Chair's presentation

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1098]

2nd Appraisal Committee meeting

Committee C

ERG: Liverpool Reviews and Implementation Group

NICE technical team: Abi Senthinathan, Nicola Hay

Company: Pfizer

21st February 2018

Slides for public [redacted]

Key issues

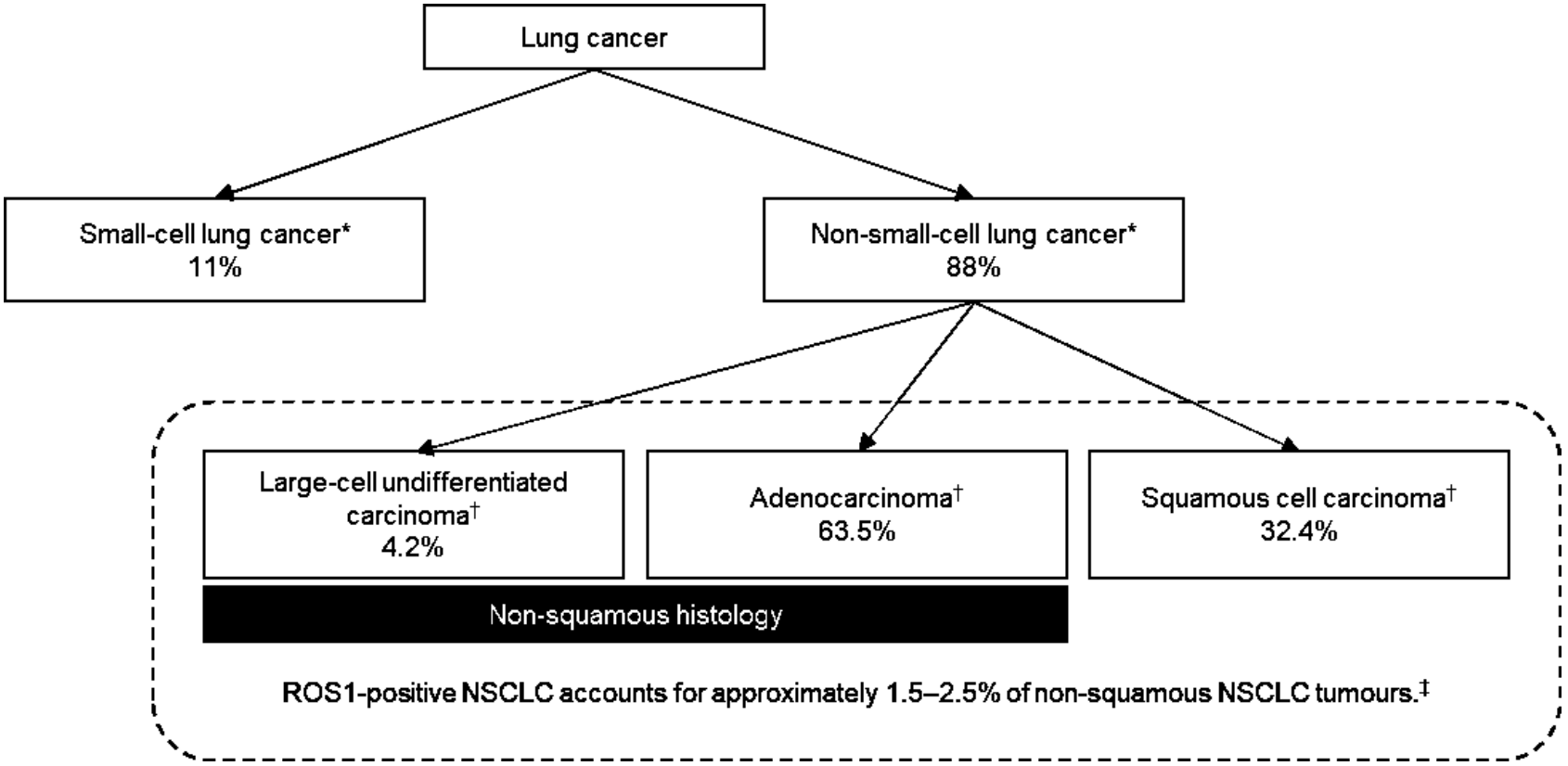
- What additional clinical benefit is plausible for crizotinib in the progressed state for first and subsequent line therapy?
- Should the higher utility value (0.75) for pemetrexed be applied
  - for the whole PFS state or
  - only apply for patients who are off treatment?
- Is sequential testing for subsequent line treatment appropriate?
- Should the model include an increased cost for treating pulmonary embolism?
- ROS-1 case is reliant on proxy data from ALK-pos patients
- Are there any additional equalities issues?
- Most plausible ICER?
- Is CDF appropriate?

Crizotinib (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 21st July 2016: *'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 December 2016
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

~ 1% of all lung cancer
~ 300 cases per year



* 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)

Treatment Pathway
First-line treatment

Advanced NSCLC
Molecular testing

Targeted therapy

ALK-1
Crizotinib [TA406]

ROS-1
Crizotinib

EGFR
EGFR-TKIs
[TA310], [TA258],
TA192] ,

PD-L1
Pembrolizumab
[TA447]

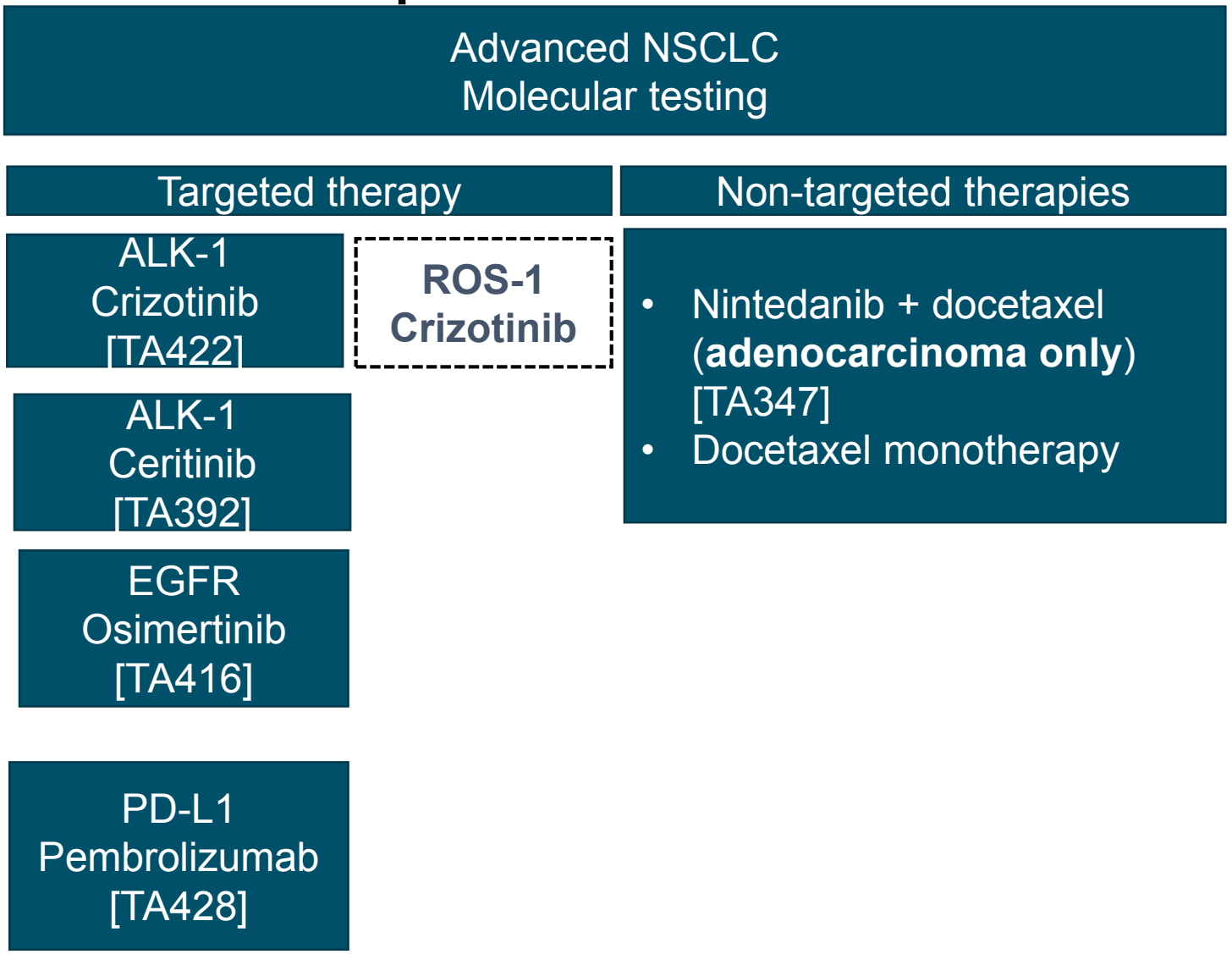
Non-targeted therapies

- Pemetrexed (**non-squamous**) plus platinum* [TA181]
- Third-generation (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus platinum* [CG121]
- Single agent chemotherapy with third-generation drug (if platinum* not tolerated) [CG121]

Pemetrexed monotherapy as maintenance [TA402]

*platinum: carboplatin/cisplatin

Treatment Pathway
Subsequent treatment



Clinical trials

	PROFILE 1001	PROFILE 1014 (1st line)	PROFILE 1007 (subsequent therapy)
Study design	single-arm, open-label, phase 1 study	Randomised, open-label, active-controlled, cross-over, phase III study	
Population	53 patients with ROS1+ locally advanced or metastatic NSCLC • untreated (n=7) • at least 1 prior chemotherapy (n=46)	343 adults with ALK+ locally advanced or metastatic non-squamous NSCLC who had not had any treatment for advanced disease	347 patients with ALK+ locally advanced or metastatic NSCLC that progressed after 1 platinum based therapy and eligible for additional chemotherapy
Intervention	crizotinib (250 mg) until disease progression	crizotinib (250 mg) allowed to continue beyond progression	crizotinib (250 mg)
Comparator	N/A	pemetrexed plus platinum-based therapy	docetaxel or pemetrexed

ACD: preliminary recommendation

- Crizotinib is not recommended for people with untreated or previously treated ROS1-positive advanced NSCLC
  - Limited clinical effectiveness data (one single arm trial)
  - Cost effectiveness results are extremely uncertain because based on proxy data
  - Meets end of life (EOL) criteria but most plausible ICERs for crizotinib vs. standard care not clearly in range normally considered cost effective
  - Company would prefer routine use rather than CDF

ACD summary

ACD section	Committee conclusion
ROS1 testing (3.2)	Only a few centres test for ROS1, and assay methods vary. ROS1 status should be tested upfront in all non-squamous NSCLC
Comparator (3.3)	In clinical practice, crizotinib likely be used for non-squamous NSCLC: • Untreated disease: Pemetrexed plus platinum-based therapy • Previously treated: docetaxel alone and docetaxel plus nintedanib ○ Company excluded docetaxel plus nintedanib as a comparator for previously treated population and considered docetaxel alone to be the best comparator
Use of proxy data (3.8, 3.9)	Limited clinical effectiveness data from ROS1-positive population. Use of proxy data (from ALK positive NSCLC) is far from ideal. Therefore both clinical and cost effectiveness estimates are extremely uncertain. • Clinical experts state that in their experience ROS1-positive advanced NSCLC is even more sensitive to crizotinib than ALK-positive NSCLC. • ERG note that any documented similarities between ALK-positive and ROS1-positive advanced NSCLC may not hold true as more patients with ROS1-positive advanced NSCLC are identified

ACD summary

ACD section	Committee conclusion

Clinical effectiveness (3.6 to 3.8)	Lack of comparative data makes assessing comparative effectiveness very challenging.
	• Evidence is from small single-armed study (PROFILE 1001)
	• Only comparative data is from proxy data in ALK positive population
	  o PROFILE 1014 in untreated population
	  o PROFILE 1007 in previously treated population
	• Untreated and previously treated: Comparison with chemotherapy based on ALK-positive population so is highly uncertain

Cost effectiveness (3.9 to 3.14)	• All cost effectiveness results extremely uncertain as use proxy data • Modelled OS is improbably high and ERG scenario analyses no more accurate due to proxy data o Company modelled OS gain crizotinib 28.7 months untreated disease and 16.3 months for previously treated disease • Utilities underestimated for comparator in untreated disease • Company's ICERs severely underestimated, most plausible ICERs above £50,000 (EOL met) and highly uncertain.

Cancer drugs fund

- Company propose a case for routine commissioning and no CDF proposal
- Crizotinib is promising treatment but more data is needed to establish clinical and cost effectiveness
- Further comparative trials may be unethical
  - ongoing single-arm studies in ROS1-positive population will only partly address uncertainties (no relevant comparator)
- Crizotinib has plausible potential to be cost-effective for **untreated** ROS1-positive population because ICER was around £50,000 per QALY gained (highly uncertain)
- Using crizotinib in CDF would provide important data and encourage standardisation of ROS1 testing
  - data may address comparability to ALK-positive population and survival benefit with crizotinib

ACD consultation (1)

Comments: Company, Royal colleges, Roy Castle Lung Cancer foundation (RCLCF), NHSE, 11 web

Theme	Comments
CDF	**Royal colleges:** If uncertainty around ICERs not resolved, CDF funding would be preferred (if not recommended for routine commissioning). But there is concern over data collection aspects for PFS if were approved on CDF. **NHS England:** Huge uncertainty in 1st line setting (so little data) makes the CDF an excellent opportunity for national data collection for a large number of patients, thus providing help to NICE (and Pfizer) in a post-CDF re-appraisal of crizotinib and to the world literature on crizotinib use in ROS1 NSCLC
ROS1 testing	**Royal colleges:** How will testing be reimbursed? **Web comments:** A testing programme is needed **NHS England:** most practical testing strategy for ROS1 would be screening of all adenocarcinoma patients at diagnosis. Cost of testing should be included in cost effectiveness analyses.
Inconsistent decision making	**RCLCF & web comments:** Committee inconsistent in accepting crizotinib for ALK+ group but not ROS1 group

ACD consultation (2)

Theme	Comments
Inaccuracies	**Company**: identify some factual inaccuracies in ACD
Incorrect costs	**NHS England:** correct cost for the HRG chemotherapy tariff for crizotinib administration has not been used by the company: a figure of £14-60 has been used whereas the 2017/18 oral chemotherapy tariff is £120 per month
Inequality in access	**Web comment:** Crizotinib is available as a 1st line treatment in France. Making it available in the CDF reduces access in some parts of the UK. It is unfair to discriminate rare disease
Unmet need and clinically similar to ALK+	**Web comments**: Although its rare, ROS1 tumours clinically similar to ALK+ and there is a need for treatment options for this group of patients. Good response with crizotinib.
Treatment duration	**NHS England:** Durations of treatment with 1st and subsequent line crizotinib are highly likely to significantly exceed the durations of progression-free survival observed in Profile 1001 and therefore this treatment period beyond disease progression must be included in the model.

Company's new evidence
Response to committee's preferred assumptions

Committee preferred assumption	Company response
1. Higher utility value (0.75) for treatment with pemetrexed	Should only apply when patients are off treatment (company's new base case)
2. Include disutility for adverse reactions	• Utilities from trials should reflect AE profiles. • Including disutility could be double-counting.
3. Adjust OS curve so crizotinib PPS similar to comparator PPS but with additional benefit for crizotinib	New analyses submitted
4. Include docetaxel plus nintedanib as a comparator (subsequent-line)	Company's use of pooled chemotherapy (docetaxel or pemetrexed in PROFILE 1007) • conservative (pemetrexed more effective) • mitigates incremental difference for docetaxel plus nintedanib
5. Increase cost of treating PE and crizotinib administration	Cost of treating PE (company's new base case). Administration costs previously accepted

- Company present analyses without cost of ROS1 testing because this may become part of routine healthcare commissioning in the near future

Company's new evidence
Additional PPS benefit for crizotinib

- Company: same PPS for crizotinib and comparator is not clinically plausible
  - 1st line: clinical experts expect mean OS gain (without cross over) between 13.1 to 18.2 months (i.e. at least that accepted in TA406)
  - Subsequent line: clinical experts expect mean OS gain (without cross over) between 16.2 to 20.9 months (i.e. at least that accepted in TA422)
  - UK audit data: 1 year OS rate 81%, 2 year OS rate 66%
- Company's clinically plausible scenarios:
  - Mean OS gain in line with clinical experts or meet mid point between company's and ERG's mean OS gain
- Company tested clinical plausibility of alternative OS survival models:
  1) Original ERG scenario
  2) Adapted ERG scenario (adjusted crizotinib curve with additional benefit)
  3) Threshold analysis (adjusted crizotinib curve to threshold £50,000 per QALY gained)
  4) Minimum OS gain analysis (adjusted crizotinib curve to mean OS gain that is clinically plausible)

Slide amended following ACM2

Company's new evidence scenarios (1)

Additional PPS benefit for crizotinib (first line)

	ICER vs pemetrexed	
	No testing cost	Testing cost
Original ERG scenario (no additional benefit for crizotinib in progressed state, PFS utility 0.75) • Mean OS gain 9.5 months *not clinically valid*	[redacted]	[redacted]
Adapted ERG scenario (no additional benefit in progressed state, adjusted curve with HR 0.64*) • Mean OS gain 9.5 months *not clinically valid*	[redacted]	[redacted]
Threshold analysis** (survival benefit to £50,000 threshold*) • Mean OS gain [redacted] months with testing cost & [redacted] months without testing costs *not clinically valid*	[redacted]	[redacted]
Minimum OS gain analysis* • Mean OS gain 13.1 months, PPS gain 3.5 months	[redacted]	[redacted]
Use mid point OS gain (company and ERG analysis)* • Mean OS gain 18.2 months, PPS gain 8.6 months	[redacted]	[redacted]

*includes PFS utility 0.72 on treatment & 0.75 off treatment and increased PE cost, ** [redacted] with testing cost and [redacted] without. NB: figures in **bold,** company consider clinically relevant

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Company's new evidence scenarios (2)

Additional PPS benefit for crizotinib (subsequent line)

	ICER vs docetaxel
Original ERG scenario (no additional benefit for crizotinib in progressed state) • Mean OS gain 5.8 months *not clinically valid*	No testing cost: [redacted] Testing cost: Sequential test:
Adapted ERG scenario (no additional benefit after progression, adjusted curve HR 0.73 & PE cost) • Mean OS gain 5.7 months *not clinically valid*	No testing cost: [redacted] Testing cost: Sequential test:
Adapted ERG scenario (use PFS HR from PROFILE 1014 for OS, additional benefit for crizotinib after progression, adjusted curve HR 0.49 and PE cost) • Mean OS gain 16.3, PPS gain 10.7 months	**No testing cost:** [redacted] **Testing cost:** **Sequential test:**
Original ERG scenario using PFS HR for OS and unadjusted data • Mean OS gain 19.7, PPS gain 14 months *less clinically plausible**	No testing cost: [redacted] Testing cost: Sequential test:

NB: figures in **bold,** company consider to be clinically relevant, *company consider these less plausible due to high mean OS in docetaxel arm

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Slide amended following ACM2

Company's new evidence scenarios (3)

Additional PPS benefit for crizotinib (subsequent line)

	ICER vs docetaxel
Threshold analysis* (survival benefit to £50,000 threshold and PE cost) • Mean OS gain ranges from [redacted] months *not clinically valid*	No testing cost: [redacted] Testing cost: [redacted] Sequential test: [redacted]
Minimum OS gain analysis (and PE cost) • Mean OS gain 16.2, PPS gain 10.5 months	**No testing cost** [redacted] **Testing cost:** [redacted] **Sequential test:** [redacted]
Use mid point OS gain (PROFILE 1007 HR 0.38 and ERG scenario using PFS HR from PROFILE 1014) and PE cost • Mean OS gain 20.9, PPS gain 15.2 months	**No testing cost:** [redacted] **Testing cost:** [redacted] **Sequential test:** [redacted]
NB: figures in **bold,** company consider to be clinically relevant *[redacted] with testing cost, [redacted] without testing cost and [redacted] with sequential testing	

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Overall survival curves (1st line ACM1)

Mean OS Crizotinib 46.4 months, Pemetrexed+platinum17.6 months, modelled OS gain; 28.7 months.

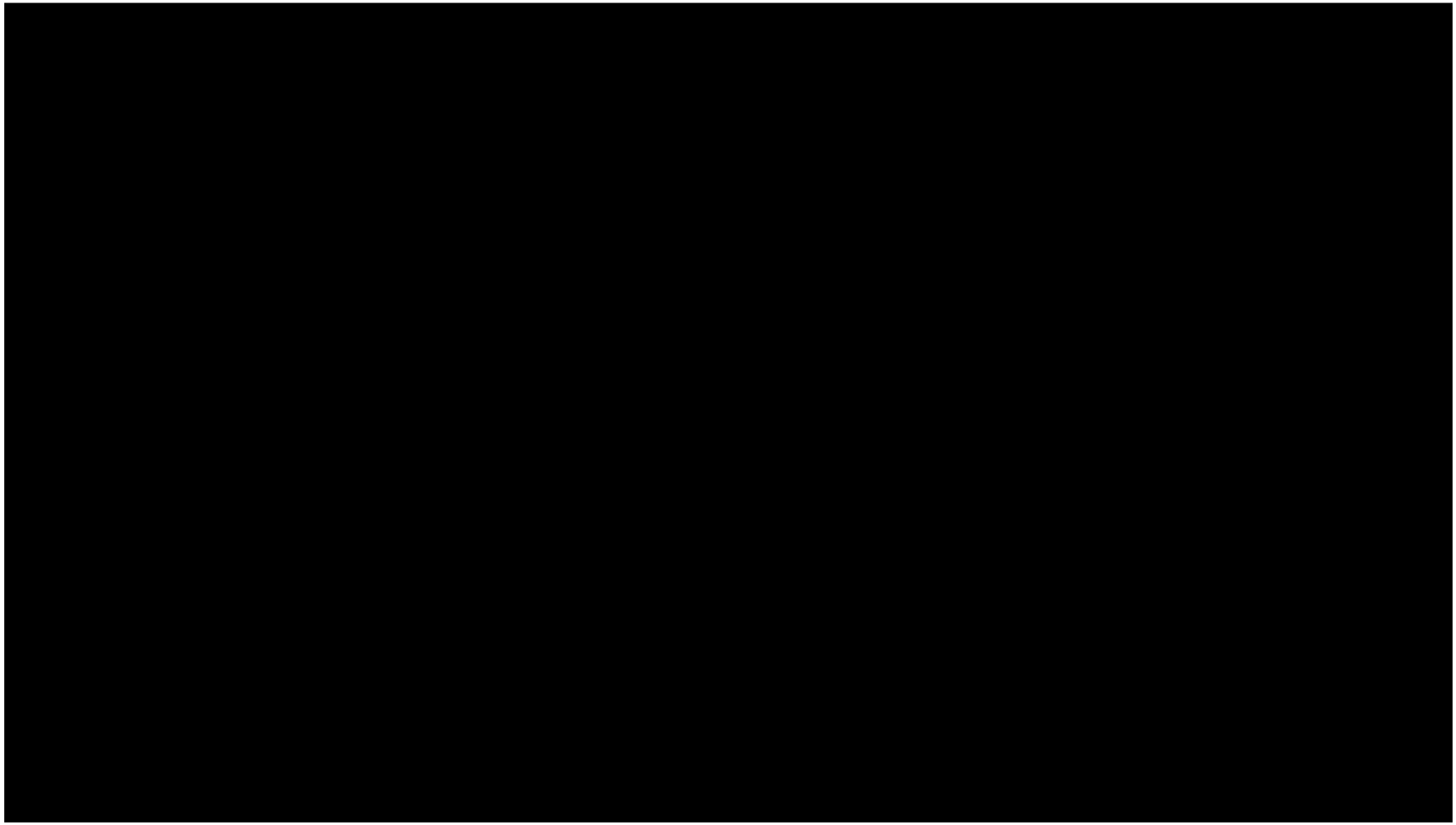
Overall survival curves (1st line ACM2)

Overall survival curves (subsequent line ACM1)

- 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.

Overall survival curves (subsequent line ACM2)



Company's new base case

Assumption	Company ACM1	ERG	Company's revised base case
Utility values pre-progression pemetrexed off treatment	0.72	0.75 (whole PFS period)	0.75 (off treatment PFS period only)
Increased cost of treating pulmonary embolism	£26.34	£26.34	£1,485.76 (consistent with TA500 and in line with ERG comments
Sequential testing for 2nd line crizotinib	Up-front testing	Up-front testing	Sequential testing in line with ERG comments

- Company conclude most clinically plausible scenarios produce ICERs that range from:
  - First line treatment: [redacted] to [redacted] per QALY
  - Subsequent line: [redacted] to [redacted] per QALY

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Slide amended following ACM2

ERG comments on company's new evidence

Additional PPS benefit for crizotinib (1)

	Company OS gain	Source	Survival gain after progression	ERG
First line	13.1 months	TA406 (crizotinib for ALK positive disease)	3.6 months (27.6%)	Based on earlier data cut from PROFILE 1014, ERG prefer recent data
	18.2 months	Midpoint between ERG's exploratory analysis (PFS=PPS) & company's original base case*	9.6 months (47.6%)	Almost 50% survival gain after progression implausible – need biological justification
Sub line	16.2 months	TA422 (crizotinib for ALK positive disease)	10.5 months (64.9%)	ERG's clinical advice: PPS gain twice that PFS implausible without justification
	20.9 months	Apply HR (0.43) to crizotinib OS curve**	15.2 months (72.8%)	Not clinically plausible for OS < PFS

*ERG exploratory analysis 0 months and company's base case 19.2 months, **midpoint between the crossover-adjusted OS HR 0.38 & PFS HR 0.49 from PROFILE 1007

ERG comments on company's new evidence

Additional PPS benefit for crizotinib (2)

	Mean (months)			
OS scenario (1st line)	OS gain	survival gain after progression	% survival gain after progression	ICER
ERG report lower estimate	9.5	0.0*	0.8%	[redacted]
Company lower bound (ACD)	13.1	3.6	27.6%	
Company upper bound (ACD)	18.2	9.6	47.6%	
Company original base case	28.7	19.2	66.7%	

*rounded

	Mean (months)			
OS scenario (subsequent line)	OS gain	survival gain after progression	% survival gain after progression	ICER
ERG report lower estimate	5.8	0.1	2.0%	[redacted]
Company lower bound (ACD)	16.2	10.5	64.9%	
Company original base case	16.3	10.7	65.2%	
Company upper bound (ACD)	20.9	15.2	72.3%	

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ERG comments on company's new evidence
Summary

Proxy data	• All ICER estimates extremely uncertain (company's new evidence still uses proxy data) • ERG considers there to be more uncertainty in the ICER estimates than is represented in the company's revised range of base case ICERs (estimates of survival gain lack sufficient justification)
Post progression benefit	• Some benefit for crizotinib is clinically plausible but size of benefit is uncertain
Utility for pemetrexed	• ERG agree 0.72 during treatment and 0.75 after treatment but only small impact on ICER
Sequential testing	• 1st line: likely to test at diagnosis • Subsequent line: sequential testing in line with clinical advice to ERG
PE costs	• Adding PE costs has small impact on ICER

Cost effectiveness of crizotinib (first-line)

Changes	ICER vs pemetrexed	
	Company	ERG
ACM1 company's base case (crizotinib mean OS gain 28.7 months, median 19.7 months)	[redacted]	N/A
ACM1 ERG's scenario with equal PPS (crizotinib mean OS gain 9.5 months, median 6.9 months)	N/A	[redacted]
Company's new base case (modelled mean OS gain 18.2 months, median 12.8 months) • Add crizotinib benefit in progressed state by applying mid-point OS gain (from company base case and ERG scenario with equal PPS), HR 0.48 • PFS utility 0.72 (on treatment) and 0.75 (off treatment) • Increased cost treating PE • Includes testing cost	[redacted]	
*ERG scenario of no survival benefit in progressed state with PFS utilities 0.75 (ICER [redacted] with utility 0.81 for both and [redacted] with utility of 0.72 for both)		

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Cost effectiveness of crizotinib (subsequent-line)

Changes	ICER vs docetaxel	
	Company	**ERG**
ACM1 company's base case (crizotinib mean OS gain 16.3 months, median 11.9 months)	[redacted]	N/A
ACM1 ERG's scenario with equal PPS (crizotinib mean OS gain 5.8 months, median 3.9 months)	N/A	[redacted]
Company's new base case (modelled mean OS gain 20.9 months) • Add crizotinib benefit in progressed state by applying mid-point OS gain from PROFILE 1007 HR 0.38 and ERG's scenario using PFS HR from PROFILE 1014 • PFS utility 0.72 (on treatment) and 0.75 (off treatment) • Increased cost treating PE • Sequential testing	[redacted]	

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Equality

- ACD: If crizotinib is available as a treatment option, ROS1 testing should be done at diagnosis to help prevent potential inequality of access

CDF recommendation decision pathway