NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

**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 Roche**

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

# Appraisal title

## 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<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| 1 | Company | Roche Products Ltd. | **Comparators (ACD, Section 3.2, 3.5)**<br><br>**Untreated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: "*If their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed. Although pembrolizumab combination might also be offered, a professional organisation noted that immunotherapy is believed to be less effective in cancer with oncogene drivers such as RET fusion compared with the broader advanced NSCLC population*"<br>"*the clinical expert […] highlighted that platinum-based chemotherapy with or without pemetrexed was missing as first-line treatment*"<br>"*The committee recalled that it had heard from the clinical experts that, in the NHS, once people have a confirmed RET fusion-positive status they would likely be offered platinum-based chemotherapy with or without pemetrexed as a first-line treatment*"<br><br>We have taken on board the clinical expert's and committee's advice regarding the inclusion of platinum-based chemotherapy +/- pemetrexed. An overview of the indirect treatment comparison for pralsetinib to platinum-based chemotherapy +/- pemetrexed is provided in ACD Company Response point 5. Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment comparison analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B.<br><br>**Untreated comparison to pembrolizumab + pemetrexed + chemotherapy**<br><br>The ACD notes: "*However, if their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or* | Thank you for your comment. Section 3.5 of the Final Appraisal Document has been updated to reflect the updated choice of comparators in the company's analyses. The committee considered that the comparators presented by the company were aligned with NHS practice. |

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| | | | *without pemetrexed*."<br><br>We would like to draw a distinction between how patients *should* be treated based on available evidence regarding the effectiveness of pembrolizumab in *RET* patients and how patients *are* currently treated nationally. Roche were advised in a clinical advisory board that the clinical experts consulted in that advisory board and those in the current appraisal (who typically specialise in NSCLC and worked in main centres) may not be a perfect representation of clinicians nationally. The clinical experts in the first appraisal committee meeting (10th February, 2022) discussed that the reason platinum-based chemotherapy +/- pemetrexed was recommended as the relevant comparator in the *RET* untreated setting is due to the limited efficacy of pembrolizumab in this population. However, feedback from clinical experts suggests that this relationship is not well understood by clinicians nationally. Clinicians nationally may be more likely to prescribe pembrolizumab + pemetrexed + chemotherapy to *RET* identified patients in comparison to the clinical experts consulted in this appraisal.<br><br>We agree that based on clinical expert feedback platinum-based chemotherapy +/- pemetrexed can be considered a main comparator for this appraisal in the untreated setting. However, we suggest that pembrolizumab + pemetrexed + chemotherapy remains a relevant secondary comparator for consideration given the high quantity of patients who receive this nationally.<br><br>**Untreated comparison to pembrolizumab monotherapy**<br><br>Based on the discussion at the appraisal committee meeting, pembrolizumab monotherapy has been excluded as a comparator in this appraisal.<br><br>**Pre-treated comparisons to docetaxel monotherapy and docetaxel + nintedanib**<br><br>The ACD notes: "*Second-line treatment for people whose RET fusion status is known is usually docetaxel monotherapy or docetaxel plus nintedanib. The clinical experts noted that docetaxel and nintedanib use is decreasing due to the limited benefit and increased side effects compared with docetaxel alone*"<br><br>We agree with the above statement. As per the company submission, docetaxel monotherapy remains the primary comparison for the pre-treated population. Docetaxel + nintedanib remains a secondary comparator. We note that the limited use and limited additional benefit from nintedanib | |

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| | | | is in line with feedback received by the company during the advisory board.<br><br>**Pre-treated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: The committee "*noted that platinum-based chemotherapy with or without pemetrexed was not a relevant comparator for the previously treated subgroup*"<br><br>We agree that, following the exclusion of pembrolizumab monotherapy as a comparator in the untreated setting, it makes logical sense to exclude platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. Therefore, this has been removed from the analysis.<br><br>**Conclusion**<br><br>In conclusion, the comparators have been updated in the cost-effectiveness analysis to reflect the committee's preferred choice:<br><br>Untreated<br>• Platinum-based chemotherapy +/- pemetrexed (primary)<br>• Pembrolizumab + pemetrexed + chemotherapy (secondary)<br><br>Pre-treated<br>• Docetaxel monotherapy (primary)<br>• Docetaxel + nintedanib (secondary)<br><br>Therefore we believe the committee can consider the concerns regarding comparators to be addressed. | |
| 2 | Company | Roche Products Ltd. | **Trial uncertainty (ACD, Section 3.6)**<br><br>The assessment of pralsetinib in the treatment of *RET* fusion-positive NSCLC is based on ARROW, a single-arm, first-in-human, pivotal Phase 1/2 dose-escalation and dose-expansion trial. A conventional RCT for a rare genomic alteration such as *RET* fusion-positive NSCLC was not chosen to ensure timely patient access to the treatment, given the rarity of *RET* rearrangements. | Thank you for your comments. The committee considered evidence from the ARROW |

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| | | | The ACD references the ERG's Downs and Black checklist (ERG report, Section 3.24, page 51). In areas where there was disagreement between company and ERG checklists, further clarification has been provided in Appendix G. | trial. The committee were aware that there was a lack of comparative data to assess pralsetinib's effectiveness with other systemic treatment options. The committee concluded that data from the ARROW study is relevant and suggests pralsetinib could be clinically effective, but it is uncertain because it comes from 1 single-arm study. Please see section 3.6 of the Final Appraisal Document. |
| 3 | Company | Roche Products Ltd. | **Generalisability to UK practice (ACD, Section 3.7)**<br><br>The company agrees with the clinical expert and the committee that the trial population in the | Thank you for your comments. |

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| | | | ARROW study is generalisable to UK practice. | The committee agreed that the ARROW study is likely to be generalisable to the NHS population. Please see section 3.7 of the Final Appraisal Document. |
| 4 | Company | Roche Products Ltd. | **Indirect treatment comparison (ACD, Section 3.8)**<br><br>**Inclusion of platinum-based chemotherapy +/- pemetrexed**<br><br>Platinum-based chemotherapy +/- pemetrexed was included in the evidence search criteria as outlined in Section B.2.9 of the Company Submission (pages 65-93). Identical methodology in analysis selection was applied to select an analysis for platinum-based chemotherapy +/- pemetrexed as other comparators in the appraisal.<br><br>The most robust form of evidence available was to inform an indirect treatment comparison by using a propensity scoring analysis using individual patient-level data from a WT population from IMpower132 to model efficacy for platinum-based chemotherapy +/- pemetrexed in the comparator arm. This reflected an identical approach to the analysis used in the pre-treated comparison to docetaxel monotherapy (ARROW vs OAK). Patients in the comparator arm were matched based on age, gender, ECOG PS, CNS metastases, smoking status, histology and race to reflect a *RET* fusion-positive population as per ARROW. After matching, pralsetinib demonstrated significantly superior OS to platinum-based chemotherapy +/- pemetrexed (OS HR [redacted]).<br><br>Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B. | Thank you for your comments. The committee considered the company's updated indirect treatment comparisons at the second committee meeting. The ERG noted that there were the methodological problems with the systematic literature review, baseline differences |

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| | | | **Updates to pembrolizumab + pemetrexed + chemotherapy**<br><br>Following the inclusion of platinum-based chemotherapy +/- pemetrexed to the indirect treatment comparison, the relationship of modelled survival between platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy was assessed. It was not considered feasible that patients would demonstrate superior OS on platinum-based chemotherapy +/- pemetrexed compared to pembrolizumab + pemetrexed + chemotherapy. Three different options for analysis were considered:<br><br>• Flatiron EDM: [redacted]<br>Given pembrolizumab + pemetrexed + chemotherapy is comparable in treatments to the platinum-based chemotherapy +/- pemetrexed regimen but also contains the addition of pembrolizumab, it did not seem logical to assume greater efficacy in the platinum-based chemotherapy +/- pemetrexed arm compared to pembrolizumab + pemetrexed + chemotherapy. This would imply a negative treatment effect of pembrolizumab. Further, as outlined in the ACD, the committee express concerns regarding the comparison between trial data and real world evidence.<br><br>• WT SLR propensity scoring of ARROW vs IMpower132 - assumption of equivalence to platinum-based chemotherapy +/- pemetrexed: ([redacted])<br>The propensity scoring informed from WT SLR (Appendix A) is considered a more robust comparison than the comparison to the Flatiron EDM dataset (Company Submission, Section B.2.9.5, pages 80-91). The assumption of equivalence of efficacy to the IMpower132 indirect treatment comparison assumes no additional efficacy benefit from the addition of pembrolizumab to the regimen. This is in line with feedback from the clinical experts in the appraisal committee meeting (and the motivation for the inclusion of platinum-based chemotherapy +/- pemetrexed as the main comparator). However, the extent to which there is limited benefit of the addition of pembrolizumab to this regimen compared to no benefit is unclear. We differ to clinical expert judgment on this matter.<br><br>• Naïve comparison ([redacted])<br>The naïve comparison was informed by a comparison to KEYNOTE-189 (Company Submission, | between the studies and the validity of the naïve comparisons. There were also other issues with the description of the search methods, no other methods of adjustment considered, and overlap was not explicitly assessed. The committee concluded that the results of the indirect treatment comparisons were uncertain. Please see section 3.8 of the Final Appraisal Document.<br><br>The committee noted that the |

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| | | | Section B.2.9.4, pages 67-80). No individual patient level data was available for this comparison and therefore no adjustment for *RET* characteristics was conducted. The impact of not adjusting for *RET* characteristics is not known. Further, the committee heard that the justification for inclusion of platinum-based chemotherapy +/- pemetrexed as the primary comparator in the untreated setting was due to the lack of survival benefit of pembrolizumab in *RET* patients. Therefore, to use a data source from a WT population to estimate efficacy in a *RET* population is likely to overestimate efficacy in the comparator arm. Therefore, this would likely underestimate the cost-effectiveness of pralsetinib.<br><br>On balance, it is likely that the true estimate of efficacy for pembrolizumab + pemetrexed + chemotherapy in *RET* fusion positive advanced NSCLC may lie somewhere between the IMpower132 and KEYNOTE-189 indirect treatment comparisons depending on the extent of the additional treatment benefit of pembrolizumab in this regimen. An assumption was used to model efficacy for pembrolizumab + pemetrexed + chemotherapy as per the naïve indirect treatment comparison against KEYNOTE-189. The impact of this assumption was explored in a scenario analysis (Appendix E). This assumption does not include the impact of a *RET* characteristics adjustment due to lack of individual patient-level data. The potential impact of this is unknown.<br><br>**Use of real-world data**<br><br>The ACD notes: "*The committee expressed concerns about the appropriateness of the real-world data in the Flatiron database, due to the challenges in assessing its quality*."<br>"*It also noted that an indirect treatment comparison of clinical trial data to with real-world data can be expected to introduce bias because the care that people have in each setting is likely to be different*"<br>"*For these reasons, the hazard ratio results of the indirect treatment comparison may have overestimated the relative clinical effectiveness of pralsetinib*"<br><br>As per the advice of the committee (ACD, Section 3.5), pembrolizumab monotherapy has been excluded as a comparator. The indirect treatment comparison for pembrolizumab + pemetrexed + chemotherapy has been updated to use the naïve comparison against KEYNOTE-189 instead of the real-world data from Flatiron. Hence, in the updated company base case, no real-world evidence comparison is used. Therefore we believe the committee can consider these concerns to be addressed. | comparison with docetaxel and docetaxel plus nintedanib assumed equal efficacy between both arms. This was considered implausible as clinical experts explained that docetaxel plus nintedanib use is decreasing due to its limited benefit and increased side effects (see section 3.2 of the Final Appraisal Document). |

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| | | | **Naïve comparison**<br><br>The ERG note that there were differences in characteristics in the naïve comparison between the GOIRC trial and ARROW. Given, as per the advice on the committee (ACD, Section 3.5), platinum-based chemotherapy +/- pemetrexed has been excluded as a comparator, we believe the committee can consider these concerns to be addressed.<br><br>In the case of docetaxel + nintedanib OS and PFS, it was originally planned to use the naïve indirect treatment comparison as per the to the company submission. However, it was not considered feasible for survival in the docetaxel + nintedanib arm to be less than in the docetaxel monotherapy arm. Therefore, to maintain internal consistency, an approach was taken to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. This assumption was made after it was noted by clinical experts there is "limited benefit" associated with the addition of nintedanib. In the case of docetaxel + nintedanib, the naïve HR for TTD as per the company submission was applied to the pralsetinib TTD arm to estimate TTD for docetaxel + nintedanib.<br><br>In the case of pembrolizumab + pemetrexed + chemotherapy, as outlined earlier in this section, a naïve comparison was deemed the best and most conservative available analysis to inform the comparison against pralsetinib. All usual limitations with naïve analyses apply.<br><br>**Conclusion**<br><br>The updates conducted on the economic model by the company have substantially increased robustness and reduced uncertainty across the indirect treatment comparison. | |
| 5 | Company | Roche Products Ltd. | **Propensity scoring for platinum-based chemotherapy +/- pemetrexed (ACD, Section 3.9)**<br><br>**Untreated setting**<br><br>The ACD notes: "*The committee concluded that propensity score weighting analysis should have been done for platinum-based chemotherapy with or without pemetrexed*"<br><br>Platinum-based chemotherapy +/- pemetrexed in the untreated setting was not included in the company submission as a comparator. As per the ACD Company Response points 2, 5 and Appendix A, platinum-based chemotherapy +/- pemetrexed has been included. Propensity scoring | Thank you for your comments. The committee acknowledged the use of propensity score analysis for the comparison |

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| | | | using an indirect treatment comparison between ARROW and IMpower132 was conducted. Therefore we believe the committee can consider these concerns to be addressed.<br><br>**Pre-treated setting**<br><br>The ACD notes: "*The ERG was concerned that the company presented this naive comparison despite having access to the Flatiron database, which was used to inform other comparisons. The ERG explained that this comparison should have been made using the Flatiron database because platinum-based chemotherapy with or without pemetrexed was used more (16.1%) than pembrolizumab plus pemetrexed and chemotherapy (14.1%) and pembrolizumab monotherapy (7.6%).*"<br><br>The naïve comparison in question relates to the indirect comparison to platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. As outlined in the Company Technical Engagement Response (Key Issue 6, pages 21-24), the numbers quoted in this quote relate to an untreated setting. The usage in the Flatiron database in the pre-treated setting was smaller ([redacted]) and did not facilitate matching. As per advice from the committee (ACD, Section 3.2, 3.5) platinum-based chemotherapy +/- pemetrexed has been removed as a comparator in the pre-treated setting. Therefore we believe the committee can consider these concerns to be addressed. | with platinum-based chemotherapy with or without pemetrexed in the untreated setting (please see section 3.8 of the Final Appraisal Document). As per section 3.5 of the Final Appraisal Document, the committee was aware of the updated choice of comparators in the company's analyses. |
| 6 | Company | Roche Products Ltd. | **Differences between deterministic and probabilistic result (ACD, Section 3.10)**<br><br>The ACD notes "*There were concerns about the validity of the model due to the large difference between the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) seen for all the comparators. The company nor the ERG were able to provide an explanation for this*."<br><br>This issue has been addressed in the updated version of the cost-effectiveness model (Appendix C) with the updated survival parameters for independent curves. Updated base case probabilistic results are provided in Appendix E and can be considered suitable for decision making. | Thank you for your comments. The committee used the probabilistic results in its decision making. This is in line with NICE's Guide to the methods of technology |

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| | | | | appraisal 2013, which states that probabilistic sensitivity analysis is preferred. |
| 7 | Company | Roche Products Ltd. | **Constant treatment benefit and proportional hazards (ACD, Section 3.11)**<br><br>**Proportional hazards**<br><br>The ACD notes: "*The ERG explained that the hazard ratios used by the company are based on a small sample size, immature data, and highly uncertain indirect treatment comparison results*"<br><br>The company understands the ERG's and committee's concerns regarding the proportional hazard assumption in the context of short median follow-up, small sample size, immature data, and uncertainty in the indirect treatment comparison. It should be highlighted that we believe concerns regarding the indirect treatment comparison have been addressed (as per ACD Company Response point 5).<br><br>The ACD notes: "*The committee considered that proportional hazards is a strong assumption and it is unreasonable to apply this over the full time horizon of the model given the immature and highly uncertain data available on relative effectiveness. The committee concluded that the assumption of pralsetinib's constant benefit over time is implausible, and the model needs adjusting to account for this*."<br><br>In response to this, we have adjusted the model to reject the proportional hazards assumption in the case of the main comparators in the untreated and pre-treated settings.<br><br>**Independent curves**<br><br>We have updated the latest version of the economic model to remove the proportional hazards assumption. Independent curves have been fitted to model survival for OS/PFS for pralsetinib against the main comparators in the untreated and pre-treated settings. In the untreated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW | Thank you for your comments. The committee was aware that the proportional hazards assumption had been removed for the comparisons with platinum-based chemotherapy with or without pemetrexed, docetaxel monotherapy and docetaxel plus nintedanib. The committee noted that the proportional hazards assumption |

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| | | | and IMpower132 to model pralsetinib and platinum-based chemotherapy +/- pemetrexed respectively (Appendix A). In the pre-treated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW and OAK to model pralsetinib and docetaxel monotherapy respectively (Company Submission B.2.9.4, pages 67-80).<br><br>In the case of docetaxel + nintedanib OS and PFS, an assumption was made to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. Therefore, the docetaxel + nintedanib arm uses the independent curves (as per the docetaxel monotherapy indirect treatment comparison) and does not assume proportional hazards for OS and PFS.<br><br>In the case of the secondary comparison to pembrolizumab + pemetrexed + chemotherapy (untreated) separate independent models were not fitted. This decision is considered a pragmatic approach given the time constraints and in order to maintain simplicity in the model. Therefore, the proportional hazards assumption was retained and survival was modelled by applying a HR from the respective indirect treatment comparison to the pralsetinib arms.<br><br>Full details are outlined in Appendix A and Appendix B. | had not been removed for pembrolizumab plus pemetrexed and chemotherapy. It noted that independent curves had been fitted to model overall and progression free survival for pralsetinib compared with the main comparators. The ERG considers this to be an improvement but highlight that there is still some uncertainty remaining. This is because a constant treatment benefit is still seen throughout the |

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| | | | | model, the trial data is immature, and the sample size is small. Please see section 3.10 of the Final Appraisal Document. |
| 8 | Company | Roche Products Ltd. | **Curve extrapolations (ACD, Section 3.12)**<br><br>**Curve extrapolations update**<br><br>The ACD notes: "*the committee agreed that the extrapolations presented could not be considered sufficiently reliable for decision making*"<br><br>We accept the committee did not see the previous extrapolations as suitable for decision making. We note that the key reasons for this appear to be that the committee considers the lifetime treatment benefit as per the proportional hazards assumption as unreasonable and that this leads to differences between clinical expert's landmark survival and extrapolation predictions.<br><br>In order to address this, the proportional hazards assumption was rejected and independent curves were used to model survival for pralsetinib compared to the main model comparators (ACD Company Response point 8; Appendix A; Appendix B).<br><br>With the updated extrapolations, curve selection was re-conducted for pralsetinib and comparators in the untreated and pre-treated settings. Methods of curve selection were in line with NICE technical guidance. Curve selection was based on statistical fit, visual fit, clinical expert's preferred clinical plausibility and alignment to clinical expert long-term landmark predictions. The updated curves were validated in a consultation with a clinical expert and against the previously provided landmark survival predictions.<br><br>**Untreated setting** | Thank you for your comments. At the second committee meeting, the committee discussed the company's updated approach. The committee concluded that the overall survival and progression free survival extrapolations were uncertain but acceptable for decision making. Please see section 3.11 of the Final |

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| | | | • OS: the exponential distribution was selected to model pralsetinib and comparators. In the case of pralsetinib at the 5-year time point, the exponential curve under predicted the clinical expert's landmark survival by 4%. In the case of platinum-based chemotherapy +/- pemetrexed, the exponential model substantially over predicts OS compared to clinical experts predictions – for example, at the 5-year time point, the exponential curve over predicted the clinical expert's upper range of landmark survival by 7% (8% to mid-point). One potential reason for this could be increased use of pemetrexed in the trial data compared to what is anticipated in UK practice<br>• PFS/TTD: the generalised gamma distribution showed the best combination of fit to the observed data, fit to clinical expert's landmark survival predictions and was recommended by a clinical expert. In the case of pralsetinib TTD, the generalised gamma model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Pre-treated setting**<br><br>• OS: Both the exponential and Weibull extrapolations demonstrated good combinations of fit to the observed data, fit to clinical expert's landmark survival predictions and were recommended by a clinical expert. However, the Weibull curve demonstrated an increasing hazard of mortality over time which was not thought to be clinically plausible. In the case of pralsetinib at the 5-year time point, the exponential curve over predicted the clinical expert's landmark survival by 8%. At the 5-year time point the exponential curve accurately predicted the clinical expert's landmark survival estimate in the docetaxel monotherapy arm.<br>• PFS/TTD: Across both endpoints, the Weibull model showed the best combination of fit to the observed data and fit to clinical expert's landmark survival predictions. In the case of pralsetinib TTD, the exponential model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Proposed ERG alternative set of HRs**<br><br>The ACD notes: "*To explore the uncertainty, the ERG produced a scenario using an alternative set of hazard ratios at 3 years. These hazard ratios resulted in overall survival and progression-free survival curves that better reflected the clinical expert advice. The ERG's calibration reduced the underprediction of the comparator survival curves*." | Appraisal Document |

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| | | | We do not agree with the ERG's proposed alternative set of hazard ratios which were estimated by calibrating HRs based on clinical expert's 3-year landmark survival estimates.<br>• This is an inferior and less robust methodology than the systematic ITC conducted in the company submission which includes observed data from clinical trials and real world evidence datasets<br>• The approach ignores the entirety of the observed clinical trial efficacy data in favour of point estimates in an advisory board. The 3-year point estimates themselves contain inconsistencies both with the observed data and internal inconsistencies. For example in the pre-treated setting, the clinical expert's predicted 35% of patients would be alive at 3-years and 30-35% would be both in PFS and on treatment. This implies that after 3 years 86-100% of patients who are alive would be in PFS and on treatment and therefore that every patient who progresses or discontinues treatment dies instantly or close to.<br>• Results are sensitive to clinical expert's predictions which clinicians stated to be a difficult exercise and were often rounded to multiples of 5/10 and can therefore considered to be approximations instead of an exact science which when translated into HRs can impact results<br>• The ERG calibration approach is a poor predictor of the observed data<br><br>Therefore, the updated company approach with the independent models to model OS and PFS in the main comparisons using propensity scoring from clinical trial data should be considered the preferred method by the committee. It represents a more robust approach, more accurately predicts the observed data and represents a closer fit to clinical expert's long term landmark survival predictions in comparison to the submission company approach.<br><br>**Conclusion**<br><br>The updated curve selection resulting from the introduction of independent models has reduced the differences between model and clinical expert predictions at landmark survival points. This has reduced uncertainty and increased robustness in results. However, in the case of platinum-based chemotherapy +/- pemetrexed in the untreated setting, model extrapolations still over predict clinical expert's expectations of survival which may bias cost-effectiveness results against pralsetinib. | |
| 9 | Company | Roche | **End-of-life in pre-treated setting (ACD, Section 3.13)** | Thank you for |

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| | | Products Ltd. | We agree with the committee's assertion that pralsetinib meets the end-of-life criteria in the pre-treated setting. | your comments. The committee concluded that end of life criteria had been met for the previously treated subgroup. Please see section 3.12 of the Final Appraisal Document. |
| 10 | Company | Roche Products Ltd. | **End-of-life in untreated setting (ACD, Section 3.14)**<br><br>We understand the committee's concerns and appreciate that at the time of the first appraisal committee meeting, there was insufficient evidence available to draw a robust conclusion regarding end-of-life.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy: 3-month life extension criterion**<br><br>In the updated company base case results in the untreated setting, the undiscounted OS for patients receiving pralsetinib is [redacted] months compared to [redacted] months in the case of platinum-based chemotherapy +/- pemetrexed and [redacted] months in the case of pembrolizumab + pemetrexed + chemotherapy. This translates to a survival benefit of [redacted] and [redacted] against platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy respectively. Therefore we consider the 3-month life extension criterion to be comfortably satisfied.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed: <24-month short life criterion** | Thank you for your comments. The committee recalled that treatments in the untreated subgroup are platinum-based chemotherapy with or without pemetrexed and pembrolizumab plus pemetrexed and chemotherapy. It was aware |

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| | | | There is previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced WT NSCLC NICE HTA appraisals. In the case of pembrolizumab + pemetrexed + chemotherapy in the WT population (TA683), pembrolizumab + pemetrexed + chemotherapy meets NICE's end-of-life criteria. However, it should be acknowledged that this is not a direct precedent due to the impact of adjustment on from WT to RET status in the platinum-based chemotherapy +/- pemetrexed population is to increase survival. The impact of the weighting on median survival in platinum-based chemotherapy +/- pemetrexed was from [redacted] (95% CI [redacted]) to [redacted] (95% CI [redacted]). This represented a 1.9m increase in median survival. In previous NICE HTA appraisals in a ROS1 positive population, which may represent a more comparable population to the current indication in terms of survival, precedence for the end-of-life short life criterion being met exists. In the case of entrectinib (TA643) and crizotinib (TA529), both treatments met both criteria to be considered a life-extending, end-of-life treatment compared with platinum-based chemotherapy +/- pemetrexed (2, 3).<br><br>In the indirect treatment comparison for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (Appendix A), the median OS in the adjusted platinum-based chemotherapy +/- pemetrexed arm is [redacted] months. OS in the economic model was modelled by the exponential curve for pralsetinib and platinum-based chemotherapy +/- pemetrexed. The modelled mean undiscounted OS for platinum-based chemotherapy +/- pemetrexed is [redacted] months. However, the exponential model overestimates the clinical expert's upper range of landmark survival at the 3-year time point by 7% (12% to the mid-point) and at the 5-year time point by 7% (8% to the mid-point). Therefore, the current model (predicting [redacted] months OS) can be considered an optimistic prediction of OS compared to clinical expert's predictions. The modelled mean represents the adjusted IMpower132 population where a higher proportion of patients received pemetrexed compared to that which would be expected in UK practice.<br><br>Therefore, based on the previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced NSCLC appraisals; the IMpower132 modelled median; and the closeness of the modelled mean to the 24 month cut-off despite the overestimation compared to clinical expert landmark predictions, we consider the end-of-life short life criterion to be met in the comparison to platinum-based chemotherapy +/- pemetrexed.<br><br>**Comparison to pembrolizumab + pemetrexed + chemotherapy: <24-month short life** | that clinicians nationally may be more likely to prescribe pembrolizumab plus pemetrexed and chemotherapy to people untreated RET-fusion positive advanced NSCLC. The committee noted that people having pembrolizumab plus pemetrexed and chemotherapy tend to live longer than 24 months. On balance, the committee concluded that the end of life criteria were not met for this subgroup. Please see section 3.13 of |

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| | | | **criterion**<br><br>We note that with the updated company base case analysis, the undiscounted predicted OS for patients receiving pembrolizumab + pemetrexed + chemotherapy is [redacted] months. It is noted that this may be an over prediction of survival given a conservative assumption was used to assume the additional survival benefit of pembrolizumab is identical in a WT population and a *RET* population.<br><br>Feedback from the ACD suggested that in previous NICE appraisals in untreated advanced NSCLC where pembrolizumab + pemetrexed + chemotherapy has been used as a comparator, the precedence has been set for appraisals not meeting the end-of-life threshold based on the short life (<24 month) criterion. We note that this precedence would not apply if, as per the clinical expert's comments, a limited survival benefit of pembrolizumab in this population is assumed.<br><br>However, given the modelled mean is comfortably above the 24 month cut-off, we do not consider that the short life criterion is met in this instance. | the Final Appraisal Document |
| 11 | Company | Roche Products Ltd. | **Cancer Drugs Fund**<br><br>The ACD notes "*the comparators used by the company* [in AcceleRET-Lung] *were not aligned with NHS practice*"<br><br>Comparators in AcceleRET-Lung for non-squamous patients consist of:<br>• Carboplatin or cisplatin + pemetrexed followed by optional pemetrexed maintenance<br>• Pembrolizumab + carboplatin or cisplatin + pemetrexed followed by pembrolizumab and optional pemetrexed maintenance.<br><br>The comparators in AcceleRET-Lung closely align with standard of care in the current appraisal (following the updated comparator list) and UK clinical practice. | Thank you for your comments. Section 3.16 of the FAD gives an overview of AcceleRET, |
| 12 | Company | Roche Products Ltd. | **Further evidence provided/other amendments to the economic model**<br><br>As per Appendix C, amendments have been made to the latest version of the economic model to amend minor errors:<br>• A fix of an adverse event which was incorrectly applied | Thank you for your comments. |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | • A fix in the application of the life tables adjustment to ensure model survival does not drop below general population mortality<br>• The issue of the PSA error was addressed as per ACD Company Response point 7 | |
| 13 | Company | Roche Products Ltd. | **Updated company base case results**<br><br>The following changes were made to the company base case as part of the ACD Company Response:<br>• Introduction of platinum-based chemotherapy +/- pemetrexed as comparator (ACD Company Response point 2; Appendix A)<br>• Life tables fix (ACD Company Response point 13; Appendix C)<br>• Adverse events fix (ACD Company Response point 13; Appendix C)<br>• Naïve comparison for pembrolizumab + pemetrexed + chemotherapy (ACD Company Response point 5)<br>• Inclusion of independent models in main comparisons with updated curve extrapolations (ACD Company Response point 8-9, Appendix B)<br>[redacted]<br>In the updated company base case in the untreated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to platinum-based chemotherapy +/- pemetrexed<br>• A dominant ICER compared to pembrolizumab + pemetrexed + chemotherapy<br><br>In the updated company base case in the pre-treated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to docetaxel monotherapy<br>• [redacted] per QALY gained compared to docetaxel + nintedanib<br><br>Full results are shown in Appendix E. Scenario analysis demonstrates the results of cost-effectiveness are robust to a range of varied assumptions. | Thank you for your comments. The committee considered the company's updated base-case results in its decision making. |
| 14 | Company | Roche Products Ltd. | **Conclusion**<br><br>We note the five concerns outlined by the committee in Section 3.10 of the ACD response. We | Thank you for your comments. |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | feel that each of these five concerns have been adequately addressed as part of this company response:<br>• The differences between the deterministic and probabilistic models have been addressed as per ACD Company Response point 7<br>• The comparators included in the analysis have been updated to reflect the committee's wishes as per ACD Company Response point 2<br>• The relative treatment benefit has been amended with updates made to the indirect treatment comparison in the untreated setting as per ACD Company Response point 5<br>• The assumption of proportional hazards has been dropped and independent curves have been fitted in the main comparisons in the untreated and pre-treated settings as per ACD Company Response point 8<br>• Following the introduction of the independent curves, the OS and PFS extrapolations have been reviewed with model predictions now being considered more plausible (when compared to clinical expert landmark survival predictions) as per ACD Company Response point 9. However, it should be noted that in the main comparison to platinum-based chemotherapy +/- pemetrexed, model OS in the comparator still over predicts clinical expert landmark predictions which may bias cost-effectiveness results against pralsetinib<br><br>This has increased the robustness and reduced the uncertainty in the analysis. We now consider that the cost-effectiveness model is suitable for decision-making. [redacted] In the updated economic model, pralsetinib is estimated to cost the healthcare payer an additional [redacted] per QALY gained in comparison to platinum-based chemotherapy +/- pemetrexed in the untreated setting and an additional [redacted] per QALY gained in comparison to docetaxel monotherapy in the pre-treated setting. Therefore, the updated results meet NICE's cost-effectiveness thresholds in both the untreated and pre-treated settings when the end-of-life threshold is considered.<br><br>Roche are available for all routes to access. Given the updates to the model to address the committee's concerns [redacted], we believe the committee should consider pralsetinib for baseline funding in the untreated and pre-treated populations. | These concerns have been addressed in the Final Appraisal Document. Please see section 3.5, section 3.8, section 3.10 and section 3.11.<br><br>The committee used the probabilistic results in its decision making. This is in line with NICE's Guide to the methods of technology appraisal 2013, which states that probabilistic sensitivity analysis is preferred. |
| 15 | Web commentato | | In relation to the comparators for the previously treated group, docetaxel monotherapy and docetaxel plus nintedanib would be suitable comparators and also reflective of the agreed | Thank you for your comment. |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | r | | comparators in the committee discussion for selpercatinib in RET-fusion positive NSCLC. | Section 3.5 of the Final Appraisal Document has been updated to reflect the updated choice of comparators in the company's analyses. The committee considered that the comparators presented by the company were aligned with NHS practice. |

**Comments received from clinical experts and patient experts**

None received

NICE National Institute for Health and Care Excellence

**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 24 March. Please submit via NICE Docs.

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced. |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Roche Products Ltd. |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | -- |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row. |
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NICE National Institute for Health and Care Excellence

**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 24 March. Please submit via NICE Docs.

| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
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| 1 | **Squamous patients (ACD, Section 3.4)**<br><br>The ACD notes "*the company did not present any information for squamous NSCLC*". The ACD also highlights that comparators chosen for this appraisal were determined using the current standard of care for the population in NICE's non-squamous treatment pathway.<br><br>The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced NSCLC. Due to the unmet medical need in all *RET* fusion-positive patients in the UK, it is important that all *RET* fusion-positive advanced NSCLC patients (non-squamous and squamous histologies) have a *RET* inhibitor available as a treatment option in line with the proposed licensed indication.<br><br>The presentation in the committee meeting considered this issue "unresolvable". However, in the selpercatinib appraisal consultation document (ID3743) (1), the committee faced a near identical issue. The clinical expert in the appraisal expected there would still be some level of response for squamous patients. The Cancer Drugs Fund clinical lead stated that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. Therefore, the committee agreed that, despite a low incidence of *RET* fusion positive patients with squamous histology, the technology appraisal recommendation would apply to both squamous and non-squamous patients with *RET*-fusion advanced NSCLC. Given the similar nature of the squamous issues across the two appraisals, the precedent set by ID3743 should be considered adequate to cover the appraisal for pralsetinib and that the relevant population for this appraisal should be the full licenced indication including squamous patients.<br><br>We consider this issue as unresolved but resolvable. The issue can be resolved if the committee aligns to the recommendation made in the selpercatinib appraisal and broadens the recommendation to include squamous patients as per the licenced indication. |
| 2 | **Comparators (ACD, Section 3.2, 3.5)**<br><br>**Untreated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: "*If their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed. Although pembrolizumab combination might also be offered, a professional organisation noted that immunotherapy is believed to be less effective in cancer with oncogene drivers such as RET fusion compared with the broader advanced NSCLC population*"<br>"*the clinical expert […] highlighted that platinum-based chemotherapy with or without pemetrexed was missing as first-line treatment*"<br>"*The committee recalled that it had heard from the clinical experts that, in the NHS, once people have a confirmed RET fusion-positive status they would likely be offered platinum-based chemotherapy with or without pemetrexed as a first-line treatment*"<br><br>We have taken on board the clinical expert's and committee's advice regarding the inclusion of platinum-based chemotherapy +/- pemetrexed. An overview of the indirect treatment comparison for pralsetinib to platinum-based chemotherapy +/- pemetrexed is provided in ACD Company Response point 5. Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment comparison analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B. |

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**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 24 March. Please submit via NICE Docs.

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| | **Untreated comparison to pembrolizumab + pemetrexed + chemotherapy**<br><br>The ACD notes: "*However, if their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed*."<br><br>We would like to draw a distinction between how patients *should* be treated based on available evidence regarding the effectiveness of pembrolizumab in *RET* patients and how patients *are* currently treated nationally. Roche were advised in a clinical advisory board that the clinical experts consulted in that advisory board and those in the current appraisal (who typically specialise in NSCLC and worked in main centres) may not be a perfect representation of clinicians nationally. The clinical experts in the first appraisal committee meeting (10th February, 2022) discussed that the reason platinum-based chemotherapy +/- pemetrexed was recommended as the relevant comparator in the *RET* untreated setting is due to the limited efficacy of pembrolizumab in this population. However, feedback from clinical experts suggests that this relationship is not well understood by clinicians nationally. Clinicians nationally may be more likely to prescribe pembrolizumab + pemetrexed + chemotherapy to *RET* identified patients in comparison to the clinical experts consulted in this appraisal.<br><br>We agree that based on clinical expert feedback platinum-based chemotherapy +/- pemetrexed can be considered a main comparator for this appraisal in the untreated setting. However, we suggest that pembrolizumab + pemetrexed + chemotherapy remains a relevant secondary comparator for consideration given the high quantity of patients who receive this nationally.<br><br>**Untreated comparison to pembrolizumab monotherapy**<br><br>Based on the discussion at the appraisal committee meeting, pembrolizumab monotherapy has been excluded as a comparator in this appraisal.<br><br>**Pre-treated comparisons to docetaxel monotherapy and docetaxel + nintedanib**<br><br>The ACD notes: "*Second-line treatment for people whose RET fusion status is known is usually docetaxel monotherapy or docetaxel plus nintedanib. The clinical experts noted that docetaxel and nintedanib use is decreasing due to the limited benefit and increased side effects compared with docetaxel alone*"<br><br>We agree with the above statement. As per the company submission, docetaxel monotherapy remains the primary comparison for the pre-treated population. Docetaxel + nintedanib remains a secondary comparator. We note that the limited use and limited additional benefit from nintedanib is in line with feedback received by the company during the advisory board.<br><br>**Pre-treated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: The committee "*noted that platinum-based chemotherapy with or without pemetrexed was not a relevant comparator for the previously treated subgroup*"<br><br>We agree that, following the exclusion of pembrolizumab monotherapy as a comparator in the untreated setting, it makes logical sense to exclude platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. Therefore, this has been removed from the analysis.<br><br>**Conclusion**<br><br>In conclusion, the comparators have been updated in the cost-effectiveness analysis to reflect the committee's preferred choice: |

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| | Untreated<br>• Platinum-based chemotherapy +/- pemetrexed (primary)<br>• Pembrolizumab + pemetrexed + chemotherapy (secondary)<br><br>Pre-treated<br>• Docetaxel monotherapy (primary)<br>• Docetaxel + nintedanib (secondary)<br><br>Therefore we believe the committee can consider the concerns regarding comparators to be addressed. |
| 3 | **Trial uncertainty (ACD, Section 3.6)**<br><br>The assessment of pralsetinib in the treatment of *RET* fusion-positive NSCLC is based on ARROW, a single-arm, first-in-human, pivotal Phase 1/2 dose-escalation and dose-expansion trial. A conventional RCT for a rare genomic alteration such as *RET* fusion-positive NSCLC was not chosen to ensure timely patient access to the treatment, given the rarity of *RET* rearrangements.<br><br>The ACD references the ERG's Downs and Black checklist (ERG report, Section 3.24, page 51). In areas where there was disagreement between company and ERG checklists, further clarification has been provided in Appendix G. |
| 4 | **Generalisability to UK practice (ACD, Section 3.7)**<br><br>The company agrees with the clinical expert and the committee that the trial population in the ARROW study is generalisable to UK practice. |
| 5 | **Indirect treatment comparison (ACD, Section 3.8)**<br><br>**Inclusion of platinum-based chemotherapy +/- pemetrexed**<br><br>Platinum-based chemotherapy +/- pemetrexed was included in the evidence search criteria as outlined in Section B.2.9 of the Company Submission (pages 65-93). Identical methodology in analysis selection was applied to select an analysis for platinum-based chemotherapy +/- pemetrexed as other comparators in the appraisal.<br><br>The most robust form of evidence available was to inform an indirect treatment comparison by using a propensity scoring analysis using individual patient-level data from a WT population from IMpower132 to model efficacy for platinum-based chemotherapy +/- pemetrexed in the comparator arm. This reflected an identical approach to the analysis used in the pre-treated comparison to docetaxel monotherapy (ARROW vs OAK). Patients in the comparator arm were matched based on age, gender, ECOG PS, CNS metastases, smoking status, histology and race to reflect a *RET* fusion-positive population as per ARROW. After matching, pralsetinib demonstrated significantly superior OS to platinum-based chemotherapy +/- pemetrexed (OS HR [redacted]).<br><br>Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B.<br><br>**Updates to pembrolizumab + pemetrexed + chemotherapy**<br><br>Following the inclusion of platinum-based chemotherapy +/- pemetrexed to the indirect treatment comparison, the relationship of modelled survival between platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy was assessed. It was not considered |

feasible that patients would demonstrate superior OS on platinum-based chemotherapy +/- pemetrexed compared to pembrolizumab + pemetrexed + chemotherapy. Three different options for analysis were considered:

- Flatiron EDM: ([redacted])

Given pembrolizumab + pemetrexed + chemotherapy is comparable in treatments to the platinum-based chemotherapy +/- pemetrexed regimen but also contains the addition of pembrolizumab, it did not seem logical to assume greater efficacy in the platinum-based chemotherapy +/- pemetrexed arm compared to pembrolizumab + pemetrexed + chemotherapy. This would imply a negative treatment effect of pembrolizumab. Further, as outlined in the ACD, the committee express concerns regarding the comparison between trial data and real world evidence.

- WT SLR propensity scoring of ARROW vs IMpower132 - assumption of equivalence to platinum-based chemotherapy +/- pemetrexed: ([redacted])

The propensity scoring informed from WT SLR (Appendix A) is considered a more robust comparison than the comparison to the Flatiron EDM dataset (Company Submission, Section B.2.9.5, pages 80-91). The assumption of equivalence of efficacy to the IMpower132 indirect treatment comparison assumes no additional efficacy benefit from the addition of pembrolizumab to the regimen. This is in line with feedback from the clinical experts in the appraisal committee meeting (and the motivation for the inclusion of platinum-based chemotherapy +/- pemetrexed as the main comparator). However, the extent to which there is limited benefit of the addition of pembrolizumab to this regimen compared to no benefit is unclear. We differ to clinical expert judgment on this matter.

- Naïve comparison ([redacted])

The naïve comparison was informed by a comparison to KEYNOTE-189 (Company Submission, Section B.2.9.4, pages 67-80). No individual patient level data was available for this comparison and therefore no adjustment for *RET* characteristics was conducted. The impact of not adjusting for *RET* characteristics is not known. Further, the committee heard that the justification for inclusion of platinum-based chemotherapy +/- pemetrexed as the primary comparator in the untreated setting was due to the lack of survival benefit of pembrolizumab in *RET* patients. Therefore, to use a data source from a WT population to estimate efficacy in a *RET* population is likely to overestimate efficacy in the comparator arm. Therefore, this would likely underestimate the cost-effectiveness of pralsetinib.

On balance, it is likely that the true estimate of efficacy for pembrolizumab + pemetrexed + chemotherapy in *RET* fusion positive advanced NSCLC may lie somewhere between the IMpower132 and KEYNOTE-189 indirect treatment comparisons depending on the extent of the additional treatment benefit of pembrolizumab in this regimen. An assumption was used to model efficacy for pembrolizumab + pemetrexed + chemotherapy as per the naïve indirect treatment comparison against KEYNOTE-189. The impact of this assumption was explored in a scenario analysis (Appendix E). This assumption does not include the impact of a *RET* characteristics adjustment due to lack of individual patient-level data. The potential impact of this is unknown.

**Use of real-world data**

The ACD notes: "*The committee expressed concerns about the appropriateness of the real-world data in the Flatiron database, due to the challenges in assessing its quality*."
"*It also noted that an indirect treatment comparison of clinical trial data to with real-world data can be expected to introduce bias because the care that people have in each setting is likely to be different*"
"*For these reasons, the hazard ratio results of the indirect treatment comparison may have overestimated the relative clinical effectiveness of pralsetinib*"

As per the advice of the committee (ACD, Section 3.5), pembrolizumab monotherapy has been excluded as a comparator. The indirect treatment comparison for pembrolizumab + pemetrexed + chemotherapy has been updated to use the naïve comparison against KEYNOTE-189 instead of the

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| | real-world data from Flatiron. Hence, in the updated company base case, no real-world evidence comparison is used. Therefore we believe the committee can consider these concerns to be addressed.<br><br>**Naïve comparison**<br><br>The ERG note that there were differences in characteristics in the naïve comparison between the GOIRC trial and ARROW. Given, as per the advice on the committee (ACD, Section 3.5), platinum-based chemotherapy +/- pemetrexed has been excluded as a comparator, we believe the committee can consider these concerns to be addressed.<br><br>In the case of docetaxel + nintedanib OS and PFS, it was originally planned to use the naïve indirect treatment comparison as per the to the company submission. However, it was not considered feasible for survival in the docetaxel + nintedanib arm to be less than in the docetaxel monotherapy arm. Therefore, to maintain internal consistency, an approach was taken to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. This assumption was made after it was noted by clinical experts there is "limited benefit" associated with the addition of nintedanib. In the case of docetaxel + nintedanib, the naïve HR for TTD as per the company submission was applied to the pralsetinib TTD arm to estimate TTD for docetaxel + nintedanib.<br><br>In the case of pembrolizumab + pemetrexed + chemotherapy, as outlined earlier in this section, a naïve comparison was deemed the best and most conservative available analysis to inform the comparison against pralsetinib. All usual limitations with naïve analyses apply.<br><br>**Conclusion**<br><br>The updates conducted on the economic model by the company have substantially increased robustness and reduced uncertainty across the indirect treatment comparison. |
| 6 | **Propensity scoring for platinum-based chemotherapy +/- pemetrexed (ACD, Section 3.9)**<br><br>**Untreated setting**<br><br>The ACD notes: "*The committee concluded that propensity score weighting analysis should have been done for platinum-based chemotherapy with or without pemetrexed*"<br><br>Platinum-based chemotherapy +/- pemetrexed in the untreated setting was not included in the company submission as a comparator. As per the ACD Company Response points 2, 5 and Appendix A, platinum-based chemotherapy +/- pemetrexed has been included. Propensity scoring using an indirect treatment comparison between ARROW and IMpower132 was conducted. Therefore we believe the committee can consider these concerns to be addressed.<br><br>**Pre-treated setting**<br><br>The ACD notes: "*The ERG was concerned that the company presented this naive comparison despite having access to the Flatiron database, which was used to inform other comparisons. The ERG explained that this comparison should have been made using the Flatiron database because platinum-based chemotherapy with or without pemetrexed was used more (16.1%) than pembrolizumab plus pemetrexed and chemotherapy (14.1%) and pembrolizumab monotherapy (7.6%).*"<br><br>The naïve comparison in question relates to the indirect comparison to platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. As outlined in the Company Technical Engagement Response (Key Issue 6, pages 21-24), the numbers quoted in this quote relate to an untreated |

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| | setting. The usage in the Flatiron database in the pre-treated setting was smaller ([redacted]) and did not facilitate matching. As per advice from the committee (ACD, Section 3.2, 3.5) platinum-based chemotherapy +/- pemetrexed has been removed as a comparator in the pre-treated setting. Therefore we believe the committee can consider these concerns to be addressed. |
| 7 | **Differences between deterministic and probabilistic result (ACD, Section 3.10)**<br><br>The ACD notes "*There were concerns about the validity of the model due to the large difference between the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) seen for all the comparators. The company nor the ERG were able to provide an explanation for this*."<br><br>This issue has been addressed in the updated version of the cost-effectiveness model (Appendix C) with the updated survival parameters for independent curves. Updated base case probabilistic results are provided in Appendix E and can be considered suitable for decision making. |
| 8 | **Constant treatment benefit and proportional hazards (ACD, Section 3.11)**<br><br>**Proportional hazards**<br><br>The ACD notes: "*The ERG explained that the hazard ratios used by the company are based on a small sample size, immature data, and highly uncertain indirect treatment comparison results*"<br><br>The company understands the ERG's and committee's concerns regarding the proportional hazard assumption in the context of short median follow-up, small sample size, immature data, and uncertainty in the indirect treatment comparison. It should be highlighted that we believe concerns regarding the indirect treatment comparison have been addressed (as per ACD Company Response point 5).<br><br>The ACD notes: "*The committee considered that proportional hazards is a strong assumption and it is unreasonable to apply this over the full time horizon of the model given the immature and highly uncertain data available on relative effectiveness. The committee concluded that the assumption of pralsetinib's constant benefit over time is implausible, and the model needs adjusting to account for this*."<br><br>In response to this, we have adjusted the model to reject the proportional hazards assumption in the case of the main comparators in the untreated and pre-treated settings.<br><br>**Independent curves**<br><br>We have updated the latest version of the economic model to remove the proportional hazards assumption. Independent curves have been fitted to model survival for OS/PFS for pralsetinib against the main comparators in the untreated and pre-treated settings. In the untreated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW and IMpower132 to model pralsetinib and platinum-based chemotherapy +/- pemetrexed respectively (Appendix A). In the pre-treated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW and OAK to model pralsetinib and docetaxel monotherapy respectively (Company Submission B.2.9.4, pages 67-80).<br><br>In the case of docetaxel + nintedanib OS and PFS, an assumption was made to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. Therefore, the docetaxel + nintedanib arm uses the independent curves (as per the docetaxel monotherapy indirect treatment comparison) and does not assume proportional hazards for OS and PFS. |

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| | In the case of the secondary comparison to pembrolizumab + pemetrexed + chemotherapy (untreated) separate independent models were not fitted. This decision is considered a pragmatic approach given the time constraints and in order to maintain simplicity in the model. Therefore, the proportional hazards assumption was retained and survival was modelled by applying a HR from the respective indirect treatment comparison to the pralsetinib arms.<br><br>Full details are outlined in Appendix A and Appendix B. |
| 9 | **Curve extrapolations (ACD, Section 3.12)**<br><br>**Curve extrapolations update**<br><br>The ACD notes: "*the committee agreed that the extrapolations presented could not be considered sufficiently reliable for decision making*"<br><br>We accept the committee did not see the previous extrapolations as suitable for decision making. We note that the key reasons for this appear to be that the committee considers the lifetime treatment benefit as per the proportional hazards assumption as unreasonable and that this leads to differences between clinical expert's landmark survival and extrapolation predictions.<br><br>In order to address this, the proportional hazards assumption was rejected and independent curves were used to model survival for pralsetinib compared to the main model comparators (ACD Company Response point 8; Appendix A; Appendix B).<br><br>With the updated extrapolations, curve selection was re-conducted for pralsetinib and comparators in the untreated and pre-treated settings. Methods of curve selection were in line with NICE technical guidance. Curve selection was based on statistical fit, visual fit, clinical expert's preferred clinical plausibility and alignment to clinical expert long-term landmark predictions. The updated curves were validated in a consultation with a clinical expert and against the previously provided landmark survival predictions.<br><br>**Untreated setting**<br><br>• OS: the exponential distribution was selected to model pralsetinib and comparators. In the case of pralsetinib at the 5-year time point, the exponential curve under predicted the clinical expert's landmark survival by 4%. In the case of platinum-based chemotherapy +/- pemetrexed, the exponential model substantially over predicts OS compared to clinical experts predictions – for example, at the 5-year time point, the exponential curve over predicted the clinical expert's upper range of landmark survival by 7% (8% to mid-point). One potential reason for this could be increased use of pemetrexed in the trial data compared to what is anticipated in UK practice<br>• PFS/TTD: the generalised gamma distribution showed the best combination of fit to the observed data, fit to clinical expert's landmark survival predictions and was recommended by a clinical expert. In the case of pralsetinib TTD, the generalised gamma model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Pre-treated setting**<br><br>• OS: Both the exponential and Weibull extrapolations demonstrated good combinations of fit to the observed data, fit to clinical expert's landmark survival predictions and were recommended by a clinical expert. However, the Weibull curve demonstrated an increasing hazard of mortality over time which was not thought to be clinically plausible. In the case of pralsetinib at the 5-year time point, the exponential curve over predicted the clinical expert's landmark survival by 8%. At the 5-year time point the exponential curve accurately predicted |

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| | the clinical expert's landmark survival estimate in the docetaxel monotherapy arm.<br>• PFS/TTD: Across both endpoints, the Weibull model showed the best combination of fit to the observed data and fit to clinical expert's landmark survival predictions. In the case of pralsetinib TTD, the exponential model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Proposed ERG alternative set of HRs**<br><br>The ACD notes: "*To explore the uncertainty, the ERG produced a scenario using an alternative set of hazard ratios at 3 years. These hazard ratios resulted in overall survival and progression-free survival curves that better reflected the clinical expert advice. The ERG's calibration reduced the underprediction of the comparator survival curves*."<br><br>We do not agree with the ERG's proposed alternative set of hazard ratios which were estimated by calibrating HRs based on clinical expert's 3-year landmark survival estimates.<br>• This is an inferior and less robust methodology than the systematic ITC conducted in the company submission which includes observed data from clinical trials and real world evidence datasets<br>• The approach ignores the entirety of the observed clinical trial efficacy data in favour of point estimates in an advisory board. The 3-year point estimates themselves contain inconsistencies both with the observed data and internal inconsistencies. For example in the pre-treated setting, the clinical expert's predicted 35% of patients would be alive at 3-years and 30-35% would be both in PFS and on treatment. This implies that after 3 years 86-100% of patients who are alive would be in PFS and on treatment and therefore that every patient who progresses or discontinues treatment dies instantly or close to.<br>• Results are sensitive to clinical expert's predictions which clinicians stated to be a difficult exercise and were often rounded to multiples of 5/10 and can therefore considered to be approximations instead of an exact science which when translated into HRs can impact results<br>• The ERG calibration approach is a poor predictor of the observed data<br><br>Therefore, the updated company approach with the independent models to model OS and PFS in the main comparisons using propensity scoring from clinical trial data should be considered the preferred method by the committee. It represents a more robust approach, more accurately predicts the observed data and represents a closer fit to clinical expert's long term landmark survival predictions in comparison to the submission company approach.<br><br>**Conclusion**<br><br>The updated curve selection resulting from the introduction of independent models has reduced the differences between model and clinical expert predictions at landmark survival points. This has reduced uncertainty and increased robustness in results. However, in the case of platinum-based chemotherapy +/- pemetrexed in the untreated setting, model extrapolations still over predict clinical expert's expectations of survival which may bias cost-effectiveness results against pralsetinib. |
| 10 | **End-of-life in pre-treated setting (ACD, Section 3.13)**<br><br>We agree with the committee's assertion that pralsetinib meets the end-of-life criteria in the pre-treated setting. |
| 11 | **End-of-life in untreated setting (ACD, Section 3.14)**<br><br>We understand the committee's concerns and appreciate that at the time of the first appraisal committee meeting, there was insufficient evidence available to draw a robust conclusion regarding |

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| | end-of-life.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy: 3-month life extension criterion**<br><br>In the updated company base case results in the untreated setting, the undiscounted OS for patients receiving pralsetinib is [redacted] months compared to [redacted] months in the case of platinum-based chemotherapy +/- pemetrexed and [redacted] months in the case of pembrolizumab + pemetrexed + chemotherapy. This translates to a survival benefit of [redacted] and [redacted] against platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy respectively. Therefore we consider the 3-month life extension criterion to be comfortably satisfied.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed: <24-month short life criterion**<br><br>There is previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced WT NSCLC NICE HTA appraisals. In the case of pembrolizumab + pemetrexed + chemotherapy in the WT population (TA683), pembrolizumab + pemetrexed + chemotherapy meets NICE's end-of-life criteria. However, it should be acknowledged that this is not a direct precedent due to the impact of adjustment on from WT to RET status in the platinum-based chemotherapy +/- pemetrexed population is to increase survival. The impact of the weighting on median survival in platinum-based chemotherapy +/- pemetrexed was from [redacted] (95% CI [redacted]) to [redacted] (95% CI [redacted]). This represented a 1.9m increase in median survival. In previous NICE HTA appraisals in a ROS1 positive population, which may represent a more comparable population to the current indication in terms of survival, precedence for the end-of-life short life criterion being met exists. In the case of entrectinib (TA643) and crizotinib (TA529), both treatments met both criteria to be considered a life-extending, end-of-life treatment compared with platinum-based chemotherapy +/- pemetrexed (2, 3).<br><br>In the indirect treatment comparison for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (Appendix A), the median OS in the adjusted platinum-based chemotherapy +/- pemetrexed arm is [redacted] months. OS in the economic model was modelled by the exponential curve for pralsetinib and platinum-based chemotherapy +/- pemetrexed. The modelled mean undiscounted OS for platinum-based chemotherapy +/- pemetrexed is [redacted] months. However, the exponential model overestimates the clinical expert's upper range of landmark survival at the 3-year time point by 7% (12% to the mid-point) and at the 5-year time point by 7% (8% to the mid-point). Therefore, the current model (predicting [redacted] months OS) can be considered an optimistic prediction of OS compared to clinical expert's predictions. The modelled mean represents the adjusted IMpower132 population where a higher proportion of patients received pemetrexed compared to that which would be expected in UK practice.<br><br>Therefore, based on the previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced NSCLC appraisals; the IMpower132 modelled median; and the closeness of the modelled mean to the 24 month cut-off despite the overestimation compared to clinical expert landmark predictions, we consider the end-of-life short life criterion to be met in the comparison to platinum-based chemotherapy +/- pemetrexed.<br><br>**Comparison to pembrolizumab + pemetrexed + chemotherapy: <24-month short life criterion**<br><br>We note that with the updated company base case analysis, the undiscounted predicted OS for patients receiving pembrolizumab + pemetrexed + chemotherapy is [redacted] months. It is noted that this may be an over prediction of survival given a conservative assumption was used to assume the additional survival benefit of pembrolizumab is identical in a WT population and a *RET* population.<br><br>Feedback from the ACD suggested that in previous NICE appraisals in untreated advanced NSCLC where pembrolizumab + pemetrexed + chemotherapy has been used as a comparator, the precedence has been set for appraisals not meeting the end-of-life threshold based on the short life |

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| | (<24 month) criterion. We note that this precedence would not apply if, as per the clinical expert's comments, a limited survival benefit of pembrolizumab in this population is assumed.<br><br>However, given the modelled mean is comfortably above the 24 month cut-off, we do not consider that the short life criterion is met in this instance. |
| 12 | **Cancer Drugs Fund**<br><br>The ACD notes "*the comparators used by the company* [in AcceleRET-Lung] *were not aligned with NHS practice*"<br><br>Comparators in AcceleRET-Lung for non-squamous patients consist of:<br>• Carboplatin or cisplatin + pemetrexed followed by optional pemetrexed maintenance<br>• Pembrolizumab + carboplatin or cisplatin + pemetrexed followed by pembrolizumab and optional pemetrexed maintenance.<br><br>The comparators in AcceleRET-Lung closely align with standard of care in the current appraisal (following the updated comparator list) and UK clinical practice. |
| 12 | **Further evidence provided/other amendments to the economic model**<br><br>As per Appendix C, amendments have been made to the latest version of the economic model to amend minor errors:<br>• A fix of an adverse event which was incorrectly applied<br>• A fix in the application of the life tables adjustment to ensure model survival does not drop below general population mortality<br>• The issue of the PSA error was addressed as per ACD Company Response point 7 |
| 14 | **Updated company base case results**<br><br>The following changes were made to the company base case as part of the ACD Company Response:<br>• Introduction of platinum-based chemotherapy +/- pemetrexed as comparator (ACD Company Response point 2; Appendix A)<br>• Life tables fix (ACD Company Response point 13; Appendix C)<br>• Adverse events fix (ACD Company Response point 13; Appendix C)<br>• Naïve comparison for pembrolizumab + pemetrexed + chemotherapy (ACD Company Response point 5)<br>• Inclusion of independent models in main comparisons with updated curve extrapolations (ACD Company Response point 8-9, Appendix B)<br>[redacted]<br><br>In the updated company base case in the untreated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to platinum-based chemotherapy +/- pemetrexed<br>• A dominant ICER compared to pembrolizumab + pemetrexed + chemotherapy<br><br>In the updated company base case in the pre-treated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to docetaxel monotherapy |

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| | • [redacted] per QALY gained compared to docetaxel + nintedanib<br><br>Full results are shown in Appendix E. Scenario analysis demonstrates the results of cost-effectiveness are robust to a range of varied assumptions. |
| 15 | **Conclusion**<br><br>We note the five concerns outlined by the committee in Section 3.10 of the ACD response. We feel that each of these five concerns have been adequately addressed as part of this company response:<br>• The differences between the deterministic and probabilistic models have been addressed as per ACD Company Response point 7<br>• The comparators included in the analysis have been updated to reflect the committee's wishes as per ACD Company Response point 2<br>• The relative treatment benefit has been amended with updates made to the indirect treatment comparison in the untreated setting as per ACD Company Response point 5<br>• The assumption of proportional hazards has been dropped and independent curves have been fitted in the main comparisons in the untreated and pre-treated settings as per ACD Company Response point 8<br>• Following the introduction of the independent curves, the OS and PFS extrapolations have been reviewed with model predictions now being considered more plausible (when compared to clinical expert landmark survival predictions) as per ACD Company Response point 9. However, it should be noted that in the main comparison to platinum-based chemotherapy +/- pemetrexed, model OS in the comparator still over predicts clinical expert landmark predictions which may bias cost-effectiveness results against pralsetinib<br><br>This has increased the robustness and reduced the uncertainty in the analysis. We now consider that the cost-effectiveness model is suitable for decision-making. [redacted] In the updated economic model, pralsetinib is estimated to cost the healthcare payer an additional [redacted] per QALY gained in comparison to platinum-based chemotherapy +/- pemetrexed in the untreated setting and an additional [redacted] per QALY gained in comparison to docetaxel monotherapy in the pre-treated setting. Therefore, the updated results meet NICE's cost-effectiveness thresholds in both the untreated and pre-treated settings when the end-of-life threshold is considered.<br><br>Roche are available for all routes to access. Given the updates to the model to address the committee's concerns [redacted], we believe the committee should consider pralsetinib for baseline funding in the untreated and pre-treated populations. |

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 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd 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.

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- 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.

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# References

1. National institute for Health and Care Excellence. Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer: Appraisal consultation document. 2021.
2. National Institute for Health and Care Excellence. TA643: Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer 2020 [Available from: https://www.nice.org.uk/guidance/ta643 accessed July 2021.
3. National Institute for Health and Care Excellence (NICE). TA529 Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer, July 2018 [online]. Available at: https://www.nice.org.uk/guidance/ta529 [Last accessed: 06/11/2020].

# Comments on the ACD received from the public through the NICE Website

| | |
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| **Name** | [redacted] |
| **Role** | Not specified |
| **Other role** | Not specified |
| **Organisation** | Not specified |
| **Location** | Not specified |
| **Conflict** | No |
| **Notes** | |
| **Comments on the ACD:** | |
| In relation to the comparators for the previously treated group, docetaxel monotherapy and docetaxel plus nintedanib would be suitable comparators and also reflective of the agreed comparators in the committee discussion for selpercatinib in RET-fusion positive NSCLC. | |

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Roche Products Ltd. |

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| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | -- |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. | ERG response |
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| 1 | **Squamous patients (ACD, Section 3.4)**<br><br>The ACD notes "*the company did not present any information for squamous NSCLC*". The ACD also highlights that comparators chosen for this appraisal were determined using the current standard of care for the population in NICE's non-squamous treatment pathway.<br><br>The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced NSCLC. Due to the unmet medical need in all *RET* fusion-positive patients in the UK, it is important that all *RET* fusion-positive advanced NSCLC patients (non-squamous and squamous histologies) have a *RET* inhibitor available as a treatment option in line with the proposed licensed indication.<br><br>The presentation in the committee meeting considered this issue "unresolvable". However, in the selpercatinib appraisal consultation document (ID3743) (1), the committee faced a near identical issue. The clinical expert in | The ERG acknowledges the decision of the committee in the appraisal of selpercatinib that the recommendation should apply to also to the squamous population. The reason given is the "wording of the marketing authorisation" and the small size of the squamous population. However, neither of these facts have any bearing on the uncertainty in effectiveness and cost-effectiveness in the squamous population.<br><br>The ERG therefore reiterates that only a small number of people with squamous NSCLC were included in ARROW trial (see Table 8 of Document B of the company submission and |

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| | the appraisal expected there would still be some level of response for squamous patients. The Cancer Drugs Fund clinical lead stated that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. Therefore, the committee agreed that, despite a low incidence of *RET* fusion positive patients with squamous histology, the technology appraisal recommendation would apply to both squamous and non-squamous patients with *RET*-fusion advanced NSCLC. Given the similar nature of the squamous issues across the two appraisals, the precedent set by ID3743 should be considered adequate to cover the appraisal for pralsetinib and that the relevant population for this appraisal should be the full licenced indication including squamous patients.<br><br>We consider this issue as unresolved but resolvable. The issue can be resolved if the committee aligns to the recommendation made in the selpercatinib appraisal and broadens the recommendation to include squamous patients as per the licenced indication. | Table 3.8 of the ERG report) and no separate effectiveness evidence for the squamous population was provided. To the ERG this implies uncertainty about the extent to which the evidence provided in the company submission applies to squamous patients. |
| 2 | **Comparators (ACD, Section 3.2, 3.5)**<br><br>**Untreated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: "*If their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed. Although pembrolizumab combination might also be offered, a professional organisation noted that immunotherapy is believed to be less effective in cancer with oncogene drivers such as RET fusion compared with the broader advanced NSCLC population*"<br>"*the clinical expert […] highlighted that platinum-based chemotherapy with or without pemetrexed was missing as first-line treatment*"<br>"*The committee recalled that it had heard from the clinical experts that, in the NHS, once people have a confirmed RET fusion-positive status they would likely be offered platinum-based chemotherapy with or without pemetrexed as a first-line treatment*"<br><br>We have taken on board the clinical expert's and committee's advice regarding the inclusion of platinum-based chemotherapy +/- pemetrexed. An overview of the indirect treatment comparison for pralsetinib to platinum-based chemotherapy +/- pemetrexed is provided in ACD Company Response point 5. Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment comparison analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B. | **Untreated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ERG acknowledges that the company added an indirect treatment comparison (ITC), which they described in Appendix A to this document. The ITC compared platinum-based chemotherapy +/- pemetrexed to address the issue that platinum-based chemotherapy with or without pemetrexed was missing as first-line treatment in the company submission. This issue was noted in the ERG report (sections 1.1 and 3.3), and not addressed in the technical engagement stage.<br><br>The ERG has a number of comments on the ITC:<br><br><u>Searches</u> |

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| | | The company claim to have identified one suitable trial (the IMpower132 trial) to inform the comparator arm in the economic model. The company did not describe the methods used to search for and identify suitable trials for the ITC, making it at a potentially high risk of having excluded relevant studies.<br><br><u>Analysis</u><br>The company reported conducting a propensity score weighted indirect comparison comparing results in the IMpower132 trial with results in the ARROW trial. The company cited the technical report of the docetaxel monotherapy analysis presented in the company submission. The company acknowledged that weighting reduced the baseline imbalances between Impower132 and ARROW in most ways, but that differences regarding CNS metastases and gender remained. A clinical expert consulted by the company was reported by the company to claim that they did not expect any imbalances in patient characteristics to impact efficacy between the two treatment arms. The ERG notes that indirect comparisons depend for their reliability on the comparability of trials included in the comparison (in this case, the IMpower132 and ARROW trials). With reference to TSD 17, the ERG also notes the following aspects of the analysis:<br><br>• The technical report states that the analysis was intended to estimate the average treatment effect of the treated |

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| | **Untreated comparison to pembrolizumab + pemetrexed + chemotherapy**<br><br>The ACD notes: "*However, if their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed*."<br><br>We would like to draw a distinction between how patients *should* be treated based on available evidence regarding the effectiveness of pembrolizumab in *RET* patients and how patients *are* currently treated nationally. Roche were advised in a clinical advisory board that the clinical experts consulted in that advisory board and those in the current appraisal (who typically specialise in NSCLC and worked in main centres) may not be a perfect representation of clinicians nationally. The clinical experts in the first appraisal committee meeting (10th February, 2022) discussed that the reason platinum-based chemotherapy +/- pemetrexed was recommended as the relevant comparator in the *RET* untreated setting is due to the limited efficacy of pembrolizumab in this population. However, feedback from clinical experts suggests that this relationship is not well understood by clinicians nationally. Clinicians nationally may be more likely to prescribe pembrolizumab + pemetrexed + chemotherapy to *RET* identified patients in comparison to the clinical experts consulted in this appraisal.<br><br>We agree that based on clinical expert feedback platinum-based chemotherapy +/- pemetrexed can be considered a main comparator for this appraisal in the untreated setting. However, we suggest that pembrolizumab + pemetrexed + chemotherapy remains a relevant secondary comparator for consideration given the high quantity of patients who receive this nationally.<br><br>**Untreated comparison to pembrolizumab monotherapy**<br><br>Based on the discussion at the appraisal committee meeting, pembrolizumab monotherapy has been excluded as a comparator in this appraisal.<br><br>**Pre-treated comparisons to docetaxel monotherapy and docetaxel + nintedanib**<br><br>The ACD notes: "*Second-line treatment for people whose RET fusion status is known is usually docetaxel monotherapy or docetaxel plus nintedanib. The clinical experts noted that docetaxel and nintedanib use is* | (ATT) i.e., the only comparator data were weighted to better match the pralsetinib baseline characteristics, which the ERG considers to be appropriate given that the comparator population was wild-type.<br>• Not other methods of adjustment such as regression adjustment or matching seem to have been considered, which is a potential limitation.<br>• The assumption of selection on observables i.e., prognosis only depends on characteristics that could be adjusted for was not explicitly assessed and only one clinical expert seems to have been consulted to determine those characteristics.<br>• Overlap was not explicitly assessed e.g., using normalised (standardised) differences. However, post-weighting there seemed to remain large differences in baseline characteristics, especially with gender and CNS metastases.<br>Therefore, the ERG considers that the results of the ITC need to be regarded with some caution.<br><br>The ERG acknowledges the company's conclusion that "platinum-based chemotherapy +/- pemetrexed can be considered a main comparator for this appraisal in the untreated setting." |

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| | *decreasing due to the limited benefit and increased side effects compared with docetaxel alone*"<br><br>We agree with the above statement. As per the company submission, docetaxel monotherapy remains the primary comparison for the pre-treated population. Docetaxel + nintedanib remains a secondary comparator. We note that the limited use and limited additional benefit from nintedanib is in line with feedback received by the company during the advisory board.<br><br>**Pre-treated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>The ACD notes: The committee "*noted that platinum-based chemotherapy with or without pemetrexed was not a relevant comparator for the previously treated subgroup*"<br><br>We agree that, following the exclusion of pembrolizumab monotherapy as a comparator in the untreated setting, it makes logical sense to exclude platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. Therefore, this has been removed from the analysis.<br><br>**Conclusion**<br><br>In conclusion, the comparators have been updated in the cost-effectiveness analysis to reflect the committee's preferred choice:<br><br>Untreated<br>• Platinum-based chemotherapy +/- pemetrexed (primary)<br>• Pembrolizumab + pemetrexed + chemotherapy (secondary)<br><br>Pre-treated<br>• Docetaxel monotherapy (primary)<br>• Docetaxel + nintedanib (secondary)<br><br>Therefore we believe the committee can consider the concerns regarding comparators to be addressed. | **Untreated comparison to pembrolizumab + pemetrexed + chemotherapy**<br><br>The ERG reiterates the uncertainty with respect to this issue, due to a few factors:<br>• The company notes the difference between "how patients should be treated…and how patients are currently treated." This distinction, while useful in theory, is problematic in this case. For one, it is difficult to establish what is actually done in the absence of a rigorous audit. The clinical expert opinions cited by the company do not overcome this problem. Additionally, an exclusive focus on what is done (for example, in most cases) does not account for the need to improve practice. |

**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 24 March. Please submit via NICE Docs.

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| | | **Untreated comparison to pembrolizumab monotherapy**<br><br>No further comment.<br><br>**Pre-treated comparisons to docetaxel monotherapy and docetaxel + nintedanib**<br><br>No further comment.<br><br>**Pre-treated comparison to platinum-based chemotherapy +/- pemetrexed**<br><br>No further comment. |

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| | | **Conclusion**<br><br>In light of the ERG comments above, the ERG accepts that these issues have been partially but not fully resolved. |
| 3 | **Trial uncertainty (ACD, Section 3.6)**<br><br>The assessment of pralsetinib in the treatment of *RET* fusion-positive NSCLC is based on ARROW, a single-arm, first-in-human, pivotal Phase 1/2 dose-escalation and dose-expansion trial. A conventional RCT for a rare genomic alteration such as *RET* fusion-positive NSCLC was not chosen to ensure timely patient access to the treatment, given the rarity of *RET* rearrangements.<br><br>The ACD references the ERG's Downs and Black checklist (ERG report, Section 3.24, page 51). In areas where there was disagreement between company and ERG checklists, further clarification has been provided in Appendix G. | The ERG acknowledges the company's comments in Appendix G to their ACD response. In their comments, the company largely agrees with the ERG assessment. The ERG's concerns about trial uncertainty therefore remain. |
| 4 | **Generalisability to UK practice (ACD, Section 3.7)**<br><br>The company agrees with the clinical expert and the committee that the trial population in the ARROW study is generalisable to UK practice. | No additional comments. |
| 5 | **Indirect treatment comparison (ACD, Section 3.8)**<br><br>**Inclusion of platinum-based chemotherapy +/- pemetrexed**<br><br>Platinum-based chemotherapy +/- pemetrexed was included in the evidence search criteria as outlined in Section B.2.9 of the Company Submission (pages 65-93). Identical methodology in analysis selection was applied to select an analysis for platinum-based chemotherapy +/- pemetrexed as other comparators in the appraisal. | The ERG reiterates the problems with the indirect treatment comparisons (see response to point 2, above). The ERG also notes that the assumption to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib, while based on an inference from the expert view that there is "limited benefit" associated with the addition of nintedanib, |

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| | The most robust form of evidence available was to inform an indirect treatment comparison by using a propensity scoring analysis using individual patient-level data from a WT population from IMpower132 to model efficacy for platinum-based chemotherapy +/- pemetrexed in the comparator arm. This reflected an identical approach to the analysis used in the pre-treated comparison to docetaxel monotherapy (ARROW vs OAK). Patients in the comparator arm were matched based on age, gender, ECOG PS, CNS metastases, smoking status, histology and race to reflect a *RET* fusion-positive population as per ARROW. After matching, pralsetinib demonstrated significantly superior OS to platinum-based chemotherapy +/- pemetrexed (OS HR [redacted]).<br><br>Full details of the inclusion of platinum-based chemotherapy +/- pemetrexed are provided in Appendix A including details of the treatment regimen, indirect treatment analysis and the inclusion of costs/utilities in the cost-effectiveness analysis. Details of clinical efficacy are provided in Appendix B.<br><br>**Updates to pembrolizumab + pemetrexed + chemotherapy**<br><br>Following the inclusion of platinum-based chemotherapy +/- pemetrexed to the indirect treatment comparison, the relationship of modelled survival between platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy was assessed. It was not considered feasible that patients would demonstrate superior OS on platinum-based chemotherapy +/- pemetrexed compared to pembrolizumab + pemetrexed + chemotherapy. Three different options for analysis were considered:<br><br>• Flatiron EDM: ([redacted])<br>Given pembrolizumab + pemetrexed + chemotherapy is comparable in treatments to the platinum-based chemotherapy +/- pemetrexed regimen but also contains the addition of pembrolizumab, it did not seem logical to assume greater efficacy in the platinum-based chemotherapy +/- pemetrexed arm compared to pembrolizumab + pemetrexed + chemotherapy. This would imply a negative treatment effect of pembrolizumab. Further, as outlined in the ACD, the committee express concerns regarding the comparison between trial data and real world evidence.<br><br>• WT SLR propensity scoring of ARROW vs IMpower132 - assumption of equivalence to platinum-based chemotherapy +/- pemetrexed: ([redacted])<br>The propensity scoring informed from WT SLR (Appendix A) is considered a more robust comparison than the comparison to the Flatiron EDM dataset (Company Submission, Section B.2.9.5, pages 80-91). The assumption of equivalence of efficacy to the IMpower132 indirect treatment comparison assumes no additional efficacy | requires additional justification.<br><br>Therefore, the ERG accepts that the uncertainty regarding the results of the indirect comparison have been reduced, it remains high. |

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| | benefit from the addition of pembrolizumab to the regimen. This is in line with feedback from the clinical experts in the appraisal committee meeting (and the motivation for the inclusion of platinum-based chemotherapy +/- pemetrexed as the main comparator). However, the extent to which there is limited benefit of the addition of pembrolizumab to this regimen compared to no benefit is unclear. We differ to clinical expert judgment on this matter.<br><br>• Naïve comparison ([redacted])<br>The naïve comparison was informed by a comparison to KEYNOTE-189 (Company Submission, Section B.2.9.4, pages 67-80). No individual patient level data was available for this comparison and therefore no adjustment for *RET* characteristics was conducted. The impact of not adjusting for *RET* characteristics is not known. Further, the committee heard that the justification for inclusion of platinum-based chemotherapy +/- pemetrexed as the primary comparator in the untreated setting was due to the lack of survival benefit of pembrolizumab in *RET* patients. Therefore, to use a data source from a WT population to estimate efficacy in a *RET* population is likely to overestimate efficacy in the comparator arm. Therefore, this would likely underestimate the cost-effectiveness of pralsetinib.<br><br>On balance, it is likely that the true estimate of efficacy for pembrolizumab + pemetrexed + chemotherapy in *RET* fusion positive advanced NSCLC may lie somewhere between the IMpower132 and KEYNOTE-189 indirect treatment comparisons depending on the extent of the additional treatment benefit of pembrolizumab in this regimen. An assumption was used to model efficacy for pembrolizumab + pemetrexed + chemotherapy as per the naïve indirect treatment comparison against KEYNOTE-189. The impact of this assumption was explored in a scenario analysis (Appendix E). This assumption does not include the impact of a *RET* characteristics adjustment due to lack of individual patient-level data. The potential impact of this is unknown.<br><br>**Use of real-world data**<br><br>The ACD notes: "*The committee expressed concerns about the appropriateness of the real-world data in the Flatiron database, due to the challenges in assessing its quality*."<br>"*It also noted that an indirect treatment comparison of clinical trial data to with real-world data can be expected to introduce bias because the care that people have in each setting is likely to be different*"<br>"*For these reasons, the hazard ratio results of the indirect treatment comparison may have overestimated the relative clinical effectiveness of pralsetinib*"<br><br>As per the advice of the committee (ACD, Section 3.5), pembrolizumab monotherapy has been excluded as a | |

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| | comparator. The indirect treatment comparison for pembrolizumab + pemetrexed + chemotherapy has been updated to use the naïve comparison against KEYNOTE-189 instead of the real-world data from Flatiron. Hence, in the updated company base case, no real-world evidence comparison is used. Therefore we believe the committee can consider these concerns to be addressed.<br><br>**Naïve comparison**<br><br>The ERG note that there were differences in characteristics in the naïve comparison between the GOIRC trial and ARROW. Given, as per the advice on the committee (ACD, Section 3.5), platinum-based chemotherapy +/- pemetrexed has been excluded as a comparator, we believe the committee can consider these concerns to be addressed.<br><br>In the case of docetaxel + nintedanib OS and PFS, it was originally planned to use the naïve indirect treatment comparison as per the to the company submission. However, it was not considered feasible for survival in the docetaxel + nintedanib arm to be less than in the docetaxel monotherapy arm. Therefore, to maintain internal consistency, an approach was taken to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. This assumption was made after it was noted by clinical experts there is "limited benefit" associated with the addition of nintedanib. In the case of docetaxel + nintedanib, the naïve HR for TTD as per the company submission was applied to the pralsetinib TTD arm to estimate TTD for docetaxel + nintedanib.<br><br>In the case of pembrolizumab + pemetrexed + chemotherapy, as outlined earlier in this section, a naïve comparison was deemed the best and most conservative available analysis to inform the comparison against pralsetinib. All usual limitations with naïve analyses apply.<br><br>**Conclusion**<br><br>The updates conducted on the economic model by the company have substantially increased robustness and reduced uncertainty across the indirect treatment comparison. | |
| 6 | **Propensity scoring for platinum-based chemotherapy +/- pemetrexed (ACD, Section 3.9)**<br><br>**Untreated setting** | With respect to the untreated setting, see responses to points 2 and 5, above.<br><br>With respect to the treated setting, the ERG agrees that the committee stated in Section 3.5 |

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| | The ACD notes: "*The committee concluded that propensity score weighting analysis should have been done for platinum-based chemotherapy with or without pemetrexed*"<br><br>Platinum-based chemotherapy +/- pemetrexed in the untreated setting was not included in the company submission as a comparator. As per the ACD Company Response points 2, 5 and Appendix A, platinum-based chemotherapy +/- pemetrexed has been included. Propensity scoring using an indirect treatment comparison between ARROW and IMpower132 was conducted. Therefore we believe the committee can consider these concerns to be addressed.<br><br>**Pre-treated setting**<br><br>The ACD notes: "*The ERG was concerned that the company presented this naive comparison despite having access to the Flatiron database, which was used to inform other comparisons. The ERG explained that this comparison should have been made using the Flatiron database because platinum-based chemotherapy with or without pemetrexed was used more (16.1%) than pembrolizumab plus pemetrexed and chemotherapy (14.1%) and pembrolizumab monotherapy (7.6%).*"<br><br>The naïve comparison in question relates to the indirect comparison to platinum-based chemotherapy +/- pemetrexed in the pre-treated setting. As outlined in the Company Technical Engagement Response (Key Issue 6, pages 21-24), the numbers quoted in this quote relate to an untreated setting. The usage in the Flatiron database in the pre-treated setting was smaller ([redacted]) and did not facilitate matching. As per advice from the committee (ACD, Section 3.2, 3.5) platinum-based chemotherapy +/- pemetrexed has been removed as a comparator in the pre-treated setting. Therefore we believe the committee can consider these concerns to be addressed. | of the ACD that platinum-based chemotherapy +/- pemetrexed is not a comparator in the pre-treated setting. Therefore, the ERG considers this issue regarding the inadequacy of the naïve comparison to be resolved. |
| 7 | **Differences between deterministic and probabilistic result (ACD, Section 3.10)**<br><br>The ACD notes "*There were concerns about the validity of the model due to the large difference between the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) seen for all the comparators. The company nor the ERG were able to provide an explanation for this*." | The ERG agrees that the difference between deterministic and probabilistic estimates has been substantially reduced. It appears to be the case however that there was not a particular error corrected or fix applied, but that it was just the application of the changed (individual fit) survival curves that made the difference diminish. The ERG is still slightly concerned that |

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| | This issue has been addressed in the updated version of the cost-effectiveness model (Appendix C) with the updated survival parameters for independent curves. Updated base case probabilistic results are provided in Appendix E and can be considered suitable for decision making. | the original issue with the PSA was not resolved, but only less visible, maybe reflected also in the rather typical shape of the cloud in the incremental cost-effectiveness plane. It is difficult to say what this implies for decision making, but the impact is probably limited. |
| 8 | **Constant treatment benefit and proportional hazards (ACD, Section 3.11)**<br><br>**Proportional hazards**<br><br>The ACD notes: "*The ERG explained that the hazard ratios used by the company are based on a small sample size, immature data, and highly uncertain indirect treatment comparison results*"<br><br>The company understands the ERG's and committee's concerns regarding the proportional hazard assumption in the context of short median follow-up, small sample size, immature data, and uncertainty in the indirect treatment comparison. It should be highlighted that we believe concerns regarding the indirect treatment comparison have been addressed (as per ACD Company Response point 5).<br><br>The ACD notes: "*The committee considered that proportional hazards is a strong assumption and it is unreasonable to apply this over the full time horizon of the model given the immature and highly uncertain data available on relative effectiveness. The committee concluded that the assumption of pralsetinib's constant benefit over time is implausible, and the model needs adjusting to account for this*."<br><br>In response to this, we have adjusted the model to reject the proportional hazards assumption in the case of the main comparators in the untreated and pre-treated settings.<br><br>**Independent curves**<br><br>We have updated the latest version of the economic model to remove the proportional hazards assumption. Independent curves have been fitted to model survival for OS/PFS for pralsetinib against the main comparators in the untreated and pre-treated settings. In the untreated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW and IMpower132 to model pralsetinib and platinum-based | The ERG appreciates the efforts of the company to amend the survival curves. The ERG would like to highlight that the ACD did not literally recommend to use independent curves (nor did the ERG), it merely said that 'The committee concluded that the assumption of pralsetinib's constant benefit over time is implausible, and the model needs adjusting to account for this' (section 3.11).<br><br>The ERG evaluated the updated survival curves and concluded that the process of curve selection was performed in an accurate way.<br><br>The ERG considers the current approach to the survival extrapolations an improvement to the previous version of the model. However, as also stated in response to point 5 above, the ERG considers remaining uncertainty in the indirect treatment comparison to be high. The issues with immature data and small sample size were also not resolved. In addition, the fact that there is no explicit assumption of constant hazards anymore does not guarantee that there is no sustained benefit of pralsetinib. More information on 'implied' (implicit?) HR would be necessary to see to what extent a sustained benefit is still |

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| | chemotherapy +/- pemetrexed respectively (Appendix A). In the pre-treated setting, independent curves were fit to the propensity scoring indirect treatment comparison for ARROW and OAK to model pralsetinib and docetaxel monotherapy respectively (Company Submission B.2.9.4, pages 67-80).<br><br>In the case of docetaxel + nintedanib OS and PFS, an assumption was made to assume equal efficacy between docetaxel monotherapy and docetaxel + nintedanib. Therefore, the docetaxel + nintedanib arm uses the independent curves (as per the docetaxel monotherapy indirect treatment comparison) and does not assume proportional hazards for OS and PFS.<br><br>In the case of the secondary comparison to pembrolizumab + pemetrexed + chemotherapy (untreated) separate independent models were not fitted. This decision is considered a pragmatic approach given the time constraints and in order to maintain simplicity in the model. Therefore, the proportional hazards assumption was retained and survival was modelled by applying a HR from the respective indirect treatment comparison to the pralsetinib arms.<br><br>Full details are outlined in Appendix A and Appendix B. | present. Also, a scenario which imposes a limit to the benefit would be informative to assess its impact on the ICERs. In conclusion, the proportional hazards issue is resolved, but the constant treatment benefit issue is not.<br><br>Therefore, the ERG considers this issue to be only partly resolved. |
| 9 | **Curve extrapolations (ACD, Section 3.12)**<br><br>**Curve extrapolations update**<br><br>The ACD notes: "*the committee agreed that the extrapolations presented could not be considered sufficiently reliable for decision making*"<br><br>We accept the committee did not see the previous extrapolations as suitable for decision making. We note that the key reasons for this appear to be that the committee considers the lifetime treatment benefit as per the proportional hazards assumption as unreasonable and that this leads to differences between clinical expert's landmark survival and extrapolation predictions.<br><br>In order to address this, the proportional hazards assumption was rejected and independent curves were used to model survival for pralsetinib compared to the main model comparators (ACD Company Response point 8; Appendix A; Appendix B).<br><br>With the updated extrapolations, curve selection was re-conducted for pralsetinib and comparators in the | Given that curve extrapolations and constant treatment benefit were very much interrelated issues in this STA, the ERG considers the reply to point 8 to also apply here. In short, although the ERG appreciates the efforts made and considers the changes to the model to be improvements, substantial uncertainty remains given that underlying all of it is still immature data and uncertain indirect treatment comparisons.<br><br>As for the ERG's proposed set of alternative HRs, these were only put forward by the ERG to demonstrate the potential impact on cost-effectiveness results when hazard ratios would better reflect the landmark expert opinion estimates. The ERG acknowledged and still |

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| | untreated and pre-treated settings. Methods of curve selection were in line with NICE technical guidance. Curve selection was based on statistical fit, visual fit, clinical expert's preferred clinical plausibility and alignment to clinical expert long-term landmark predictions. The updated curves were validated in a consultation with a clinical expert and against the previously provided landmark survival predictions.<br><br>**Untreated setting**<br><br>• OS: the exponential distribution was selected to model pralsetinib and comparators. In the case of pralsetinib at the 5-year time point, the exponential curve under predicted the clinical expert's landmark survival by 4%. In the case of platinum-based chemotherapy +/- pemetrexed, the exponential model substantially over predicts OS compared to clinical experts predictions – for example, at the 5-year time point, the exponential curve over predicted the clinical expert's upper range of landmark survival by 7% (8% to mid-point). One potential reason for this could be increased use of pemetrexed in the trial data compared to what is anticipated in UK practice<br>• PFS/TTD: the generalised gamma distribution showed the best combination of fit to the observed data, fit to clinical expert's landmark survival predictions and was recommended by a clinical expert. In the case of pralsetinib TTD, the generalised gamma model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Pre-treated setting**<br><br>• OS: Both the exponential and Weibull extrapolations demonstrated good combinations of fit to the observed data, fit to clinical expert's landmark survival predictions and were recommended by a clinical expert. However, the Weibull curve demonstrated an increasing hazard of mortality over time which was not thought to be clinically plausible. In the case of pralsetinib at the 5-year time point, the exponential curve over predicted the clinical expert's landmark survival by 8%. At the 5-year time point the exponential curve accurately predicted the clinical expert's landmark survival estimate in the docetaxel monotherapy arm.<br>• PFS/TTD: Across both endpoints, the Weibull model showed the best combination of fit to the observed data and fit to clinical expert's landmark survival predictions. In the case of pralsetinib TTD, the exponential model sits within the expected range of the clinical expert's landmark survival prediction at the 5-year time point.<br><br>**Proposed ERG alternative set of HRs** | agrees that the expert estimates were uncertain but the company selected many of the survival curves distributions based on this expert opinion. The ERG agrees with the company that the HR calibration is not to be preferred when there are better ways to reliably estimate survival curves. |

**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

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| | The ACD notes: "*To explore the uncertainty, the ERG produced a scenario using an alternative set of hazard ratios at 3 years. These hazard ratios resulted in overall survival and progression-free survival curves that better reflected the clinical expert advice. The ERG's calibration reduced the underprediction of the comparator survival curves*."<br><br>We do not agree with the ERG's proposed alternative set of hazard ratios which were estimated by calibrating HRs based on clinical expert's 3-year landmark survival estimates.<br>• This is an inferior and less robust methodology than the systematic ITC conducted in the company submission which includes observed data from clinical trials and real world evidence datasets<br>• The approach ignores the entirety of the observed clinical trial efficacy data in favour of point estimates in an advisory board. The 3-year point estimates themselves contain inconsistencies both with the observed data and internal inconsistencies. For example in the pre-treated setting, the clinical expert's predicted 35% of patients would be alive at 3-years and 30-35% would be both in PFS and on treatment. This implies that after 3 years 86-100% of patients who are alive would be in PFS and on treatment and therefore that every patient who progresses or discontinues treatment dies instantly or close to.<br>• Results are sensitive to clinical expert's predictions which clinicians stated to be a difficult exercise and were often rounded to multiples of 5/10 and can therefore considered to be approximations instead of an exact science which when translated into HRs can impact results<br>• The ERG calibration approach is a poor predictor of the observed data<br><br>Therefore, the updated company approach with the independent models to model OS and PFS in the main comparisons using propensity scoring from clinical trial data should be considered the preferred method by the committee. It represents a more robust approach, more accurately predicts the observed data and represents a closer fit to clinical expert's long term landmark survival predictions in comparison to the submission company approach.<br><br>**Conclusion**<br><br>The updated curve selection resulting from the introduction of independent models has reduced the differences between model and clinical expert predictions at landmark survival points. This has reduced uncertainty and increased robustness in results. However, in the case of platinum-based chemotherapy +/- pemetrexed in the untreated setting, model extrapolations still over predict clinical expert's expectations of survival which may bias cost-effectiveness results against pralsetinib. | |

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| 10 | **End-of-life in pre-treated setting (ACD, Section 3.13)**<br><br>We agree with the committee's assertion that pralsetinib meets the end-of-life criteria in the pre-treated setting. | No additional comments. |
| 11 | **End-of-life in untreated setting (ACD, Section 3.14)**<br><br>We understand the committee's concerns and appreciate that at the time of the first appraisal committee meeting, there was insufficient evidence available to draw a robust conclusion regarding end-of-life.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy: 3-month life extension criterion**<br><br>In the updated company base case results in the untreated setting, the undiscounted OS for patients receiving pralsetinib is [redacted] months compared to [redacted] months in the case of platinum-based chemotherapy +/- pemetrexed and [redacted] months in the case of pembrolizumab + pemetrexed + chemotherapy. This translates to a survival benefit of [redacted] and [redacted] against platinum-based chemotherapy +/- pemetrexed and pembrolizumab + pemetrexed + chemotherapy respectively. Therefore we consider the 3-month life extension criterion to be comfortably satisfied.<br><br>**Comparison to platinum-based chemotherapy +/- pemetrexed: <24-month short life criterion**<br><br>There is previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced WT NSCLC NICE HTA appraisals. In the case of pembrolizumab + pemetrexed + chemotherapy in the WT population (TA683), pembrolizumab + pemetrexed + chemotherapy meets NICE's end-of-life criteria. However, it should be acknowledged that this is not a direct precedent due to the impact of adjustment on from WT to RET status in the platinum-based chemotherapy +/- pemetrexed population is to increase survival. The impact of the weighting on median survival in platinum-based chemotherapy +/- pemetrexed was from [redacted] (95% CI [redacted]) to [redacted] (95% CI [redacted]). This represented a 1.9m increase in median survival. In previous NICE HTA appraisals in a ROS1 positive population, which may represent a more comparable population to the current indication in terms of survival, precedence for the end-of-life short life criterion being met exists. In the case of entrectinib (TA643) and crizotinib (TA529), both treatments met both criteria to be considered a life-extending, end-of-life treatment compared with platinum-based chemotherapy +/- | Subject to the comments above regarding the comparators and analyses, the ERG acknowledges the additional evidence presented by the company which suggests that the 3 month extension of life has been met. The ERG also acknowledges the company's assertion that they do not consider that the short life criterion is met in this instance. |

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| | pemetrexed (2, 3).<br><br>In the indirect treatment comparison for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (Appendix A), the median OS in the adjusted platinum-based chemotherapy +/- pemetrexed arm is [redacted] months. OS in the economic model was modelled by the exponential curve for pralsetinib and platinum-based chemotherapy +/- pemetrexed. The modelled mean undiscounted OS for platinum-based chemotherapy +/- pemetrexed is [redacted] months. However, the exponential model overestimates the clinical expert's upper range of landmark survival at the 3-year time point by 7% (12% to the mid-point) and at the 5-year time point by 7% (8% to the mid-point). Therefore, the current model (predicting [redacted] months OS) can be considered an optimistic prediction of OS compared to clinical expert's predictions. The modelled mean represents the adjusted IMpower132 population where a higher proportion of patients received pemetrexed compared to that which would be expected in UK practice.<br><br>Therefore, based on the previous precedent set for platinum-based chemotherapy +/- pemetrexed meeting the short life criterion in previous untreated advanced NSCLC appraisals; the IMpower132 modelled median; and the closeness of the modelled mean to the 24 month cut-off despite the overestimation compared to clinical expert landmark predictions, we consider the end-of-life short life criterion to be met in the comparison to platinum-based chemotherapy +/- pemetrexed.<br><br>**Comparison to pembrolizumab + pemetrexed + chemotherapy: <24-month short life criterion**<br><br>We note that with the updated company base case analysis, the undiscounted predicted OS for patients receiving pembrolizumab + pemetrexed + chemotherapy is [redacted] months. It is noted that this may be an over prediction of survival given a conservative assumption was used to assume the additional survival benefit of pembrolizumab is identical in a WT population and a *RET* population.<br><br>Feedback from the ACD suggested that in previous NICE appraisals in untreated advanced NSCLC where pembrolizumab + pemetrexed + chemotherapy has been used as a comparator, the precedence has been set for appraisals not meeting the end-of-life threshold based on the short life (<24 month) criterion. We note that this precedence would not apply if, as per the clinical expert's comments, a limited survival benefit of pembrolizumab in this population is assumed.<br><br>However, given the modelled mean is comfortably above the 24 month cut-off, we do not consider that the short life criterion is met in this instance. | |

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| 12 | **Cancer Drugs Fund**<br><br>The ACD notes "*the comparators used by the company* [in AcceleRET-Lung] *were not aligned with NHS practice*"<br><br>Comparators in AcceleRET-Lung for non-squamous patients consist of:<br>• Carboplatin or cisplatin + pemetrexed followed by optional pemetrexed maintenance<br>• Pembrolizumab + carboplatin or cisplatin + pemetrexed followed by pembrolizumab and optional pemetrexed maintenance.<br><br>The comparators in AcceleRET-Lung closely align with standard of care in the current appraisal (following the updated comparator list) and UK clinical practice. | The committee provided a number of reasons why pralsetinib should did not meet the criteria for inclusion within the Cancer Drugs Fund including: uncertainty regarding clinical effectiveness, outcomes[check] availability of data within the relevant timeframe, and comparators not be aligned with NHS practice. The company has addressed only one of these, namely the comparators. All of the committee's concerns would have to be addressed in order for pralsetinib to meet the criteria for inclusion in the Cancer Drugs Fund.<br><br>In the absence of additional evidence (including from independent clinical experts), it is not possible to confirm whether the comparators used in the AcceleRET-lung trial overlap to a great degree with those in the ARROW trial, but not completely. |
| 12 | **Further evidence provided/other amendments to the economic model**<br><br>As per Appendix C, amendments have been made to the latest version of the economic model to amend minor errors:<br>• A fix of an adverse event which was incorrectly applied<br>• A fix in the application of the life tables adjustment to ensure model survival does not drop below general population mortality<br>• The issue of the PSA error was addressed as per ACD Company Response point 7 | The issue with the PSA difference was addressed in response to point 7. As for the fix for an adverse event, the ERG took note of this but would like to point at another AE issue in the model, which is the AE incidence for pembrolizumab + chemotherapy. This incidence can be adjusted via a switch in the incidence column of the model (AErates worksheet column E) but the incidence is not translated to the |

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| | | percentages in column F, which means effectively the AEs for this comparator are not taken into account in any of the model calculations. But as in the company base-case the AE incidences for this comparator were set to zero, the error does not impact the company base-case ICERs, and therefore the ERG considers this something that could be ignored. |
| 14 | **Updated company base case results**<br><br>The following changes were made to the company base case as part of the ACD Company Response:<br>• Introduction of platinum-based chemotherapy +/- pemetrexed as comparator (ACD Company Response point 2; Appendix A)<br>• Life tables fix (ACD Company Response point 13; Appendix C)<br>• Adverse events fix (ACD Company Response point 13; Appendix C)<br>• Naïve comparison for pembrolizumab + pemetrexed + chemotherapy (ACD Company Response point 5)<br>• Inclusion of independent models in main comparisons with updated curve extrapolations (ACD Company Response point 8-9, Appendix B)<br>[redacted]<br>In the updated company base case in the untreated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to platinum-based chemotherapy +/- pemetrexed<br>• A dominant ICER compared to pembrolizumab + pemetrexed + chemotherapy<br><br>In the updated company base case in the pre-treated setting, pralsetinib ([redacted]) represents an ICER of:<br>• [redacted] per QALY gained compared to docetaxel monotherapy<br>• [redacted] per QALY gained compared to docetaxel + nintedanib<br><br>Full results are shown in Appendix E. Scenario analysis demonstrates the results of cost-effectiveness are robust to a range of varied assumptions. | No additional comments. |

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**Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]**

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| | | |
|---|---|---|
| 15 | **Conclusion**<br><br>We note the five concerns outlined by the committee in Section 3.10 of the ACD response. We feel that each of these five concerns have been adequately addressed as part of this company response:<br>• The differences between the deterministic and probabilistic models have been addressed as per ACD Company Response point 7<br>• The comparators included in the analysis have been updated to reflect the committee's wishes as per ACD Company Response point 2<br>• The relative treatment benefit has been amended with updates made to the indirect treatment comparison in the untreated setting as per ACD Company Response point 5<br>• The assumption of proportional hazards has been dropped and independent curves have been fitted in the main comparisons in the untreated and pre-treated settings as per ACD Company Response point 8<br>• Following the introduction of the independent curves, the OS and PFS extrapolations have been reviewed with model predictions now being considered more plausible (when compared to clinical expert landmark survival predictions) as per ACD Company Response point 9. However, it should be noted that in the main comparison to platinum-based chemotherapy +/- pemetrexed, model OS in the comparator still over predicts clinical expert landmark predictions which may bias cost-effectiveness results against pralsetinib<br><br>This has increased the robustness and reduced the uncertainty in the analysis. We now consider that the cost-effectiveness model is suitable for decision-making. [redacted] In the updated economic model, pralsetinib is estimated to cost the healthcare payer an additional [redacted] per QALY gained in comparison to platinum-based chemotherapy +/- pemetrexed in the untreated setting and an additional [redacted] per QALY gained in comparison to docetaxel monotherapy in the pre-treated setting. Therefore, the updated results meet NICE's cost-effectiveness thresholds in both the untreated and pre-treated settings when the end-of-life threshold is considered.<br><br>Roche are available for all routes to access. Given the updates to the model to address the committee's concerns [redacted], we believe the committee should consider pralsetinib for baseline funding in the untreated and pre-treated populations. | As far as the 5 points raised by the committee in section 3.10 of the ACD response:<br>• Point 1 is mostly resolved (as per response to comment 7 above)<br>• Point 2 has been partly resolved (as per response to comment 2 above)<br>• Point 3 has been partly resolved (as per response to comment 5 above)<br>• Point 4 has been partly resolved (as per response to comment 8 above)<br>• Point 5 has been partly resolved (as per response to comment 9 above) |

Insert extra rows as needed

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- 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 2nd 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.
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