: non-small cell lung cancer; PFS: progression-free survival.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 4. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for PFS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable)**



**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

#### **OS (secondary endpoint)**

The relative treatment effects for interventions of interest for OS versus docetaxel plus placebo are presented in Table 5 for the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 5. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of death compared to docetaxel plus placebo (HR: [REDACTED]; 95% CrI: [REDACTED]).

**Table 5. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for OS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

<b>Treatment</b>	<b>Median HR (95% CrI) versus docetaxel + placebo</b>
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	[REDACTED]
Nintedanib + docetaxel	[REDACTED]

**Abbreviations:** CrI: credible interval; HR: hazard ratio; NSCLC: non-small cell lung cancer; OS: overall survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>



**Figure 5. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for OS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable)**



**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

3

**Uncertainty in the OS and PFS survival extrapolations**

Lilly would like to address the concerns of the Committee regarding the uncertainty in OS and PFS survival extrapolations. As discussed during the Committee meeting, the increase in OS in the simulated control arm was because of the adjustment processes for *RET* fusion status used in its generation. Given the revisions to the generation of the pseudo-control arm to produce more clinically plausible survival estimates for *RET* fusion-positive NSCLC patients treated with docetaxel monotherapy (see Comment 2), it was necessary to review an updated set of survival extrapolations for selpercatinib and docetaxel monotherapy for PFS and OS.

PFS and OS functions for the other relevant comparator (nintedanib plus docetaxel) were constructed through the application of the HR generated in the revised NMA to the reference (docetaxel) arm extrapolation (Table 6). For the selpercatinib arm, as IPD were available to inform long-term extrapolations for PFS, it was not necessary to apply a HR to the reference arm to generate these.

**Table 6. HRs (95% CrI) applied to reference arm (fixed effects hierarchical exchangeable)**

Drug (patient subgroup)	PFS	OS
Nintedanib + docetaxel		

**Abbreviations:** CrI: credible interval; HR: hazard ratio; NA: not applicable; OS: overall survival; PFS: progression-free survival.

**Progression-free survival**

Model fit statistics for the parametric survival functions are available below in Table 7 and long-term extrapolations for PFS are available in Appendix A, Figure 8 and

Figure 9. Among all the curves explored, minimal difference between the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics was observed, although the best fitting curves, as indicated by both the AIC and BIC statistics, was the unstratified Gamma and Weibull.

**Table 7. Model fit statistics for PFS second line parametric survival functions for selpercatinib and reference arm**

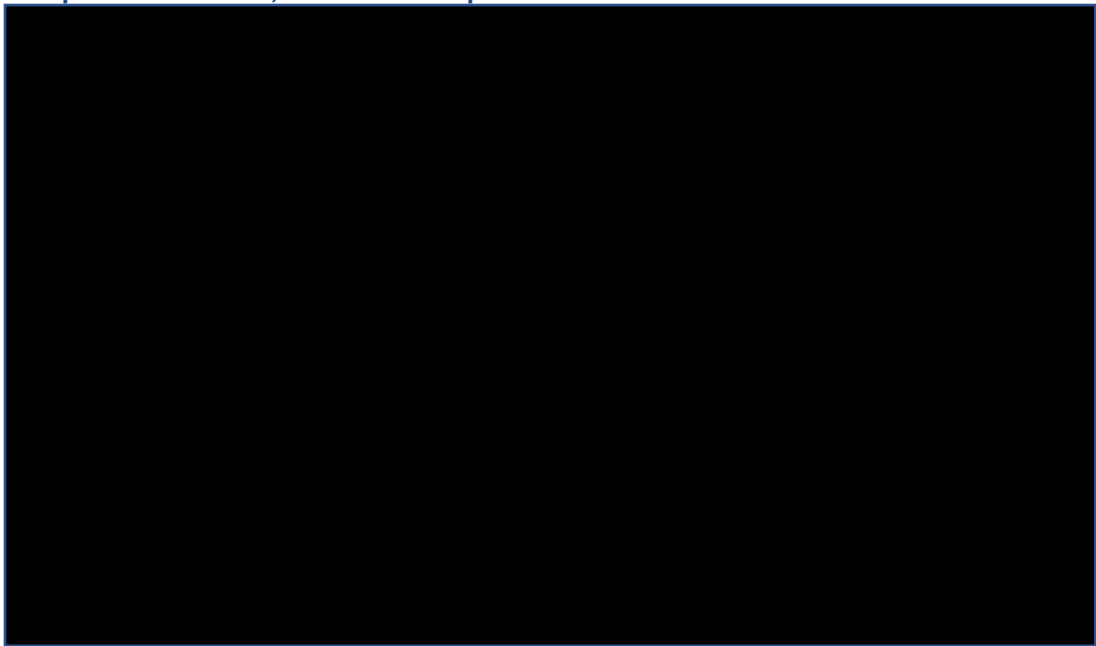
Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
<b>Unstratified</b>				
Exponential	██████	██████	█	█
Weibull	██████	██████	█	█
Log-normal	██████	██████	█	█
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	█	█
Spline/knot=2	██████	██████	█	█
Spline/knot=3	██████	██████	█	█
<b>Stratified</b>				
Weibull	██████	██████	█	█
Log-normal	██████	██████	█	█
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	█	█
Spline/knot=2	██████	██████	█	█
Spline/knot=3	██████	██████	█	█

**Abbreviations:** AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Lilly considers that the stratified Gompertz function remains the most appropriate choice for extrapolating the selpercatinib PFS curve. The reasoning for this choice is provided in the Company’s response to Key Issue 8 at Technical Engagement. In addition, Lilly considers that the stratified Gompertz is the most appropriate function for the docetaxel comparator arm, because it produces consistent predictions to trial data published in the literature (predicted: █████ months versus REVEL: 3.0 months;<sup>6</sup> LUME-Lung 1: 2.7 months)<sup>9</sup> and only has a small percentage of patients remaining progression-free after five years.

The revised Company base case extrapolations for selpercatinib and comparators for PFS is presented in Figure 6.

**Figure 6. Revised Company base case extrapolations for selpercatinib and comparators for PFS, stratified Gompertz**



**Abbreviations:** KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; PFS: progression-free survival.

**Overall survival**

Model fit statistics for the parametric survival functions are provided in Table 8, and long-term extrapolations for OS are available in Appendix A, Figure 10 and Figure 11. Among all the curves explored, minimal differences between the AIC and BIC statistics were observed, although the best fitting curves, as indicated by both the AIC and BIC statistics, was the unstratified exponential and log-logistic.

**Table 8. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm**

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
<b>Unstratified</b>				
Exponential	██████	██████	█	█
Weibull	██████	██████	█	█
Log-normal	██████	██████	█	█
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	█	█
Spline/knot=2	██████	██████	█	█
Spline/knot=3	██████	██████	█	█
<b>Stratified</b>				
Weibull	██████	██████	█	█
Log-normal	██████	██████	█	█
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█

Spline/knot=1	████	████	█	█
Spline/knot=2	████	████	█	█
Spline/knot=3	████	████	█	█

**Abbreviations:** AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Given the absence of published evidence on the long-term survival of pre-treated patients with advanced non-squamous *RET* fusion-positive NSCLC treated with docetaxel monotherapy or selpercatinib, clinical expert opinion was sought at Technical Engagement. Estimates for long term survival, provided by clinical experts at Technical Engagement, are presented again in Table 9 below for ease of reference.

**Table 9. Survival projections for previously treated patients receiving docetaxel monotherapy or selpercatinib provided by clinical experts at Technical Engagement**

Population	5-year survival (%)	10-year survival (%)	20-year survival (%)	25 year-survival (%)
<b>Clinical expert one</b>				
Patient receiving docetaxel monotherapy after prior immunotherapy	█	██	█	█
<i>RET</i> fusion-positive patient receiving docetaxel monotherapy after immunotherapy	█	██	█	█
<i>RET</i> fusion-positive patient receiving selpercatinib <sup>a</sup>	████	██	████	████
<b>Clinical expert two</b>				
Patient receiving docetaxel monotherapy after prior immunotherapy	██	█	█	█
<i>RET</i> fusion-positive patient receiving docetaxel monotherapy after immunotherapy	██	█	█	█
<i>RET</i> fusion-positive patient receiving selpercatinib <sup>a</sup>	████	████	████	████

**Footnotes:** <sup>a</sup> both clinical experts were hesitant to give a reliable prediction beyond 5 years, due to lack of long-term data for *RET*-targeted therapies in NSCLC; therefore, predictions for selpercatinib beyond 5 or 10 years are uncertain and listed as unknown.

**Abbreviations:** *RET*: rearranged during transfection.

Predicted survival rates from a selection of curves are shown in Table 10 below. Only the unstratified Gompertz and stratified Weibull curves produced 10-year survival rates for selpercatinib that were consistent with the estimates provided by clinical experts at Technical Engagement (clinician estimates: █████; unstratified Gompertz: 8.5%; stratified Weibull: 9.9%). In addition, while no curve predicted a 5-year survival rate that closely aligned with estimates provided by clinical experts, the unstratified Gompertz and stratified Weibull curves produced the closest estimates for selpercatinib (clinician estimates: █████; unstratified Gompertz: 38.8%; stratified Weibull: 36.1%). With the exception of the stratified Gompertz, which was deemed clinically implausible due to significantly underestimating survival for selpercatinib compared to clinician estimates (stratified Gompertz: 3.9% at 5-years and 0% at 10-years) and predicting shorter long-term survival than docetaxel, these two curves represent the most conservative choices of survival functions.

To further support these estimates, in Tan et al. (2020), patients treated with a selective *RET* tyrosine kinase inhibitor had a median OS of 49.3 months, which aligns with the median OS estimated by the unstratified Gompertz (████ months) and stratified Weibull (████ months) curves. While the analysis reported by Tan et al. (2020) was performed

using a mixture of treatment naive and pre-treated patients, a small study population (n=60) and a retrospective design, this analysis does lend evidence to provide external validity for the predicted OS estimates. In addition, the survival values reported by Tan et al. (2020) could suggest that the clinician 5-year survival estimates may be pessimistic (see Table 9).<sup>10</sup>

As such, Lilly considers that the unstratified Gompertz and stratified Weibull curves provide the most clinically plausible extrapolations for the selpercatinib arm, while also being the most conservative. As the unstratified Gompertz provided a slightly lower 10-year survival estimate compared to the stratified Weibull curve, the Gompertz was applied in the revised base case. Lilly acknowledges that immaturity in the LIBRETTO-001 survival data presents challenges with regards to parametric survival curve fitting, particularly to the tail ends of the Kaplan-Meier curves, where few patients remain. However, ongoing data collection under the CDF, including more mature estimates of OS, would help to reduce this uncertainty.

For the docetaxel comparator arm, the unstratified Gompertz function was also considered to be the most appropriate choice for extrapolation, as it produced median OS predictions that were consistent with estimates provided by expert clinicians, who estimated survival could be slightly more than 10 months, given that *RET* fusion-positive patients often have baseline characteristics associated with improved survival (see Comment 2 in this response).<sup>1</sup> Furthermore, the median OS prediction, using the unstratified Gompertz function, was broadly consistent with published trial data in advanced NSCLC patients without a *RET* fusion, treated with docetaxel monotherapy (predicted: 13.38 months versus REVEL: 9.1 months;<sup>6</sup> LUME-Lung 1: 7.9 months).<sup>9</sup>

**Table 10. Long-term predicted survival estimates for docetaxel monotherapy and selpercatinib with a selection of survival functions**

	Median PFS <sup>a</sup> (months)	Median OS (months)	5-year survival (%)	10-year survival (%)	25-year survival (%)
<b>Exponential</b>					
Docetaxel	4.62	13.15	4.1	0.2	0
Selpercatinib	████	████	45.6	20.8	2.0
<b>Weibull</b>					
Docetaxel	4.62	13.15	2.9	0.1	0
Selpercatinib	████	████	41.7	15.8	0.7
<b>Loglogistic</b>					
Docetaxel	4.62	12.69	11.4	5	1.5
Selpercatinib	████	████	42.8	23.3	8.1
<b>Gompertz</b>					
Docetaxel	4.62	13.38	2.2	0.0	0.0
Selpercatinib	████	████	38.8	8.5	0.0
<b>Gamma</b>					
Docetaxel	4.62	13.15	3.1	0.1	0.0
Selpercatinib	████	████	41.4	15.9	0.8
<b>Stratified Weibull</b>					
Docetaxel	4.62	13.15	3.2	0.1	0.0
Selpercatinib	████	████	36.1	9.9	0.1
<b>Spline/Knot 1</b>					

Docetaxel	4.62	13.15	2.2	0.1	0.0
Selpercatinib	■	■	39.2	17.3	0.1
<b>Stratified Gamma</b>					
Docetaxel	4.62	13.15	3.3	0.1	0.0
Selpercatinib	■	■	39.3	13.8	0.5

**Footnotes:** <sup>a</sup> fixed by applying the stratified Gompertz.

**Abbreviations:** OS: overall survival; PFS: progression-free survival.

The recommended base case extrapolations for selpercatinib and comparators for OS is presented in Figure 7.

**Figure 7. Base case extrapolations for selpercatinib and comparators for OS, unstratified Gompertz**



**Abbreviations:** KM: Kaplan-Meier; OS: overall survival. ■

**Scenario analyses**

Scenario analyses for PFS included using the unstratified Gompertz, Gamma, stratified Weibull and Spline/Knot=1 survival functions. Scenario analyses for OS included applying the unstratified exponential, Weibull, stratified Weibull and stratified Gamma survival functions. Results from the scenario analyses are presented in Table , Appendix B.

4

**The economic model should use time to discontinuation (TTD) when calculating the cost of selpercatinib**

Lilly understands the Committee's rationale for suggesting that TTD extrapolations, based on LIBRETTO-001 data, be used to inform time on treatment for selpercatinib in the cost-effectiveness analysis, instead of PFS. Namely, as described in the ACD, clinicians may deem that patients can derive further benefit from continued treatment with selpercatinib following progression. This may be because an initially large tumour may have substantially decreased in size with selpercatinib treatment, and so 'progressed disease' is less severe than the patient's original disease status, or alternatively because a secondary tumour in the body has progressed, but there is still a positive effect of treatment on the first tumour.

Lilly would like to clarify the approach taken to model time on treatment for selpercatinib during the technical engagement stage. To account for the fact that patients may continue treatment following progression (as discussed above), the mean time from progression to treatment discontinuation was sourced directly from LIBRETTO-001 and

applied to the PFS curve. This was [REDACTED] days (approximately [REDACTED]) in the IAS (Table 11). Accordingly, this approach to modelling time on treatment takes into account treatment that may be received following disease progression and is not solely informed by PFS.

**Table 11. Mean time (days) between meeting the PFS endpoint and treatment discontinuation for NSCLC pre-treated patients in LIBRETTO-001**

	Pre-treated NSCLC (IAS) (N=184)
Discontinued treatment during trial follow-up, n (%)	[REDACTED]
<b>Time between PFS and treatment discontinuation</b>	
Mean (days)	[REDACTED]
SD	[REDACTED]
Min, max (days)	[REDACTED]
95% CI	[REDACTED]

**Abbreviations:** CI: confidence interval; IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progress-free survival; SD: standard deviation.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

For completeness, Lilly have assessed the time on treatment estimates generated by the TTD extrapolations based on LIBRETTO-001 for face validity. Clinical expert feedback from the first Committee meeting was that patients would be unlikely to be on treatment two years after progression. Estimates of time on treatment as per the different extrapolation models compared to PFS (as informed by the stratified Gompertz extrapolation) are presented in

Table 12. Based on the expert feedback received, these results suggest that all eight TTD extrapolations consistently overestimate time on treatment after progression from three years; it can be seen that the proportion of patients on treatment two years later (at five years) is greater than the proportion of patients who were progression free at three years.



**Table 12. Time on treatment versus PFS estimates for selpercatinib**

Time (yrs)	PFS: Stratified Gompertz (%)	On Treatment (based on TTD curves)							
		Exponential (%)	Weibull (%)	Lognormal (%)	Loglogistic (%)	Gompertz (%)	Gamma (%)	Spline Knot 1 (%)	Spline Knot 2 (%)
1	■	■	■	■	■	■	■	■	■
2	■	■	■	■	■	■	■	■	■
3	■	■	■	■	■	■	■	■	■
4	■	■	■	■	■	■	■	■	■
5	■	■	■	■	■	■	■	■	■
6	■	■	■	■	■	■	■	■	■
7	■	■	■	■	■	■	■	■	■
8	■	■	■	■	■	■	■	■	■
9	■	■	■	■	■	■	■	■	■
10	■	■	■	■	■	■	■	■	■

**Abbreviations:** PFS: progression free survival; TTD: time to treatment discontinuation.

Since use of TTD extrapolations based on LIBRETTO-001 data are observed to over-estimate time on treatment relative to progression, Lilly have maintained the approach to time on treatment adopted during Technical Engagement. In addition, to assist the Committee’s decision-making, sensitivity analyses have also been conducted in which time to discontinuation following progression is varied through the 95% confidence intervals to the mean (please see Appendix B), which show only a small variation to the base case ICER.

5

**Revised base-case cost-effectiveness results**

Lilly has updated the results from the economic model to incorporate the change in pseudo-control arm generation (see Comment 2) and the revised PAS (see Comment 1). As deemed acceptable by the Committee, Lilly have retained the progressed disease (PD) utility value that was applied at Technical Engagement (0.628). As such, utility values for progression free and PF health states were ■ and 0.628, respectively (please see the Company’s response to Key Issue 9 of the Technical Engagement Response for further details). Lilly has also retained the approach for time-on-treatment adopted during Technical Engagement, applying the mean time from progression to treatment discontinuation from LIBRETTO-001 (please see the Company’s Comment 4 above for further details).

A summary of the results for the revised company base case analysis for *RET* fusion-positive NSCLC, using LIBRETTO-001 data from the 16<sup>th</sup> December 2019 data cut, is presented in Appendix B.

6

**Evidence is not sufficiently robust to determine if selpercatinib meets the criteria to be an end-of-life treatment**

Lilly is in agreement with the Appraisal Committee’s conclusion that NICE’s end-of-life Criterion 1 (the treatment is indicated for patients with a short life expectancy, normally less than 24 months) is met for pre-treated patients with advanced non-squamous *RET* fusion-positive NSCLC in England and Wales.

To address the concerns of the Committee that uncertainty around the OS estimate for docetaxel monotherapy meant that it is unclear whether treatment with selpercatinib met Criterion 2 (treatment offers an extension to life, normally of at least an additional 3 months), Lilly has revised its approach to generating the pseudo-control arm (please see Lilly’s Comment 2). These updates produced a median OS for docetaxel monotherapy (██████████) that more closely aligns with clinical expectation and the published literature.<sup>1, 9</sup> Two key consequences of this are as follows. Application of the NMA-derived HR for nintedanib plus docetaxel to docetaxel in the model gives rise to a more clinically plausible estimate of OS for nintedanib plus docetaxel. Secondly, a more reliable estimate of the difference in survival likely to be achieved by patients treated with selpercatinib, compared to docetaxel or nintedanib plus docetaxel, can be obtained from the model.

As presented in Table 13, selpercatinib is associated with an extension to survival of ██████ and ██████ median months compared to nintedanib plus docetaxel and docetaxel monotherapy, respectively. Nintedanib plus docetaxel and docetaxel monotherapy are themselves associated with an estimated survival of ██████ years and ██████ years, respectively, using the revised approach outlined above. As noted in Comment 2, the median OS estimate for docetaxel monotherapy aligns with clinician estimates and the published literature.<sup>9</sup> Similarly, median OS estimates for treatment with nintedanib plus docetaxel more closely align with the published literature in adenocarcinoma patients who progressed within 9 months of initiating first line treatment (10.9 months)<sup>9</sup> and reflect comments from clinical experts that the addition of nintedanib to docetaxel only results in a modest improvement to survival.<sup>1</sup>

**Table 13. Revised base case survival outcomes (PFS and OS) and clinical outcomes**

Intervention/comparator	Median PFS (months)	Mean PFS (months)	Median OS (months)	Discounted LYs	Undiscounted LYs
<b>Revised base case survival outcomes</b>					
Selpercatinib	██████	██████	██████	██████	██████
Docetaxel monotherapy	██████	██████	██████	██████	██████
Nintedanib + docetaxel	██████	██████	██████	██████	██████

**Abbreviations:** OS: overall survival; PFS: progression-free survival.

Given the above, Lilly believes that:

- Uncertainty in the OS estimate for docetaxel monotherapy has been addressed through revisions to the method for generating the pseudo-control arm, providing a reliable measure of effect from the economic model that aligns with clinician estimates and clinical practice
- Pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second line or beyond in England and Wales have a life expectancy <24 months and are highly likely to experience an extension to life >3 months if they were to receive selpercatinib monotherapy
- Lilly’s revisions confirm that selpercatinib monotherapy meets Criterion 1 and Criterion 2 of NICE’s end-of-life criteria, when used in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- 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 submitted under [REDACTED] and all information submitted under [REDACTED]. If confidential information is submitted, please also send a 2<sup>nd</sup> version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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 appraisal consultation document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

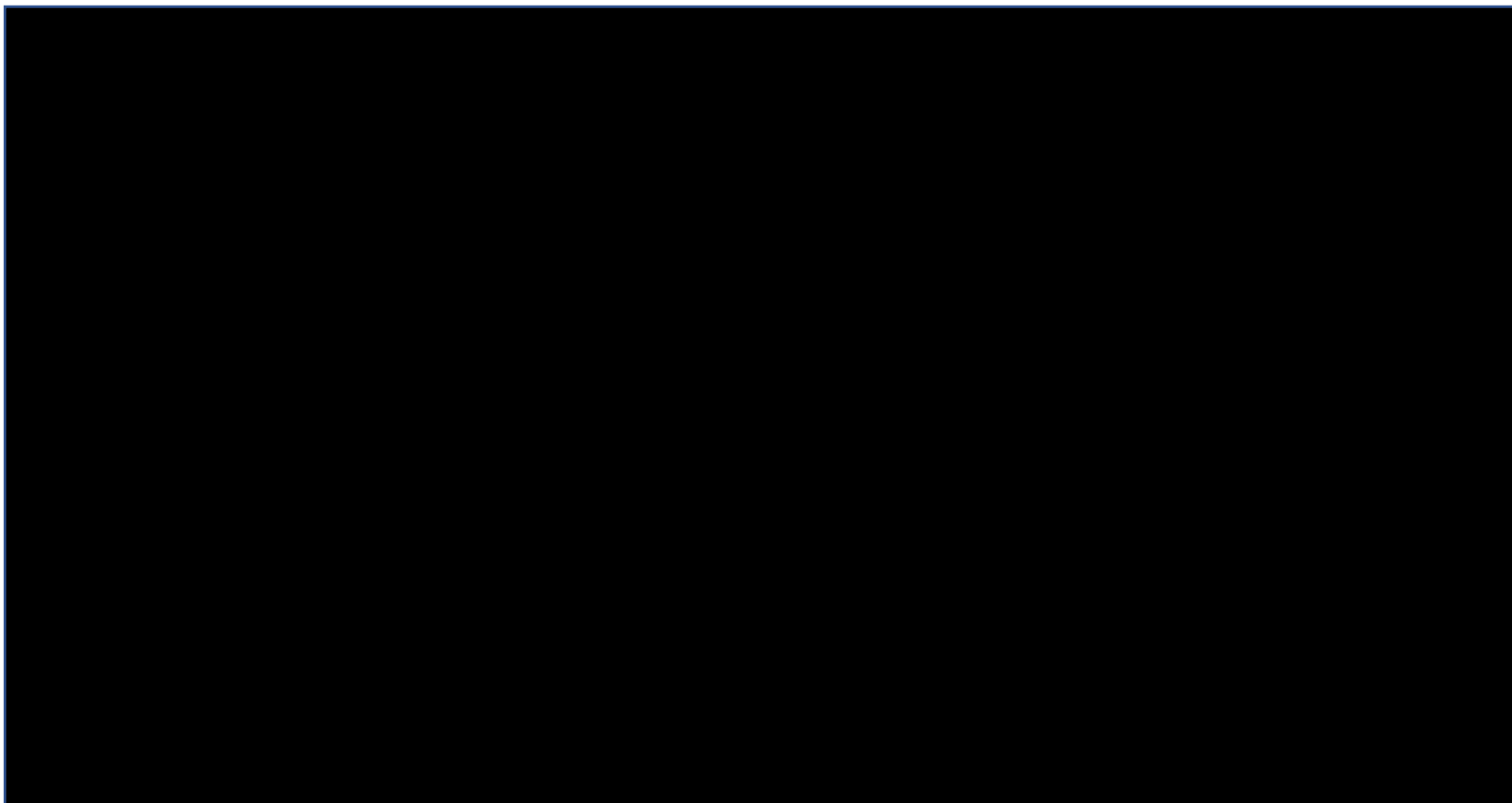
Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

**Appendix A**

***PFS***

Long term extrapolations for PFS are provided below in Figure 8 and Figure 9.

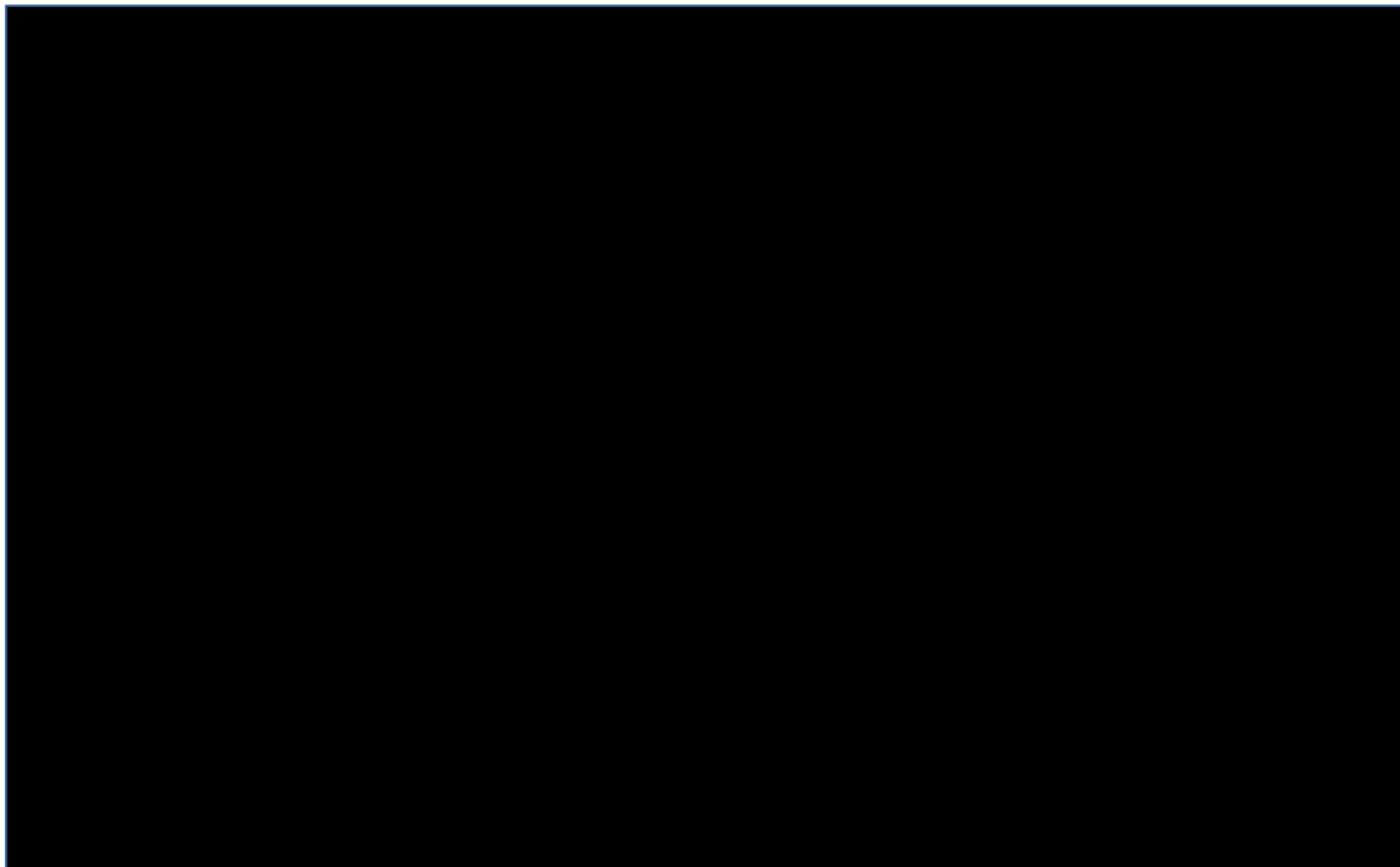
**Figure 8. Selpercatinib PFS parametric survival function extrapolations in second line advanced NSCLC patients**



**Abbreviations:** NSCLC: non-small cell lung cancer; PFS: progression free survival.

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Figure 9. Reference arm (docetaxel) PFS parametric survival function extrapolations in second line advanced NSCLC patients



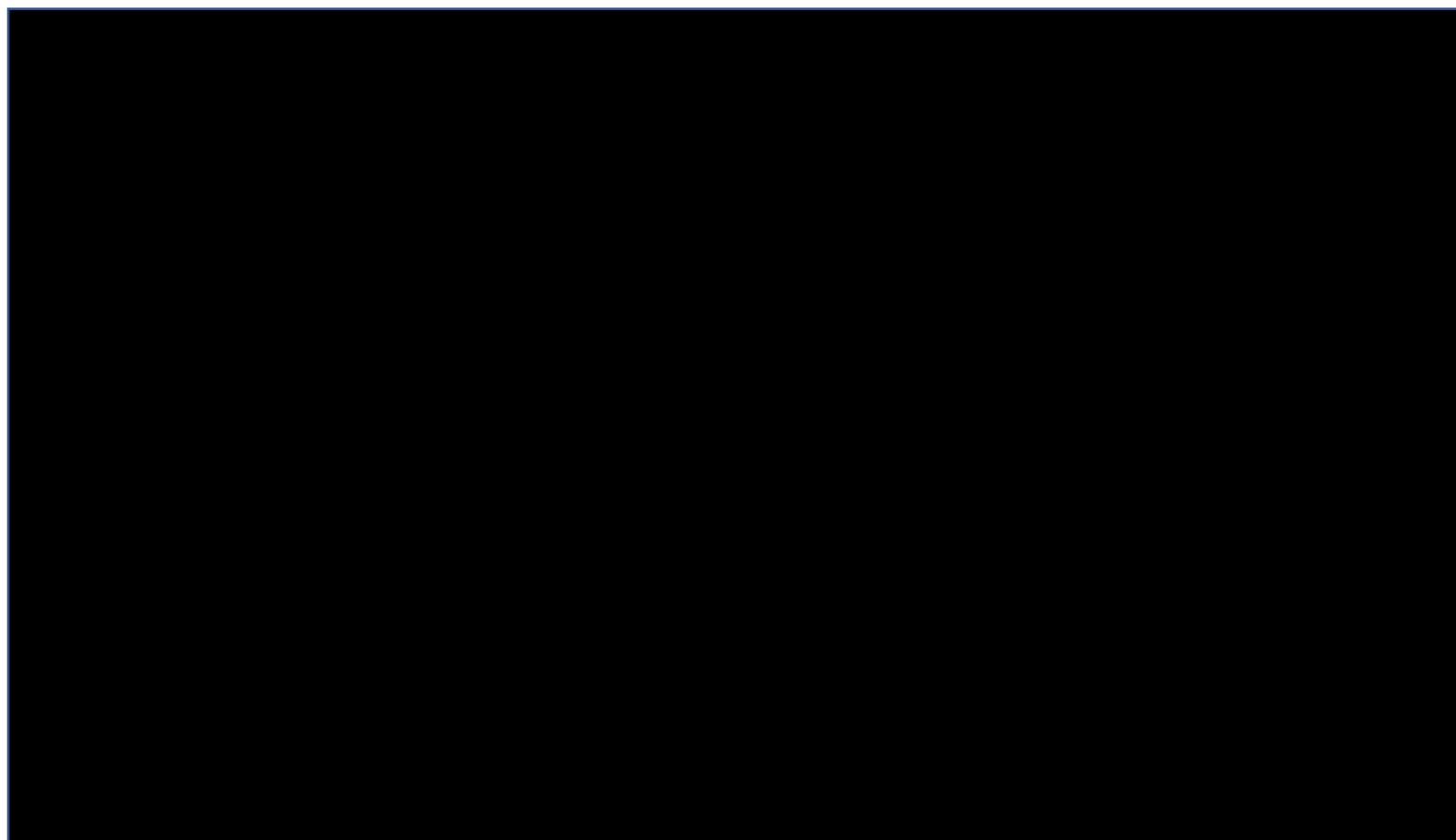
**Abbreviations:** NSCLC: non-small cell lung cancer; PFS: progression free survival.

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**OS**

Long term extrapolations for OS are provided below in Figure 10 and Figure 11.

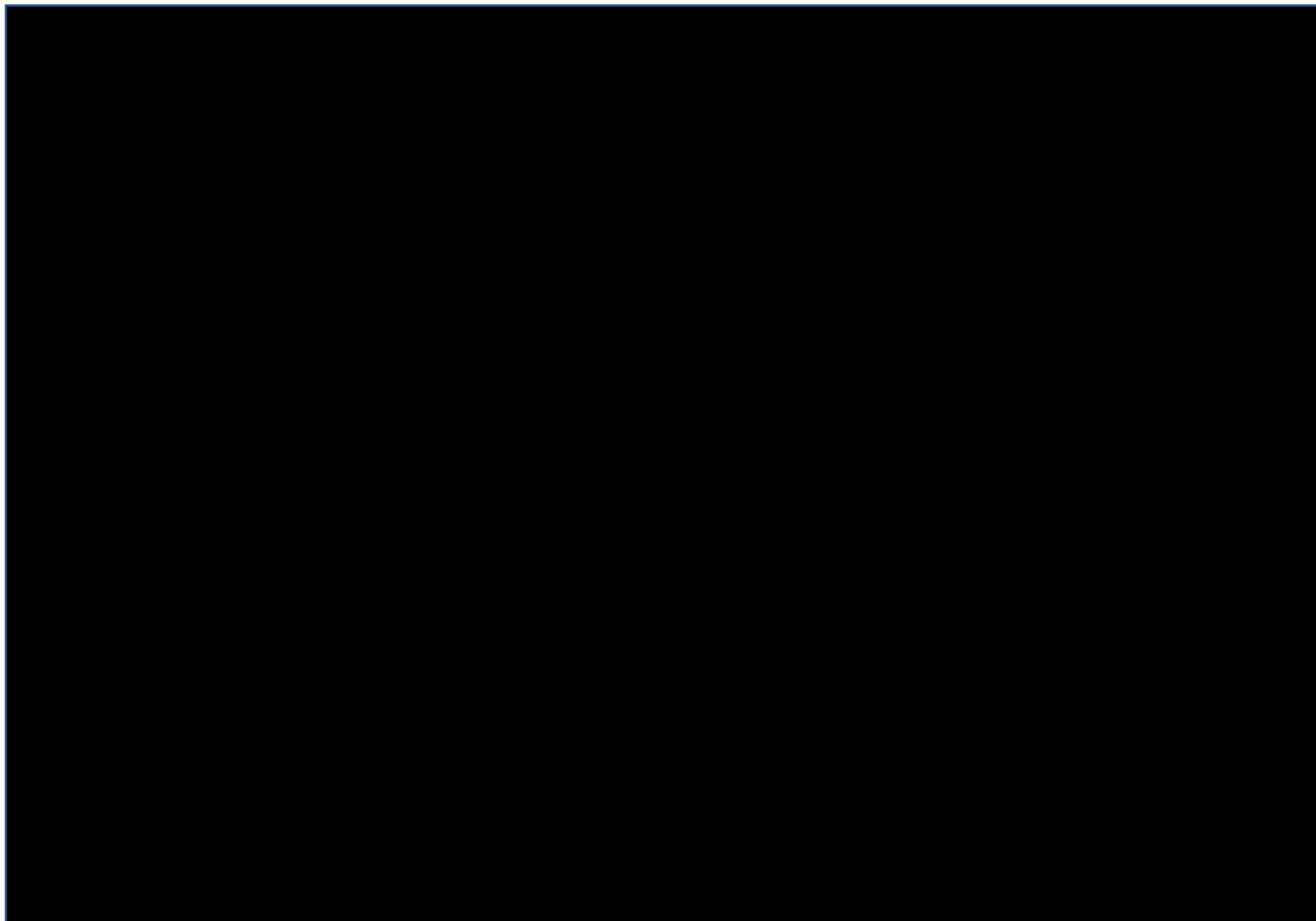
**Figure 10. Selpercatinib OS parametric survival function extrapolations in second line advanced NSCLC patients**



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival.

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Figure 11. Reference arm (docetaxel) OS parametric survival function extrapolations in second line advanced NSCLC patients





**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival.

## Appendix B

A summary of the base case analysis results (with PAS) is presented in Table 14. The results illustrate that versus all comparators, selpercatinib is associated with greater QALYs, reflecting the high levels of efficacy of selpercatinib in the second line *RET* fusion-positive NSCLC population.

**Table 14. Base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	████	██	██	-	-	-	-	55,119
Nintedanib + docetaxel	████	██	██	████	██	██	118,952 <sup>a</sup>	48,800
Selpercatinib	████	██	██	████	██	██	55,119	-

**Footnotes:** <sup>a</sup> Nintedanib plus docetaxel is extendedly dominated.

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

### Probabilistic sensitivity analysis

The probabilistic base case results are presented in Table 15. The PSA results illustrate that versus both comparators, selpercatinib is associated with greater QALYs. The deterministic and probabilistic base case results are observed to be in close alignment.

**Table 15. Probabilistic base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price**

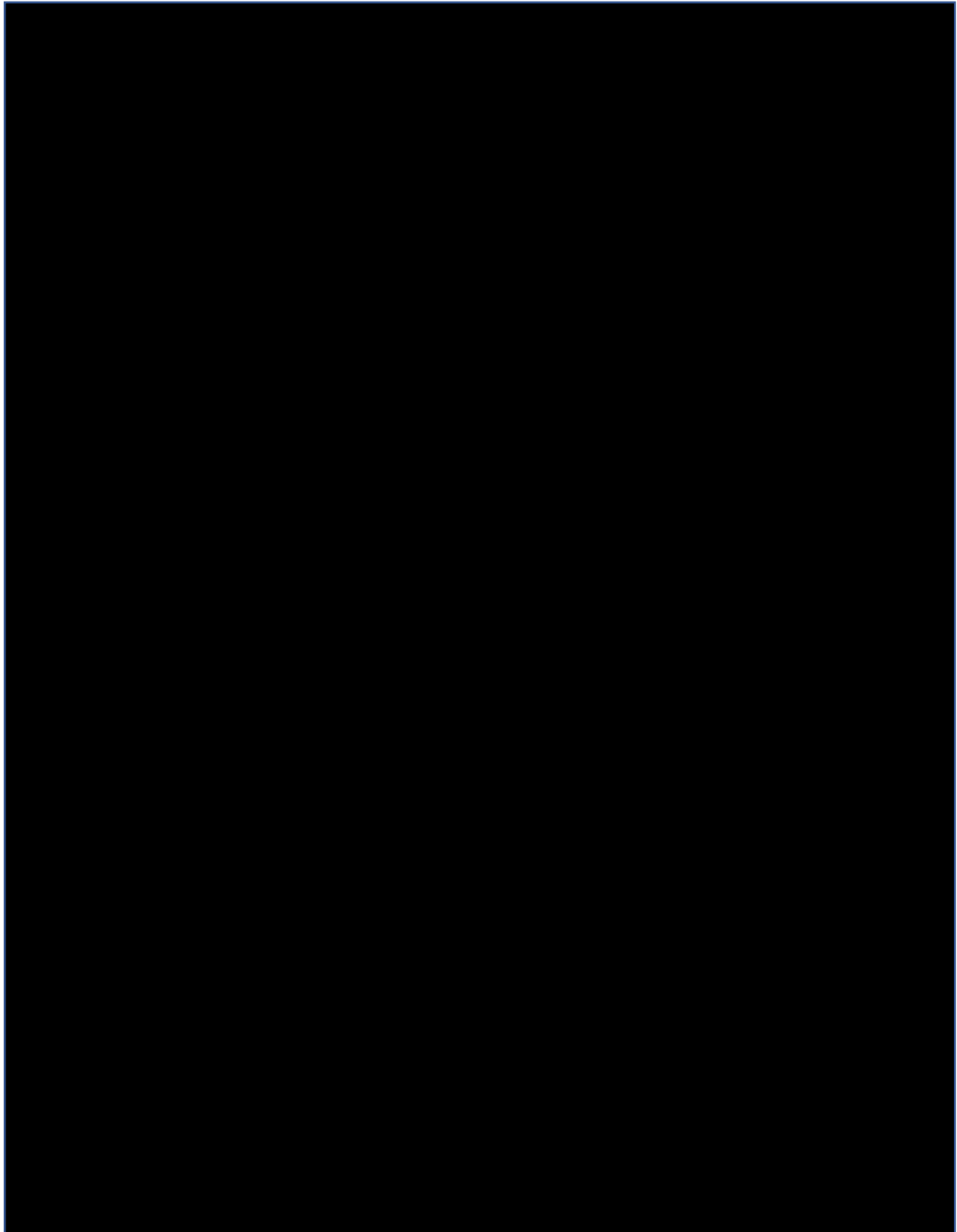
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	████	██	██	-	-	-	55,595
Nintedanib + docetaxel	████	██	██	████	██	██	49,238

Selpercatinib	██████	████	████	██████	████	████	-
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**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel are presented in Figure 12.

**Figure 12. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel**

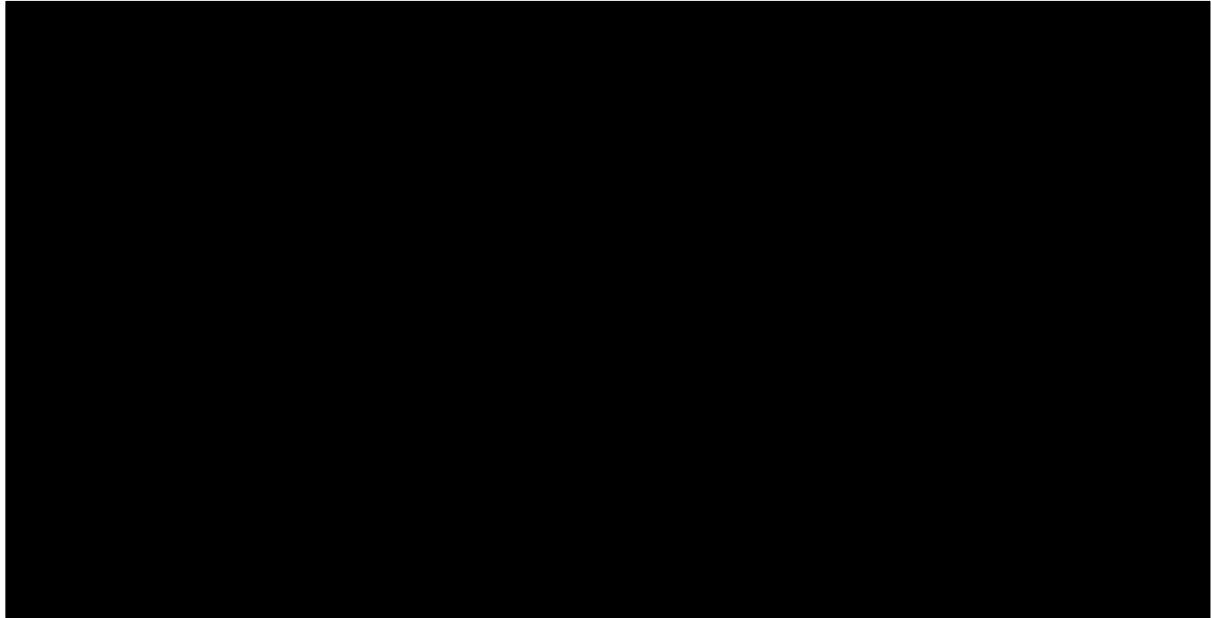


**Abbreviations:** QALY: quality-adjusted life year.

### Deterministic sensitivity analysis

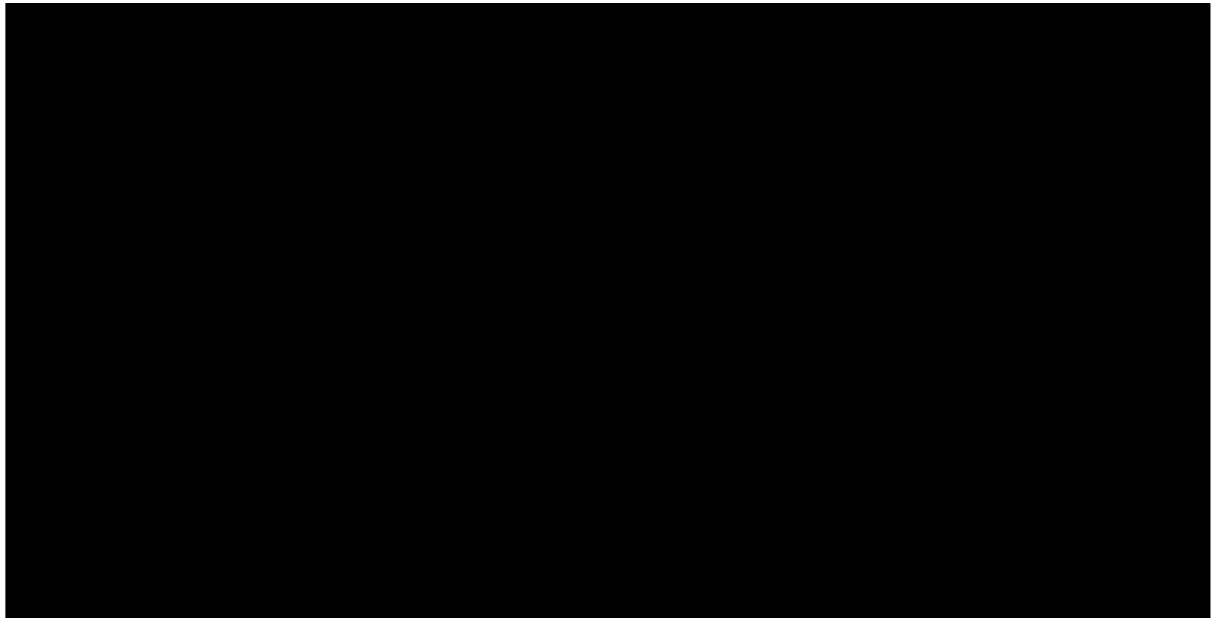
The tornado diagram by parameter for selpercatinib versus docetaxel is presented in Figure 13. The tornado diagram and by parameter for selpercatinib versus nintedanib plus docetaxel is presented in Figure 14.

**Figure 13. DSA tornado diagram for selpercatinib versus docetaxel monotherapy**



**Abbreviations:** DSA: deterministic sensitivity analysis; QALY: quality-adjust life year.

**Figure 14. DSA tornado diagram for selpercatinib versus nintedanib plus docetaxel**



**Abbreviations:** DSA: deterministic sensitivity analysis; QALY: quality-adjust life year.

### Scenario analyses

A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table . It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and all comparator arms.

**Table 16. Scenario analysis results for selpercatinib versus relevant comparators**

Scenario		Pairwise ICER vs. docetaxel (£)	% ICER change	Pairwise ICER vs. nintedanib + docetaxel (£)	% ICER change
	<b>Base case</b>	<b>55,199</b>	<b>-</b>	<b>48,800</b>	<b>-</b>
1	Alternative TTD assumptions: [REDACTED] (mid-point of lower limit of 95% CI and mean [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	54,006	-2.16%	47,577	-2.51%
2	Alternative TTD assumptions: [REDACTED] (mid-point of upper limit of 95% CI and mean [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	56,596	2.53%	50,423	3.33%
3	Alternative TTD assumptions: [REDACTED] (upper limit of 95% [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	59,540	7.86%	53,659	9.96%
4	Curve choice: OS – Exponential	43,781	-20.69%	38,719	-20.66%
5	Curve choice: OS – Weibull	48,511	-12.12%	42,455	-13.00%
6	Curve choice: OS – stratified Weibull	55,647	0.81%	49,669	1.78%
7	Curve choice: OS – stratified Gamma (selpercatinib and docetaxel arms only) <sup>a</sup>	47,811	-13.38%	42,013	-13.91%
8	Curve choice: OS – spline knot 1	46,740	-15.32%	41,259	-15.45%

9	Curve choice: PFS – Gompertz	54,018	-2.14%	47,534	-2.59%
10	Curve choice: PFS – Gamma (selpercatinib and docetaxel arms only) <sup>a</sup>	58,029	5.13%	52,083	6.73%
11	Curve choice: PFS – stratified Weibull	58,128	5.31%	52,229	7.03%
12	Curve choice: PFS – spline knot 1	61,250	10.96%	55,609	13.95%

**Footnotes:** <sup>a</sup> AFT models were only applied to the selpercatinib arm, whilst base case extrapolations were utilised for docetaxel and nintedanib plus docetaxel so that the hazard ratio from the NMA could be applied.

**Abbreviations:** ICER: incremental cost-effectiveness ratio; OS: overall survival; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity; TA: technology appraisal.

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**Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]**

**Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 27 August 2021. Please submit via NICE Docs.**

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>• 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;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Roche Products Limited</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>████████████████████</p>
<p><b>Name of commentator person completing form:</b></p>	<p>Commercial in confidence information removed</p>
<p><b>Comment number</b></p>	<p style="text-align: center;"><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>

**Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]**

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	<p>As per the ACD papers Section 3.10, page 12, in reference to the use of TTD to model treatment costs, "The company stated that this approach overestimated TTD, and therefore costs, because the data was immature."</p> <p>Roche note there is an inconsistency in the company approach with LIBRETTO-001 clinical trial data used to inform the OS and PFS endpoints in the cost-effectiveness model but stating that TTD is too immature to model treatment costs. A consistent approach to modelling endpoints should be used across OS, PFS and TTD where appropriate. Therefore, Roche agree with the committee's preference of using TTD to inform the treatment costs for this appraisal.</p>
2	<p>As per the ACD papers Section 3.11, page 13, NHS England provided a cost per test for use in the economic model which was accepted by the company. This cost per test remains confidential. Given the expected upcoming roll-out of widespread NGS testing, it is Roche's view that if a cost of testing is to be included in the economic model for this appraisal, the cost of testing attributed to selpercatinib should represent a percentage of overall testing costs. This percentage should represent the short term additional uptake in testing over and above what the expected testing roll-out would have been.</p>

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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**Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]**

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NICE, its officers or advisory committees.

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>• 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;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Eli Lilly and Company Limited (Lilly)</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p><b>Name of commentator person completing form:</b></p>	<p>Hamish Lunagaria, Health Economics Adviser &amp; New Product Planning</p>
<p><b>Comment number</b></p>	<p><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>

Do not paste other tables into this table, because your comments could get lost – type directly into this table.	
1	<p>Lilly would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for selpercatinib for previously treated rearranged during transfection (<i>RET</i>) fusion-positive advanced non-small cell lung cancer (NSCLC) [ID3743].</p> <p>We are disappointed that the Appraisal Committee have made the preliminary decision not to recommend selpercatinib for this patient group, as advanced non-squamous <i>RET</i> fusion-positive NSCLC, previously treated with immunotherapy and/or platinum-based chemotherapy, is a disease with considerable unmet need and poor outcomes with current therapies. We understand the Committee’s concerns, and hope that the Committee will consider the additional evidence provided within this response document sufficient to make selpercatinib available for this patient group.</p> <p>To address the Committee’s concerns regarding uncertainty resulting from the generation of the pseudo-control arm for LIBRETTO-001, Lilly present further analyses in which the pseudo-control arm has been generated without an adjustment for <i>RET</i> status, whilst maintaining an adjustment for other available relevant prognostic factors using propensity score matching. This approach aligns with feedback from clinical experts that the effect of <i>RET</i> fusion on treatment effectiveness for people with advanced NSCLC is unknown,<sup>1</sup> and that previous OS estimations for the docetaxel arm were clinically implausible. In addition, to offer further value for money to the NHS, Lilly have increased the Patient Access Scheme (PAS) from █████ to █████ (80mg 60Xcapsule pack: █████; 40mg 60Xcapsule pack: █████). Crucially, while Lilly acknowledges the uncertainties caused by immature survival data from LIBRETTO-001, further data collection from LIBRETTO-001 would resolve these uncertainties while under the Cancer Drug’s Fund (CDF).</p> <p>Lilly therefore welcomes the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of these further analyses, hope that the Committee will recommend selpercatinib as a treatment option for patients with pre-treated advanced non-squamous <i>RET</i> fusion-positive NSCLC.</p>
<u>ERG comment</u>	No comment
2	<p><b>Uncertainty resulting from generation of the pseudo-control arm for LIBRETTO-001</b></p> <p>Lilly would first like to address the concerns of the Appraisal Committee that patient survival in the pseudo-control arm is overestimated, and the implications that this has on the validity of subsequent clinical and economic analyses. As outlined in Section B.1.3.1 of the Company’s original submission, patients that exhibit <i>RET</i> fusions tend to be younger, female, have a better tumour performance status and more frequently have a non-smoking status, when compared with advanced NSCLC patients whose tumour does not exhibit a <i>RET</i> fusion.<sup>2-4</sup> These social and clinical factors are known to be prognostic. However, evidence for the independent prognostic effect of <i>RET</i> fusion, in people with advanced NSCLC, is currently inconclusive, as confirmed by expert clinicians during the Appraisal Committee discussion.<sup>1</sup></p> <p>Considering this uncertainty, Lilly deemed it appropriate in their original submission to take the conservative approach of adjusting survival outcomes in the pseudo-comparator arm to account for an independent prognostic effect of the presence of a <i>RET</i> fusion. To Lilly’s knowledge, the best currently available dataset that provides an insight into survival outcomes of <i>RET</i> fusion-positive NSCLC patients is the Flatiron Clinico-Genomic</p>

Database (CGDB). Data from *RET* fusion-positive and -negative patients from this dataset were used to calculate a time acceleration factor for *RET* fusion-positive status. This adjustment appeared to artificially increase overall survival (OS) in the pseudo-control arm, thus overestimating length of survival, as informed by expert clinician opinion, in advanced *RET* fusion-positive NSCLC patients treated with docetaxel monotherapy.<sup>1</sup>

Since the development of the original submission, Lilly has identified the analysis reported by Hess et al. (2021), who assessed tumour response outcomes in 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761) in the United States using data from the Flatiron CGDB.<sup>5</sup> In unadjusted analyses, Hess et al. (2021) found that there was no significant difference in progression free survival (PFS) by *RET* fusion status ( $p=0.06$ ), but that OS did differ significantly (hazard ratio [HR]: 1.91; 95% CI: 1.22–3.0;  $p=0.005$ ). However, after adjusting for baseline covariates, there was no statistically significant difference identified for either PFS (HR: 1.24; 95% CI: 0.86–1.78;  $p=0.25$ ) or OS (HR: 1.52; 95% CI: 0.95–2.43;  $p=0.08$ ) in patients treated with standard therapy prior to the availability of selective *RET* inhibitors.<sup>5</sup> While Lilly acknowledges that the study is limited due to the small sample size of the *RET* fusion-positive population and potential unmeasured confounding,<sup>5</sup> the lack of statistically significant difference in adjusted survival outcomes by *RET* status suggests that the adjustment for *RET* in the original submission was not necessary to calculate a clinically plausible estimate of OS in the pseudo-comparator arm, given these recent findings.

Given the above analysis and feedback from expert clinicians on probable survival times for *RET* fusion-positive patients treated with docetaxel, Lilly therefore considers it appropriate to remove the *RET* adjustment step from the process used to generate the pseudo-control arm (further details on the revised methodology is provided below). This avoids the artificial inflation of OS caused by Flatiron CGDB adjustment, providing a more clinically plausible reflection of OS in *RET* fusion-positive patients treated with docetaxel monotherapy. As outlined below, differences in prognostic baseline characteristics between the LIBRETTO-001 selpercatinib arm and the pseudo-control arm continued to be adjusted for in the Company's approach.

#### **Revised approach to the generation of the pseudo-control arm for LIBRETTO-001**

As described in the Company's response to Key Issue 6 at Technical Engagement, the pseudo-control arm was simulated for the LIBRETTO-001 trial using individualised patient data (IPD) from the docetaxel plus placebo arm of the REVEL RCT, which included patients with advanced non-squamous NSCLC who had progressed after a first line platinum-based chemotherapy regimen.<sup>6</sup> The IPD from the REVEL trial were adjusted for prognostic factors through matching with IPD from the LIBRETTO-001 trial, using propensity scores with a logistic regression model.<sup>7</sup> The covariates that were used as adjustment factors during propensity score matching remain the same from the Company's Technical Engagement responses and are listed in Table 3 in the Technical Engagement response document. This adjustment was necessary to account for any differences in characteristics between trial populations, and to generate a reliable treatment effect estimate for the two treatments.

Table 1 provides a summary of the baseline patient characteristics of the LIBRETTO-001 and REVEL trial populations, alongside data showing the impact of matching using propensity scores. The matching process can be seen to have aligned key population characteristics between the selpercatinib and pseudo-control arm.

**Table 1. Summary of patient characteristics of the REVEL and LIBRETTO-001 pre-treated NSCLC trial populations, before and after propensity score matching**

Characteristic	Baseline characteristics		After propensity score matching <sup>a</sup>	
	LIBRETTO-001, IAS (selpercatinib) (N=174) <sup>b</sup>	REVEL (docetaxel + placebo) (N=447) <sup>c</sup>	Docetaxel + placebo arm (N=174)	Difference
Age (mean, years)	████	████	████	████
Female, %	██	██	██	██
Race: White, %	██	██	██	██
Race: Asian, %	██	██	██	██
Race: Other, %	█	█	█	██
Never smoked, %	██	██	██	█
Histology: Non-squamous	████	████	████	█
Stage III, %	█	█	█	█
Stage IV, %	██	██	██	██
ECOG ≥ 1, %	██	██	██	██
Time since diagnosis to start of trial (median months)	██	██	██	██

**Notes:** <sup>a</sup> The analysis followed greedy match as the matching algorithm. <sup>b</sup> The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the need to exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on covariates required for the matching process. <sup>c</sup> A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to generate the pseudo-control arm.

**Abbreviations:** ECOG: Eastern Cooperative Oncology Group; IAS: Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.

Non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process, to obtain significance tests for the treatment effect and estimate log HRs and standard errors for selpercatinib versus the pseudo-control arm (Table 2). The HRs were then introduced into the network meta-analyses (NMA) of second line treatments, described previously in the Company submission.

**Table 2. Estimated treatment effects for selpercatinib versus docetaxel (pseudo-control arm) in pre-treated advanced non-squamous NSCLC patients**

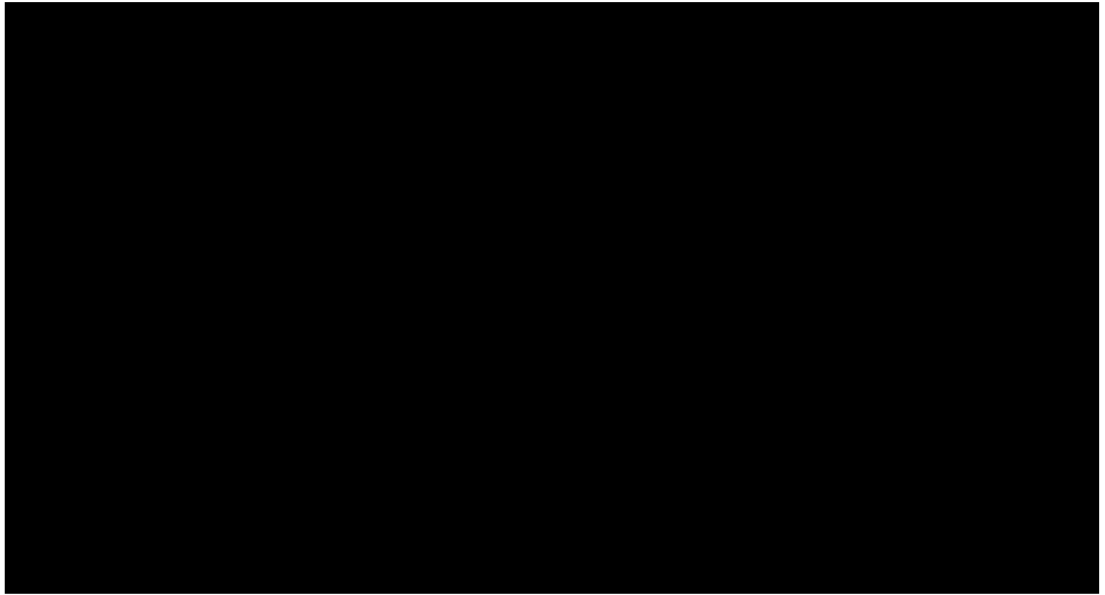
Endpoint	HR (95% CrI)	P value
PFS	██████████	██████████
OS	██████████	██████████

**Abbreviations:** CrI: credible interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

The Kaplan-Meier outputs for PFS and OS, following propensity score matching, are presented in Figure 1 and Figure 2, respectively.

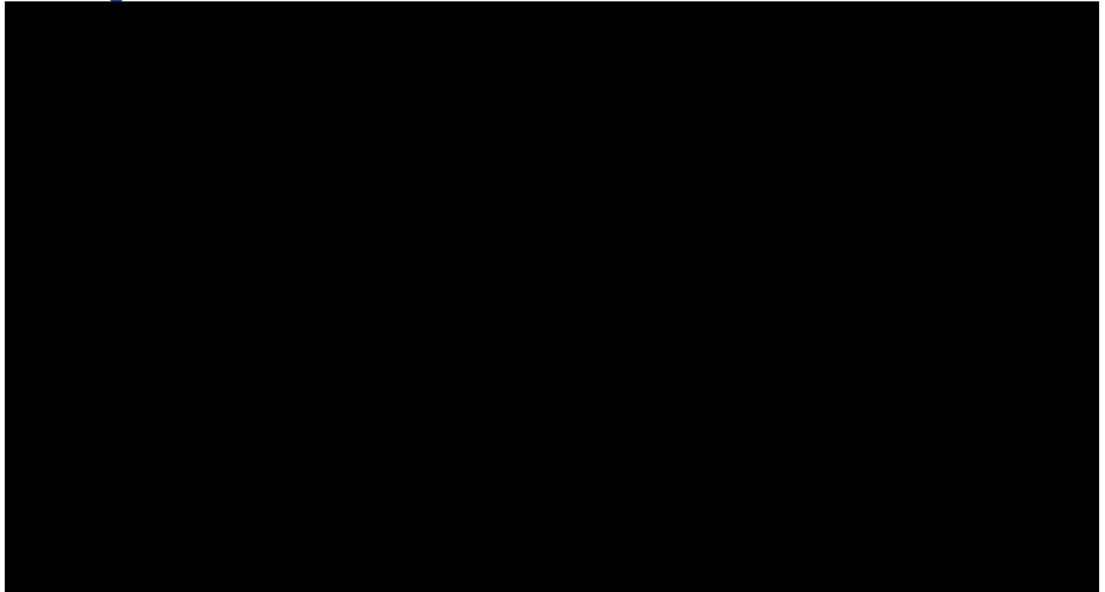
**Figure 1. Revised Kaplan-Meier chart for PFS for selpercatinib and docetaxel pseudo-control arm in pre-treated advanced NSCLC patients following propensity score matching**



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 2. Revised Kaplan-Meier chart for OS for selpercatinib and docetaxel pseudo-control arm in pre-treated advanced NSCLC patients following propensity score matching**



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

The impact of the Company's revised adjustment approach produced a median OS of [REDACTED] in the pseudo-control arm. Clinical experts estimated survival to be slightly more than 9–10 months during Committee consultation, because patients with *RET* fusion-positive advanced NSCLC tend to be younger and non-smokers.<sup>1</sup> Consequently,



median OS in the pseudo-control arm, using the Company's revised approach, more closely aligns with the estimates given by clinical experts, when compared to the median OS produced when the pseudo-control arm was adjusted for *RET* status (( [REDACTED] [REDACTED] in Company's submission at Technical Engagement. In addition, the revised approach more closely aligns with the median OS reported in pretreated adenocarcinoma patients without a *RET* fusion receiving docetaxel monotherapy (7.9 months).<sup>9</sup> The median PFS produced by the revised adjustment process ([REDACTED]) also closely aligns with the median PFS reported in pretreated adenocarcinoma patients without a *RET* fusion receiving docetaxel monotherapy (2.7 months).<sup>9</sup>

Given the above, Lilly considers that the updated NMA method, which does not adjust the pseudo-control arm for the effect of *RET* status, provides more robust PFS and OS estimates for docetaxel and will ultimately lead to a more plausible measure of the treatment effect of selpercatinib in the economic analysis.

### **NMA meta-regression and model selection**

Consistent with the Company's submission at Technical Engagement, a meta-regression was explored to relate the size of the treatment effects obtained from the meta-analysis to certain numerical characteristics of the included trials. The study-covariates explored align with those explored at Technical Engagement, and the same models were selected for OS, PFS and objective response rate (ORR) (i.e. a fixed effects [FE] hierarchical exchangeable model without age adjustment was used for OS and PFS, while a FE hierarchical exchangeable model with adjustment for the proportion of Asian patients was used for ORR). Further information is available in the Company's response to Key Issue 6 at Technical Engagement.

### **NMA results**

Updated results from the NMA, generated using the amended approach to adjusting the pseudo-control arm and using a FE hierarchical exchangeable model for OS and PFS are presented in the following section. ORR results are reported using a FE hierarchical exchangeable model, adjusted for the proportion of Asian patients, and remain unchanged since Technical Engagement, but are reported below for completeness. The results of the revised NMA have also been incorporated into the cost-effectiveness results presented in this ACD response (See Comment 5). Treatment effects are presented versus the common comparator in the network, docetaxel plus placebo.

### **ORR by RECIST v1.1 (primary endpoint)**

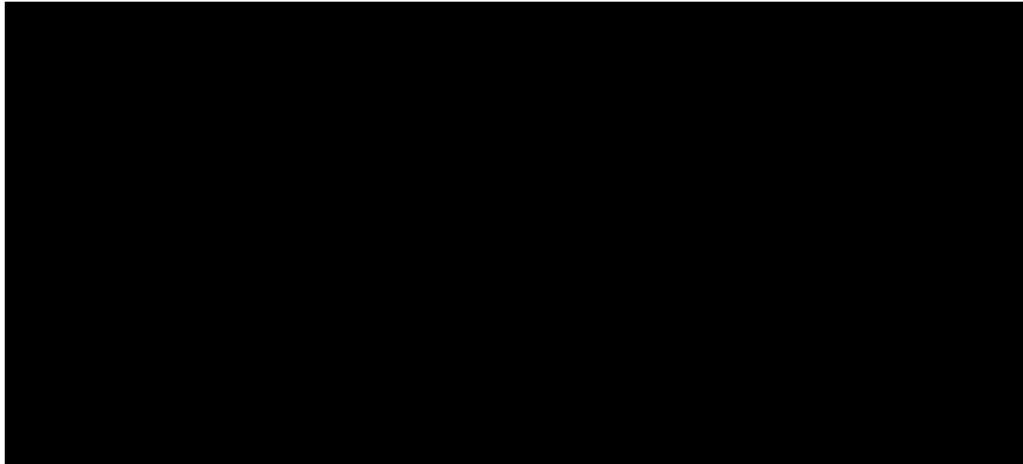
The relative treatment effects using the FE hierarchical exchangeable model, adjusted for the proportion of Asian patients, for interventions of interest for ORR versus docetaxel plus placebo are presented in Table 3, and the forest plot is presented in Figure 3. Relative to nintedanib plus docetaxel, selpercatinib demonstrated higher odds of inducing a tumour response compared to docetaxel plus placebo placebo (ORR: [REDACTED]; 95% CrI: [REDACTED]).

**Table 3. Relative treatment effects expressed as odds ratios versus docetaxel plus placebo (with 95% CrI) for ORR in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

<b>Treatment</b>	<b>Median OR (95% CrI) versus docetaxel + placebo</b>
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	[REDACTED]
Nintedanib + docetaxel	[REDACTED]

**Footnotes:** <sup>a</sup>Fixed effects hierarchical exchangeable model adjusted for the proportion of Asian patients.  
**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 3. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for ORR in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable model adjusted for the proportion of Asian patients)**



**Abbreviations:** CrI: Credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

#### **PFS (secondary endpoint)**

The relative treatment effects for interventions of interest for PFS versus docetaxel plus placebo are presented in Table 4, using the FE hierarchical exchangeable model. The forest plot is presented in Figure 4. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of disease progression compared to docetaxel plus placebo (HR: [REDACTED]; 95% CrI: [REDACTED]).

**Table 4. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for PFS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

<b>Treatment</b>	<b>Median HR (95% CrI) versus docetaxel + placebo</b>
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	[REDACTED]
Nintedanib + docetaxel	[REDACTED]

**Abbreviations:** CrI: credible interval; HR: hazard ratio; NSCLC: non-small cell lung cancer; PFS: progression-free survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 4. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for PFS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable)**



**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

### OS (secondary endpoint)

The relative treatment effects for interventions of interest for OS versus docetaxel plus placebo are presented in Table 5 for the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 5. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of death compared to docetaxel plus placebo (HR: [REDACTED]; 95% CrI: [REDACTED]).

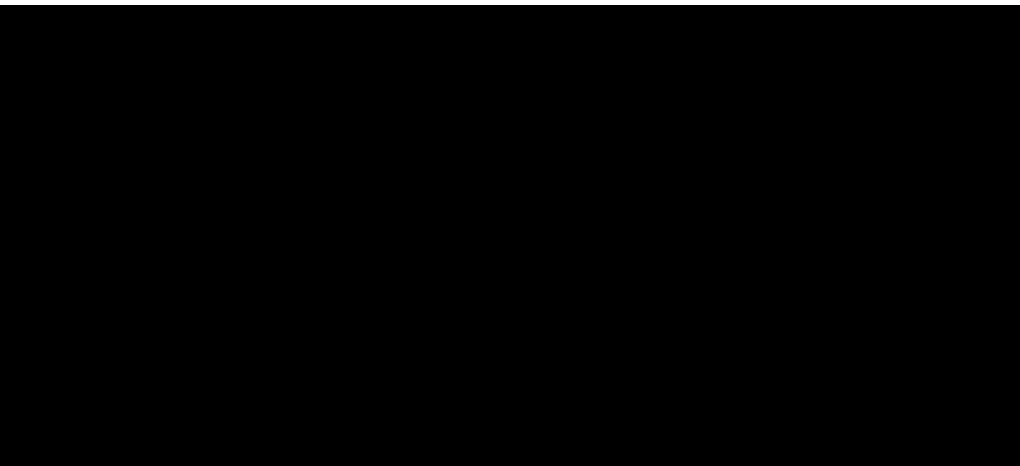
**Table 5. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for OS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients**

Treatment	Median HR (95% CrI) versus docetaxel + placebo
<b>Fixed effects (hierarchical exchangeable)</b>	
Selpercatinib	[REDACTED]
Nintedanib + docetaxel	[REDACTED]

**Abbreviations:** CrI: credible interval; HR: hazard ratio; NSCLC: non-small cell lung cancer; OS: overall survival.

**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

**Figure 5. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel plus placebo for OS in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients (fixed effects hierarchical exchangeable)**



**Abbreviations:** CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

<p><u>ERG comment</u></p>	<p>The ERG agrees with the Appraisal Committee concerns that OS is overestimated in the pseudo-control arm and considers that this overestimation seems to primarily originate from the first stage of the company adjustment of the pseudo-control arm; this adjustment had been made to account for the presence of <i>RET+</i> fusion (Company Response to Technical Engagement, Figure 1B). Therefore, the ERG considers it is appropriate and informative for decision making for the company to present a revised approach to the generation of the pseudo-control arm (i.e., without an adjustment for the presence of <i>RET+</i> fusion).</p> <p>The revised company approach uses a propensity score matching adjustment only, in line with the methods described by the company for their revised approach to the generation of the pseudo-control arm (Company Response to Technical Engagement, Issue 6).</p> <p>Results from the revised company NMAs demonstrated statistically significant advantages for selpercatinib versus docetaxel plus placebo and nintedanib+docetaxel versus docetaxel plus placebo for both PFS (Table 4) and OS (Table 5). The selpercatinib versus docetaxel plus placebo HRs are smaller (i.e., larger advantages for selpercatinib compared with docetaxel plus placebo) compared to the original NMA results (CS, Table 36 and Table 37) and the revised NMA results presented in Technical Engagement (Company Response to Technical Engagement, Table 26 and Table 27).</p> <p>The ERG emphasises that it is not possible to mitigate all uncertainty in the company estimation of indirect treatment effect estimates for selpercatinib compared to relevant comparators.</p> <p>It should be noted that many other concerns regarding data input and methods used within the NMAs, as highlighted within the ERG report (Section 3.6.3 and Appendix 9.2) and within propensity score matching approach, as highlighted in the ERG critique of the company response to Issue 6 of technical engagement. Namely:</p> <ul style="list-style-type: none"> <li>• the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a <i>RET+</i> NSCLC population, nor have these networks been adjusted for any prognostic factors associated with <i>RET+</i> NSCLC</li> <li>• the inclusion of data from comparators in the NMAs which are not relevant to the decision problem introduces uncertainty into the NMA results</li> <li>• the ORR NMA used raw (unadjusted) data from the docetaxel+placebo control arm of the REVEL trial and selpercatinib data from the LIBRETTO-001 trial; this approach introduces uncertainty into the ORR NMA results</li> <li>• differences in the definition of PFS between the REVEL trial, the LIBRETTO-001 trial, and the Flatiron database (used in the first stage of generating the pseudo-control arms) are likely to have introduced uncertainty into the generation of the PFS pseudo-control arm, and therefore into the PFS NMA results</li> <li>• there was evidence of violation of the assumption of proportion hazards (PH) for three trials in the PFS NMA and for two trials in the OS NMA (see Section 3.6.3 of the ERG report for details of the trials). Additional analyses using a fractional polynomial approach were conducted by the company for the PFS NMA. Using a fractional polynomial approach was deemed inappropriate by the company for OS due to the immaturity of the LIBRETTO-001 trial OS data. The impact of PH violation on the results of the OS NMA is not known</li> <li>• the company has not presented any evidence to demonstrate that formal checks of overlap of covariate distribution, before or after propensity score matching, were carried out</li> </ul>
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	<ul style="list-style-type: none"> <li>the company has not explained their rationale for the choice of regression model for propensity score matching (logistic and/or generalised boosted model), nor presented any assessments of the statistical model specification or model fit</li> <li>compared with the original approach, data from fewer patients were included in the propensity score matching approach.</li> </ul>																																																																	
3	<p><b>Uncertainty in the OS and PFS survival extrapolations</b></p> <p>Lilly would like to address the concerns of the Committee regarding the uncertainty in OS and PFS survival extrapolations. As discussed during the Committee meeting, the increase in OS in the simulated control arm was because of the adjustment processes for <i>RET</i> fusion status used in its generation. Given the revisions to the generation of the pseudo-control arm to produce more clinically plausible survival estimates for <i>RET</i> fusion-positive NSCLC patients treated with docetaxel monotherapy (see Comment 2), it was necessary to review an updated set of survival extrapolations for seliperatinib and docetaxel monotherapy for PFS and OS.</p> <p>PFS and OS functions for the other relevant comparator (nintedanib plus docetaxel) were constructed through the application of the HR generated in the revised NMA to the reference (docetaxel) arm extrapolation (Table 6). For the seliperatinib arm, as IPD were available to inform long-term extrapolations for PFS, it was not necessary to apply a HR to the reference arm to generate these.</p> <p><b>Table 6. HRs (95% CrI) applied to reference arm (fixed effects hierarchical exchangeable)</b></p> <table border="1" data-bbox="347 976 1449 1061"> <thead> <tr> <th>Drug (patient subgroup)</th> <th>PFS</th> <th>OS</th> </tr> </thead> <tbody> <tr> <td>Nintedanib + docetaxel</td> <td>██████████</td> <td>██████████</td> </tr> </tbody> </table> <p><b>Abbreviations:</b> CrI: credible interval; HR: hazard ratio; NA: not applicable; OS: overall survival; PFS: progression-free survival.</p> <p><b>Progression-free survival</b></p> <p>Model fit statistics for the parametric survival functions are available below in Table 7 and long-term extrapolations for PFS are available in Appendix A, Figure 8 and Figure 9. Among all the curves explored, minimal difference between the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics was observed, although the best fitting curves, as indicated by both the AIC and BIC statistics, was the unstratified Gamma and Weibull.</p> <p><b>Table 7. Model fit statistics for PFS second line parametric survival functions for seliperatinib and reference arm</b></p> <table border="1" data-bbox="347 1532 1422 2038"> <thead> <tr> <th rowspan="2">Function</th> <th colspan="4">PFS</th> </tr> <tr> <th>AIC</th> <th>BIC</th> <th>Rank (AIC)</th> <th>Rank (BIC)</th> </tr> </thead> <tbody> <tr> <td colspan="5"><b>Unstratified</b></td> </tr> <tr> <td>Exponential</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Weibull</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Log-normal</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Log-logistic</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Gompertz</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Gamma</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Spline/knot=1</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Spline/knot=2</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> <tr> <td>Spline/knot=3</td> <td>██████████</td> <td>██████████</td> <td>█</td> <td>█</td> </tr> </tbody> </table>	Drug (patient subgroup)	PFS	OS	Nintedanib + docetaxel	██████████	██████████	Function	PFS				AIC	BIC	Rank (AIC)	Rank (BIC)	<b>Unstratified</b>					Exponential	██████████	██████████	█	█	Weibull	██████████	██████████	█	█	Log-normal	██████████	██████████	█	█	Log-logistic	██████████	██████████	█	█	Gompertz	██████████	██████████	█	█	Gamma	██████████	██████████	█	█	Spline/knot=1	██████████	██████████	█	█	Spline/knot=2	██████████	██████████	█	█	Spline/knot=3	██████████	██████████	█	█
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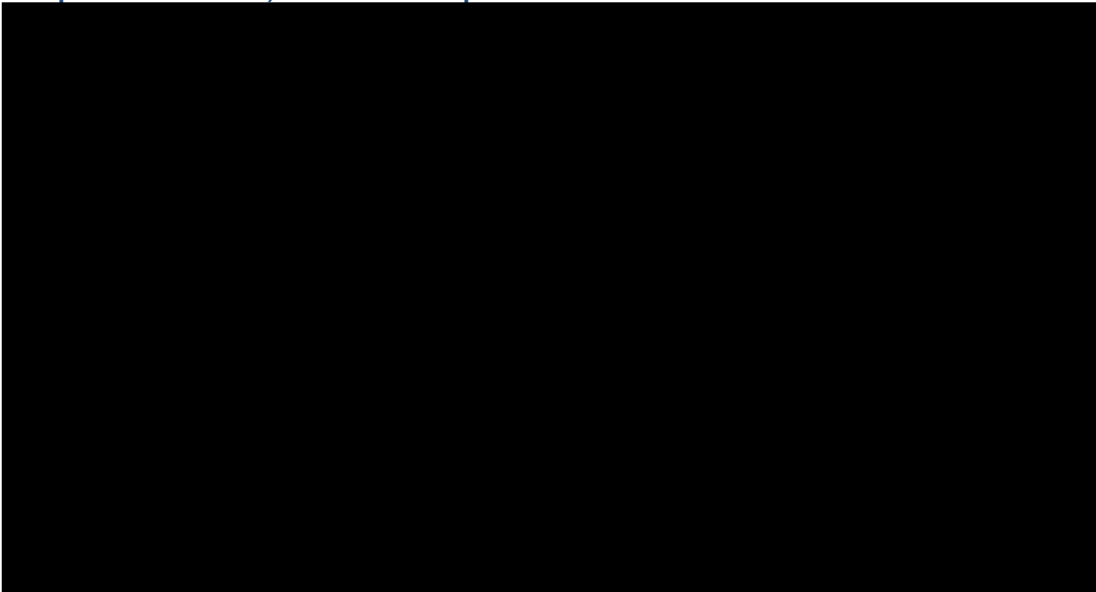
Stratified				
Weibull	██████	██████	█	█
Log-normal	██████	██████	██	██
Log-logistic	██████	██████	██	██
Gompertz	██████	██████	██	██
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	██	██
Spline/knot=2	██████	██████	█	██
Spline/knot=3	██████	██████	█	██

**Abbreviations:** AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Lilly considers that the stratified Gompertz function remains the most appropriate choice for extrapolating the selpercatinib PFS curve. The reasoning for this choice is provided in the Company’s response to Key Issue 8 at Technical Engagement. In addition, Lilly considers that the stratified Gompertz is the most appropriate function for the docetaxel comparator arm, because it produces consistent predictions to trial data published in the literature (predicted: █████ months versus REVEL: 3.0 months;<sup>6</sup> LUME-Lung 1: 2.7 months)<sup>9</sup> and only has a small percentage of patients remaining progression-free after five years.

The revised Company base case extrapolations for selpercatinib and comparators for PFS is presented in Figure 6.

**Figure 6. Revised Company base case extrapolations for selpercatinib and comparators for PFS, stratified Gompertz**



**Abbreviations:** KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; PFS: progression-free survival.

**Overall survival**  
 Model fit statistics for the parametric survival functions are provided in Table 8, and long-term extrapolations for OS are available in Appendix A,

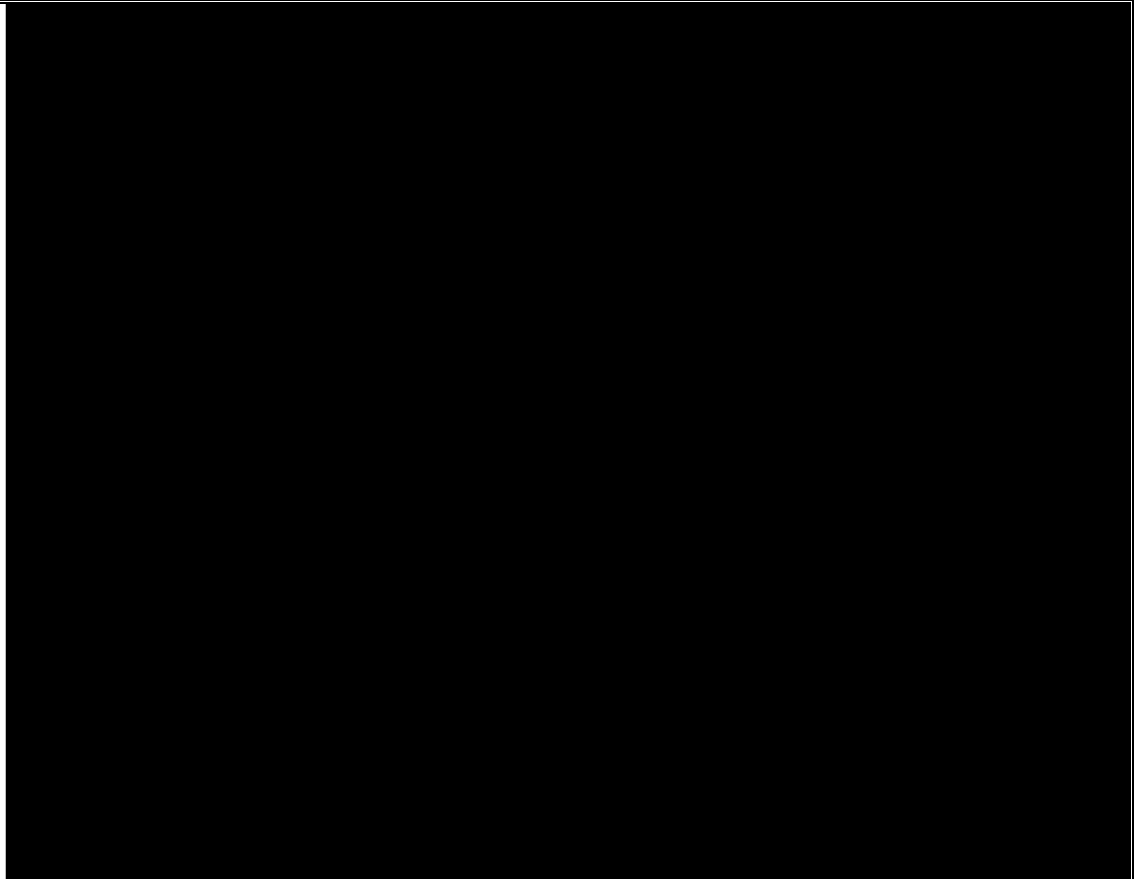


Figure 10 and Figure 11. Among all the curves explored, minimal differences between the AIC and BIC statistics were observed, although the best fitting curves, as indicated by both the AIC and BIC statistics, was the unstratified exponential and log-logistic.

**Table 8. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm**

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
<b>Unstratified</b>				
Exponential	██████	██████	█	█
Weibull	██████	██████	█	█
Log-normal	██████	██████	██	██
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	██	██
Spline/knot=2	██████	██████	██	██
Spline/knot=3	██████	██████	██	██
<b>Stratified</b>				
Weibull	██████	██████	█	█
Log-normal	██████	██████	██	██
Log-logistic	██████	██████	█	█
Gompertz	██████	██████	█	█
Gamma	██████	██████	█	█
Spline/knot=1	██████	██████	██	██
Spline/knot=2	██████	██████	██	██

Spline/knot=3

**Abbreviations:** AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Given the absence of published evidence on the long-term survival of pre-treated patients with advanced non-squamous *RET* fusion-positive NSCLC treated with docetaxel monotherapy or selpercatinib, clinical expert opinion was sought at Technical Engagement. Estimates for long term survival, provided by clinical experts at Technical Engagement, are presented again in Table 9 below for ease of reference.

**Table 9. Survival projections for previously treated patients receiving docetaxel monotherapy or selpercatinib provided by clinical experts at Technical Engagement**

Population	5-year survival (%)	10-year survival (%)	20-year survival (%)	25 year-survival (%)
<b>Clinical expert one</b>				
Patient receiving docetaxel monotherapy after prior immunotherapy	■	■	■	■
<i>RET</i> fusion-positive patient receiving docetaxel monotherapy after immunotherapy	■	■	■	■
<i>RET</i> fusion-positive patient receiving selpercatinib <sup>a</sup>	■	■	■	■
<b>Clinical expert two</b>				
Patient receiving docetaxel monotherapy after prior immunotherapy	■	■	■	■
<i>RET</i> fusion-positive patient receiving docetaxel monotherapy after immunotherapy	■	■	■	■
<i>RET</i> fusion-positive patient receiving selpercatinib <sup>a</sup>	■	■	■	■

**Footnotes:** <sup>a</sup> both clinical experts were hesitant to give a reliable prediction beyond 5 years, due to lack of long-term data for *RET*-targeted therapies in NSCLC; therefore, predictions for selpercatinib beyond 5 or 10 years are uncertain and listed as unknown.

**Abbreviations:** *RET*: rearranged during transfection.

Predicted survival rates from a selection of curves are shown in Table 10 below. Only the unstratified Gompertz and stratified Weibull curves produced 10-year survival rates for selpercatinib that were consistent with the estimates provided by clinical experts at Technical Engagement (clinician estimates: ■; unstratified Gompertz: 8.5%; stratified Weibull: 9.9%). In addition, while no curve predicted a 5-year survival rate that closely aligned with estimates provided by clinical experts, the unstratified Gompertz and stratified Weibull curves produced the closest estimates for selpercatinib (clinician estimates: ■; unstratified Gompertz: 38.8%; stratified Weibull: 36.1%). With the exception of the stratified Gompertz, which was deemed clinically implausible due to significantly underestimating survival for selpercatinib compared to clinician estimates (stratified Gompertz: 3.9% at 5-years and 0% at 10-years) and predicting shorter long-term survival than docetaxel, these two curves represent the most conservative choices of survival functions.

To further support these estimates, in Tan et al. (2020), patients treated with a selective *RET* tyrosine kinase inhibitor had a median OS of 49.3 months, which aligns with the median OS estimated by the unstratified Gompertz (■ months) and stratified Weibull (■ months) curves. While the analysis reported by Tan et al. (2020) was performed using a mixture of treatment naïve and pre-treated patients, a small study population (n=60) and a retrospective design, this analysis does lend evidence to provide external



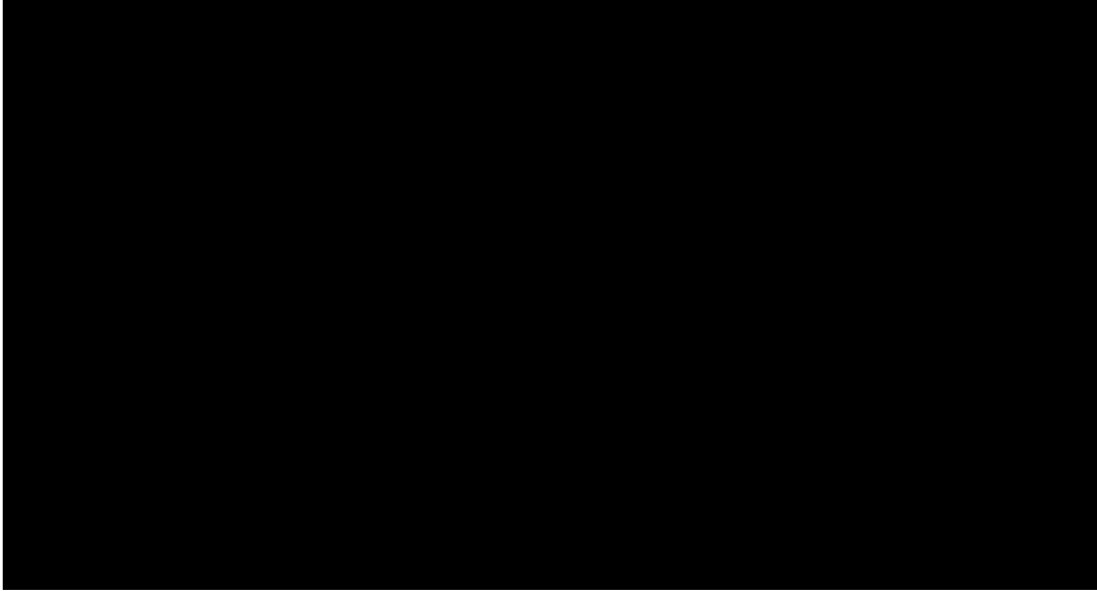
validity for the predicted OS estimates. In addition, the survival values reported by Tan et al. (2020) could suggest that the clinician 5-year survival estimates may be pessimistic (see Table 9).<sup>11</sup>

As such, Lilly considers that the unstratified Gompertz and stratified Weibull curves provide the most clinically plausible extrapolations for the selpercatinib arm, while also being the most conservative. As the unstratified Gompertz provided a slightly lower 10-year survival estimate compared to the stratified Weibull curve, the Gompertz was applied in the revised base case. Lilly acknowledges that immaturity in the LIBRETTO-001 survival data presents challenges with regards to parametric survival curve fitting, particularly to the tail ends of the Kaplan-Meier curves, where few patients remain. However, ongoing data collection under the CDF, including more mature estimates of OS, would help to reduce this uncertainty.

For the docetaxel comparator arm, the unstratified Gompertz function was also considered to be the most appropriate choice for extrapolation, as it produced median OS predictions that were consistent with estimates provided by expert clinicians, who estimated survival could be slightly more than 10 months, given that *RET* fusion-positive patients often have baseline characteristics associated with improved survival (see Comment 2 in this response).<sup>1</sup> Furthermore, the median OS prediction, using the unstratified Gompertz function, was broadly consistent with published trial data in advanced NSCLC patients without a *RET* fusion, treated with docetaxel monotherapy (predicted: 13.38 months versus REVEL: 9.1 months;<sup>6</sup> LUME-Lung 1: 7.9 months).<sup>9</sup>

**Table 10. Long-term predicted survival estimates for docetaxel monotherapy and selpercatinib with a selection of survival functions**

	Median PFS <sup>a</sup> (months)	Median OS (months)	5-year survival (%)	10-year survival (%)	25-year survival (%)
<b>Exponential</b>					
Docetaxel	4.62	13.15	4.1	0.2	0
Selpercatinib	██████	██████	45.6	20.8	2.0
<b>Weibull</b>					
Docetaxel	4.62	13.15	2.9	0.1	0
Selpercatinib	██████	██████	41.7	15.8	0.7
<b>Loglogistic</b>					
Docetaxel	4.62	12.69	11.4	5	1.5
Selpercatinib	██████	██████	42.8	23.3	8.1
<b>Gompertz</b>					
Docetaxel	4.62	13.38	2.2	0.0	0.0
Selpercatinib	██████	██████	38.8	8.5	0.0
<b>Gamma</b>					
Docetaxel	4.62	13.15	3.1	0.1	0.0
Selpercatinib	██████	██████	41.4	15.9	0.8
<b>Stratified Weibull</b>					
Docetaxel	4.62	13.15	3.2	0.1	0.0
Selpercatinib	██████	██████	36.1	9.9	0.1
<b>Spline/Knot 1</b>					
Docetaxel	4.62	13.15	2.2	0.1	0.0

	Selpercatinib	████	████	39.2	17.3	0.1
	<b>Stratified Gamma</b>					
	Docetaxel	4.62	13.15	3.3	0.1	0.0
	Selpercatinib	████	████	39.3	13.8	0.5
	<p><b>Footnotes:</b> <sup>a</sup> fixed by applying the stratified Gompertz.</p> <p><b>Abbreviations:</b> OS: overall survival; PFS: progression-free survival.</p> <p>The recommended base case extrapolations for selpercatinib and comparators for OS is presented in Figure 7.</p> <p><b>Figure 7. Base case extrapolations for selpercatinib and comparators for OS, unstratified Gompertz</b></p>  <p><b>Abbreviations:</b> KM: Kaplan-Meier; OS: overall survival.</p> <p><b>Scenario analyses</b>            Scenario analyses for PFS included using the unstratified Gompertz, Gamma, stratified Weibull and Spline/Knot=1 survival functions. Scenario analyses for OS included applying the unstratified exponential, Weibull, stratified Weibull and stratified Gamma survival functions. Results from the scenario analyses are presented in Table , Appendix B.</p>					
<u>ERG comment</u>	<p>As stated in the NICE ACD (Section 3.9), the Appraisal Committee (as well as clinical experts and the CDF lead) considered that the company model overestimated OS for patients treated with selpercatinib and for those treated with chemotherapy. The data presented in Figure 7 (above) show that this is still the case for patients treated with selpercatinib. This means that the ICERs per QALY gained generated by the company model are likely to be optimistic for the comparison of selpercatinib versus chemotherapy.</p>					
4	<p><b>The economic model should use time to discontinuation (TTD) when calculating the cost of selpercatinib</b></p> <p>Lilly understands the Committee’s rationale for suggesting that TTD extrapolations, based on LIBRETTO-001 data, be used to inform time on treatment for selpercatinib in the cost-effectiveness analysis, instead of PFS. Namely, as described in the ACD, clinicians may deem that patients can derive further benefit from continued treatment with selpercatinib following progression. This may be because an initially large tumour may have substantially decreased in size with selpercatinib treatment, and so ‘progressed disease’ is less severe than the patient’s original disease status, or alternatively because a secondary tumour in the body has progressed, but there is still a positive effect of treatment on the first tumour.</p>					

Lilly would like to clarify the approach taken to model time on treatment for selpercatinib during the technical engagement stage. To account for the fact that patients may continue treatment following progression (as discussed above), the mean time from progression to treatment discontinuation was sourced directly from LIBRETTO-001 and applied to the PFS curve. This was [REDACTED] days (approximately [REDACTED]) in the IAS (Table 11). Accordingly, this approach to modelling time on treatment takes into account treatment that may be received following disease progression and is not solely informed by PFS.

**Table 11. Mean time (days) between meeting the PFS endpoint and treatment discontinuation for NSCLC pre-treated patients in LIBRETTO-001**

	Pre-treated NSCLC (IAS) (N=184)
Discontinued treatment during trial follow-up, n (%)	[REDACTED]
<b>Time between PFS and treatment discontinuation</b>	
Mean (days)	[REDACTED]
SD	[REDACTED]
Min, max (days)	[REDACTED]
95% CI	[REDACTED]

**Abbreviations:** CI: confidence interval; IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progress-free survival; SD: standard deviation.  
**Source:** Eli Lilly and Company Ltd. Data on File.<sup>8</sup>

For completeness, Lilly have assessed the time on treatment estimates generated by the TTD extrapolations based on LIBRETTO-001 for face validity. Clinical expert feedback from the first Committee meeting was that patients would be unlikely to be on treatment two years after progression. Estimates of time on treatment as per the different extrapolation models compared to PFS (as informed by the stratified Gompertz extrapolation) are presented in Table 12. Based on the expert feedback received, these results suggest that all eight TTD extrapolations consistently overestimate time on treatment after progression from three years; it can be seen that the proportion of patients on treatment two years later (at five years) is greater than the proportion of patients who were progression free at three years.

**Table 12. Time on treatment versus PFS estimates for selpercatinib**

Time (yrs)	PFS: Stratified Gompertz (%)	On Treatment (based on TTD curves)							
		Exponential (%)	Weibull (%)	Lognormal (%)	Loglogistic (%)	Gompertz (%)	Gamma (%)	Spline Knot 1 (%)	Spline Knot 2 (%)
1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
4	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
5	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
6	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
7	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
8	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
9	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

	<div style="display: flex; justify-content: space-between; border: 1px solid black; padding: 2px;"> <span>10</span> <span>■</span> <span>■</span> <span>■</span> <span>■</span> <span>■</span> <span>■</span> <span>■</span> <span>■</span> </div> <p><b>Abbreviations:</b> PFS: progression free survival; TTD: time to treatment discontinuation.</p> <p>Since use of TTD extrapolations based on LIBRETTO-001 data are observed to over-estimate time on treatment relative to progression, Lilly have maintained the approach to time on treatment adopted during Technical Engagement. In addition, to assist the Committee's decision-making, sensitivity analyses have also been conducted in which time to discontinuation following progression is varied through the 95% confidence intervals to the mean (please see Appendix B), which show only a small variation to the base case ICER.</p>
ERG comment	<p>The Appraisal Committee considered that fitting a parametric distribution to LIBRETTO-001 trial TTD data was the most appropriate method to model time on treatment (ACD, Section 3.10). The company has not presented new evidence to support their alternative approach to modelling time on treatment (which was based on LIBRETTO-001 PFS data). The company considers that using a distribution fitted to LIBRETTO-001 trial TTD data is a flawed approach that produces unrealistically high TTD estimates. However, there are more LIBRETTO-001 trial TTD data than OS data available and the company appears to consider that fitting a distribution to LIBRETTO-001 trial OS data generates robust results.</p>
5	<p><b>Revised base-case cost-effectiveness results</b></p> <p>Lilly has updated the results from the economic model to incorporate the change in pseudo-control arm generation (see Comment 2) and the revised PAS (see Comment 1). As deemed acceptable by the Committee, Lilly have retained the progressed disease (PD) utility value that was applied at Technical Engagement (0.628). As such, utility values for progression free and PF health states were ■ and 0.628, respectively (please see the Company's response to Key Issue 9 of the Technical Engagement Response for further details). Lilly has also retained the approach for time-on-treatment adopted during Technical Engagement, applying the mean time from progression to treatment discontinuation from LIBRETTO-001 (please see the Company's Comment 4 above for further details).</p> <p>A summary of the results for the revised company base case analysis for <i>RET</i> fusion-positive NSCLC, using LIBRETTO-001 data from the 16<sup>th</sup> December 2019 data cut, is presented in Appendix B.</p>
ERG comment	No comment
6	<p><b>Evidence is not sufficiently robust to determine if selpercatinib meets the criteria to be an end-of-life treatment</b></p> <p>Lilly is in agreement with the Appraisal Committee's conclusion that NICE's end-of-life Criterion 1 (the treatment is indicated for patients with a short life expectancy, normally less than 24 months) is met for pre-treated patients with advanced non-squamous <i>RET</i> fusion-positive NSCLC in England and Wales.</p> <p>To address the concerns of the Committee that uncertainty around the OS estimate for docetaxel monotherapy meant that it is unclear whether treatment with selpercatinib met Criterion 2 (treatment offers an extension to life, normally of at least an additional 3 months), Lilly has revised its approach to generating the pseudo-control arm (please see Lilly's Comment 2). These updates produced a median OS for docetaxel monotherapy (■) that more closely aligns with clinical expectation and the published literature.<sup>1,9</sup> Two key consequences of this are as follows. Application of the NMA-derived HR for nintedanib plus docetaxel to docetaxel in the model gives rise to a more clinically plausible estimate of OS for nintedanib plus docetaxel. Secondly, a more</p>

reliable estimate of the difference in survival likely to be achieved by patients treated with seliperatinib, compared to docetaxel or nintedanib plus docetaxel, can be obtained from the model.

As presented in Table 13, seliperatinib is associated with an extension to survival of 30.70 and 33.24 median months compared to nintedanib plus docetaxel and docetaxel monotherapy, respectively. Nintedanib plus docetaxel and docetaxel monotherapy are themselves associated with an estimated survival of 1.74 years and 1.47 years, respectively, using the revised approach outlined above. As noted in Comment 2, the median OS estimate for docetaxel monotherapy aligns with clinician estimates and the published literature.<sup>9</sup> Similarly, median OS estimates for treatment with nintedanib plus docetaxel more closely align with the published literature in adenocarcinoma patients who progressed within 9 months of initiating first line treatment (10.9 months)<sup>9</sup> and reflect comments from clinical experts that the addition of nintedanib to docetaxel only results in a modest improvement to survival.<sup>1</sup>

**Table 13. Revised base case survival outcomes (PFS and OS) and clinical outcomes**

Intervention/comparator	Median PFS (months)	Mean PFS (months)	Median OS (months)	Discounted LYs	Undiscounted LYs
<b>Revised base case survival outcomes</b>					
Seliperatinib	████	████	████	████	████
Docetaxel monotherapy	4.62	5.98	13.38	1.44	1.47
Nintedanib + docetaxel	5.77	7.47	15.92	1.69	1.74

**Abbreviations:** OS: overall survival; PFS: progression-free survival.

Given the above, Lilly believes that:

- Uncertainty in the OS estimate for docetaxel monotherapy has been addressed through revisions to the method for generating the pseudo-control arm, providing a reliable measure of effect from the economic model that aligns with clinician estimates and clinical practice
- Pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second line or beyond in England and Wales have a life expectancy <24 months and are highly likely to experience an extension to life >3 months if they were to receive seliperatinib monotherapy
- Lilly's revisions confirm that seliperatinib monotherapy meets Criterion 1 and Criterion 2 of NICE's end-of-life criteria, when used in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients

**ERG comment**

The company has not addressed the uncertainty around the reliability of model OS estimates for patients treated with seliperatinib and, therefore, the ERG considers that the evidence remains insufficiently robust to conclude that treatment with seliperatinib meets the NICE End-of-Life criteria.

Insert extra rows as needed

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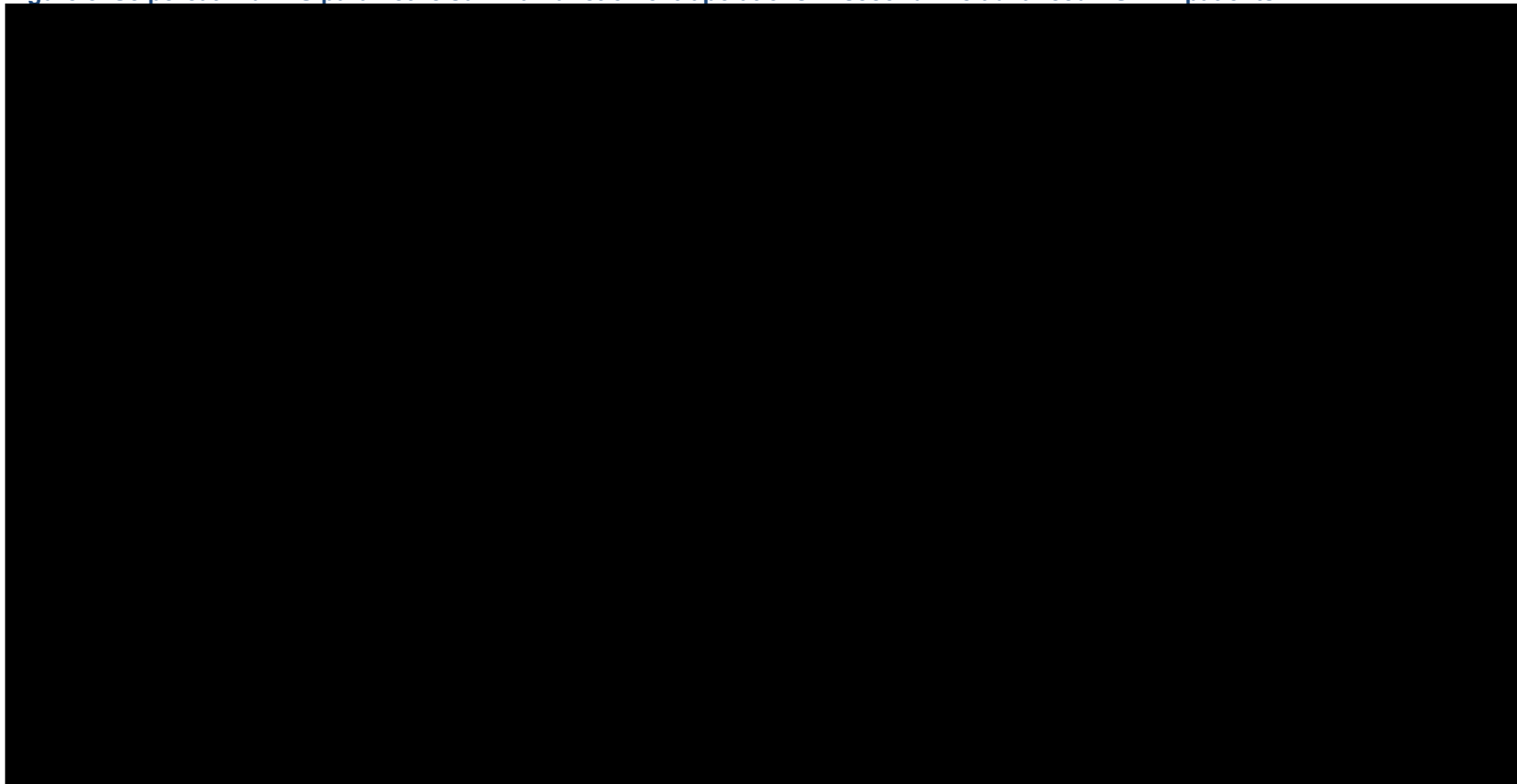
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Appendix A

*PFS*

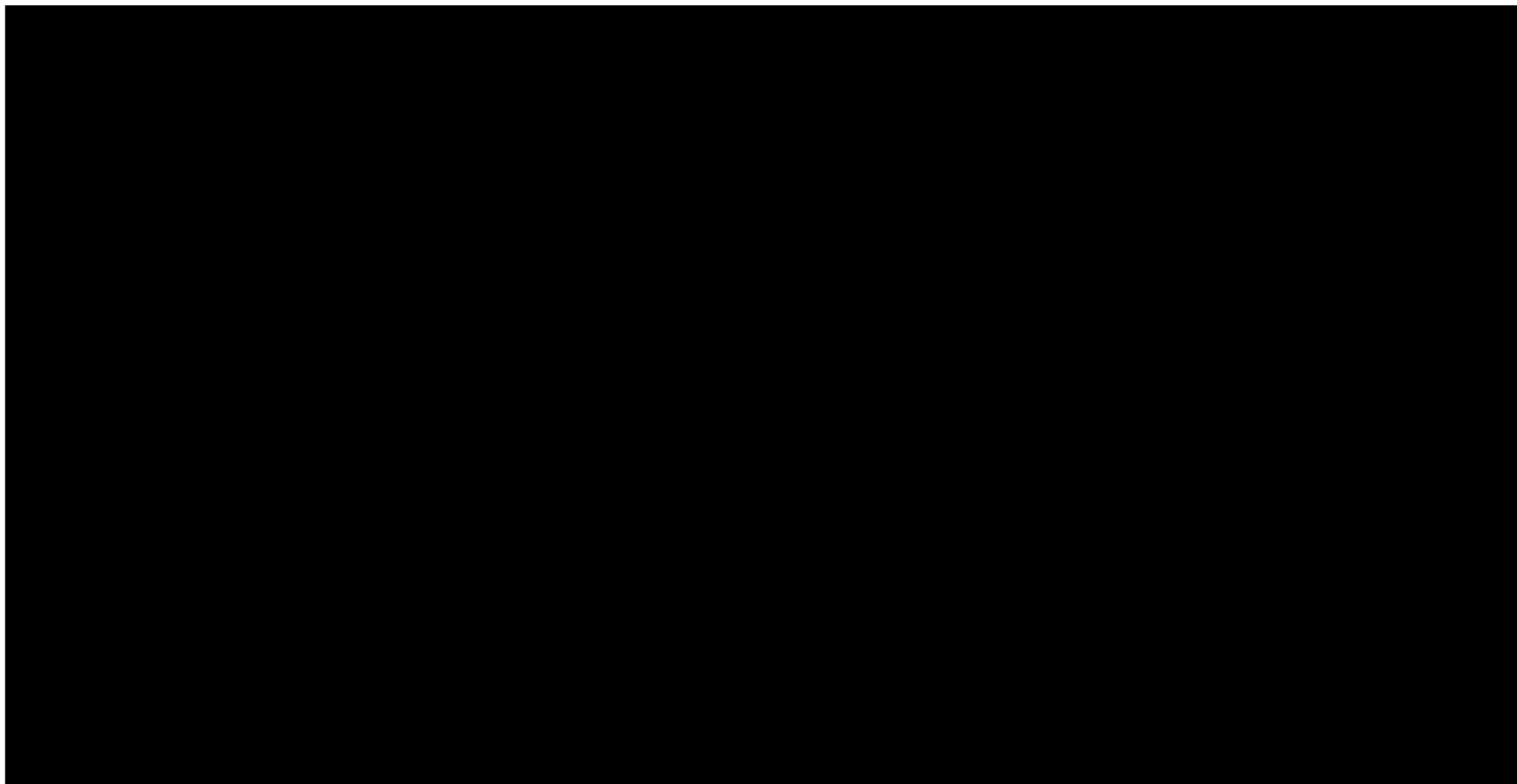
Long term extrapolations for PFS are provided below in Figure 8 and Figure 9.

**Figure 8. Selpercatinib PFS parametric survival function extrapolations in second line advanced NSCLC patients**



**Abbreviations:** NSCLC: non-small cell lung cancer; PFS: progression free survival.

Figure 9. Reference arm (docetaxel) PFS parametric survival function extrapolations in second line advanced NSCLC patients



**Abbreviations:** NSCLC: non-small cell lung cancer; PFS: progression free survival.

OS



Long term extrapolations for OS are provided below in

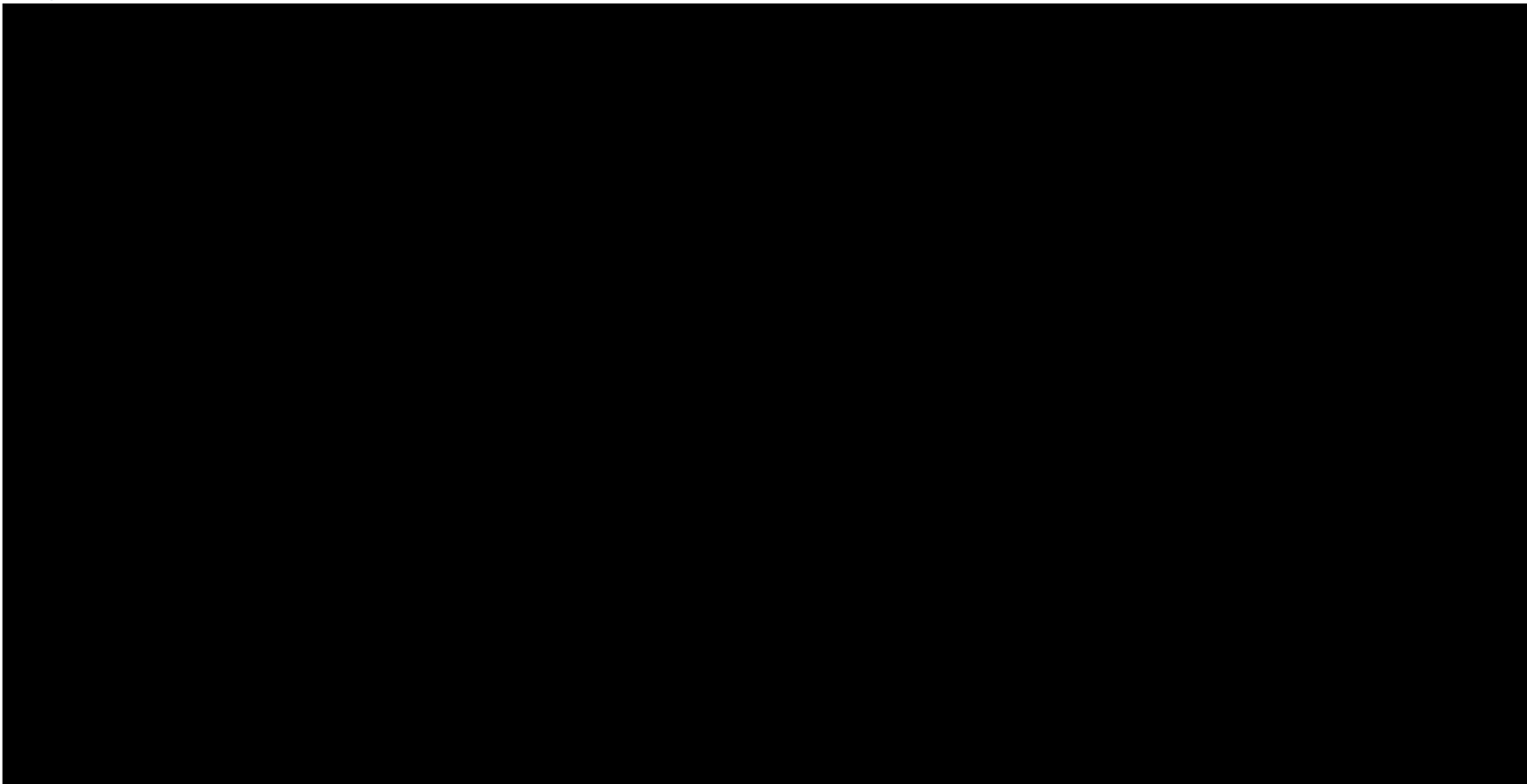


Figure 10

and Figure 11.

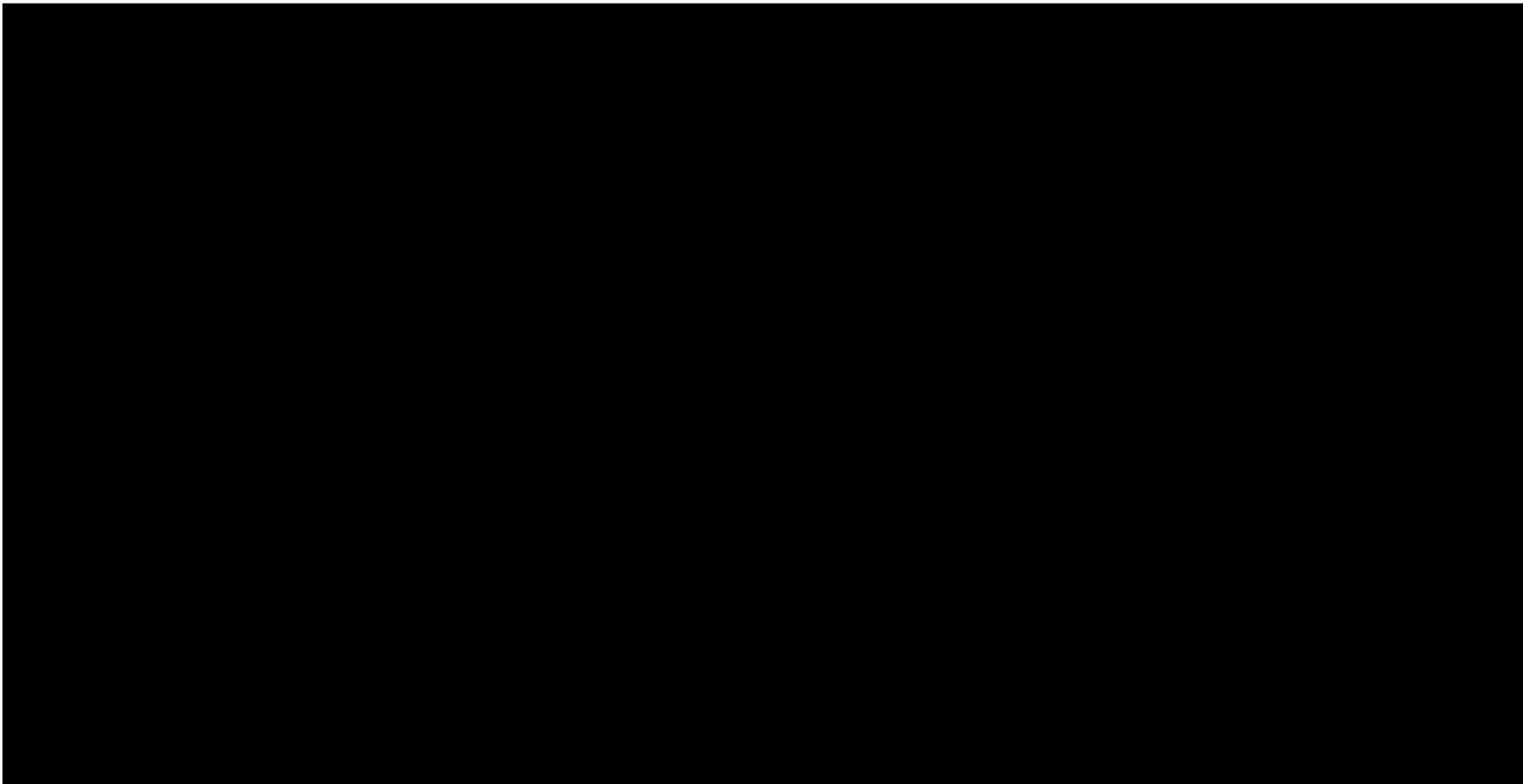
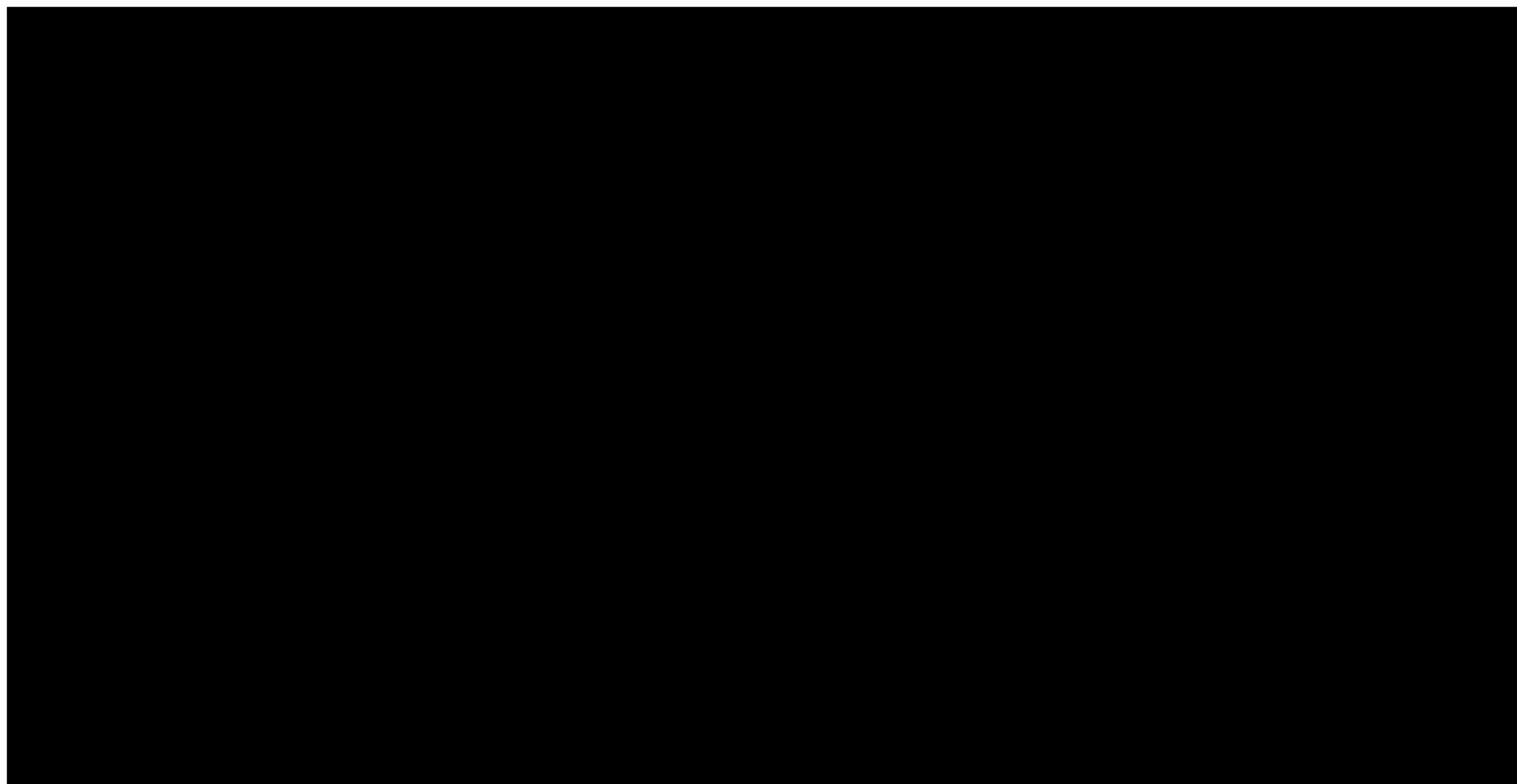


Figure 10.

Selpercatinib OS parametric survival function extrapolations in second line advanced NSCLC patients

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

Figure 11. Reference arm (docetaxel) OS parametric survival function extrapolations in second line advanced NSCLC patients



**Abbreviations:** NSCLC: non-small cell lung cancer; OS: overall survival.

## Appendix B

A summary of the base case analysis results (with PAS) is presented in Table 14. The results illustrate that versus all comparators, selpercatinib is associated with greater QALYs, reflecting the high levels of efficacy of selpercatinib in the second line *RET* fusion-positive NSCLC population.

**Table 14. Base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	██████	████	████	-	-	-	-	55,119
Nintedanib + docetaxel	██████	████	████	██████	████	████	118,952 <sup>a</sup>	48,800
Selpercatinib	██████	████	████	██████	████	████	55,119	-

**Footnotes:** <sup>a</sup> Nintedanib plus docetaxel is extendedly dominated.

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

### Probabilistic sensitivity analysis

The probabilistic base case results are presented in Table 15. The PSA results illustrate that versus both comparators, selpercatinib is associated with greater QALYs. The deterministic and probabilistic base case results are observed to be in close alignment.

**Table 15. Probabilistic base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price**

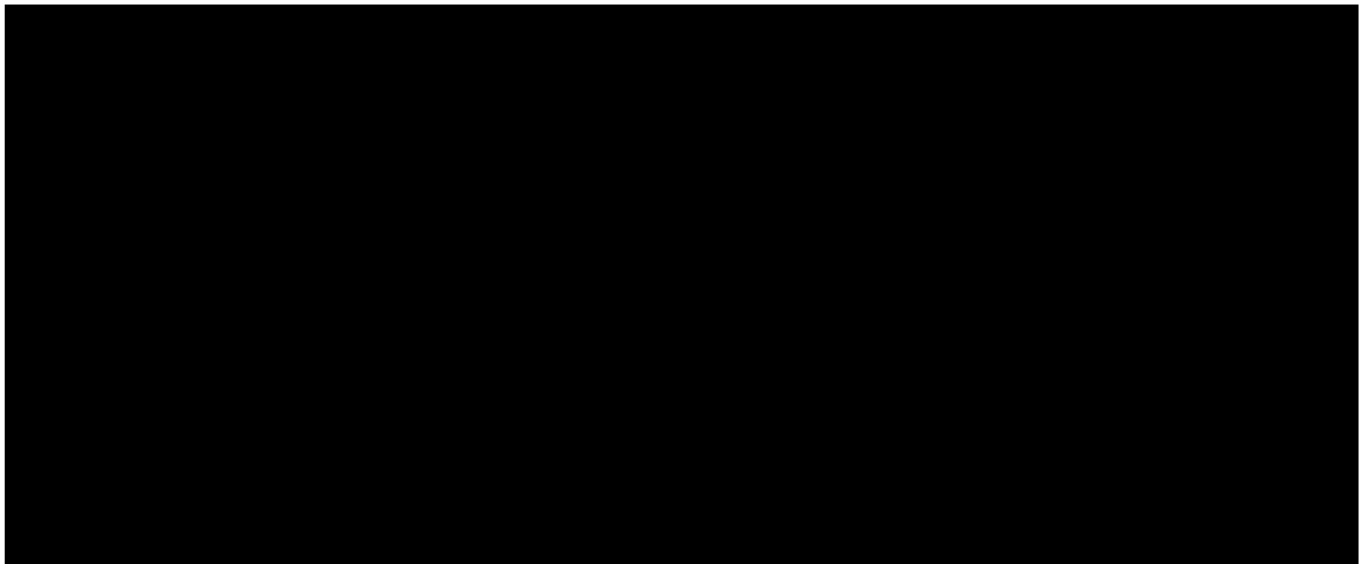
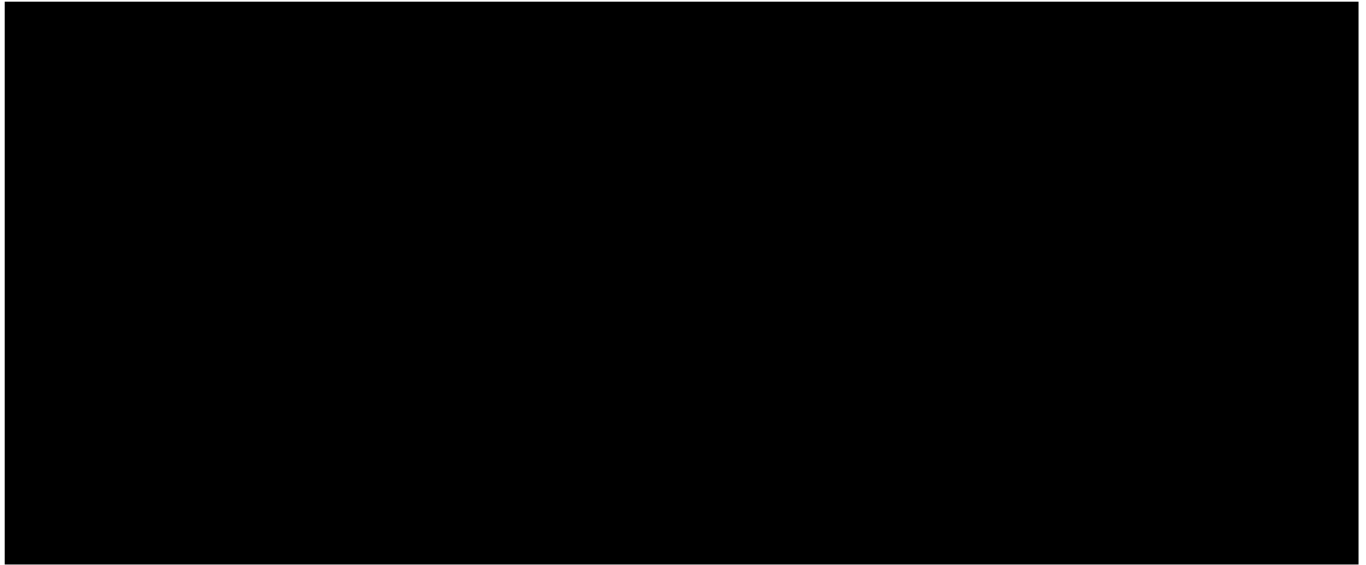
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	██████	████	████	-	-	-	55,595
Nintedanib + docetaxel	██████	████	████	██████	████	████	49,238

Selpercatinib	████████	████	████	████████	████	████	-
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**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel are presented in Figure 12.

**Figure 12. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel**

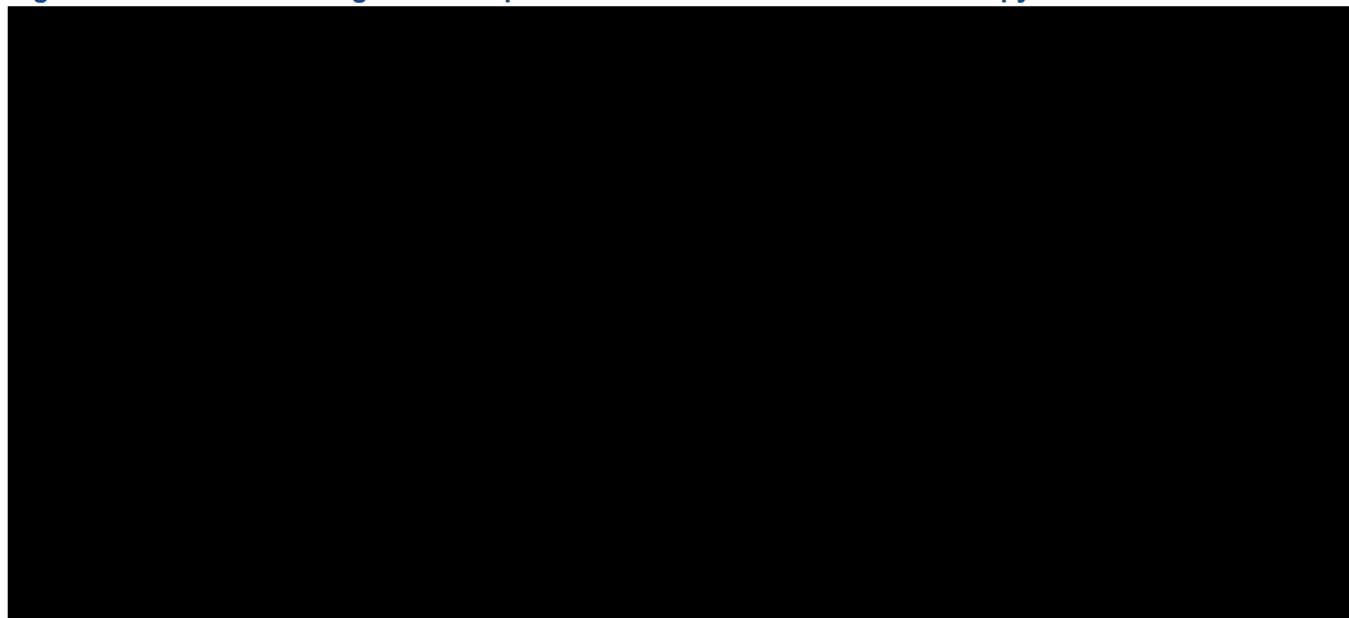


**Abbreviations:** QALY: quality-adjusted life year.

### Deterministic sensitivity analysis

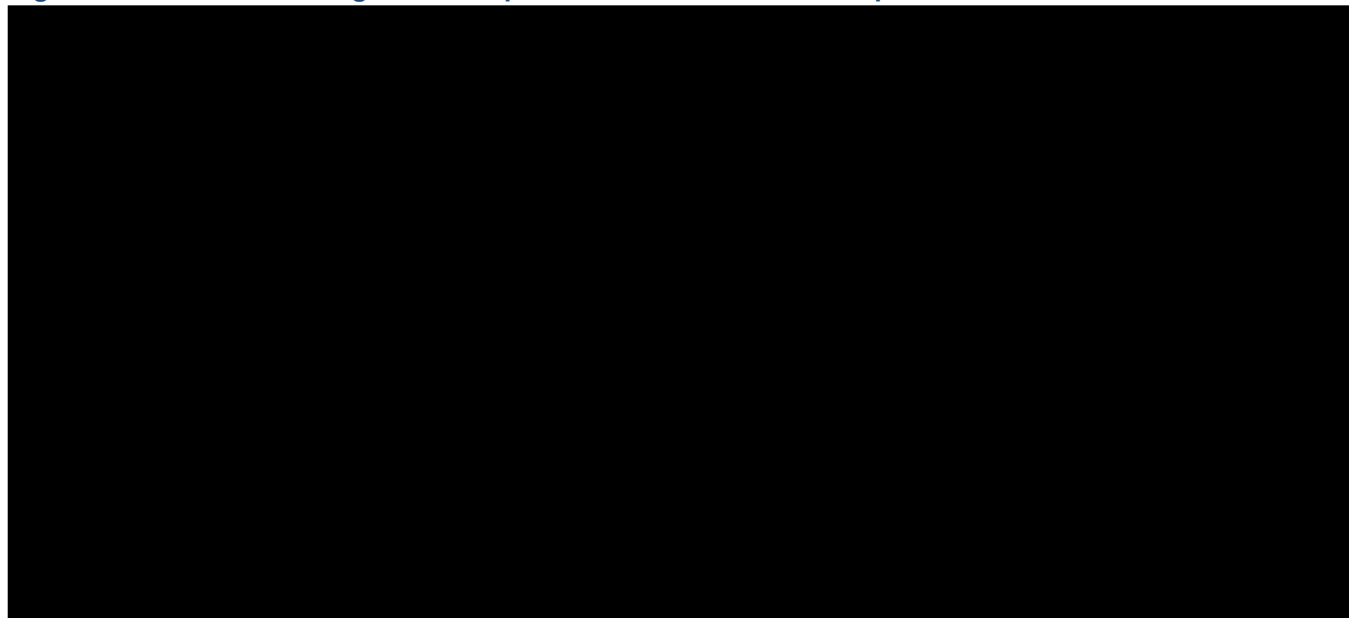
The tornado diagram by parameter for selpercatinib versus docetaxel is presented in Figure 13. The tornado diagram and by parameter for selpercatinib versus nintedanib plus docetaxel is presented in Figure 14.

**Figure 13. DSA tornado diagram for selpercatinib versus docetaxel monotherapy**



**Abbreviations:** DSA: deterministic sensitivity analysis; QALY: quality-adjust life year.

**Figure 14. DSA tornado diagram for selpercatinib versus nintedanib plus docetaxel**



**Abbreviations:** DSA: deterministic sensitivity analysis; QALY: quality-adjust life year.

## Scenario analyses

A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table . It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and all comparator arms.

**Table 16. Scenario analysis results for selpercatinib versus relevant comparators**

Scenario		Pairwise ICER vs. docetaxel (£)	% ICER change	Pairwise ICER vs. nintedanib + docetaxel (£)	% ICER change
	<b>Base case</b>	<b>55,199</b>	<b>-</b>	<b>48,800</b>	<b>-</b>
1	Alternative TTD assumptions: [REDACTED] (mid-point of lower limit of 95% CI and mean [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	54,006	-2.16%	47,577	-2.51%
2	Alternative TTD assumptions: [REDACTED] (mid-point of upper limit of 95% CI and mean [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	56,596	2.53%	50,423	3.33%
3	Alternative TTD assumptions: [REDACTED] (upper limit of 95% [REDACTED] for mean time between PFS and treatment discontinuation in LIBRETTO-001)	59,540	7.86%	53,659	9.96%
4	Curve choice: OS – Exponential	43,781	-20.69%	38,719	-20.66%
5	Curve choice: OS – Weibull	48,511	-12.12%	42,455	-13.00%
6	Curve choice: OS – stratified Weibull	55,647	0.81%	49,669	1.78%
7	Curve choice: OS – stratified Gamma (selpercatinib and docetaxel arms only) <sup>a</sup>	47,811	-13.38%	42,013	-13.91%
8	Curve choice: OS – spline knot 1	46,740	-15.32%	41,259	-15.45%
9	Curve choice: PFS – Gompertz	54,018	-2.14%	47,534	-2.59%



10	Curve choice: PFS – Gamma (selpercatinib and docetaxel arms only) <sup>a</sup>	58,029	5.13%	52,083	6.73%
11	Curve choice: PFS – stratified Weibull	58,128	5.31%	52,229	7.03%
12	Curve choice: PFS – spline knot 1	61,250	10.96%	55,609	13.95%

**Footnotes:** <sup>a</sup> AFT models were only applied to the selpercatinib arm, whilst base case extrapolations were utilised for docetaxel and nintedanib plus docetaxel so that the hazard ratio from the NMA could be applied.

**Abbreviations:** ICER: incremental cost-effectiveness ratio; OS: overall survival; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity; TA: technology appraisal.

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