NICE National Institute for Health and Care Excellence

Version for public
Contains no ACIC data

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

Lead team presentation

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ERG: Kleijnen Systematic Reviews in collaboration with Groningen Medical Center

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Company: Roche

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NSCLC: Disease overview

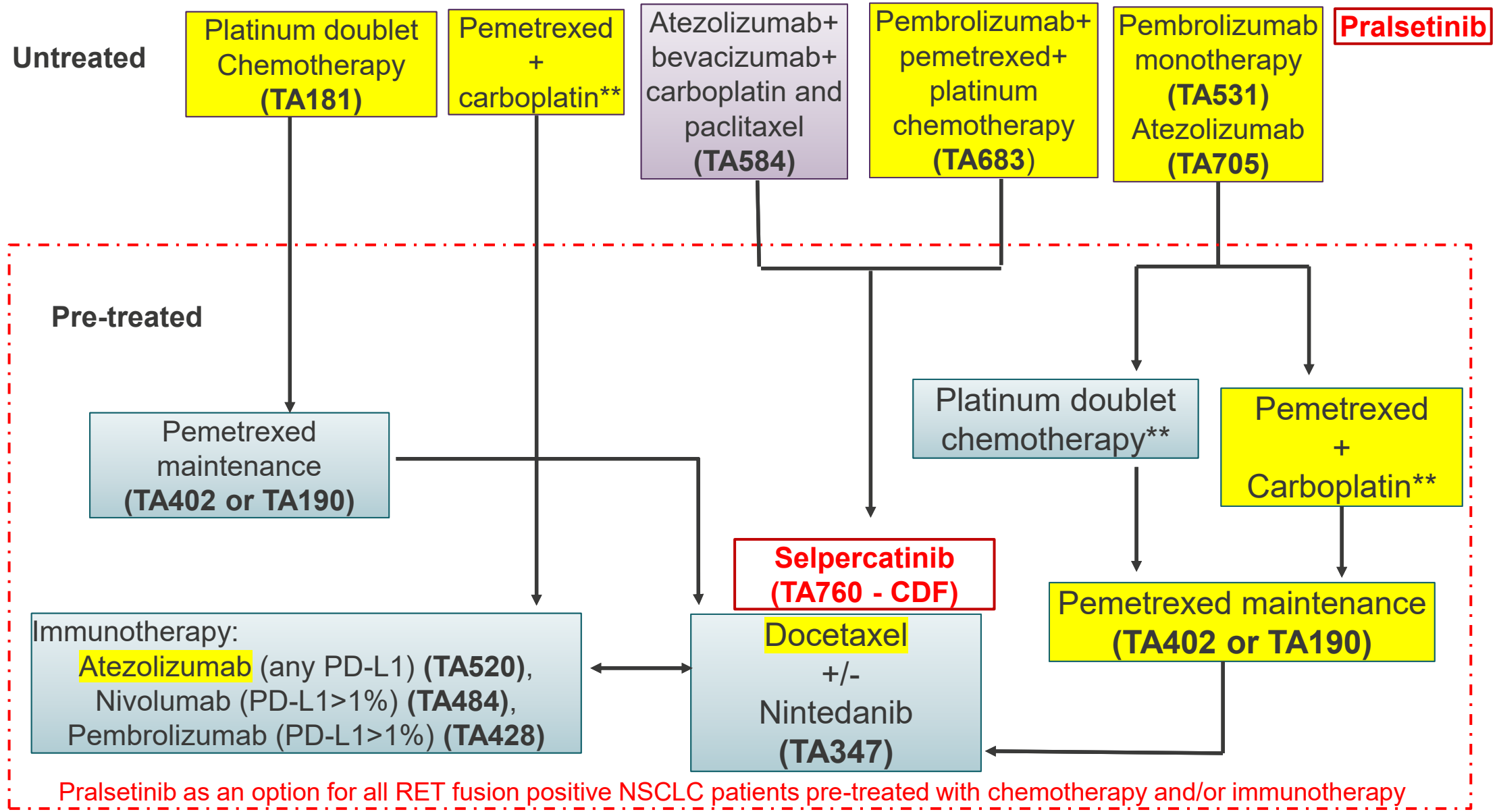
- More than 47,000 people are diagnosed with lung cancer each year in the UK, and there are over 35,000 deaths.
- 48% of lung cancers in England are stage 4 (metastatic) at diagnosis. 5-year survival for people diagnosed at stage 4 is around 3%.
- 80 to 85% of lung cancer cases are non-small cell lung cancer (NSCLC). There are 2 major histological subtypes of NSCLC:
  - Squamous cell carcinoma (25 to 30% of cases)
  - Non-squamous cell carcinoma which comprises adenocarcinoma (40% of cases) and large cell carcinoma (5-10% of lung cancer cases)
- 75% lung adenocarcinomas have oncogenic driver alterations like KRAS, EGFR, ALK, ROS1, BRAF, MET,NTRK and RET.
- Rearranged during transfection (RET) gene fusions are rare and occur in 1-2% of NSCLC
- Typically affects people under 60 years old, females, and non-smokers.
- Symptoms are non-specific and may be disregarded leading to advanced cancer diagnosis.
- Advanced lung cancer frequently metastasise to the central nervous system (brain metastasis 25%).

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)	[redacted]
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. Average cost of treatment course in untreated people: [redacted] Average cost of treatment course in pre-treated people: [redacted] Simple patient access scheme has been approved.

Treatment options and pathway

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.

Patient and carer perspectives

Roy Castle Lung Cancer Foundation

ROY CASTLE LUNG CANCER FOUNDATION

Living with the condition

- 1 year survival for lung cancer is 37% (National Lung cancer audit).
- RET alterations comprise 1-2% of all patients with NSCLC.
- Particularly affects young people who are likely to be non-smokers; often diagnosed at late stage as do not fit "typical" profile.
- Condition has poor prognosis and significant impact on family and carers.
- Symptoms of breathlessness, cough and weight loss are difficult to manage without active treatment and can be distressing for family members.

Current experience of treatment in the NHS

- There are no treatments recommended by NICE targeted specifically at RET-fusion positive lung cancer.[a]
- Current treatment includes a combination of chemotherapy and immunotherapy.
- If selpercatinib (ID3743) was to be recommended, it would be the new standard of care.

New treatment advantages

- Pralsetinib is a once daily oral pill, in COVID times, oral therapy has a clear advantage over in-hospital attendance for intravenous treatment.

[a] TA760 was published after this evidence was submitted

Clinician perspective

British Thoracic Oncology Group

Unmet need

- No NHS guidelines or approved drugs specific to RET-fusion NSCLC.[a]

Current treatment

- Single agent immunotherapy is an option but less effective for RET fusion positive patients.
- Consensus that patients with RET-fusion NSCLC should be treated with a RET TKI but unclear whether selpercatinib or pralsetinib is more effective, and whether it should be first or second line.

New treatment advantages

- Evidence of benefit with RET tyrosine kinase inhibitors (TKIs) in 1st line and relapsed settings.
- Oral treatment pralsetinib→ easier to use than current intravenous standard of care.
- Could reduce demand on oncologists, chemotherapy units and associated services.
- Fewer side effects and more convenient (no need for long treatment cycles nor day-case attendance for treatment).

[a] TA760 was published after this evidence was submitted

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 1. Dose Escalation

N=62, Complete

BOIN design
- Advanced MTC, NSCLC or other solid tumor
- 30-600 mg (PO QD or BID)
- *RET* alteration required at doses > 120 mg QD

400 mg QD

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.

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.

Key efficacy results from ARROW
Modelled 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 (xx)	xx(xxx)	xx (xxxx)
Patients Censored, n (%)	xxxx (xx)	xx (xxx)	xx(xxxx)
Progression free survival Kaplan Meier estimate, Months			
Median	xxxxx	xxxx	xxx
(95% CI)	(xx, xx)	(xx, xx)	(xx, xx)
Overall survival analyses			
Deaths, n (%)[a]	xx(xx)	xx(xxx)	xx (xxxx)
Censored, n (%)	xx (xx)	xx (xxx)	xx(xxxx)
Overall survival Kaplan Meier estimate, Months			
Median (95% CI)	xx (xx)	xx (xx)	xx (xx)
Overall follow-up time Kaplan Meier estimate[a], Months			
Median (95% CI)	xx(xxxx)	xx(xxxx)	xx(xxxx)

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 xx (xx) months (95% CI: xx (xx))
- xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Indirect treatment comparison of pralsetinib versus comparators - Background

- Most appropriate study for pembrolizumab and pembrolizumab plus chemotherapy was Flatiron US database.
- **Matching in Flatiron dataset not to RET+** patients only as n=10 patients were eligible. ERG→ plausible to assume equivalent prognosis among RET positive and negative NSCLC after controlling for other prognostic factors.
- Matched patients to Flatiron were ECOG 0-1 (as in ARROW study), non-squamous histology and other drivers such as EGFR, ALK or ROS were excluded.

Trial and baseline characteristics	ARROW (NCT03037385) (N=233)	Docetaxel monotherapy OAK trial (N=425)	Pemetrexed + carboplatin (GOIRC) (N=119)	Docetaxel + nintedanib (LUME-Lung 1) (N=322)
Trial characteristics				
Blinding	Open label	Open label	Open label	Double-blinded
Inclusion criteria	• RET + untreated or pre-treated with platinum based chemotherapy • ECOG 0 to 1	• Squamous or non-squamous NSCLC • ECOG 0 to 1	• Non-squamous only • ECOG PS ≤ 2	• Locally advanced or metastatic NSCLC • ECOG 0 to 1
Baseline characteristics				
Gender (% female)	52.4%	39%	72.3%	37%
Brain metastases(%)	37.3%	NR	NR	8%
Performance status (ECOG; % PS 1)	63.9%	62%	37.8%	70%
Histology (% non-squamous)	96.1% had adenocarcinoma	74%	71.4% had adenocarcinoma	100%

Source: ERG report Table 3.17 and 3.18 ECOG = European Co-operative Oncology Group; NR = not reported; PD-L1 = programmed death-ligand 1; PS = performance status

Indirect treatment comparison of pralsetinib versus comparators

- ERG noted differences in studies and states it is not possible to match them. The validity of results is uncertain.

	Hazard ratios vs pralsetinib in ITC			
Treatment	**OS HR (95% CIs)**	**PFS HR (95% CIs)**	**TTD HR (95% CIs)**	**Source**
1st line treatment				
Pembrolizumab + pemetrexed + chemotherapy	xxxx (xx)	xxxx (xx)	xxxx (xx)	Flatiron Health dataset (propensity score weighting)
Pembrolizumab monotherapy	xxxx (xx)	xxxx (xx)	xxxx (xx)	Flatiron Health dataset (propensity score weighting)
2nd line treatment				
Docetaxel	xxxx (xx)	xxxx (xx)	xx	OAK trial (propensity score weighting)
Docetaxel + nintedanib	xxxx (xx)	xxxx (xx)	xx	LUME-Lung 1 (naïve comparison); PFS assumed equal to docetaxel monotherapy.
Pemetrexed + carboplatin	xxxx (xx)	xxxx (xx)	xx	GOIRC 02-2006 + NVALT7 (naïve comparison)

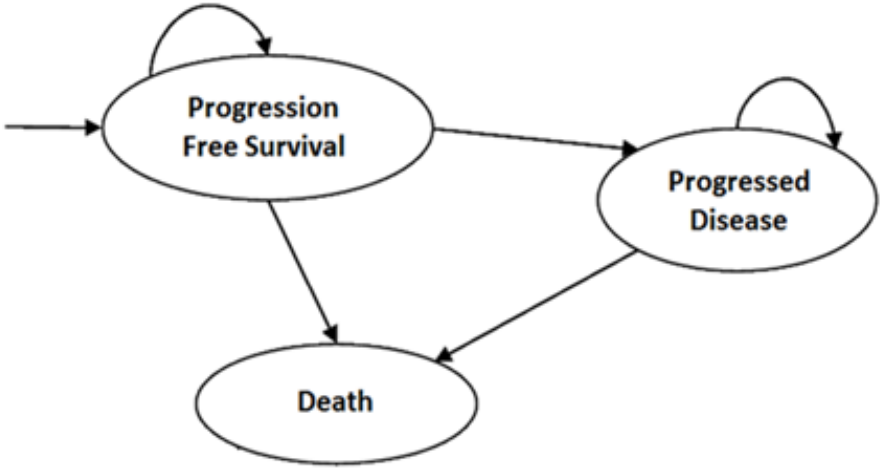
Source: ERG report, critique of trials identified and included in the indirect comparison, table 3.16 HR: hazard ratio; OS: overall survival; PFS: progression free survival; TTD: time to treatment discontinuation.

- Company acknowledge naïve comparisons used for docetaxel + nintedanib and pemetrexed + carboplatin in pre-treated patients show treatment effects favouring pralsetinib which may be attributed to bias due to key cross-population differences.

Also see Issue 6: ERG recommended using Flatiron data to inform comparison with platinum-based chemotherapy +/- pemetrexed

Economic model

- Partitioned survival model comprising 3 mutually exclusive health states: progression-free, progressed disease and death



Source: company submission, document B, figure 31.

Parameter	Source
Pralsetinib	ARROW
Comparators	Flatiron, KEYNOTE-189, KEYNOTE-042, OAK, LUME-lung 1 and GOIRC 02-2006
Time horizon, cycle length	Lifetime horizon of 25 years, model cycle length is 1 month with a half-cycle correction.
Discount rate	3.5%
Utility values	HSUVs from previous NICE NSCLC appraisals treated as relevant source (TA654, TA713)
Costs and resource use	PSSRU, NHS reference costs, British National Formulary, and electronic market information tool.

HSUV: Health state utility value; PSSRU: Personal Social Services Reference Unit

Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1)The population is restricted to non-squamous NSCLC which limits generalisability to patients with squamous NSCLC		Unresolvable
2)Exclusion of potentially relevant comparators listed in the NICE scope		
3)Questionable generalisability to UK population		Unresolvable
4)Methodological problems with systematic literature reviews		Unresolvable
5)Lack of comparative safety data		Unresolvable
6)Propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed		
7)No correction for crossing curves in probabilistic sensitivity analysis		
8)Constant benefit of pralsetinib assumed without justification and based on immature data		
9)Substantial uncertainty in survival curve extrapolations due to immaturity of data		
10)Adverse event incidences included in the model potentially subject to error		
11)Lack of direct evidence to inform health-related quality of life		Unresolvable
12) End of life		

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Key:
Model driver;  Unknown impact;  Small/moderate impact 

Issues unresolvable after technical engagement and contributing to uncertainty

Summary	Company responses	ERG response
Key issue 1: Population restricted to non-squamous NSCLC Scope includes people with RET fusion-positive NSCLC but submission limited to patients with non-squamous NSCLC.	• Marketing authorisation does not differentiate squamous and non-squamous advanced NSCLC. • Selpercatinib- Committee agreed recommendation would apply to both squamous and non-squamous advanced NSCLC.	• Scope includes all patients with NSCLC; currently restricted to non-squamous NSCLC. • ITCs for squamous histology used only non-squamous histology data from Flatiron.
Key issue 3: Questionable generalisability to UK population Only 13 UK patients included.	• UK clinical experts confirmed population in ARROW is similar to LIBRETTO-001 selpercatinib clinical trial.	• Unclear how comparison with LIBRETTO-001 informs generalisability to UK clinical practice.
Key issue 4: Methodological problems with systematic literature reviews	• Company disagrees with methodological issues pointed out by the ERG.	• ERG's concerns about methodological quality of SLR remain.
Key issue 5: Lack of comparative safety data Evidence comes from single arm study so no comparative safety data for pralsetinib versus comparators.	• ITC on safety outcomes not feasible. • Impact of comparative safety data on cost-effectiveness results is negligible.	• ERG reiterates concern that comparative safety data should be provided.
Key issue 11:Lack of direct evidence to inform health-related quality of life Utility values from previous appraisals and not specific to RET fusion positive NSCLC.	• Used utility values previously approved by NICE committees in patient populations comparable to the current appraisal.	• No observational data submitted to evaluate magnitude of difference in HRQoL.

Issue 2: Exclusion of potentially relevant comparators listed in the NICE scope

Background: summary of issue from ERG report

- Numerous comparators in NICE final scope omitted from company's submission.
- Justification for omitting best supportive care also missed.

Company technical engagement response

Comparators chosen to reflect standard of care for RET fusion-positive patients in NICE pathway.

Untreated disease → Platinum based chemotherapy not considered as an appropriate comparator

- Other comparators excluded due to not being recommended by NICE (Nivolumab with ipilimumab TA724) and minimal usage (Atezolizumab, bevacizumab, carboplatin plus paclitaxel [ABCP] TA584)

Pre-treated disease → (selpercatinib TA760) recommended through CDF so not a comparator.

- Immunotherapies are usually given in untreated disease (ABCP, pembrolizumab).
- Best supportive care not an option for patients who can tolerate/want pharmacological intervention.

Stakeholder technical engagement responses

- Untreated → carboplatin-pemetrexed is a fundamental comparator. Agree to exclude immunotherapy in relapsed patients.
- TA683 recommends pembrolizumab combination for untreated NSCLC without markers.

ERG views after technical engagement

- Comparators not in line with NICE final scope→ pralsetinib's relative effects remains uncertain.
- Justification based on expert opinion and not from rigorous quantitative data

Other information

- TA760 stated docetaxel is main comparator for pre-treated (docetaxel + nintedanib also appropriate)

Issue 6:Propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed

Background: summary of issue from ERG report

- Platinum-based chemotherapy comparison made using GOIRC 02-2006 + NVALT. No adjustment for confounding made.
- Flatiron study (data source that allows propensity score weighting analysis) could have been used to inform the comparison with platinum-based chemotherapy +/- pemetrexed.

Company technical engagement response

- Does not consider platinum-based chemotherapy+/- pemetrexed as standard of care in untreated setting →comparison using Flatiron EDM dataset not required.
- Naïve comparison between pralsetinib and platinum-based chemotherapy+/- pemetrexed used in pre-treated setting. Flatiron EDM data not adjustable.

Stakeholder technical engagement responses

- Naïve estimates likely underestimate effectiveness of platinum-based chemotherapy+/- pemetrexed. RET-fusion positive patient characteristics differ from those with broader NSCLC.
- Reasonable to request population-adjusted ITC based on aggregated data from docetaxel + nintedanib trial- LUME-Lung 1.

ERG views after technical engagement

- Untreated setting – refer to Key Issue 2
- Pre-treated setting – imbalances in populations, but PSWA could have been conducted to compare platinum-based chemotherapy +/- pemetrexed.
- TSD17 →regression on matched sample to explore lack of overlap in covariates.

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Would a propensity score weighting analysis for platinum-based chemotherapy be more appropriate?

Issue 8: Constant benefit assumed without justification and based on immature data

Background: summary of issue from ERG report

- Pralsetinib's benefit assumed to be constant over time → evidence from ARROW insufficient to substantiate it.
- Treatment waning exclusion was not justified.
- Median follow up in ARROW trial is 9.5 months, suggest implementing treatment waning at 2 years over a 3-year period.

Company technical engagement response

- Evidence suggests no waning of treatment effect in observed period ~[redacted] months.
- Used clinical experts landmark OS predictions. Clinical experts consulted do not believe there will be treatment waning in first 5 years.
- Previous appraisals of selpercatinib & entrectinib → base-case assumes no waning of OS treatment effect.
- Scenarios exploring varying treatment waning provided → cost-effectiveness results not sensitive to treatment waning assumptions

Stakeholder technical engagement responses

- Do not agree with treatment waning effect. Uncertainty could be handled by exploring the impact of alternative survival curve choices

ERG views after technical engagement

- Given the low patient numbers, no inference should be made on OS curve tails → therefore assumption of no treatment waning seems optimistic.
- Treatment waning included in recent NSCLC appraisals – usually 3 to 5 year duration of treatment effect.

Is it appropriate to assume that pralsetinib has a constant treatment benefit? Should treatment effect waning be applied in the modelling?

Issue 9: Substantial uncertainty in survival curve extrapolations due to immaturity of data 1/2

Background: summary of issue from ERG report

- Hazard ratios and survival curve extrapolations are uncertain due to the small sample size and immaturity of data.
- Difficulty in choosing appropriate curve distribution therefore hazard ratios were calibrated to fit expert's estimates.

Company technical engagement response

- Acknowledge immaturity of ARROW data. Low events during the follow up, patient's survival modelled in unobserved period in the economic model.
- Current appraisal comparable in terms of size and maturity data to previous NICE appraisals in NSCLC (entrectinib and selpercatinib).
- Absolute errors in over/under prediction of 5-10% in extrapolations represent an acceptable range of error.
- Over/under prediction landmark survival compared to clinical expert resulted from taking absolute values which should have precedence.
- ERG's calibration of HR based on clinical expert landmark survival prediction at 3 years is inferior to methodology used in systematic ITC conducted by the company.
- Immaturity data concerns will be addressed with upcoming AcceleRET-Lung clinical trial in XXXX.

Issue 9: Substantial uncertainty in survival curve extrapolations due to immaturity of data 2/2

Stakeholder technical engagement responses

- Technical support document 14 should be followed in absence of longer survival follow-up.
- External validation to clinical datasets and to landmark survival estimates from clinical experts are most appropriate methods to validate survival extrapolations.

ERG views after technical engagement

- Although clinical expert landmark predictions although lack accuracy, it is best available data for long-term predictions.
- Both absolute and relative prediction error should be considered → relative error holds less value when the absolute predictions are close to zero.
- Neither the absolute nor relative net combined errors for untreated OS fall in an acceptable range of error → even a single absolute error is questionable.
- Additional analyses of uncertainty through scenario analysis provided insight in the effects on ICERs → more robust conclusions.

Are the calibrated hazard ratios appropriate for decision making?

Modelled OS and PFS extrapolation

	3 years			5 years			10 years		
	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono
Validation for model untreated OS									
EO	50%	30%	25%	40%	10%	8%	10%	3-5%	2%
Weibull*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation for model untreated PFS									
EO	30-35%	15%	5%	10-15%	5%	1%	5%	1%	0-1%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report tables 4.6 and 4.7. EO = expert opinion; OS = overall survival; PFS=progression free survival; *base-case selection.

	3 years				5 years				10 years			
	Pra	DoM	DoN	PBC+/- pem	Pra	DoM	DoN	PBC+/- pem	Pra	DoM	DoN	PBC+/- pem
Validation for model pre-treated OS												
EO	35%	5%	5%	15%	20%	2%	2%	5%	7%	0%	0%	1%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation for model pre-treated PFS												
EO	30-35%	1-2%	1-2%	5%	10-15%	0%	0%	1%	5%	0%	0%	0%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report tables 4.9 and 4.10. EO = expert opinion; OS = overall survival; Pra = pralsetinib; DoM = docetaxel monotherapy; DoN = docetaxel plus nintedanib; PBC +/- pem = pemetrexed +/- platinum-based chemotherapy;*base-case selection.

- Company's submitted modelled OS and PFS.
- ERG critique- under and overpredictions in comparators.

Modelled OS and PFS extrapolation (ERG's calibrated estimates)

	3 years			5 years			10 years		
	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono
Validation for model untreated OS									
EO	50%	30%	25%	40%	10%	8%	10%	3-5%	2%
Weibull*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation for model untreated PFS									
EO	30-35%	15%	5%	10-15%	5%	1%	5%	1%	0-1%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

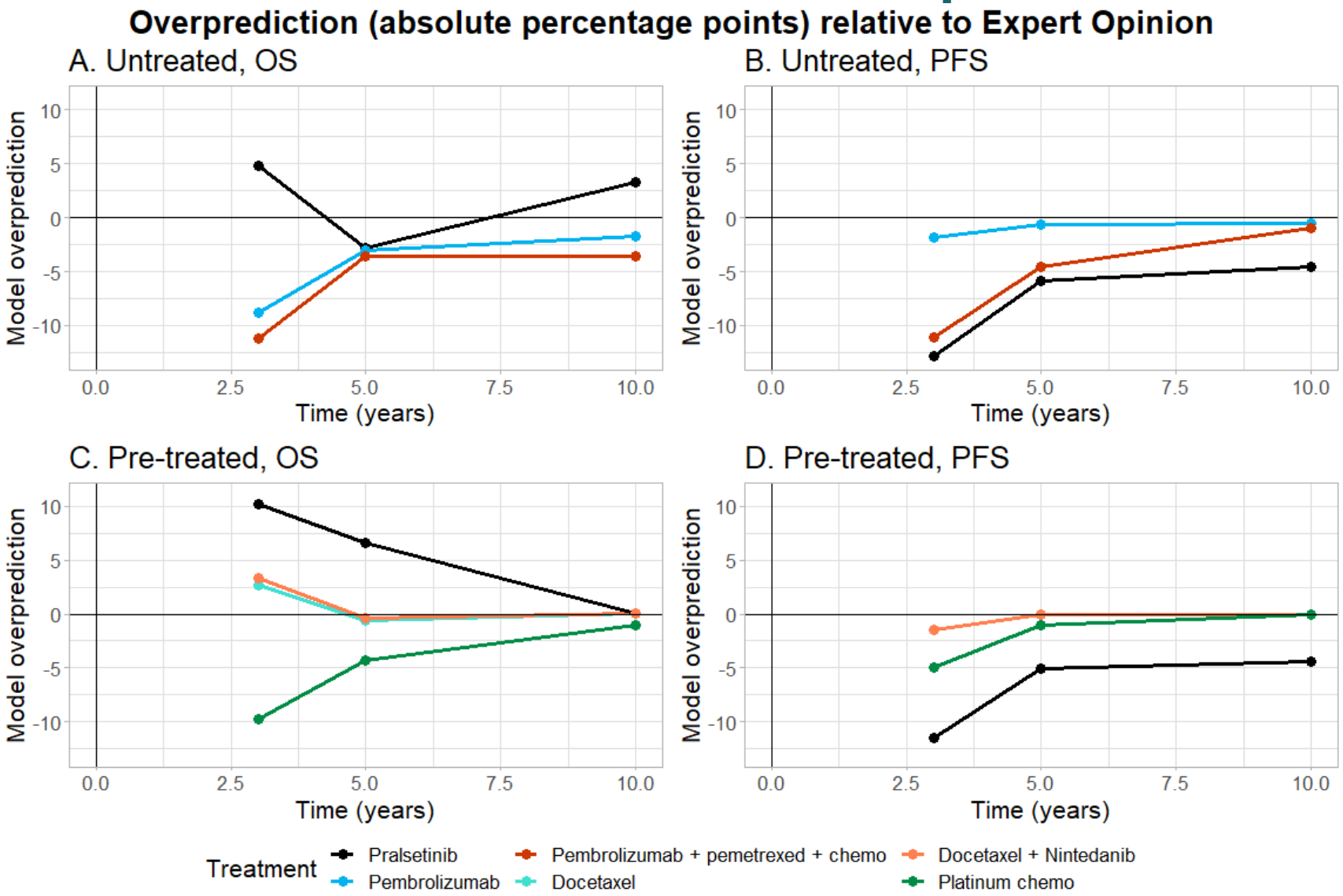
Source: ERG report tables 4.6 and 4.7. EO = expert opinion; OS = overall survival; PFS=progression free survival; *base-case selection. (ERG calibrated HR)

	3 years				5 years				10 years			
	Pra	DoM	DoN	PBC+/- pem	Pra	DoM	DoN	PBC+/- pem	Pra	DoM	DoN	PBC+/- pem
Validation for model pre-treated OS												
EO	35%	5%	5%	15%	20%	2%	2%	5%	7%	0%	0%	1%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Validation for model pre-treated PFS												
EO	30-35%	1-2%	1-2%	5%	10-15%	0%	0%	1%	5%	0%	0%	0%
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report tables 4.9 and 4.10. EO = expert opinion; OS = overall survival; Pra = pralsetinib; DoM = docetaxel monotherapy; DoN = docetaxel plus nintedanib; PBC +/- pem = pemetrexed +/- platinum-based chemotherapy;*base-case selection. (ERG calibrated HR)

- The ERG applied an alternative set of hazard ratios that were calibrated on the expert opinion landmark estimates at 3 years.

Modelled OS and PFS extrapolation



Source: Visual representation of ERG report tables 4.6, 4.7,4.8 and 4.9.

- The curves reflect at each time point, the difference between the modelled OS and PFS from the expert estimates. Graphs show base-case curve distributions.

End of life

Summary of mean/ median life expectancy from the economic model and literature (months)

Technology	Literature Median OS	Company base-case Mean OS	ERG calibrated HR Mean OS
Untreated			
Pralsetinib	-	XXX	XXX
Pembrolizumab + pemetrexed + chemotherapy	22	XXX	XXX
Pembrolizumab monotherapy	20	XXX	XXX
Pre-treated			
Pralsetinib	-	XXX	XXX
Docetaxel	7.9	XXX	XXX
Docetaxel + nintedanib	10.9	XXX	XXX
Pemetrexed + carboplatin	10.6	XXX	XXX

Source: CS report table 34, company and ERG model outputs, KEYNOTE-042, KEYNOTE-189, LUME LUNG 1.

ERG:

1. Life expectancy of <24 months met.
2. Extension of life ≥ 3 months; Economic model vs all comparators-gain in life years >2 years. Issues 2, 4 and 5 not sufficiently resolved to overcome concerns in validity of evidence.
3. To demonstrate second criterion, robust comparative data needed. No formal comparison performed for some comparisons.

Key issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1)The population is restricted to non-squamous NSCLC which limits generalisability to patients with squamous NSCLC		Unresolvable
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10)Adverse event incidences included in the model potentially subject to error		
11)Lack of direct evidence to inform health-related quality of life		Unresolvable
12) End of life		

NICE

Key:
Model driver;  Unknown impact;  Small/moderate impact 

Cost-effectiveness results

- Because of confidential discounts, results will be presented in part 2.
- Note: some estimates in the company's analyses are over £30,000 per quality adjusted life year gained.
- Deterministic and probabilistic ICERs differ in first line treatment.

Cancer Drugs Fund

Committee decision-making criteria:

- ARROW final analysis is TBC, but expected to be available by XXXX
- Phase 3 AcceleRET Lung recruiting, results expected in XXXX

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.

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

BACK-UP SLIDES

Key efficacy results from ARROW
Secondary efficacy points in patients with RET fusion positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC n=216	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
Duration of response (DOR)							
DOR, months (95% CI)	22.3 (15.1, NR)	NR (9.0, NR)	11.0 (7.4, NR)	NR (NR, NR)	22.3 (15.1, NR)	22.3 (15.1, NR)	NR (9.2, NR)
Clinical benefit rate (CBR)							
CBR, % (95% CI)	77 (71, 82)	82 (71, 91)	79 (64, 90)	88 (69, 98)	74 (67, 81)	74 (65, 81)	77 (55, 92)
Disease control rate (DCR)							
DCR, % (95% CI)	92 (87, 95)	93 (84, 98)	91 (78, 97)	96 (80, 100)	91 (85, 95)	91 (85, 96)	91 (71, 99)

Sources: ERG report, efficacy results table 3.11 NR: Not reported

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

Clinical cut-off date is 6 November 2020

- Follow up times for CBR and DCR not provided.

Safety results from ARROW trial
Adverse Events

Parameter, n (%)	Overall (All tumour types) n=528	RET fusion-positive NSCLC n=281	Prior systemic treatment xxx	No prior systemic treatment xxx
Any adverse event	525 (99.4)	279 (99.3)	xxx	xxx
≥Grade 3	406 (76.9)	212 (75.4)	xxx	xxx
Treatment related adverse event	493 (93.4)	264 (94.0)	xxx	xxx
≥Grade 3	296 (56.1)	155 (55.2)	xxx	xxx
Serious adverse events	288 (54.5)	166 (59.1)	xxx	xxx
≥Grade 3	251 (47.5)	137 (48.8)	xxx	xxx
Related serious adverse events	111 (21.0)	70 (24.9)	xxx	xxx
Deaths due to adverse events	71 (13.4)	38 (13.5)	xxx	xxx
Deaths related to pralsetinib	6 (1.1)	2 (<1)	xxx	xxx
Sources: ERG report, safety results from ARROW trial, table 3.14				

- No comparative safety data for Pralsetinib against comparators listed in NICE final scope.
- Available evidence from single arm study.

Issue 7:No correction for crossing curves in probabilistic sensitivity analysis

Impact = 

Background: summary of issue from ERG report

- Overall survival curve of probabilistic sensitivity analysis crosses progression free survival and time to treatment discontinuation curve leading to negative post-progression survival in a proportion of simulations.
- ERG corrected model with preferred assumptions which leads to increased probabilistic ICER.
- Deterministic ICER remains unaffected.

Company technical engagement response

- Issue resolved by the ERG as part of technical engagement clarification call.

Stakeholder technical engagement responses

- Issue seems resolved according to ERG.

ERG views after technical engagement

Issue 10:Adverse event (AE) incidences included in the model potentially subject to error

Impact =

Background: summary of issue from ERG report

- Incidence of adverse events used to inform the model subject to inconsistencies and errors.
- Issue on both pralsetinib and comparator arms.

Company technical engagement response

- Inconsistency in sample sizes of safety population due to different ARROW populations used in each section.
- Safety population used in clinical section represents published measurable disease population consistent with the rest of the section.
- Safety population used in economic section represents safety/unrestricted efficacy population and used in model to align with population used for efficacy.
- Typographical errors amended; negligible impact on ICER.

Stakeholder technical engagement responses

- No comment.

ERG views after technical engagement

- Agrees with the new AE incidences and used them in its updated analyses.
- New AE only used in absolute incidences, not in percentages→ nothing changed.
- ERG amended model to include new AE incidences in cost-effectiveness calculations → Minor impact.

Issue 1: Population restricted to non-squamous NSCLC

Background: summary of issue from ERG report

- Population in scope "People with advanced rearranged during transfection (RET) fusion-positive NSCLC who require systemic therapy" but population in submission limited to patients with non-squamous NSCLC.

Company technical engagement response

- Marketing authorisation does not differentiate squamous and non-squamous advanced NSCLC.
- RET fusion positive squamous NSCLC is rare → ARROW trial (1.4%), reflective of UK clinical practice.
- European medicines agency granted a licence in squamous indication because results are generalisable.
- Due to unmet need, crucial to have RET inhibitor in both histology types.
- Selpercatinib → committee agreed recommendation would apply to both histological types.

Stakeholder technical engagement responses

- Reasonable to generalise results to squamous RET positive NSCLC as the numbers are negligible.
- Prevalence might increase when RET testing becomes wider adopted.
- Recommendation should comprise both histological types of RET positive NSCLC.

ERG views after technical engagement

- Population in NICE final scope includes all patients with NSCLC; currently restricted to non-squamous non-small cell lung cancer.
- ITCs for squamous histology used only non-squamous histology data from Flatiron study.

Issue 3: Questionable generalisability to UK population

Background: summary of issue from ERG report

- The ARROW trial in which conclusions are based only includes 13 UK patients.

Company technical engagement response

- UK clinical experts confirmed that the enrolled population in ARROW is similar to LIBRETTO-001 selpercatinib clinical trial.

Stakeholder technical engagement responses

- Unlikely there are major differences between ARROW trial and UK population. RET fusion positive behaves similar regardless of ethnic difference.

ERG views after technical engagement

- Acknowledge clinical expert confirm that ARROW trial population similar to other oncogenic driver clinical trials used in UK technology appraisals → unclear how comparison with LIBRETTO-001 informs generalisability to UK clinical practice.
- Reiterates the value of empirical data to support expert opinion.
- Generalisability of ARROW trial in terms of demographic and disease characteristics remains unclear.

Issue 4:Methodological problems with systematic literature reviews (SLR)

Background: summary of issue from ERG report

- Methodological problems with SLR such as inconsistency of response rate definitions, no dual independent data extraction, exclusion of non-randomised studies and lack of comprehensive assessment of included studies which limits the conclusions on safety and effectiveness.

Company technical engagement response

- Company disagrees with the methodological issues pointed out by the ERG.
- No evidence that relevant studies/evidence were missed.
- Network analysis was not possible so prioritised studies with individual patient data. Results from different studies are not connected which led to the decision of using one study per comparator.

Stakeholder technical engagement responses

- SLR done to expected standard, reviews always have heterogeneity in outcome measurements and the way they are reported but the outcomes are broadly similar.

ERG views after technical engagement

- Methodological quality concerns→ does not seem to adhere to NICE guidance or Cochrane methods in some areas.
- “no evidence that relevant studies/evidence were missed” → inadequate response to relevant data sources not searched; no evidence on searching trial registers submitted.
- ITC for adverse events could have been conducted.
- ERG’s concerns regarding the methodological quality of the SLRs remain.

NICE

Have the systematic literature reviews been conducted appropriately? Are they suitable for decision making?

Issue 5:Lack of comparative safety data

Background: summary of issue from ERG report

- Evidence comes from a single arm study so there is no comparative safety data for pralsetinib versus comparators
- Impossible to draw conclusions about relative safety and tolerability of pralsetinib.

Company technical engagement response

- Indirect treatment comparison on safety outcomes not feasible; different mechanism of action, different treatment duration, follow up and trial design which could be misleading.
- Limited data available for comparators and adverse events usually grouped (any adverse event (AE) or any treatment related adverse event) which does not allow for differentiation.
- Naïve comparisons would have been possible with few safety endpoints per comparator with no adjustment.
- Impact of comparative safety data on cost-effectiveness results is negligible.
- Selpercatinib (ID3747) also submitted single arm trial and no comparative safety data was provided; not viewed as key issue.
- Upcoming AcceleRET-lung clinical trial in [redacted]. Pralsetinib versus standard of care for 1st line.

Stakeholder technical engagement responses

- Single arm trial due to rarity of RET fusion positive NSCLC.
- Randomised clinical trial in progress, unclear if will continue due to recruitment and COVID issues.
- ITC worth exploring; safety been explored by European Medicines Agency who granted approval.

ERG views after technical engagement

- ERG reiterates the concern that comparative safety data should be provided.

Should the ITC be used to inform the comparative safety?

Issue 11:Lack of direct evidence to inform health-related quality of life (HRQoL)

Background: summary of issue from ERG report

- Utility values used in the economic model are not from the ARROW study.
- Company used utility values from previous appraisals and are not specific to patients with RET fusion positive NSCLC.
- Difference between treated and untreated populations not reflected in mapped EORTC QLQ-C30.

Company technical engagement response

- Acknowledge utilities uncertainty as not informed from trial outcomes. Used utility values that have been previously approved by NICE committees in appraisals in patient populations which represent the most comparable to the current appraisal.
- Untreated utility value → all three sources/populations could arguably represent suitable proxies
- Pre-treated utility value 0.628 represents a mid-point between the HRQoL in LIBRETTO-001 (0.688) and approved value in TA713 (0.569).
- HRQoL evidence gap will be addressed with upcoming AcceleRET-Lung clinical trial in XXX.

Stakeholder technical engagement responses

- Company's approach is reasonable. RET fusion positive patients behave similar to other NSCLC patients.

ERG views after technical engagement

- Best approach → collect comparative HRQoL data.
- No observational data submitted to evaluate magnitude of difference in HRQoL.