NICE National Institute for Health and Care Excellence

Slides for committee only – Contains ACIC

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

Chair's presentation

Chair: Lindsay Smith

ERG: Kleijnen Systematic Reviews in collaboration with Groningen Medical Center

Technical team: Anne Murray, Caron Jones, Linda Landells

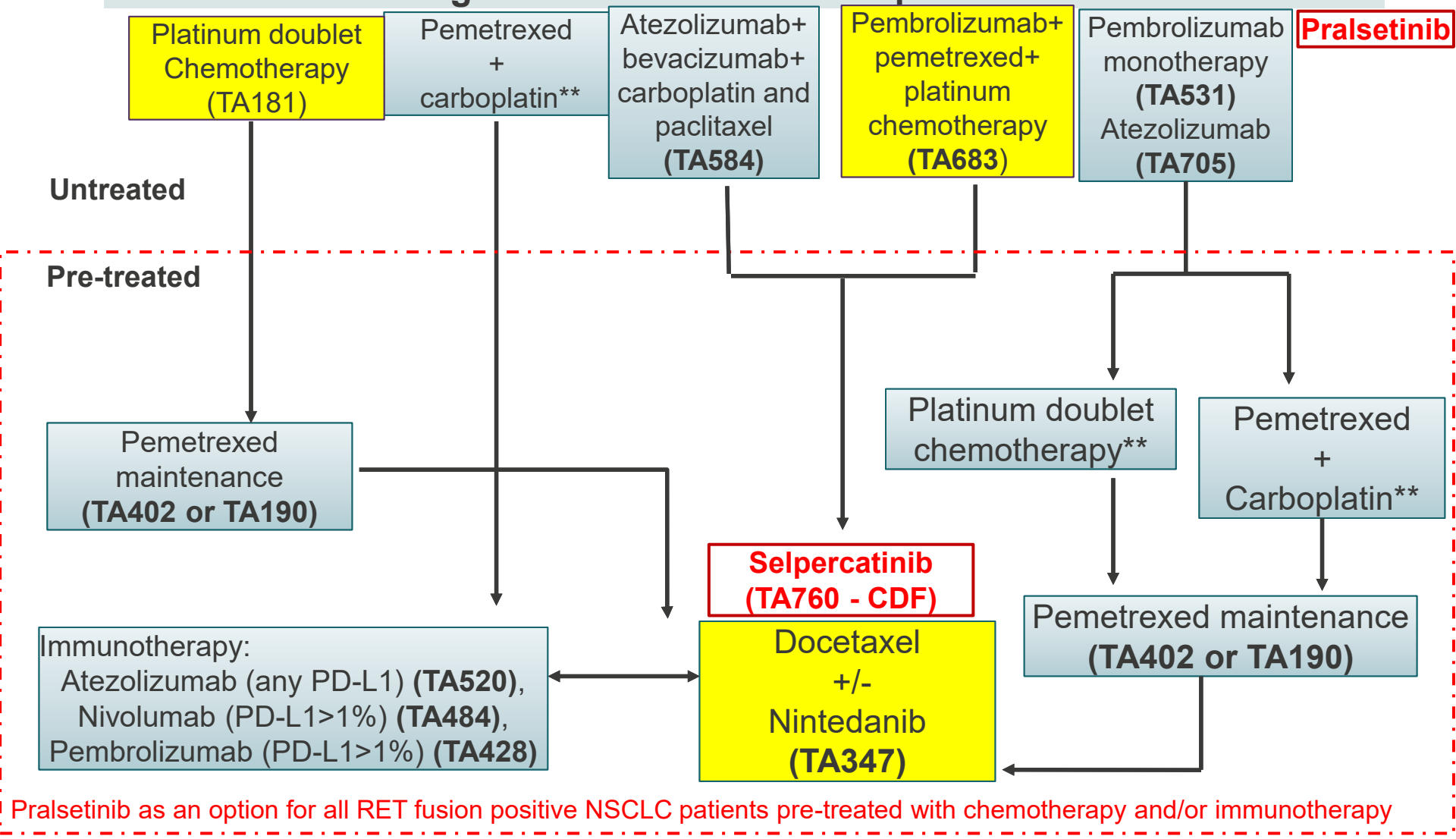
Company: Roche

7th April 2022

Treatment options and pathway

RECAP

RET-fusion positive patients with non-squamous NSCLC and no other gene mutations or fusion proteins



Source: Adapted from company submission, document B, figure 2. CDF: cancer drugs fund

** This/some combinations do not have UK MA for 1 or more indications

Drugs highlighted in yellow represent the main treatment options as per ACM1.

Pralsetinib (Gavreto, Roche)

Mechanism of action	Selective and potent tyrosine kinase inhibitor of WT RET and RET-altered kinases due to targeting fusions (KIF5B-RET and CCDC6-RET) and mutations (RET M918T and RET C634W), including gatekeeper mutations (RET V804M and RET V804L) associated with cabozantinib and vandetanib resistance. Pralsetinib inhibits abnormal activation of signalling pathways that may lead to uncontrolled cell proliferation in tumours harbouring RET alterations.
Marketing authorisation (MA)	Monotherapy for the treatment of adult patients with rearranged during transfection (*RET*) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a *RET* inhibitor.
Dosage and Administration	Oral, 400 mg once-daily tablet. (May be adjusted according tolerability) To be taken on an empty stomach (no food intake for at least two hours before and at least one hour after).
Price	List price: £7,044 Price per pack of 100mg 120 capsules. [redacted]

ARROW study design (Single arm trial)

Phase I & II, Multicentre, non-randomised, open-label, multi-cohort study
Phase I determined maximum tolerated dose & Phase II assessed clinical efficacy, safety and tolerability

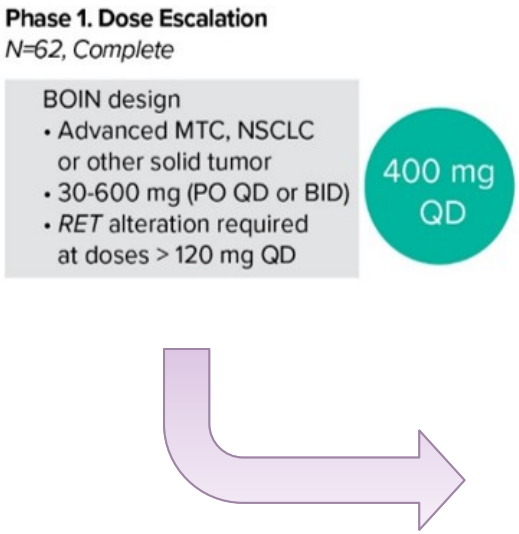
Population

- Patients must have non-resectable disease

Phase I: Adults with advanced solid tumour confirmed by histopathology.

Phase II: Adults must have oncogenic RET fusion or mutation solid tumour.

Key exclusions:
- Phase II excludes synonymous, frameshift and nonsense mutations
- Other non RET alteration
- CNS metastases



Phase 2: Dose expansion
N:310 population of interest

Group 1: RET fusion NSCLC, prior platinum. N~80

Group 2:RET fusion NSCLC, platinum naive. N~ 200

Group 8: RET fusion NSCLC, prior platinum (China). N~30

Primary outcome:
- Objective response rate by RECIST v1.1 criteria by patients' disease type (RET-altered status and/or prior treatment status) if applicable.
- Safety and tolerability.

Source: Company submission doc B, Summary of methodology of the relevant clinical effectiveness evidence, Figure 3. CNS: central nervous system PO: orally QD: once a day BID: twice a day.

RECAP

Key efficacy results from ARROW
Overall response rate (ORR) in measurable disease population

	Measurable Disease Population						
	All *RET* positive NSCLC n=216	Treatment-naïve			Prior Systemic Treatment		
		All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
ORR, % (95% CI)	69 (62, 75)	79 (68, 88)	74 (59, 87)	88 (69, 98)	64 (55, 71)	62 (53, 70)	73 (50, 89)
Best Overall Response, n (%)							
Complete response	9 (4)	4 (6)	4 (9)	0	5 (3)	5 (4)	0
Partial response	139 (64)	50 (74)	28 (65)	22 (88)	89 (60)	73 (58)	16 (73)
Stable disease	50 (23)	9 (13)	7 (16)	2 (8)	41 (28)	37 (29)	4 (18)
Progressive disease	10 (5)	3 (4)	3 (7)	0	7 (5)	5 (4)	2 (9)
Not estimated	8 (4)	2 (3)	1 (2)	1 (4)	6 (4)	6 (5)	0

Source: ERG report, efficacy results table 3.10. Clinical cut-off date is 6 November 2020

[a]Protocol amendment 07/2019; Allowing recruitment of treatment-naïve patients eligible for standard platinum-based therapy which was previously not been permitted.

- **Measurable disease population**: All patients in the efficacy population who had measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for tumour type) at baseline according to blinded central review and sufficient evidence of a *RET* alteration.
- ORR results were similar among treatment-naïve and prior systemic treatment subgroups.

RECAP

Key efficacy results from ARROW
OS and PFS in RET fusion positive NSCLC (unrestricted population)

	Unrestricted Efficacy Population		
	All *RET* positive NSCLC n=281	Prior Systemic Treatment n=165	Treatment Naïve n=116
Progression free survival analyses			
Patients with event, n (%)	xxx	xxx	xxx
Patients Censored, n (%)	xxx	xxx	xxx
Progression free survival Kaplan Meier estimate, Months			
Median (95% CI)	xxx	xxx	xxx
Overall survival analyses			
Deaths, n (%)[a]	xxx	xxx	xxx
Censored, n (%)	xxx	xxx	xxx
Overall survival Kaplan Meier estimate, Months			
Median (95% CI)	xxx	xxx	xxx
Overall follow-up time Kaplan Meier estimate[a], Months			
Median (95% CI)	xxx	xxx	xxx

Source: ERG report, efficacy results, table 3.12 and 3.13.
a: overall follow-up time is based on reverse KM method. NR = not reported
Clinical cut-off date is 6 November 2020.

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- Median PFS of xxx months (95% CI: xxx, xxx)
- xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

ACD preliminary recommendation

Pralsetinib is not recommended, within its marketing authorisation, for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults who have not had a RET inhibitor before.

Recap: ACD considerations

RECAP

Issue	Committee's considerations
The company's comparators are incomplete and not aligned with NHS practice (ACD 3.5)	• Platinum-based chemotherapy with or without pemetrexed missing as first-line treatment. Not relevant for previously treated subgroup.
The indirect treatment comparison results are highly uncertain (ACD 3.8)	• Baseline differences between studies used in systematic literature review. • Use of real world data challenge: quality of data concerns and different setting to an RCT. • Hazard ratios results may have been overestimated. • Comparators issue also apply to the results of the ITC.
The model assumes a constant treatment benefit which is implausible (ACD 3.11)	• Unrealistic to assume a constant and unending treatment effect for pralsetinib. • Hazard ratios used by company based on a small sample size, immature data, and highly uncertain ITC results.
OS and PFS extrapolations are implausible (ACD 3.12)	• Evidence from a single-arm trial compared with real-world evidence and data from ITC highly uncertain. • Implausibility of a lifetime relative treatment benefit.
End of life criteria (section 3.13 and 3.14)	• End of life criteria met in previously treated subgroup but not for the untreated subgroup.
Cancer Drugs Fund (section 3.16)	• Pralsetinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

ACD consultation responses

- Roche (company)
- 1 web comment

Key issues after ACD consultation

Issue	Impact	Slides
Issue 1: Comparators		11
Issue 2: Indirect treatment comparison		12-13
Issue 3: Constant treatment benefit & proportional hazards		14-15
Issue 4: Curve extrapolations		16-20
Issue 5: End of life		21-22
Issue 6: Cancer Drugs Fund		23

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 Model driver

 Unknown impact

 Small/Moderate impact

Issue 1: Comparators

ACD	*Section 3.5 "The company's comparators are incomplete and not aligned with NHS practice"*
Company response	• Provided comparison for **platinum-based chemotherapy +/- pemetrexed** • Clinicians nationally are more likely to prescribe **pembrolizumab + pemetrexed + chemotherapy** to the RET identified untreated subgroup ➔ considered secondary comparator
Web comment	• Previously treated ➔ docetaxel monotherapy and docetaxel plus nintedanib would be suitable comparators & aligns with TA760 selpercatinib.
ERG response	− Platinum-based chemotherapy +/- pemetrexed (primary) ➢ Acknowledges company's conclusion that this can be considered a main comparator. − Pembrolizumab + pemetrexed + chemotherapy (secondary) ➢ Difficult to establish what is actually done in the absence of a rigorous audit ➢ An exclusive focus on what is done e.g. in most cases does not account for the need to improve practice.

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○ **Is the committee satisfied with the comparisons presented in the consultation response?**

Issue 2: Indirect treatment comparison

ACD	*Section 3.8 "The indirect treatment comparison results are highly uncertain".*
Company response	• ITC for **platinum-based chemotherapy +/- pemetrexed** updated using propensity score analysis from IMpower132 used to model efficacy. • ITC used in the base case for **pembrolizumab + pemetrexed + chemotherapy** updated using naïve comparison against KEYNOTE-189 instead of real world data from Flatiron. • For docetaxel monotherapy and docetaxel + nintedanib OS and PFS ➔ equal efficacy assumed.
ERG response	• ITC results need to be regarded with caution. • Inherent limitations with ITC remain, e.g. no description of search methods, no other methods of adjustment considered, some baseline characteristic differences remain, and overlap not explicitly assessed. • Assuming equal efficacy between docetaxel monotherapy and docetaxel + nintedanib requires additional justification as it is currently based on the inference from an expert's point of view.

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○ **Are the ITCs suitable for decision making?**

New ITC results: HR for OS & PFS pralsetinib (ARROW) versus platinum based chemotherapy +/- pemetrexed (IMPower132)

Comparison	Method	Median, months (95% CI) Pralsetinib	Median, months (95% CI) platinum-based chemotherapy +/- pemetrexed	Hazard ratio (95% CI)OS
OS pralsetinib vs platinum-based chemotherapy +/- pemetrexed	Weighted	[redacted]	XXXX	XXXX
PFS pralsetinib vs platinum-based chemotherapy +/- pemetrexed	Weighted	[redacted]	[redacted]	XXXX
Company's ACD response, Appendix A, Analysis.				

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Issue 3: Constant treatment benefit & proportional hazards

ACD	*Section 3.11 "The model assumes a constant treatment benefit which is implausible".*
Company response	• Model has been adjusted to remove proportional hazards assumption. • <u>Untreated setting:</u> − Independent curves fit to propensity scoring ITC for ARROW and IMpower132 (platinum-based chemotherapy +/- pemetrexed) − Proportional hazards retained for (pembrolizumab + pemetrexed + chemotherapy) – time constraints and simplicity. • <u>Pre-treated setting:</u> − Independent curves fit to propensity scoring ITC for ARROW and OAK to model pralsetinib and docetaxel monotherapy respectively. − Independent curves fit to ITC for docetaxel monotherapy. Equal efficacy is assumed between docetaxel monotherapy & docetaxel + nintedanib.

Issue 3: Constant treatment benefit & proportional hazards

ERG response	**Consider this issue only partly resolved** • Improvement in survival extrapolations presented although there is high uncertainty in ITCs • Immature data and small sample size were not resolved • Proportional hazards issue is resolved, but the constant treatment benefit issue is not ➔ more information on implied HR needed to examine if sustained benefit is still present • Suggests scenario with imposed limit to the benefit ➔ informative of the impact on ICER

○ **Is the company's new approach appropriate for decision making?**

Issue 4: Curve extrapolations

ACD	*Section 3.12 "The overall survival and progression-free survival extrapolations are implausible".*
Company response	• Company tested different extrapolation curves (see company's ACD response appendices for details). • Curve selection re-conducted aligned with NICE technical guidance ➢ Untreated: exponential for OS, generalised gamma for PFS/TTD ➢ Pre-treated: exponential for OS, Weibull for PFS/TTD • Updated curves validated in a consultation with a clinical expert • Do not agree with EAG's proposed alternative set of calibrated hazard ratios.
ERG response	• Curve extrapolations & constant treatment benefit very much interrelated issues. • Changes in the model are considered improvements however substantial uncertainty remain. • Agrees with company that HR calibration is not to be preferred when there are better ways to reliably estimate survival curves.

○ **Are the company's chosen extrapolation curves plausible?**

OS extrapolation: untreated

Exponential distribution to model untreated OS for pralsetinib and comparators

Company note:

- Exponential curve demonstrated the closest fit to the long term landmark survival for pralsetinib and comparators ➔ most clinically plausible curves to represent untreated OS in UK clinical practice. Used in the economic model base case.

PFS/TTD extrapolation: untreated

Progression-free survival (PFS)

Time to treatment discontinuation (TTD)

Generalised gamma distribution used to model untreated PFS/TTD for pralsetinib and comparators.

OS extrapolation: pre-treated

Exponential distribution to model pre-treated OS for pralsetinib and comparators

Company note:

- Exponential curves demonstrated the best fit to observed data and clinical expert's landmark survival for pralsetinib and comparators ➔ most clinically plausible curves to represent untreated OS in UK clinical practice. Used in the economic model base case.

PFS/TTD extrapolation: pre-treated

Progression-free survival (PFS)

Time to treatment discontinuation (TTD)

Weibull curves used to model previously treated PFS/TTD for pralsetinib and comparators.

Issue 5: End of life (1)

ACD	*Section 3.13 "The end of life criteria are met for people with previously treated RET fusion-positive advanced NSCLC"* *Section 3.14 "There is not enough evidence to conclude if people with untreated RET fusion-positive advanced NSCLC meet the end of life criteria"*
Company response	**EoL in the pre-treated setting** • Agrees with committee that pralsetinib meets end of life criteria in the pre-treated subgroup. **EoL in the untreated setting** • Consider that the 3-month life extension criterion is met. Undiscounted OS for pralsetinib is xxx months compared to xxx months in platinum-based chemotherapy +/- pemetrexed and xxx months in pembrolizumab + pemetrexed + chemotherapy ➔ survival benefit of xxx and xxx, respectively. • Previous NICE HTA appraisals in ROS1 positive population, entrectinib (TA643) and crizotinib (TA529), met the EOL compared with platinum-based chemotherapy +/- pemetrexed. • ITC against platinum-based chemotherapy +/- pemetrexed shows median OS xxxx months and mean undiscounted OS xxxx months (considered an overestimation).

Issue 5: End of life (2)

Company response	• Considers EOL criteria is met in the comparison against platinum-based chemotherapy +/- pemetrexed. • Consider the OS of xxx months modelled for pembrolizumab + pemetrexed + chemotherapy an overprediction. However, do not consider the 24 month cut-off is met for this comparator.
ERG response	• EoL in the pre-treated setting - no further comment. • EoL in untreated setting ➢ Acknowledges additional evidence suggesting 3 month extension of life has been met. ➢ Acknowledges company do not consider that the short life criterion is met.

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- **Does pralsetinib meets the EOL criteria?**

Issue 6: Cancer Drugs Fund

- ARROW final analysis is TBC, but expected to be available by [redacted]
- Phase 3 AcceleRET Lung recruiting, results expected in [redacted]. Comparators ➔ closely align with standard of care in the current appraisal and UK clinical practice.

Committee decision-making criteria:

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

Other issues submitted in response to consultation

Issue	Company response	ERG response
Pralsetinib's clinical evidence is based on non-squamous NSCLC alone (ACD 3.4)	• Marketing authorisation does not differentiate between squamous and non-squamous NSCLC.	• Uncertainty about the extent to which the evidence applies to squamous patients.
Trial uncertainty (ACD 3.6)	• A conventional RCT for RET fusion-positive NSCLC was not chosen to ensure timely patient access to the treatment.	• ERG's concerns about trial uncertainty remains.
Generalisability to the UK practice (ACD 3.7)	• Agrees with the clinical expert and the committee that the trial population in the ARROW study is generalisable to UK practice.	• No further comment.
Propensity scoring for platinum-based chemotherapy +/- pemetrexed (ACD 3.9)	• Untreated: propensity scoring conducted where appropriate • Pre-treated: no longer required.	• Untreated: see ERG's response to ITC. • Pre-treated: resolved.
Differences between deterministic and probabilistic result (ACD 3.10)	• Updated model addresses this issue	• Still concerned that the original PSA issue was not resolved. No error corrected or fix applied.

Key issues after consultation

Issue at ACM2	Questions for committee
Issue 1: Comparators update	Is the committee satisfied with the comparisons presented in the consultation response?
Issue 2: Indirect treatment comparison update	Are the ITCs suitable for decision making?
Issue 3: Constant treatment benefit & proportional hazards	Is the company's new approach appropriate for decision making?
Issue 4: Curve extrapolations	Are the company's chosen extrapolation curves plausible?
Issue 5: End of life	Does pralsetinib meet the EOL criteria?
Issue 6: Cancer Drugs Fund	Is pralsetinib a candidate for the CDF?

Cost-effectiveness results

All cost-effectiveness results are reported in private PART 2 slides because they include confidential PAS discounts for other treatments.

The committee will consider the following:

- The company's post-ACD base-case (probabilistic, fully incremental analyses)
- The company's post-ACD base-case (pairwise ICERs calculated by the NICE technical team)

BACKUP

AcceleRET Lung

- Open-label, randomized, phase 3 study of pralsetinib vs standard of care (SOC) in first-line treatment of advanced RET fusion+ NSCLC
- Approximately 250 patients randomised 1:1 to pralsetinib or SOC (non-squamous: platinum/pemetrexed ± pembrolizumab followed by maintenance pemetrexed ± pembrolizumab; squamous: platinum/gemcitabine)
- Primary endpoint is progression-free survival
- Secondary endpoints include overall response rate, overall survival, safety/tolerability and quality of life
- Recruitment expected in North America, Europe, Asia, and Australia