NICE National Institute for Health and Care Excellence

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Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Lead team presentation

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Company: Roche

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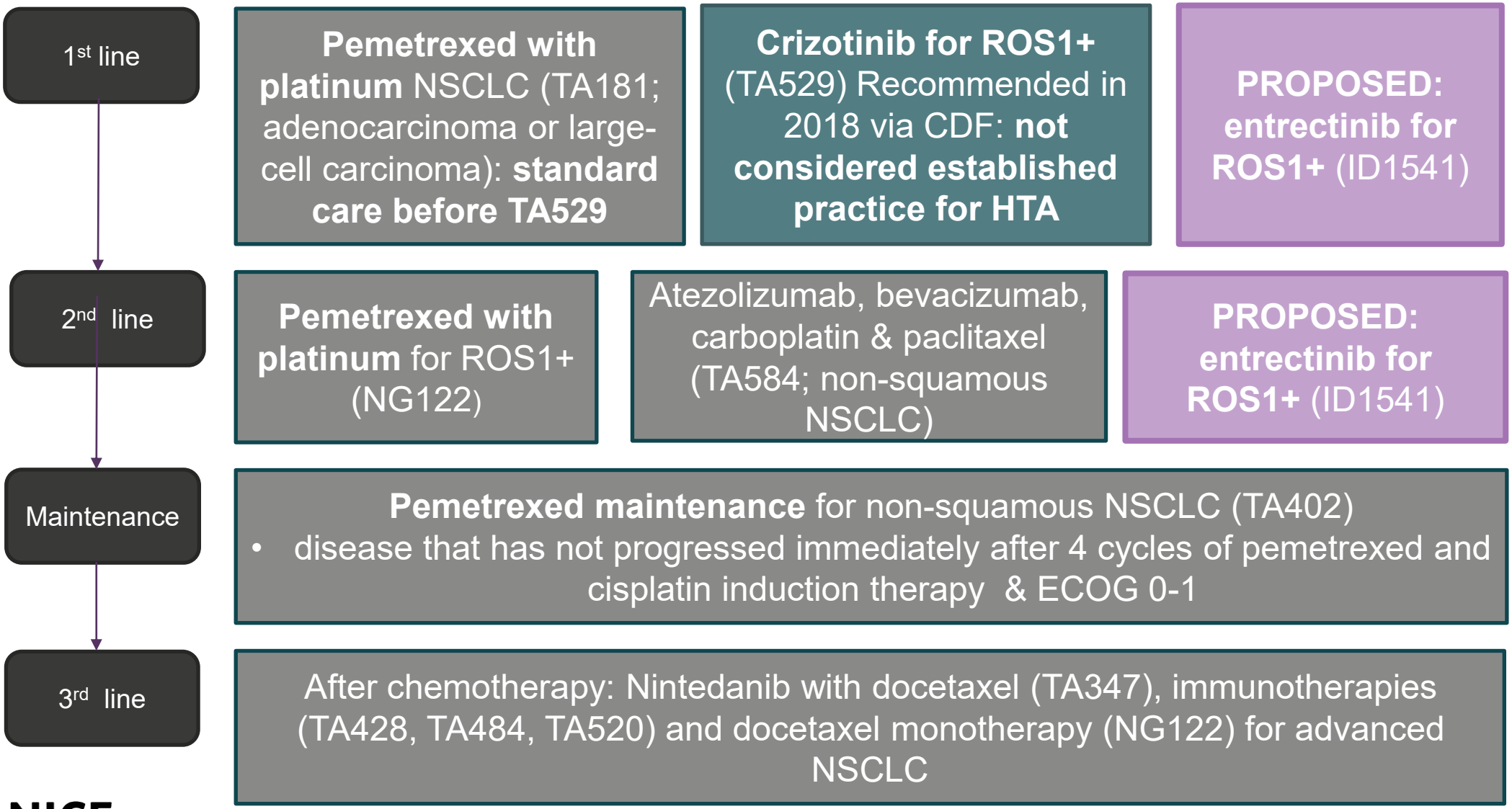
ROS1-positive advanced NSCLC

- Lung cancer is third most common cancer in the UK (~13% of all cancer).
- Most (~ 88%) lung cancers are non-small cell lung cancer (NSCLC).
- Prognosis is often poor due to late diagnosis.
- In 2016, approximately 32,533 people were diagnosed with NSCLC in England, of whom 53% had stage IV disease.
- CNS metastasis are common in advanced NSCLC.
- ROS1 is a rare mutation that occurs in around 1-2% of NSCLC, mostly in non-squamous tumours, with the majority in adenocarcinoma (80 - 100%).
- Similarly to ALK mutations, ROS1 mutations are more common in younger people who have never smoked and have adenocarcinoma and were associated with worse prognosis.

Treatment pathway

- **Advanced ROS1-positive NSCLC**



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Entrectinib (Rozlytrek, Roche)

Anticipated marketing authorisation	Indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors
Administration	600mg given orally (as three 200mg capsules), once daily. Treatment is recommended until disease progression or unacceptable toxicity.
CHMP opinion	Due on 12th December 2019

- The company have proactively positioned entrectinib for funding via the Cancer Drugs Fund (CDF) as opposed to by routine commissioning in the NHS.

Key issues

Issue for discussion:

- **Issue 4 – OS and PFS modelling** (slides 12 to 18)
  - Technical team: compared with company's, ERG's approach is more appropriate.

Issues for consideration:

- **Issue 5 – End-of-Life** (slide 11)
  - Technical team: considers that entrectinib meets EoL vs PEM+PLAT.
- **Issue 10 – Cancer Drugs Fund** (slide 22)
  - Technical team: entrectinib meets the criteria for inclusion in CDF.

What is the committee view of technical team's conclusions?

Background

Comparator	**Pemetrexed with platinum (PEM+PLAT)**
Key clinical trial	STARTRK-2, phase II, single-arm, multicentre, basket study of entrectinib in solid tumours • ROS1-positive NSCLC SG (n=78) PFS: [redacted] OS: [redacted]
Issue 4: ERG's approach to PFS & OS modelling	MAIC Entrectinib vs PEM+PLAT: • Entrectinib: STARTRK-2 SG • PEM+PLAT: ASCEND-4
Issue 4: company's approach to PFS & OS modelling	MAIC Entrectinib vs crizotinib (step 1): • Entrectinib: STARTRK-2 SG • Crizotinib: PROFILE 1001 HR crizotinib vs PEM+PLAT from PROFILE 1014 (step 2):
Model	Cohort based partitioned survival model: Progression-free, Progressed disease & Death states.
Technical team's preferred ICER	**£37,910 to £42,572 /QALY gained** • with company's approach to PFS & OS: £21,607 to £23,457 /QALY gained

Patient and carer perspectives

- Entrectinib is an oral therapy taken once a day.
- The side effects including changes in taste, weight gain and dizziness are easily manageable by patients.
- Pre-screening of NSCLC patients for the ROS1 fusion is required for treatment selection.
- Targeting the ROS1 fusion found in 1-2% of patients with NSCLC has clear patient benefits.
- Current treatments for NSCLC have limited activity towards brain metastases which are seen in around one third of patients at initial diagnosis.
- Entrectinib is able to penetrate the central nervous system which is beneficial to NSCLC patients who have brain metastases.

Equality issues and Innovation

- No equality issues have been raised during this appraisal.

Company on innovation:

- Entrectinib is the first ROS1 Inhibitor to show intracranial activity against ROS1-driven CNS metastases, which has led to entrectinib receiving Promising Innovative Medicine.
- However, due to small patient numbers, this group could not be separately modelled. Therefore, the impact of entrectinib on health-related benefits in this difficult-to-treat patient population with significant unmet need in current practice, is not fully captured in QALY calculation.

Issues resolved after technical engagement I.

	Summary	Stakeholder responses	Technical team	Base case
1	Comparators: company presented comparison vs PEM+PLAT and a scenario analysis comparing entrectinib with crizotinib.	Stakeholders agree that PEM+PLAT is the key comparator.	PEM+PLAT is the key comparator.	Company ✓ ERG ✓
2	Relevant population: company's efficacy set (n=53) vs ERG's STARTRK-2 SG (n=78)	Stakeholders agree that STARTRK-2 SG is the relevant population	STARTRK-2 SG is the relevant population	Company ✓ ERG ✓
3	Indirect comparison: entrectinib versus PEM+PLAT using ALK data (ASCEND-4 MAIC)	ALK-positive data as proxy for ROS1-positive NSCLC is reasonable.	MAIC results are appropriate for decision making. However: • **PFS & OS estimates are uncertain** • **not possible to estimate direction & size of this uncertainty** Note: modelled PFS & OS discussed in Issue 4	Company ✓ ERG ✓

Issues resolved after technical engagement II.

	Summary	Stakeholder responses	Technical team	Base case
6	Company: pemetrexed maintenance only after induction with cisplatin with no maintenance therapy in base case.	Expected: 3-6 cycles. ASCEND-4: 8 cycles. Company: scenarios with 4, 6 & 8 cycles after cisplatin or carboplatin.	Considers results assuming 4, 6 & 8 cycles after induction with cisplatin or carboplatin.	Company ✓ ERG ✓
7	Subsequent treatments (ST): company assumed range of treatments, and only some patients had it.	50-70% patients would have ST. PEM+PLAT after entrectinib. Atezolizumab (TA584) is unlikely to be used.	Considers results assuming 60% & 70% of patients having ST and PEM+PLAT after entrectinib.	Company ✓ ERG ✓
8	STARTRK-2: only PFS utilities, but issues with the regression model. ERG: utilities from TA529 more appropriate.	The utility values seems similar.	Utilities as used in TA529, 0.81 for PFS and 0.66 for PPS are appropriate for decision making.	Company ✓ ERG ✓
9	Company based costs on previous appraisals. However, some of the assumptions did reflect clinical practice.	ERG's approach was considered more appropriate.	ERG's approach is appropriate for decision making.	Company ✓ ERG ✓

Issue 5 – End-of-Life: for consideration

	Evidence:	Entrectinib vs PEM+PLAT	
		ERG	Company
Life expectancy: < 24 months	• Retrospective Korean study: median OS of 20.7 months in people who did not have TKI • TA529: considered PEM+PLAT survival < 24 months.	**Mean OS:** [redacted] vs 39.2 [redacted] months	**Mean OS:** [redacted] vs 15.57 [redacted] months
Extension to life: ≥3 months	• Entrectinib survival data are immature; crizotinib median OS is 51.4 months (PROFILE 1001). • TA529: crizotinib survival gain versus PEM+PLAT is ≥ 3 months.	**Median OS:** [redacted] vs 26.6 [redacted] months	**Median OS:** [redacted] vs 10.8 [redacted] months
Stakeholders comments	• Life expectancy with PEM+PLAT ≤ 24 months: audits of NSCLC patients with other molecular drivers (e.g. ALK), we know that their median survival was < 24 months. It is reasonable to assume same life expectancy for ROS1 patients. • Entrectinib gain ≥ 3 months: it is definitely plausible that entrectinib increases. survival vs PEM+PLAT by ≥ 3 months.		
Technical team conclusions	• Considers ERG's approach to modelling OS is more appropriate (Issue 4): The model in this case overestimate PEM+PLAT survival, however entrectinib survival gain of [redacted] months is clinically plausible. **Entrectinib is likely to meet both criteria to be considered a life-extending, end-of-life treatment when compared with PEM+PLAT**.		

Does the committee agree with the technical team conclusions?

Outstanding issues after technical engagement

Issue 4: OS and PFS modelling

- No direct evidence for entrectinib vs PEM+PLAT (STARTRK-2 SG was single arm study)
- Two distinct approaches to modelling the indirect comparison, choice driven by preference for managing bias in the PEM+PLAT data source
  - Which study minimises biases in PEM+PLAT data?
- Important as choice of approach to modelling OS has large impact on ICER

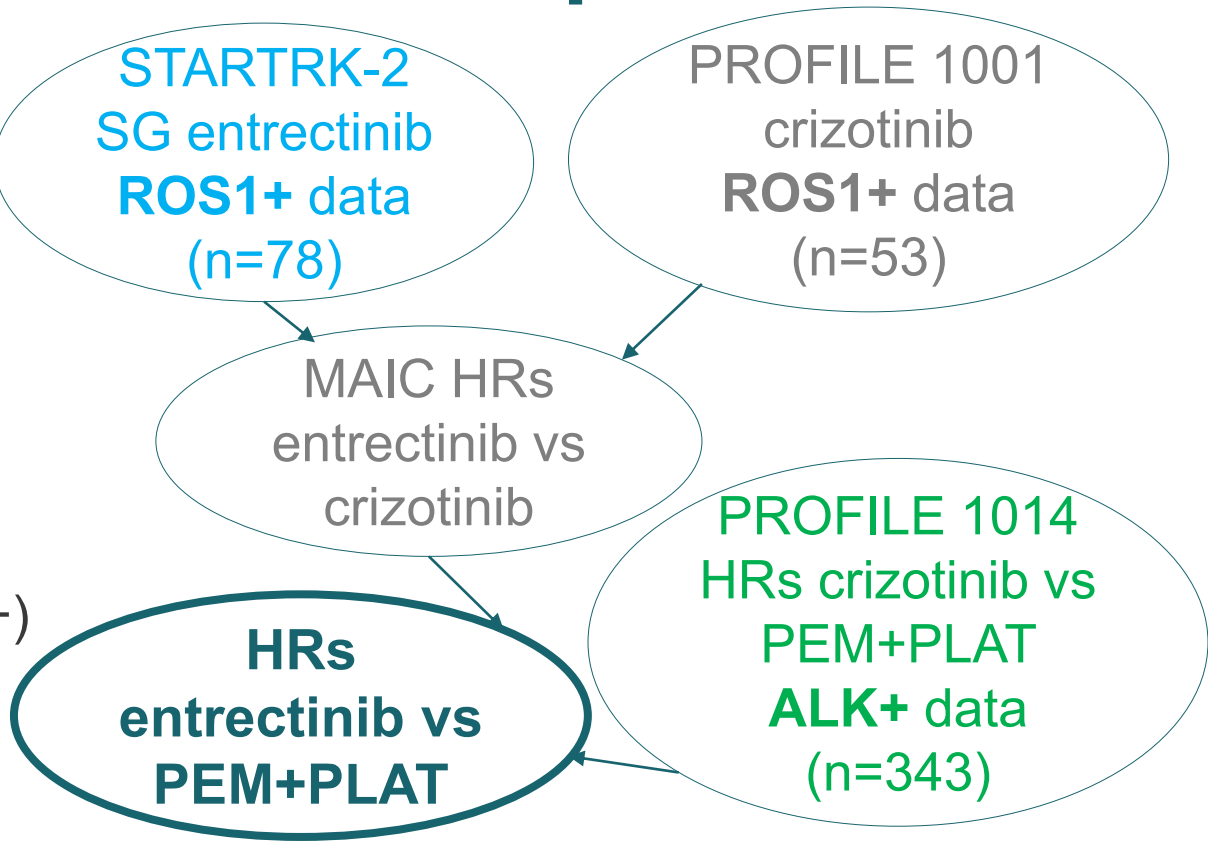
Background:

- both approaches have considerable limitations, mainly due to using evidence from ALK+ NSCLC and due to differences in prior and subsequent treatments used in trials providing indirect evidence

Indirect evidence: entrectinib vs pemetrexed

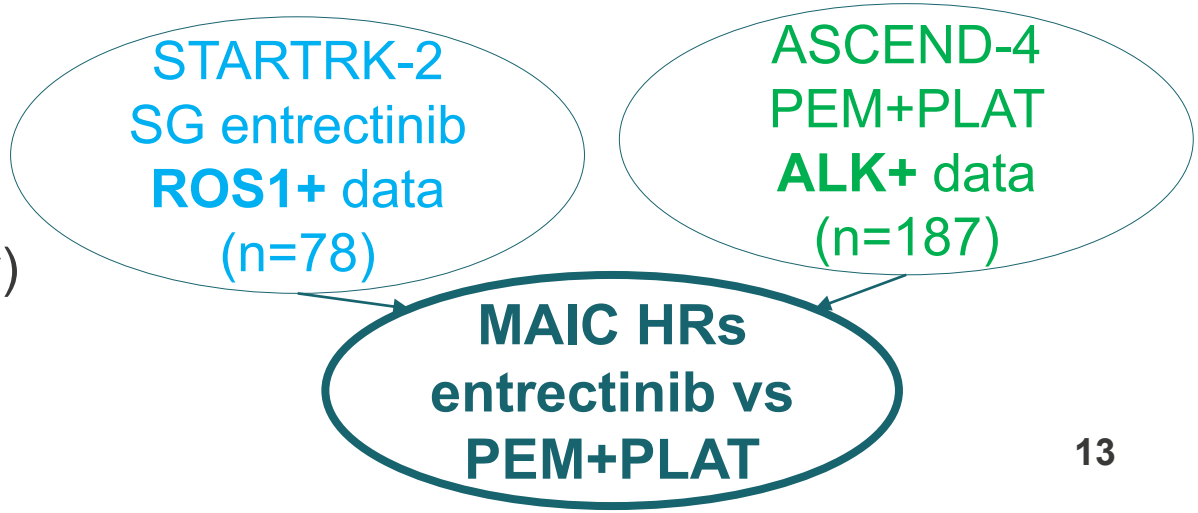
Company preferred:

- Step 1: Matching-adjusted indirect comparison (MAIC) is used to generate a HR for entrectinib vs crizotinib (ROS1+) that is inverted and applied to the entrectinib survival curve.
- Step 2: The HR for crizotinib vs PEM+PLAT from PROFILE 1014 (ALK+) is inverted and applied to the crizotinib survival curve (note study did not have maintenance therapy)



ERG preferred:

- The HR for the PEM+PLAT ALK+ (ASCEND-4 with maintenance therapy) vs entrectinib (STARTRK-2 subgroup) comes directly from the MAIC.



PFS: Entrectinib and PEM+PLAT curves

OS: Entrectinib and PEM+PLAT curves

ERG's and company's approach compared

	ERG (ASCEND-4 MAIC)	Company (PROFILE 1001 MAIC & PROFILE 1014)
Key assumptions	1) Absolute effect of PEM+PLAT is the same for ALK+ and ROS1+ NSCLC.	1) PROFILE 1001 MAIC is a sound basis for estimating crizotinib curves and applying the PROFILE 1014 HRs. 2) Relative effect of crizotinib vs PEM+PLAT is the same for ALK+ and ROS1+ NSCLC.
Population	Both recruited untreated populations which may favour PEM+PLAT.	
Design	Both are multicentre, open-label, RCTs.	
Pemetrexed maintenance	Yes, as per UK clinical practice.	No, doesn't reflect UK clinical practice and may favour entrectinib.
Crossover	46% (to ceritinib)	84% (to crizotinib) in PROFILE 1014
Crossover adjustment	None, likely to favour PEM+PLAT.	Yes, but ERG TA529 deemed the adjustment unfit and used unadjusted OS instead (19% crossover).
Proportional hazards	Not assessed.	HRs are the basis of the company's method and this key assumption does not hold for PFS.
Possible confounding factors	Prior treatment and crossover to ceritinib may overestimate PEM+PLAT relative to entrectinib.	Of applying PROFILE 1014 HRs: unlikely as retains randomisation between crizotinib and PEM+PLAT. Of PROFILE 1001 MAIC: disease stage/ brain metastases - unknown direction.

Entrectinib vs PEM+PLAT results compared

OS, PFS and PPS (undiscounted) using STARTRK-2 subgroup (n=78)

Entrectinib vs PEM+PLAT		ERG (ASCEND-4 MAIC)	Company (PROFILE 1014 HRs)
OS (months)	Mean	[redacted] vs 39.2 ([redacted] gain)	[redacted] vs 15.6 ([redacted] gain)
	Median	[redacted] vs 26.6 ([redacted] gain)	[redacted] vs 10.8 ([redacted] gain)
PFS (months)	Mean	[redacted] vs 11.4 ([redacted] gain)	[redacted] vs 11.7 ([redacted] gain)
	Median	[redacted] vs 7.9 ([redacted] gain)	[redacted] vs 7.9 ([redacted] gain)
PPS (months)	Mean	[redacted] vs 27.78 ([redacted] gain)	[redacted] vs 3.87 ([redacted] gain)
	Median	[redacted] vs 18.7 ([redacted] gain)	[redacted] vs 2.9 ([redacted] gain)

Percentage of patients alive using STARTRK-2 subgroup (n=78)

Years	Entrectinib	PEM+PLAT	
		ERG (ASCEND-4 MAIC)	Company (PROFILE 1014 HRs)
2.0	[redacted]	54.1%	19.9%
4.0	[redacted]	28.1%	3.6%
5.0	[redacted]	20.5%	1.6%
10.0	[redacted]	4.2%	0.0%
15.0	[redacted]	0.8%	0.0%
30.0	[redacted]	0.0%	0.0%

Issue 4: OS and PFS modelling: comments

BTOG-NCRI-ACP-RCP-RCR

- The use of data from ASCEND-4, in principle, is the most appropriate comparator as this study included maintenance pemetrexed.
- However, median OS of PEM+PLAT in ASCEND-4 (26.6 months) is, higher than expected and, this is inevitably due to the crossover of patients on to ceritinib in this study.
- Equally, the median OS of 10.8 months in PROFILE 1014 seems low, even accounting for the absence of maintenance pemetrexed. One would expect the OS in the comparator arm to be in the region of 12-14 months or potentially higher given cross-over onto crizotinib.
- On balance, irrespective of the absolute figures, a survival gain of median [redacted] months (ERG approach) or median [redacted] months (company approach) both seem plausible and the true figure may lie between the two.
- Considering mean OS, survival gain of [redacted] months (ERG approach) seems more likely than survival advantage of [redacted] months (company approach) but both may be plausible.

Clinical expert

- There are arguments for both approaches.
- The survival modelling from the ERG's approach is implausibly high.

Which approach is appropriate for decision making?

Cost effectiveness results

Including PAS for entrectinib and list prices for comparators	ICER
Technical team's base-case before TE (draft TR base-case) • **8** maintenance cycles & **100%** of patients have subsequent treatments	£36,728
Company's post TE base-case: draft TR base-case with company's OS & PFS modelling (4 induction cycles & assuming HRs entrectinib vs crizotinib = 1)	**£21,470**
Technical team's base-case after TE	**£37,910 to £42,572**
Technical team preferred assumptions and: • **4, 6, 8** maintenance cycles & **60%** of patients have subsequent treatments	£42,572 £40,279 £38,304
Technical team preferred assumptions and: • **4, 6, 8** maintenance cycles & **70%** of patients have subsequent treatments	£42,179 £39,885 £37,910
Technical team's base-case with company's OS & PFS modelling and HRs entrectinib vs crizotinib = 1	**£21,607 to £23,457**
Company's approach to OS & PFS and: • **4, 6, 8** maintenance cycles & **60%** of patients have subsequent treatments	£22,978 £21,924 £21,607
Company's approach to OS & PFS and: **4, 6, 8** maintenance cycles & **70%** of patients have subsequent treatments	£23,457 £22,460 £21,623

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Note: results with commercial arrangements will be presented in Part 2

Company's new results: not checked by ERG

- **STARTRK-2 subgroup (n=78) updated results**

Data set	May 2018 (n=78)	Draft SPC (n=94)	May 2019 (n=78)
Patients with response, n (%)	[redacted]	[redacted]	[redacted]
95% CI for response	[redacted]	[redacted]	[redacted]
Median PFS months (95% CI)	[redacted]	[redacted]	[redacted]
Median OS months (95% CI)	[redacted]	[redacted]	[redacted]

	Draft TR results (May 2018 data)		Updated draft TR results (May 2019 data)	
	Entrectinib	PEM+PLAT	Entrectinib	PEM+PLAT
Mean OS	[redacted]	39.21	[redacted]	38.12
Mean PFS	[redacted]	11.43	[redacted]	11.87
Mean PPS	[redacted]	27.78	[redacted]	26.25
Mean ToT	[redacted]	11.43	[redacted]	11.87

	Draft TR (May 2018 data)	Updated draft TR (May 2019 data)
ICER vs PEM+PLAT	£36,728	£33,749
• With company's approach to OS and PFS modelling (company's post TE base-case)		
ICER vs PEM+PLAT	£21,470	£21,023

What is the committee view of the updated results?

Additional areas of uncertainty

Issue	Impact on ICER
The clinical trial evidence is based on a small subgroup (n=78) from a single arm trial	unknown
Because of the small size of the clinical evidence, it was not possible to differentiate between naïve and previously treated patients and so an “all-lines” approach has been used.	STARTRK-2 is more representative of patients treated with entrectinib in second- rather than first-line.
The clinical trial evidence is immature; median overall survival has not been met	unknown
No direct comparative evidence, and no indirect comparative evidence in ROS1-positive advanced NSCLC is available. Indirect comparison with PEM+PLAT has been drawn using data from ALK-positive NSCLC in ASCEND-4 trial (see issue 3).	unknown
Comparative data for specific adverse events used in the economic model are based on unadjusted data from the company’s preferred efficacy set for entrectinib (n = 53) and the PEM+PLAT arm of PROFILE 1014 trial (n = 171).	unknown
No data for PEM+PLAT induction treatment duration is available. The company assumed 6 cycles in its base case and the ERG and technical team assumed 4 cycles.	Assuming 6 cycles as in the company’s approach decreases ICERs slightly.

Issue 10 – Cancer Drugs Fund

Background

- Roche has proactively proposed entry of entrectinib into the CDF
- The technical team considers that entrectinib meets the criteria for inclusion in the Cancer Drugs Fund

Company's comments:

- We acknowledge that there are a number of clinical- and cost-effectiveness uncertainties due to the limited and immature data. Longer-term, comparative data in a larger number of patients with ROS1-positive NSCLC would improve the robustness of the economic evaluation presented and reduce the outstanding uncertainty
- [redacted]
- Other stakeholders: data collection in CDF would be useful

If entrectinib cannot be recommended for routine commissioning due to clinical uncertainty: does it meet criteria for inclusion in CDF?

Key issues

Issue for discussion:

- **Issue 4 – OS and PFS modelling** (slides 12 to 18)
  - Technical team: compared with company's, ERG's approach is more appropriate.

Issues for consideration:

- **Issue 5 – End-of-Life** (slide 11)
  - Technical team: considers that entrectinib meets EoL vs PEM+PLAT.
- **Issue 10 – Cancer Drugs Fund** (slide 22)
  - Technical team: entrectinib meets the criteria for inclusion in CDF.

What is the committee view of technical team's conclusions?