National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche Products Limited	Yes	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Eli Lilly & Company Ltd.	No. According to the title of the appraisal in development (ID3875) and Lilly's understanding of pralsetinib's expected license[1], the wording should be changed to: '*To appraise the clinical and cost effectiveness of pralsetinib within its marketing authorisation for treating RET fusion-positive advanced non-small-cell lung cancer after platinum-based chemotherapy*.' [1] Specialist Pharmacy Service. Pralsetinib, updated 11th January 2021. Accessed at https://www.sps.nhs.uk/medicines/pralsetinib/	Thank you for your comment. The wording of the title will remain broad to align with the main global trial for pralsetinib.
Timing Issues	Roche Products Limited	Given the existing gap between marketing authorisation and access, Roche encourage this appraisal to continue in line with usual NICE scheduling to ensure there is no further delay to patient access.	Thank you for your comment. In any appraisal NICE aims to publish guidance within 90 days of marketing authorisation. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche Products Limited	Roche acknowledge that the background section correctly outlines all possible treatments available for metastatic non-small-cell lung cancer (NSCLC) patients depending on: • Whether patients are untreated or previously treated • Non-squamous/squamous • Programmed death-ligand 1 (PD-L1) status. However, the background section does not currently recognise the distinction that exists between rearranged during transfection (RET) fusion-positive patients and non-RET fusion-positive patients. Therefore, Roche propose adding the following between the second and third paragraphs. "Patients with RET fusion-positive NSCLC have a different profile to other NSCLC patients and standard therapies may provide limited benefit for patients with RET fusion-positive tumours.[1] Testing for RET fusion mutations is not routinely carried out as standard of care (SoC) in the UK. RET fusion patients are currently unidentified in the treatment pathway. As it stands, there is no specific treatment pathway for RET fusion patients and therefore unidentified patients go into the standard NSCLC treatment pathway. The remainder of this section outlines the standard NSCLC treatment pathway. " See the Comparators row for further details on how clinicians are treating RET fusion patients as SoC.	Thank you for your comment. The background information has been amended to clarify that testing for RET fusion/mutations is not currently standard in the UK.

Section	Consultee/ Commentator	Comments [sic]	Action
		[1] Gandhi, Leena, et al. "Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer." New England journal of medicine 378.22 (2018): 2078-2092. Hellmann, Matthew D., et al. "Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden." New England Journal of Medicine 378.22 (2018): 2093-2104. Mok, Tony SK, et al. "Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial." The Lancet.10183 (2019): 1819-1830. Sandler, Alan, et al. "Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer." New England Journal of Medicine 355.24 (2006): 2542-2550.	
	Eli Lilly & Company Ltd.	Nivolumab (TA484) is currently recommended through the CDF as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after chemotherapy, only if their tumours are PD-L1 positive[2]. [2] National Institute of Health and Care Excellence (2017). Nivolumab for previously treated non-squamous non-small-cell lung cancer. NICE Technology Appraisal 484 [TA484]	Thank you for your comment. This clarification will be made in the text.
The technology/ intervention	Roche Products Limited	Yes	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Roche Products Limited	The population is appropriately defined. The description does not make reference to a particular line of therapy which aligns with the main global trial for pralsetinib and its intended use in clinical practice as a line agnostic treatment. However, although the anticipated licence is for all RET fusion-positive NSCLC patients, [redacted][2] See Innovation row for further information on the ARROW trial. [2] Phase 1/2 Study of the Highly-selective RET Inhibitor, Pralsetinib (BLU-667), in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors (ARROW). https://clinicaltrials.gov/ct2/show/NCT03037385	Thank you for your comment. No action needed.
	Eli Lilly & Company Ltd.	No. Please amend to the expected licensed population[1]: '*People with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy after prior platinum-based chemotherapy*' [1] Specialist Pharmacy Service. Pralsetinib, updated 11th January 2021. Accessed at https://www.sps.nhs.uk/medicines/pralsetinib/	Thank you for your comment. The population is usually left broad. The committee will consider the clinical evidence presented to it and make recommendations based on that.

Comparators	Roche Products Limited	Conducting an STA with a high quantity of comparators is not practical and not an efficient use of NICE and company resources. The list of relevant comparators for appraisal should be confined not to all available treatments but only those that are typically used to treat RET fusion-positive NSCLC patients. Roche have the following comments on potential comparators outlined in the Draft Scope: • Selpercatinib is indicated for the treatment of adults with advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.[3] Given selpercatinib does not have a licence in untreated patients, it should not be considered as a comparator for untreated patients in this appraisal • The ARROW trial consisted of low patient numbers with squamous NSCLC [redacted]. Therefore a squamous specific comparison is not feasible due to small sample size. Given non-squamous patients represent 70% of NSCLC patients, this appraisal will focus on the non-squamous treatment pathway • With regards to best supportive care (BSC), given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate, or are willing to have pharmacological intervention will be eligible for pralsetinib, hence, BSC is not an appropriate comparator for this appraisal. Roche consulted clinical experts in NSCLC to establish the SoC in non-squamous untreated and treated patients. Roche propose that the comparators in this appraisal should align with the current SoC and are outlined below.	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee. The positioning of selpercatinib has been noted. The scope has been updated to remove it from the list of comparators for untreated NSCLC.

		Untreated • Pembrolizumab, with pemetrexed and platinum chemotherapy (TA557) **Treated** • Docetaxel, with or without nintedanib Pembrolizumab, with pemetrexed and platinum chemotherapy is available regardless of PD-L1 status and is seen as the most effective and most commonly used treatment option in untreated patients. After treatment, patients typically receive docetaxel, with or without nintedanib, aligned with NICE Guidance 122.[4] [3] Retsevmo CHMP opinion. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/retsevmo [4] NICE Guidance 122. https://www.nice.org.uk/guidance/ng122	

Section	Consultee/ Commentator	Comments [sic]	Action
	Eli Lilly & Company Ltd.	No. According to pralsetinib's expected license[1], comparators should be limited to those listed for previously treated squamous and non-squamous disease only. Furthermore, for previously treated non-squamous NSCLC, atezolizumab combinations (TA584) is only recommended as a second-line treatment for people who have had EGFR or ALK-targeted treatment at first line[3]. Therefore, it is not a relevant comparator for pralsetinib. Atezolizumab (TA520) is an option for previously treated disease regardless of PD-L1 expression[4]. Selpercatinib (subject to ongoing appraisal ID3743) is a relevant comparator for previously treated disease for people with RET-fusion positive NSCLC. 1. Specialist Pharmacy Service. Pralsetinib, updated 11th January 2021. Accessed at https://www.sps.nhs.uk/medicines/pralsetinib/ 3. National Institute of Health and Care Excellence (2019). Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. NICE Technology Appraisal 584 [TA584] 4. National Institute of Health and Care Excellence (2018). Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. NICE Technology Appraisal 520 [TA520]	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee.
Outcomes	Roche Products Limited	Yes, the listed outcomes capture the most important health-related benefits and harms.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Economic analysis	Roche Products Limited	Pralsetinib has demonstrated considerable patient benefit, thus a cost-effectiveness analysis is the most appropriate economic analysis. This will be expressed in terms of incremental cost per quality-adjusted life-year. The time horizon should be sufficient to capture all health related benefits and costs of treatment. A lifetime horizon that captures the full expected overall survival of patients is the appropriate time horizon. The cost of RET fusion testing will be included in the appraisal. The extent to which the cost of testing is included in the economic analysis will be subject to the extent to which national genomic testing will be expected to be implemented at the time of the launch of pralsetinib. Scenario analysis will explore the uncertainty around testing by providing cost-effectiveness results for a range of plausible testing scenarios.	Thank you for your comment. No action needed.
Equality and Diversity	Roche Products Limited	No equality issues have been identified.	Thank you for your comment. No action needed.
Other considerations	Roche Products Limited	The draft scope suggests that if evidence allows, subgroup analysis could be conducted by previous therapy. It is important to note here that it is unlikely that the evidence package will be sufficient for a subgroup analysis via previous therapy.	Thank you for your comment. No action needed.
Innovation	Roche Products Limited	• Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it	Thank you for your comment. The appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		might improve the way that current need is met (is this a 'step-change' in the management of the condition)? • Yes, pralsetinib can be considered innovative in its potential to make a substantial impact. Pralsetinib is a selective and highly potent RET inhibitor targeting fusions and mutations. There is currently a high unmet need in RET fusion-positive patients as currently there are no targeted therapies available for RET fusion-positive patients and standard therapies may provide limited benefit.[1] Pralsetinib may provide a step-change in the management of the condition by creating a new RET fusion-positive treatment pathway in a similar fashion to entrectinib and crizotinib in ROS1-positive NSCLC.[5] [redacted][6] • Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No • Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. ARROW (NCT03037385) is a phase I/II, global, single-arm, open-label, multicentre study in patients with RET fusion–positive NSCLC and other advanced solid tumours. ARROW will inform the evidence base pertaining to this submission.[2] [5] Entrectinib (NICE TA643) https://www.nice.org.uk/guidance/ta643	committee will consider the innovative nature of the technology. Thank you for your comment. No action needed. Thank you for your comment. The data provided has been noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Crizotinib (NICE TA529) https://www.nice.org.uk/guidance/ta529 6 [redacted]	

Questions for consultation	Roche Products Limited	• **Have all relevant comparators for pralsetinib been included in the scope?** Roche have amended the proposed comparator list in order to align with SoC for RET fusion-positive patients. See the Comparators row under Comment 2: the draft scope for further details. • **Where in the treatment pathway is pralsetinib expected to be used (i.e. previously treated RET fusion-positive)?** As per the expected licence, it is anticipated that, subject to the selpercatinib appraisal[7] and the full implementation of RET fusion testing, pralsetinib will create a new treatment pathway for RET fusion-positive patients.[8] All patients who test RET fusion-positive will be eligible for this pathway and it is anticipated they will be able to receive pralsetinib in any line of therapy. • **Which treatments are considered to be established clinical practice in the NHS for RET fusion-positive advanced non-small-cell lung cancer?** Roche have amended the proposed comparator list in order to align with SoC for RET fusion-positive patients. See the Comparators row under Comment 2: the draft scope for further details. • **How should best supportive care be defined?** Only patients who can tolerate or are willing to have pharmacological intervention will be eligible for pralsetinib. Therefore, BSC is not considered to be an appropriate comparator in this appraisal. See the Comparators row under Comment 2: the draft scope for further details. • **Are the outcomes listed appropriate?** Yes, the listed outcomes capture the most important health-related benefits and harms and are appropriate for this appraisal. • **Are the subgroups suggested in 'other considerations appropriate?** Yes	Thank you for your comment. As noted above, the comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee. Thank you for your comment. No action needed. Thank you for your comment. As noted above, the comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

		• **Are there any other subgroups of people in whom pralsetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No [7] Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10618 [8] In a similar fashion to entrectinib (NICE TA643) and crizotinib (NICE TA529) in ROS1-positive NSCLC • **Do you consider pralsetinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, pralsetinib can be considered innovative in its potential to make a substantial impact. See the Innovation row under Comment 2: the draft scope for further details. • **Do you consider that the use of pralsetinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** No • **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** ARROW (NCT03037385) is a phase I/II, global, single-arm, open-label, multicentre study in patients with RET fusion–positive NSCLC and other advanced solid tumours. ARROW will inform the evidence base pertaining to this submission.[2] • **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**	Thank you for your comment. No action needed. Thank you for your comment. The appraisal committee will consider the innovative nature of the technology. Thank you for your comment. No action needed. Thank you for your comment. The data provided has been noted.

		Nationwide RET fusion testing of NSCLC patients will have to be implemented in order to facilitate the adoption of pralsetinib. Any delay to this implementation would represent a barrier to patient access. • **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** This is an appropriate process with which to appraise this technology. • **NICE has published an addendum to its guide to the methods of technology appraisal, which states the methods to be used where a cost comparison case is made. Would it be appropriate to use the cost comparison methodology for this topic?** Cost comparison methodology is not relevant for this appraisal. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Pralsetinib is likely to be similar in clinical efficacy and resource use to selpercatinib.[4] Selpercatinib is an in-class competitor. • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Primary outcomes measured in the trial include: ○ Determination of maximum tolerated dose ○ Number of patients with adverse events and serious adverse events ○ Objective response rate (ORR) Secondary outcomes include (but are not limited to): ○ Duration of response (DOR) ○ Progression-free survival (PFS) ○ Overall survival (OS) Although clinically relevant, primary outcome measures in the ARROW trial are not key drivers of the economic model. The model will be driven by secondary trial outcomes such as PFS and OS.	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. This has been noted. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

		• **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** To complement ARROW, (although not available in time for the initial NICE appraisal), the AcceleRET Lung trial was initiated in June 2020. AcceleRET Lung (NCT04222972) is a phase III multicentre trial that will evaluate pralsetinib at 400 mg QD against platinum-based chemotherapy in patients with RET fusion–positive NSCLC.[9] [redacted] The AcceleRET trial will have PFS as a primary outcome. [9] AcceleRET Lung Study of Pralsetinib for 1L RET Fusion-positive, Metastatic NSCLC. https://www.clinicaltrials.gov/ct2/show/NCT04222972	Thank you for your comment. NICE notes the initiation of this trial. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Pfizer Inc. responded to confirm receipt but had no comment for the consultation.
British Lung Foundation responded to confirm receipt but would not be taking part in the consultation.