Handout for public: confidential information redacted

Lead team presentation
Crizotinib for ROS1-positive advanced non-small cell lung cancer– STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee C

Lead team: John Hampson, Judith Wardle and Matt Stevenson

ERG: Liverpool Reviews and Implementation Group

NICE technical team: Anwar Jilani, Nicola Hay

12 December 2017

Key issues (1): NICE scope

- Company consider pemetrexed+ platinum as the comparator for first-line and docetaxel for subsequent-line
- Company did not include the following comparators which were stated in the scope
  - First line
    - Third generation chemotherapy plus platinum (cisplatin/carboplatin)
    - Single agent chemotherapy (with 3rd generation for platinum intolerant)
    - Pemetrexed maintenance
  - Second line
    - Docetaxel plus nintedanib
    - Best supportive care

Is it appropriate for the company to exclude these comparators?

Key issues (2): Testing for ROS1

- How is ROS 1 tested in practice?
- Potential testing scenarios
  - all patients with non-squamous NSCLC will be tested for ROS1 upfront alongside EGFR and ALK,
  - also explored sequential testing i.e. ROS1 tested only in those tested negative for EGFR and ALK.

Which strategy is more likely to happen in clinical practice?

Key issues (3): ALK+ as a proxy for ROS1

- Is it appropriate for the company to use outcome data from patients with ALK-positive advanced NSCLC as a proxy for the outcome data of patients with ROS1-positive advanced NSCLC?
- Are the result from PROFILE 1014 and 1007 reliable?
  - Pemetrexed + platinum (for untreated) and docetaxel + nintedanib (for treated) are standard of care in NHS for adenocarcinoma (non-squamous NSCLC) . Only 43.4% of patients in comparator arm received pemetrexed + platinum in the first-line crizotinib trial (in ALK+ NSCLC) while none of the patients received docetaxel + nintedanib in the subsequent-line trial.
  - Substantial patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both trials

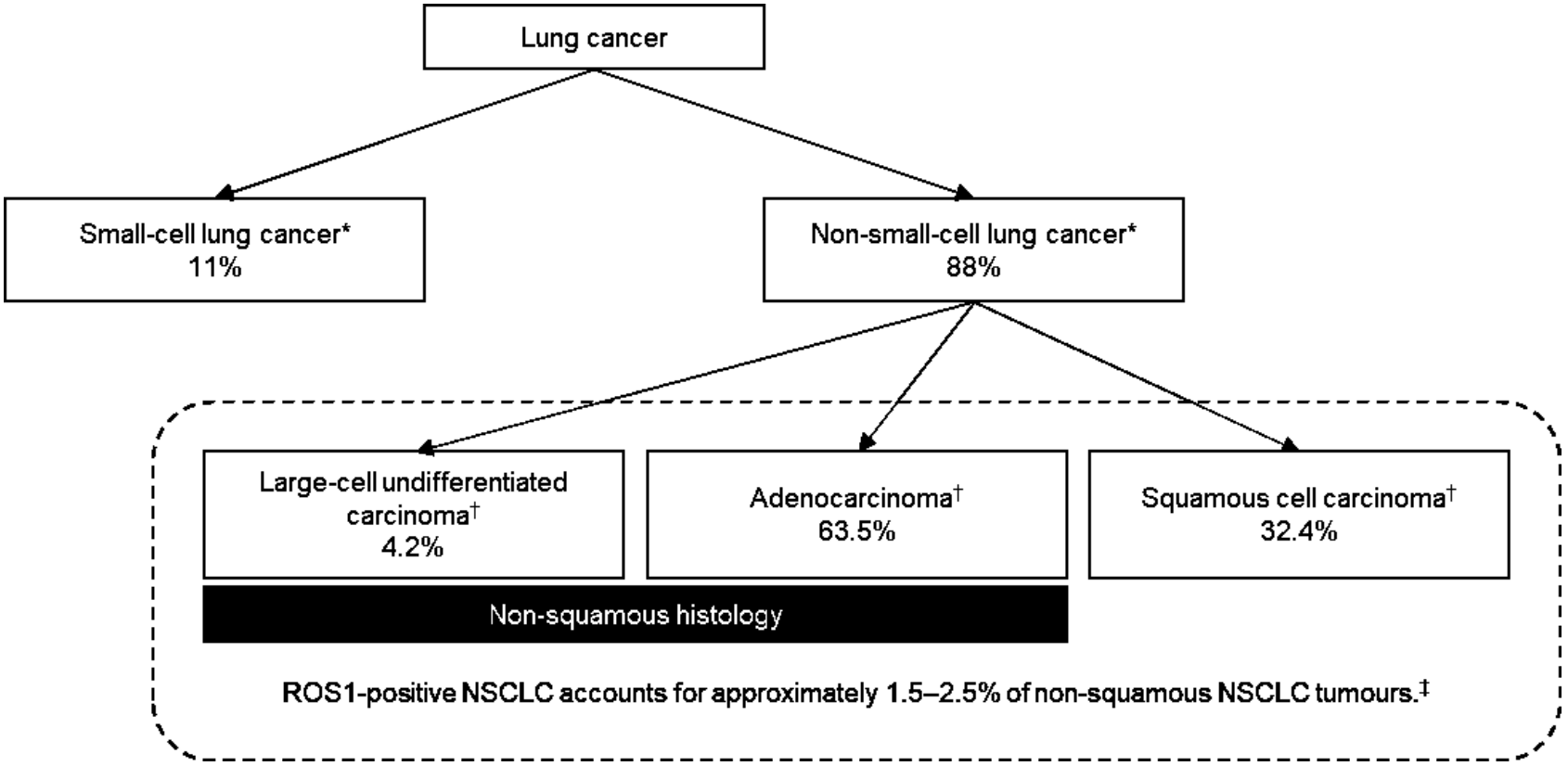
Key issues (4): Clinical effectiveness

- How robust are the PFS data from PROFILE 1014 and 1007?
  - ERG concluded that the proportional hazards assumption was not valid for PFS, and that the hazard ratios for PFS data from both trials should be interpreted with caution
- How robust is the OS data from PROFILE 1001, 1014 and 1007?
  - OS data from PROFILE 1001 were immature, with only 30% of patients having died at the latest data cut-off date (2014)
  - ERG considers the **RPSFTM-adjusted hazard ratios for OS in PROFILE 1014** are unlikely to be valid and **should be interpreted with caution**
  - ERG considers the **PFS hazard ratio in PROFILE 1001** is likely to be closer to the true OS hazard ratio than the RPSFTM-adjusted OS hazard ratio. However, the ERG also noted that the true OS hazard ratio may still be less than the PFS hazard ratio, and that **the company's hazard ratio for "crossover-adjusted" OS should be interpreted with caution**

Crizotinib (Xalkori, Pfizer)

Mechanism of action		Tyrosine kinase inhibitor, inhibits ROS 1 proto-oncogene receptor tyrosine kinase (and anaplastic lymphoma kinase [ALK]) which leads to inhibition of tumour cell growth.
Administration and dosage		Oral 250 mg twice daily (a total of 500 mg daily)
Marketing authorisation	**New (subject of this appraisal)**	• On 25th August 2017: *'for the treatment of adults with ROS1-positive advanced NSCLC.'*
	Existing licensed indications	• first-line treatment of ALK-positive advanced NSCLC (November 2015) recommended in NICE TA 406 • for the previously treated ALK-positive advanced NSCLC (October 2012) recommended in NICE TA 422
Companion diagnostic		Accurate and validated assay for either ROS1 or ALK
List price		£4,689.00 for 60 capsules of 200 mg or 250 mg
PAS discount		simple discount (magnitude: commercial in confidence)

ROS1-positive advanced NSCLC

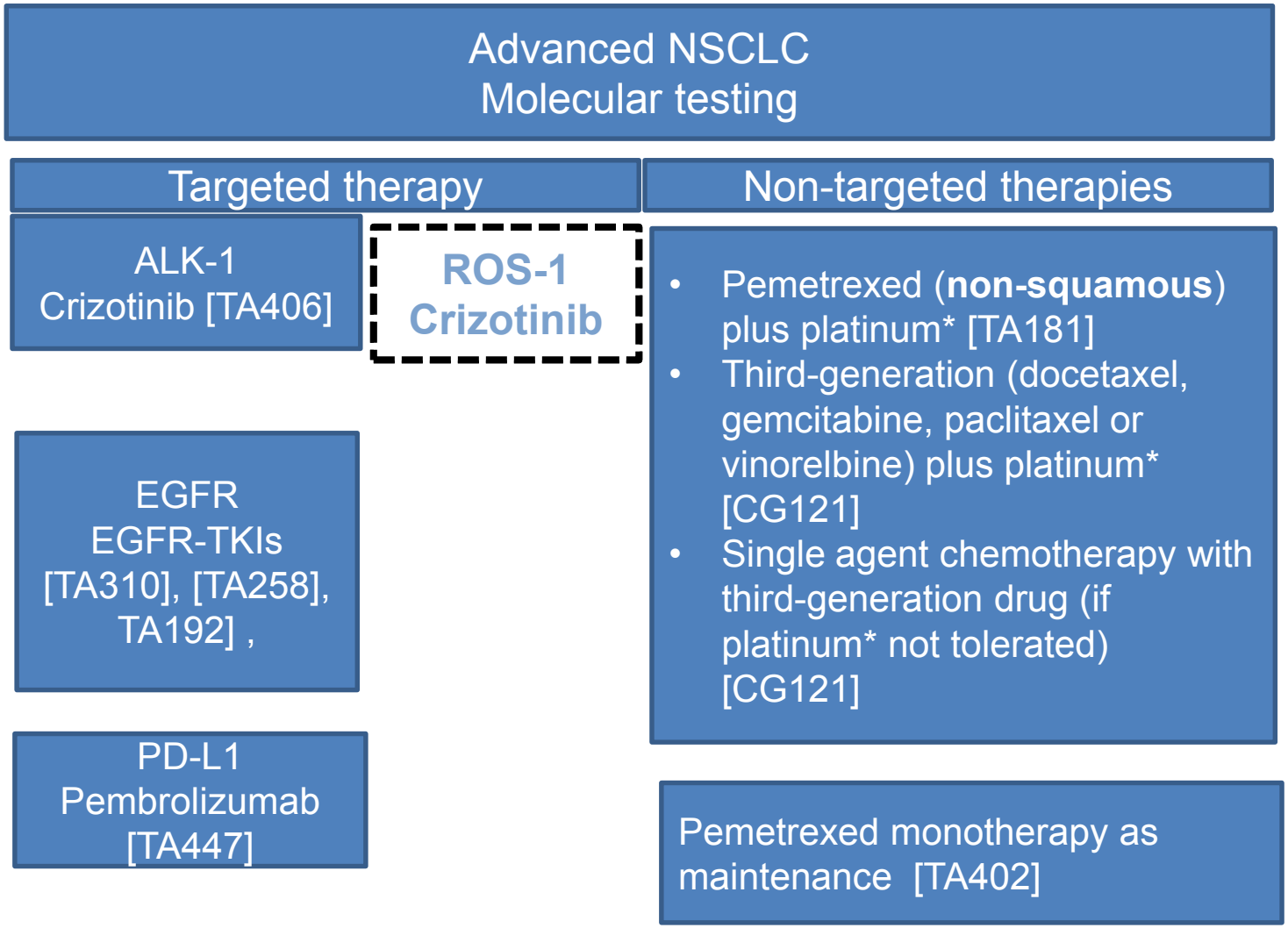


* National Lung Cancer Audit Report (2016) for England and Wales
† Clinical Lung Cancer Genomics Project (2013)
‡ Clavé et. Al (2016), Scheffler et al. (2015) and Takeuchi et al. (2012)

ROS1-positive advanced NSCLC

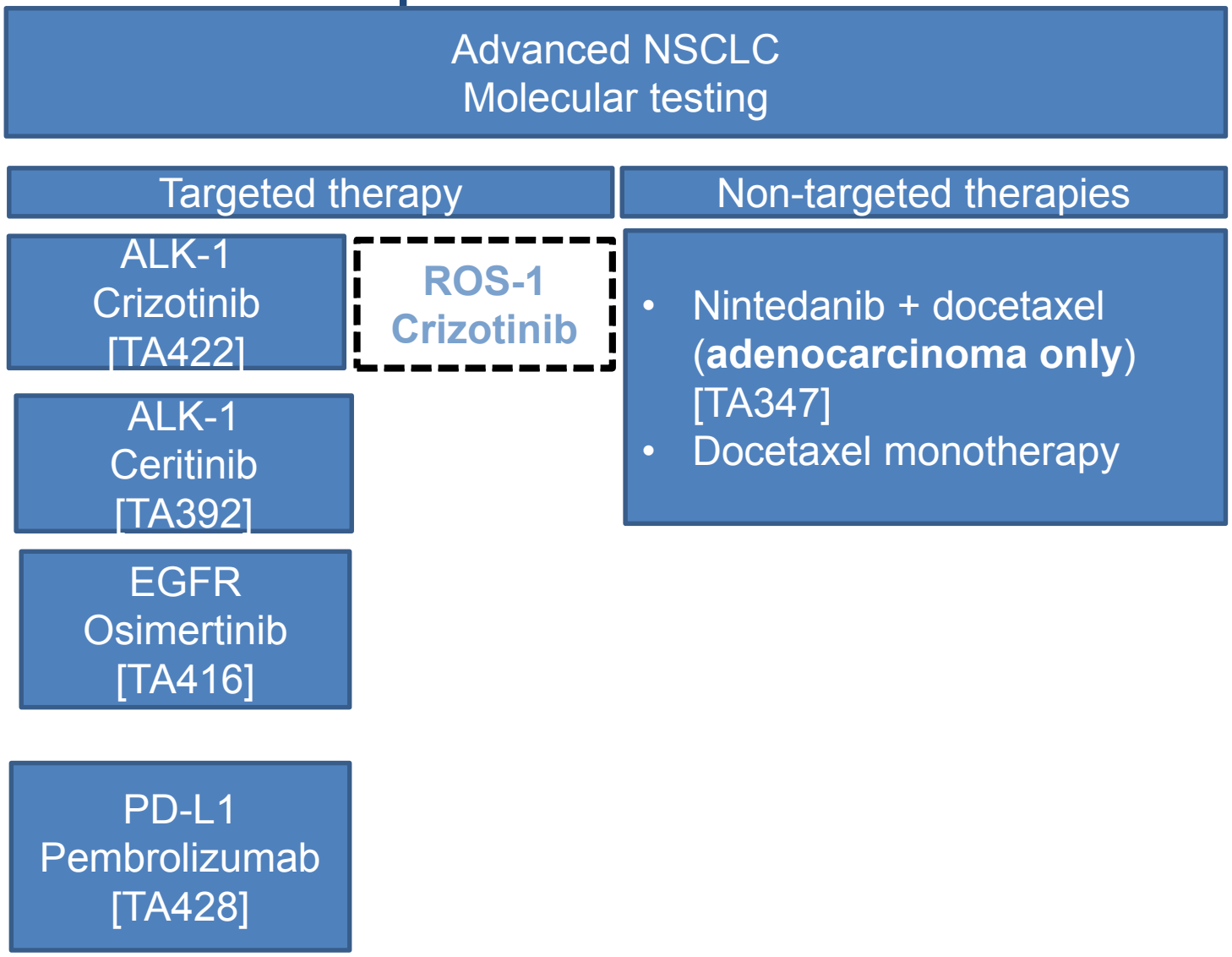
- ROS1-positivity occurs in only 1.1–1.8% of NSCLC patients
  - exclusively in **non-squamous tumours**
  - predominantly in **adenocarcinoma** tumour types
- ROS1 is mutually exclusive to other oncogenic markers such as ALK or EGFR or KRAS
- Similar to ALK-positive NSCLC, ROS1-positive NSCLC is more prevalent among
  - **younger patients , never-smokers**
- Diagnostic testing for ROS1-positivity is not established
- Patients with ROS1-positive advanced NSCLC do not have access to any targeted therapy
- Estimated number of patients with ROS1-positive advanced NSCLC in England and Wales
  - Company 289, ERG 307

Treatment Pathway
First-line treatment



*platinum: carboplatin/cisplatin

Treatment Pathway
Subsequent treatment



Clinical aspects

- Crizotinib is taken orally, therefore resource saving in terms of clinician, pharmacy, nursing, day unit time and radiology time.
- **Innovation**: represents a first in class targeted therapy for patients with ROS 1 – positive NSCLC.
- Received “breakthrough therapy designation” and was granted “priority review” by the FDA.
- EMA approved crizotinib for ROS 1 positive NSCLC based on the strength of a single arm study.
- ROS 1 is not routinely tested. No provision for ROS 1 directed therapies in the NHS at present.

Impact on Patients and Carers

- People with advanced or metastatic NSCLC often debilitated by multiple and distressing symptoms, e.g. breathlessness, difficult to manage
- Recent addition of targeted therapies and immunotherapy has given active treatment options: availability of new targets & therapy choices important
- Since outlook for these patients is poor, improved QoL and even small extension of life is significant for patients & family

Patient/carer views on Crizotinib

- Crizotinib has been standard practice for ALK+ patients for some time so side effect profile well known.
- Wide range of side effects, but all appear to be well tolerated, especially compared with standard cytotoxic therapies
- Diagnostic testing ensures segmentation of therapy
- Patient group highlights importance of End of Life considerations for these patients

Decision Problem: Scope (1)

	Scope	Company's decision problem and Justification
Comparator	**Untreated:** • Chemotherapy* plus platinum** For people with non-squamous NSCLC only • Chemotherapy* plus platinum** with pemetrexed maintenance treatment For people with adenocarcinoma or large cell carcinoma (non-squamous cell) only • Pemetrexed plus platinum** • Pemetrexed plus platinum with pemetrexed maintenance (if received first-line cisplatin) For people who cannot tolerate platinum • Single agent chemotherapy*	No data for effectiveness of comparators available in people with ROS1 positive NSCLC • For comparison company extrapolated data from patient with ALK positive NSCLC for pemetrexed+ platinum** **Excluded** • **Pemetrexed maintenance** (rationale: only small proportion [~15%] being eligible and insufficient evidence) • **Chemotherapy* plus platinum**** (rationale: clinical opinion against use in non-squamous NSCLC) • **Single agent chemotherapy with third generation for platinum intolerant** (rationale: unavailability of evidence)

- *chemotherapy: (docetaxel, gemcitabine, paclitaxel or vinorelbine)
- **platinum: carboplatin/cisplatin

Decision Problem: Scope (2)

	Scope	Company's decision problem and justification
Comparator	**Treated**: • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	Docetaxel monotherapy **Excluded** (rationale: unavailability of evidence) • **Docetaxel with nintedanib** (for adenocarcinoma histology) • **Best supportive care**

ERG agreed with company's rationale for excluding the comparators specified in the scope

PROFILE1001 (pivotal trial)

Study design	single-arm, open-label, phase 1 study
Location	8 locations across US, Australia and South Korea
Population	People with ROS1+ locally advanced or metastatic NSCLC N=53, 7 untreated and 46 had at least 1 prior chemotherapy 3 ALK-negative patients were included when retrospectively identified to be ROS1+ 2 patients retrospectively determined to be ROS1-negative
Intervention	250 mg of crizotinib twice daily until disease progression
Primary outcome	objective response rate (ORR): % of patients with complete or partial response (CR or PR) according to RECIST v1.0/v1.1*
Secondary outcome	disease control rate (DCR) at weeks 8 and 16, duration of response (DR), time to tumour response (TTR), progression-free survival (PFS), time to progression (TTP), time to treatment failure (TTF), overall survival (OS), safety
Duration	Recruitment: October 2010 to September 2013 Data cut-off: 30 November 2014/24 June 2014 * Median follow-up: 25.4 months

*for 3 patients who retrospectively identified as ROS1 positive

PROFILE 1014 (NCT01154140)

Study design	Randomised, open-label, active-controlled, cross-over, phase III study
Location	251 locations across USA, Canada, Mexico, Australia, Asia, Europe (9 UK sites) South America and South Africa
Population	Adults with ALK+ locally advanced or metastatic non-squamous NSCLC who had not had any treatment for advanced disease (n=343)
Intervention	250 mg of crizotinib twice daily (n=172) Patients allowed to continue crizotinib beyond RECIST-defined PD, at investigator's discretion
Comparator	pemetrexed, 500 mg/m^2, plus platinum-based therapy (cisplatin, 75 mg/m^2, or carboplatin, target AUC of 5–6 mg/mL/min); iv every 3 weeks for a maximum of 6 cycles (n=171)
Primary outcome	Progression-free survival: duration from randomisation to disease progression according to RECIST v1.1 (as by independent radiological review) or death
Secondary outcome	overall survival (OS), time to treatment failure (TTF), safety , health-related quality of life (EQ-5D)

PROFILE 1007 (NCT00932893)

Study design	Randomised, open-label, active-controlled, cross-over, phase III study
Location	North America, Australia, Brazil, China, Japan, Korea, Taiwan, Hong Kong and Europe (9 UK sites)
Population	People with ALK+ locally advanced or metastatic NSCLC that progressed after 1 platinum based therapy and considered eligible for additional chemotherapy
Intervention	250 mg of crizotinib twice daily (n=173)
Comparator	docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 (n=174)
Primary outcome	Progression-free survival: duration from randomisation to disease progression according to RECIST v1.0
Secondary outcome	overall survival (OS), time to treatment failure (TTF), safety , health-related quality of life (EQ-5D)

ERG's critique: design of studies

- PROFILE 1001,1014 and 1007 trials were generally well designed and well conducted
- PROFILE 1001
  - Population in the study matches the patient population specified in the final scope issued by NICE
  - Clinical advice to the ERG suggests that the eligibility criteria used in PROFILE 1001 are appropriate
  - Main limitations of the study are:
    - Small sample size (n=53)
    - no comparator arm to provide direct evidence of the effectiveness of crizotinib in comparison to a relevant comparator in the patient population of interest

Base-line characteristics (1)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Age (years): median, (min, max)		55 (25–81)	52.0 (22–76)	54 (19–78)	51 (22–81)	49 (24–85)
Category (years) – no. (%)	<65	38 (71.7)	[redacted]	[redacted]	146 (84.4)	[redacted]
	≥65	15 (28.3)	[redacted]	[redacted]	27 (15.6)	[redacted]
Sex – no. (%)	Male	23 (43.4)	68 (39.5)	63 (36.8)	75 (43.4)	78 (44.8)
	Female	30 (56.6)	104 (60.5)	108 (63.2)	98 (56.6)	96 (55.2)
Race – no. (%)	White	30 (56.6)	91 (52.9)	85 (49.7)	90 (52.0)	91 (52.3)
	Black	2 (3.8)	[redacted]	[redacted]	2 (1.2)	3 (1.7)
	Asian	21 (39.6)	77 (44.8)	80 (46.8)	79 (45.7)	78 (44.8)
	Other	NR	4 (2.3)	2 (1.2)	2 (1.2)	2 (1.2)
Weight (kg)	Mean (SD)	71.9 (16.0)	[redacted]	[redacted]	65.3 (17.3)	[redacted]
	Median (range)	70.0 (48.0-106.3)	[redacted]	62.5 (35.8–151.6)[a]	62.0 (35.2-160.0)	[redacted]

a: One person's weight incorrectly reported as 151.6kg instead of 151.6 pounds

Base-line characteristics (2)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
ECOG performance status	0	23 (43.4)	[redacted]	[redacted]	72 (41.6)	65 (37.4)
	1	29 (54.7)	[redacted]	[redacted]	84 (48.6)	95 (54.6)
	2	1 (1.9)	9 (5.2)	[redacted]	16 (9.2)	14 (8.0)
Smoking status – no. (%)	Never smoker	40 (75.5)	106 (61.6)	112 (65.5)	108 (62.4)	111 (63.8%)
	Ex-smoker	13 (24.5)	56 (32.6)	54 (31.6)	59 (34.1)	54 (31.0%)
	Current smoker	NR	10 (5.8)	5 (2.9)	5 (2.9)	9 (5.2%)
Histological classification – no. (%)	Adenocarcinoma	51 (96.2)	158 (91.9)	159 (93.0)	163 (94.2)	160 (92.0%)
	Non-adenocarcinoma	2 (3.8)	14 (8.1)	12 (7.0)	9 (5.2)	14 (8.0)
Prior radiation therapies – no. (%)	No	34 (64.2)	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	19 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]

b Two patients in the crizotinib group did not report their prior radiation therapy status

ERG's critique: baseline characteristics (1)

- ERG stated that there were no important differences in baseline characteristics between the treatment arms in PROFILE 1014 and PROFILE 1007.
- ERG commented that the following 2 assumptions must hold if the company's approach is to be valid, that is, using results from PROFILE 1014 and PROFILE 1007 to estimate effectiveness of crizotinib for ROS1-positive advanced NSCLC (first-line and subsequent-line):
  1. ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations must be comparable in terms of baseline characteristics
  2. Patients recruited to the ALK-positive advanced NSCLC trials must be representative of the ALK-positive advanced NSCLC patient population (and consequently the ROS1-positive advanced NSCLC patient population, if assumption 1 holds) that would be seen in NHS clinical practice

ERG's critique: baseline characteristics (2)

- For assumption 1, clinical advice to the ERG suggested that ROS1-positive advanced NSCLC and ALK-positive advanced NSCLC patient populations are comparable in terms of baseline characteristics
- For assumption 2, as noted in the development of TA406, patients in PROFILE 1014 tended to be younger than patients seen in clinical practice. However, clinical advice to the ERG suggested that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS

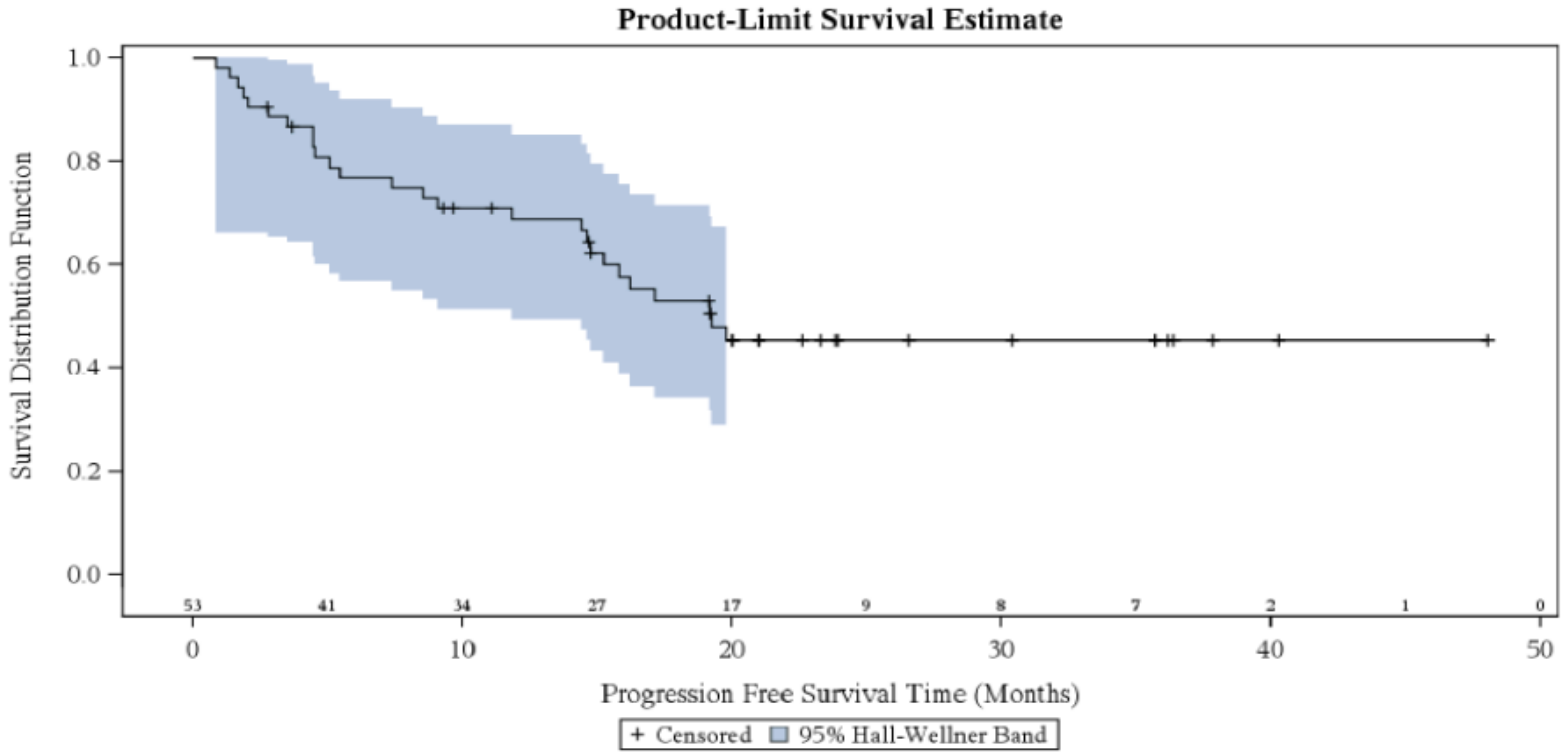
ERG's critique: baseline characteristics (3)

- PROFILE 1001
  - Of the patients who had received previous treatment, 37% had not received treatment with pemetrexed + platinum in the first-line setting; which is the standard first-line treatment for adenocarcinoma histology
- PROFILE 1007
  - 56.6% of patients did not receive treatment with pemetrexed + platinum in the first-line setting
  - No patients received treatment with docetaxel + nintedanib in the second line setting (NHS standard care)

Results (PROFILE 1001)

Outcome		Result
Objective response rate (ORR) investigator (n=53)	ORR (%) (95% CI)	37 (69.8 [55.7 to 81.7])
	Complete response (%)	5 (9.4)
	Partial response (%)	32 (60.4)
	Stable Disease (≥6 weeks) (%)	11 (20.8)
	Progressive Disease (%)	3 (5.7)
	Early death (%)	1 (1.9)
	Indeterminate (%)	1 (1.9)
Overall survival	Median months	NR
	HR (95% CI, p-value)	N/A
	Probability of survival at 6 months (95% CI)	90.6% (78.8 to 96.0)
	Probability of survival at 12 months (95% CI)	79.0% (65.3 to 87.8)
	Median duration of follow up months (95% CI)	25.4 (22.5 to 28.5)

Progression-free survival (PROFILE 1001)

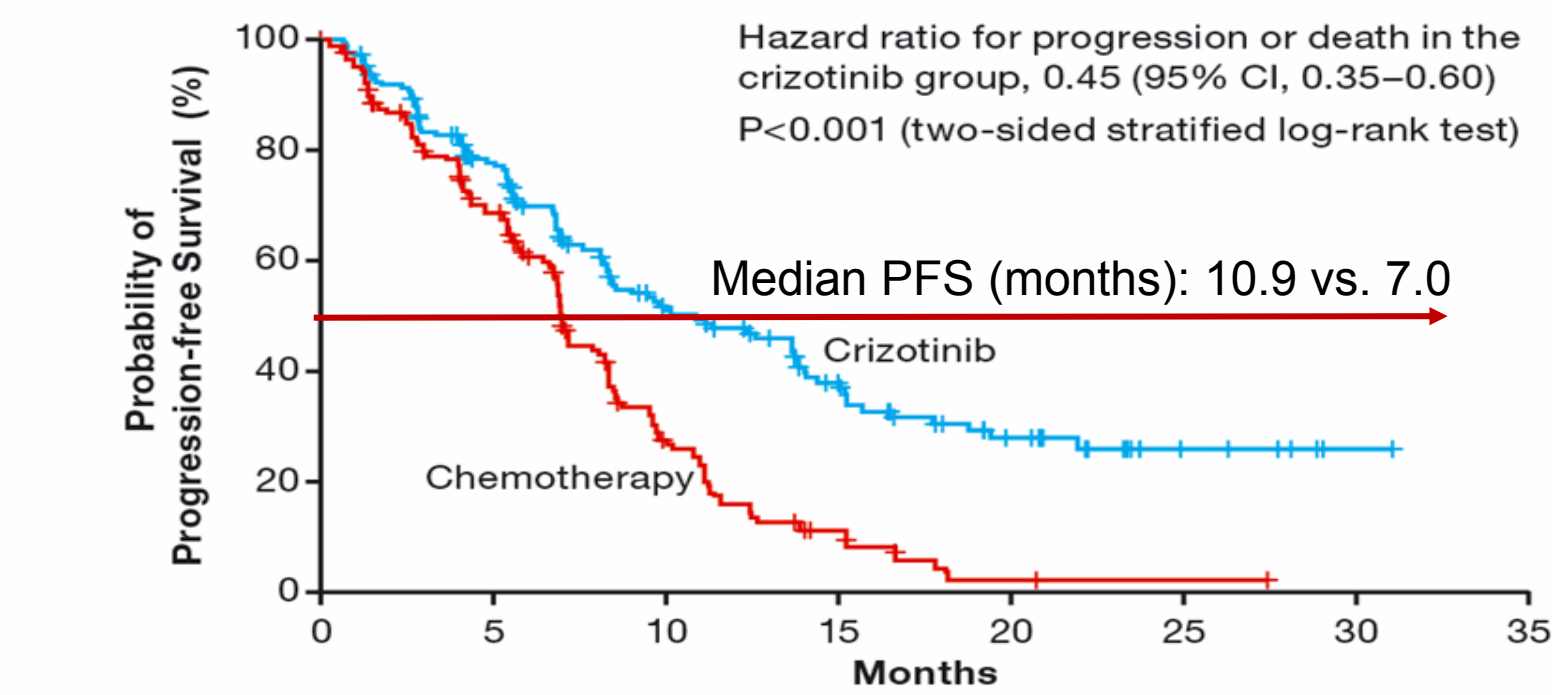


Progression free survival	Patients with event (%)	26 (49.1)
	Median months (95% CI)	**19.3** (14.8 to NR)
Time to Tumour Progression	Patients with event (%)	23 (43.4)
	Median months (95% CI)	**19.8** (15.2 to NR)

Results (PROFILE 1014 & 1007)

Outcome	PROFILE 1014 (N=347)	PROFILE 1007 (N=343)
Median PFS		
Crizotinib, months (95% CI)	10.9 (8.3 to 13.9)	7.7 (6.0 to 8.8)
Chemotherapy, months (95% CI)	7.0 (6.8 to 8.2)	3.0 (2.6 to 4.3)
HR, (95% CI; p-value)	0.45 (0.35 to 0.60; p<0.001)	0.487 (0.371 to 0.638; p<0.0001)
Patients who crossed-over		
Crizotinib	33/172 (19.2%)	39/173 (22.5%)
Chemotherapy	[redacted]	151/174 (86.8%)
ORR		
Crizotinib, no. of patients (%) [95%	128 (74.4 [67.2 to 80.8])	112 (65.3 [57.7 to 72.4])
Chemotherapy, no. of patients (%) [95% CI]	77 (45 [37 to 53])	34 (19.5 [13.9 to 26.2])
Median OS		
Crizotinib, months (95% CI)	[redacted]	21.7 (18.9 to 30.5)
Chemotherapy, months (95% CI)	[redacted]	21.9 (16.8 to 26.0)
Unadjusted HR, (95% CI, p-value)	[redacted]	0.854 (0.66 to 1.10; p=0.11)
Crossover adjusted HR, (95% CI, p-value)	[redacted]	0.49 (0.37 to 0.64)

Progression-free survival in patients with untreated ALK-positive disease (PROFILE 1014)



No. at Risk

Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

Overall survival in patients with previously treated ALK-positive disease (PROFILE 1007)

ERG's critique (1) results from PROFILE 1001, 1014 and 1007

- **PROFILE 1001**
  - OS data were immature, with only 30% of patients having died at the latest data cut-off date (2014)
    - The ERG stated that there was no robust OS data available for patients with ROS1-positive advanced NSCLC
  - No HRQoL data were collected during the study
- **PROFILE 1014 and 1007**: The ERG concluded that the proportional hazards assumption was not valid for PFS, and that the hazard ratios for PFS data from both trials should be interpreted with caution
- Median PFS varied across **PROFILE 1001, 1014 and 1007**. ERG stated that the variation in PFS brings into question the comparability of the ALK-positive and ROS1-positive patient populations

ERG's critique (2) adjusting for cross over PROFILE 1014 and 1007

- ERG considered the RPSFTM-adjusted hazard ratios for OS in PROFILE 1014 was unlikely to be valid and should be interpreted with caution
- For the PROFILE 1007 trial, company presented the PFS hazard ratio as a proxy for the true OS hazard ratio, instead of using the RPSFTM-adjusted OS hazard ratio.
  - ERG considered the PFS hazard ratio to be most likely closer to the true OS hazard ratio than the RPSFTM-adjusted OS hazard ratio.
  - However, the ERG also noted that the true OS hazard ratio may still be less than the PFS hazard ratio, and that the company's hazard ratio for "crossover-adjusted" OS should be interpreted with caution
- The ERG stated that there are no reliable OS data available from either PROFILE 1014 or 1007 to support treatment with crizotinib

Common treatment related adverse events (PROFILE 1001)

AEs	% patients experiencing
Vision disorder	84.9
Nausea	49.1
Oedema	45.3
Diarrhoea	41.5
Vomiting	37.7
Constipation	34
Elevated aminotransferases	30.2

AEs	% patients experiencing
Bradycardia	20.8
Dysgeusia	18.9
Dizziness	18.9
Fatigue	18.9
Hypophosphataemia	15.1
Rash	13.2
Neutropenia	13.2
Decreased appetite	11.3
Neuropathy	9.4

Treatment related grade 3 or 4 adverse event (PROFILE 1001)

Grade 3 or 4 adverse event	Crizotinib (N=53) No. of patients (%)
Hypophosphatemia	7 (13.2)
Neutropenia	5 (9.4)
Vomiting	1 (1.9)
Electrocardiogram QT prolonged	1 (1.9)
Elevated transaminases	2 (3.8)
Total	16 (30.2)

Extrapolating ALK+ data to ROS1+ (1) Company's view

- ROS1+ and ALK+ advanced NSCLC are similar in terms of
  - structure of their receptor tyrosine kinases: kinase domains for both have 77% common amino acids within the ATP-binding site (where crizotinib binds)
  - in clinical behaviour, including response to crizotinib
  - patient characteristics (tend to be non-smokers and younger than unselected NSCLC)
  - Histology (predominantly adenocarcinoma)
- European Medicines Agency (EMA) recognised the generalisability of data from ALK+ to the ROS1+
- 12 UK clinical experts from a company sponsored advisory board supported generalisability of clinical effectiveness data from ALK+ to ROS1+ patients
  - during clarification, company reconfirmed it with a targeted mutation specialist clinician
- RCT of crizotinib in ROS1+ is unlikely, given the small number of ROS1+ and the clinical efficacy from PROFILE 1001, clinical equipoise is not feasible, therefore, unethical to conduct an RCT

Extrapolating ALK+ data to ROS1+ (2)
ERG's view

- ERG accepts the company's view that biological and clinical similarities exist between ROS1+ and ALK+ advanced NSCLC and that there are similarities between patients with ROS1+ and ALK+ advanced NSCLC
- Clinical advice to the ERG
  - uncertain if the currently documented similarities between ROS1+ and ALK+ will be supported as more patients with ROS1+ are identified
  - small number of ROS1+ patients so far identified does not allow robust comparisons between the outcomes from patients with ROS1+ and ALK+ treated with crizotinib

Extrapolating ALK+ data to ROS1+ (3)
Clinical expert's view

- ROS1+ NSCLC would behave in a similar manner as ALK+ NSCLC.
  - Both tend to present with metastatic disease, at a younger age than average NSCLC, and usually in never-smokers
  - Both have similar symptoms and distribution of disease at presentation
  - Both respond very well to crizotinib with rapid durable responses
  - Quality of life is markedly improved in both ROS1 and ALK+ NSCLC with crizotinib to near baseline/premorbid status

"My clinical experience is of ROS1+ patients gaining similar benefit of crizotinib as ALK+ patients and markedly superior to chemotherapy. Given the marked rarity of the ROS1 genotype it would be reasonable to generalize outcomes for the ROS1+ NSCLC group from that of the ALK+ group"

Key issues (1): NICE scope

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- Company did not include following comparators which were stated in the scope
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    - Docetaxel plus nintedanib
    - Best supportive care

Is it appropriate for the company to exclude these comparators?

Key issues (2): Testing for ROS1

- How is ROS 1 tested in practice?
- Potential testing scenarios
  - all patients with non-squamous NSCLC will be tested for ROS1 upfront alongside EGFR and ALK,
  - also explored sequential testing i.e. ROS1 tested only in those tested negative for EGFR and ALK.

Which strategy is more likely to happen in clinical practice?

Key issues (3): ALK+ as a proxy for ROS1

- Is it appropriate for the company to use outcome data from patients with ALK-positive advanced NSCLC as a proxy for the outcome data of patients with ROS1-positive advanced NSCLC?
- Are the result from PROFILE 1014 and 1007 reliable?
  - Pemetrexed + platinum (for untreated) and docetaxel + nintedanib (for treated) are standard of care in NHS for adenocarcinoma (non-squamous NSCLC) and in trial for first-line crizotinib (in ALK+ NSCLC) only 43.4% of patients in comparator arm received pemetrexed + platinum while none of the patients received docetaxel + nintedanib in trial of crizotinib for subsequent-lines.
  - Substantial patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both trials

Key issues (4): Clinical effectiveness

- How robust are the PFS data from PROFILE 1014 and 1007?
  - ERG concluded that the proportional hazards assumption was not valid for PFS, and that the hazard ratios for PFS data from both trials should be interpreted with caution
- How robust is the OS data from PROFILE 1001, 1014 and 1007?
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  - ERG considers the **RPSFTM-adjusted hazard ratios for OS in PROFILE 1014** are unlikely to be valid and **should be interpreted with caution**
  - ERG considers the **PFS hazard ratio in PROFILE 1001** is likely to be closer to the true OS hazard ratio than the RPSFTM-adjusted OS hazard ratio. However, the ERG also noted that the true OS hazard ratio may still be less than the PFS hazard ratio, and that the company's hazard ratio for "crossover-adjusted" **OS should be interpreted with caution**

Lead team presentation Crizotinib for ROS1+ advanced non-small cell lung cancer– STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee C

Lead team: John Hampson, Judith Wardle and Matt Stevenson

ERG: Liverpool Reviews and Implementation Group

NICE technical team: Anwar Jilani, Nicola Hay

12 December 2017

Key issues (1): Cost effectiveness

- Is the company's economic model appropriate for determining the cost effectiveness of crizotinib for ROS1+ advanced non-small cell lung cancer?
  - The evidence underpinning the base case first- and subsequent-line models is from a proxy population (ALK+ advanced NSCLC) rather than the population of interest (ROS1+ advanced NSCLC). ERG stated that the impact of this assumption on cost effectiveness estimates is unknown, since the evidence for the ROS1+ advanced NSCLC population is severely limited
- How appropriate are the assumptions in the company's economic model?
  - ERG stated that the company submission relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296) and company has not provided sufficient justification for use of these assumptions and approaches, except that they were previously accepted.
  - ERG was unable to investigate the effects of specific key assumptions in the model as a result of the limited functionality of the model

Key issues (2): Cost effectiveness

- How robust are the company's estimates of post progression survival ?
  - Estimates of post progression survival gain in the first- and subsequent-line base cases are substantially greater than estimates of progression-free survival gain. This means that treatment effect on overall survival is greater than treatment effect on progression-free survival, which the ERG does not consider to be supported by the evidence available
- ERG explored 2 additional scenarios for overall survival modelling
  - assuming continued treatment effect on survival (as seen in pre-progression stage) after progression
  - assuming no benefit of crizotinib after progression

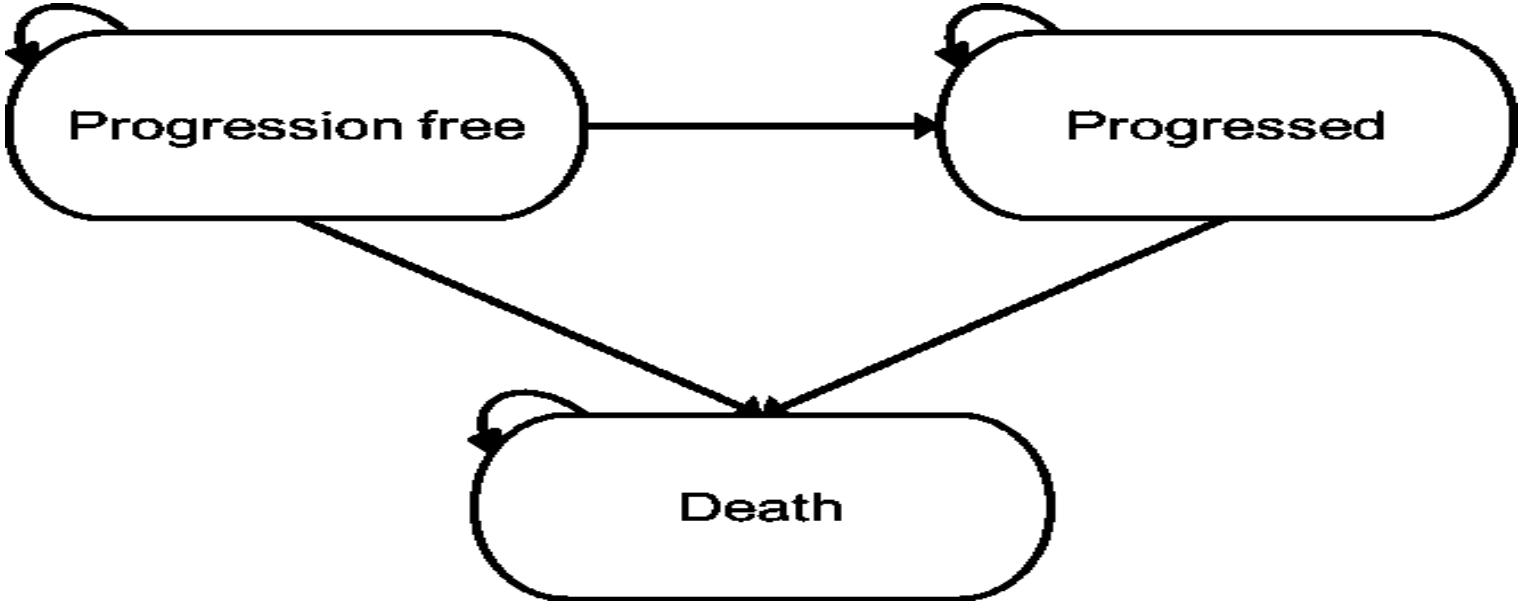
  Which is the committee's preferred method?
- How robust are the company's progression-free survival utility values?
  - For patients who received treatment with pemetrexed + platinum in the first-line model?
    - ERG was concerned that the progression-free survival utility value may not be representative of the whole time that these patients spend in the progression-free state, as it is based on EQ-5D responses collected only whilst patients are on treatment

Key issues (3): Cost effectiveness

- How robust is the company's PROFILE 1001 scenario analysis?
  - The ERG stated that estimates of overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTTD) were based on parametric models with low levels of face validity and clinical plausibility
- What are the most plausible ICERs for crizotinib for treating ROS1+ advanced NSCLC?

Model structure

- Partition survival model
- Based on the models considered in previous appraisals for crizotinib in ALK+ NSCLC (TA406 and TA422)
- Same structure for first- and subsequent-line treatment with crizotinib
- 3 health states: PFS, progressed disease (PD) and death
- Cycle length: 30-day with half-cycle correction
- Time horizon 20 years, costs and benefits are discounted at a rate of 3.5% per annum, NHS and personal social services perspective



The conceptual model

- Patients begin in PFS are at risk of progression or death
- Patients in PD are at risk of death
- PFS was associated with a higher quality of life than the PD
- For the crizotinib treatment arm, patients in PD who continue to receive crizotinib were assumed to have the same quality of life as those in PFS
  - The PD value is used once crizotinib treatment is discontinued

Model Population

- Clinical advisors to company suggested that patients in clinical practice may be less healthy and 5 to 10 years older (TA406)
  - Patients from a retrospective real-world, Western, cohort study conducted by Davis et al. (2015) considered to be more representative of patients seen in UK clinical practice
- Company conducted an analysis of key covariates by fitting Cox regression models to the patient-level trial data and evaluated the effect of each of these factors on PFS and OS
- The company used parametric curves (OS, PFS and TTTD) adjusted for the following patient characteristics in order to match Davis et al. (2015)
  - Race [Asian vs. non-Asian]
  - Eastern Cooperative Oncology Group [ECOG] status [2 vs. 1 or 0]
  - Brain metastases [yes vs. no]
  - Age group [≥65 vs. <65]
  - Sex [male vs. female]
  - Smoking status [never smoked vs. former smokers or current smoker]
  - Adenocarcinoma [yes vs. no]

Baseline characteristics used in the covariate-adjustment

Covariate	Real-world data (Davis et al. [2015])	Crizotinib (PROFILE 1014)	Pemetrexed plus platinum therapy (PROFILE 1014)	Pooled treatments (PROFILE 1014)
% non-Asian	87.6%	55.2%	53.2%	54.2%
% age ≥ 65	29.2%	13.4%	18.7%	16.0%
% male	67.9%	39.5%	36.8%	38.2%
% smoker or ex-smoker	62.8%	38.4%	34.5%	36.4%
% ECOG PS 0-1	78.1%	94.2%	95.3%	94.7%
% ECOG PS 2	21.9%*	5.8%	4.7%	5.3%
% with brain metastases	NR	26.2%	27.5%	26.8%
% non-adenocarcinoma	NR	6.4%	5.8%	6.1%

*16.8% were ECOG PS 2, and 5.1% were ECOG PS 3, only ECOG PS 0–1 and 2 included in the PROFILE 1014 trial, therefore n=7 (5.1%) ECOG PS 3 patients have been pooled into the ECOG PS 2 category.

Modelling clinical effectiveness

- In the base case analysis, the company used effectiveness data from ALK+ advanced NSCLC as a proxy for ROS1+ advanced NSCLC for both first-line and subsequent-line treatment with crizotinib because
  - Data from ROS+ are limited and immature
  - Biological and clinical similarities between the ROS1 and ALK oncogenes
  - Similarities in patient characteristics of ROS1- and ALK+ NSCLC patients,
  - Generalisability of ALK+ data to ROS1+ patients supported by 12 UK leading clinical experts
- Company used data from PROFILE 1001 (in ROS1+ NSCLC) as a scenario
- *ERG accepted company's view about biological and clinical similarities between ROS1+ and ALK+ advanced NSCLC and similarities between patients with ROS1+ and ALK+ advanced NSCLC*

Summary of modelled effectiveness

		First-line (PROFILE 1014)	Subsequent-line (PROFILE 1007)
OS	Crizotinib	Exponential	Exponential (PH) adjusted from comparator HR=0.49 (CI=0.37 to 0.64)
	Comparator	Exponential	Exponential
PFS	Crizotinib	Log-normal	Weibull
	Comparator	Generalised Gamma	Log-normal
TTD	Crizotinib	Exponential	Weibull
	Comparator	Gompertz	3 cycles

PFS curves

- Data from the PROFILE 1014 trial (data cut-off: 30 November 2013) used
- Company chose fully stratified curves, adjusted for the baseline characteristics
  - Log-normal for crizotinib
  - Generalised–gamma for pemetrexed plus platinum
  - Rationale: accepted by the Appraisal Committee during TA406

Mean PFS
Crizotinib 16.8 months, docetaxel 7.3 months, modelled PFS gain; 9.5 months.

PFS curves

- Data from the PROFILE 1007 trial
- Company chose
  - Weibull for crizotinib arm
  - Log-normal for docetaxel arm
- Rationale: accepted by the Appraisal Committee during TA422

OS

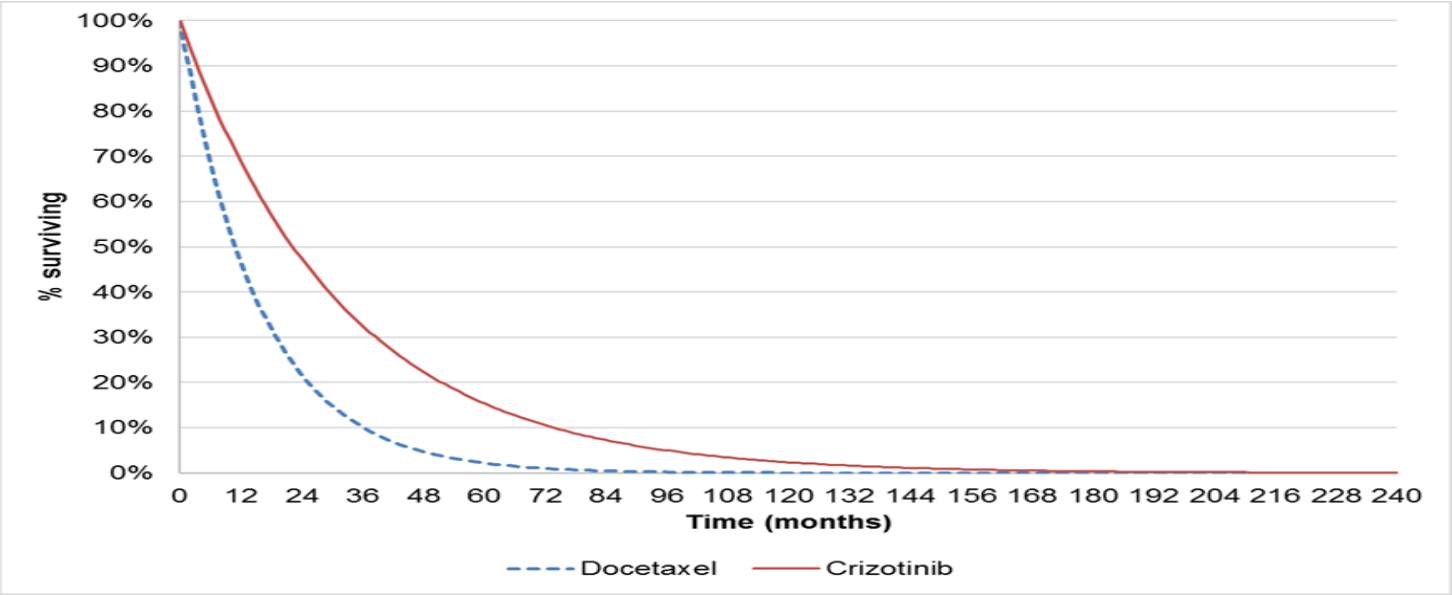
- Separate parametric survival curves were fitted to OS data from the latest data cut from PROFILE 1014 (2017), for crizotinib and pemetrexed plus platinum
  - OS data for pemetrexed plus platinum adjusted for crossover (RPFSTM: Wilcoxon)
- Based on; visual inspection, Akaike information criterion (AIC) & Bayesian information criterion (BIC) and clinical plausibility of expected survival from long-term extrapolation, the company chose
  - Exponential curves for its base case
  - Alternative curve fits are tested in sensitivity analysis
- Selected curves adjusted for patient characteristics

OS curves

Subsequent-line

OS curves

- Data from PROFILE 1007
- Company used extrapolation accepted in TA422
  - Exponential curve fitted to OS data from docetaxel (comparator) arm
  - Assuming proportional hazards, HR of 0.49 applied to model OS for crizotinib arm



Mean OS

Crizotinib 33.0 months, docetaxel16.7 months, modelled OS gain; 16.3 months.

Time on treatment

First-line

- Data from PROFILE 1014
- Company chose the following curves, adjusted for the baseline characteristics
  - exponential for crizotinib
  - gompertz for pemetrexed plus platinum (up to a maximum 6 cycles)
- Rationale: accepted by the Appraisal Committee during TA406

Subsequent-line

- Data from PROFILE 1007
- Company chose the Weibull curve, adjusted for the baseline characteristics for crizotinib
- 3 cycles of docetaxel assumed
- Rationale: accepted by the Appraisal Committee during TA422

PROFILE 1001 scenario: Summary of modelled effectiveness

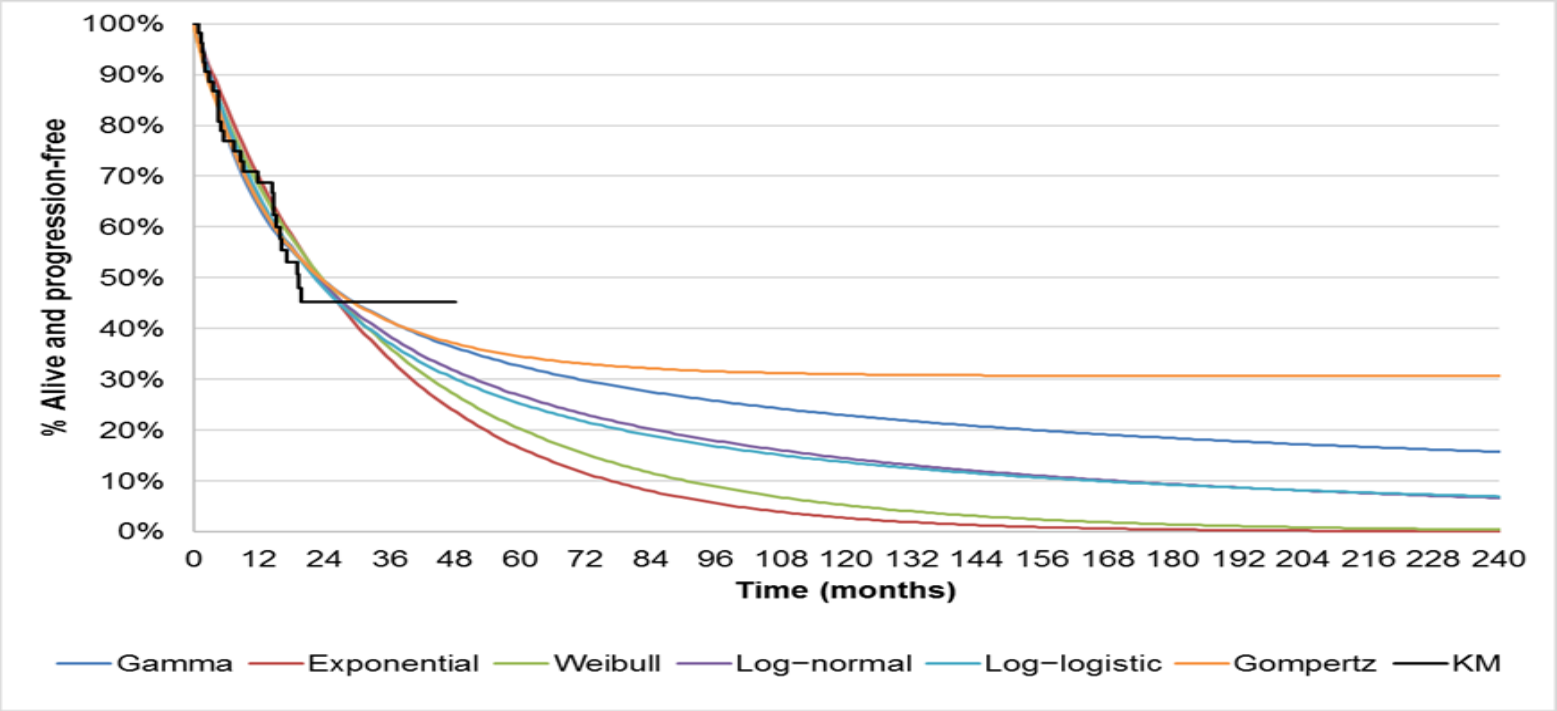
		First-line (PROFILE 1001)	Subsequent-line (PROFILE 1001)
OS	Crizotinib	Exponential	Same as first-line
	Comparator	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=2.61, CI=1.01 to 23.81
PFS	Crizotinib	Exponential	Same as first-line
	Comparator	Exponential (PH) adjusted from intervention HR=2.20 (CI=1.68 to 2.89)	Exponential (PH) adjusted from intervention HR=2.05 (CI=1.57 to 2.70)
TTTD	Crizotinib	Exponential	Same as first-line
	Comparator	Gompertz 6-cycles maximum	3 cycles

Parametric curve fitting for PROFILE 1001 scenario

- For the crizotinib treatment arm, standard parametric curve fitting was done for OS, PFS, and TTTD, data from PROFILE 1001
- For the comparator treatment arm, inverse of hazard ratios (from ALK+ trials)
  - PROFILE 1014 for pemetrexed plus platinum (first-line)
  - PROFILE 1007 for docetaxel (subsequent-line)

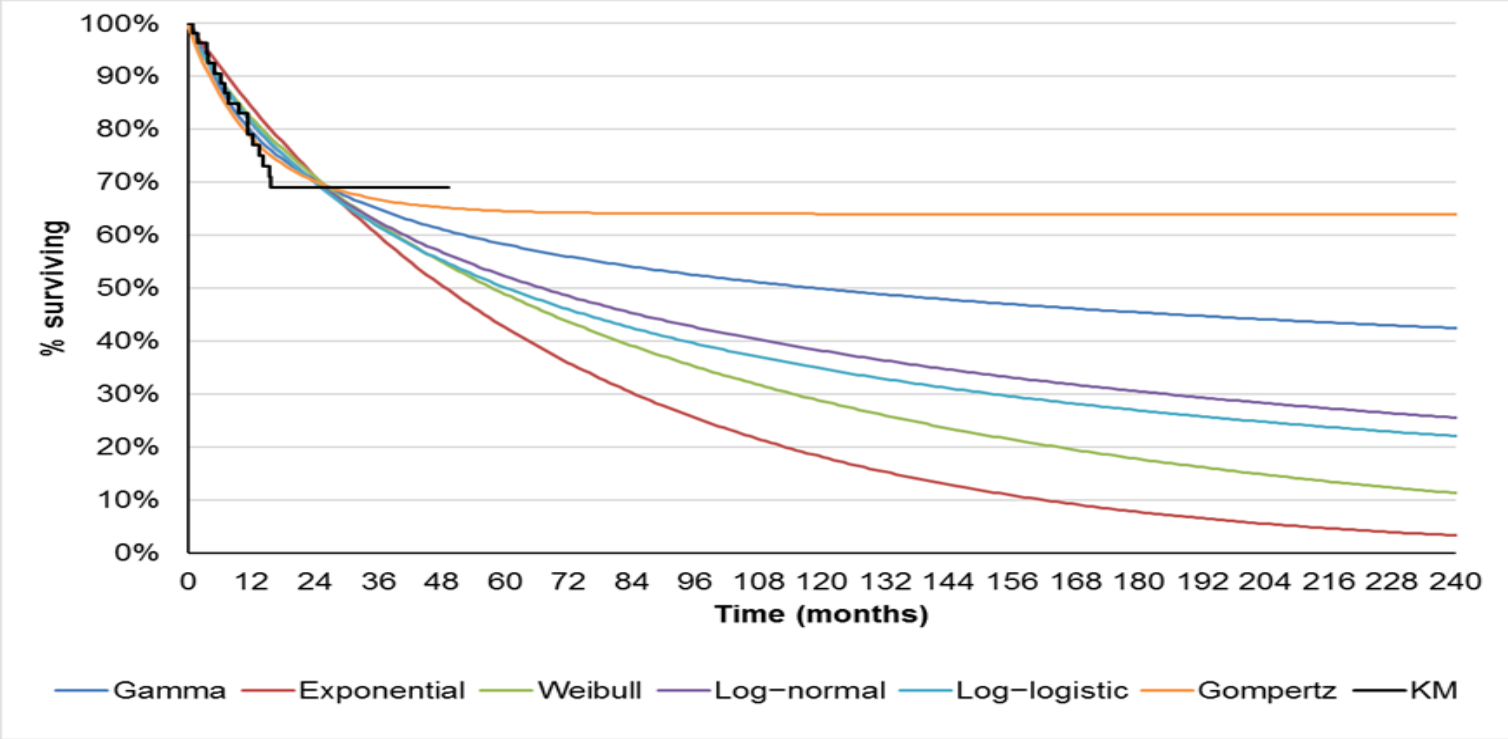
  were applied to OS and PFS curves from PROFILE 1001
- No distinction was made between first and subsequent lines of treatment with crizotinib because of the small number of people receiving treatment as first line (n=7)

PROFILE 1001 scenario: Parametric curves: PFS



Model	AIC	BIC
Log-normal	412.36	416.3
Gompertz	413.27	417.21
Generalised Gamma	413.51	419.42
Log-logistic	413.6	417.54
Exponential	**414**	**415.97**
Weibull	415.48	419.42

PROFILE 1001 scenario: Parametric curves: OS



Model	AIC	BIC
Gompertz	276.54	280.48
Log-normal	278.01	281.95
Generalised Gamma	278.59	284.5
Log-logistic	279.34	283.28
Exponential	**279.41**	**281.38**
Weibull	280.42	284.36

PROFILE 1001 scenario: Parametric curves: TTD

Modelling of health-related quality of life

- HRQoL data were not collected in PROFILE 1001
- Company used utility value data from PROFILE 1014 and PROFILE 1007 assuming that HRQoL of ALK+ population could be used as proxy for HRQoL for the ROS1+ population
- Disutility as a result of adverse events were not modelled
  - Company stated ‘utility estimates ….are taken directly from patients on treatment in the PROFILE 1014 and PROFILE 1007 trials, and hence this HRQoL reporting is expected to already reflect the negative changes in utility incurred through the adverse event profiles of the treatments’.

Utility values

State	Utility Value	95% CI	Source
First-line			
Treatment with crizotinib (both PFS and PD)	0.81	0.79 to 0.82	PROFILE 1014 (measured whilst on treatment)
PFS: Pemetrexed plus platinum therapy	0.72	0.70 to 0.74	PROFILE 1014
PD: second-line treatment with docetaxel monotherapy	0.66	0.58 to 0.74	PROFILE 1007
PD: third-line treatment with BSC	0.47	0.38 to 0.56	From literature Nafees et al. (2008) utility values for third-line treatment of NSCLC
Subsequent-lines			
Treatment with crizotinib (both PFS and PD)	0.81	0.79 to 0.82	PROFILE 1007 (measured whilst on treatment)
PFS on docetaxel	0.66	0.58 to 0.74	PROFILE 1007
PD – third line treatment with BSC	0.47	0.38 to 0.56	Nafees et al. (2008)

Resource use and costs

Company included the following costs in the model

1. ROS1+ testing
2. Drug acquisition cost
3. Drug administration cost
4. Adverse event costs
5. Health state cost including monitoring costs
6. Palliative care cost

Resource use and costs
ROS1 testing

- Introduction of crizotinib to treat ROS1+ advanced NSCLC would require additional resource for ROS1 testing
- Company envisaged
  - all patients with non-squamous NSCLC will be tested for ROS1 rearrangements
  - testing strategy was modelled as IHC (83% specificity and 100% sensitivity) followed by confirmatory FISH (diagnostic accuracy 100%)
  - no impact of ROS1 testing on resource use except cost of the tests as NHS already has infrastructure to carry out testing
- Company modelled
  - upfront testing (with ALK and EGFR testing) in the base case and
  - sequential testing (after patients have been found to be for ALK and EGFR negative) in a scenario analysis

Cost for ROS1 testing

Upfront ROS1 testing cost (base case)	
Test	**Cost**
IHC	£50
FISH	Cost per FISH test: £120 Proportion of true positive and false positive patients from IHC: (1.69%+17%)= 18.7% Cost of FISH testing: £120*18.7% = £22.44
Total cost of testing	£50 + £22.44 = £72.44
Total cost per ROS1+ patient diagnosed	ROS1 incidence in non-squamous patients: 1.69% £72.44 / 1.69% = **£4,287.92**
Scenario analysis – sequential testing	
IHC	Cost per IHC test: £50 Number of EGFR-negative and ALK-negative non-squamous NSCLC patients: (100% - 24.54% - 4.73%)= 70.73% Cost of IHC testing: £50*70.73% = £35.37
FISH	Cost per FISH test: £120 Number of true-positive and false-positive patients from IHC: (70.73%*17%)+1.69% = 13.72% Cost of FISH testing: £120*13.72% = £16.50
Total cost of testing	£35.37 + £16.50 = £51.84
Total cost per ROS1+ patient diagnosed	£51.84 / 1.69% = **£3,068.08**

Drug acquisition cost

- Crizotinib costs in the first- and subsequent-line models calculated according to proportion of patients on treatment in each cycle according to TTTD curve from relevant trials
- For pemetrexed + platinum in first-line model, costs are applied according to the proportion of patients on treatment in each cycle according to TTTD data from the PROFILE 1014 trial
  - In the base case the company used cisplatin (54%) + carboplatin (46%)
  - Investigated alternative proportions in a sensitivity analysis.
- For docetaxel costs in the subsequent-line model, company assumed 3 cycles
  - based on a median PFS of 2.6 months PROFILE 1007 trial
- Drug wastage for all treatments except for crizotinib
- Dosing for pemetrexed, cisplatin and docetaxel is based on body surface area
  - 1.73m^2 for first-line (TA406)
  - 1.80m^2 for subsequent-line (TA422)
- Dosing for carboplatin based on a target area under the concentration versus time curve (AUC in mg/mL/min)
  - Company assumed a target AUC for carboplatin of 5 mg/mL/min, which translates to 500 mg

Drug administration cost

- Cisplatin-containing regimens incurred a day case administration appointment (£406.63)
- Carboplatin-containing regimens and docetaxel monotherapy were assumed to incur an outpatient administration appointment (£304.30)

- The administration cost modelled for crizotinib was £14.50 based on 12 minutes of dispensing time. NHS England report that the HRG chemo tariff is £120 per month

Adverse event costs

- Company used treatment-related adverse events of Grade 3/4 occurring in ≥5% of patients
  - From PROFILE 1014 for first-line and
  - From PROFILE 1007 subsequent-line
  - From PROFILE 1001, for scenario analysis (hypophosphatemia was an additional Grade 3/4 adverse event that occurred in ≥5% of patients)

Proportions of patients experiencing each adverse event

Adverse event	Crizotinib, First-line (PROFILE 1014)	Pemetrexed plus platinum (PROFILE 1014)	Crizotinib, subsequent-line (PROFILE 1007)	Docetaxel monotherapy (PROFILE 1007)	Crizotinib, in PROFILE 1001 analyses (PROFILE 1001)
Elevated transaminases	14.04%	2.37%	15.70%	2.34%	0.00%
Neutropenia	11.11%	15.38%	13.37%	19.30%	9.43%
Anaemia	0.00%	8.88%	2.33%	5.26%	0.00%
Leukopenia	1.75%	5.33%	1.16%	4.68%	0.00%
Thrombocytopenia	0.00%	6.51%	0.00%	0.00%	0.00%
Hypophosphatemia	0.00%	0.00%	0.00%	0.00%	13.21%
Pulmonary embolism	6.43%	6.51%	5.23%	1.75%	0.00%

Cost of treating AEs in the company model

Adverse event	Resource required (hospital days)	Source	Unit cost	Total cost	Reference for unit cost (NHS reference costs 2015/16)
Anaemia	1.7	Consistent with TA296 (replaced by TA422) and TA406	£335.57 per day	£570.47	Iron Deficiency Anaemia with CC Score 0-1 SA04L
Thrombocytopenia	2.0		£303.52 per day	£607.04	Thrombocytopenia with CC Score 0-1 SA12K
Neutropenia	Managed by dose reduction (assumed)		-	-	-
Leukopenia			-	-	-
Elevated transaminases			-	-	-
Hypophosphatemia	1	Assumption	£287.19 per day	£287.19	Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Pulmonary embolism	1		£26.34 per day	£26.34	Weighted average of Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4 (YR23B) and Anticoagulant Services (Outpatient Attendances)

Health state and palliative care cost

- Company assumed 2 separate monthly costs for
  - Patients in PFS or PD whilst receiving second-line treatment (£185.53)
  - Patients in PD who were receiving third-line treatment with best supportive care (£181.65)
- Company applied a one-off cost of £7,415 for palliative care before death
  - based on Georghiou and Bardsley (2014)
  - in line with previous NICE appraisal in untreated ALK+ NSCLC, TA406

Company results (deterministic)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]
Base case: subsequent-line							
Docetaxel	£11,076	1.39	0.71				
Crizotinib	[redacted]	2.75	1.63	[redacted]	1.36	0.93	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,570	2.15	1.29				
Crizotinib	[redacted]	5.75	3.25	[redacted]	3.60	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£12,706	2.32	1.29				
Crizotinib	[redacted]	5.75	3.24	[redacted]	3.43	1.95	[redacted]

Company results (probabilistic)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]
Base case: subsequent-line							
Docetaxel	£11,092	1.40	0.71				
Crizotinib	[redacted]	2.76	1.63	[redacted]	1.37	0.92	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,913	2.41	1.39				
Crizotinib	[redacted]	5.82	3.34	[redacted]	3.42	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£13,378	2.83	1.47				
Crizotinib	[redacted]	5.82	3.33	[redacted]	2.99	1.86	[redacted]

Company's deterministic sensitivity analysis

- Company's deterministic sensitivity analysis showed the results were most sensitive to:
- For first-line, base case analysis
  - TTTD and OS parametric model coefficients for crizotinib
  - utility value for comparator
- For subsequent-line, base case analysis
  - HR for OS
  - OS and PFS parametric curves for crizotinib
  - utility values for treatment with the comparators
- For first-line and subsequent-line PROFILE 1001 analysis HR for OS
  - OS, PFS and TTTD parametric curves for crizotinib
  - utility value for comparator.

Company's scenario analysis (base-case)

Scenario	Scenario setting	First-line ICER	Subsequent-line ICER
	Base case	[redacted]	[redacted]
1	Time horizon 5 years	[redacted]	[redacted]
2	Time horizon 10 years	[redacted]	[redacted]
3	Time horizon 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	N/A
7	Crossover adjustment method: Log-rank	[redacted]	N/A
8	Weibull OS models	[redacted]	N/A
9	Gamma OS models	[redacted]	N/A
10	Log normal OS models	[redacted]	N/A
11	Log logistic OS models	[redacted]	N/A
12	Gompertz OS models	[redacted]	N/A
13	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Company's scenario analysis (PROFILE 1001 analysis)

S. No	Scenario	First-line ICER	Subsequent-line ICER
	PROFILE 1001	[redacted]	[redacted]
1	Time horizon 5 years	[redacted]	[redacted]
2	Time horizon 10 years	[redacted]	[redacted]
3	Time horizon 15 years	[redacted]	[redacted]
4	Excluding wastage	[redacted]	[redacted]
5	Sequential testing for ROS1	[redacted]	[redacted]
6	25% of patients receive carboplatin	[redacted]	[redacted]
7	Maximum of 4 pemetrexed cycles	[redacted]	[redacted]
8	Include covariate for line of treatment for crizotinib	[redacted]	[redacted]
9	Weibull OS model	[redacted]	[redacted]
10	Weibull PFS model	[redacted]	[redacted]
11	Weibull TTF model	[redacted]	[redacted]
12	Weibull OS, PFS, TTF model	[redacted]	[redacted]
13	OS HR (1st line): RPSFTM Log-rank (new data cut)	[redacted]	N/A
14	OS HR (Subsequent-line): RPSFTM Wilcoxon	N/A	[redacted]
15	OS HR (Subsequent-line): RPSFTM Cox	N/A	[redacted]
16	PFS HR (Subsequent-line): crizotinib versus docetaxel	N/A	[redacted]
17	Include a basket of subsequent therapies based on PROFILE 1014	[redacted]	N/A

Probabilistic sensitivity analysis

- Company run 10,000 probabilistic iterations and total costs, and QALYs obtained from each simulation were recorded and averaged

Scenario	Probabilistic ICER	Probability of being cost effective at a cost-effectiveness threshold		
		£20K/QALY	£30K/QALY	£50K/QALY
Base-case				
First-line	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent-line	[redacted]	[redacted]	[redacted]	[redacted]
PROFILE 1001 scenario				
First-line	[redacted]	Not reported	Not reported	[redacted]
Subsequent-line	[redacted]	Not reported	Not reported	[redacted]

* Extracted from the model

ERG's comments (1)

- The evidence underpinning the company's base case analyses is from a proxy population (ALK+ advanced NSCLC)
- The ERG identified issues that prevented it from providing a detailed critique
  - The company used assumptions and modelling approaches from 3 previous NICE appraisals (TA406, TA422 and TA296) without providing sufficient justification
  - The ERG could not investigate the effects of key assumptions because of the lack of model functionality

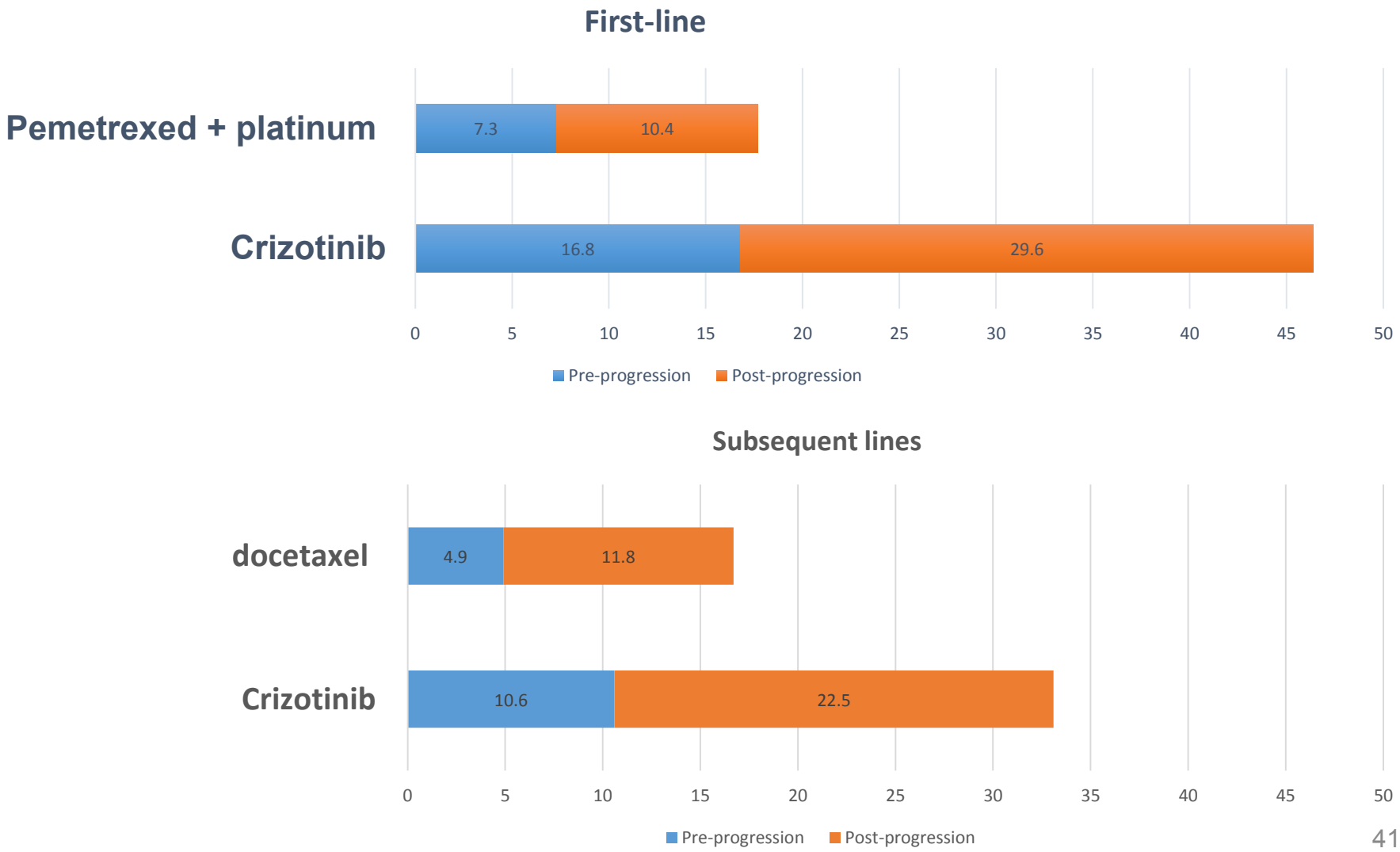
ERG's comments (2)

Post-progression survival

- Difference between OS gain and PFS gain is improbably high

Health state	Crizotinib (months)	Pemetrexed + platinum (months)	Increment (months)	Increment
First-line				
Pre-progression	16.8	7.3	9.5	33.3%
Post-progression	29.6	10.4	19.2	66.7%
Total	46.4	17.7	28.7	100%
Subsequent-line				
Pre-progression	10.6	4.9	5.7	34.8%
Post-progression	22.5	11.8	10.6	65.2%
Total	33.0	16.7	16.3	100.0%

Modelled survival (months)



ERG's comments (3)

PROFILE 1001 analysis

- PROFILE 1001 data are immature and heavily censored
  - modelling of PROFILE 1001 data resulted in very long survival projections
  - company estimated time-to-event curves for comparator by using inverse HRs from the PROFILE 1014 and PROFILE 1007 trials
  - These HRs based on RPSFTM crossover adjustments which resulted in implausible difference in overall survival

ERG's comments (4)

PFS utility values: first-line treatment

- ERG agreed that the EQ-5D scores from PROFILE 1014 trial show greater HRQoL benefit with crizotinib than with pemetrexed + platinum
- However the ERG questioned the magnitude of that benefit noting
  - lack of long-term off-treatment EQ-5D data for pemetrexed + platinum treatment arm,
  - lack of a statistically significant difference between mean EQ-5D for those cycles where data have been recorded
  - open-label nature of the trial
- The ERG explored other scenarios
  - no HRQoL benefit with crizotinib
  - using a PFS utility value of 0.75 (preferred by committee during TA406) for treatment with pemetrexed + platinum.
- The ERG commented that utility values reflect PROFILE 1014 trial population, whereas, in the first-line base case model, the time-to-event estimates have been adjusted to reflect the population observed in clinical practice

ERG's comments (5)

Cost of pulmonary embolism

- The ERG considered the company's estimated cost for pulmonary embolism (£26.34) to be underestimated
  - Hospital Episode Statistics report mean time in hospital for pulmonary embolism to be 6 days.
  - NICE guidance on treating thromboembolism indicates that patients should be initially treated for at least 5 days with a low molecular weight heparin (LMWH) and that a LMWH should be given for 6 months if a patient with active cancer develops a pulmonary embolism.

ERG's comments (6)

Testing for ROS1 rearrangements

- The ERG questioned the company's approach that assumed upfront testing for subsequent-line model
  - Clinical advice to ERG: only a small percentage of patients who are eligible to receive crizotinib as a subsequent-line treatment would not have already been tested for ALK and EGFR mutations earlier in their treatment pathway.
  - In the subsequent-line model sequential testing (ROS1 testing in EGFR- and ALK-negative population) would be more appropriate
- The ERG noted that NHS laboratory services may offer a discount when testing for more than one mutation at the same time.
  - All Wales Genetic Laboratory list price for FISH analysis (ALK) is £120 and for EGFR is £175 when both test undertaken at the same time is price is £250, (15% discount)
  - Similar discount plausible for upfront cost of carrying testing for ROS1 alongside other tests

The ERG stated that the issues raised on this and the previous slide only had a slight impact on the ICER

ERG's exploratory analyses (1)

Citing the lack of transparency of data and model functionality issue, the ERG did not provide its preferred assumptions for the base-case

ERG explored alternative modelling approaches for time to event data and utility values

OS: first-line treatment

- ERG explored 2 scenarios
  - PFS treatment effect is the same as the PPS treatment effect*
    - Implemented using PFS HR to modelled crizotinib OS estimates
    - ERG noted that this analysis should be treated with caution as PH assumption did not hold for PFS in the PROFILE 1014
  - no benefit with crizotinib after progression
    - PPS is equal for both treatments and any gain in OS is attributable only to difference in PFS
    - implemented by adjusting the exponential OS curve for pemetrexed so that PPS is equal to PPS for treatment with crizotinib

* Technically incorrect, but I will stick to it.

ERG's exploratory analyses (2)

OS: subsequent-line treatment

- ERG questioned company's approach of applying PFS HR from PROFILE 1007 trial to the RPSFTM-adjusted docetaxel OS curve
  - 'applying a HR to OS data that has already been adjusted for crossover somewhat defeats the point of trying to find a method that avoids the pitfalls of the RPSFTM approach'

- ERG explored 2 OS scenarios
  - OS HR = PFS HR and
  - OS gain = PFS gain

- ERG commented that not adjusting for patients who receive further active treatment is an optimistic assumption for treatment with crizotinib

ERG's exploratory analyses (3)

PFS utility values: first-line treatment

- The ERG explored the impact of assuming no difference in PFS utility values between the crizotinib treatment arm and the pemetrexed + platinum treatment arm
  - Using crizotinib utility value (0.81) for both treatments
  - Using pemetrexed utility value (0.72) for both treatments
- The ERG also used PFS utility value (0.75) for the pemetrexed utility value

ERG's Scenario

- ERG presented a series of ICERs combining aforementioned modelling approaches and utility values

ERG's exploratory analyses (first-line)

ERG revisions	Incremental		ICER £/QALY
	Cost (£)	QALYs	
First-line base-case			
Company base case	[redacted]	1.28	[redacted]
OS treatment effect: use PFS HR from 1014	[redacted]	1.11	[redacted]
OS treatment effect: no PPS gain	[redacted]	0.62	[redacted]
PFS utility: crizotinib utility (0.81) for both	[redacted]	1.23	[redacted]
PFS utility: pemetrexed utility (0.72) for both	[redacted]	1.15	[redacted]
PFS utility: pemetrexed utility = 0.75	[redacted]	1.26	[redacted]

ERG's scenarios (first-line)

ERG scenarios		Incremental		ICER
		Cost	QALYs	£/QALY
Company base case		[redacted]	1.28	[redacted]
OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	1.05	[redacted]
	PFS utility=0.72 for both	[redacted]	0.98	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.09	[redacted]
OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	0.57	[redacted]
	PFS utility=0.72 for both	[redacted]	0.49	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	0.60	[redacted]

ERG's exploratory analyses (subsequent-line)

Model scenario and ERG revisions	Incremental		ICER
	Cost	QALYs	£/QALY
Subsequent-line			
Company base case	[redacted]	0.93	[redacted]
OS treatment effect: apply PFS HR to unadjusted crizotinib estimate	[redacted]	1.03	[redacted]
OS treatment effect: no PPS treatment effect	[redacted]	0.55	[redacted]

ERG's exploratory analyses: PROFILE 1001 analysis (1)

- ERG did not consider data from PROFILE 1001 to be robust enough to provide reliable estimates of time-to-event outcomes
- Comparative effectiveness of crizotinib and chemotherapy remained uncertain in ROS1+ advanced NSCLC
  - Treatment effect of pemetrexed + platinum, or docetaxel on ROS1+ advanced NSCL remains unknown
- To improve the face validity of the results, the ERG explored
  - different assumptions of treatment effect applied to the company's modelling of OS data of crizotinib
  - different modelling approaches for OS, PFS and TTD.

ERG's exploratory analyses: PROFILE 1001 analysis (2)

Different treatment effect

- First line: company used RPSFTM (Wilcoxon)-adjusted hazard ratio from PROFILE 1014 to estimate the treatment effect for OS for the ROS1+ advanced NSCLC population in the first-line setting.
  - The ERG applied PFS HR from PROFILE 1014 and assumed equal PPS for each treatment.
- Subsequent line: Company used the PFS HR from PROFILE 1007 in its PROFILE 1001 scenario for subsequent-line treatment.
  - The ERG explored the effect of assuming equal PPS for docetaxel and crizotinib.

Different modelling approaches for time to event data

- ERG explored the impact of remodelling OS, PFS and TTTD from PROFILE 1001 by using 'all-lines' Kaplan-Meier data directly as far as possible and then appending an exponential tail to project out to the time horizon

ERG's exploratory analyses: PROFILE 1001 analysis (3)

ERG exploratory analyses	Incremental		ICER
	Cost	QALYs	£/QALY
First-line			
Company PROFILE 1001 scenario	[redacted]	1.95	[redacted]
OS treatment effect: use PFS HR from 1014	[redacted]	1.71	[redacted]
OS treatment effect: no PPS gain	[redacted]	1.13	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	1.43	[redacted]
PFS utility: crizotinib utility (0.81) for both	[redacted]	1.84	[redacted]
PFS utility: pemetrexed utility (0.72) for both	[redacted]	1.70	[redacted]
PFS utility: pemetrexed utility = 0.75	[redacted]	1.91	[redacted]

ERG's exploratory scenarios: PROFILE 1001 (first-line) (4)

Model scenarios		Incremental		ICER
		Cost	QALYs	£/QALY
Company PROFILE 1001 scenario		[redacted]	1.95	[redacted]
OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	1.59	[redacted]
	PFS utility=0.72 for both	[redacted]	1.46	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.67	[redacted]
OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	1.02	[redacted]
	PFS utility=0.72 for both	[redacted]	0.89	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.09	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	PFS utility=0.81 for both	[redacted]	1.33	[redacted]
	PFS utility=0.72 for both	[redacted]	1.18	[redacted]
	PFS utility=0.75 for pemetrexed	[redacted]	1.40	[redacted]

ERG's exploratory analyses: PROFILE 1001 (subsequent-lines) (5)

ERG exploratory analyses	Incremental		ICER
	Cost	QALYs	£/QALY
Subsequent-line			
Company PROFILE 1001 scenario	[redacted]	1.95	[redacted]
OS treatment effect: no PPS gain	[redacted]	1.21	[redacted]
Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	1.45	[redacted]

End-of-life

1. **Short life expectancy (less than 24 months)**

- The company expected life expectancy to be less than 24 months
  - no conclusive evidence that ROS1-positivity is a better prognostic factor for survival, compared to unselected NSCLC.
  - opinion from 12 UK clinical experts, supports similar PFS in chemotherapy-treated ROS1+ patients than chemotherapy-treated ALK+ patients.
  - limited data on OS for ROS1+ advanced NSCLC patients
  - Estimated median OS in ALK+ range from 6 to 22 months, with median OS in the chemotherapy arm of PROFILE 1007 reaching 21.9 months at the final analysis.

ERG commented that evidence for life expectancy in the ROS1+ advanced NSCLC population is uncertain

End-of-life

2. Evidence of extension to life (at least an additional 3 months)

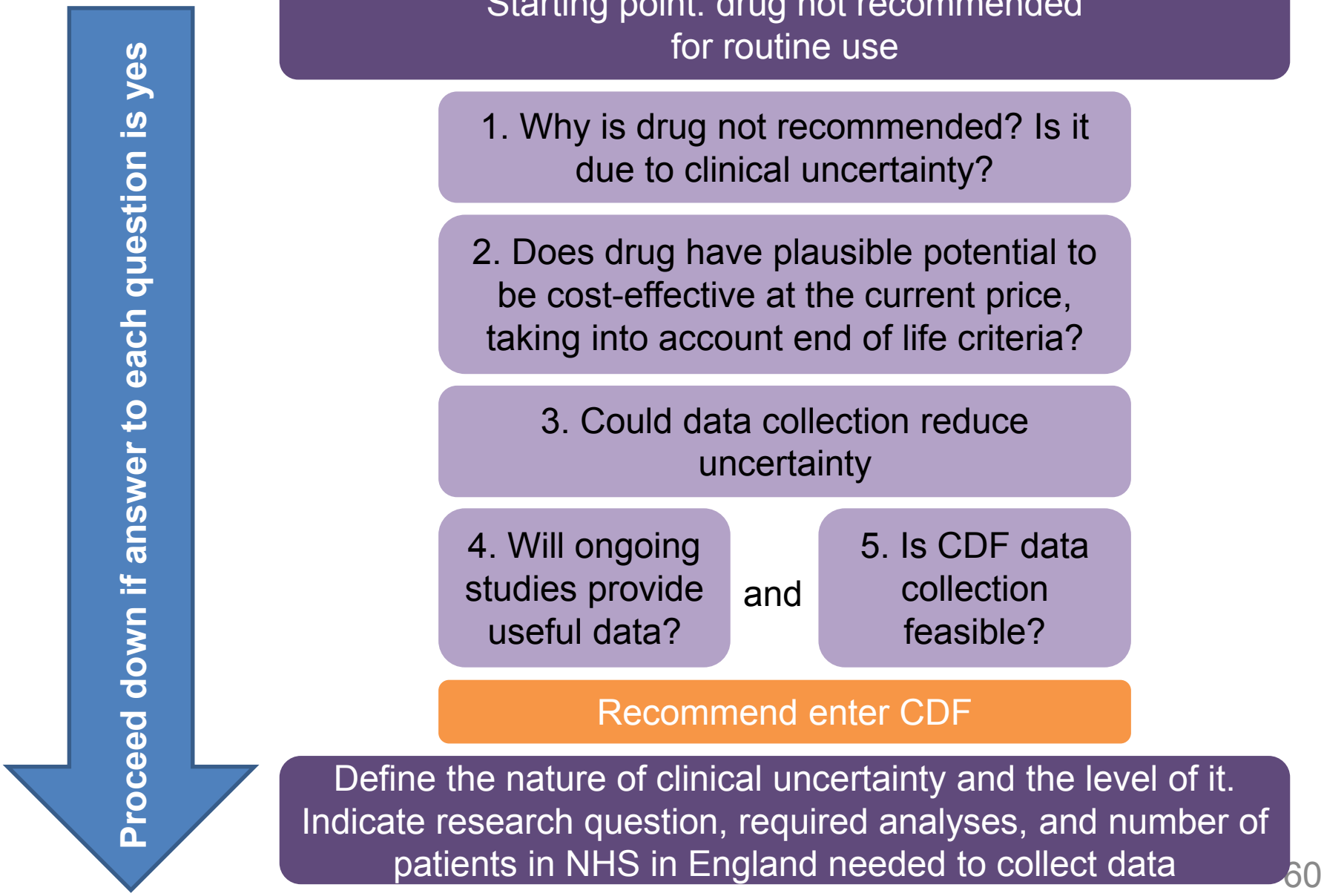
- in PROFILE 1001, median PFS was 19.3 months,
- In a previous appraisal (TA422) of it was acknowledged that PFS is a conservative indicator of OS
- Crizotinib demonstrated clear benefits in terms of tumour response in PROFILE 1001,
- In both first-line and subsequent-line settings, NICE has accepted an extension of life of more than 3 months in ALK+ NSCLC patients receiving crizotinib
- The model predicts an extension to life associated with crizotinib in ROS1+ patients of 2.39 years compared with pemetrexed plus platinum therapy and 1.36 years compared with docetaxel therapy

ERG noted that given the lack of a comparator to crizotinib in the PROFILE 1001 study, the duration of extension to life in the ROS1+ advanced NSCLC population is uncertain.

Potential equality issues

- Company commented that if there are regional variations in the access to ROS1 testing, this could lead to inequitable access.
- Company noted the upfront testing strategy of all non-squamous NSCLC as proposed by the company would reduce the inequality associated with access of targeted therapy to ROS1+ patients.
- Company considered sequential testing strategy may increase inequities, as ROS1+ patients would experience a delay in access to targeted therapy, compared to EGFR+ and ALK+ patients.

CDF recommendation decision pathway



Key issues (1): Cost effectiveness

- Is the company's economic model appropriate for determining the cost effectiveness of crizotinib for ROS1+ advanced non-small cell lung cancer?
  - The evidence underpinning the base case first- and subsequent-line models is from a proxy population (ALK+ advanced NSCLC) rather than the population of interest (ROS1+ advanced NSCLC). ERG stated that the impact of this assumption on cost effectiveness estimates is unknown, since the evidence for the ROS1+ advanced NSCLC population is severely limited
- How appropriate are the assumptions in the company's economic model?
  - ERG stated that the company submission relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296) and company has not provided sufficient justification for use of these assumptions and approaches, except that they were previously accepted.
  - ERG was unable to investigate the effects of specific key assumptions in the model as a result of the limited functionality of the model

Key issues (2): Cost effectiveness

- How robust are the company's estimates of post progression survival ?
  - Estimates of post progression survival gain in the first- and subsequent-line base cases are substantially greater than estimates of progression-free survival gain. This means that treatment effect on overall survival is greater than treatment effect on progression-free survival, which the ERG does not consider to be supported by the evidence available
- ERG explored 2 additional scenarios for overall survival modelling
  - assuming continued treatment effect on survival (as seen in pre-progression stage) after progression
  - assuming no benefit of crizotinib after progression

  Which is the committee's preferred method?
- How robust are the company's PFS utility values?
  - For patients who received treatment with pemetrexed + platinum in the first-line model?
    - ERG was concerned that the PFS utility value may not be representative of the whole time that these patients spend in the progression-free state, as it is based on EQ-5D responses collected only whilst patients are on treatment

Key issues (3): Cost effectiveness

- How robust is the company's PROFILE 1001 scenario analysis?
  - The ERG stated that estimates of OS, PFS and TTD were based on parametric models with low levels of face validity and clinical plausibility.
- What are the most plausible ICERs for crizotinib for treating ROS1+ advanced NSCLC?