NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Pfizer

2. **Clarification questions and company responses**

3. **Expert personal perspectives** from:
   a. Debra Montague, patient expert nominated by ALK Positive UK
   b. Professor Fiona Blackhall, clinical expert nominated by Royal College of Physicians
   c. Dr Alastair Greystoke, clinical expert nominated by Pfizer

4. **Evidence Review Group report** prepared by Aberdeen HTA Group
   a. ERG report
   b. ERG addendum
   c. ERG second addendum

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Pfizer

7. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group

8. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lorlatinib for treating ALK-positive advanced non-small cell lung cancer [ID1338]

Document B

Company evidence submission

July 2019

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Abbreviations

AE	adverse event
AIC	Akaike information criterion
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under curve
AV	atrioventricular
BIC	Bayesian information criterion
BID	twice daily
BOR	best overall response
B-M	Brookmeyer-Cowley
BMI	body-mass index
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
CBPD	crizotinib beyond progressive disease
CC	complication and comorbidity
CD137	TNF receptor superfamily member 9
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
cm	centimetre
CNS	central nervous system
CPK	creatinine phosphokinase
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA 4	cytotoxic T-lymphocyte-associated antigen 4
CYP3A4	cytochrome P450 3A4
CYP3A5	cytochrome P450 3A5
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	electronic market information tool
EML4	echinoderm microtubule-associated protein-like 4
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL 5 Dimensional scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
EXP	expansion
FAS	full analysis set
HBV	hepatitis B virus
HCV	hepatitis C virus
HELP	hydrophobic EML protein
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology assessment
IC	intracranial
IC_{50}	half-maximal inhibitory concentration
ICER	incremental cost-effectiveness ratio

ICR	Institute of Clinical Research
INV	investigator-assessed
IPD	individual patient-level data
IRC	independent review committee
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
kg	kilogram
KM	Kaplan–Meier
LFT	liver function test
LS	least square
LVEF	left ventricular ejection fraction
LY	life year
LYG	life years gained
MAIC	matching-adjusted indirect comparison
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
mL	millilitre
MRI	magnetic resonance imaging
N/A	not applicable
NE	not experienced
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reached
NSCLC	non-small cell lung cancer
OD	once daily
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PartSA	partitioned survival analysis
PAS	patient access scheme
PD	pharmacodynamic
PD-1	programmed cell death receptor-1
PDC	platinum doublet chemotherapy
PD-L1	programmed death-ligand 1
PD-L2	programmed cell death receptor-ligand-2
PF	progression free
PFS	progression-free survival
P-gp	P-glycoprotein
PH	proportional hazards assumption
PIM	Promising Innovative Medicine
PK	pharmacokinetic
PRO	patient-reported outcomes
PSA	probabilistic sensitivity analysis
PS	performance status
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QC	quality control
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire – Cancer
QLQ-LC-13	Quality of Life Questionnaire – Lung cancer
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted mean survival time
ROS1	c-ROS oncogene 1
RTK	receptor tyrosine kinase

RP2D	recommended Phase 2 dose
SAE	serious adverse event
SE	standard error
SF-36	36-Item Short Form Health Survey
SLR	systematic literature review
SMC	Scottish Medicine Consortium
SmPC	summary of product characteristic
ST	systemic therapy
TA	technology appraisal
TKI	tyrosine kinase inhibitor
ToT	time on treatment
TRAE	treatment-related adverse event
TSD	Technical Support Document
TTP	time to tumour progression
TTR	time to response
vs	versus
WD	WD repeat protein
WHO	World Health Organization
WTP	willingness to pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced ALK-positive NSCLC that has: • progressed after treatment with alectinib or ceritinib as the first ALK-tyrosine inhibitor or • progressed after treatment with crizotinib and at least one other ALK-tyrosine kinase inhibitor.	As per final scope.	N/A
Intervention	Lorlatinib	As per final scope.	N/A
Comparator(s)	For people who have not had previous chemotherapy: • Pemetrexed with cisplatin/carboplatin (adenocarcinoma or large cell carcinoma only) o with or without pemetrexed maintenance • Atezolizumab with bevacizumab, paclitaxel and carboplatin (non-squamous only) [subject to NICE appraisal]. For people who have had previous chemotherapy (but not a PD-L1 immunotherapy): • Atezolizumab (for adults with locally advanced or metastatic NSCLC who have previously received chemotherapy and targeted ALK treatment) • Pembrolizumab (for adults with locally advanced or metastatic PD-L1-NSCLC who have had at least one chemotherapy and targeted ALK treatment) • Best supportive care.	PDC (pemetrexed with cisplatin/carboplatin) as the standard of care comparator for the vast majority of patients in this indication.	Pfizer does not propose making a comparison on the basis of whether or not patients have had prior chemotherapy, for the following reasons: • The vast majority of patients will not have had prior chemotherapy, as multiple ALK TKIs are currently recommended by NICE in the first-line setting. The population who have had previous chemotherapy is shrinking at least as quickly as the population of patients who had crizotinib in first line. • The small number of patients receiving prior chemotherapy as a first-line therapy (i.e. pre-ALK TKI) would not receive lorlatinib until the fourth line, as they must first progress to crizotinib then ceritinib or brigatinib according to the NICE pathway. As the number of patients who remain alive and fit to undergo treatment reduces following each treatment through the pathway, the number of patients receiving lorlatinib as a fourth-line therapy represents a small fraction of the total

	For people who have had previous treatment with an immunotherapy (PD-L1 inhibitor): • Nintedanib with docetaxel (adenocarcinoma only) • Docetaxel • Best supportive care.		population and does not warrant a 'standard of care' comparison. • Those who have received chemotherapy at a later line (i.e. post-ALK TKI) are a temporary population that exists only in the short term because no further ALK TKIs are currently available. The recommendation of lorlatinib would render such a population (i.e. those receiving chemotherapy after an ALK TKI) obsolete. • For the small numbers of patients in these two groups, sensitivity to pemetrexed can return, thereforePDC would be the relevant comparator for many of these. Considering the above, it is important not to restrict this small number of patients who have had prior chemotherapy from the recommendation, for purposes of equity. The submitted lorlatinib trial data demonstrate the efficacy and safety of lorlatinib post-ALK TKI, regardless of whether or not patients have had prior chemotherapy. The EMA marketing authorisation does not restrict based on prior chemotherapy status and it is understood from UK clinical experts that lorlatinib will be used after a second-generation ALK TKI, irrespective of prior chemotherapy or not. It is thus suggested that lorlatinib is considered in line with its expected marketing authorisation (i.e. post-second-generation ALK TKIs, regardless of prior chemotherapy). This perspective was

			supported by repeated independent validations with clinical experts. Best supportive care (i.e. no systemic anti-cancer therapy) cannot be a comparator irrespective of previous treatment because patients receive this when they cannot tolerate or respond to ALK-inhibitors or PDC. The remaining treatments for which use is stated as being conditional on previous immunotherapy (nintedanib with docetaxel and docetaxel) cannot be comparators in this appraisal because virtually no patients have had immunotherapies in any line – this is supported by published data from the UK ALK-positive database.[1] Docetaxel is considered by clinical experts to be harder to tolerate than pemetrexed and PDC but with less likelihood of response, suggesting that it would come after PDC (if tolerable). Although atezolizumab in combination with bevacizumab, paclitaxel and carboplatin has recently been recommended for the treatment of metastatic, non-squamous NSCLC (TA584),[2] Pfizer does not believe there is any evidence to suggest that this combination constitutes a 'standard of care' comparator in the specific ALK-positive population for the following reasons: • The uptake of this combination is expected to be very small in the ALK-positive population. This combination was approved by MHRA in December 2018 for the early access to medicines scheme (EAMS) with an indication

			including ALK-positive patients. However, there is no precedent for use in the ALK-positive population via EAMS or any other free access programme. Data from the lorlatinib compassionate use programme show that no included patients (enrolled up to April 2019) had the combination in any reported lines (i.e. lines 1 to 5). The UK ALK database also shows no evidence of use in any line. Lack of previous patient and clinician use suggests low uptake. • Pfizer consulted an additional four clinical experts on the inclusion of this combination as a comparator. These experts suggested that the combination is more relevant for EGFR patients and that based on ALK patient fitness and high levels of brain metastases, uptake would be low. • The only available clinical evidence for efficacy in ALK-positive patients is the small subgroup from IMpower150 (41 patients, only 11 of which ALK-positive). Recent data indicate a non-significant benefit (HR: 0.65) in the ALK-positive population when atezolizumab is added to the combination of bevacizumab, paclitaxel and carboplatin.[3] The latter combination has not been approved for the treatment of ALK-positive patients. • Experts in the TA584 committee meeting also expected eligible patients in the ALK-positive population to be small particularly because of the levels of brain metastases (around 70% in Study 1001)

Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates (including intercranial response) • AEs • HRQoL.	As per final scope.	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of lorlatinib is conditional on ALK status. The economic modelling should include the costs associated with diagnostic testing for ALK status in	The economic analysis does not include the cost of testing for ALK status.	ALK testing is not relevant in this population as all patients will have already received an ALK TKI.

	people with advanced NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per final scope.	N/A

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; EAMS = Early Access to Medicines Scheme; EGFR = epidermal growth factor receptor; EMA = European Medicines Agency; HR = hazard ratio; HRQoL = health-related quality of life; MHRA = Medicines and Healthcare Products Regulatory Agency; N/A = not applicable; NHS = National Health Service; NICE = National Institute For Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TKI = tyrosine kinase inhibitor; UK = United Kingdom

B.1.2 Description of the technology being appraised

A summary of lorlatinib is shown in Table 2 and the draft summary of product characteristics is included in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Lorlatinib (Lorviqua®)
Mechanism of action	Lorlatinib (previously PF-06463922) is a macrocyclic, selective, adenosine triphosphate-competitive, brain penetrant, small molecule inhibitor of ALK and ROS1 RTKs.[4, 5] ALK is a member of the insulin receptor superfamily of receptors and is expressed in a number of adult human tissues, including the brain, small intestine, testis, prostate and colon.[6] ALK activates multiple cellular signalling pathways and is thought to play a role in the development and function of the nervous system. Rearrangements, mutations or amplifications of *ALK* have been identified in a number of tumour types,[7] and play an essential role in the regulation of tumour cell survival, growth and metastasis.[8] Lorlatinib has shown potent growth-inhibitory activity and induced apoptosis *in vitro*. *In vivo*, lorlatinib demonstrated marked cytoreductive activity in mice-bearing tumour xenografts that express *ALK* or *ROS1* fusion variants. In addition, lorlatinib was specifically designed to cross the blood-brain barrier through the introduction of a macrocyclic ring, and has demonstrated CNS penetrance in animal models.[9]
Marketing authorisation/CE mark status	Lorlatinib received conditional approval in the EU for the indication in this submission on 7 May 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Lorlatinib as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after: • Alectinib or ceritinib as the first ALK TKI therapy • Crizotinib and at least one other ALK TKI.[10] Lorlatinib is contraindicated or not recommended in patients who are: • Hypersensitive to lorlatinib or any of the excipients • Taking strong CYP3A4/5 inducers • Pregnant • Breast-feeding during treatment and for 7 days after the last dose.[11]
Method of administration and dosage	The recommended dose schedule of lorlatinib is 100 mg OD taken orally. Lorlatinib may be taken with or without food.

Additional tests or investigations	For the population of patients within the scope of this submission, *ALK* mutation testing is already considered standard of care in the NICE clinical guideline. In addition, as lorlatinib will be licensed following treatment with a prior ALK TKI, no additional testing is required.
List price and average cost of a course of treatment	List prices will be £5,283 for the 100 mg strength (pack of 30) and £7,044 for the 25 mg strength (pack of 120).
Patient access scheme (if applicable)	The simple PAS will be a discount of [redacted] on the list price.

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; CYP3A4/5 = cytochrome P450 3A4/5; EU = European Union; mg = milligram; NICE = National Institute For Health and Care Excellence; NSCLC = non-small cell lung cancer; OD = once daily; PAS = patient access scheme; ROS1 = ROS proto-oncogene 1; RTK = receptor tyrosine kinases; TKI = tyrosine kinase inhibitor

B.1.3 Health condition and position of the technology in the treatment pathway

Executive summary

Lung cancer

- Lung cancer is the third most common cancer in the UK,[12] with over 39,000 cases diagnosed in England and Wales in 2016.[13]
- Non-small cell lung cancer (NSCLC) is the most common subtype, accounting for 88.5% of all lung cancer cases in England and Wales.[13]
- Tumours bearing translocations of the anaplastic lymphoma kinase (*ALK*) gene represent a subset of NSCLCs, with estimated prevalence rates of between 1.6% and 5%.[14-19]
- ALK-positive NSCLCs are associated with advanced clinical stage at presentation,[20] and are more frequently observed in non-smokers and younger patients, compared with ALK-negative disease.[20-23]

Burden of ALK-positive NSCLC

- Lung cancer is the leading cause of cancer-related mortality in the UK, with an age-standardised mortality rate of 61.4 per 100,000 persons.[12]
- Survival is strongly associated with stage at diagnosis, with 1-year survival of 83% at Stage I and 17% at Stage IV.[24]
- The symptom burden of NSCLC is high, with symptoms such as fatigue, dyspnoea, cough, pain, weight loss, depression, shortness of breath and haemoptysis having a considerable impact on patients' quality of life (QoL).[25, 26]
- As ALK-positive NSCLC is associated with younger age,[20, 23] patients are more likely to be of working age, have dependents, or be carers, than those with ALK-negative disease. Therefore, the impact on both QoL and productivity loss may be particularly high in this population.
- A common site for progression in ALK-positive NSCLC is the brain,[27] with a particularly high incidence (45–70%) in patients with a history of prior ALK tyrosine kinase inhibitor (TKI) treatment.[28] Brain metastases are associated with a poor prognosis and represent a significant challenge, due to the inadequate penetration of some current treatment options, difficult accessibility and neurological symptoms.[28]

Clinical pathway of care

- In the UK, the majority of lung cancers present as locally advanced or metastatic disease with no curative treatment option.[13] The aim of treatment is therefore to prolong survival, improve QoL, and control disease-related symptoms.
- According to current National Institute for Health and Care Excellence (NICE) guidelines, first-line treatment options for ALK-positive NSCLC include chemotherapy, the first-generation ALK TKI crizotinib, and the second-generation ALK TKIs ceritinib and alectinib.[29-32]
- NICE recommended second-line treatment options include chemotherapy, crizotinib and ceritinib and brigatinib (if previously treated with crizotinib).[29, 33, 34]

Lorlatinib and unmet need

- Resistance to ALK TKIs is common, with the frequency of resistance mutations following treatment with second-generation ALK TKIs ranging from 53% to 71%.[35, 36]
    - Lorlatinib is effective against tumours bearing ALK mutations responsible for progression following treatment with current ALK TKIs.[35] As such, lorlatinib addresses the high unmet medical need for broader mutational coverage, and provides an additional treatment option for patients who progress following second-generation ALK TKIs.
- Brain metastases occur in up to 70% of patients with a history of prior ALK TKI treatment,[28] contributing to the high levels of morbidity and mortality.[37]
    - Lorlatinib was specifically designed to allow CNS penetration and retention in the intracranial (IC) space, thereby addressing the unmet need for additional treatment options for patients who develop brain metastases.

B.1.3.1 Disease overview

Lung cancer arises from the cells of the respiratory epithelium and consists of two major histological types, small-cell lung cancer and non-small cell lung cancer (NSCLC).[21] NSCLC is the most common type, accounting for 88.5% (approximately 34,500 cases in 2016) of all lung cancers in England and Wales,[13] and is further classified histologically into adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma.[13, 22]

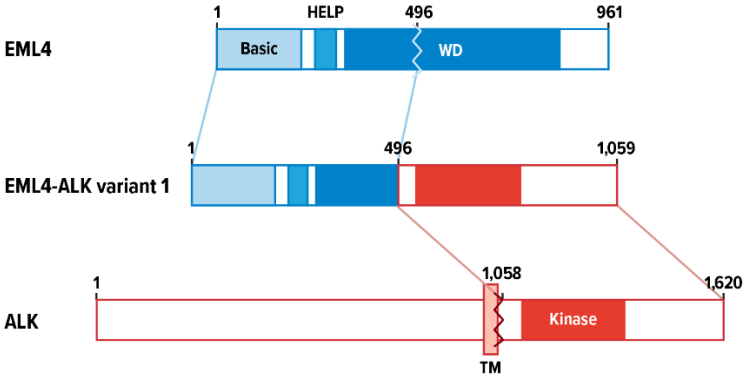
Due to the usually asymptomatic nature of lung cancer in the early stages, it is typically diagnosed at an advanced stage. In the UK, the majority of lung cancers present as inoperable locally advanced (Stage IIIb: 8%) or metastatic (Stage IV: 53%) disease with no curative treatment option.[13]

ALK fusion oncogenes are direct drivers of lung tumourigenesis

Although the pathophysiology of NSCLC is complex and not completely understood, a number of cellular and genetic mechanisms have been identified in recent years, leading to the recognition of distinct molecular subsets of NSCLC. In particular, the identification of oncogenic activation of tyrosine kinases in some advanced NSCLCs, principally mutations in the epidermal growth factor receptor (*EGFR*) and translocations of the anaplastic lymphoma kinase (*ALK*) gene or ROS proto-oncogene 1 (*ROS1*), has led to advances in the molecular diagnosis and personalised treatment of NSCLC.[38]

ALK is a member of the insulin receptor superfamily of receptors, and plays an important role in the development of the brain.[7, 39] *ALK* rearrangements, mutations or amplifications have been identified in a number of tumour types, including anaplastic large cell lymphomas, neuroblastoma and NSCLC.[7] Oncogenic fusions of *ALK* in NSCLC were first reported in 2007,[8] in which the normally inactive *ALK* gene is fused with another gene (such as echinoderm microtubule-associated protein-like 4 [*EML4*]), leading to the production of an ALK fusion protein (see Figure 1).[39] These fusion proteins play an essential role in the regulation of tumour cell survival, growth and metastasis.[8]

Figure 1. Fusion of the N-terminal portion of EML4 to the intracellular region of ALK



Abbreviations: ALK = anaplastic lymphoma kinase; EML4 = echinoderm microtubule-associated protein-like 4; HELP = hydrophobic EML protein; WD = WD repeat protein
Source: Soda et al. 2007[8]

At least 28 different *ALK* rearrangements have been identified to date, of which *EML4-ALK* is the predominant isoform, having been identified in 63.5% of *ALK*-rearranged cases.[40] At least 37 *EML4-ALK* variants have been reported to date, with variant 1 being the most common type of fusion transcript (50%), followed by variant 3a/b (26%) and variant 2 (10%).[41] Other *ALK* fusion variants present in NSCLC include kinesin family member 5B-*ALK*, kinesin light chain 1-*ALK*, *TRK*-fused gene-*ALK* and *ALK*-protein tyrosine phosphatase.[42]

Lung cancer is the most common cancer in the world

Globally, there were over 1.8 million new cases of lung cancer diagnosed in 2012, representing 12.9% of all incident cancer cases.[43] In the UK, lung cancer is the third most common cancer, accounting for 13% of all incident cancer cases (excluding non-melanoma skin cancer).[12] In 2016, there were over 39,000 new cases of lung cancer in England and Wales.[13] As of 2015, the UK age-standardised incidence of lung cancer was 78.1 cases per 100,000 persons.[12]

The incidence of lung cancer is strongly associated with age, with incidence rates rising sharply from age 45–49 years (6.8 cases and 5.5 cases per 100,000 persons for men and women, respectively).[12]

While lung cancer incidence rates have decreased by 7% in the UK since the early 1990s, there has been a 4% increase in the past decade (between 2003–2005 and 2012–2014).[12, 44-47]

Patients with ALK-positive NSCLC represent a unique lung cancer subpopulation

ALK translocation occurs almost exclusively in adenocarcinoma NSCLCs, which represent 36% of NSCLC cases in England and Wales (approximately 14,040 in 2016).[13] Estimates of the prevalence of the *ALK* fusion oncogene in NSCLC vary, with studies in non-selected patients with NSCLC reporting a prevalence of between 1.6% and 5%.[14-19] *ALK* mutations have been reported at a rate of 3.4% in patients with adenocarcinomas, which is the predominant histological subtype in NSCLC.[48] An estimation of the incidence of ALK-positive NSCLC in the UK is shown in Table 3.

Table 3. Estimated number of patients with ALK-positive NSCLC in England and Wales

Assumption		Estimated number of patients	Calculation
A	Number of patients diagnosed with lung cancer per year[13]	39,001	N/A
B	Number of patients with NSCLC (88.5%)[13]	34,516	A × 0.885
C	Number of patients with Stage IIIB–IV NSCLC (61%)[13]	21,055	B × 0.610
D	Number of patients with adenocarcinoma pathological subtype (52.5% of patients with confirmed pathological subtype)[13]	11,054	C × 0.525
E	Number of adenocarcinoma patients with ALK-positive Stage III–IV NSCLC (3.4%)[48]	376	D × 0.034
F	Number of patients with ALK-positive Stage III–IV NSCLC, all subtypes (93.9%)[49]	400	E/0.939

Abbreviations: ALK = anaplastic lymphoma kinase; N/A = not applicable; NSCLC = non-small cell lung cancer

Patients with ALK-positive NSCLC are generally younger than other patients with NSCLC, with brain metastases a more frequent complication

ALK-positive NSCLCs are associated with advanced clinical stage at presentation, and are mostly adenocarcinomas.[20, 22] Compared with ALK-negative patients, those with ALK-positive NSCLC are more often non-smokers,[20, 21] and are typically younger, with a median age in the early 50s for ALK-positive patients, compared with mid-to-late 60s for ALK-negative NSCLC.[20, 23] In addition, brain metastases are a frequent complication of ALK-positive NSCLC, occurring in approximately 30% of ALK-positive patients.[27]

B.1.3.2 Burden to patients, carers and society

The prognosis of ALK-positive NSCLC is poor and is likely worse than that of ALK-negative NSCLC, but the introduction of ALK tyrosine kinase inhibitors is improving survival

As well as being the most common cancer, lung cancer is the leading cause of cancer-related mortality worldwide, estimated to be responsible for 19.4% of total cancer deaths.[43] As such, more patients die of lung cancer than of breast, colon and prostate cancers combined.[43] The prognosis of locally advanced or metastatic lung cancer is poor, with survival strongly associated with stage at diagnosis. In England, 1-year survival rates decrease from 83% at Stage I to 17% for patients diagnosed at Stage IV.[24] Unlike the majority of cancers, 5-year and 10-year survival rates for lung cancer have shown little improvement since the 1970s. For individuals in the UK diagnosed between 2010 and 2011, the predicted 5-year and 10-year survival rates were 9.5% and 4.9%, respectively.[12]

The majority of analyses that controlled for known confounding factors suggest that ALK positivity is a negative prognostic factor in NSCLC.[50] However, ALK-targeted therapies have yielded promising results in clinical trials, with median overall survival (OS) not reached after 46 months of follow-up following treatment with crizotinib.[51] Further innovation in the development of agents directed at ALK would therefore be expected to improve outcomes further.

Reduced quality of life and functioning is particularly burdensome in patients with ALK-positive NSCLC

While the majority of the burden of lung cancer is related to mortality, it also has a significant negative impact on patients' quality of life (QoL), well-being and social functioning. A number of symptoms of NSCLC can affect patients' QoL, including fatigue, dyspnoea, cough, pain, weight loss, depression, shortness of breath and haemoptysis.[25, 26] Increasing symptom severity and the number of symptoms experienced are both negatively correlated with QoL,[52-54] and patients with the most debilitating symptoms at presentation typically continue to report symptom-related distress, primarily fatigue and pain.[26]

Health-related QoL (HRQoL) has been shown to be associated with survival, with global QoL and physical functioning scores of the disease-specific European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Cancer (QLQ-C30) being predictive of survival among 1,194 patients with NSCLC, most of whom (55%) were diagnosed with Stage IV disease. For every 10-point improvement in global QoL or physical functioning scores, there was a 9% and 10% increase in survival, respectively.[55] In addition, better 36-Item Short Form Health Survey (SF-36) general health and QLQ-C30 global QoL scores are associated with a lower risk of death among patients with NSCLC who have undergone initial therapy.[56]

As ALK-positive NSCLC is associated with younger age (median age in the early 50s),[20, 23] ALK-positive patients are more likely to be of working age, have dependents, or be carers, than those with ALK-negative disease. Therefore, the impact of reduced QoL and functioning may be particularly burdensome in this population. In addition, the high incidence of brain metastases in ALK-positive NSCLC is likely to have a further negative impact on QoL; brain metastases may result in neurological dysfunction and cognitive impairment,[28] and are associated with significant reductions in QoL.[57]

The direct and indirect economic costs of NSCLC increase with disease progression and are particularly high in patients with ALK-positive NSCLC

In addition to the high clinical burden of disease, lung cancer has a significant economic impact through increased healthcare resource use, as well as indirect medical and non-medical costs. Studies assessing the overall economic burden of lung cancer have consistently found that lung cancer is a costly illness, and that hospitalisation and medical treatment account for a large portion of direct costs.[58],[59]

As patients with ALK-positive NSCLC are typically younger than patients who are ALK-negative,[20, 23] and are therefore more likely to be of working age, costs associated with productivity loss can be expected to be higher in this population. The economic burden of NSCLC on carers is also substantial, and has been shown to increase over time with disease progression;[60, 61] this burden is compounded when ALK-positive patients are themselves carers.

B.1.3.3 Clinical pathway of care

The European Society for Medical Oncology (ESMO) currently recommends that ALK rearrangement testing is carried out in all patients with advanced non-squamous cell carcinoma.[62] NICE recommends that ALK status testing should be performed for all patients

with non-squamous NSCLC at diagnosis,[63] and clinical experts have confirmed that testing is widespread.

The identification of the mutations and genetic rearrangements present in subsets of NSCLC patients has enabled the development of selective, pathway-directed systemic therapies tailored to individual patients.[49, 64-67] For patients with ALK-positive NSCLC, ALK TKIs are now approved as first- and second-line therapies; the ALK TKIs currently available in the UK are shown in Table 4.

Table 4. ALK TKIs currently approved for the treatment of ALK-positive NSCLC in the UK

Generation	Name	Indication
First	Crizotinib (Xalkori®)	Crizotinib as monotherapy is indicated for: • The first-line treatment of adults with ALK-positive advanced NSCLC • The treatment of adults with previously treated ALK-positive advanced NSCLC • The treatment of adults with ROS1-positive advanced NSCLC.[68]
Second	Ceritinib (Zykadia®)	Ceritinib as monotherapy is indicated for: • The first-line treatment of adult patients with ALK-positive advanced NSCLC • The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[69]
	Alectinib (Alecensa®)	Alectinib as monotherapy is indicated for: • The first-line treatment of adult patients with ALK-positive advanced NSCLC • The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[70]
	Brigatinib (Alunbrig®)	Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK-positive NSCLC previously treated with crizotinib.

Abbreviations: ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor; UK = United Kingdom

Crizotinib, ceritinib, alectinib and brigatinib are currently recommended for the treatment of ALK-positive NSCLC by both NICE and ESMO.[30-34, 62, 71] A summary of NICE recommendations for the treatment of advanced ALK-positive NSCLC is shown in Table 5.

Table 5. Current NICE guidelines for the treatment of advanced ALK-positive NSCLC

Treatment line	Recommendation
First	• PDC (patients with Stage III or IV NSCLC and good PS) or single-agent chemotherapy for patients who are unable to tolerate a platinum combination[29] • Crizotinib[31] • Ceritinib[30] • Alectinib[32]
Second	• Chemotherapy[29] • Crizotinib[34] • Ceritinib, if previously treated with crizotinib[33] • Brigatinib, if previously treated with crizotinib[71]

Abbreviations: ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PS = performance status

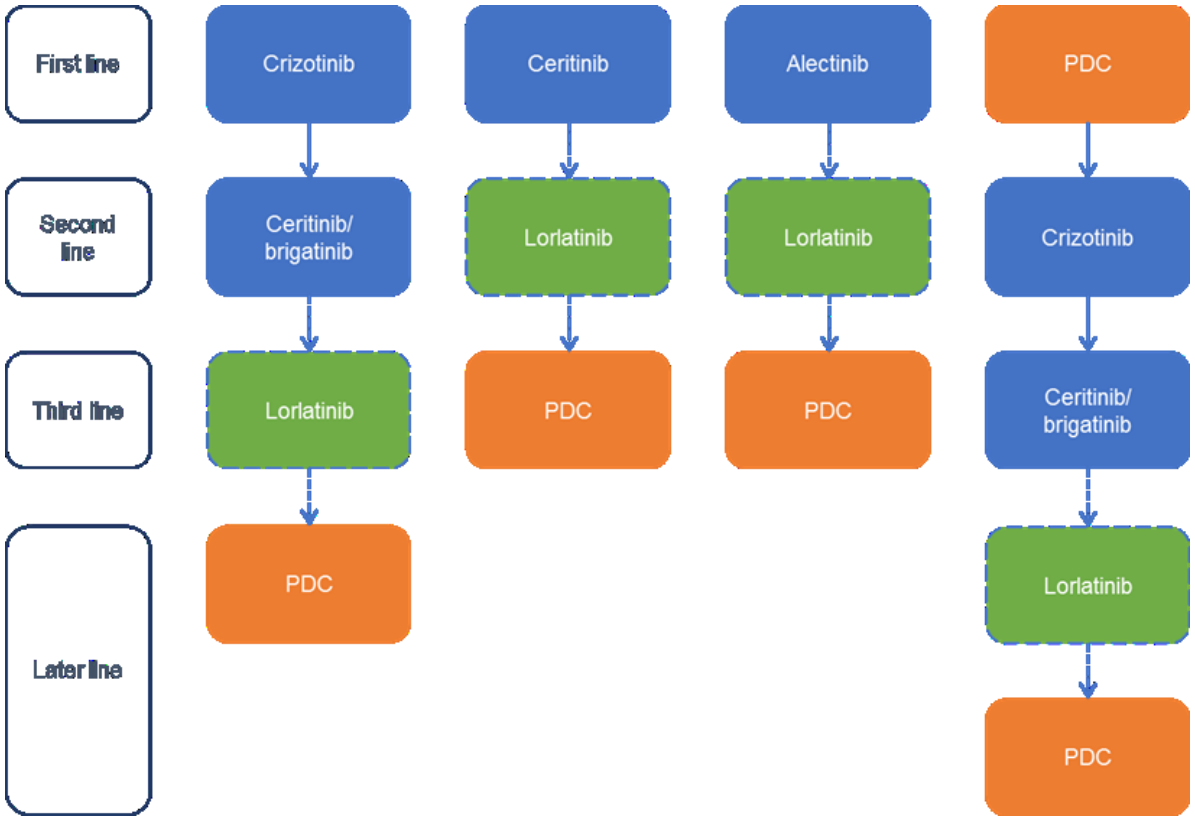
The introduction of second-generation ALK TKIs provided the opportunity to sequence multiple targeted therapies, with ceritinib or brigatinib as options for patients who have

progressed following treatment with crizotinib. However, data on the sequencing of therapies for ALK-positive NSCLC are limited and the optimal treatment pathway is not yet clear. Expert opinion suggests that clinicians aim to maximise the time patients are treated with targeted ALK TKIs. When the current choice of ALK TKIs is exhausted, platinum doublet chemotherapy (PDC) is generally preferred before immunotherapy (pembrolizumab/atezolilumab), with or without chemotherapy.

Following approval by the European Medicines Agency (EMA), lorlatinib will provide an additional treatment option for patients with ALK-positive advanced NSCLC previously treated with one or more second-generation ALK TKIs.[11] The possible treatment pathways following NICE approval of lorlatinib are shown in Figure 2; with the introduction of lorlatinib extending the possible treatment time with targeted ALK TKIs, thereby delaying the need for subsequent chemotherapy. Real-world evidence from the lorlatinib compassionate use programme demonstrates that the cohort used to inform the cost-effectiveness model closely reflects the population expected to receive lorlatinib in England and Wales (see Appendix R), and clinical expert opinion has consistently suggested that:

- The pathway beginning with Alectinib will become the standardised pathway for up to 90% of ALK+ NSCLC patients in the near future;
- The pathway beginning with chemotherapy represents a small and rapidly shrinking patient pool.

Figure 2. Treatment pathways for patients with ALK-positive NSCLC, based on licensed indications and current NICE guidance, following the introduction of lorlatinib



Abbreviations: ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy

B.1.3.4 Lorlatinib and unmet need

A number of limitations exist in the current treatment pathway for ALK-positive NSCLC, including resistance to existing ALK TKIs, suboptimal efficacy against brain tumours, and chemotherapy-related toxicities and the associated impact on QoL and functioning.[72]

Resistance to ALK TKIs is common and immunotherapies (with or without chemotherapy) have limited efficacy in patients with ALK-positive NSCLC

Crizotinib was the first targeted therapy to be approved for the treatment of ALK-positive advanced NSCLC, having demonstrated superior efficacy compared with chemotherapy.[49] Although most patients with ALK-positive NSCLC experience rapid and durable disease control from crizotinib treatment, some patients with ALK-positive NSCLC will not derive any benefit (intrinsic resistance), and other patients who initially experience benefit will later develop resistance (acquired resistance) due to the emergence of secondary *ALK* mutations and the activation of bypass resistance mechanisms.[73] Progression of pre-existing, or development of new brain metastases is also a common manifestation of acquired resistance to crizotinib.[74] Approximately 20–30% of patients develop ALK-related resistance following crizotinib treatment,[35, 36] and most patients tend to relapse within the first year of treatment.[75]

To address the issue of crizotinib treatment failure through intrinsic and acquired resistance, second-generation ALK TKIs have been developed. These compounds - alectinib, ceritinib, and brigatinib - have shown therapeutic benefit in clinical trials.[49, 64-67] However, as with the development of resistance to treatment with crizotinib, a number of *ALK* mutations have been observed following treatment with second-generation ALK TKIs in clinical settings.[76] The frequency of resistance mutations following treatment with second-generation ALK TKIs is significantly higher than that reported following treatment with crizotinib, with reported resistance rates of 53–71% (including patients previously treated with crizotinib), compared with 20–30% following crizotinib therapy.[35, 36]

Each ALK TKI is associated with a distinct spectrum of resistance mutations, with the most common mutation among patients who progress following treatment with second-generation ALK TKIs being *EML4-ALK*^{G1202R}, which has been identified in 21–50% of cases.[35] Crizotinib, ceritinib, alectinib and brigatinib have all been shown to be inactive against *EML4-ALK*^{G1202R}, and the double mutants *EML4-ALK*$^{D1203N+E1210K}$ and *EML4-ALK*$^{D1203N+F1174C}$ *in vitro*. In addition, while *EML4-ALK*^{F1174C} and *EML4-ALK*^{I1171T} appear sensitive to ceritinib and alectinib, respectively, *in vitro*, prior clinical reports suggest that these mutations may not be susceptible to these agents *in vivo* (see Section B.2.11, Figure 18).[35, 77-79]

In patients with ALK-positive NSCLC, 5-year OS has been reported as 42.9%.[80] Extended survival is possible with access to optimum therapy consisting of sequential ALK TKIs, with a reported median OS of 51 months among patients who received crizotinib followed by ceritinib, compared with 18 months for those who received crizotinib alone.[81]

Among patients whose disease has progressed on ceritinib, alectinib or brigatinib, chemotherapy is the standard of care, as no other ALK TKIs are currently licensed in this setting. However, outcomes with chemotherapy in this population have been modest—in a randomised Phase 3 trial of alectinib versus chemotherapy in patients with ALK-positive NSCLC previously treated with chemotherapy and crizotinib, chemotherapy had an objective response rate (ORR) of 11.4%, and a median progression-free survival (PFS) of just 1.6

months.[64] In addition, adverse events (AEs) related to chemotherapy, such as neutropenia, fatigue, nausea and alopecia, are burdensome to patients and have a detrimental effect on QoL,[64, 66] with 41.2% of patients in the chemotherapy arm of the above trial experiencing severe to fatal AEs.[64]

While the immune checkpoint inhibitors pembrolizumab and atezolizumab have been approved for the treatment of patients with advanced NSCLC, including later-line treatment of ALK-positive NSCLC, both are recommended only for patients who have received chemotherapy and a prior ALK TKI.[82, 83] In addition, there are limited data on their activity in patients with ALK-positive NSCLC. Phase 3 trials enrolled very few patients (<1%) who were ALK-positive, and subgroup analyses found that these patients did not benefit from immune checkpoint inhibitors.[84] Retrospective data have also indicated that *ALK* rearrangements are associated with low response rates to programmed death-ligand 1 (PD-L1) pathway blockade in NSCLC.[85] For the combination of atezolizumab with bevacizumab, paclitaxel and carboplatin, recent IMpower150 subgroup analyses demonstrated a non-significant effect in ALK-positive patients with NSCLC versus the combination without atezolizumab.[3] For patients who are considered unfit to undergo chemotherapy and not eligible for treatment with PD-L1 inhibitors, there are currently no further treatments available.

Therefore, despite the introduction of effective ALK and immune checkpoint inhibitors over the past several years, for patients who progress following second-generation ALK TKIs, there is a lack of treatment options to enable sequential targeted therapy. In addition, existing ALK TKIs have proven ineffective against some resistance mutations. Lorlatinib was specifically designed for activity against tumours bearing ALK TKI-resistance mutations, including the G1202R mutation, which is the most common ALK mutation among patients who have progressed following treatment with first- and/or second-generation ALK TKIs.[35] As such, lorlatinib addresses the high unmet medical need for broader mutational coverage, and provides an additional treatment option for patients who have developed resistance to existing ALK TKIs (see Section B.2.11 for further information on lorlatinib's mutational coverage).

Brain metastases occur in up to 70% of patients with a history of prior ALK TKI treatment, and contribute to high levels of morbidity and mortality

The brain is a common site for progression in metastatic NSCLC.[27] ALK-positive NSCLC patients with a history of prior ALK TKI treatment (including second-generation ALK TKIs) have a particularly high incidence of brain metastases, with estimates ranging from approximately 45% to 70%.[28] Brain metastases are associated with a poor prognosis and represent a significant challenge, due to the inadequate penetration of some current treatment options, difficult accessibility and neurological symptoms.[28] Central nervous system (CNS) progression in relapsed patients therefore contributes substantially to the high levels of morbidity and mortality associated with ALK-positive NSCLC.[37]

In patients with brain metastases, crizotinib has shown limited clinical activity[74, 86-88] due to low CNS penetration,[89] and progression in the brain is particularly common among patients who relapse following crizotinib treatment.[74, 90] Ceritinib has also demonstrated lower intracranial (IC) disease control rates in patients previously treated with crizotinib, compared with crizotinib-naïve patients.[91] Systemic chemotherapy is of limited use in this setting, with low IC-ORRs.[67] For example, in the recent Phase 3 trial of alectinib in patients previously treated with crizotinib and platinum-based chemotherapy, the IC-ORR in patients with brain metastases in

the chemotherapy control arm (n=35) was 0%.[64] Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is also of limited use in this population, with clinical experts suggesting that brain metastases will limit access to this combination (see the TA584 committee discussion).

Due to the lack of effective treatment options for patients with CNS progression following treatment with second-generation ALK TKIs, additional treatment options are required with improved activity against brain metastases. Lorlatinib was specifically designed to allow CNS penetrance and retention in the IC space, thereby addressing the unmet need for an effective therapy for patients with ALK-postive NSLC with brain metastases.

B.1.4 Equality considerations

There are no known equality issues relating to the use of lorlatinib in patients with ALK-positive NSCLC.

B.2. Clinical effectiveness

Summary of clinical evidence

The clinical effectiveness of lorlatinib as a single agent in adult patients with ALK-positive advanced NSCLC, previously treated with first- and/or second-generation ALK TKIs, has been established in the ongoing multicentre, Phase 1/2, multiple-dose, dose escalation, safety, PK, PD, and anti-tumour activity study (Study 1001). Data are reported in this submission for the latest data cut-off, 2 February 2018. The sample consisting of expansion cohorts EXP-3B, EXP-4 and EXP-5 (patients who have progressed after one or more prior ALK TKIs) is the most relevant population for this submission and is the data used to inform efficacy in the model (see Section B.2.3.1). Data are summarised below for the pooled EXP-3B:5 cohort.

Co-primary outcomes – tumour response

- Over one-third of patients achieved a tumour response to lorlatinib with a majority of patients experiencing tumour shrinkage (ORR: 40.3% [95% confidence interval, CI: 32.1–48.9])
  - The proportion of patients who achieved an objective response with lorlatinib treatment after one or more prior ALK TKIs contrasts with the poor responses seen after chemotherapy
  - The lower boundary of the 95% CI (32.1%) around the observed proportions of patients with objective response exceeded the proportions of patients with objective response reported for single-agent chemotherapy in the ALUR (2·9–11·4%)[64, 92] and ASCEND-5 trials (6·9%)[66]
- Almost half of patients with brain metastases achieved intercranial tumour response to lorlatinib with a majority of patients experiencing tumour shrinkage (IC-ORR: 47.9% [95% CI: 37.5–58.4]), consistent with the ability of lorlatinib to cross the blood brain barrier

Secondary outcomes

- Time to first tumour response (TTR) was less than 2 months for the majority of patients, including patients with brain metastases (TTR: 1.4 months [range 1.2–16.6]; IC-TTR: 1.4 months [range 1.2–16.2])
- Responses were sustained for a median of 7 months and 15 months for patients with brain metastases (DOR: 7.1 months [95% CI: 5.6–24.4]; IC-DOR: 14.5 months [95% CI: 11.1–NR])
- Disease control rate (DCR) was observed for over half of patients at 12 weeks (DCR: 59.7% [95% CI: 51.1–67.9]) and almost half of patients at 24 weeks (DCR: 43.2% [95% CI: 34.8–51.8])
- For patients with brain metastases, disease control rate was observed for approximately three-quarters of patients at 12 weeks (IC-DCR: 73.4% [95% CI: 63.3–82.0]) and over half of patients at 24 weeks (IC-DCR: 55.3% [95% CI: 44.7–65.6])
- Lorlatinib provided a median progression-free survival (PFS) of 7 months (median PFS: 6.9 months [95% CI: 5.4–8.2]) and a median overall survival (OS) of 20 months (median OS: 20.4 months [95% CI: 16.1–NR]) with an OS probability of 67.8% and 55.6% at 12 and 18 months, respectively.
- The median PFS also numerically exceeded the median PFS for chemotherapy in ALUR and ASCEND-5 (1·6 months for both trials).[64, 66, 92]
- Treatment with lorlatinib led to a clinically meaningful improvement in global QoL, functioning and patient-reported symptoms.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant literature regarding the efficacy and safety of lorlatinib as a second-line or later-line of therapy for ALK-positive advanced/metastatic NSCLC. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to lorlatinib.

B.2.2 List of relevant clinical effectiveness evidence

This submission is supported by data from the ongoing Phase 1/2 B7461001 study (NCT01970865; Study 1001). An overview of Study 1001 is provided in Table 6. Data sources for this submission include the Study 1001 clinical study report,[93] Solomon et al. 2018, which reported Phase 2 data to a cut-off date of March 2017[94] and Pfizer data on file (latest data cut-off date of February 2018).[95]

Table 6. Clinical effectiveness evidence

Study	B7461001 (NCT01970865; Study 1001; latest data cut-off date: 2 February 2018)				
Study design	Open-label, multicentre Phase 1/2 study				
Population	Adult patients with metastatic ALK-positive or ROS1-positive NSCLC				
Intervention(s)	Lorlatinib				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Efficacy data for lorlatinib is used in the model because this is the only study that currently provides data for lorlatinib in the population and line of relevance to this submission.				
Reported outcomes specified in the decision problem	• **OS** • **PFS** • Response rates (ORR) • **AEs** • **HRQoL**				
All other reported outcomes	• IC-ORR • TTR and IC-TTR • DOR and IC-DOR • DCR and IC-DCR • TTP and IC-TTP				

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; DCR = disease control rate; DOR = duration of response; HRQoL = health-related quality of life; IC = intracranial; N/A = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; ROS1 = ROS proto-oncogene 1; TTP = time to tumour progression; TTR = time to tumour response

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of Study 1001 methodology is provided in Table 7.

Table 7. Study 1001 methodology

Trial number	B7461001 (NCT01970865; Study 1001)
Location (number of centres in which patients were randomised to lorlatinib)	Australia (2), Canada (1), France (4), Germany (1), Hong Kong (1), Italy (4), Japan (10), Korea (1), Singapore (2), Spain (4), Switzerland (2), Taiwan (1), US (11)
Study design	Ongoing Phase 1/2, open-label, multicentre, multiple-dose, dose escalation, safety, PK, PD, and anti-tumour activity study of lorlatinib as a single agent in adult patients with metastatic (Stage IV) ALK-positive or ROS1-positive NSCLC
Study objectives	Phase 1 primary objective: • Assess the safety and tolerability of lorlatinib as a single agent at increasing dose levels in patients with advanced ALK- or ROS1-positive NSCLC in order to estimate and select the recommended phase II dose (RP2D) Phase 2 primary objective: • Evaluate overall and IC anti-tumour activity of single-agent lorlatinib at RP2D in patients with advanced ALK- or ROS1-positive NSCLC

Eligibility criteria	Inclusion criteria:
	• Age ≥18 years (or ≥20 years, if required by local regulations)
	• Histologically or cytologically-confirmed diagnosis of metastatic (Stage IV) NSCLC
	• Confirmed presence of an *ALK* or *ROS1* gene rearrangement
	• At least one measurable target extracranial lesion according to RECIST version 1.1
	• Adequate bone marrow, renal and hepatic function
	• ECOG PS of:
	  ○ 0 or 1 in Phase 1
	  ○ 0, 1, or 2 in Phase 2
	• Prior treatment:
	  ○ Phase 1: treatment naïve in the advanced setting or disease progression after at least 1 previous ALK or ROS1 inhibitor
	  ○ Phase 2: treatment naïve in the metastatic setting or disease progression after 1–3 ALK TKIs, with or without prior chemotherapy (ALK-positive patients), or any number of ROS1 therapies
	• Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 (except for AEs that did not constitute a safety risk)
	• Serum pregnancy test negative at screening (for females of childbearing potential) and the use of two highly effective methods of contraception from screening, until 90 days after the last dose
	Exclusion criteria:
	• Spinal cord compression, unless the patient demonstrated good pain control with therapy and stabilisation or recovery of neurological function for four weeks prior to study entry
	• Major surgery within four weeks of study entry

	• Radiation therapy within two weeks of study entry, unless palliative to relieve bone pain and completed at least 48 hours prior to study entry. Stereotactic/small field brain irradiation and whole brain radiation had to be completed at least two or four weeks prior to study entry, respectively • Systemic anti-cancer therapy completed within 5 half-lives of study entry • Prior T-cell co-stimulation- or immune checkpoint pathway-targeted therapy (including, but not limited to anti-PD-1, PD-L1, PD-L2, CD137 or CTLA-4 therapy) • Previous high-dose chemotherapy requiring stem cell rescue • Prior irradiation to >25% of the bone marrow • Active and clinically significant bacterial, fungal, or viral infection including HBV, HCV, HIV or AIDS-related illness • Clinically significant cardiovascular disease or abnormal LVEF • Predisposing characteristics for acute pancreatitis • History of extensive, disseminated, bilateral or presence of Grade 3/4 interstitial fibrosis or interstitial lung disease • Active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease or previous gastric resection or lap band • Other severe acute or chronic medical or psychiatric condition
Trial drugs	• Phase 1: lorlatinib (n=55) • Phase 2: lorlatinib (n=275)
Permitted and disallowed concomitant medication	Allowed concomitant therapies included: • Bisphosphonate therapy for metastatic bone disease • Palliative radiotherapy for the treatment of painful bony lesions • Granulocyte-colony stimulating factors for treatment-emergent neutropenia • Erythropoietin for the supportive treatment of anaemia • Anti-diarrhoeal, anti-emetic and acid-reducing therapy, except in the first cycle of Phase 1 • Anti-inflammatory or narcotic analgesics • Palliative and supportive care for disease-related symptoms • Topical or oral corticosteroids • Testosterone replacement therapy • Statins (recommended at the first signs of elevated cholesterol and/or triglycerides. Statins of choice were pitavastatin or pravastatin, followed by rosuvastatin. Similarly, if hypertriglyceridemia required treatment, fenofibrate or fish oils, followed by nicotinic acid were recommended). The following concomitant therapies were disallowed, or caution warranted: • Additional systemic anti-tumour therapy • Strong/moderate CYP3A4 inhibitors or strong CYP3A4 inducers • CYP2C9 or CYP2B6 substrates • CYP3A4 or P-gp substrates with a narrow therapeutic index • Surgical procedures
Primary outcomes	• ORR • IC-ORR
Secondary outcomes	• TTR and IC-TTR • DOR and IC-DOR • DCR and IC-DCR at 12 weeks and 24 weeks • TTP and IC-TTP • PFS • OS

	• Probabilities of survival at 1 year and 18 months
PROs	• EORTC QLQ-C30 • EORTC QLQ-LC13
Safety assessments	• AEs • SAEs • Vital signs and physical examination • ECG • Echocardiogram or multi-gated acquisition scan • Laboratory assessments • Neurological assessments • Deaths
Pre-planned subgroups	N/A

Abbreviations: AE = adverse event; AIDS = acquired immunodeficiency syndrome; ALK = anaplastic lymphoma kinase; CD137 = TNF receptor superfamily member 9; CTCAE = Common Terminology Criteria for Adverse Events; CTLA 4 = cytotoxic T-lymphocyte-associated antigen 4; CYP3A4 = cytochrome P450 3A4; CYP2B6 = cytochrome P450 2B6; CYP2C9 = cytochrome P450 2C9; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IC = intracranial; LVEF = left ventricular ejection fraction; N/A not applicable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic; PD-1 = programmed cell death receptor-1; P-gp = P-glycoprotein; PD-L1 = programmed cell death receptor-ligand-1; PD-L2 = programmed cell death receptor-ligand-2; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; QLQ-C30 = Quality of Life Questionnaire – Cancer; QLQ-LC13 = Quality of Life Questionnaire – Lung Cancer; ROS1 = ROS proto-oncogene 1; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TKI = tyrosine kinase inhibitor; TTP = time to tumour progression; TTR = time to tumour response
Source: Pfizer Limited, 2017[93]

B.2.3.1 Study cohorts

In Phase 2, efficacy was explored in expansion (EXP) cohorts of patients defined by ALK/ROS1 status, prior treatment and treatment line (see Table 8).[93] Cohorts EXP-3B, EXP-4 and EXP-5 reflect the population most relevant to this submission. Data from pooled cohorts EXP-3B, EXP-4 and EXP-5 (EXP-3B:5) were used to inform efficacy in the cost-effectiveness model.

Table 8. Study 1001 EXP cohorts

ALK/ROS1 status	Cohort	Prior treatment regimen
ALK-positive	EXP-1	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI therapy)
	EXP-2	Patients relapsing after crizotinib therapy only
	EXP-3A	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Patients relapsing after one ALK TKI therapy other than crizotinib with or without any number of prior chemotherapy regimens
	EXP-4	Patients relapsing after two prior ALK TKI therapies with or without any number of prior chemotherapy regimens
	EXP-5	Patients relapsing after three or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens
ROS1-positive	EXP-6	Treatment naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor
Source: Pfizer Limited, 2017[93]

B.2.3.2 Study treatment

In the Phase 1 portion of the study, lorlatinib was administered once daily (OD) or twice daily (BID), in 21-day cycles. The starting dose was 10 mg OD, with escalating doses of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg and 400 mg OD, depending on toxicities observed. BID dosing was not originally planned, but was also tested to support identification of the recommended Phase 2 dose (RP2D).[93]

A dose of 100 mg OD was identified as the RP2D, based on safety, efficacy and clinical pharmacology data, and was administered in 21-day cycles in each EXP cohort in the Phase 2 portion of the study.[93] The 100 mg OD dose was identified as the lowest dose that would exceed the minimum efficacious concentration of 150 ng/mL to inhibit ALK^{G1202R},[93] which is the most common *ALK* mutation among patients who have progressed following treatment with second-generation ALK TKIs.[35]

In the event of significant toxicity, dosing was allowed to be withheld and/or reduced. Following dosing interruption or cycle delay due to toxicity, the lorlatinib dose could be reduced when treatment was resumed. In Phase 2, dose reduction levels were 75 mg, 50 mg and 25 mg OD. Dose re-escalation was allowed at the discretion of the investigator.[93]

B.2.3.3 Assessments and outcomes

A complete list of the efficacy outcomes (and their definitions) is provided in Table 9. The evaluation of anti-tumour activity was based on objective tumour response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and the modified RECIST for IC response assessment. Tumour assessments included all known or suspected disease sites. Computed tomography (CT) scans of the chest, abdomen and pelvis, and magnetic resonance imaging (MRI) of the brain were performed at screening and every six weeks for the first 25 cycles or 38 cycles, and then every 12 weeks, in Phase 1 and 2, respectively, until documented disease progression. Gadolinium contrast enhanced MRI was used to assess

CNS lesions. A bone scan was required at screening and every 12 weeks during the treatment period if bone was a disease site at screening. Primary and secondary efficacy analyses (except OS), were performed according to Institute of Clinical Research (ICR) and derived investigator assessment. The analyses based on ICR assessment were considered primary.[93]

Table 9. Study 1001 efficacy outcomes

Effiacy outcome	Definition
Primary	
ORR	Proportion of patients with a BOR,* defined as confirmed CR or PR
IC-ORR	Proportion of patients with a best overall IC response, defined as confirmed CR or PR, considering only the brain as the disease site, relative to patients with brain lesions at study entry
Secondary	
TTR	Time from C1D1 to first documentation of objective response (CR or PR)
IC-TTR	Time from C1D1 to first documentation of IC objective response (CR or PR, considering only the brain as the disease site)
DOR	Time from the first documentation of objective tumour response (CR or PR), to the first documentation of disease progression or death associated with any cause, whichever occurs first
IC-DOR	Time from the first documentation of objective IC tumour response (CR or PR, considering only the brain as the disease site), to the first documentation of disease progression or death associated with any cause, whichever occurs first
DCR	The proportion of patients with disease control (CR, PR or stable disease) at 12 weeks and 24 weeks
IC-DCR	The proportion of patients with IC disease control (CR, PR or stable disease, considering only the brain as the disease site) at 12 weeks and 24 weeks
TTP	Time from C1D1 to the date of the first documentation of objective tumour progression
IC-TTP	Time from C1D1 to the date of the first documentation of objective progression of IC disease, based on either new brain metastases or progression of existing brain metastases
PFS	Time from C1D1 to first documentation of objective disease progression or death on study due to any cause, whichever came first
OS	Time from C1D1 to the date of death due to any cause

Abbreviations: BOR = best overall response; C1D1 = Cycle 1 Day 1; CR = complete response; DCR = disease control rate; DOR = duration of response; IC = intracranial; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TTP = time to tumour progression; TTR = time to tumour response
*BOR was defined as the best response recorded from the start of treatment (C1D1) until progression or start of new anti-tumour therapy (based on objective tumour response according to RECIST version 1.1, and the modified RECIST for IC response assessment), whichever occurred earlier
Source: Pfizer Limited, 2017[93]

Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30 and the corresponding lung cancer module (QLQ-LC13).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population

Analysis sets defined in Study 1001 included:

- Full analysis set (FAS): All enrolled patients, regardless of whether or not treatment was received.

- Intention-to-treat (ITT) analysis set: All enrolled patients with documented *ALK* or *ROS1* gene rearrangement who received at least one dose of lorlatinib. Patients without documentation of an *ALK* or *ROS1* rearrangement were excluded (the ITT population was considered to be the primary analysis set for all efficacy evaluations).
- Safety analysis set: All enrolled patients who received at least one dose of lorlatinib (including lead-in dose).
- PRO-evaluable analysis set: All enrolled patients who received at least one dose of lorlatinib and completed a baseline and at least one post-baseline PRO assessment.[93]

In Phase 2, analyses of efficacy endpoints were conducted by EXP cohorts. However, to allow for a broader HRQoL assessment, PRO analyses were performed using the PRO-evaluable analysis set, which included the entire patient population (cohorts EXP-1 to EXP-6).

B.2.4.2 Statistical tests

No formal statistical hypothesis was planned for Phase 1. In Phase 2, for subpopulations EXP-1:5 the goal of the primary analysis of objective response was to estimate the ORR and their exact 95% confidence intervals (CIs).[96]

Binary data: Binary endpoints were summarised by percentage rates along with the 95% CIs using an exact method.

Continuous data: Descriptive statistics, including the mean, standard deviation, median, minimum and maximum values, was provided for continuous endpoints.

Categorical data: The number and percentage of patients in each category was provided for categorical variables. Missing data for a variable was included in the denominator and a row was included for the number and percent with missing values.

Time to event data: For each endpoint, the median, quartiles; and for TTP, IC-TTP, PFS and OS only the probabilities at 1 year and 18 months were estimated using the Kaplan–Meier (KM) method. CIs for the median and quartiles were generated using the Brookmeyer-Cowley (B-M) method. Two-sided 95% CIs for the 1-year and 18-month survival probability were calculated for the log [-log(1-year (18-month) survival probability)] using a normal approximation and then back transformed to give a CI for the 1-year (18-month) survival probability itself.[96]

B.2.4.2.1 Patient withdrawals

Patients were allowed to withdraw from treatment at any time at their own request, or withdraw at the discretion of the investigator or sponsor due to safety or behavioural reasons, or to the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.[96]

B.2.4.3 Quality assessment of the relevant clinical effectiveness evidence

The design of Study 1001 was assessed using the Downs and Black checklist for assessing the quality of both randomised control trials (RCTs) and non-randomised studies.[97] The results of the quality assessment are presented in Appendix D.

B.2.5 Clinical effectiveness results of the relevant trials

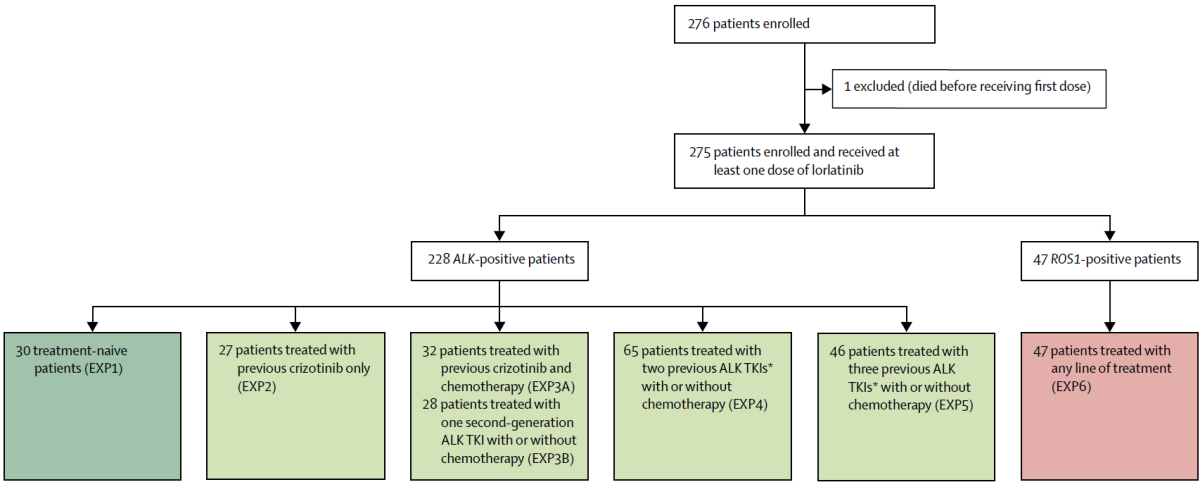
Baseline and efficacy data are presented for patients relapsing after one prior second-generation ALK TKI (EXP-3B) with or without chemotherapy, two prior ALK TKIs (EXP-4) with or without chemotherapy, and three or more prior ALK TKIs (EXP-5) with or without chemotherapy, along with pooled data representing the licensed population (i.e. patients relapsing after one or more prior ALK TKIs with or without chemotherapy [EXP-3B:5]). This latter pooled data is the focus of this submission and the data used to inform efficacy in the cost-effectiveness model. Phase 1 and Phase 2 EXP-1, EXP-2 and EXP-3A data are provided in Appendix D. Data are presented as of the data cut-off date of 2 February 2018, at which time the study was ongoing, but enrolment in both phases was complete.[93]

B.2.5.1 Study population

B.2.5.1.1 Patient disposition

Patient disposition for Phase 2 is shown in Figure 3. A total of 276 patients were enrolled and allocated to EXP cohorts based on ALK/ROS1 positivity and prior treatment regimens (FAS), with 275 patients receiving at least one dose of lorlatinib (one patient assigned to EXP-4 died before receiving the first dose).

Figure 3. Patient disposition (Study 1001; Phase 2 FAS)



Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; FAS = full anaysis set; ROS1 = c-ROS oncogene 1; TKI = tyrosine kinase inhibitor
*If the same TKI was given twice, it was counted as two previous lines of treatment
Source: Solomon et al. 2018[94]

As of the data cut-off date (2 February 2018), 139 patients assigned to EXP-3B (n=28), EXP-4 (n=65) and EXP-5 (n=46) received at least one dose of lorlatinib and were analysed for efficacy (ITT population). Of these 139 patients, 94 (67.6%) had brain metastases. A summary of patient disposition for the pooled cohort (EXP-3B:5) at data cut-off (2 February 2018) is shown in Table 10. The most common reason for treatment discontinuation was disease progression or relapse (66 [47.5%] patients).[95]

Table 10. Patient disposition (Study 1001; Phase 2 ITT population)

	EXP-3B:5 (n=139)
Treated, n (%)	139 (100.0)
Treatment discontinued, n (%)	98 (70.5)
Treatment ongoing at data cut-off, n (%)	41 (29.5)
Study discontinued, n (%)	81 (58.3)
Study ongoing at data cut-off, n (%)	59 (42.4)

Abbreviations: EXP = expansion; ITT = intention-to-treat; n = number of patients
Source: Pfizer Limited, 2018[95]

B.2.5.1.2 Demographics and baseline characteristics

A summary of demographics and baseline characteristics is shown in Table 11. The majority of patients in Study 1001 were female, white, and had brain metastases at baseline. Although there were some slight imbalances in gender and ethnicity, demographics were generally similar to that expected of patients with ALK-positive NSCLC (see Table 24).[94, 98]

Table 11. Demographics and baseline characteristics (Study 1001; Phase 2 ITT population)

Demographics/characteristics	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
Mean (SD) age, years	55.0 (11.6)	52.2 (11.8)	51.5 (11.2)	52.5 (11.6)
Gender, n (%)				
Female	16 (57.1)	37 (57.0)	25 (54.3)	78 (56.1)
Male	12 (42.9)	28 (43.1)	21 (45.7)	61 (43.9)
Race, n (%)				
White	7 (25.0)	32 (49.2)	27 (58.7)	66 (47.5)
Black	1 (3.6)	0 (0.0)	0 (0.0)	1 (0.7)
Asian	16 (57.1)	23 (35.4)	14 (30.4)	53 (38.1)
Other	1 (3.6)	3 (4.6)	2 (4.3)	6 (4.3)
Unspecified	3 (10.7)	7 (10.8)	3 (6.5)	13 (9.4)
ECOG PS, n (%)				
0	14 (51.9)	25 (38.5)	21 (45.7)	60 (43.5)
1	13 (48.1)	37 (56.9)	22 (47.8)	72 (52.2)
2	0 (0.0)	3 (4.6)	3 (6.5)	6 (4.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Brain metastases present, n (%)	12 (42.9)	44 (67.7)	37 (80.4)	93 (66.9)
Prior cancer treatment, n (%)				
Surgery	16 (57.1)	33 (50.8)	29 (63.0)	78 (56.1)
Radiotherapy	12 (42.9)	49 (75.4)	34 (73.9)	95 (68.3)
Systemic therapies	28 (100.0)	65 (100.0)	46 (100.0)	139 (100.0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EXP = expansion; ITT = intention-to-treat; n = number of patients; PS = performance status; SD = standard deviation
Source: Pfizer Limited, data on file[98]; Solomon et al. 2018[94]

B.2.5.2 Duration of treatment

In Phase 2, the median duration of treatment was 8.7 months (range 0.3–25.8 months) for patients in EXP-3B, 11.8 months (range 0.2–27.7 months) for patients in EXP-4, 9.3 months (range 0.4–27.9 months) for EXP-5 and 10.1 months (range 0.2–27.9 months) for EXP-3B:5.[95]

B.2.5.3 Primary efficacy outcomes

In Phase 2, the co-primary efficacy endpoints were ORR and IC-ORR in the ITT population.

B.2.5.3.1 Objective response rate

Over one-third of patients achieved a tumour response to lorlatinib with a majority of patients experiencing tumour shrinkage

A summary of ORR and best overall response (BOR) in patients relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 12. In the pooled EXP-3B:5 cohort, lorlatinib treatment led to an ORR of 40.3%.[95]

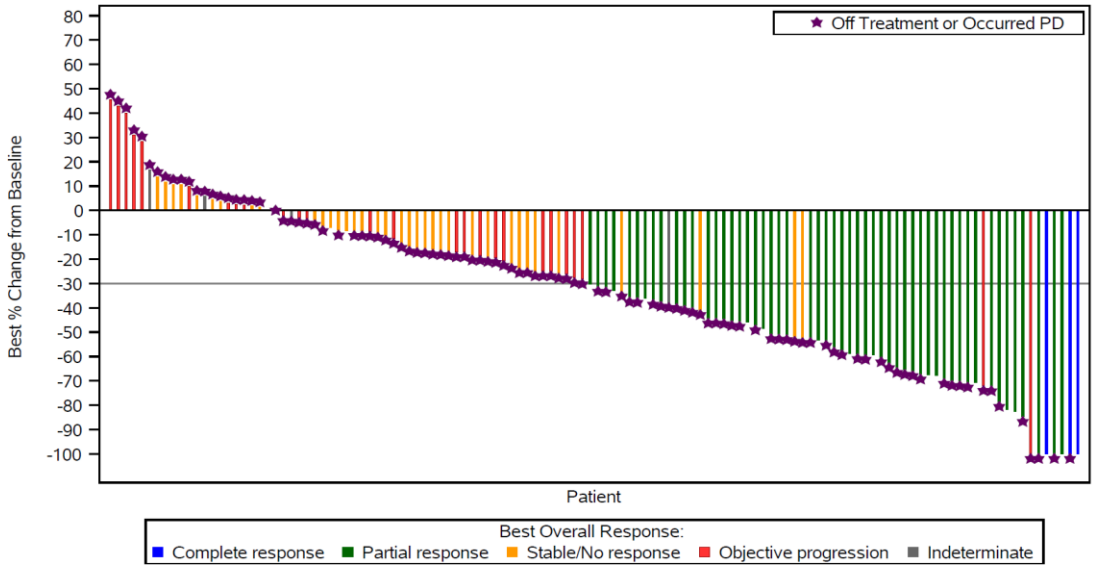
Table 12. Co-primary efficacy analysis – ORR and BOR (Study 1001; Phase 2 ITT population)

Endpoint	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
ORR (CR + PR)				
n (%)	12 (42.9)	27 (41.5)	17 (37.0)	56 (40.3)
95% CI	24.5, 62.8	29.4, 54.4	23.2, 52.5	32.1, 48.9
BOR, n (%)				
CR	1 (3.6)	2 (3.1)	0 (0.0)	3 (2.2)
PR	11 (39.3)	25 (38.5)	17 (37.0)	53 (38.1)
Stable	8 (28.6)	22 (33.8)	15 (32.6)	45 (32.4)
Disease progression	6 (21.4)	10 (15.4)	10 (21.7)	26 (18.7)
Indeterminate	2 (7.1)	6 (9.2)	4 (8.7)	12 (8.6)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; EXP = expansion; ITT = intention-to-treat; ORR = objective response rate; PR = partial response
Source: Pfizer Limited, 2018[95]

The best percentage change from baseline in target lesion dimensions for patients in cohort EXP-3B:5 is shown in Figure 4. Most patients had at least some degree of tumour shrinkage during the study in all three individual cohorts and in the pooled cohort.[99]

Figure 4. Best percentage change from baseline in tumour size (Study 1001; Phase 2 ITT population: EXP-B3:5)



Abbreviations: EXP = expansion; ITT = intention-to-treat; PD = progressed disease
Source: Pfizer Limited, 2018[99]

B.2.5.3.2 Intracranial objective response

Almost half of patients with brain metastases achieved a tumour response to lorlatinib, with a majority of patients experiencing tumour shrinkage, consistent with the ability of lorlatinib to cross the blood brain barrier

A summary of IC-ORR for patients with brain metastases relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 13.

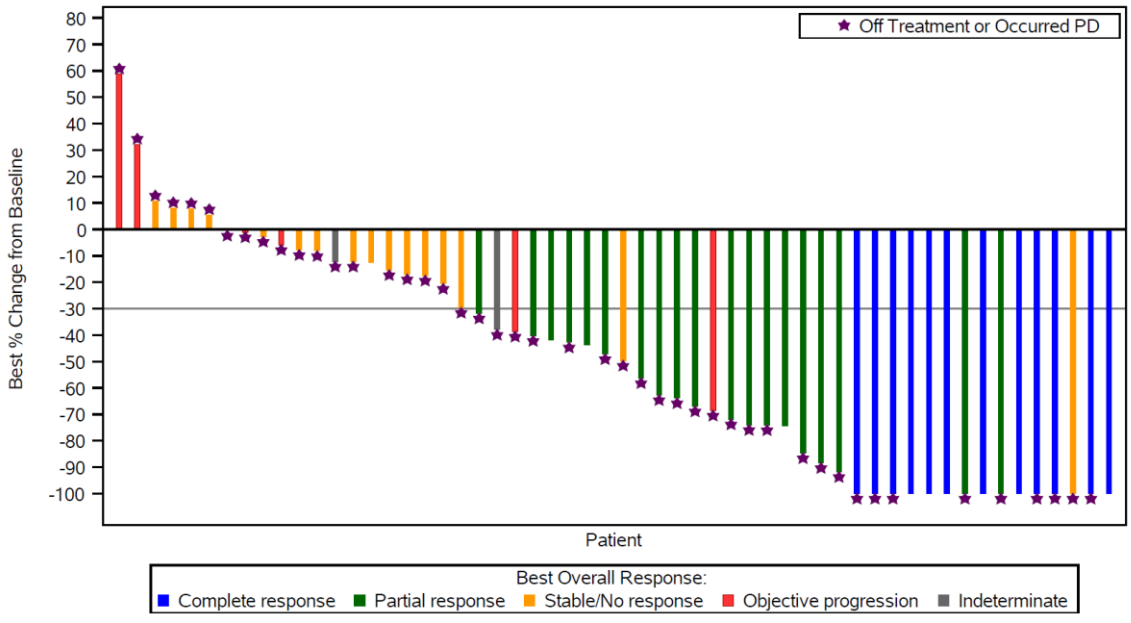
Table 13. Co-primary efficacy analysis – IC-ORR and IC-BOR (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline)

Endpoint	EXP-3B (n=13)	EXP-4 (n=44)	EXP-5 (n=37)	EXP-3B:5 (n=94)
IC-ORR (CR + PR)				
n (%)	6 (46.2)	23 (52.3)	16 (43.2)	45 (47.9)
95% CI	19.2, 74.9	36.7, 67.5	27.1, 60.5	37.5, 58.4
IC-BOR, n (%)				
CR	2 (15.4)	15 (34.1)	9 (24.3)	26 (27.7)
PR	4 (30.8)	8 (18.2)	7 (18.9)	19 (20.2)
Stable/no response	3 (23.1)	15 (34.1)	13 (35.1)	31 (33.0)
Disease progression	3 (23.1)	3 (6.8)	2 (5.4)	8 (8.5)
Indeterminate	1 (7.7)	3 (6.8)	6 (16.2)	10 (10.6)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; EXP = expansion; IC = intracranial; n = number; ORR = objective response rate; PR = partial response
Source: Pfizer Limited, 2018[95]

The best percentage change from baseline in target IC lesion dimensions for patients in cohort EXP-3B:5 is shown in Figure 5. The majority of patients in the pooled cohort had at least some degree of tumour shrinkage during the study.[95]

Figure 5. Best percentage change from baseline in brain lesion size (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline: EXP-3B:5)



Abbreviations: EXP = expansion; PD = progressed disease
Source: Pfizer Limited, 2018[99]

B.2.5.4 Secondary efficacy outcomes

B.2.5.4.1 Time to tumour response

Time to first tumour response was less than 2 months for the majority of patients, including patients with brain metastases

A summary of TTR for patients relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 14. For those patients in the pooled cohort (EXP-3B:5) with a confirmed objective tumour response, the median TTR was 1.4 months (95% CI: 1.2, 16.6).[95]

Table 14. TTR (Study 1001; Phase 2 ITT population)

Endpoint	EXP-3B (n=12)	EXP-4 (n=27)	EXP-5 (n=17)	EXP-3B:5 (n=56)
Median (range) TTR, months	1.4 (1.2–16.6)	2.6 (1.2–16.4)	1.4 (1.2–9.3)	1.4 (1.2–16.6)
0–<2 months, n (%)	7 (58.3)	12 (44.4)	13 (76.5)	32 (57.1)
2–<4 months, n (%)	3 (25.0)	6 (22.2)	2 (11.8)	11 (19.6)
4–<6 months, n (%)	0 (0.0)	2 (7.4)	1 (5.9)	3 (5.4)
≥6 months, n (%)	2 (16.7)	7 (25.9)	1 (5.9)	10 (17.9)

Abbreviations: Exp = expansion; ITT = intention-to-treat; n = number of patients; TTR = time to tumour response
Source: Pfizer Limited, 2018[95]

A summary of IC-TTR for patients with brain metastases relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 15. For those patients in the pooled cohort (EXP-3B:5) with a confirmed objective tumour response and brain metastases, the median IC-TTR was 1.4 months (95% CI: 1.2, 16.2).[99]

Table 15. IC-TTR (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline)

Endpoint	EXP-3B (n=6)	EXP-4 (n=23)	EXP-5 (n=16)	EXP-3B:5 (n=45)
Median (range) IC-TTR, months	1.4 (1.2–3.0)	1.5 (1.2–16.2)	1.4 (1.2–10.6)	1.4 (1.2–16.2)
0–<2 months, n (%)	4 (66.7)	13 (56.5)	11 (68.8)	28 (62.2)
2–<4 months, n (%)	2 (33.3)	5 (21.7)	3 (18.8)	10 (22.2)
4–<6 months, n (%)	0 (0.0)	3 (13.0)	0 (0.0)	3 (6.7)
≥6 months, n (%)	0 (0.0)	2 (8.7)	2 (12.5)	4 (8.9)

Abbreviations: EXP = expansion; IC = intracranial; ITT = intention-to-treat; n = number of patients; TTR = time to tumour response
Source: Pfizer Limited, 2018[99]

B.2.5.4.2 Duration of response

Tumour responses were sustained for a median of 7 months and a median of 15 months for patients with brain metastases

A summary of DOR for patients relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 16, and a KM plot of DOR is shown in Figure 6. For those patients in the pooled cohort (EXP-3B:5) with a confirmed objective tumour response, the median DOR was 7.1 months (95% CI: 5.6–24.4). Among 33 responding patients who

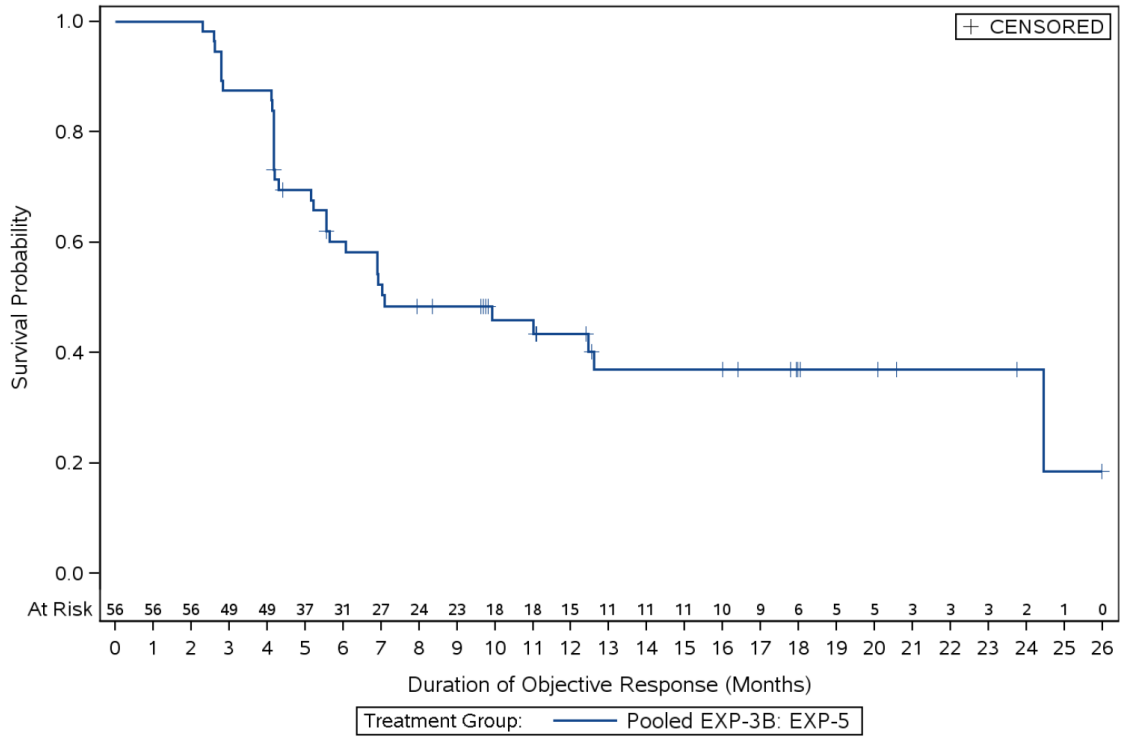
subsequently progressed or died, 11 (44.0%) patients had a response lasting at least 6 months. Among 23 responding patients who were alive and without disease progression at the data cut-off date, 20 (86.7%) had a response lasting at least 6 months.[95]

Table 16. Duration of response (Study 1001; Phase 2 ITT population)

Endpoint	EXP-3B (n=12)	EXP-4 (n=27)	EXP-5 (n=17)	EXP-3B:5 (n=56)
Patients with events, n (%)	7 (58.3)	14 (51.9)	12 (70.6)	33 (58.9)
<3 months	0 (0.0)	3 (11.1)	4 (23.5)	7 (12.5)
3–<6 months	6 (50.0)	6 (22.2)	3 (17.6)	15 (26.8)
6–<9 months	1 (8.3)	3 (11.1)	2 (11.8)	6 (10.7)
9–<12 months	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.6)
12–<15 months	0 (0.0)	1 (3.7)	1 (5.9)	2 (3.6)
15–<18 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18–<21 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
21–<24 months	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
≥24 months	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.8)
Patients censored, n (%)	5 (41.7)	13 (48.1)	5 (29.4)	23 (41.1)
<3 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3–<6 months	1 (8.3)	1 (3.7)	1 (5.9)	3 (5.4)
6–<9 months	0 (0.0)	1 (3.7)	1 (5.9)	2 (3.6)
9–<12 months	2 (16.7)	4 (14.8)	0 (0.0)	6 (10.7)
12–<15 months	0 (0.0)	2 (7.4)	0 (0.0)	2 (3.6)
15–<18 months	0 (0.0)	4 (14.8)	1 (5.9)	5 (8.9)
18–<21 months	1 (8.3)	1 (3.7)	1 (5.9)	3 (5.4)
21–<24 months	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.8)
≥24 months	0 (0.0)	0 (0.0)	1 (5.9)	1 (1.8)
Median DOR (95% CI), months	5.6 (4.2, NR)	12.5 (5.6, 24.4)	7.0 (4.2, 12.6)	7.1 (5.6, 24.4)

Abbreviations: CI = confidence interval; DOR = duration of response; ITT = intention-to-treat; n = number of patients; NR = not reached
Source: Pfizer Limited, 2018[95]

Figure 6. KM plot of DOR in objective responders (Study 1001; Phase 2 ITT population: EXP-3B:5)



Abbreviations: DOR = duration of response; EXP = expansion; ITT = intention-to-treat; KM = Kaplan–Meier
Source: Pfizer Limited, 2018[95]

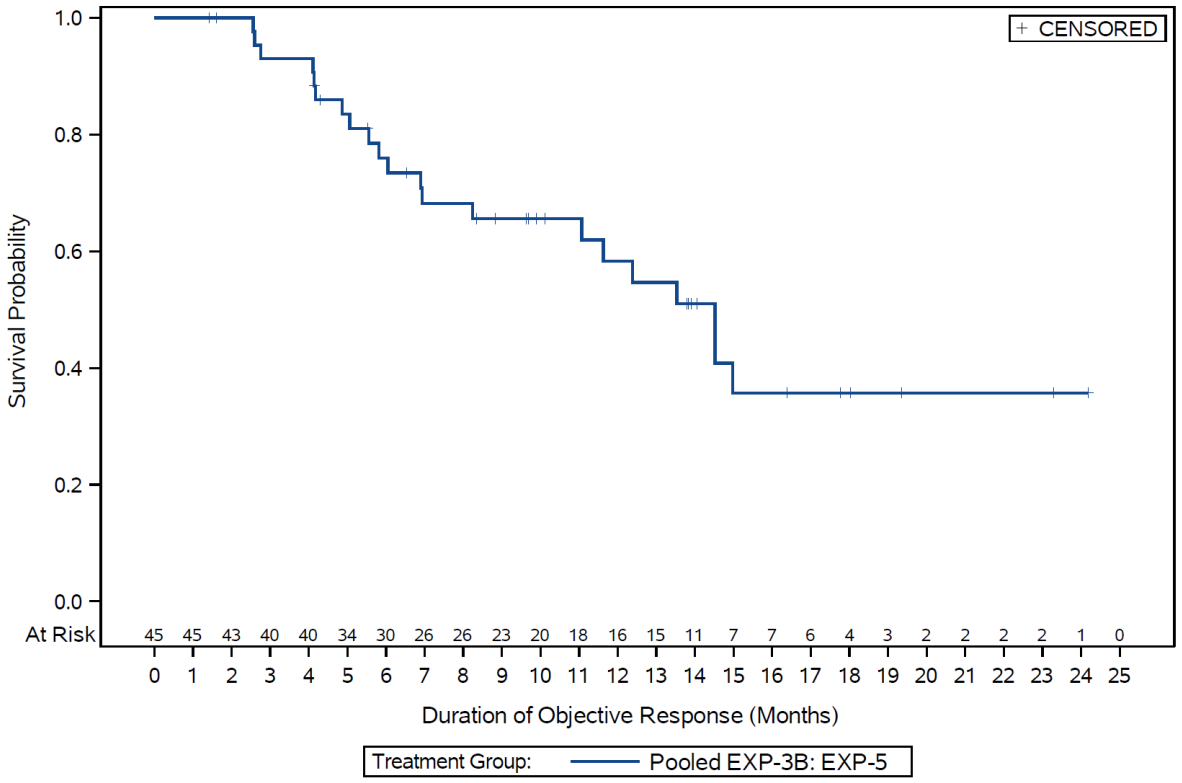
A summary of IC-DOR for patients with brain metastases relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 17, and a KM plot of IC-DOR is shown in Figure 7. In the pooled cohort of patients (EXP-3B:5), the median IC-DOR was 14.5 months (95% CI: 11.1, NR). Among 21 responding patients who subsequently progressed or died, 11 (52.4%) patients had a response lasting at least six months. Among 24 responding patients who were alive and without disease progression at the data cut-off date, 19 (79.2%) had a response lasting at least six months.[95]

Table 17. IC-DOR (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline)

Endpoint	EXP-3B (n=6)	EXP-4 (n=23)	EXP-5 (n=16)	EXP-3B:5 (n=45)
Patients with events, n (%)	3 (50.0)	9 (39.1)	9 (56.3)	21 (46.7)
<3 months	0 (0.0)	2 (8.7)	1 (6.3)	3 (6.7)
3–<6 months	3 (50.0)	2 (8.7)	2 (12.5)	7 (15.6)
6–<9 months	0 (0.0)	1 (4.3)	3 (18.8)	4 (8.9)
9–<12 months	0 (0.0)	2 (8.7)	0 (0.0)	2 (4.4)
12–<15 months	0 (0.0)	2 (8.7)	3 (18.8)	5 (11.1)
15–<18 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18–<21 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
21–<24 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥24 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients censored, n (%)	3 (50.0)	14 (60.9)	7 (43.8)	24 (53.3)
<3 months	0 (0.0)	2 (8.7)	0 (0.0)	2 (4.4)
3–<6 months	0 (0.0)	3 (13.0)	0 (0.0)	3 (6.7)
6–<9 months	0 (0.0)	1 (4.3)	2 (12.5)	3 (6.7)
9–<12 months	1 (16.7)	3 (13.0)	1 (6.3)	5 (11.1)
12–<15 months	1 (16.7)	2 (8.7)	1 (6.3)	4 (8.9)
15–<18 months	0 (0.0)	2 (8.7)	1 (6.3)	3 (6.7)
18–<21 months	0 (0.0)	1 (4.3)	1 (6.3)	2 (4.4)
21–<24 months	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.2)
≥24 months	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.2)
Median IC-DOR (95% CI), months	NR (4.1, NR)	13.5 (11.1, NR)	14.5 (6.9, NR)	14.5 (11.1, NR)

Abbreviations: CI = confidence interval; DOR = duration of response; EXP = expansion; IC = intracranial; ITT= intention-to-treat; n = number of patients; NR = not reached
Source: Pfizer Limited, 2018[95]

Figure 7. KM plots of IC-DOR in objective responders (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline: EXP-3B:5)



Abbreviations: DOR = duration of response; EXP = expansion; IC = intracranial; ITT = intention-to-treat; KM = Kaplan–Meier
Source: Pfizer Limited, 2018[99]

B.2.5.4.3 Disease control

Disease control was observed for over half of patients at 12 weeks and approximately half of patients at 24 weeks. For patients with brain metastases, disease control was observed for approximately three-quarters of patients at 12 weeks and over half of patients at 24 weeks

A summary of disease control for patients relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown Table 18. For patients in the pooled cohort (EXP-3B:5), the DCR at 12 weeks and 24 weeks was 59.7% and 43.2%, respectively.[99]

Table 18. Disease control (Study 1001; Phase 2 ITT population)

DCR	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
At 12 weeks, n (%)	16 (57.1)	43 (66.2)	24 (52.2)	83 (59.7)
95% CI	37.2, 75.5	53.4, 77.4	36.9, 67.1	51.1, 67.9
At 24 weeks, n (%)	11 (39.3)	33 (50.8)	16 (34.8)	60 (43.2)
95% CI	21.5, 59.4	38.1, 63.4	21.4, 50.2	34.8, 51.8

Abbreviations: CI = confidence interval; DCR = disease control rate; EXP = expansion; ITT = intention-to-treat; n = number of patients
Source: Pfizer Limited, 2018[99]

A summary of IC disease control for patients with brain metastases relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) is shown in Table 19. For patients in the

pooled cohort (EXP-3B:5), the IC-DCR at 12 weeks and 24 weeks was 73.4% and 55.3%, respectively.[99]

Table 19. IC disease control (Study 1001; Phase 2 ITT population, patients with brain metastases at baseline)

IC-DCR	EXP-3B (n=13)	EXP-4 (n=44)	EXP-5 (n=37)	EXP-3B:5 (n=94)
At 12 weeks, n (%)	9 (69.2)	35 (79.5)	25 (67.6)	69 (73.4)
95% CI	38.6, 90.9	64.7, 90.2	50.2, 82.0	63.3, 82.0
At 24 weeks, n (%)	6 (46.2)	28 (63.6)	18 (48.6)	52 (55.3)
95% CI	19.2, 74.9	47.8, 77.6	31.9, 65.6	44.7, 65.6

Abbreviations: CI = confidence interval; DCR = disease control rate; EXP = expansion; IC = intracranial; ITT = intention-to-treat; n = number of patients
Source: Pfizer Limited, 2018[99]

B.2.5.4.4 Progression-free survival and overall survival

Lorlatinib provided a median PFS of 7 months and a median OS of 20 months

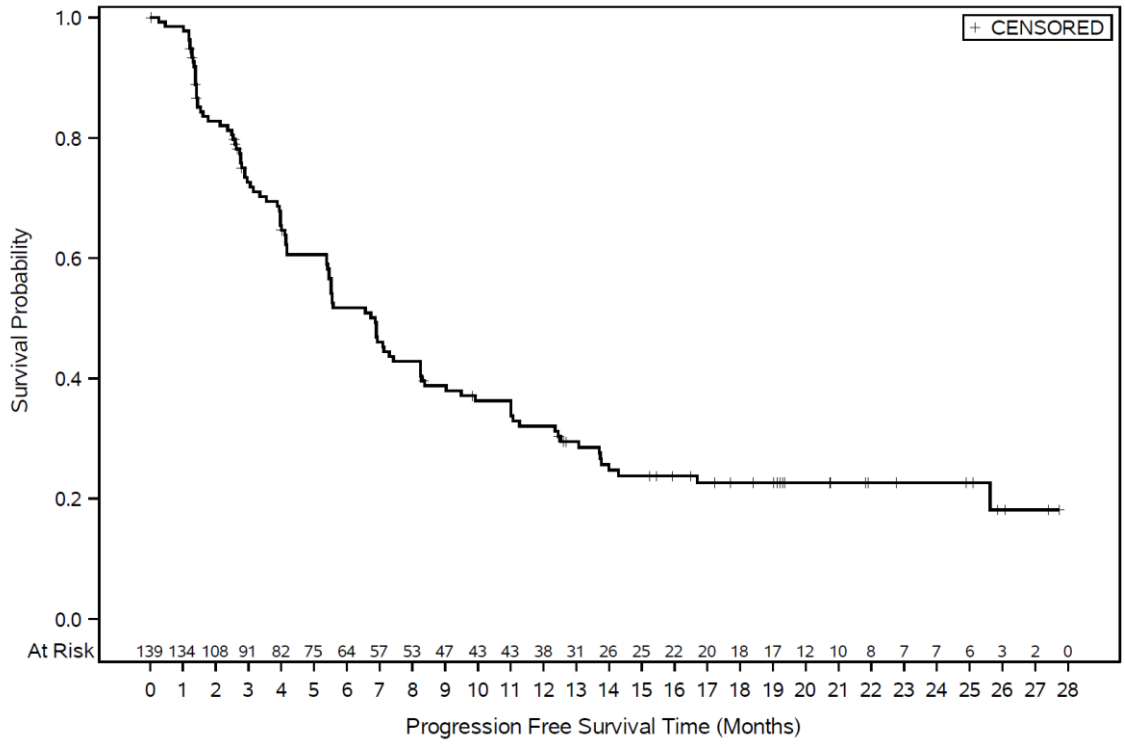
Summaries of PFS and OS for patients relapsing after one or more prior ALK TKIs (cohorts EXP-3B, EXP-4 and EXP-5) are shown in Table 20. KM plots of PFS and OS for the pooled cohort (EXP-3B:5) are shown in Figure 8 and Figure 9, respectively. In the pooled cohort, 97 (69.8%) patients subsequently progressed or died, and 22 (15.8%) patients were alive and still in follow-up at the date of data cut-off.[95] The median PFS and OS were 6.9 months and 20.4 months, respectively, with an OS probability of 0.678 at 12 months and 0.556 at 18 months.[95]

Table 20. PFS and OS (Study 1001; Phase 2 ITT population)

Endpoint	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
Median (95% CI) PFS, months	5.5 (2.9, 8.2)	7.4 (5.4, 11.1)	5.6 (4.0, 8.3)	6.9 (5.4, 8.2)
Median (95% CI) OS, months	21.1 (12.3, NR)	18.7 (15.1, NR)	19.2 (10.5, NR)	20.4 (16.1, NR)
OS probability, % (95% CI)				
12 months	0.698 (0.485, 0.836)	0.696 (0.566, 0.795)	0.641 (0.482, 0.762)	0.678 (0.591, 0.750)
18 months	0.616 (0.402, 0.772)	0.512 (0.376, 0.633)	0.572 (0.414, 0.702)	0.556 (0.155, 0.306)

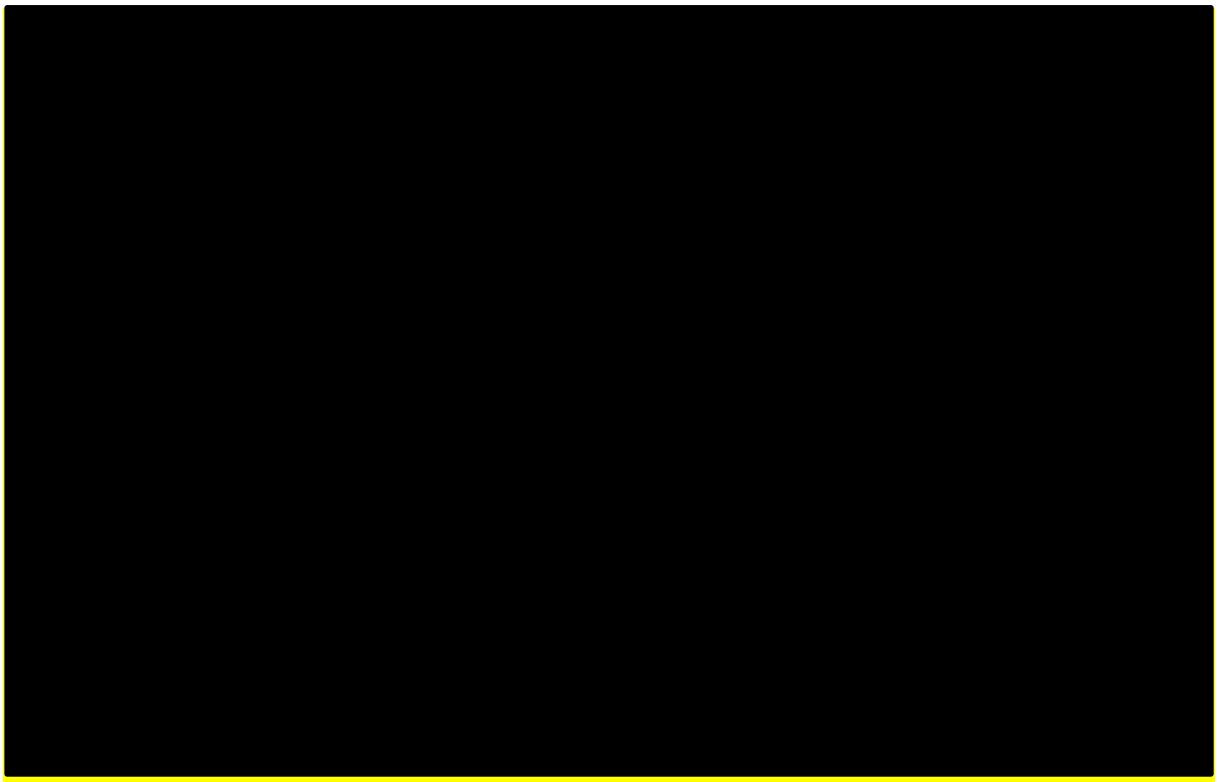
Abbreviations: CI = confidence interval; EXP = expansion; ITT = intention-to-treat; n = number of patients; NR = not reached; OS = overall survival; PFS = progression-free survival
Source: Pfizer Limited, 2018[95]

Figure 8. KM plot of PFS (Study 1001; Phase 2 ITT population: EXP-3B:5)



Abbreviations: EXP = expansion; ITT = intention-to-treat; KM = Kaplan–Meier; PFS = progression-free survival
Source: Pfizer Limited, 2018[99]

Figure 9. KM plot of OS (Study 1001; Phase 2 ITT population; EXP-3B:5)



Abbreviations: EXP = expansion; ITT = intention-to-treat; KM = Kaplan–Meier; OS = overall survival
Source: Pfizer Limited, 2018[99]

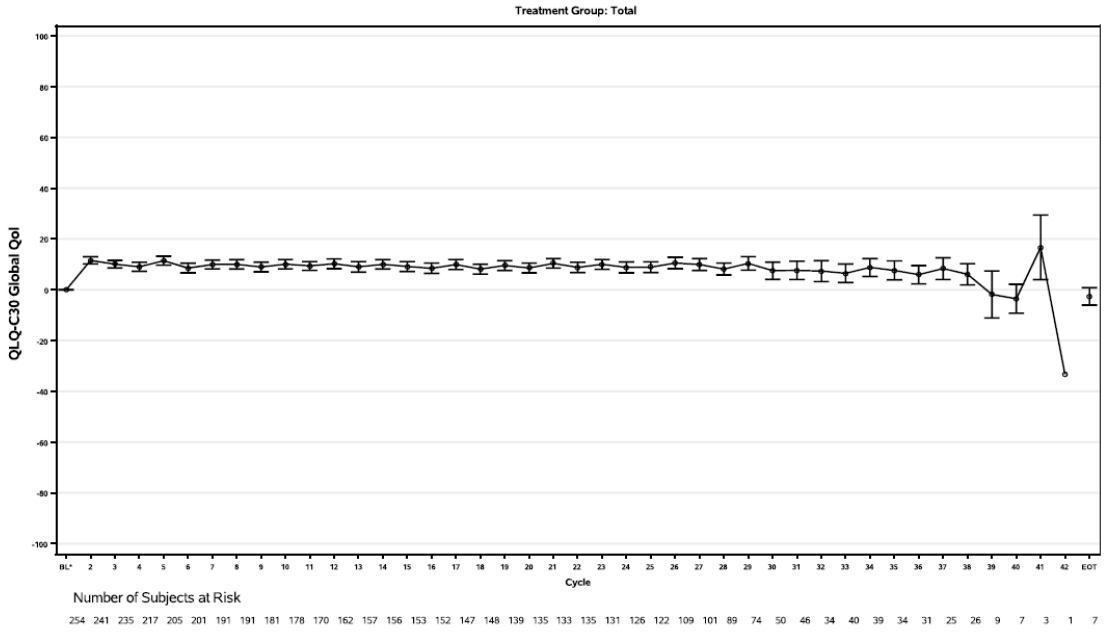
B.2.5.5 Patient-reported outcomes

Treatment with lorlatinib led to a clinically meaningful improvement in global QoL, functioning and patient-reported symptoms

Rates of completion for the EORTC QLQ-C30 and QLQ-LC13 instruments were high, with 94.5–100% of patients completing at least one question, and 84.4–100% of patients completing all questions over the first 26 cycles.[100]

The mean change from baseline in global QoL in the PRO-evaluable population (EXP-1:6) is shown in Figure 10. As of the first data cut-off date (15 March 2017), a statistically significant and clinically meaningful (≥10-point) improvement from baseline was observed in Cycles 2 (11.55), Cycle 3 (10.07) and Cycle 5 (11.42).[93]

Figure 10. Mean change from baseline in EORTC QLQ-C30 global QoL (Study 1001; Phase 2 PRO-evaluable population)



Abbreviations: BL = baseline; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire – Cancer; QoL = quality of life
Source: Pfizer Limited, 2018[100]

A summary of change from baseline in EORTC QLQ-C30 global QoL and functional domains (PRO-evaluable population [EXP-1:6]) is shown in Table 21. The majority of patients had either improved (42.4%) or stable (38.0%) global QoL scores during treatment. Similarly, most patients had improved or stable scores for each of the functional domains.[100, 101]

Table 21. Change in EORTC QLQ-C30 global QoL and functional scales (Study 1001; PRO-evaluable population)

Domain	n (%), all cycles (N=255)			
	Improved	Stable	Worsening	Missing
Global QoL	108 (42.4)	97 (38.0)	49 (19.2)	1 (0.4)
Physical functioning	76 (29.8)	143 (56.1)	35 (13.7)	1 (0.4)
Role functioning	96 (37.6)	106 (41.6)	51 (20.0)	2 (0.8)
Emotional functioning	94 (36.9)	134 (52.5)	26 (10.2)	1 (0.4)
Cognitive functioning	57 (22.4)	135 (52.9)	62 (24.3)	1 (0.4)
Social functioning	79 (31.0)	132 (51.8)	43 (16.9)	1 (0.4)

Abbreviations: EORTC = European Organisation for Research and Treatment of Cancer; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire – Cancer; QoL = quality of life
Source: Pfizer Limited, 2018[100]

A summary of change from baseline in EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales (PRO-evaluable population [EXP-1:6]) is shown in Table 22. As with EORTC QLQ-C30 global QoL and functional domain scores, the majority of patients reported improved or stable symptoms during treatment. Key lung cancer symptoms that improved most from baseline (≥10-point decrease) among treated patients were coughing (42.7%), pain in other parts (32.9%), pain in chest (29.8%) and dyspnoea (27.5%).[100, 101]

Table 22. Change in EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales (Study 1001; PRO-evaluable population)

Instrument	Symptom	n (%), all cycles (N=255)			
		Improved	Stable	Worsening	Missing
QLQ-C30	Fatigue	126 (49.4)	94 (36.9)	34 (13.3)	1 (0.4)
	Nausea and vomiting	63 (24.7)	181 (71.0)	10 (3.9)	1 (0.4)
	Pain	104 (40.8)	111 (43.5)	39 (15.3)	1 (0.4)
	Dyspnoea	86 (33.7)	117 (45.9)	51 (20.0)	1 (0.4)
	Insomnia	118 (46.3)	105 (41.2)	31 (12.2)	1 (0.4)
	Appetite loss	107 (42.0)	141 (55.3)	6 (2.4)	1 (0.4)
	Constipation	64 (25.1)	152 (59.6)	38 (14.9)	1 (0.4)
	Diarrhoea	47 (18.4)	171 (67.1)	36 (14.1)	1 (0.4)
QLQ-LC13	Dyspnoea	70 (27.5)	140 (54.9)	44 (17.3)	1 (0.4)
	Coughing	109 (42.7)	111 (43.5)	34 (13.3)	1 (0.4)
	Haemoptysis	25 (9.8)	218 (85.5)	11 (4.3)	1 (0.4)
	Sore mouth	23 (9.0)	192 (75.3)	39 (15.3)	1 (0.4)
	Dysphagia	23 (9.0)	203 (79.6)	28 (11.0)	1 (0.4)
	Peripheral neuropathy	35 (13.7)	124 (48.6)	95 (37.3)	1 (0.4)
	Alopecia	34 (13.3)	171 (67.1)	49 (19.2)	1 (0.4)
	Pain in chest	76 (29.8)	152 (59.6)	25 (9.8)	2 (0.8)
	Pain in arm or shoulder	66 (25.9)	144 (56.5)	44 (17.3)	1 (0.4)
	Pain in other parts	84 (32.9)	103 (40.4)	66 (25.9)	2 (0.8)

Abbreviations: EORTC = European Organisation for Research and Treatment of Cancer; n/N = number of patients; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire – Cancer; QLQ-LC13 = Quality of Life Questionnaire – Lung Cancer; QoL = quality of life
Source: Pfizer Limited, 2018[100]

B.2.5.6 Efficacy conclusions

In the Phase 2 portion of the study, a total of 139 patients with ALK-positive NSCLC that had progressed on prior ALK TKI therapy were treated with lorlatinib at the RP2D of 100 mg OD as of the data cut-off date (2 February 2018). Lorlatinib exhibited anti-tumour activity in patients previously treated with prior second-generation ALK TKIs. For patients whose disease has progressed after prior ALK TKI therapy (pooled cohort EXP-3B:5), the ORR (40.3%) and PFS (6.9 months) following lorlatinib treatment exceeded historical outcomes with standard-of-care chemotherapy, for which an ORR of 6.9% and a median PFS of 1.6 months has been reported in patients previously treated with crizotinib and chemotherapy.[102] Treatment with lorlatinib also led to a clinically meaningful improvement in QoL, functioning, and patient-reported symptoms.

In Phase 2, the clinical benefit of lorlatinib was also evident in patients who presented with brain metastases at baseline. Consistent with its ability to cross the blood-brain barrier, high IC-ORRs were observed; in the pooled cohort IC-ORR was determined to be 47.9%. Analyses of Phase 2 secondary endpoints supported the primary efficacy results with rapid TTR and IC TTR.

Overall, the results of Study 1001 indicate that lorlatinib treatment provides a clinically meaningful benefit to patients with ALK-positive advanced NSCLC as evidenced by rapid, deep, and durable systemic and IC responses. Lorlatinib has demonstrated anti-tumour activity both *in vitro* and *in vivo* against ALK mutations responsible for resistance to first- and second-generation ALK TKIs, as well as efficacy in patients who have experienced disease

progression despite prior second-generation ALK TKI therapy, and the ability to cross the blood-brain barrier.

Among patients whose disease has progressed on second-generation TKIs, chemotherapy is the standard of care, and outcomes are poor, with an ORR and IC-ORR of 11.4% and 0%, respectively, and a median PFS of <2 months.[64] Therefore, lorlatinib offers a much-needed treatment option for patients with resistance to current ALK TKIs, due to acquired mutations in the ALK kinase domain, and patients with brain metastases - both of which are patient groups with a high unmet need and significant burden of disease.

B.2.6 Subgroup analysis

There were no pre-specified subgroup analyses based on baseline demographics and characteristics. Results of post-hoc subgroup analyses for the patient population relevant to the licensed indication and cost-effectiveness model (EXP-3B:5) are presented in Appendix E.

B.2.7 Meta-analysis

There is only one relevant study (Study 1001) for this submission, therefore a meta-analysis was not performed.

B.2.8 Indirect and mixed treatment comparisons

- Study 1001 is a single arm trial and the SLR identified no direct head-to-head trials of lorlatinib versus pemetrexed with cisplatin/carboplatin.
- The SLR identified two external trial sources of chemotherapy PFS data, Novello et al. (ALUR)[64] and Shaw et al. (ASCEND-5).[66]
- A published retrospective analysis of PROFILE 1001 and PROFILE 1005 trials (Ou et al.[103]) was used as the source of chemotherapy OS data.
- An exploratory analysis was used to select likely treatment effect modifiers and a matching-adjusted indirect comparison (MAIC) was conducted that applied weights to Study 1001 patients to balance these prognostic factors with the external sources of chemotherapy PFS and OS data.
- For the purposes of precision and robustness two alternative matching cohorts from Study 1001 were used in the MAIC (EXP-2:3A and EXP-3B:5).After weighting, lorlatinib was found to significantly reduce the risk of disease progression for the EXP-2:3A (hazard ratio [HR] = [redacted], 95% CI: [redacted]) and EXP-3B:5 cohorts (HR: [redacted], 95% CI: [redacted]) with PFS KM curves showing a significant plateau (up to [redacted] in the lorlatinib arm and [redacted] in the chemotherapy arm by [redacted] months).
- After weighting, lorlatinib was found to significantly reduce the risk of mortality in the EXP-2:3A (HR: [redacted], 95% CI: [redacted]) and EXP-3B:5 cohorts (HR: [redacted], 95% CI: [redacted]) with KM curves showing a notable difference between treatments.
- These results suggest that lorlatinib offers significant benefits over chemotherapy in this population of ALK-positive NSCLC, with results consistent across adjusted versus naïve analyses and robust to different Study 1001 matching cohorts.

B.2.8.1 Introduction, objectives and feasibility

In the absence of a comparator arm in Study 1001, it is not possible to obtain survival outcomes from individual patient-level data (IPD) for the comparator of interest in this submission. Standard techniques such as indirect treatment comparison (ITC) and network meta-analysis (NMA) could not be used to estimate relative treatment effects for the same reason. A matching-adjusted indirect comparison (MAIC),[104] was deemed the most appropriate approach to estimate relative treatment effects, as MAICs allow ITCs to be conducted when treatments are not connected via a common comparator or 'anchor' arm (see Appendix D for more information on the methodology of the MAIC). A MAIC was conducted for lorlatinib versus chemotherapy for the outcomes of PFS and OS.

The key aim of these analyses was to estimate the relative efficacy of lorlatinib compared with chemotherapy as treatments for ALK-positive advanced NSCLC, in the population of relevance to this submission. In short, the MAIC indirectly compared the two treatments by weighting the individuals in the IPD sample in Study 1001 so as to match the patient characteristics of the trial population that provided the chemotherapy efficacy data.[104]

After the matching procedure was conducted and the weights derived, weighted KM curves were generated for PFS and OS. Hazard ratios (HRs) comparing lorlatinib cohort(s) and the comparative evidence source were estimated using weighted Cox proportional hazards models and the corresponding 95% CIs were calculated using bootstrapping to account for the within-subject correlation.

The MAIC was deemed feasible based on satisfaction of the following criteria:

- Availability of literature sources that provide post ALK TKI chemotherapy KM curves for OS or PFS and baseline characteristics data for matching purposes;
- Chemotherapy data populations are similar to the relevant Study 1001 population, particularly on factors for which matching is not possible (e.g. population and treatment history);
- The establishment of a set of baseline characteristics that are likely effect modifiers or prognostic factors for OS and PFS in the ALK-positive NSCLC population.

B.2.8.2 Systematic literature review and relevant lorlatinib cohorts

A SLR (previously described) was conducted to identify relevant studies providing evidence for the efficacy and safety of lorlatinib and chemotherapy in ALK-positive NSLC patients (see Appendix D). The ALUR[64] and ASCEND-5[66] studies were identified and provided chemotherapy arm PFS data for ALK-positive NSCLC patients after they had progressed on crizotinib and previous chemotherapy. Given the similarity in baseline characteristics and population these two sources were pooled for the purposes of the MAIC (see Appendix D). These studies did not provide any OS data.

A retrospective analysis of the crizotinib arm of the trials PROFILE 1001 and PROFILE 1005 (Ou et al. 2014)[103] for the subgroup of patients receiving systemic therapy (likely chemotherapy) after progression on crizotinib was used as the source for OS data.

The majority of patients in ALUR, ASCEND-5. and PROFILE 1001/1005 studies received both chemotherapy and crizotinib previously and so arguably the most precise Study 1001 cohort for matching is EXP-3A (i.e. relapse after previous crizotinib and one or two regimens of

chemotherapy given before or after crizotinib). However, a pooled EXP-3A and EXP-2 (i.e. relapse after crizotinib only) cohort was used to ensure that the sample size on which matching was conducted was not too small (effectively doubling the matching cohort). The larger the number of matching variables in proportion to the size of the Study 1001 matching sample, the more extreme the weights that are required and the lower the effective sample size for the efficacy analysis. In addition, outcomes are not expected to vary greatly with pre-treatment by crizotinib alone versus crizotinib and at least one regimen of chemotherapy. This is consistent with the license indication and clinical expert opinion.

An additional analysis was conducted that uses the pooled EXP-3B:5 as the matching cohort instead of EXP-2:3A. This analysis requires the assumption that only patient characteristics and not treatment line – i.e. pre-treatment by different ALK TKIs – affects outcomes. Each MAIC is summarised in Table 23. Unadjusted or 'naïve' results are also presented for comparison. The EXP-3B:5 cohort was less of a match to the comparator sources than the EXP-2:3A cohort, in terms of previous treatments. However, the sample size was substantially larger and the matching cohort reflects the sample used in the cost-effectiveness model.

Table 23. Study 1001 cohorts used in the MAIC

Comparator arm used	Outcome	Studies	Final lorlatinib population matching	Associated method in Section B.3.3.2
Chemotherapy (pemetrexed or docetaxel)	PFS	Pooled ALUR[64] and ASCEND-5[66]	EXP-2 and EXP-3A EXP-3B:5 (model cohort)	Method 1 PFS Method 2 PFS
Chemotherapy (pemetrexed or docetaxel)	OS	PROFILE 1001/1005[103]	EXP-2 and EXP-3A EXP-3B:5 (model cohort)	Method 1 OS Method 2 OS

Abbreviations: EXP = expansion; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival

B.2.8.3 Identified matching covariates

There were some imbalances in baseline characteristics between the lorlatinib and comparative evidence sources'. As such, it was necessary to attempt to adjust any comparisons made between the lorlatinib cohort(s) and each comparator evidence source for these differences in order to provide comparisons that minimise selection bias.

Based on clinical feedback, the most important factors to match on were ECOG performance status (PS) (potentially grouped as 0-1 and >1), brain metastases and race.

Exploratory analyses using Study 1001 data were conducted on eight variables to determine the relevant set of matching characteristics. KM curves for OS and PFS were produced for each of the levels of these variables so as to judge differences visually. Univariate and multivariate cox proportional hazards models were estimated and p-values calculated so as to further identify statistically significant effect modifiers (see Appendix D). Based on this analysis the final prognostic variables/effect modifiers selected for the matching were:

- ECOG PS (1/2, 0)
- Race (Asian, Non-Asian)
- Sex (male, female)
- Brain metastases (yes, no).

ECOG PS and body-mass index (BMI) were identified as potential important effect modifiers/prognostic factors in the lorlatinib IPD. However, BMI is not reported in the comparator studies and so is not used in the MAIC process.

Age and adenocarcinoma were considered sufficiently consistent across the lorlatinib IPD and the comparator studies therefore these characteristics have not been used to conduct the matching (Table 24).

ECOG PS has been summarised into a binary variable, due to the presentation of the information for comparator studies – ALUR[64] only reports baseline ECOG PS 0 and ECOG PS 1/2.

When matching on race, the lorlatinib data were matched based on the proportion of Asian patients as the comparator studies included a large percentage of the population as either Asian or White with small numbers in other categories, such as Other and Unknown. The 22 patients in the lorlatinib trial with missing information on race were considered 'Non-Asian' for purposes of the matching.

Matching of the baseline characteristics required only mild weighting and the distribution of weights in the dataset was relatively uniform (see Appendix D).

Table 24. Baseline characteristics across identified comparator studies

Treatment	Study	Median age (range), years	Baseline characteristics (%)						
			Male, %	Asian	White	ECOG PS 0/1	ECOG PS 1/2	% Brain metastases	Adenocarcinoma
Lorlatinib	Study 1001 (EXP-2 and EXP-3A)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy (PFS)	ALUR[64]	59 (37-80)	48.6	20	Not required		14.3	74.3	100
	ASCEND-5[66]	54 (47-64)	47	33			56 (WHO)	59	97
Chemotherapy (OS)	PROFILE 1001/1005*[103]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]

Abbreviations: CBPD = crizotinib beyond progressive disease ; ECOG = Eastern Cooperative Oncology Group; EXP = expansion; OS = overall survival; PFS = progression-free survival; PS = performance status; ST = systemic therapy; WHO = World Health Organization

*These baseline characteristics are for the 37 patients that did not continue crizotinib but received systemic therapy (i.e. not CBPD, +ST) and cannot be found in Ou et al. 2014

** Defined as the percentage who had progressed disease at the site of the brain at baseline

B.2.8.4 MAIC results: Progression-free survival

The results of the MAIC show that lorlatinib is associated with a notably decreased hazard of progression compared with chemotherapy

The results for the MAIC analyses for PFS are presented in Table 25. Lorlatinib is associated with a notably decreased hazard of progression compared with chemotherapy (pemetrexed or docetaxel), which is consistent across both the naïve and adjusted comparisons and matching cohorts. As neither CI crosses one, the analyses indicate that there is a significant difference in PFS between lorlatinib and chemotherapy.

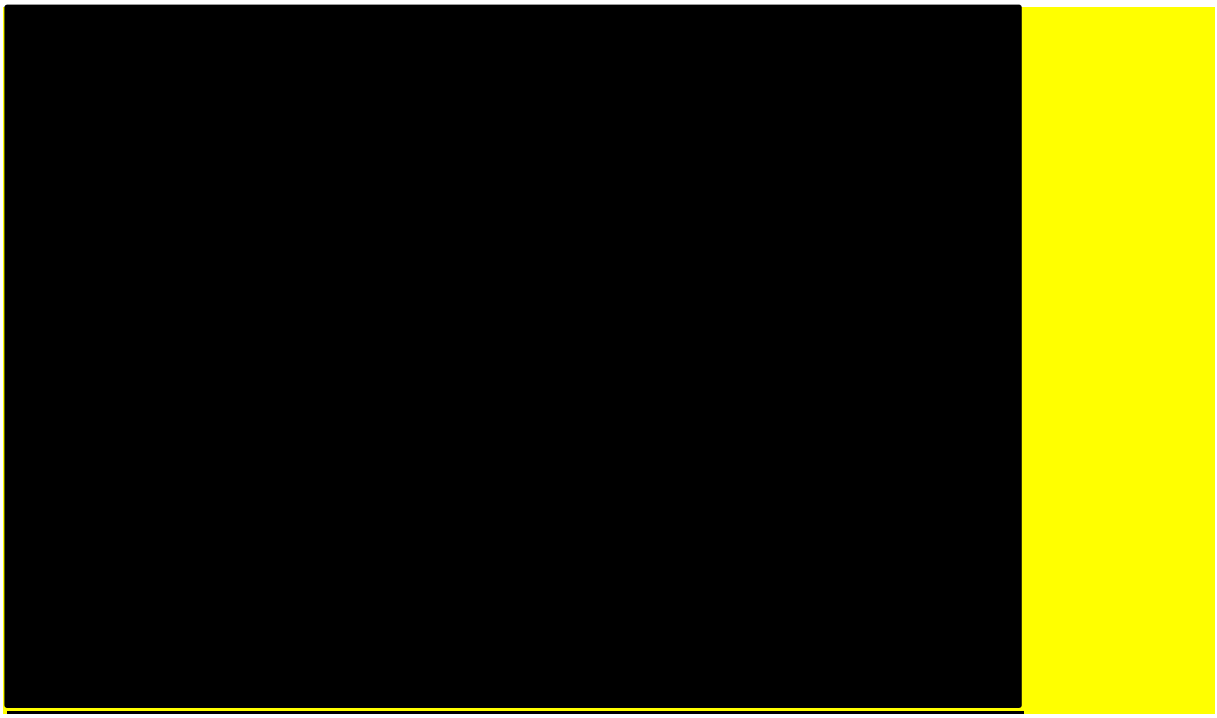
Table 25. Unadjusted and adjusted HR results for progression-free survival

Weighted matching cohort (Study 1001)	Naïve		Adjusted	
	HR	95% CI	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; EXP = expansion; HR = hazard ratio
*bootstrapped 95% CI

The large difference between the treatments indicated based on the low HR in each case is also seen clearly in Figure 11 and Figure 12. There is only a very minor difference between the observed and weighted lorlatinib KMs which is reflected in the approximate equivalence of the naïve and adjusted HRs.

Figure 11. KMs for observed and MAIC (EXP-2:3A) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel)



Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison

Figure 12. PFS KMs for observed and MAIC (EXP-3B:5) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel)

Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

B.2.8.5 MAIC results: overall survival

The results of the MAIC show that lorlatinib is associated with a notably decreased hazard of mortality compared with chemotherapy

The results for the MAIC analyses for OS are presented in Table 26. It should be noted that the baseline brain metastases variable associated with the PROFILE 1001/1005[103] data was defined as 'the percentage who had progressed disease at the site of the brain at baseline', which may not correspond precisely to the definition of brain metastases at baseline as defined in Study 1001 and other trials. Therefore, a sensitivity analysis is conducted with the brain metastases excluded from matching.

Lorlatinib is associated with a substantial decreased hazard of death compared with chemotherapy, which is consistent across both the naïve and adjusted comparisons and matching cohorts. HRs are similar with the inclusion and exclusion of the brain metastases variables, especially when using EXP-2:3A as the matching cohort.

Table 26. Unadjusted and adjusted HR results for overall survival

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases variable)		Adjusted (not including brain metastases variable)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio
*bootstrapped 95% CI

The large difference between the treatments indicated based on the low HR in each case is also seen clearly in Figure 13, Figure 14, Figure 15 and Figure 16. There is only a very minor difference between the observed and weighted lorlatinib KMs which is reflected in the approximate equivalence of the naïve and adjusted HRs.

Figure 13. OS KMs for observed and MAIC (EXP-2:3A) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel) – with adjustment for brain metastases

Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

Figure 14. OS KM plots for observed and MAIC (EXP-2:3A) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel) - without adjustment for brain metastases

Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

Figure 15. OS KM plots for observed and MAIC (EXP-3B:5) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel) - with adjustment for brain metastases

Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

Figure 16. OS KM plots for observed and MAIC (EXP-3B:5) adjusted lorlatinib versus chemotherapy (pemetrexed or docetaxel) - without adjustment for brain metastases

Abbreviations: EXP = expansion; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

B.2.8.6 Discussion

In the absence of head-to-head clinical trial evidence comparing lorlatinib with PDC, MAIC methodology was used to assess the efficacy of lorlatinib compared with chemotherapy for the outcomes of PFS and OS. The methodology was also suggested to be a viable approach by clinicians at a ad-board (July 2018). MAICs and indirect naïve comparisons have been widely used and accepted in health technology submissions to NICE,[105] including the submission for ceritinib (TA395) and more recently brigatinib (TA571), both of which were in the ALK-positive NSCLC population. The methodology employed in this submission was influenced by the Evidence Review Group (ERG) critique of MAICs found in previous submissions. In particular:

- Evidence of correlation with outcomes as well as clinical opinion is used to determine choice of matching variables;
- Methods to measure correlation are transparently reported and involve visual comparison of KMs and both univariate and multivariate Cox proportional hazard models;
- Study 1001 baseline characteristics are presented before and after matching, and compared with comparator sources (see Appendix D).

After adjusting for differences in baseline characteristics between Study 1001 and comparator data sources, lorlatinib shows a statistically significant decrease in hazard compared with chemotherapy (pemetrexed or docetaxel) for both PFS and OS.

A MAIC is an example of an indirect comparison and so invariably there is the possibility that unknown variables are confounding the estimated relative treatment effects. However, the systematic choice of matching variables can help to reduce selection bias of this type. The current MAIC was preceded by an exploratory analysis that selected adjustment factors from a list that is consistent with previously reported prognostic factors for NSCLC outcomes.[106-109] Being selective in this way allows adjustment of the appropriate baseline characteristics while maximising the effective sample size used in the subsequent analyses.

Inevitably, in this sort of indirect comparison there will be some heterogeneity in factors that cannot be adjusted for by matching. As already stated, the EXP-2:3A cohort does not perfectly match the chemotherapy data sources in terms of proportions pre-treated with both crizotinib and chemotherapy. However, clinical expert opinion suggests that this difference in previous chemotherapy should not make a clinically significant difference to outcomes. This view is also consistent with the license indication for lorlatinib, in that its' efficacy is not conditional on previous chemotherapy treatment.

As an alternative methodology, MAICs could have been conducted with each source of PFS chemotherapy data separately and the resultant HRs combined via a meta-analysis. However, this was deemed unnecessary because of the similarity between ALUR and ASCEND-5 studies in terms of inclusion and exclusion criteria and baseline characteristics.[64, 66] Indeed, a comparable scenario analysis was conducted in the appraisal of brigatinib (TA571) and both methods gave similar results.

In summary, the MAIC presented here represents the best available comparative evidence for lorlatinib versus chemotherapy in ALK-positive NSCLC.

B.2.9 Adverse reactions

B.2.9.1 Extent of exposure

The safety of lorlatinib has been evaluated in seven completed clinical pharmacology studies in healthy volunteers (Study 1004, Study 1005, Study 1007, Study 1008, Study 1011, Study 1012 and Study 1016), as well as the ongoing (closed to further enrolment) Phase 1/2 Study 1001 in adults with ALK and c- ROS1-positive NSCLC.

Safety data are presented for all patients who received lorlatinib at 100 mg OD in Study 1001, as of the data cut-off date of 2 February 2018. This cohort consisted of 17 patients from Phase 1, 275 patients from Phase 2, and three patients from the Japan lead-in-cohort.[110] These 295 patients constitute the 100 mg OD group. In addition, Phase 2 data are presented for the pooled EXP-3B:5 cohort (n=139).

As of the data cut-off date (2 February 2018), the median duration of lorlatinib treatment was 16.3 months for the 100 mg OD group, with a median relative dose intensity (RDI) of [redacted]. In the pooled EXP-3B:5 cohort, the median duration of treatment was [redacted] months, with a median RDI of [redacted].[99]

In the 100 mg OD group, dose reductions and temporary discontinuations due to AEs occurred in [redacted] and [redacted] patients, respectively. Permanent discontinuations of lorlatinib associated with all-causality AEs were reported in [redacted] patients; nine [redacted] were considered treatment-related.[95]

In the pooled EXP-3B:5 cohort, dose reductions and temporary discontinuations due to AEs occurred in [redacted] and [redacted] patients, respectively.[111] Permanent discontinuations of lorlatinib associated with all-causality AEs were reported in [redacted]; [redacted] were considered treatment-related.

B.2.9.2 Incidence of adverse events

A summary of all-causality and treatment-related AEs is shown in Table 27.

Table 27. Overview of Adverse events (Study 1001; safety analysis population)

Event	100 mg OD group* (n=295)	EXP-3B:5 (n=139)
All-causality AEs, n (%)	294 (99.7)	[redacted]
Grade 3 or 4 AEs	209 (70.8)	[redacted]
Grade 5 AEs	37 (12.5)	[redacted]
SAEs	112 (38.0)	[redacted]
Dose reduction due to AEs	73 (24.7)	[redacted]
Discontinuations due to AEs	26 (8.8)	[redacted]
Temporary discontinuations due to AEs	147 (49.8)	[redacted]
TRAEs, n (%)	281 (95.3)	[redacted]
Grade 3 or 4 AEs	134 (45.4)	[redacted]
Grade 5 AEs	0 (0.0)	[redacted]
SAEs	23 (7.8)	[redacted]
Dose reduction due to AEs	69 (23.4)	[redacted]
Discontinuations due to AEs	9 (3.1)	[redacted]
Temporary discontinuations due to AEs	99 (33.6)	[redacted]

Abbreviations: AE = adverse event; EXP = expansion; mg = milligram; n = number of patients; OD = once daily; SAE = serious adverse event; TRAE = treatment-related adverse event
* Includes all Phase 1 patients treated at a lorlatinib starting dose of 100 mg OD, all Phase 2 patients and three patients who were part of the Japanese lead-in cohort
Source: Pfizer Limited, 2018;[99] Pfizer Limited, 2019[111]

B.2.9.3 Most frequent adverse events

In the 100 mg OD group, 294 (99.7%) patients experienced all-causality AEs in Study 1001 (Table 28). The most frequent all-causality AE was hypercholesterolemia (84.4%). In terms of severity, 140 (47.5%) patients, 36 (12.2%) patients and 37 (12.5%) patients experienced grade 3, grade 4 and grade 5 (fatal) AEs, respectively.[95]

In the pooled EXP-3B:5 cohort, [redacted] patients experienced all-causality AEs (Table 28). The most frequent all-causality AE was hypercholesterolemia ([redacted]). In terms of severity, [redacted] patients, [redacted] patients and [redacted] patients experienced grade 3, grade 4 and grade 5 (fatal) AEs, respectively.[111]

Table 28. Most frequent (≥10% of patients in either group) AEs (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
All-causality AEs, n (%)	294 (99.7)	[redacted]
Hypercholesterolemia*	249 (84.4)	[redacted]
Hypertriglyceridemia*	198 (67.1)	[redacted]
Oedema*	161 (54.6)	[redacted]
Peripheral neuropathy*	141 (47.8)	[redacted]
Cognitive effects*	85 (28.8)	[redacted]
Fatigue	83 (28.1)	[redacted]
Dyspnoea	82 (27.8)	[redacted]
Weight increase	78 (26.4)	[redacted]
Arthralgia	73 (24.7)	[redacted]
Mood effects*	67 (22.7)	[redacted]
Diarrhoea	67 (22.7)	[redacted]
Cough	57 (19.3)	[redacted]
Nausea	54 (18.3)	[redacted]
Headache	53 (18.0)	[redacted]
Dizziness	49 (16.6)	[redacted]
Anaemia	47 (15.9)	[redacted]
Constipation	47 (15.9)	[redacted]
Vision disorder*	45 (15.3)	[redacted]
AST increased	43 (14.6)	[redacted]
Pyrexia	42 (14.2)	[redacted]
Lipase increased	41 (13.9)	[redacted]
ALT increased	40 (13.6)	[redacted]
Back pain	40 (13.6)	[redacted]
Pain in extremity	40 (13.6)	[redacted]
Myalgia	36 (12.2)	[redacted]
Vomiting	36 (12.2)	[redacted]
Upper respiratory tract infection	35 (11.9)	[redacted]
Amylase increased	30 (10.2)	[redacted]
Rash	30 (10.2)	[redacted]
Hypertension	29 (9.8)	[redacted]
Disease progression	27 (9.2)	[redacted]
Electrocardiogram QT prolonged	19 (6.4)	[redacted]
Chest pain	27 (9.2)	[redacted]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EXP = expansion; mg = milligram; OD = once daily
*AE cluster term
Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.4 Most frequent treatment-related adverse events

In the 100 mg OD group, [redacted] patients experienced TRAEs in Study 1001 (Table 29). The most frequent TRAEs were hypercholesterolemia ([redacted]) and hypertriglyceridemia ([redacted]). In terms of severity, [redacted] patients and [redacted] patients experienced grade 3 and grade 4 TRAEs, respectively. No grade 5 (fatal) TRAEs were reported [95]

In the pooled EXP-3B:5 cohort, [redacted] patients experienced TRAEs (Table 29). The most frequent TRAEs were hypercholesterolemia ([redacted]) and hypertriglyceridemia ([redacted]). In terms of severity, [redacted] patients and [redacted] patients experienced grade 3 and grade 4 TRAEs, respectively. No grade 5 (fatal) TRAEs were reported [111]

Table 29. Most frequent (≥3% of patients in either group) TRAEs (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
TRAE, n (%)	281 (95.3)	[redacted]
Hypercholesterolemia*	247 (83.7)	[redacted]
Hypertriglyceridemia*	196 (66.4)	[redacted]
Oedema*	131 (44.4)	[redacted]
Peripheral neuropathy*	99 (33.6)	[redacted]
Cognitive effects*	68 (23.1)	[redacted]
Weight increase	66 (22.4)	[redacted]
Mood effects*	46 (15.6)	[redacted]
Fatigue	45 (15.3)	[redacted]
Diarrhoea	37 (12.5)	[redacted]
AST increased	36 (12.2)	[redacted]
ALT increased	32 (10.8)	[redacted]
Arthralgia	32 (10.8)	[redacted]
Constipation	27 (9.2)	[redacted]
Lipase increased	27 (9.2)	[redacted]
Dizziness	26 (8.8)	[redacted]
Nausea	26 (8.8)	[redacted]
Speech effects*	25 (8.5)	[redacted]
Vision disorder*	22 (7.5)	[redacted]
Amylase increased	22 (7.5)	[redacted]
Anaemia	20 (6.8)	[redacted]
Headache	20 (6.8)	[redacted]
Myalgia	20 (6.8)	[redacted]
Rash	17 (5.8)	[redacted]
ECG QT prolonged	16 (5.4)	[redacted]
Tinnitus	16 (5.4)	[redacted]
Alopecia	14 (4.7)	[redacted]
Hypertension	14 (4.7)	[redacted]
Blood CPK increased	13 (4.4)	[redacted]
Insomnia	13 (4.4)	[redacted]
Vomiting	13 (4.4)	[redacted]
Abdominal distension	12 (4.1)	[redacted]
Dysgeusia	12 (4.1)	[redacted]
Pain in extremity	12 (4.1)	[redacted]
Thrombocytopenia	11 (3.7)	[redacted]
Hallucination	10 (3.4)	[redacted]
Hyperuricaemia	10 (3.4)	[redacted]
Muscle spasms	10 (3.4)	[redacted]
Dyspnoea	9 (3.1)	[redacted]
Hyperhidrosis	9 (3.1)	[redacted]
Increased appetite	9 (3.1)	[redacted]
Stomatitis	9 (3.1)	[redacted]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; ECG = electrocardiogram; EXP = expansion; mg = milligram; n = number of patients; OD = once daily; TRAE = treatment-related adverse event

*AE cluster term

Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.5 Serious adverse events

In the 100 mg OD group, 112 (38.0%) patients experienced all-causality SAEs in Study 1001 (Table 30). The most frequent all-causality SAE was disease progression 27 (9.2%). In terms of severity, 44 (14.9%) patients, 12 (4.1%) patients and 37 (12.5%) patients experienced grade 3, grade 4 and grade 5 (fatal) SAEs, respectively.[95]

In the pooled cohort, [redacted] ([redacted]) patients experienced all-causality SAEs (Table 30). The most frequent all-causality SAE was disease progression ([redacted]). In terms of severity, 22 ([redacted]) patients, [redacted] ([redacted]) patients and [redacted] ([redacted]) patients experienced grade 3, grade 4 and grade 5 (fatal) SAEs, respectively.[111]

Table 30. Most frequent SAEs (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
All-causality SAEs, n (%)	112 (38.0)	[redacted]
Disease progression	27 (9.2)	[redacted]
Dyspnoea	8 (2.7)	[redacted]
Pyrexia	7 (2.4)	[redacted]
Pneumonia	6 (2.0)	[redacted]
Mental status change	5 (1.7)	[redacted]
Fall	4 (1.4)	[redacted]
Pericardial effusion	4 (1.4)	[redacted]
Cognitive effects*	3 (1.0)	[redacted]
Pleural effusion	3 (1.0)	[redacted]
Pulmonary embolism	3 (1.0)	[redacted]
Respiratory failure	3 (1.0)	[redacted]
Vomiting	3 (1.0)	[redacted]
Oedema*	2 (0.7)	[redacted]
Peripheral neuropathy*	2 (0.7)	[redacted]
Acute respiratory failure	2 (0.7)	[redacted]
ALT increased	2 (0.7)	[redacted]
AST increased	2 (0.7)	[redacted]
Atrial fibrillation	2 (0.7)	[redacted]
Chest pain	2 (0.7)	[redacted]
Embolism	2 (0.7)	[redacted]
Femoral neck fracture	2 (0.7)	[redacted]
Headache	2 (0.7)	[redacted]
Lower respiratory tract infection	2 (0.7)	[redacted]
Lung disorder	2 (0.7)	[redacted]
Lung infection	2 (0.7)	[redacted]
Pain	2 (0.7)	[redacted]
Pneumonitis	2 (0.7)	[redacted]
Respiratory tract infection	2 (0.7)	[redacted]
Sepsis	2 (0.7)	[redacted]
Superior vena cava syndrome	2 (0.7)	[redacted]
Thrombosis	2 (0.7)	[redacted]
Upper respiratory tract infection	2 (0.7)	[redacted]
Urinary tract infection	2 (0.7)	[redacted]
Vertigo	2 (0.7)	[redacted]
Pleural effusion	0 (0.0)	[redacted]
Respiratory failure	0 (0.0)	[redacted]
Vomiting	0 (0.0)	[redacted]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EXP = expansion; mg = milligram; n = number of patients; OD = once daily; SAE = serious adverse event
* AE cluster term
Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.6 Treatment-related serious adverse events

In the 100 mg OD group, 23 (7.8%) patients experienced treatment-related SAEs (Table 31). The most frequent treatment-related SAE was cognitive effects (1.0%). In terms of severity, 13 (4.4%) and 5 (1.7%) patients experienced grade 3 and grade 4 treatment-related SAEs, respectively. No grade 5 (fatal) treatment-related SAEs were reported.[95]

In the pooled cohort, [redacted] ([redacted]) patients experienced treatment-related SAEs (Table 31). In terms of severity, [redacted] ([redacted]) and [redacted] ([redacted]) patients experienced grade 3 and grade 4 treatment-related SAEs, respectively.. No grade 5 (fatal) treatment-related SAEs were reported.[111]

Table 31. Treatment-related SAEs (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
Treatment-related SAE, n (%)	23 (7.8)	[redacted]
Cognitive effects*	3 (1.0)	[redacted]
Oedema*	1 (0.3)	[redacted]
Hypercholesterolemia*	1 (0.3)	[redacted]
Hypertriglyceridemia*	1 (0.3)	[redacted]
Peripheral neuropathy*	1 (0.3)	[redacted]
Acute respiratory failure	1 (0.3)	[redacted]
ALT increased	1 (0.3)	[redacted]
AST increased	1 (0.3)	[redacted]
Cerebral infarction	1 (0.3)	[redacted]
Coronary artery disease	1 (0.3)	[redacted]
Dyspnoea exertional	1 (0.3)	[redacted]
Erysipelas	1 (0.3)	[redacted]
Gastritis	1 (0.3)	[redacted]
Glossitis	1 (0.3)	[redacted]
Hallucination	1 (0.3)	[redacted]
Headache	1 (0.3)	[redacted]
Interstitial lung disease	1 (0.3)	[redacted]
Mental status changes	1 (0.3)	[redacted]
Pancreatitis	1 (0.3)	[redacted]
Pneumonia	1 (0.3)	[redacted]
Pneumonitis	1 (0.3)	[redacted]
Presyncope	1 (0.3)	[redacted]
Respiratory failure	1 (0.3)	[redacted]
Lung disorder	1 (0.3)	[redacted]
Thrombosis	1 (0.3)	[redacted]
Vagus nerve disorder	1 (0.3)	[redacted]
Cerebral infarction	0 (0.0)	[redacted]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EXP = expansion; mg = milligram; n = number of patients; OD = once daily; SAE = serious adverse event
* AE cluster term
Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.7 Deaths

During the study treatment or within 28 days of the last dose of lorlatinib, 32 (10.8%) patients in the 100 mg OD group died, and 69 (23.4%) patients died more than 28 days after the last dose of lorlatinib (during follow-up).[95] None of the deaths were treatment-related and the majority (29.5%) of deaths were due to disease progression.[95]

B.2.9.8 Adverse events associated with permanent treatment discontinuation

In the 100 mg OD group, 26 (8.8%) patients permanently discontinued lorlatinib treatment due to AEs (Table 32).[95] In the pooled cohort, [redacted] ([redacted]) patients permanently discontinued lorlatinib treatment due to AEs (Table 32).[111]

Table 32. AEs as the primary reason for permanent study drug discontinuation (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
Any AE, n (%)	26 (8.8)	[redacted]
Acute respiratory failure	2 (0.7)	
Dyspnoea	2 (0.7)	
Respiratory failure	2 (0.7)	
Acute leukaemia	1 (0.3)	
Acute myocardial infarction	1 (0.3)	
Affect lability	1 (0.3)	
Anxiety	1 (0.3)	
Asphyxia	1 (0.3)	
Brain compression	1 (0.3)	
Cognitive disorder	1 (0.3)	
Confusional state	1 (0.3)	
Disease progression	1 (0.3)	
Embolism	1 (0.3)	
Hallucination	1 (0.3)	
Hallucination, auditory	1 (0.3)	
Hallucination, visual	1 (0.3)	
Headache	1 (0.3)	
Hydrocephalus	1 (0.3)	
Hypoxia	1 (0.3)	
Leukocytosis	1 (0.3)	
Loss of consciousness	1 (0.3)	
Lung infection	1 (0.3)	
Mental status change	1 (0.3)	
Myocardial infarction	1 (0.3)	
Parkinsonian gait	1 (0.3)	
Peripheral swelling	1 (0.3)	
Pneumonitis	1 (0.3)	
Renal cyst haemorrhage	1 (0.3)	
Seizure	1 (0.3)	
Thrombocytopenia	1 (0.3)	
Tinnitus	1 (0.3)	
Vomiting	1 (0.3)	

Abbreviations: AE = adverse event; EXP = expansion; mg = milligram; n = number of patients; OD = once daily
Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.9 Adverse events associated with dose reductions

In the 100 mg OD group, 73 (24.7%) patients experienced dose reductions due to AEs (Table 33).[95] In the pooled cohort, [redacted] patients experienced dose reductions due to AEs (Table 33).[111]

Table 33. AEs as the primary reason for dose reduction (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
Any AE	73 (24.7)	[redacted]
Oedema*	18 (6.1)	
Peripheral neuropathy*	14 (4.7)	

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)
Cognitive effects*	13 (4.4)	[redacted]
Mood effects*	10 (3.4)	[redacted]
Hypertriglyceridemia*	6 (2.0)	[redacted]
Lipase increase	4 (1.4)	[redacted]
Fatigue	3 (1.0)	[redacted]
Hypercholesterolemia*	3 (1.0)	[redacted]
Arthralgia	3 (1.0)	[redacted]
Dizziness	3 (1.0)	[redacted]
Weight increase	3 (1.0)	[redacted]
Speech effects*	2 (0.7)	[redacted]
Amylase increase	2 (0.7)	[redacted]
Dyspnoea	2 (0.7)	[redacted]
Hypoxia	2 (0.7)	[redacted]
Pain in extremity	2 (0.7)	[redacted]
Pulmonary oedema	2 (0.7)	[redacted]
Vision disorder*	1 (0.3)	[redacted]
ALT increased	1 (0.3)	[redacted]
Axillary mass	1 (0.3)	[redacted]
Blood CPK increased	1 (0.3)	[redacted]
Brain oedema	1 (0.3)	[redacted]
Cardiac tamponade	1 (0.3)	[redacted]
Diarrhoea	1 (0.3)	[redacted]
Dyspnoea exertional	1 (0.3)	[redacted]
Ejection fraction decreased	1 (0.3)	[redacted]
Erysipelas	1 (0.3)	[redacted]
Face oedema	1 (0.3)	[redacted]
Feeling abnormal	1 (0.3)	[redacted]
Hallucination	1 (0.3)	[redacted]
Hallucination, auditory	1 (0.3)	[redacted]
Hallucination, visual	1 (0.3)	[redacted]
Hydrocephalus	1 (0.3)	[redacted]
Hypertensive crisis	1 (0.3)	[redacted]
Localised oedema	1 (0.3)	[redacted]
Neck pain	1 (0.3)	[redacted]
Pancreatitis	1 (0.3)	[redacted]
Pleural effusion	1 (0.3)	[redacted]
Presyncope	1 (0.3)	[redacted]
Tinnitus	1 (0.3)	[redacted]
Upper respiratory tract infection	1 (0.3)	[redacted]
Vertigo	1 (0.3)	[redacted]
Vomiting	1 (0.3)	[redacted]
Oedema peripheral	0 (0.0)	[redacted]
Memory impairment	0 (0.0)	[redacted]
Peripheral swelling	0 (0.0)	[redacted]
Affect lability	0 (0.0)	[redacted]
Amnesia	0 (0.0)	[redacted]
Gait disturbance	0 (0.0)	[redacted]
Neurotoxicity	0 (0.0)	[redacted]
Peripheral sensory neuropathy	0 (0.0)	[redacted]
Personality change	0 (0.0)	[redacted]

Event	100 mg OD group (n=295)	EXP-3B:5 (n=139)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; CPK = creatinine phosphokinase; EXP = expansion; mg = milligram; n = number of patients; OD = once daily
* AE cluster term
Source: Pfizer Limited, 2018;[95] Pfizer Limited, 2019[111]

B.2.9.10 Adverse events of special interest

Adverse events of special interest (AESI) are summarised in Table 34. AESIs were primarily grade 1 and grade 2 in severity and were managed by dose interruption, temporary discontinuation, or standard medical therapies. No patients experienced grade 5 AESIs and only 1 (0.3%) pneumonitis AESI (grade 4) led to permanent discontinuation of lorlatinib.[95]

Table 34. Adverse events of special interest (Study 1001; safety analysis population)

Event	100 mg OD group (n=295)				EXP-3B:5 (n=139)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Hypercholesterolemia*	249 (84.4)	43 (14.6)	6 (2.0)	0 (0.0)	[redacted]			
Hypertriglyceridemia*	198 (67.1)	41 (13.9)	8 (2.7)	0 (0.0)				
Oedema*	161 (54.6)	7 (2.4)	0 (0.0)	0 (0.0)				
Peripheral neuropathy*	141 (47.8)	8 (2.7)	0 (0.0)	0 (0.0)				
Cognitive effects*	85 (28.8)	6 (2.0)	0 (0.0)	0 (0.0)				
Mood effects*	67 (22.7)	5 (1.7)	0 (0.0)	0 (0.0)				
Speech effects*	29 (9.8)	1 (0.3)	0 (0.0)	0 (0.0)				
Weight increased	78 (26.4)	16 (5.4)	0 (0.0)	0 (0.0)				
Vision disorder*	45 (15.3)	1 (0.3)	0 (0.0)	0 (0.0)				
ALT increased	40 (13.6)	3 (1.0)	2 (0.7)	0 (0.0)				
AST increased	43 (14.6)	2 (0.7)	2 (0.7)	0 (0.0)				
Blood ALP increased	10 (3.4)	2 (0.7)	0 (0.0)	0 (0.0)				
Transaminases increased	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)				
LFT increased	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)				
Hepatic function abnormal	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)				
Blood bilirubin increased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)				
Hepatic enzyme increased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)				
Electrocardiogram QT prolongation	19 (6.4)	2 (0.7)	0 (0.0)	0 (0.0)				
Interstitial lung disease	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)				
Pneumonitis	3 (1.0)	1 (0.3)	1 (0.3)	0 (0.0)				
AV block first-degree	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)				
AV block complete	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)				
Pancreatitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)				

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; AV = atrioventricular; LFT = liver function test

* AE cluster term

Source: Pfizer Limited, 2018[95]

B.2.9.11 Safety conclusions

Safety data from Study 1001 demonstrate that lorlatinib was generally tolerable and, when needed, AEs were manageable through dosing delay, dose reduction and/or standard supportive medical therapy.

In the 100 mg OD group, the most frequent all-causality AEs were hypercholesterolemia (84.4%), hypertriglyceridemia (67.1%), oedema (54.6%) and peripheral neuropathy (47.8%).[95] The most frequent all-causality SAEs were disease progression (9.2%), dyspnoea (2.7%) and pyrexia (2.4%).[95] Although cognitive effects were reported at a rate of 28.8%, they were generally mild and rapidly reversible upon dose modification. Hyperlipidaemia was successfully managed with lipid-lowering agents. In total, 8.8% of patients permanently discontinued treatment due to all-causality AEs. There were 32 (10.8%) deaths on treatment and 69 (23.4%) deaths after the last dose of treatment, none of which were treatment-related. Thirty-seven (12.5%) patients experienced grade 5 (fatal) AEs.[95]

In the pooled EXP-3B:5 cohort, the most frequent all-causality AEs were hypertriglyceridemia ([redacted]),hypercholesterolemia ([redacted]), hypercholesterolemia ([redacted]), oedema ([redacted]) and peripheral neuropathy ([redacted]).[111] The most frequent all-causality SAEs were disease progression ([redacted]), dyspnoea ([redacted]) and falls ([redacted]). In total, [redacted] of patients permanently discontinued treatment due to all-causality AEs. [redacted] ([redacted]) patients experienced grade 5 (fatal) AEs.[111]

B.2.10 Ongoing studies

Other than Study 1001, there are no ongoing studies of lorlatinib for the indication under review. The next and final planned data cut for Study 1001 is scheduled for September 2020.

Lorlatinib is also being evaluated for the first-treatment of ALK-positive NSCLC (Study B7461006; NCT03052608). However, this population is not relevant to this submission.

B.2.11 Innovation

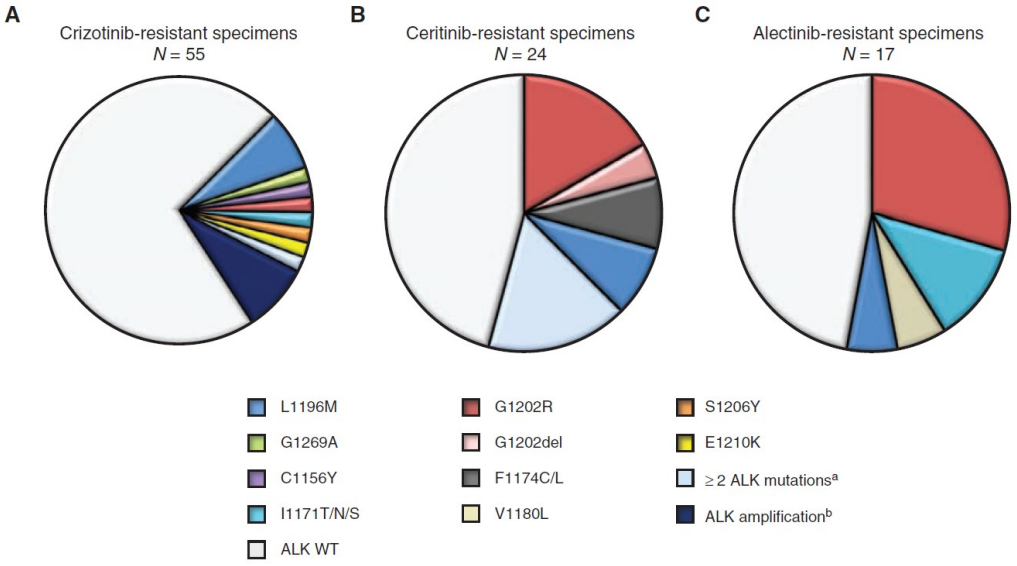
Lorlatinib is the first third-generation targeted therapy for patients with ALK-positive advanced NSCLC

Lorlatinib is the first and only licensed third-generation ALK TKI targeted therapy available in Europe for patients with ALK-positive advanced NSCLC whose disease has progressed after first- and/or second-generation ALK TKIs (alectinib or ceritinib as the first ALK TKI therapy; or crizotinib and at least one other ALK TKI).

Lorlatinib was specifically designed to inhibit resistant ALK mutations, including the ALK^{G1202R} mutation, and to penetrate the blood-brain barrier

Each ALK TKI is associated with a distinct spectrum of ALK resistance mutations and the frequency of the G1202R mutation increases significantly after treatment with second-generation agents (Figure 17).[35]

Figure 17. Overview of on-target mechanisms of resistance among ALK-positive specimens obtained from patients progressing on A , crizotinib; B , ceritinib; and C , alectinib



Abbreviations: ALK = anaplastic lymphoma kinase
Source: Gainor et al. 2016[35]

Lorlatinib is active against all single ALK resistant mutations and retains significant activity against the G1202R mutation, which is the most common ALK mutation among patients who have progressed following treatment with first- and/or second-generation ALK TKIs. *In vitro* assays demonstrate that lorlatinib is the only ALK TKI to potently inhibit ALK phosphorylation across all single ALK secondary mutations, including ALK^{G1202R}, with a half maximal inhibitory concentration (IC_{50}) of 49.9 nmol/L. In addition, lorlatinib retained significant potency against the compound $ALK^{D1203N+E1210K}$ (IC_{50}=26.6 nmol/L) mutant and intermediate potency against $ALK^{D1203N+F1174C}$ (IC_{50}=69.8 nmol/L), while crizotinib, ceritinib, alectinib and brigatinib were all inactive against these mutations (Figure 18).[35]

Figure 18. ALK TKI activity in Ba/F3 cells expressing wild-type *EML4–ALK* or *EML4–ALK* harbouring various *ALK* mutations

Mutation status	Cellular ALK phosphorylation mean IC_{50} (nmol/L)				
	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Abbreviations: ALK = anaplastic lymphoma kinase; EML4 = Echinoderm Microtubule-Associated Protein-Like 4; IC_{50} = half maximal inhibitory concentration; nmol = nanomoles; TKI = tyrosine kinase inhibitor
Green = significant potency; Yellow = intermediate potency; Red = inactive
Source: Gainor et al. 2016[35]

Patients with ALK-positive advanced NSCLC often present with brain metastases.[27] Lorlatinib's ability to cross the blood-brain barrier, along with the rapid and durable IC response, means that it is expected to provide therapeutic benefit to patients with brain metastases, a common cause of disease progression following treatment with current ALK TKIs.[74, 90]

Lorlatinib is recognised as innovative at the regulatory level

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) awarded lorlatinib a Promising Innovative Medicine (PIM) designation in 2018. Lorlatinib also received Breakthrough Therapy Designation in 2017 and Priority Review in 2018 by the United States Food and Drug Administration.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Interim findings from the clinical evidence

Despite improvements in outcomes for patients with ALK-positive NSCLC, due to the development of first- and second-generation ALK TKIs, significant unmet needs still exist.[81]

For patients who progress following treatment with first- and/or second-generation ALK TKIs, treatment options are limited, with chemotherapy regimens as the standard of care. However, outcomes are modest, particularly for patients with brain metastases,[64, 67] and AEs related to chemotherapy, such as neutropenia, fatigue, nausea and alopecia, are burdensome to patients and have a detrimental effect on QoL.[64, 66]

In Study 1001, lorlatinib demonstrated a clinically meaningful benefit in patients with ALK-positive advanced NSCLC, with rapid, deep and durable systemic and IC responses, and a manageable AE profile. Lorlatinib is the only ALK TKI with robust clinical evidence for efficacy in ALK-positive advanced NSCLC patients who have progressed on one or more prior ALK TKIs.

- Over one-third of patients achieved a tumour response to lorlatinib with a majority of patients experiencing tumour shrinkage (ORR: 40.3% [95% CI: 32.1–48.9])
    - The lower boundary of the 95% CI (32.1%) around the observed proportions of patients with objective response exceeded the proportions of patients with objective response reported for single-agent chemotherapy in the ALUR (2·9–11·4%)[64, 92] and ASCEND-5 trials (6·9%)[66]
- Almost half of patients with brain metastases achieved a tumour response to lorlatinib with a majority of patients experiencing tumour shrinkage (IC-ORR: 47.9% [95% CI: 37.5–58.4]), consistent with the ability of lorlatinib to cross the blood-brain barrier
- Lorlatinib provided a median PFS of 6.9 months (95% CI: 5.4–8.2) and a median OS of 20.4 months (95% CI: 16.1–NR) with an OS probability of 67.8% and 55.6% at 12 months and 18 months, respectively
    - The median PFS time (6.9 months), also numerically exceeded the median PFS for chemotherapy in ALUR and ASCEND-5 (1·6 months for both trials).

Taken together, data from Study 1001 indicate that lorlatinib has the potential to fill an important unmet medical need for patients (including those with brain metastases) whose disease has progressed after one or more prior ALK TKIs.

In addition to the survival benefits, a number of benefits of lorlatinib, in terms of convenience, increased work productivity (patient and carer) and reduction in patient out-of-pocket travel expenditure, are not captured in cost-effectiveness modelling. As patients with ALK-positive disease are typically younger than those with ALK-negative NSCLC,[20, 23] they are more likely to be of working age, have dependents, or be carers. The burden of disease may therefore be especially high in this population. The clinical benefits associated with lorlatinib treatment may therefore allow patients of working age to remain in employment. The burden of NSCLC on carers in terms of HRQoL and cost is also substantial, and has been shown to deteriorate over time with disease progression.[60, 61] It is plausible to assume that treatment with lorlatinib would likely reduce the carer burden compared with chemotherapy whilst patients are responding to lorlatinib treatment. Lorlatinib also delays time to chemotherapy and is administered orally. This is transformative for patients, as treatment with lorlatinib avoids the time spent in secondary care receiving chemotherapy infusions in the short-term. In addition, it negates the need for patients (and potentially carers) to spend time away from home or work to receive treatment.

B.2.12.2 Strengths and limitations of the clinical evidence base

Overall, clinical data for lorlatinib provide an appropriate evidence base for assessment of its clinical and cost-effectiveness for the treatment of ALK-positive NSCLC. The strengths of the clinical evidence base are a follows:

- Study 1001 pre-treatment patterns almost perfectly reflect those that would be seen for lorlatinib-treated patients in England and Wales (see Appendix R).
- Patients with brain metastases were included (and IC response measured), representing patients with a high unmet clinical need.
- The study evaluated PFS and OS, which are widely regarded as appropriate endpoints to assess the efficacy of anti-cancer therapies.
- The secondary efficacy endpoints of objective response, TTR, DOR, DCR and TTP are relevant to routine clinical practice.
- The study included an assessment of HRQoL, using the disease-specific EORTC QLQ-C30 and QLQ-LC13 instruments.

Single-arm trials are commonly implemented in oncology indications with a limited patient pool and acute unmet medical need, and allow for quicker patient access to new treatments. Indeed, EMA regulatory approval for all four second-line ALK TKIs were initally based on findings from Phase 1/2 single-arm trials. In addition, virtually all NICE submissions for second-line ALK TKIs have used Phase 2 single-arm trials as their pivotal studies.

While there were low patient numbers in each of the EXP cohorts, the different cohorts and patient numbers within them reflect the varied pre-treatment patterns that would be seen in clinical practice (see Appendix R). Lorlatinib demonstrated treatment benefit across cohorts, and although the trial was not designed to demonstrate that any of these groups responded significantly better than the others, patients in all groups benefited from lorlatinib.

B.2.12.3 End-of-life criteria

Lorlatinib meets the NICE end-of-life criteria (Table 35). This is in line with previous NICE appraisals of ALK-inhibitors (ceritinib [TA395] and brigatinib [TA571]) that have been approved for second-line use (after crizotinib).

Table 35. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• The median OS from Study 1001 for the cohort of most relevance to this submission (EXP-3B:5) was approximately 20 months • Median OS for PDC is expected to be lower – Ou et al. 2014 (PROFILE 1001/1005) reported a median OS of 5.4 months for patients post-crizotinib who received systemic anti-cancer therapy (i.e. chemotherapy) • The model predicts mean OS for the comparator arm (base case settings) of 9.4 months	Section B.2.5.4.4 (page 50)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Median OS differences between lorlatinib and the source used for OS (PROFILE 1001/1005) exceed 3 months (20 versus 5 months) • Model predicted mean OS differences exceed 3 months ([redacted] months versus 9 months)	Section B.2.8.5 (page 61)

Abbreviations: EXP = expansion; NHS = National Health Service; OS = overall survival; PDC = platinum-doublet chemotherapy; PFS = progression-free survival

B.3. Cost effectiveness

***De novo* cost-effectiveness model**

- The cost-utility of lorlatinib for the treatment of NSCLC was assessed with an area under the curve, partitioned survival model. The model included three core health states: progression free, progressed disease and death.
- In the base case analysis, lorlatinib was compared to PDC, which consists of pemetrexed in combination with cisplatin/carboplatin.
- OS and PFS estimates of lorlatinib were based on the EXP-3B:5 cohort from the Study 1001 trial data; parametric survival curves were fit to these data to inform anticipated survival over time.
- OS and PFS estimates for PDC were informed from the literature. Several methods have been incorporated to inform the comparison; including MAICs, unadjusted HRs and fitting independent curves to the observed KM data from the literature.
- Health-state utilities were treatment-dependent in the progression-free state to reflect differences in AE profiles and the different method of administration which is known to impact HRQoL.
- Health-state utilities were captured within the Study 1001 trial and were applied in the model to lorlatinib progression-free patients. For PDC, the progression-free health-state utility value was informed from a previous trial reported in a prior Health Technology assessment (HTA) submission. For progressed disease, health-state utilities were informed from the literature and reflected the worsening of a patients' condition upon progression. Disutilities for AEs were considered already accounted for in the progression-free health state.
- Input from expert oncologists who treat NSCLC patients in the UK was sought on nine separate and independent occasions to validate the assumptions and the clinical outcomes used in the model.

Base case results

- In the base case analysis, lorlatinib was associated with a deterministic incremental cost-effectiveness ratio (ICER) of £50,152 when applying a patient access scheme (PAS) of [redacted] to the lorlatinib list price. The probabilistic ICER (with PAS) was £46,337.

Sensitivity analyses and validation

- The mean ICER from the probabilistic analysis was similar to that in the deterministic base case analysis; at a willingness-to-pay threshold of £50,000 per quality-adjusted life year (QALY) gained, lorlatinib with the PAS discount was associated with a high probability of cost-effectiveness. The average across 1,000 iterations was under the £50,000 threshold.
- In addition to the running of probabilistic analyses, 28 sensitivity analyses were explored where model assumptions were changed. The model appears relatively robust to the most plausible scenarios.
- The model estimates for survival were credible as they were externally validated and in line with existing literature.

- Lorlatinib is an efficacious and cost-effective treatment for ALK-positive advanced NSCLC patients. The results of the model indicate that treatment with lorlatinib results in improved life years (LYs) and QALYs compared to treatment with PDC.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify cost-effectiveness studies relevant to the decision problem. All searches were conducted on 6 August 2018. Although the clinical SLR was fully updated in 2019, the cost-effectiveness SLR was not updated because of the very low probability that an alternative cost-effectiveness analysis related to lorlatinib had been published since that time. A table of results from the identified studies and a full list of the search strategy including the identification of studies, description of studies and quality assessment of the studies identified can be found in Appendix G.

B.3.2 Economic analysis

B.3.2.1 Patient population

A *de novo* economic evaluation was conducted to assess the cost effectiveness of lorlatinib in ALK-positive advanced NSCLC previously treated with one or more ALK TKIs other than crizotinib, in line with the appraisal scope and the licensed indication for lorlatinib (see Section B.1.2). Therefore, the cost-effectiveness analysis was informed by a subgroup of patients (EXP-3B:5) from Study 1001 for which pre-treatment was consistent with the expected license indication. This was to ensure that the economic evaluation results were generalisable to the population under consideration and to avoid introducing population bias into the analysis. These cohorts are discussed in more detail in Section B.2.3 and Table 8 and a summary of the populations in Study 1001 are presented in Table 36.

Table 36. Populations in Study 1001

ALK/ROS1 status	Cohort	Used in model?	Prior treatment regimen
ALK-positive	EXP-1	No	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI)
	EXP-2	No	Patients relapsing after crizotinib therapy only
	EXP-3A	No	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Yes	Patients relapsing after one ALK TKI other than crizotinib ± any number of prior chemotherapy regimens
	EXP-4	Yes	Patients relapsing after two prior ALK TKIs ± any number of prior chemotherapy regimens
	EXP-5	Yes	Patients relapsing after ≥3 prior ALK TKIs ± any number of prior chemotherapy regimens
ROS1-positive	EXP-6	No	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

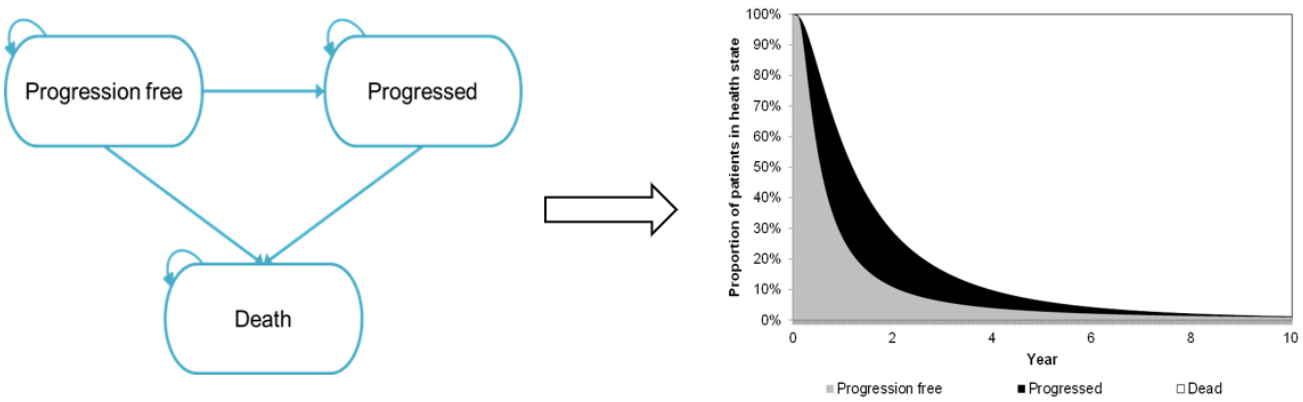
Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor
Source: Pfizer Limited, 2017[93]

B.3.2.2 Model structure

The cost-effectiveness model was developed in Microsoft Excel® using an 'area under the curve' (partitioned survival analysis) structure in both deterministic and probabilistic (Monte Carlo simulation) frameworks.

The model structure (Figure 19) has three health states: *progression free*, *progressed disease* and *death*. All patients begin the model in the *progression free* state and are at risk of progression. *Death* can occur in either the *progression free* or *progressed disease* health states, and *death* is an 'absorbing state'. The occupancy in the *progression free* state is calculated as the area under the PFS curve, while the *progressed disease* state is calculated as the area between the OS curve and the PFS curve, and *death* is calculated as 1-OS. The *progression free* health state was designed to capture the relatively higher QoL while the disease is controlled prior to progression, as patients are benefitting from an active treatment. The *progressed disease* state was designed to capture the relatively poor QoL following disease progression. The model therefore captures the changes in QoL between the *progression free* and *progressed disease* states.

Figure 19. Model structure



The model structure is fully aligned with two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life. This structure is considered appropriate for capturing the health effects and complexities of natural history/disease progression in ALK-positive NSCLC as it aligns with the efficacy outcomes of Study 1001 (Section B.2.3.3 and B.2.5.4). In addition, this structure is consistent with the vast majority of previous NICE submissions in NSCLC and published economic models.[30, 31, 33, 71]

The structure contains the three most relevant disease-related health states from patient, clinician and payer perspectives:

- **Progression free:** Within this state, it is assumed that a patients' disease is in a stable or responding state and not actively progressing. Progression is defined in the model as it was in the lorlatinib trial (Study 1001) – using RECIST v1.1 criteria. Patients in this state are assumed to incur costs associated with treatment including:
    - Drug acquisition costs
    - Drug administration costs (it is assumed that if treatment is continued beyond progression, then drug and administration costs of the first treatment are also incurred in the progressed disease state)

- Costs associated with medical management of the condition
- Costs related to the management of grade 3/4 AEs in >5% of patients
- Patients in the progression-free state are expected to experience a higher disease-related utility than those with progressed disease as their tumour and related symptoms are controlled.

- **Progressed disease:** In this state, a patients' disease is assumed to have progressed (as defined by RECIST v1.1 criteria); therefore, the patient will move on to subsequent treatment lines (if appropriate) before death. Patients in this state incur costs associated with medical management, subsequent therapy and associated administration costs. Patients in this health state also incur a cost associated with terminal care. These patients are expected to experience a lower disease-related utility than in the progression free state.
- **Death:** This is an absorbing health state, and patients can transition from any other health state.

B.3.2.3 Features of the economic analysis

The analysis was constructed from the perspective of the National Health Service (NHS) and the Personal Social Services (PSS) in England and Wales. Costs were included based on 2017–2018 prices (which were the latest available publication sources at the time of submission). A discount rate of 3.5% per annum was applied for costs and benefits in line with the NICE reference case.[112]

A lifetime horizon of 20 years was applied in the model base case. All recent NICE appraisals in NSCLC have used lifetime horizons (ranging from 10 years to 30 years).[30-33, 113] Twenty years was used in the base case as it is sufficiently long (based on survival extrapolations and clinical plausibility) to capture the relevant HRQoL and costs associated with the disease and treatments considered. It is unlikely that people with previously treated advanced ALK-positive NSCLC would survive beyond this time horizon. By the end of the time horizon (discussed in Section B.3.3) <1% of patients remain alive.

The model incorporates a 30-day cycle length; this is sufficiently short to provide the level of granularity required for this disease area and also aligns with the pack size of lorlatinib, which is available in 100 mg 30-day packs. First-line drug costs (acquisition and administration) are not incorporated in the half-cycle corrections as they are assumed to be administered at the start of each model cycle. All other costs and outcomes (health state monitoring costs, AEs, subsequent therapy and terminal care costs) are half-cycle corrected.

Table 37 presents the main features of the economic analysis. A comparison of the features of this analysis compared with the features of previous technology appraisals (TAs) for ALK-positive NSCLC is presented in Appendix K.

Table 37. Features of the economic analysis

Factor	Chosen Values	Justification
Treatment and indication	N/A	N/A
Model structure	PartSA with three health states	Regarded as appropriate for capturing the health effects and complexities of natural history/disease progression in ALK-positive NSCLC as it aligns with the endpoints of Study 1001. Precedent shows that this structure is consistent with previous NICE NSCLC appraisals and published economic models
Time horizon (years)	20 years (lifetime)	As per reference case, the time-horizon is long enough to reflect all important differences in costs or outcomes; <1% of patients are alive at 20 years.
Cycle length	30 days	To align with lorlatinib dosing
Half cycle correction applied	Yes	To increase accuracy
Health effects measured	QALYs	NICE reference case[112]
Source of utilities	Mapping from EORTC QLQ-C30 to EQ-5D, Labbe 2017	NICE reference case 5.3.9 when EQ-5D not available mapping is appropriate[112] Source most closely reflects the decision problem.
Source of drug costs	MIMS; eMIT	NICE reference case[112]
Source of other costs	NHS reference costs; PSSRU	NICE reference case[112]

Abbreviations: ALK = anaplastic lymphoma kinase; BNF = British National Formulary; eMIT = electronic market information tool; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D = EuroQoL 5 Dimensional scale; MIMS = Monthly Index of Medical Specialities; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = non-small-cell lung cancer; PartSA = partitioned survival analysis; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year

B.3.2.4 Intervention technology and comparator

The indication for lorlatinib (as monotherapy) is for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with one or more ALK TKI, except for patients treated with crizotinib as the only ALK TKI. The licensing of lorlatinib is aligned to cohorts EXP-3B:5 of Study 1001, as presented in Table 36. As outlined in Section B.1.2, lorlatinib is an ALK and ROS1 receptor TKI. Lorlatinib has a recommended dose of 100 mg to be taken once daily (available in 100 mg and 25 mg capsules) (Section B.2.3.2).

The pathway and full justification of comparators are presented in Section B.1.1. The final scope for this appraisal has been separated into two populations, in line with the lorlatinib licence:[11]

- Patients with advanced ALK-positive NSCLC that have been previously treated with crizotinib and at least one other ALK TKI;
- Patients with advanced ALK-positive NSCLC that have been previously treated with at least one ALK TKI other than crizotinib.

The populations in the NICE scope are further split based on the following conditionalities: previous chemotherapy and previous immunotherapy (PD-L1 inhibitor).

- For patients who have not had previous chemotherapy, the comparator of relevance is PDC (pemetrexed with cisplatin or carboplatin).

- Pemetrexed is indicated for the initial treatment of patients with locally advanced or metastatic, non-squamous NSCLC in combination with cisplatin.[114] Pemetrexed with carboplatin has also been identified as a treatment administered to patients with NSCLC. Previous trial evidence indicates that carboplatin and cisplatin are used roughly equally in combination with pemetrexed in UK clinical practice;[30, 31] however there is also evidence that 25% receive cisplatin and 75% receive carboplatin, which was supported by the ERG and a clinician in TA406.[31] Thus, a scenario analysis is included in which pemetrexed is used in combination with cisplatin in 25% of patients and carboplatin in 75% of patients, respectively. Reference to the use of PDC has been made in prior TA assessments and this regimen is also recommended as a combination therapy in NICE Clinical Guideline 121.[29-31]

- For patients who have received prior chemotherapy, the NICE final scope suggests that pembrolizumab, atezolizumab or best supportive care (BSC) would be comparators of relevance.
  - Pembrolizumab is currently recommended by NICE as a treatment for adults with locally advanced or metastatic PD-L1-positive NSCLC who have had at least one chemotherapy as well as a targeted ALK treatment.[82]
  - Atezolizumab is recommended for adults with locally advanced or metastatic NSCLC who have previously received chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour).[83]
  - BSC is administered to patients who are unfit to receive targeted treatment or chemotherapy, and these patients are therefore also unlikely to be fit to receive lorlatinib. As such, BSC is not considered a relevant comparator at this stage of disease.

Given that lorlatinib is indicated in patients who have previously used ALK TKIs, this is the likely setting for lorlatinib, irrespective of whether the patient has had prior chemotherapy. Due to increased use of ALK testing and increased availability of targeted treatments in UK clinical practice, a small and decreasing proportion of patients are likely to have received chemotherapy prior to an ALK TKI. Indeed, the population of patients receiving prior chemotherapy is likely to be shrinking at least as quickly as the group of patients who received crizotinib in first line, as confirmed by clinical experts (four clinicians and an advisory board), who suggested the following:

- The aim of NSCLC treatment is to maximise time on targeted therapies.
- The preference for treatment after targeted therapies is PDC.
- PDC is preferred to treatment with immunotherapies (pembrolizumab and atezolizumab), which are generally avoided by clinicians.
  - This is supported by a recently published real-world study based on a UK database of ALK patients (Gomes et al. 2019),[1] which reports that only 6% of 181 patients receive immunotherapy in any line.[1]
- For the small number of patients that receive chemotherapy in early lines, re-treatment with PDC is possible, when sensitivity to pemetrexed returns.

The treatments for which use is conditional on previous immunotherapy (docetaxel ± nintedanib) are not suitable comparators in this appraisal. This is because only a very small proportion of patients use immunotherapies in any line, as evidenced by the ALK UK database,[1] so an even smaller proportion would be eligible for docaetaxel ± nintedanib.

Furthermore, docetaxel is considered by clinical experts to be harder to tolerate than pemetrexed and PDC but with less likelihood of response, suggesting that it would come after PDC (if tolerable).

Further clinical validation was undertaken by Pfizer following the May 2019 release of the updated scope that added atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (TA10340) as a comparator for patients who have not had previous chemotherapy.[2] Additional interviews with four clinicians suggested the following:

- Uptake in the ALK-positive population is expected to be relatively small.
    - There is very little evidence to support the use of this combination in ALK-positive patients. Evidence is only available from the small subgroup of the IMpower150 trial and recent data suggests a non-significant benefit in ALK-positive patients compared with the combination without atezolizumab.[3] It is important to note that this latter combination has not been approved for the treatment of ALK-positive NSCLC.
    - This is supported by data from the Lorlatinib Pfizer compassionate use program that enrolled patients from 2016 to April 2019 and the ALK UK database. Both suggest no experience of using this combination via compassionate use programs or EAMS (approved in December 2018) in the last 3 years.
- Very few patients in the ALK-positive population will be fit enough to use the combination, particularly those with brain metastases (i.e. the majority of patients in this population). This is supported by the statements of clinical experts in the committee meetings for TA584.[2]

A standalone incremental analysis is provided seperately in an addendum at the end of this document (Appendix S). The only available evidence for this combination is in a small EGFR sample of patients (Impower150 trial; see TA10340)[2] – however, we attempt a comparison with atezolizumab with bevacizumab, paclitaxel and carboplatin in ALK-positive only patients.

In general, clinicians suggest that lorlatinib will displace PDC; PDC moves to a subsequent treatment line for those patients for which it is tolerable. Depending on sensitivity to pemetrexed and ability to tolerate doublet chemotherapy, some patients will receive pemetrexed alone, docetaxel, or BSC following lorlatinib.

B.3.3 Clinical parameters and variables

B.3.3.1 Clinical data incorporated in the model

B.3.3.1.1 Patient characteristics

The patient population from Study 1001 that is most relevant to this appraisal is the EXP-3B:5 cohort – patients who have had at least one prior ALK TKI that is not crizotinib alone. From the EXP-3B:5 cohort, 139 patients were evaluable. The patient characteristics for this cohort are presented in Table 38. As discussed in Section B.2.5.1, the baseline characteristics of patients included in the Study 1001 trial are considered to be largely representative of and generalisable to the ALK-positive patient population in the UK. Baseline characteristics are comparable between Study 1001 and other ALK-positive trials including those used to inform the MAIC (Section B.2.8.2). In addition, comparison with data from the Pfizer compassionate use programme show that Study 1001 pre-treatment patterns correspond almost perfectly with pre-treatment for patients eligible for lorlatinib in real-world practice in England and Wales (see Appendix R).

Table 38. Patient characteristics of EXP-3B:5 included in the economic model

Component	Mean Value
Age (years)	[redacted]
Proportion male (%)	[redacted]
Height (cm)	[redacted]
Weight (kg)	[redacted]

Abbreviations: cm = centimetre; kg = kilogram

B.3.3.1.2 Summary of clinical data used in the model

B.3.3.1.2.1 Lorlatinib

Within the model, efficacy data for lorlatinib were obtained from Study 1001 using the EXP-3B:5 cohort outlined in Table 36. The data from this cohort were used to inform the three health states in the model (as outlined in Section B.3.2.2 and Figure 19). KM estimates for PFS and OS are reported in Figure 20. For the outcomes of OS and PFS, parametric survival models were fitted, which extrapolated beyond the observed trial period.

Figure 20. Observed PFS and OS for lorlatinib in Study 1001 for EXP-3B:5

Abbreviations: EXP = expansion cohort; KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival. Notes: n=139

Study 1001 was used to inform other clinical data within the model; a summary is presented in Table 39.

Table 39. Application of clinical trial data in the model

Component	Application with the model	Source
PFS	Used to fit parametric survival curves to extrapolate long-term PFS estimates	Study 1001
ToT	RMST used to capture treatment beyond progression and parametric survival curves fit to extrapolate long-term ToT (scenario analysis)	
OS	Used to fit parametric survival curves to extrapolate long-term OS estimates	
Utilities	Used to inform utility of progression free patients in the progression free health state for lorlatinib	
AE incidence	Informed the proportion of patients who incur the cost (and the disutility in scenario analysis) associated with each adverse event	

Abbreviations: AE = adverse event; OS = overall survival; PFS = progression-free survival; RMST = restricted mean survival time; ToT = time on treatment

B.3.3.1.2.2 Pemetrexed in combination with cisplatin/carboplatin

Given that Study 1001 was a non-comparative single-arm study of lorlatinib, clinical inputs for PDC were informed using external evidence identified by the clinical SLR (ALUR,[92] ASCEND-5,[66] and PROFILE 1001/1005;[103] see Appendix D). Both naïve and MAIC methods were explored using these sources, in order to obtain a comparison with PDC. The MAIC methodology and results are detailed in Section B.2.8 and Appendix D.

The only remaining ALK-positive crizotinib trials – PROFILE 1007 and PROFILE 1014 – are not relevant as data sources because of the population of the trials and the levels of pre-treatment on entry to the trials. PROFILE 1007 patients were not previously treated with an ALK TKI, only PDC. PROFILE 1014 patients had no systemic pre-treatment for advanced disease.

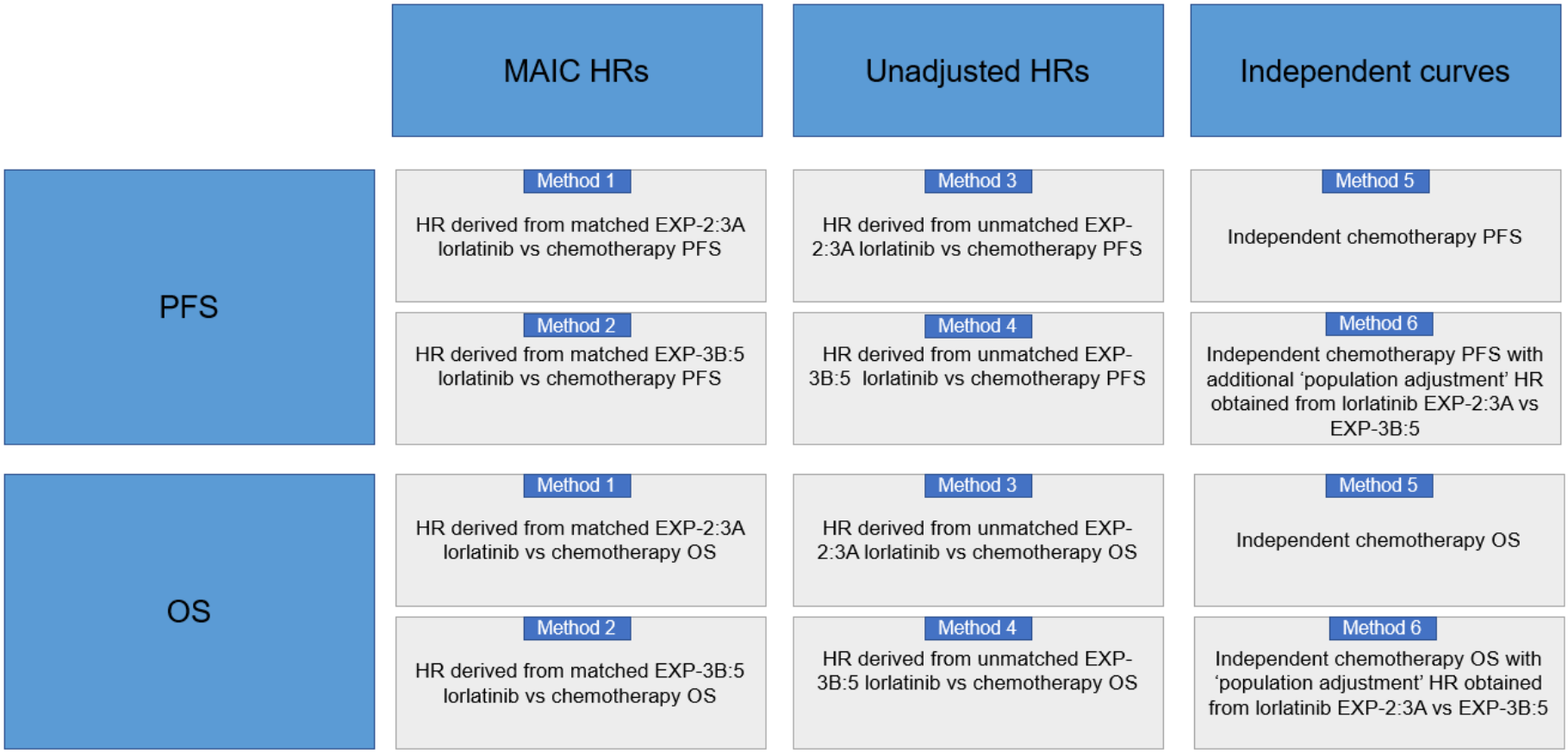
The application of PDC data and MAIC-derived treatment effects are described throughout this section. All approaches assumed that chemotherapy in the literature was an appropriate proxy for PDC in terms of efficacy. Three overarching techniques were used to compare single-arm data for lorlatinib to that of PDC:

- MAICs as described in Section B.2.8, to obtain a HR to represent the difference between lorlatinib and chemotherapy for both PFS (pooled ALUR[92] and ASCEND-5[66]) and OS (PROFILE 1001/1005).[103] HRs were derived using a weighted Cox proportional hazards model using IPD for the relevant lorlatinib cohorts, and corresponding weights – derived through the MAIC process and pseudo IPD estimates – for the PDC arm (all pseudo patients within these data were assigned weights of 1). Bootstrapping techniques were applied for CIs and variance estimates, to account for uncertainty in the MAIC process.[115]
- Unadjusted HRs derived from the differences between the pooled ALUR[92] and ASCEND-5[66] studies compared to Study 1001 for PFS, and a retrospective analysis of PROFILE 1001/1005[103] compared to Study 1001 for OS.
- Independent parametric models fitted directly to evidence sourced from the literature for the chemotherapy arm. For PFS, this was pooled data from two studies (ALUR[92] and ASCEND-5[66]). For OS, data were sourced from PROFILE 1001/1005[103] By fitting independent curves to chemotherapy data (parametric survival models generated by replicating IPD from the literature using the Guyot et al. 2012 algorithm[116]), the assumption that proportional hazards holds across the two treatments (lorlatinib and PDC) has been avoided.

Numerous scenarios associated with these three approaches were explored to fully investigate the anticipated difference (and associated uncertainty) in the effectiveness of

lorlatinib versus PDC. These scenarios are detailed throughout this section and summarised in Figure 21.

Figure 21. Summary of methods explored to derive comparator evidence



Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; vs = versus

B.3.3.2 Estimation of transition probabilities from the clinical data

The area under the curve model was populated by fitting parametric survival models to Study 1001 trial data for PFS and OS for lorlatinib.

B.3.3.3 Transition probabilities over time

B.3.3.3.1 Progression-free survival

For the economic model, the definition of PFS was derived from independent review committee (IRC) data. A benefit of using IRC PFS data over investigator-assessed (INV) PFS data is that the comparator sources (from ALUR and ASCEND-5) used IRC data (Section B.2.8). Shaw et al. only reported outcomes for ASCEND-5 derived from IRC data,[66] whereas Novello et al. reported outcomes derived from both IRC and INV assessment in ALUR.[92] Therefore, by using IRC data for lorlatinib, the approach to estimate PFS was consistent for all comparators in the economic model.

Lorlatinib

In the base case analysis, the Study 1001 trial was used to derive PFS for lorlatinib. All parametric curves were fitted to the lorlatinib PFS data, which were taken from the EXP-3B:5 cohort of patients in Study 1001. PFS curves are presented in Figure 22 for the EXP-3B:5 trial population, with corresponding Akaike information criterion (AIC)/Bayesian information criterion (BIC) statistics presented in Table 40. In all cases, standard parametric models were considered and compared, which included exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. The fit of the models was assessed by following NICE Technical Support Document (TSD) 14 ('Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data') guidance[117] and are based upon:

- Visual inspection of fitted curves;
- Comparisons of AIC and BIC statistics between the model types;
- The plausibility of long-term extrapolation based on clinical expert opinion, and expected survival from other data sources.

While all curves had a similar visual fit, the generalised gamma curve was selected for the base case. This was based on the visual fit to the observed data, statistical fit (lowest AIC and second lowest BIC), and long-term plausibility. When shown visual extrapolations and proportions in PFS, clinical experts favoured the generalised gamma or the Gompertz curve. The estimate of PFS provided by the generalised gamma curve was also in the middle of the range of estimates provided by all curves.

Figure 22. Progression-free survival parametric curves for lorlatinib (unadjusted)

Table 40. Mean, median and landmark values and AIC and BIC statistics for lorlatinib PFS parametric survival models

Model	AIC	BIC	Mean PFS (months)	Median PFS (months)	Proportion progression-free and alive at each landmark value (%)			
					6 months	1 year	2 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = progression-free survival

Pemetrexed in combination with cisplatin/carboplatin

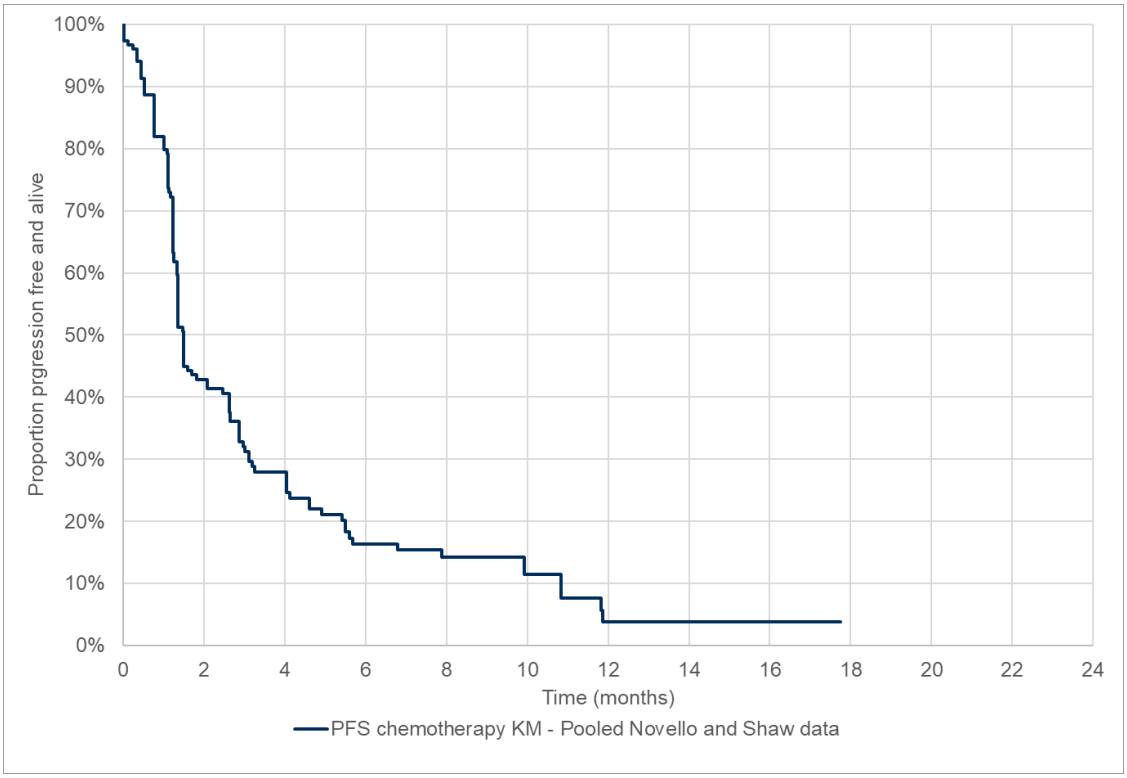
In the absence of any head-to-head evidence from which to derive a comparison of lorlatinib with chemotherapy (PDC), a variety of methods have been explored to try and accurately reflect the difference in efficacy between lorlatinib and PDC in the population of interest. These methods are outlined in Section B.3.3.1 and Section B.2.8.

As outlined, PFS for PDC was sourced from two studies: ALUR[92] and ASCEND-5.[66] Both studies assessed pemetrexed or docetaxel and reported PFS for a population that is comparable in pre-treatment terms to the combined cohort EXP-2:3A. Clinical expert opinion suggested that outcomes for chemotherapy or PDC are expected to be equally poor following treatment with a first- or second-generation TKI.

Novello et al. presented the primary results from the Phase 3 ALUR study of alectinib versus chemotherapy in previously treated ALK-positive NSCLC.[92] Key eligibility criteria indicated that patients must have: advanced disease, previous treatment with one prior line of PDC and had experienced failure on treatment with crizotinib. In this study, chemotherapy consisted of either pemetrexed 500 mg/m^2 every 21 days or docetaxel 75 mg/m^2 every 21 days. Shaw et al. presented the results of the ASCEND-5 Phase 3 RCT of ceritinib versus chemotherapy in patients with ALK-positive NSCLC who had received prior chemotherapy and crizotinib.[66] Chemotherapy within the ASCEND-5 study was aligned with ALUR, as patients were also assigned to either receive pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 every 21 days.[66]

As indicated above, ALUR and ASCEND-5 were considered the most representative of the true effectiveness of PDC, as they both reported a relatively large number of patients, and ultimately are the only sources that provide published PFS KM data for chemotherapy patients in the ALK-positive population (Section B.2.8),[66, 92] Within this analysis it was assumed that the pooled chemotherapy arms of the trials were an appropriate proxy for PDC. The PFS KM data for these pooled data are presented in Figure 23.

Figure 23. Pooled PFS KM data for chemotherapy (used to inform the PDC arm)



Abbreviations: KM = Kaplan–Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival

The model allows PDC PFS to be calculated in six different ways, as presented in Figure 21. All possible options are listed in Table 41. The methodology and merits of each option are discussed in turn throughout this section.

Table 41. Methods of deriving PFS for PDC

Method (label)	Method of deriving PFS for PDC	Cohort of lorlatinib	Adjusted curve	HR	Key assumptions
1	MAIC HRs derived from Cox-proportional hazards model after weighting	EXP-2:3A	Yes	[redacted]	• The relationship between lorlatinib and chemotherapy in EXP-2:3A is the same as EXP-3B:5 • PH holds
2		EXP-3B:5	Yes	[redacted]	• Treatment line does not affect outcomes (only patient characteristics). • PH holds
3	Unadjusted HRs derived from Cox-proportional hazards model	EXP-2:3A	No	[redacted]	• The relationship between lorlatinib and chemotherapy in EXP-2:3A is the same as in EXP-3B:5 • Patients characteristics do not affect outcomes • PH holds
4		EXP-3B:5	No	[redacted]	• Treatment line does not affect outcomes • Patients characteristics do not affect outcomes • PH holds
5	Independent curves applied to the pooled KM data from ALUR and ASCEND-5	N/A	N/A	N/A	• Treatment line does not affect outcomes • Patients characteristics do not affect outcomes
6		N/A	Population adjustment	[redacted] applied to independent curve to represent 2-3A vs 3B-5 cohort	• The HR observed for lorlatinib cohorts EXP-2:3A vs EXP-3B:5 is representative of the difference in outcomes across EXP-2:3A and EXP-3B:5 for chemotherapy • Patient characteristics do not affect outcomes

Abbreviations: EXP = expansion; HR = hazard ratio; KM = Kaplan–Meier; MAIC = matching adjusted indirect comparison; N/A = not applicable; OS = overall survival; PDC = platinum doublet therapy; PFS = progression-free survival; PH = proportional hazards assumption; SE = standard error; vs = versus

Applying MAIC methodology

Method 1 and method 2 (Table 41) derived PFS for PDC by applying a HR to the lorlatinib PFS data. The HR was derived from the MAIC methodology outlined in Appendix D, by matching patient characteristics from Study 1001 to data reported for ALUR and ASCEND-5.[66, 92]

Method 1: Application of MAIC HR for chemotherapy versus EXP-2:3A lorlatinib

Method 1 applied a HR to the lorlatinib PFS curve to obtain PFS for PDC. This HR was derived from matching lorlatinib EXP-2:3A patients to those in the ALUR[92] and ASCEND-5[66] (which also represent patients that would fall into the EXP-2:3A cohort). The benefit of this approach is that it estimates the difference in efficacy for the correct population of patients. This approach assumed that the difference in efficacy for lorlatinib versus PDC observed in the EXP-2:3A cohort would extend to the EXP-3B:5 cohort. The HR derived from the MAIC for this cohort was [redacted] (CI: [redacted]), and Figure 24 shows its application to the lorlatinib base case curve to derive PFS for PDC.

Figure 24. MAIC EXP-2:3A HR applied to lorlatinib PFS data – Method 1

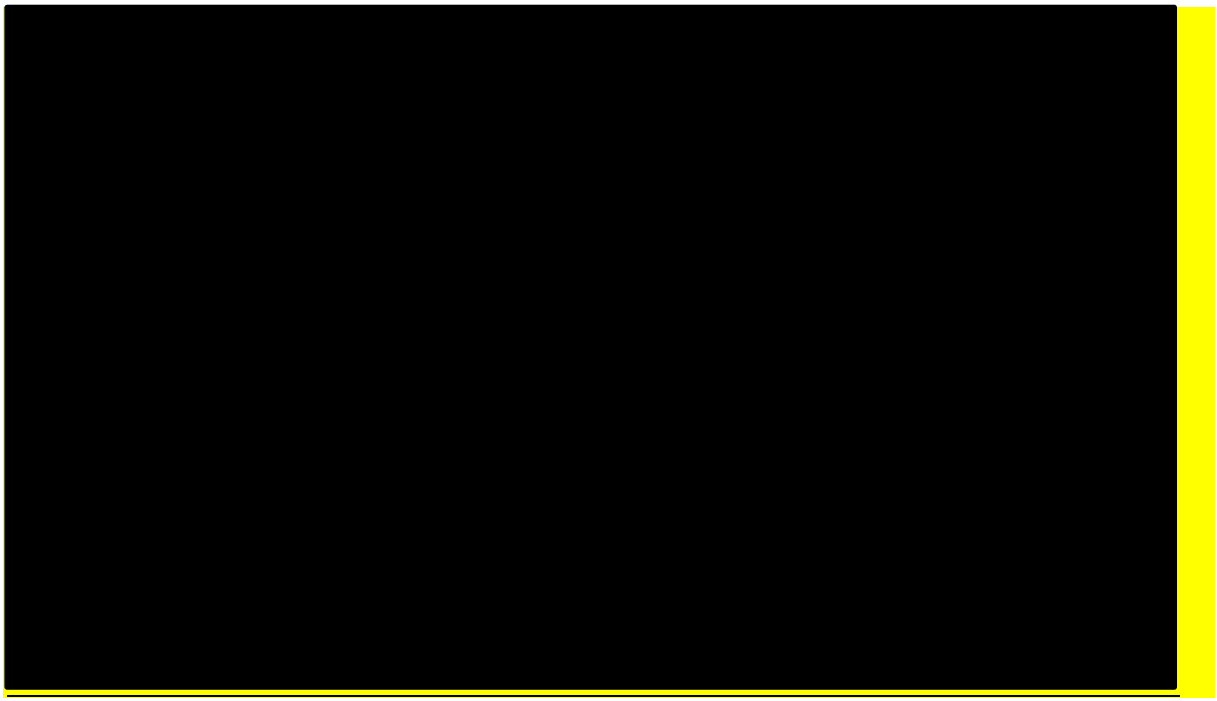
Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

Method 2: Application of MAIC HR for chemotherapy versus EXP-3B:5 lorlatinib

Method 2 applied a HR to the lorlatinib PFS curve to obtain PFS for PDC. This HR was derived from matching patient characteristics of lorlatinib EXP-3B:5 patients to those in ALUR and ASCEND-5.[66, 92] The benefit to this approach is that the HR derived is directly applicable to the patients relevant to the decision problem, and data from these patients are used to inform comparative efficacy (EXP-3B:5). The main limitation to this analysis is that it derived a HR between two cohorts with different patterns of pre-treatment. The HR derived from the MAIC

for this cohort (EXP-3B:5 lorlatinib versus chemotherapy) was was [redacted] (CI: [redacted]). Figure 25 shows its application to the lorlatinib base case curve to derive PFS for PDC.

Figure 25. MAIC EXP-3B:5 HR applied to lorlatinib PFS data – Method 2



Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

Unadjusted hazard ratios

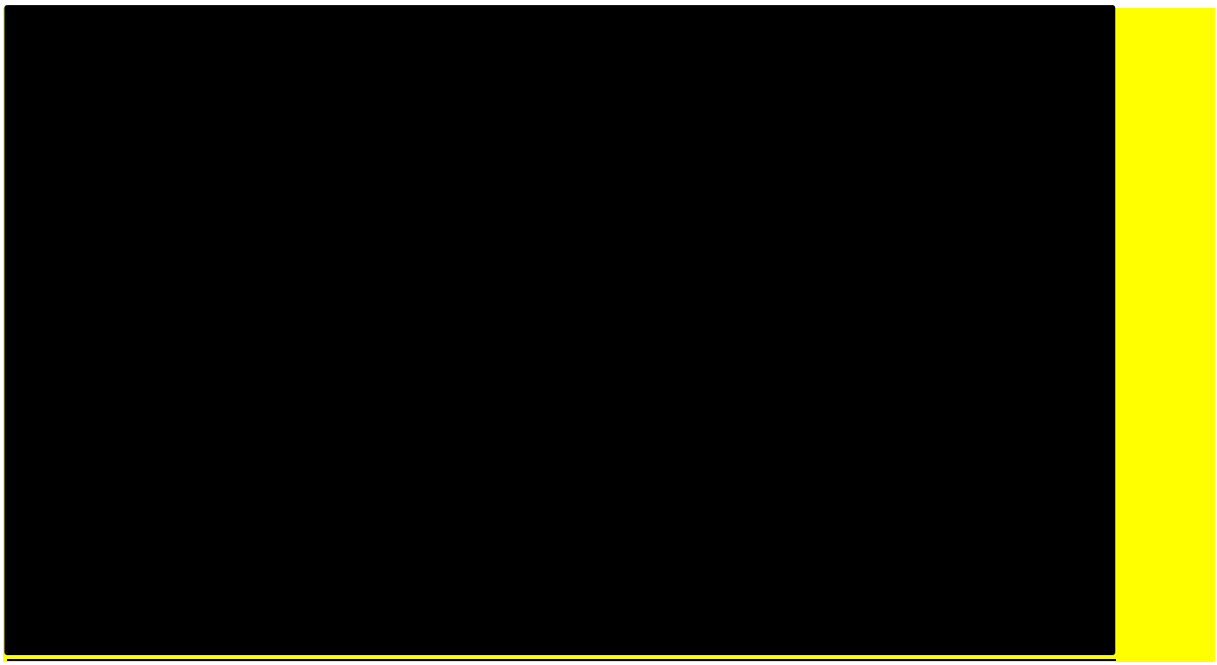
For Methods 3 and 4, unadjusted HRs were used to inform the anticipated PFS of chemotherapy (used as a proxy to estimate PDC). These methods did not apply any matching and drew a naïve comparison of lorlatinib to chemotherapy. In utilising these methods, it is assumed that patients within both the lorlatinib and PDC groups are relatively homogeneous and that all differences in outcomes are not a result of differences in patient characteristics.

Given the small difference in the obtained HRs using this unadjusted methodology compared to the MAIC HRs (see Table 41), it is unlikely that the difference in patient characteristics had a large impact on the survival estimates. Therefore, use of unadjusted or adjusted HRs is likely to have little difference on modelled outcomes; however, for transparency, both adjusted and unadjusted approaches were explored in this analysis.

Method 3: Application of an unadjusted HRs derived for chemotherapy versus EXP-2:3A lorlatinib

Method 3 applied an unadjusted HR to the lorlatinib PFS curve to obtain PFS for PDC. This HR was derived from the difference between the lorlatinib EXP-2:3A cohort data and the pooled chemotherapy data.[66, 92] The unadjusted HR for this cohort (EXP-2:3A lorlatinib versus chemotherapy) was [redacted] (CI: [redacted]), which is not too dissimilar from the matching-adjusted HR of [redacted] derived in Method 1. Figure 26 shows the application of this HR to the lorlatinib base case curve to derive PFS for the comparator arm.

Figure 26. Unadjusted EXP-2:3A HR applied to lorlatinib PFS data – Method 3



Abbreviations: EXP = expansion cohort; HR = hazard ratio; PFS = progression-free survival

Method 4: Application of unadjusted HR derived for chemotherapy versus EXP-3B:5 lorlatinib

Method 4 applied an unadjusted HR to the lorlatinib PFS data derived from the difference between lorlatinib EXP-3B:5 data and the pooled chemotherapy data. The HR obtained for this was [redacted] – similar to the MAIC HR derived in Method 3 ([redacted]). Figure 27 shows its application to the lorlatinib base case PFS curve to derive PFS for PDC.

Figure 27. Unadjusted EXP-3B:5 HR applied to lorlatinib PFS data – Method 4

Abbreviations: EXP, expansion cohort; HR, hazard ratio; PFS, progression-free survival

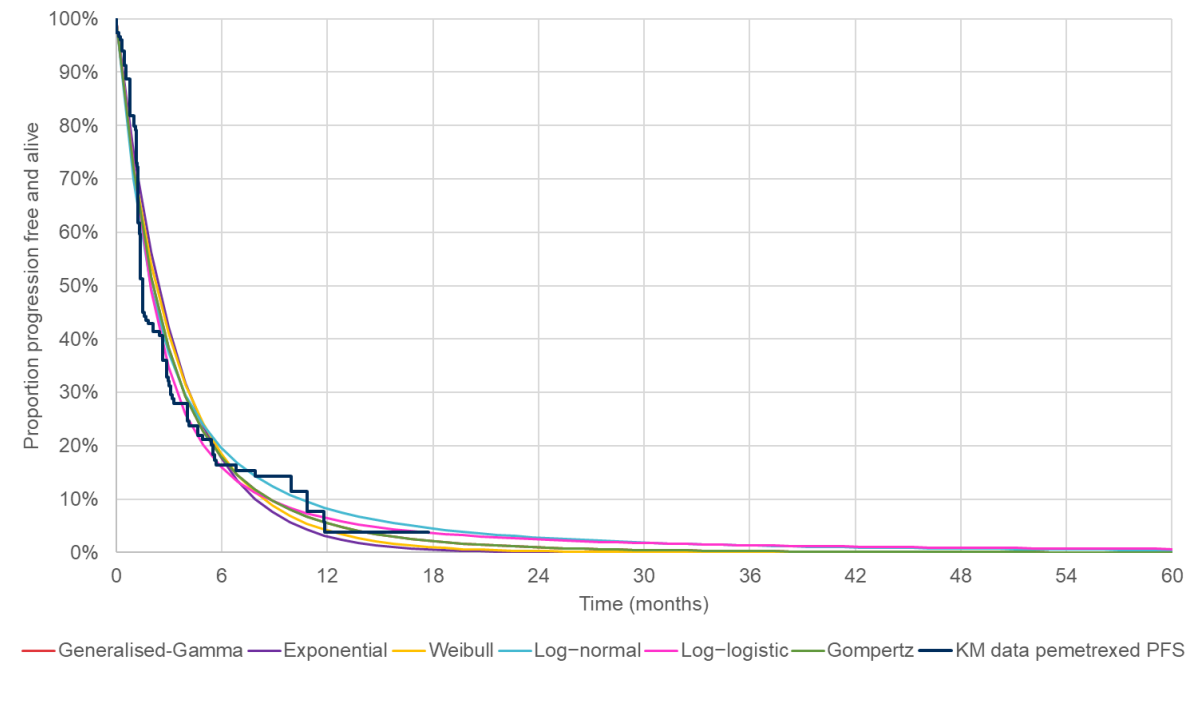
Independent curves

Independent parametric curves were also fitted to the pooled chemotherapy data from ALUR and ASCEND-5. Using independent curves relaxes the assumptions of proportional hazards and allow the parametric survival models to take a different underlying shape to survival than that which was observed in Study 1001 for lorlatinib. This is plausible because of the different mechanism of action and very different time on treatment between lorlatinib (a TKI) and a chemotherapy regimen.

Method 5: Independent chemotherapy curve

Method 5 applied an independent curve to represent PFS for PDC. Initially KM curves were digitised and IPD were replicated using the Guyot algorithm.[116] From this, parametric survival models were fitted. Figure 28 shows the parametric survival models fitted to the pooled KM data for chemotherapy used to inform the PDC arm of the model. The AIC/BIC statistics are reported in Table 42. The log-logistic curve was selected as the most plausible based on the visual fit to the KM data and the statistical fit. The means are also similar and this selection was validated with clinicians.

Figure 28. PFS parametric curves – PDC (derived from pooled KM data for chemotherapy)



Abbreviations: KM = Kaplan–Meier; PDC = platinum doublet chemotherapy; PFS = progression-free survival

Table 42. Mean, median and landmark values and AIC and BIC statistics for PDC PFS parametric survival models

Model	AIC	BIC	Mean PFS (months)	Median PFS (months)	Proportion progression-free and alive at each landmark value (%)			
					6 months	1 year	2 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum doublet chemotherapy; PFS, progression-free survival

Figure 29 shows the base-case lorlatinib PFS curve in comparison to the independent log-logistic chemotherapy curve.

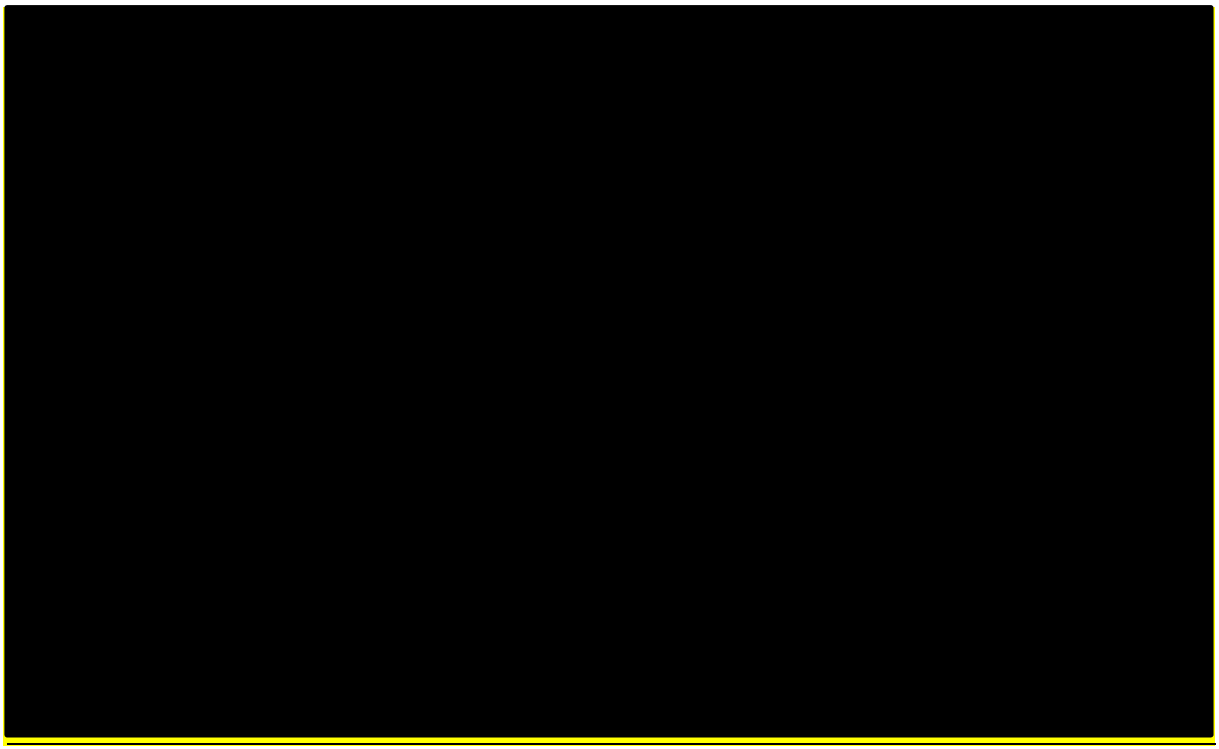
Figure 29. Independent curves fitted to pooled chemotherapy KM data compared to lorlatinib PFS data – Method 5

Abbreviations: KM = Kaplan–Meier; PFS = progression-free survival

Method 6: Independent chemotherapy curve with 'population adjustment' to EXP-3B:5 cohort

The population of the chemotherapy arm data used to represent PDC resembles the EXP-2:3A cohort most closely in terms of pre-treatments, whereas the population of relevance for lorlatinib given its licence is the EXP-3B:5 cohort. Therefore, a further analysis explored the application of a HR to the independent PFS comparator curve to calculate the PFS of patients receiving PDC in the EXP-3B:5 cohort. This represents approach Method 6 to compare PDC PFS with that of lorlatinib (Table 41).

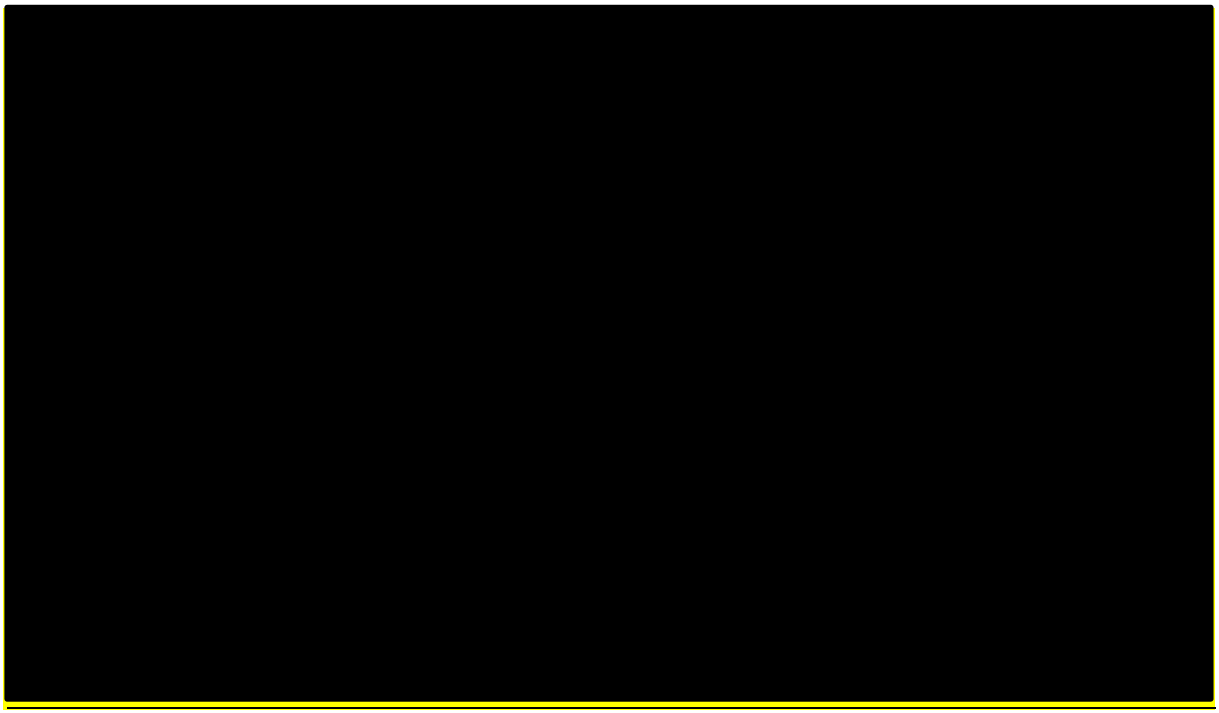
Figure 30. Lorlatinib EXP-2:3A versus EXP-3B:5 – PFS



Abbreviations: EXP = expansion cohort PFS = progression-free survival

This application of a HR to adjust the population is appropriate given that the survival of patients in the EXP-2:3A and EXP-3B:5 cohorts may differ based on the extent of prior treatment (expansion cohort definitions are provided in Table 36). The difference in PFS between the two cohorts in Study 1001 is presented in Figure 30 and gave a HR of [redacted].This HR was applied to provide a 'population adjustment' to determine PDC in the desired population. Figure 31 shows the adjustment of the independent curve (Figure 29) with the HR of [redacted] applied to produce a PFS curve for the EXP-3B:5 cohort.

Figure 31. Independent curves fitted to pooled chemotherapy KM data with 'population adjustment' compared to lorlatinib PFS data – Method 6

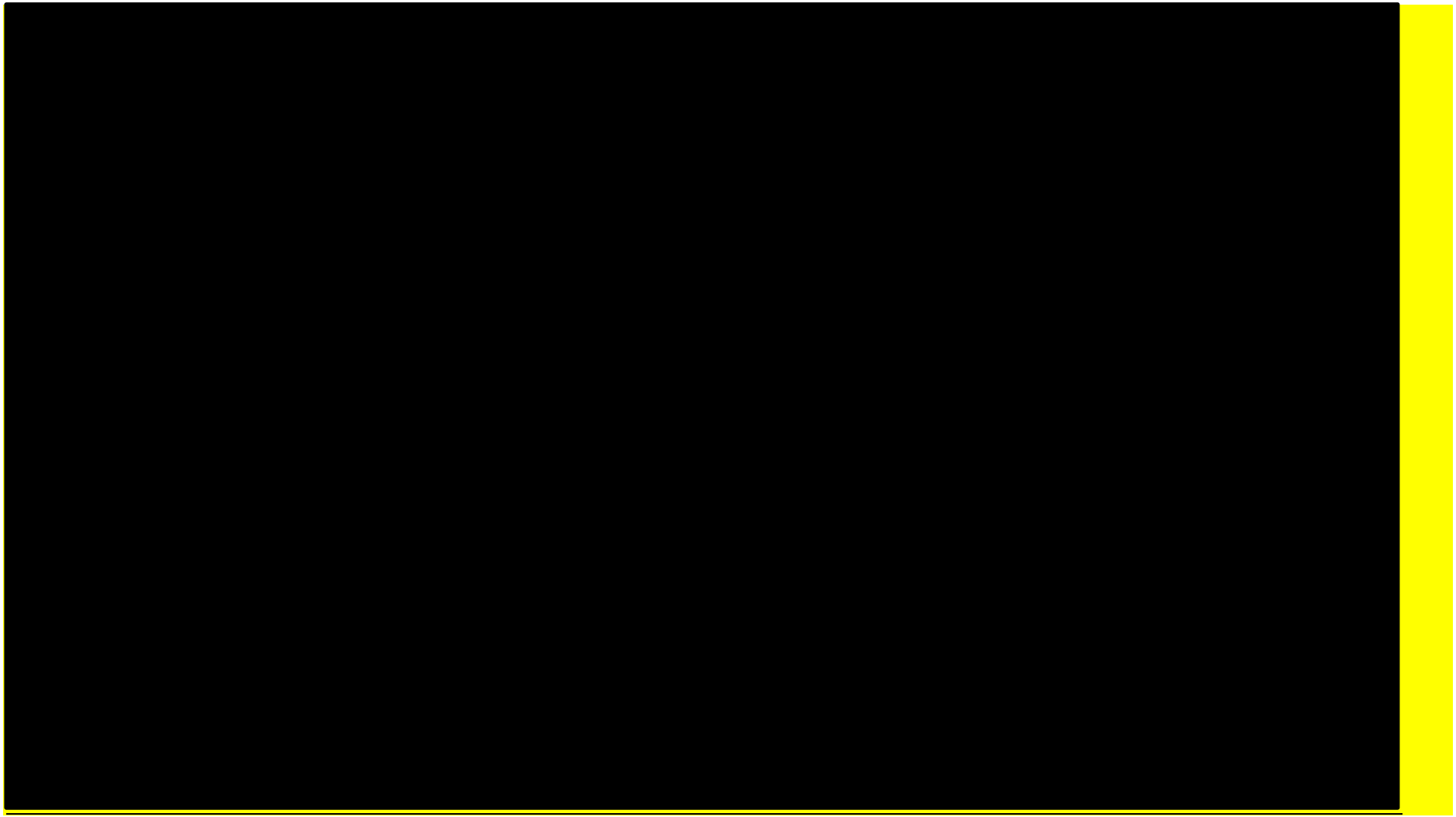


Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival

Summary of the methodology for deriving comparative PFS

Figure 32 summarises the six methods for obtaining estimates for PFS in the PDC arm.

Figure 32. Summary of methods 1–6 for considering PFS of PDC



Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PDC = platinum doublet chemotherapy; PFS = progression-free survival

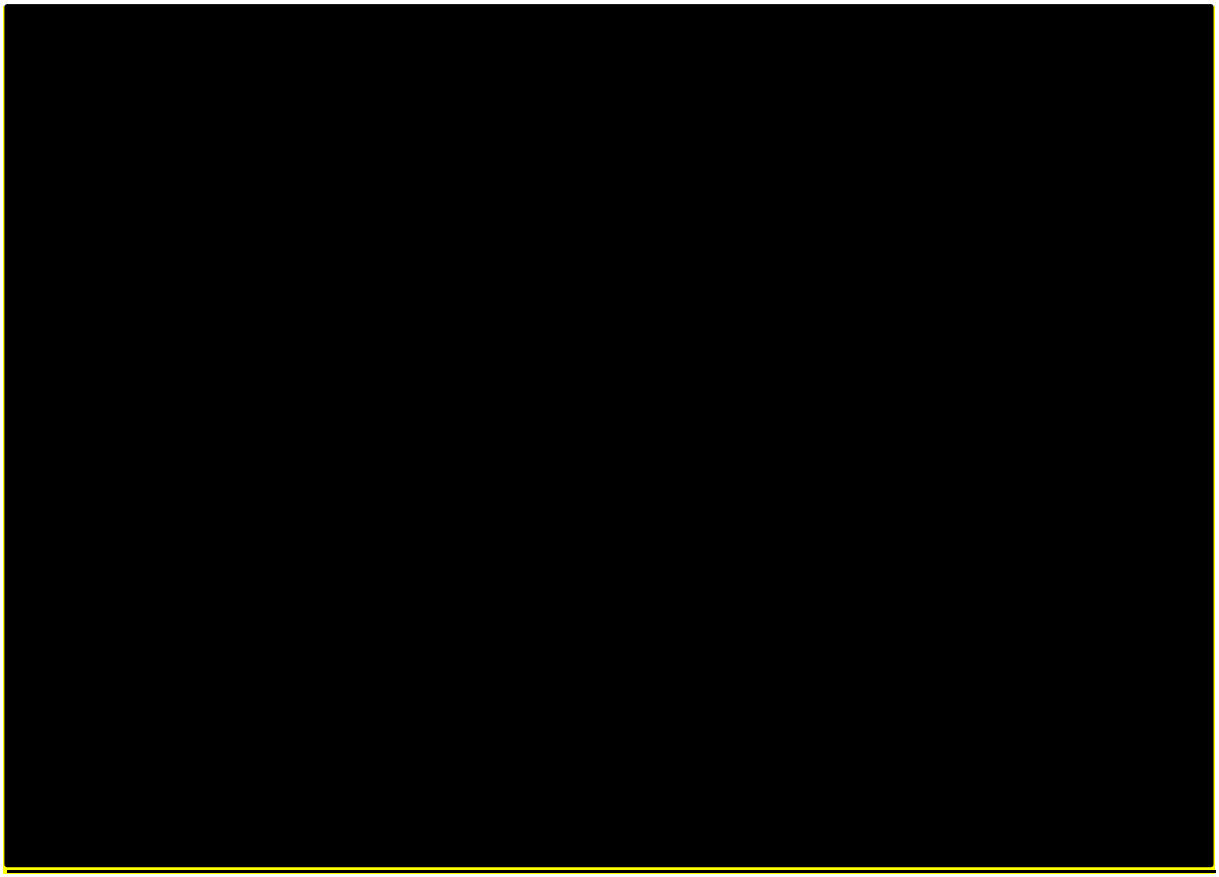
B.3.3.3.2 Time on treatment

Lorlatinib

Treatment beyond progression was permitted for lorlatinib in Study 1001. Figure 33 shows the parametric survival models fitted to the KM data. The AIC/BIC statistics are reported in Table 43. Selection of the most appropriate ToT was based on NICE TSD 14 guidance[117] with a balancing of the following criteria:

- fit statistics (AIC and BIC) which reflect the observed KM data;
- plausibility of extrapolations relative to UK real-world data;
- plausibility of extrapolations based on clinical expert opinion, and
- plausibility of extrapolations in relation to base case extrapolated PFS and OS.

Figure 33. ToT parametric curves – lorlatinib



Abbreviations: ToT = time on treatment

Table 43. Mean, median and landmark values and AIC and BIC statistics for lorlatinib ToT parametric survival models

Model	AIC	BIC	Mean ToT (months)	Median ToT (months)	Proportion still on treatment at each landmark value (%)			
					6 months	1 year	2 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; ToT = time on treatment

AIC fit statistics favour the log-normal curve. However, BIC fit statistics give almost identical scores to both the log-normal and exponential curve. The BIC fit statistics penalise model complexity – the log-normal has more parameters than the exponential function – and therefore it can be argued that AIC reflects overfitting to the plateau that begins around 18 months. Therefore, based on fit statistics alone, it is not clear which curve is the most appropriate. The Weibull is very similar to the exponential but has less favourable BIC statistics.

Clinical expert opinion suggested there would be very few patients remaining on a targeted treatment for 10 years or more – the log-normal curve also predicts [redacted] of patients remaining on lorlatinib at 20 years which is highly implausible (the exponential curve predicts [redacted] patients). In addition, at 10 years on treatment, the log-normal curve predicts a slightly greater proportion of patients on treatment ([redacted]) than are predicted to be alive according to the base case OS curve ([redacted]), which is not the case with the exponential curve ([redacted] on treatment at 10 years).

The UK database of ALK patients (Gomes et al. 2019)[1] reported median times on treatment for two ALK-inhibitors: a median of 9 months (95% CI: 5.1–12.9; n=83) for ceritinib and 9 months (95% CI: 3.1–14.9; n=49) for brigatinib. The upper bounds of the reported 95% CIs are the 95th percentile of the ordered data, because they are CIs around a median. Although the >99th percentile would be a more effective maximum value, the reported values are a reasonable proxy. The largest upper bound of the two treatments – 14.9 months – is supporting evidence for selecting the exponential curve, as this 95th percentile is also closest to the 95th percentile predicted by the exponential curve (i.e. the time point at which 5% of patents are still on treatment, which is around [redacted] months compared with [redacted] months for log-normal). The majority of patients that inform these values from Gomes et al. 2019[1] are receiving ceritinib or brigatinib in the second-line and beyond (i.e. after at least 1 previous ALK-inhibitor), so the estimates are generalisable to the population relevant to this appraisal. On this basis the exponential curve is arguably the most appropriate selection.

An additional criterion for selecting ToT curves is the plausibility of extrapolations in relation to base-case PFS selection. On this basis, an alternative method for capturing lorlatinib costs - for both patients who have not progressed and those that have progressed - was selected for the base-case.

Figure 34 shows the base-case PFS curve (generalised-gamma) over the model time horizon of 20 years, overlaid with the exponential and log-normal ToT curves. It can be seen that the exponential ToT curve crosses the PFS curve at around [redacted] months and results in up to [redacted] of patients remaining progression free while not recieving lorlatinib treatment for the remaining [redacted] months. This is not considered clinically plausible. This is in contrast to the log-normal curve; however, as previously discussed the latter does not give clinically plausible projections of time on treatment.

The weibull ToT curve is also not an appropriate selection because it crosses the PFS curve in a similar way to the exponential. The remaining ToT curves are a very similar shape to the log-normal (log-logistic, generalised-gamma) or much higher (gompertz), suggesting that these also do not give plausible projections of time on treatment.

Figure 34. Parametric PFS base-case overlaid with exponential and log-normal ToT

Abbreviations: PFS = progression-free survival; ToT = time on treatment

Figure 35 shows the exponential ToT curve overlaid with PFS curves that have projections below the base-case PFS selection (generalised-gamma). The log-logistic and log-normal curves also cross the ToT curve ([redacted] months) and again this can be considered clinically implausible. The exponential and weibull PFS curves are more plausible in this respect. However, these curves have the lowest statistical fit when compared with the other PFS survival functions according to both AIC and BIC. They also have a relatively poor visual fit to the KM compared with the other PFS curves.

Figure 35. Parametric ToT (exponential) overlaid with PFS

Abbreviations: PFS = progression-free survival; ToT = time on treatment

Therefore, given these constraints associated with parametric curve extrapolations an alternative approach was implemented. In the base-case, ToT was equated to PFS to capture the treatment costs of lorlatinib patients who are progression free. To take account of the progressed patients who received lorlatinib, newly progressed patients in each cycle accrued the treatment costs associated with [redacted] months of lorlatinib. Newly progressed patients are calculated based on the difference between cycles in PFS, adjusting for a proportion that move straight to death; the latter proportion was calculated using Study 1001 trial data. [redacted] months was calculated using IPD KM data and is the difference between the RMST for ToT ([redacted] months) and the RMST for PFS ([redacted] months) up to a time point of [redacted] months. This method overestimates ToT up to around month [redacted] and underestimated ToT from then to around [redacted] months, compared with ToT KM curve. However, it is expected to overestimate ToT in the later model cycles, based on the previous discussion (Figure 36).

This method has the following advantages:

- the most plausible parametric curve is fitted to PFS, a fundamental secondary outcome of Study 1001 (PFS);
- the relationship between PFS and ToT is clinically plausible and no patients remain off treatment and progression free for a prolonged period (Figure 36), and
- the costs of treatment in progression are accounted for in a way that preserves the relationship between the PFS and ToT that was observed during the Study 1001 trial period.

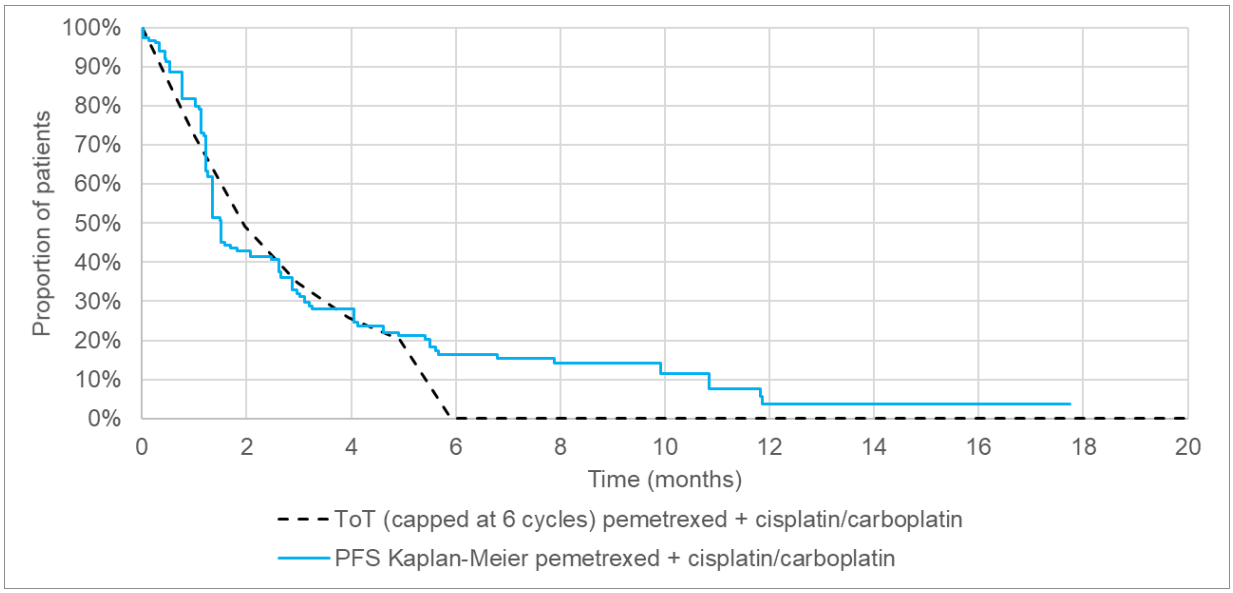
Figure 36. ToT with base-case method of calculation

Abbreviations: PFS = progression-free survival; ToT = time on treatment
Note: the synthesised ToT curve is calculated by shifting the PFS curve right by 2.6 months

PDC

In line with clinical practice, it was assumed that PDC was administered for a maximum of six cycles or until progression. Hence PFS was used as a proxy to inform ToT in the PDC arm of the model. Figure 37 presents the ToT for PDC, derived from the base case PFS curve. It is also assumed that 100% of PDC patients receive pemetrexed maintenance.

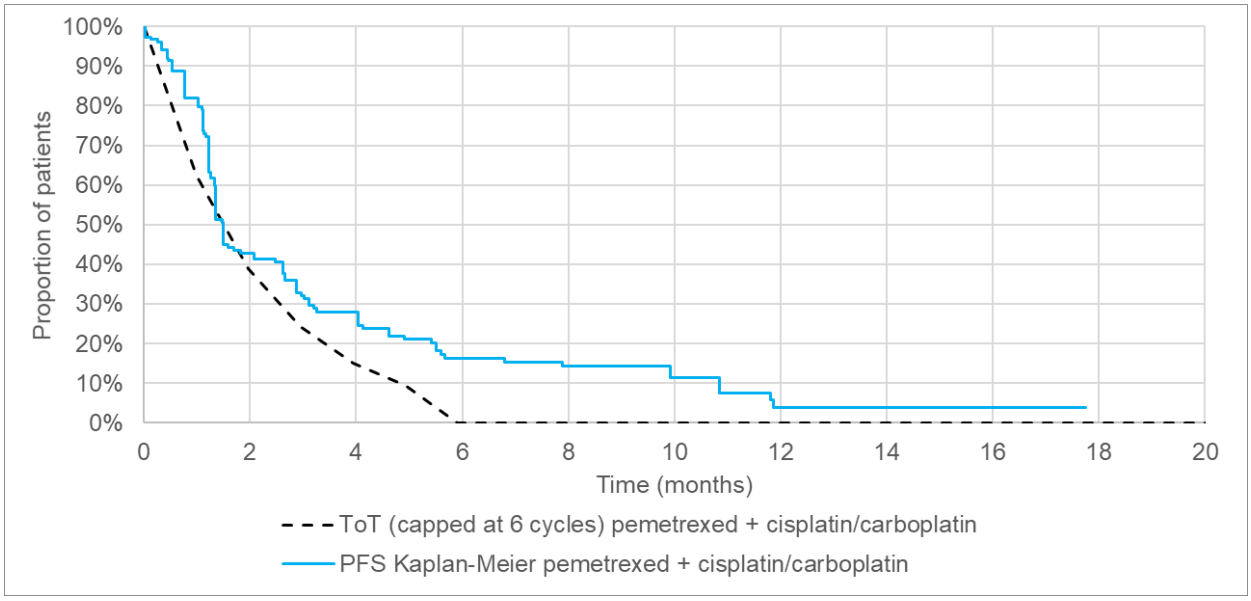
Figure 37. ToT for PDC (PFS used as a proxy for treatment, for a maximum of six cycles)



Abbreviations: PDC = platinum doublet chemotherapy; PFS = progression-free survival; ToT = time on treatment

A scenario analysis explored the application of an exponential curve to represent ToT for PDC. This was derived from the median ToT in ASCEND-5,[66] reported to be 6.3 weeks (44 days). The curve derived was very similar to that of the base case and is presented in Figure 38.

Figure 38. Exponential curve to represent ToT



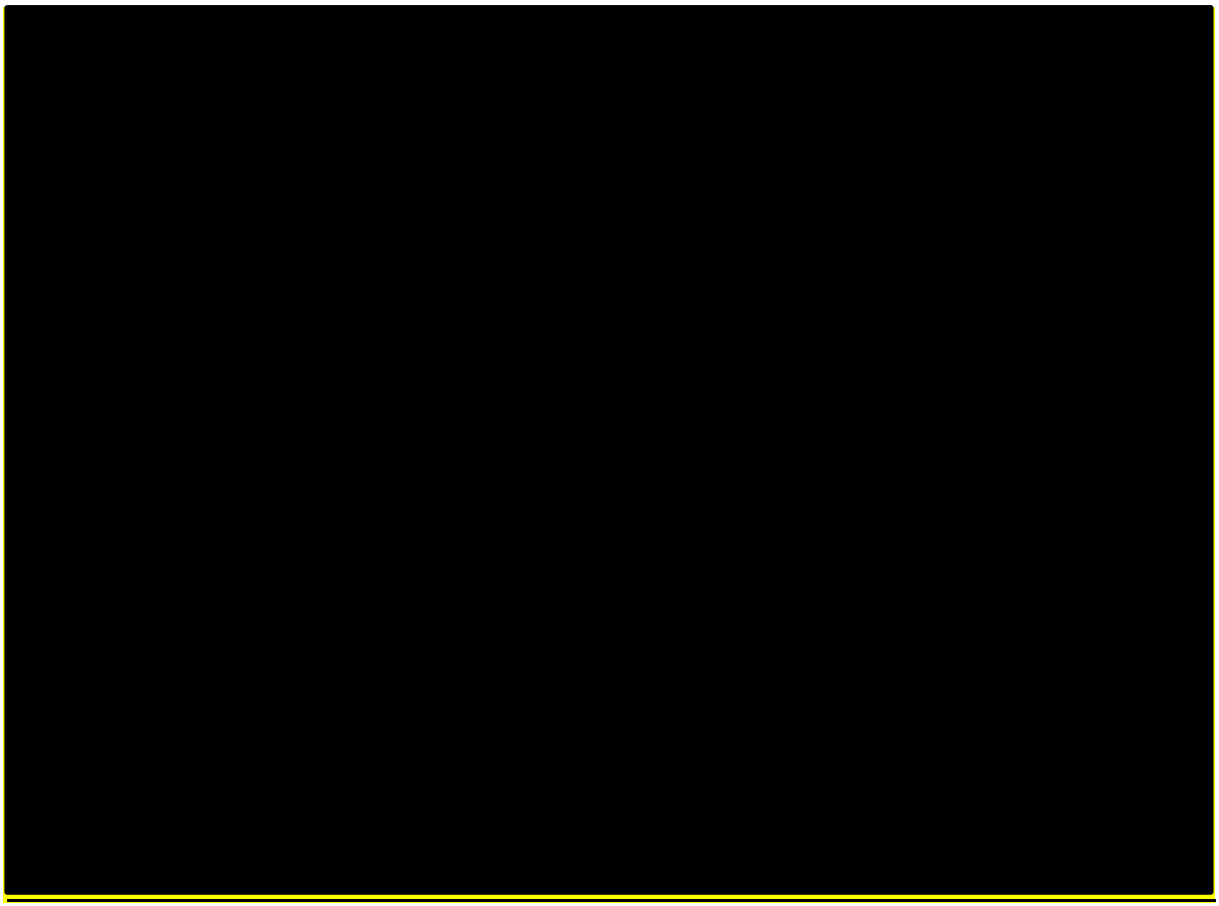
Abbreviations: PFS = progression-free survival; ToT, time on treatment

B.3.3.3.3 Overall survival

Lorlatinib

To derive long-term OS for lorlatinib, parametric curves were fitted to the lorlatinib OS data taken from the EXP-3B:5 cohort of Study 1001. Unadjusted OS curves are presented in Figure 39 for the EXP-3B:5 trial population, with corresponding AIC/BIC statistics presented in Table 44. Similar to PFS, the fit of the models was assessed in line with NICE TSD 14 guidance.[117]

Figure 39. OS parametric curves – lorlatinib



Abbreviations: OS = overall survival

Table 44. Mean, median and landmark values and AIC and BIC statistics for lorlatinib OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)				
					6 months	1 year	2 years	3 years	5 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival

Although the exponential curve has the best fit statistics, the generalised gamma curve was deemed, on balance, the most appropriate selection. Fit statistics in this case are not a useful criterion for curve selection because of the following reasons:

- The range of fit statistics between curves was not large;
- Fit statistics reflect only the observed portion of the KM curve and during this period the fitted curves are almost identical;

- Ordering on long-term extrapolations do not conform with ordering on fit statistics. For example, the log-logistic curve has the second lowest fit statistics (and so closest to the exponential curve) but has an extrapolation far more optimistic than the exponential curve and the cluster of other curves with less favourable fit statistics (Gompertz and Weibull).

Therefore, in these cases where ordering on long-term extrapolations do not conform with ordering on fit statistics, an overemphasis on the latter can lead to spurious conclusions. Even more importantly, clinical experts suggested that 10-year survival would be closer to [redacted] than [redacted]. Therefore, the generalised gamma was selected to inform the base-case.

Pemetrexed in combination with cisplatin/carboplatin

As with the PFS analysis, published literature was used to inform the chemotherapy arm of the cost-effectiveness model. Ou et al. 2014 (PROFILE 1001/1005) was identified as the best source as it was the only one that reported the OS of patients who received 'systemic therapy' following progression and discontinuation of crizotinib.[103] It is reasonable to assume that systemic therapy refers to chemotherapy; potentially PDC, given the line of treatment. The OS KM data in PROFILE 1001/1005 for those likely to be receiving chemotherapy are presented in Figure 40.

Figure 40. OS KM data for chemotherapy (used to inform the PDC arm)


[redacted]

Abbreviations: KM = Kaplan–Meier; OS = overall survival; PDC = platinum doublet chemotherapy

The model allows PDC OS to be calculated in six different ways, with all possible options listed in Table 45. The methodology and merits of each option are discussed in turn throughout this section.

Table 45. Methods to derive OS for PDC

Method (label)	Method of deriving OS for PDC	Cohort of lorlatinib used in analysis	Adjusted curve	HR	Key assumptions
1	MAIC HRs (with brain metastases variable) derived from Cox-proportional hazards model after weighting	EXP-2:3A	Yes	[redacted]	• The relationship between lorlatinib and chemotherapy in EXP-2:3A is the same as in EXP-3B:5 • PH holds
2		EXP-3B:5	Yes	[redacted]	• Treatment line does not affect outcomes (only patient characteristics) • PH holds
3	Unadjusted HRs derived from Cox proportional hazards model	EXP-2:3A	No	[redacted]	• The relationship between lorlatinib and chemotherapy in EXP-2:3A is the same as EXP-3B:5 • Patients characteristics do not affect outcomes • PH holds
4		EXP-3B:5	No	[redacted]	• Treatment line does not affect outcomes • Patients characteristics do not affect outcomes • PH holds
5	Independent curves applied to the KM data from PROFILE 1001/1005	NA	NA	NA	• Treatment line does not affect outcomes • Patients characteristics do not affect outcomes
6		NA	Population adjustment	[redacted] applied to independent curve to represent 2-3A vs 3B-5 cohort	• The HR observed for lorlatinib cohorts EXP-2:3A vs EXP-3B:5 is representative of the difference in outcomes across EXP-2:3A and EXP-3B:5 for chemotherapy • Patients characteristics do not affect outcomes

Abbreviations: EXP = expansion; HR = hazard ratio; KM = Kaplan–Meier; MAIC = match adjusted indirect comparison; NA = not applicable; OS = overall survival; PH = proportional hazards; SE = standard error

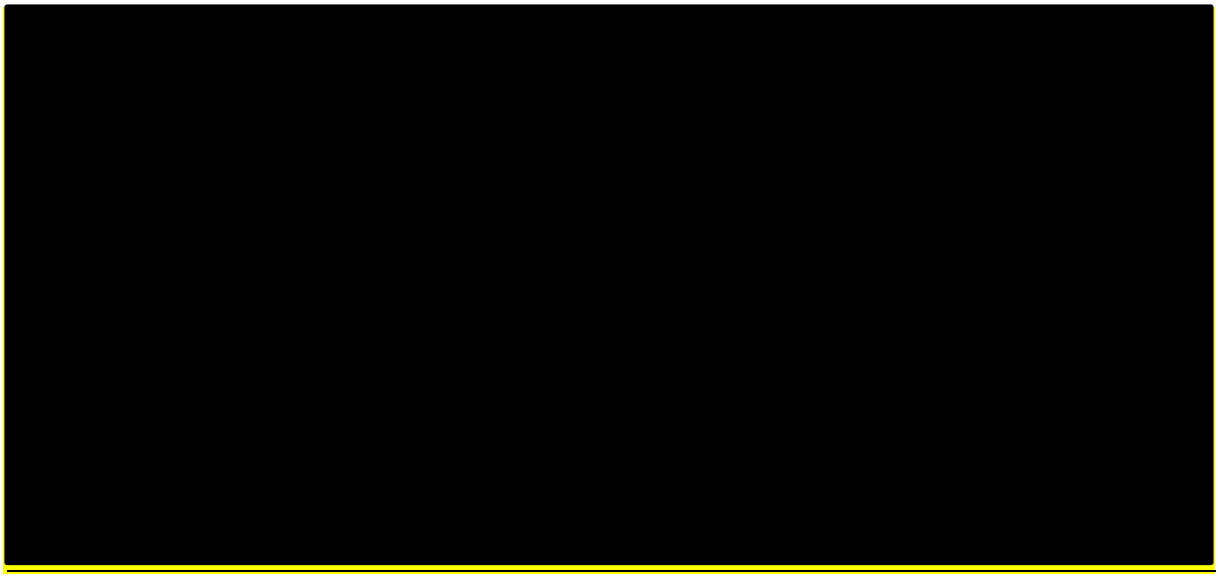
Applying MAIC methodology

Method 1 and 2 (Table 45) derived OS for PDC by applying a HR to the lorlatinib OS data. The HR was derived from the MAIC methodology outlined in Section B.2.8, by matching patient characteristics from Study 1001 to the data reported for PROFILE 1001/1005.[103] The HR applied in the model was derived from the MAIC that included the brain metastases variable.

Method 1: Application of MAIC HR for chemotherapy versus EXP-2:3A lorlatinib

Method 1 applied a HR to the lorlatinib OS curve. This HR was derived from matching lorlatinib EXP-2:3A patients to those in PROFILE 1001/1005 (representing patients that would fall into the EXP-2:3A cohort).[103] The HR derived from the MAIC for this cohort was [redacted] (CI: [redacted], [redacted]). Figure 41 shows its application to the lorlatinib base case OS curve to derive OS for the PDC arm.

Figure 41. MAIC EXP-2:3A PFS HR applied to lorlatinib OS data – Method 1



Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; OS = overall survival

Method 2: Application of MAIC HR chemotherapy versus EXP-3B:5 lorlatinib

Method 2 applied a HR to the lorlatinib OS curve to obtain OS for PDC. This HR was derived from matching the characteristics of patients in the lorlatinib EXP-3B:5 cohort to those in PROFILE 1001/1005[103] The HR for OS from the MAIC for this cohort (EXP-3B:5 lorlatinib versus chemotherapy) was [redacted] (CI [redacted], [redacted]); Figure 42 shows its application to the lorlatinib base case curve to derive OS for the comparator arm.

Figure 42. MAIC PFS EXP-3B:5 HR applied to lorlatinib OS data – Method 2

Abbreviations: EXP = expansion cohort; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; OS = overall survival

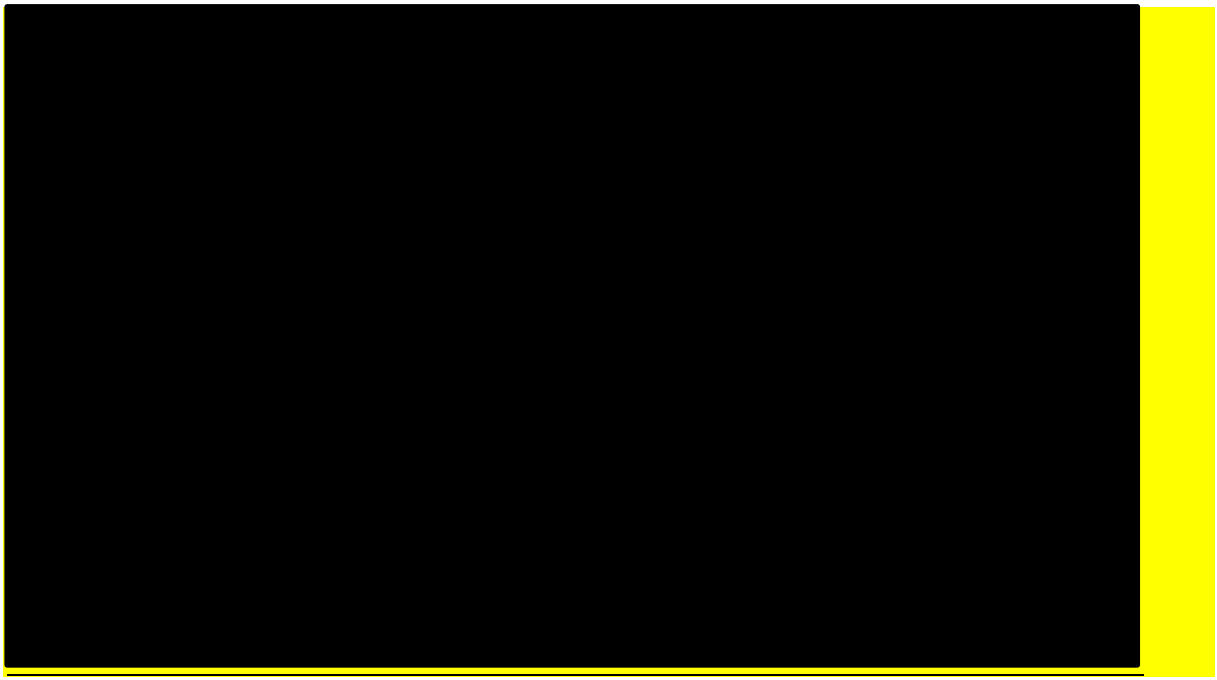
Unadjusted hazard ratios

In Methods 3 and 4, unadjusted HRs were used to inform the anticipated OS of chemotherapy (used as a proxy to estimate the OS of PDC). These methods did not apply any matching and drew a naïve comparison of lorlatinib to chemotherapy, with chemotherapy taken from PROFILE 1001/1005[103] If it is reasonable to assume that proportional hazards hold, then independent unadjusted HRs may be applied within the model.

Method 3: Application of unadjusted HR derived for chemotherapy versus EXP-2:3A lorlatinib

Method 3 applied an unadjusted HR to the lorlatinib OS curve to obtain OS for PDC. This HR was derived from the difference between the lorlatinib EXP-2:3A cohort and the PROFILE 1001/1005 chemotherapy data.[103] Given that this population is not covered by the licence of lorlatinib, in applying this method, it is assumed that the HR would also be observed in the relevant population of interest (EXP-3B:5). The HR derived from exploring the unadjusted data for this cohort (EXP-2:3A lorlatinib versus chemotherapy) was [redacted] (CI: [redacted]). Figure 43 shows its application to the lorlatinib base case curve to derive OS for the comparator arm. In utilising this method, it is inherently assumed that patients in the lorlatinib and PDC groups were relatively homogeneous and that all differences in outcomes are driven by treatment alone.

Figure 43. Unadjusted EXP-2:3A HR applied to lorlatinib OS data – Method 3

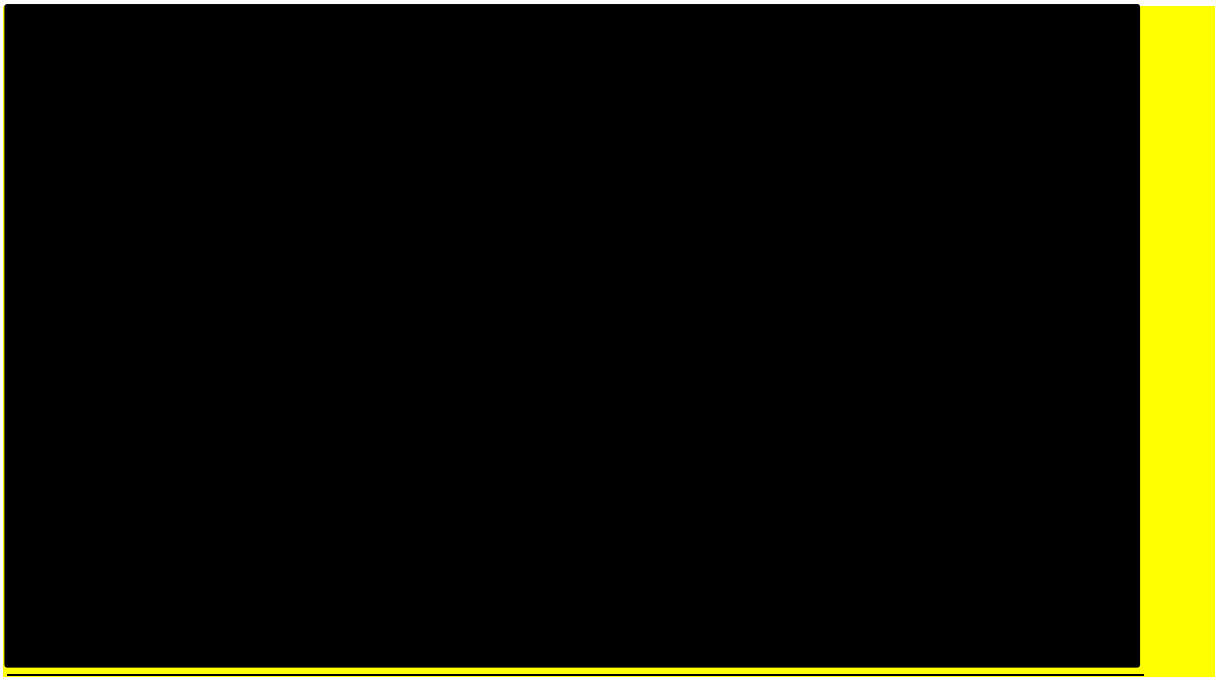


Abbreviations: EXP = expansion cohort; HR = hazard ratio; OS = overall survival

Method 4: Application of an unadjusted HR derived for chemotherapy versus EXP-3B:5 lorlatinib

Method 4 applied an unadjusted HR to the lorlatinib OS data derived from the difference between lorlatinib EXP-3B:5 data versus the PROFILE 1001/1005 chemotherapy data.[103] The HR obtained for this was [redacted] (CI: [redacted], [redacted]). Figure 44 shows its application to the lorlatinib base case OS curve to derive OS for PDC.

Figure 44. Unadjusted EXP-3B:5 HR applied to lorlatinib OS data – Method 4



Abbreviations: EXP = expansion cohort; HR = hazard ratio; OS = overall survival

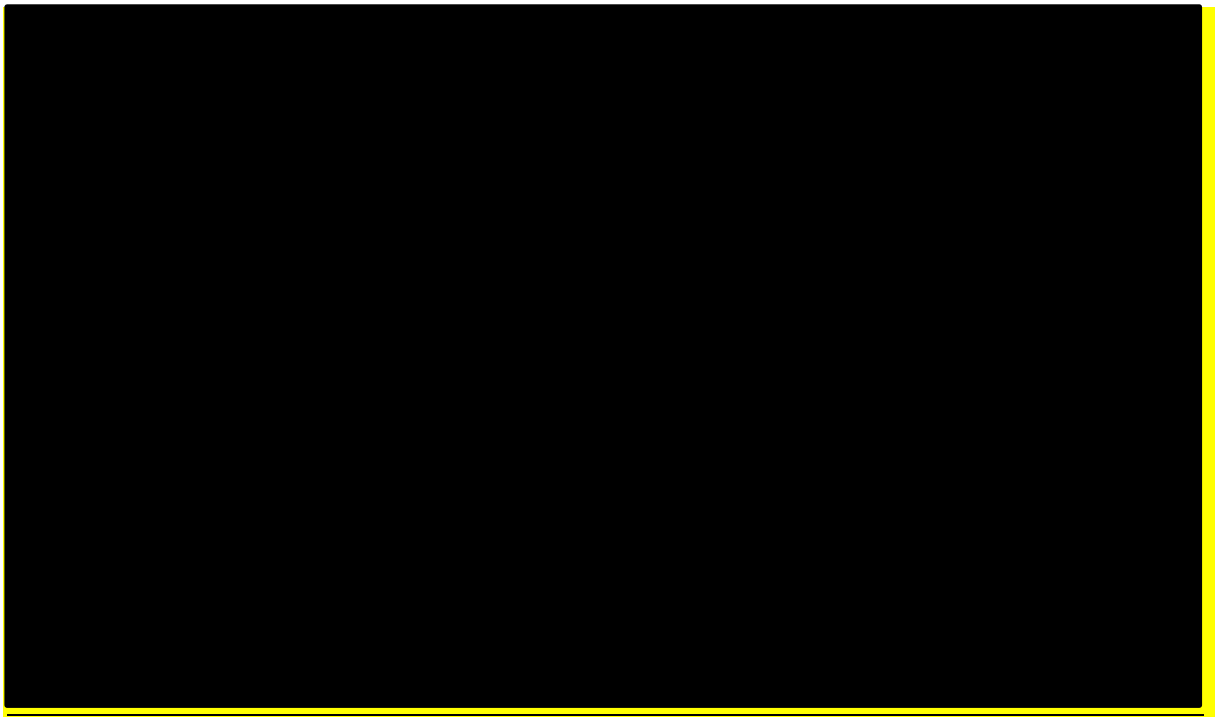
Independent curves

Independent parametric curves were also fitted to the pooled chemotherapy data from PROFILE 1001/1005[103] Fitting independent curves relaxes the assumption of proportional hazards and allows the parametric survival models to take a different underlying shape to survival projections than that which was observed in Study 1001 for lorlatinib. Given that lorlatinib is a TKI and has a different mechanism of action and very different ToT to chemotherapy, it is considered plausible that a different shaped survival curve would be observed.

Method 5: Independent chemotherapy curve from EXP-2:3A cohort

Method 5 applied an independent curve to represent OS for PDC. Initially, KM curves were digitised from PROFILE 1001/1005[103] and IPD were replicated using the Guyot algorithm.[116] From this, parametric survival models were fitted. Figure 45 shows the parametric survival models fitted to the pooled KM data for chemotherapy used to inform the PDC arm of the model. The AIC/BIC statistics are reported in Table 46. From the information presented, the log-normal curve was selected as the most plausible based on the fit to the KM data and the statistical fit.

Figure 45. OS parametric curves – PDC (derived from PROFILE 1001/1005 KM data for chemotherapy)



Abbreviations: KM = Kaplan–Meier; OS = overall survival; PDC = platinum doublet chemotherapy

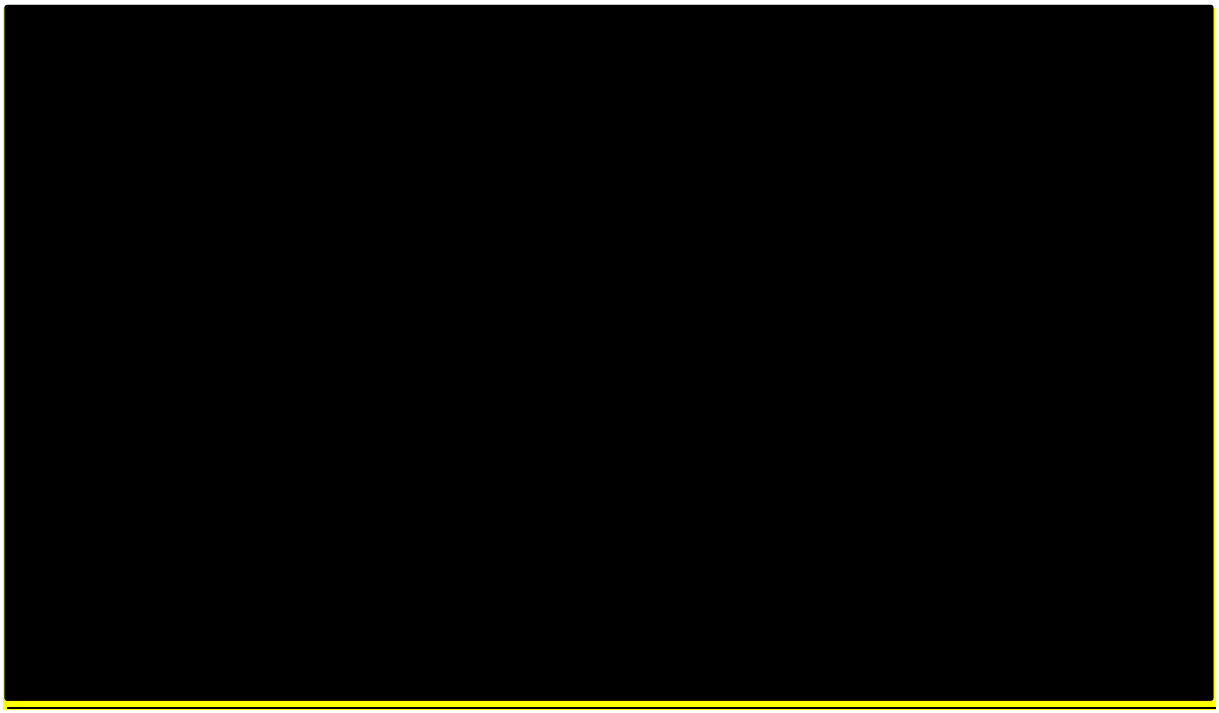
Table 46. Mean, median and landmark values and AIC and BIC statistics for PDC OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)					
					6 months	1 year	2 years	3 years	5 years	10 years
Generalised gamma	[redacted]									
Exponential	[redacted]									
Weibull	[redacted]									
Log-normal	[redacted]									
Log-logistic	[redacted]									
Gompertz	[redacted]									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion, OS = overall survival; PDC = platinum doublet chemotherapy

Figure 46 shows the base case lorlatinib OS curve in comparison to the independent log-normal chemotherapy curve (informed by PROFILE 1001/1005).[103]

Figure 46. Independent curves fitted to pooled chemotherapy KM data compared to lorlatinib OS data – Method 5



Abbreviations: KM = Kaplan–Meier; OS = overall survival

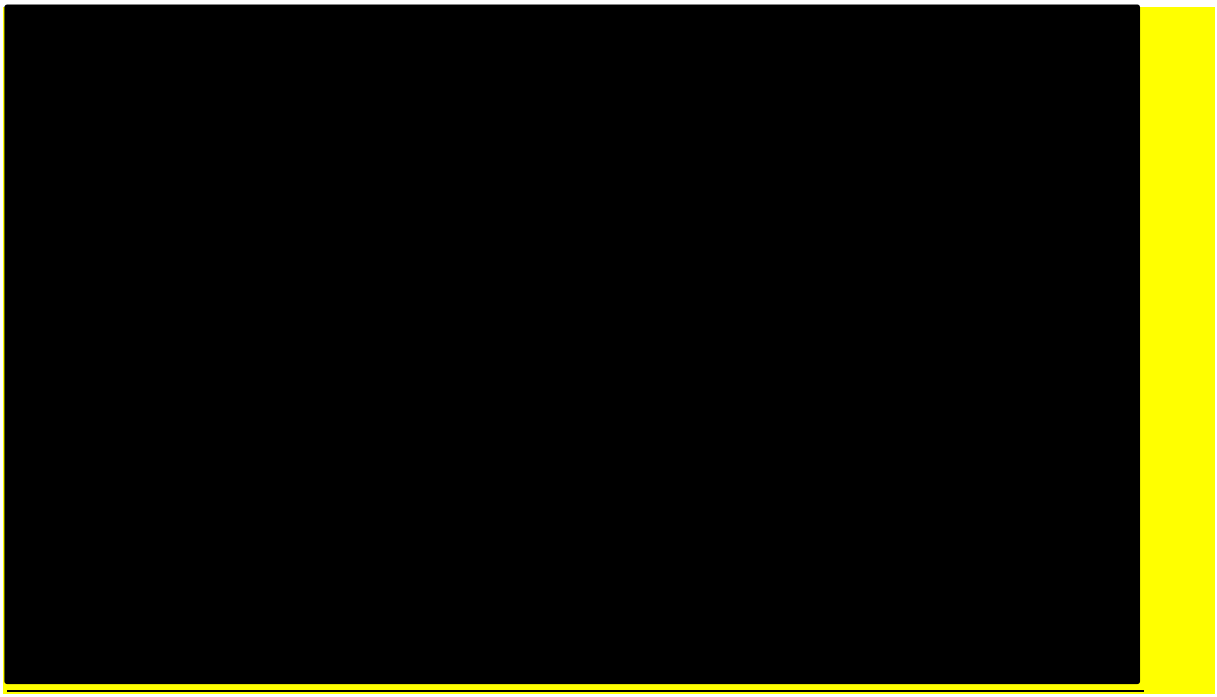
Method 6: Independent chemotherapy curve with 'population adjustment' to EXP-3B:5 cohort

Similar to the PFS analysis, the population of the chemotherapy arm used to represent PDC from PROFILE 1001/1005 was most reflective of the EXP-2:3A cohort, whereas the population of relevance for lorlatinib given its licence is EXP-3B:5. Therefore, a further analysis explored the application of a HR to the independent OS comparator curve to calculate the OS of patients receiving PDC in the EXP-3B:5 cohort.

This application of a HR to adjust the population may be appropriate given that the survival of patients in these two cohorts may be different, due to their levels of pre-treatment. The

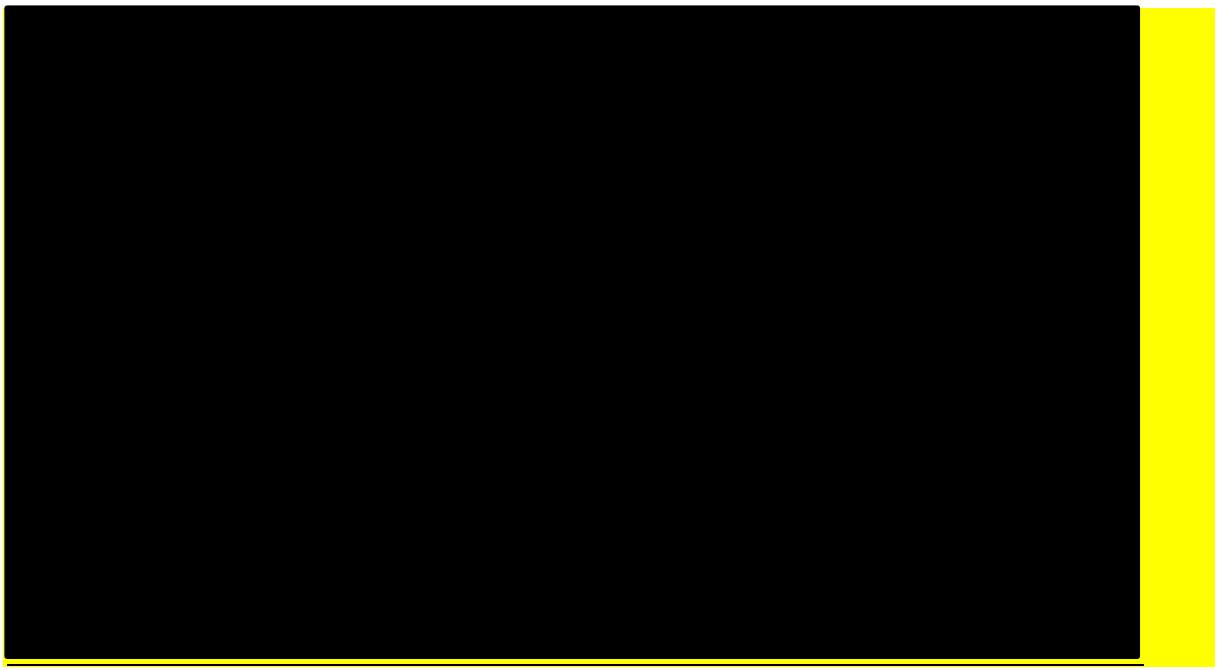
difference in OS between the two cohorts from Study 1001 is presented in Figure 47, giving an HR of [redacted].Figure 48 shows the adjustment of the independent curve (Figure 46) with the HR of [redacted] applied.

Figure 47. Lorlatinib EXP-2:3A versus EXP-3B:5 OS



Abbreviations: EXP = expansion; OS = overall survival

Figure 48. Independent curves fitted to pooled chemotherapy KM data with 'population adjustment' compared to lorlatinib OS data – Method 6



Abbreviations: KM = Kaplan–Meier; OS = overall survival

Summary of methodology for deriving comparative overall survival

Figure 49 provides a summary of the six methods of obtaining OS estimates for PDC.

Figure 49. Summary of Methods 1–6 for estimating the OS of PDC

Abbreviations: EXP = expansion; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PDC = platinum doublet chemotherapy

B.3.3.3.4 Base case PFS and OS selection

The satisfaction of several criteria were required before the base case selection of methodology for generating comparator PFS and OS (i.e. methods 1 to 6) for PDC could be made.

First, PFS and OS are closely related and correlated outcomes – therefore, it was reasoned that the same method should be used for generating the comparator PFS and OS curves. For example, it would be counterintuitive to presuppose that the assumptions required for method 1 are applied for PFS but the assumptions required for method 4 are applied for OS (see Table 41 and Table 45).

Second, methods 1 to 4 make use of survival models with a treatment covariate and so assume proportional hazards across time (i.e. Cox proportional hazards model). Evidence of a violation of proportional hazards between treatment groups may mean that the fitted HR is not a meaningful measure of a true time variant treatment effect. Log cumulative hazard plots for PFS and OS are presented in Appendix Q. These suggest that the proportional hazards assumption is likely to hold for adjusted and unadjusted PFS irrespective of matching cohort (i.e. methods 1 to 4). It is unclear if the proportional hazards assumption is satisfied for OS, particularly when EXP-3B:5 is the matching cohort. This suggests that method 2 and method 4 may not be an appropriate choice for the OS outcome.

Third, the method chosen would have to satisfy clinical expert opinion. Clinicians suggested that patients receiving PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI. This suggests that the methods that do not adjust for the prior treatment used – i.e. method 2, method 4 and method 5 – are most valid. Given that method 2 and method 4 may not be appropriate, as described above, method 5 – independent curves and no population adjustment – was deemed the most appropriate choice for generating PFS and OS data for PDC in the base case. Clinical expert opinion was used to validate selection of each curve as described in previous sections.

B.3.3.3.5 Comparative efficacy

Based on the methods selected for the base case economic model provided in B.3.3.3.1, B.3.3.3.2 and B.3.3.3.3 the following section outlines the efficacy used in the model.

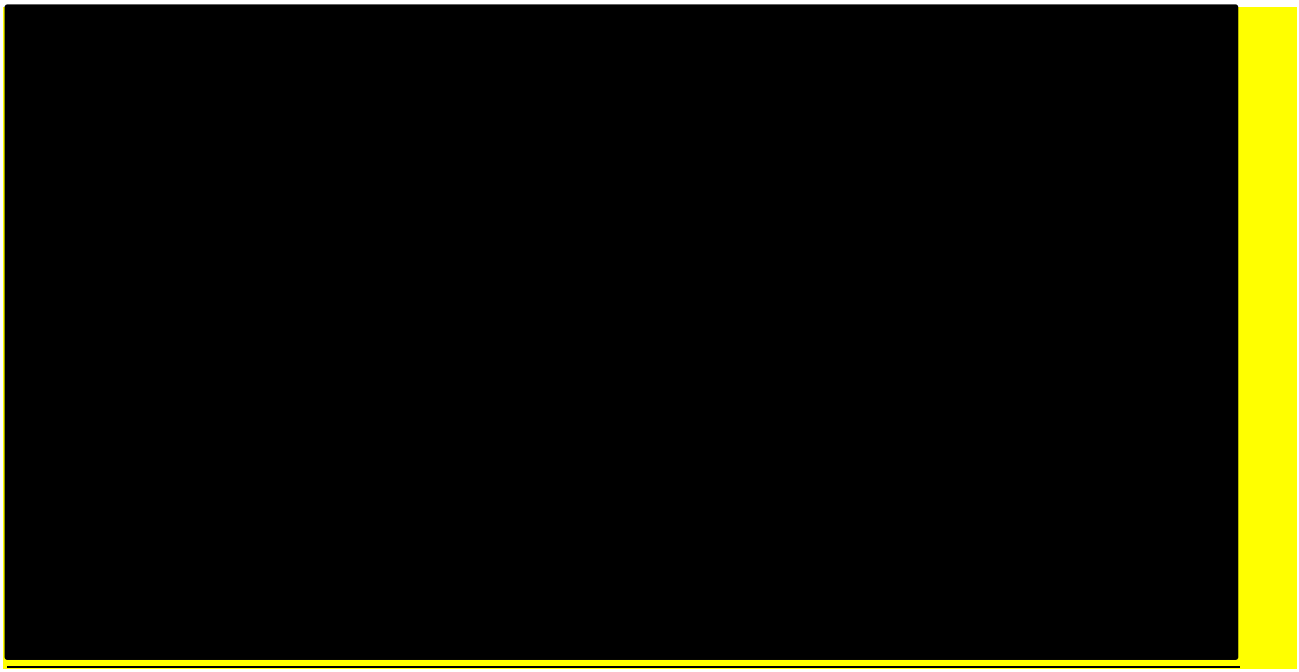
Progression-free survival

Figure 50. PFS applied in the base case model setting – lorlatinib versus pemetrexed plus cisplatin/carboplatin

Abbreviations: PFS = progression-free survival

Overall survival

Figure 51. OS applied in the base case model setting – lorlatinib versus pemetrexed plus cisplatin/carboplatin



Abbreviations: OS = overall survival

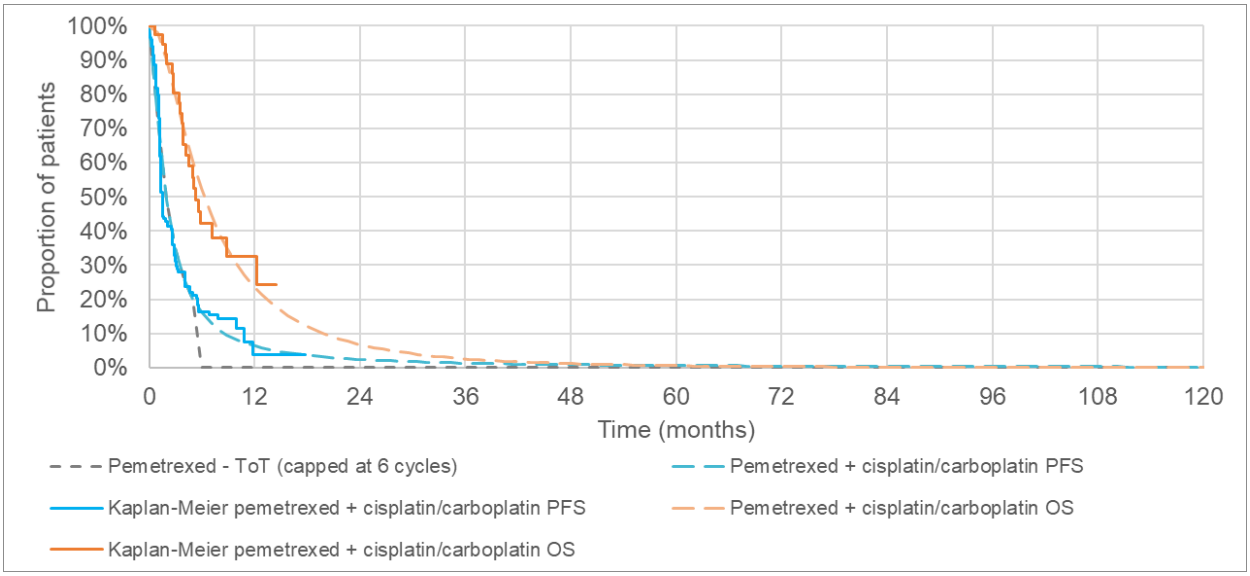
B.3.3.3.6 Summary of clinical estimates used to inform the base case model.

Figure 52 and Figure 53 present the survival applied within the base case model for lorlatinib and pemetrexed (in combination with cisplatin/carboplatin), respectively.

Figure 52. PFS, ToT and OS applied in the base case model setting - lorlatinib

Abbreviations: OS = overall survival, PFS = progression free survival, ToT = time on treatment
Note: the synthesised ToT curve was calculated by shifting the PFS curve right by 2.6 months and therefore it is above the OS curve in earlier cycles; however, dead patients do not accrue lorlatinib treatment costs in the model.

Figure 53. PFS, ToT and OS applied in the base case model setting – pemetrexed plus cisplatin/carboplatin



Abbreviations: OS = overall survival, PFS = progression free survival, ToT = time on treatment

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

Study 1001 collected information on HRQoL for lorlatinib using the following measures:

- ORTC QLQ-C30
- EORTC QLQ-LC13 (the specific lung cancer module of the EORTC QLQ-C30)

These measures were completed by patients on Day 7 (only for those patients in the lead-in cohort), Day 1 of every cycle for up to 38 cycles, Day 1 of every other cycle for cycles after Cycle 38 and at the end-of-study treatment.[93]

In order to estimate a progression-free health state utility value, EORTC QLQ-C30 responses were mapped to the EQ-5D, from which utility values could be estimated. Mapping to the EQ-5D was required in order for the model to have utilities that are both appropriate for cost-effectiveness analysis and consistent with the NICE reference case.[112]

Questionnaire compliance was high across the two measures used within Study 1001. Completion of at least one questionnaire ranged from [redacted] to [redacted] over the first 24 cycles.

B.3.4.2 Mapping

In accordance with NICE guidance, the model used data from the three-level EQ-5D (EQ-5D-3L) to estimate health state-related utility for the progression free state.[112] To do so, utility mapping from the EORTC QLQ-C30 to the EQ-5D was conducted based on IPD from Study 1001. The mapping algorithm provided by Longworth et al.[118] and Young et al.[119] was used.

Appropriate mapping algorithms were identified using Dakin 2016, which provides a database that aims to capture mapping algorithms from any questionnaire to the EQ-5D, and therefore aligns with the NICE reference case.[112, 120]

From the database, five publications were identified, which all mapped EORTC QLQ-C30 data to the EQ-5D and included some lung cancer patients in the dataset used to derive the mapping algorithm: Jang et al. 2009,[121] Khan et al. 2014,[122] Khan et al. 2016,[123] Kim et al. 2012,[124] Longworth et al. 2014[118] and Young et al. 2015[119] In addition to these publications, one further paper was identified based on investigation of previous NICE submissions: the manufacturer submission for ceritinib in previously treated ALK-positive NSCLC used a publication by Proskorovsky 2014, which used a mapping algorithm based on 154 multiple myeloma patients.[125]

Both Jang et al. 2009[121] and Kim et al. 2012[124] were considered unsuitable choices given that a non-UK tariff was used in these publications. Kim et al. 2012[124] also included patients with a large variety of cancer types. The Khan et al. papers were derived using information from patients with NSCLC only, and had a reasonably large number of patients and corresponding observations.[122, 123] The Longworth et al. 2014/Young et al. 2015 algorithm was derived from a larger number of patients (n=771), with just under 100 of these having lung cancer.[118, 119] Although the Khan et al. 2014[122] and Khan et al. 2016[123] publications were considered, there was a lack of clarity regarding the application of the mappings proposed in both publications.

Although previously used within a NSCLC NICE submission[33] (ceritinib for ALK-positive, previously treated patients), the mapping algorithm presented by Proskorovsky et al. 2014[125] did not include any patients with lung cancer and was therefore not considered as relevant (searches in the Dakin mapping database were limited to lung cancer).

While there are a number of publications available that present mapping methods, the Longworth et al. 2014/Young et al. 2015 algorithm was considered the most appropriate for the decision problem, given that it was derived from the largest population, was relevant to NSCLC, had clarity in its application and gave the best fitting results.[118, 119]

Longworth et al. 2014/Young et al. 2015 used a 'response mapping' technique that predicts the probability of a patient scoring 1, 2 or 3 for each of the five EQ-5D-3L dimensions using multinomial logistic regression models applied to the QLQ-C30 responses from each patient.[118, 119] To estimate utility, the coefficient for each domain score is multiplied by the corresponding probability derived by the Longworth algorithm to give Equation 1.

Equation 1. Utility mapping algorithm

$$\begin{aligned} Expected\ (EQ-5D) &= 1-(Prmob2\ \times 0.069)-(Prmob3\times 0.314)-(Prcare2\ \times 0.104) \\ &-(Prcare3\ \times 0.201)-(Pruact2\times 0.036)-(Pruact3\ \times 0.094) \\ &-(Prpain2\ \times 0.123)-(Prpain3\ \times 0.386)-(Pranx2\ \times 0.071) \\ &-(Pranx3\ \times 0.236)-(1-PrPerfect)\times 0.081-PrN3\ \times 0.269 \end{aligned}$$

Abbreviations: Pranx2 = probability of anxiety 2; Pranx3 = probability of anxiety 3; Prcare2 = probability of self care 2; Prcare3 = probability of self care 3; Prmob2 = probability of mobility 2; Prmob3 = probability of mobility 3; PrN3 = probability of one or more questions answered with a 3; Prpain2 = probability of pain 2; Prpain3 = probability of pain 3; PrPerfect = probability of perfect health; Pruact2 = probability of usual activities 2; Pruactb3 = probability of usual activities 3
Note: The number following the codes indicates a level 2 or level 3 response. Pr indicates probability

Utility values obtained from mapping of the EORTC QLQ-C30 scores reported in Study 1001 are reported in Table 47. These were used to inform progression-free utilities for the lorlatinib arm in the model. It is important to note that only the data from the relevant subgroups of the trial (EXP-3B:5) were used to inform the utility analyses in line with the licence.

Table 47. Mapped utility values for patients in PFS from Study 1001

Patient utility definition	N of patients	N of observations	Mean utility	SE	95% confidence interval
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N = number; PFS = progressison free survival SE = standard error

B.3.4.3 Health-related quality of life studies

To inform the utility estimates used in the model, an SLR was performed to identify published utility values associated with advanced/metastatic ALK-positive NSCLC. All searches were conducted on 6 August 2018. A table of reported utility values and summary, and a full list of the search strategy including the identification of studies, description of studies, and quality assessment of the studies identified can be found in Appendix I.

Following a review of previous NICE and SMC HTA reports in NSCLC, two other sources were identified that were considered representative of the progressed disease state within the economic model.[126-128] Labbe et al. 2017[126] was identified as it was an update to an earlier study included in the HRQL SLR (Labbe et al. 2016).[129] Labbe et al. 2017 evaluated EQ-5D-derived health-state utility scores using a longitudinal cohort of Canadian outpatients diagnosed with metastatic lung cancer (including ALK-positive patients) across various disease states.[126] Utility values for the ALK-positive population using UK preference weights (for those receiving ALK TKIs) in the progression-free and progressed disease states were 0.73 and 0.65, respectively.[126]

LUME-Lung-1 (incorporated in TA347[128] and TA416[127]) was not identified during the initial searches, but was subsequently highlighted after the review of previous appraisals and was considered to be relevant to the economic analysis. LUME-Lung-1 was a trial comparing treatment with nintedanib plus docetaxel with placebo plus docetaxel in a population of patients with previously treated locally advanced or metastatic NSCLC. The trial collected EQ-5D utilities, which were 0.687 for PFS and 0.64 for post-progression survival. Although these results were not obtained from an ALK population, they were broadly aligned to similar estimates identified elsewhere e.g. Labbe et al. 2017.[126]

For the base case, the progression-free (absolute) value from the PDC arm of the PROFILE 1014 study was chosen and applied to the PDC progression-free health state (0.72).[130] In scenario analysis, a variety of values from Zhou et al. 2015,[131] TA395[33] and from Blackhall et al. 2014[132] were tested. For progressive disease Labbe et al. 2017[126] was used in the base case (0.65) and TA422,[34] LUME LUNG-1[128] and Zhou et al. 2015[131] were tested in scenario analyses. The rationales of the utilities applied in the model are outlined in section B.3.4.6.

AE utility decrements were not included in the base case of the model but were tested in scenario analyses. HRQoL decrements for anaemia and dyspnoea could not be sourced through papers identified by the SLR, so a targeted literature review was undertaken with the aim of sourcing utility decrements for these AEs from previous NSCLC studies or NSCLC HTAs. However, as no NSCLC-specific sources could be found, searches were widened to include any appraisal or study in similar cancers. Ultimately decrements of 0.090 and 0.048 were applied to anaemia and dyspnoea, respectively, taken from Beusterin 2010[133] and TA420,[134] respectively. All other AE-related utility decrements were sourced from Nafees 2008,[135] or were assumed to be zero based upon CTCAEs guidelines[136] (see Section B.3.4.4).

B.3.4.4 Adverse reactions

In line with previous HTA submissions, the impact on costs associated with AEs (of grade 3 or higher that occurred in >5% of patients in at least one treatment of interest) are included within the model.[31-33] It is assumed that grade 1/2 AEs have negligible impact on HRQoL and costs, so these are excluded from the model. This approach was also taken in previous NSCLC appraisals.[31, 113, 137]

The impact on HRQoL associated with AEs (AE disutilities) was not included in the base case. This assumes that the lorlatinib progression-free health state utilities, which were informed by lorlatinib trial data, already captured the effect of AEs. Progression-free EQ-5D utilities for PDC were taken from PROFILE 1014 data for pemetrexed plus platinum therapy, which captured the effect of any AEs associated with pemetrexed.[130]

The probability of incurring an AE for lorlatinib was taken from Study 1001. The entire safety analysis set was used (n=295) to estimate AEs as these were not anticipated to vary by subgroup/cohort. For PDC, the incidence of AEs was informed by the literature.[66, 92] As data for TRAEs were not consistently available for all treatments, all-cause AEs were applied (as these were consistently reported between treatments). Table 48 includes the list of AEs that met the criteria and were applied in the model. Where there were data from multiple sources, a weighted average of the AEs was calculated.

Table 48. Adverse events

		Lorlatinib	PDC
Trial population size (n)		[redacted]	147
AEs (proportion)*	Anaemia	[redacted]	AEs (proportion)*
	Asthenia	[redacted]	0.054
	Dyspnoea	[redacted]	0.048
	Fatigue	[redacted]	0.054
	Febrile neutropenia	[redacted]	0.054
	Hypercholesterolemia	[redacted]	NE
	Hypertriglyceridemia	[redacted]	NE
	Lipase increased	[redacted]	NE
	Neutropenia	[redacted]	0.143
	Neutrophil count decreased	[redacted]	0.054
	Weight increased	[redacted]	NE
Reference		Study 1001	ALUR and ASCEND-5[66, 92]

Abbreviations: AE = adverse event; CSR = clinical study report; N = number; NE = not experienced; PDC = platinum doublet chemotherapy

*AEs that were spelled differently but are clearly the same have been recoded

A scenario analysis explores the inclusion of AE disutilities (Table 49), with decrements taken from the literature.[135, 136] Within this scenario, a one-off QALY decrement was estimated by multiplying the disutility with the anticipated duration of the event and the probability of the event occurring. The disutility was then summed across all AEs experienced and applied within the first cycle of the model. The total QALY decrement per arm was [redacted] for lorlatinib and [redacted] for PDC plus cisplatin/carboplatin.

Table 49. Adverse event disutilities included in scenario analysis

AE	Utility decrement (SE)	Assumed duration – days (SE)	QALY decrement for AE	Reference
Anaemia	0.090 (0.020)	16.10 (1.61)	0.119	Beusterin 2010 [133]
Asthenia	0.073 (0.018)	35.30 (3.53)	0.213	Nafees et al. 2008,[135] Assumed equal to fatigue
Dyspnoea	0.048 (0.005)	12.70 (1.27)	0.050	PEGASUS-TIMI 54 trial (TA420)[134]
Fatigue	0.073 (0.018)	2.50 (0.25)	0.015	Nafees et al. 2008[135]
Febrile neutropenia	0.090 (0.016)	7.10 (0.71)	0.052	Nafees et al. 2008[135]
Hypercholesterolemia	No decrement	2.50 (0.25)	No decrement	Assumed zero based upon CTCAE guidelines[a] [136]
Hypertriglyceridemia	No decrement	2.50 (0.25)	No decrement	Assumed zero based upon CTCAE guidelines[a] [136]
Lipase increased	No decrement	2.50 (0.25)	No decrement	Assumed zero based upon CTCAE guidelines[a] [136]
Neutropenia	0.090 (0.020)	5.00 (0.50)	0.037	Nafees et al. 2008[135]

Neutrophil count decreased	No decrement	2.50 (0.25)	No decrement	Assumed zero based upon CTCAE guidelines[a] [136]
Weight increased	No decrement	2.50 (0.25)	No decrement	Assumed zero based upon CTCAE guidelines[a] [136]

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; QALY = quality-adjusted life year; SE = standard error
Note: CTCAE guidelines suggest that lab abnormalities are not associated with symptomatic events, and therefore a utility decrement of 0 has been applied for: hypercholesterolemia, hypertriglyceridemia, lipase increased, neutrophil count decreased and weight increased[136]

B.3.4.5 Age-related disutility

Within the model, age adjustment was applied in the base case to account for the deterioration in well-being as a patient gets older. Age-related disutility was based on the formula from Ara and Brazier (Equation 2 and Table 50).[138] This was applied within the model by use of the baseline age (52.5 years) and proportion male (43.5%).

Equation 2. Age-related disutility

$$\text{General population utility} = \beta_0 + \beta_1 \text{male} + \beta_2 \text{age} + \beta_3 \text{age}^2$$

Table 50. Age adjustment – Ara and Brazier, 2010[138]

Coefficient	Value	Standard error (assumed 10% of mean)
Male (β1)	0.021213	0.0021213
Age (β1)	-0.000259	0.0000259
Age^2 (β2)	-0.000033	0.0000033
Constant (β0)	0.950857	0.0950857

B.3.4.6 Health-related quality of life data used in the cost-effectiveness analysis

Progression free utilities applied to the lorlatinib arm were calculated based upon the mapping algorithm applied to the observed utilities from Study 1001 (Section B.3.4.2). These within-trial utilities were used for lorlatinib as they are directly reflective of the efficacy observed within the trial. No alternative lorlatinib-specific utilities were observed within the SLR.

The progression free utility of lorlatinib ([redacted]) was consistent with the utility applied for previous ALK cost-effectiveness models and appraisals ([redacted]).[29, 68, 71, 112, 114, 127, 129, 131, 135, 139, 140] The value also has validity against population norms and, as expected, is lower than the estimate derived from the algorithm presented in Ara and Brazier[138] (0.855 based on the average age and gender split presented in Study 1001).

Given that Study 1001 was single arm, a progression free utility for a PDC arm was not available and needed to be informed from elsewhere. Treatment-specific utilities were applied in the base case. It was considered appropriate to apply treatment-specific utilities given that patients receiving chemotherapy are likely to have a poorer HRQoL than patients on ALK TKIs. This was found in PROFILE 1007, where utilities for the ALK TKI crizotinib (0.82, 95% CI: 0.79−0.85) were significantly greater ($p<0.05$) than for PDC (0.73, 95% CI: 0.70−0.79).[132] Further to this, within the HRQoL SLR, seven out of the 10 studies identified progression free treatment-specific utilities. For four of these studies, a comparison between ALK TKIs and chemotherapy was available and, in all instances, a utility decrement was applied for patients on chemotherapy compared to those receiving treatment with an ALK TKI (0.02–0.08).[127, 129, 131, 140] Applying treatment-specific utilities in this submission

would also inherently account for the decrement due to the method of administration with PDC (intravenous) compared with lorlatinib (oral).

Given the results of the SLR, utilities from PROFILE 1014 were applied to progression-free patients for PDC. This is because these utilities are for the correct comparator treatment (PDC), are specific to the ALK-positive population, and are representative of the source with the largest sample size (n=171 in PDC arm). The value is very similar to the value (0.74) reported in Blackhall 2017[132] for the pemetrexed/docetaxel arm in PROFILE 1007 which was accepted in previous NICE appraisals TA406[31] and TA422[34] and was therefore considered a useful validation. The main difference between the studies was that patients in PROFILE 1007 were pre-treated with platinum-based chemotherapy (i.e. PDC), whereas PROFILE 1014 patients were untreated for advanced disease. Further to this, for the base case values, the application of the progression-free utilities for lorlatinib ([redacted]) and for PDC (0.72) resulted in a decrement of 0.065 for chemotherapy, which corresponds to a realistic decrement between the two arms, in line with previous estimates of decrements identified in the literature ranging from 0.02 to 0.08.

For progressed patients, the same utility was applied to both arms. Given that Study 1001 did not capture utility for progressed patients (off treatment) – and the value calculated was unreliable – this information was obtained from published literature. Progressed disease utilities were taken from Labbe et al. 2017[126], as this represents the largest source of NSCLC ALK-positive EQ-5D utility values, and therefore is the closest that aligns with the decision problem.

In addition to also being more reflective of the disease, Labbe et al. 2017[129] was chosen in preference over LUME-Lung-1 (TA347[128] and TA416[127]) and Zhou et al. 2015[131], as it represents utilities collected from ALK-positive NSCLC patients. Utilities from LUME-Lung-1 (0.64) were not ALK specific, and Zhou[131] utilities were arbitrarily calculated using utilities from Nafees et al. 2008[135] and adjusted using utilities reported in Chouaid et al. 2013[141] (post-ALK TKI value [0.46] and post-chemotherapy value [0.59]). Details of how these utilities were adjusted were not reported. A progressed utility applied in TA422[34] (derived from PROFILE 1007) with a value of 0.61 was also considered in scenario analyses. Utilities in PROFILE 1007 were from a NSCLC population previously treated with ALK TKIs, but as the utility value in TA422[34] represents the end of treatment (as a proxy for progressed disease), this was not applied in the base case.

From the five possible utility values to apply to progressed disease, 0.650 was selected.[32, 130, 134, 142] This was done in order to more closely reflect the current treatment pathway for NSCLC patients. Patients within the progressed disease health state are typically healthier and have better outcomes than were previously achievable because of better management of the disease. Utility values for a progressed health state similar to this value have been used and accepted in recent NSCLC submissions.[71]

Table 51 summarises the utility values applied within the base case model. Within the cost-effectiveness model, patients are expected to incur different utility values in the *progression free* health state dependent on the first-line treatment received.

Table 51. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission (section)	Justification
PF lorlatinib: clinical trial data[98]	[redacted]	[redacted]	Section B.3.4.2	Mapped observed utility data collected in the clinical trial

PF pemetrexed: Blackhall 2014[132](PROFILE 1007)	0.72 (0.07 (assumed 10% of mean))	(0.70, 0.79)	Section B.3.4.2	Source most closely reflects the decision problem
Progressed disease: Labbe 2017[126]	0.650 (0.007)	Not reported	Section B.3.4.6	Source most closely reflects the decision problem

Abbreviations: CI = confidence interval; PF = progression free

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted with the objective of identifying healthcare resource use and direct and indirect costs associated with advanced/metastatic ALK-positive NSCLC. The search was conducted on 6 August 2018. All relevant search strategies, search identification, and methodology are presented in Appendix G and Appendix J.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Acquisition costs

The acquisition costs associated with lorlatinib and PDC are presented in Table 52. Drug costs were taken from the Monthly Index of Medical Specialities (MIMS) for branded products, and the electronic market information tool (eMIT) for generic products. The table also presents the costs associated with docetaxel.

PDC was selected with a split of cisplatin/carboplatin taken from PROFILE 1014 (TA406 with 46.15% of patients receiving carboplatin and 53.85% of patients receiving cisplatin). This 50/50 split is also supported by the ASCEND-4 study for first-line ceritinib (Soria et al. 2017)[67]. These proportions were used to provide a weighted cost of the comparator in the model. A scenario analysis is included with a 25% cisplatin and 75% carboplatin, which was supported by the ERG in TA406.[31]

Pravastatin is given prophylactically to counteract hypertriglyceridemia and hypercholesteremia as experienced with lorlatinib. This was assumed to be given alongside lorlatinib for the duration of treatment and was factored in as an AE cost (see Section B.3.5.3).

Table 52. Drug costs

Treatments	Pack size	Cost	Cost per unit	Source
Lorlatinib[a]	120 tab pack (25 mg)	£7,044.00	£58.70	Price supplied by Pfizer as a placeholder
	30 tab pack (100 mg)	£5,283.00	£176.10	
	[PAS]: 120 tab pack (25 mg)	[redacted]	[redacted]	
	[PAS]: 30 tab pack (100 mg)	[redacted]	[redacted]	
Pravastatin	28 tab pack (40 mg)	£0.59	£0.02	eMIT (2019) (generic)[143]
Pemetrexed	100 mg (vial)	£160.00	£160.00	MIMS (2019) (Alimta®)[144]
	500 mg (vial)	£800.00	£800.00	
Carboplatin	50 mg/5 mL solution for infusion	£3.07	£3.07	eMIT (2019) (generic)[143]
	150 mg/15 mL solution for infusion	£6.65	£6.65	
	450 mg/45 mL solution for infusion	£17.03	£17.03	
	600 mg/65 mL solution for infusion	£17.54	£17.54	
Cisplatin	10 mg/10 mL solution for infusion	£1.53	£1.53	eMIT (2019) (generic)[143]
	50 mg/50 mL solution for infusion	£4.25	£4.25	
	100 mg/100 mL solution for infusion	£9.26	£9.26	
Docetaxel	10 mg/mL, (2 mL vial)	£162.75	£162.75	MIMS (generic)[142]
	10 mg/mL, (8 mL vial)	£534.75	£534.75	MIMS (2018) (generic)[142]
	10 mg/mL, (16 mL vial)	£1,069.50	£1,069.50	MIMS (2018) (generic)[142]
	20 mg/mL, (1 mL vial)	£3.85	£3.85	eMIT (2018) (generic)[143]
	20 mg/mL, (4 mL vial)	£14.74	£14.74	eMIT (2018) (generic)[143]
	20 mg/ml, (7 mL vial)	£900.00	£900.00	MIMS (2018) (generic) [142]
	20 mg/mL, (7 mL vial)	£46.75	£46.75	eMIT (2018) (generic)[143]
Pembrolizumab	100 mg/4 mL	£2,630.00	£2,630.00	MIMS (2019) (Keytuda®)[145]
	50 mg	£1,315.00	£1,315.00	
Atezolizumab	1.2 g	£3,807.69	£3,807.69	MIMS (2019) (Tecentriq®)[146]

Abbreviations: eMIT = electronic marketing information tool; g = gram; mg = milligram; MIMS = Monthly Index of Medical Specialities; mL = millilitre; PAS = patient access scheme

A simple PAS of [redacted] agreed with the Patient Access Scheme Liaison Unit and the Department of Health has been applied to the acquisition cost of lorlatinib.

As discussed in Section B.2.3, within Study 1001, patients could continue treatment with lorlatinib beyond progression. Therefore, lorlatinib was costed throughout the model using time on treatment data, to accurately reflect the clinical trial. The dosing schedules for the treatments are provided in Table 53, and were taken from the Summary of Product characteristic (SmPC) and related sources.[114]

Table 53. Dosing information and stopping rules

Treatments	Method of administration	Dosing schedule	Dosing source	Stopping rules	Stopping rule justification
Lorlatinib	Oral	100 mg once daily (lorlatinib trial)	Lorlatinib clinical trial dosing[147]	N/A	Treatment is given while clinical benefit is being seen – this may extend beyond progression.
Pravastatin	Oral	40 mg daily	Prescribing information[148]	Applied as long as treatment of lorlatinib	Treatment is given prophylactically to counteract adverse reactions linked to lorlatinib: hypercholesteremia and hypertriglyceridemia.
Pemetrexed	IV	500 mg/m^2 every 21 days	Pemetrexed SmPC[114]	A maximum of 6 x 21-day cycles	As per SmPC[114]
Carboplatin	IV	Target AUC dose = 5; dose = 750 mg (every 21 days)	Previous NICE appraisal[149]		
Cisplatin	IV	75 mg/m^2 every 21 days	Pemetrexed and cisplatin SmPC[114]		
Docetaxel	IV	Premedication regimen recommended before docetaxel is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. Docetaxel is administered as a 1-hour infusion every 21 days, 75 mg/m^2 docetaxel is recommended every 21 days for a maximum of 10 cycles	Docetaxel SmPC[150]	6 x 21-day cycles	As per TA584[2]
Pembrolizumab	IV	2 mg/kg every 3 weeks	Applied using the same methodology as TA10340[2]	Duration assumed to be 21.59 weeks	As per TA584[2]
Atezolizumab	IV	1.2 g every 3 weeks	Applied using the same methodology as TA10340[2]	Duration assumed to be 35.8 weeks	As per TA584[2]

Abbreviations: AUC = area under curve; g = gram; IV = intravenous; kg = kilogram; mg = milligram; N/A = not applicable; NICE = National Institute for Health and Care Excellence; SmPC = summary of product characteristics; TA = technology appraisal

For lorlatinib, the median RDI was reported to be [redacted] from the trial evidence available;[93] given that tablets are prescribed in either a 25 mg or 100 mg formthis RDI is unlikely to have an impact on the direct costs. Therefore, a simplifying assumption was made within the model that all patients receive 100 mg form (RDI=100%). No information was available to inform the RDI associated with any of the other drugs used within the model and so an RDI of 100% was also assumed for these. Wastage is taken into account using method of moments for treatments that are administered with the use of vials.

B.3.5.1.2 Administration costs

In addition to the drug acquisition costs, the cost of administration was also considered for lorlatinib and PDC. Given that lorlatinib is an oral treatment and does not require hospital administration, administration costs consisted of a dispensing fee only. A dispensing fee of £9.60 per administration was applied to each treatment, which included 12 minutes of hospital pharmacist time (Hospital pharmacist [Band 6]; radiographer cost per working hour [£48]) in line with previous NICE NSCLC appraisals).[30-32, 151] Administration costs for intravenous (IV) therapies were included, in line with infusion time from their respective SmPCs, and are presented in Table 54.[114, 150, 152]

Scenario analysis explores applying different administration costs to lorlatinib. The first approach assigns a cost of £131.61, an oral chemotherapy cost from NHS references costs (code SB11Z – outpatient attendance).[153] The second is taken from the Brigatinib ERG report, which applies a £42.50 cost per cycle.[71] This cost was informed by a senior NHS pharmacist, who suggested that the appropriate cost is for home delivery, which is £42.50 according to the NHS Peninsula Purchasing Alliance.

Table 54. Administration costs per treatment

Drug	Administration method	Cost per administration	Source
Lorlatinib	Oral	£9.60	Cost of 12 minutes pharmacist time (hospital-based staff: band 6 – PSSRU 2018[151]. Based on assumptions taken in TA536, TA529 and TA520[32, 83, 137]
Pemetrexed (if monotherapy)	IV – outpatient (simple parenteral chemotherapy)	£174.40	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance; outpatient[153]
Carboplatin (with pemetrexed)	IV – outpatient (simple chemotherapy)	£174.40	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance; outpatient[153]
Cisplatin (with pemetrexed)	IV – outpatient (complex parenteral chemotherapy)	£374.52	SB14Z; Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; day case[153]
Docetaxel	IV – outpatient (simple parenteral chemotherapy)	£174.40	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance[153]
Pembrolizumab	IV	£174.40	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance; outpatient[153]
Atezolizumab	IV	£174.40	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance; outpatient[153]
Lorlatinib (scenario analysis)	Oral	£42.50	TA571[71]
Lorlatinib (scenario analysis)	Oral	£131.61	SB11Z: Deliver exclusively oral chemotherapy; outpatient [153]

Abbreviations: IV = intravenous; PSSRU = Personal Social Services Research Unit; TA = technology appraisal

B.3.5.1.3 Summary of drug acquisition and administration costs

Table 55 summarises the drug acquisition costs and administration costs associated with lorlatinib and PDC. The table presents the total anticipated cost per patient per cycle. The total cost for pemetrexed was estimated by taking a weighted average of the proportion of patients that received cisplatin and carboplatin using data from PROFILE 1014.[154]

Table 55. Total drug acquisition costs per model cycle

	Drug cost per 30-day model cycle		Administration cost per 30-day model cycle		Total cost per cycle
Lorlatinib (100 mg 30 pack)	£5,283.00		£9.60		£5,292.60
Pemetrexed	£1,807.78	£1,829.86	£249.15	£403.08	£2,232.94 (weighted average based on treatment use)
Cisplatin	£19.61		£535.03		
Carboplatin	£24.45		£249.15.		

Abbreviations: mg = miligram

B.3.5.2 Health-state unit costs and resource use

The details of the health state costs are described in Table 56. A micro-costing approach was used, whereby the frequencies of individual resources were broken down depending on patients' health states. Frequencies were estimated as usage per month and were based on prior NICE appraisals for NSCLC (TA536,[32] TA529,[137] TA500,[30] TA406,[31] TA395[33] and TA296[113] [which was subsequently replaced by TA422][34]). All monitoring costs were derived from the latest version of the NHS reference costs (2017–2018)[153] and from the PSSRU (2018).[151]

Table 56. Medical resources for monitoring NSCLC patients based on TA500, TA406, TA395 and TA296

Health state	Resources required	Frequency		Reference	Unit cost	Reference	Cost code (if applicable)	Description
Progression free	GP visit	10%	of patients per month	TA536, TA529, TA500, TA406, TA395 and TA296[30-33, 113, 137]	£37.40	PSSRU 2018[151]	N/A	Clinic consultation lasting 9.22 minutes with qualification costs (unit costs)
	Outpatient visit	100%	of patients, 0.75 times per month		£165.85	NHS reference costs 2017/18[153]	370	Outpatient Attendances Data - medical oncology
	Cancer nurse	20%	of patients per month		£89.16		N10AF	Community Health Services: Specialist Nursing, Cancer Related, Adult, Face to face
	Complete blood count	100%	of patients, 0.75 times per month		£2.51		DAPS05	Direct Access: Pathology services - haematology
	Biochemistry	100%	of patients, 0.75 times per month		£1.11		DAPS04	Direct Access: Pathology services - clinical biochemistry
	CT scan	30%	of patients, 0.75 times per month		£121.91		RD26Z	Outpatient; CT Scan of three areas, with contrast
	X-ray	100%	of patients, 0.75 times per month		£31.49		DAPF	Direct Access Plain Film
Total cost per cycle, progression free								**£196.84**
Progressed disease	GP visits	28%	of patients per month	TA536, TA529, TA500, TA406, TA395 and TA296[30-33, 113, 137]	£37.40	PSSRU 2018[151]	N/A	Clinic consultation lasting 9.22 minutes with qualification costs (unit costs)
	Outpatient visit	100%	of patients per month		£165.85	NHS reference costs 2017/18[153]	370	Outpatient Attendances Data - medical oncology
	Cancer nurse	10%	of patients per month		£89.16		N10AF	Community Health Services: Specialist Nursing, Cancer Related, Adult, Face to face
	Complete blood count	100%	of patients per month		£2.51		DAPS05	Direct Access: Pathology services - haematology
	Biochemistry	100%	of patients per month		£1.11		DAPS04	Direct Access: Pathology services - clinical biochemistry
	CT scan	5%	of patients, 0.75 times per month		£121.91		RD26Z	Outpatient; CT Scan of three areas, with contrast
	X-ray	30%	of patients, 0.75 times per month		£31.49		DAPF	Direct Access Plain Film
Total cost per cycle, progressed disease								**£197.62**

Abbreviations: CT = computed tomography; DAPF = Direct Access Plain Film; DAPS = Direct Access Pathology Services; GP = general practitioner; N/A = not applicable; NHS = National Health Service; NSCLC = non-small-cell lung cancer; PSSRU = Personal Social Services Research Unit; TA = technology appraisal

A one-off terminal care cost was applied within the model. This was assumed to cover costs of supporting patients in the palliative stage before death. The cost was calculated based on the approach reported in Brown et al. 2013 which breaks down terminal care cost based upon care in the home, in hospital and in a hospice.[155] This approach to terminal care costing is consistent with nine prior NICE TA appraisals in NSCLC.[32, 82, 83, 127, 156-160] A cost of £4,574 was used to inform the base case of the model and a summary of the costs, resource use and assumptions made are provided in Table 57. Given that TA406 and TA529 incorporated palliative care costs from Georgiou and Bardsley from 2014 (assuming a cost of £7,653 when inflated to current prices), this value was explored in scenario analyses.[151, 161]

Table 57. Terminal care costs applied in the model

Resource	Unit cost	Consumption of resource	Cost	% of patients in each care setting	Setting assumed	Assumptions/references
Community nurse visit	£64.00	28 hours	£5,119.88	27%	Home	Resource use taken from Brown et al. 2013, with cost informed from PSSRU 2018 (cost per hour Band 8a hospital based nurse)[155, 162]
GP Home visit	£95.13	7.00 visits				Resource use taken from Brown et al. 2013, with costs informed from PSSRU 2018 (including direct care staff costs, with qualifications - GP duration 9.2 minutes).[151, 155] For home visits a GP duration of 23.4 minutes was assumed (PSSRU 2015); this accounts for 11.4 minutes home visit and 12 minutes travel time per visit
Macmillan nurse visit	£42.69	50 hours				Resource use taken from Brown et al. 2013, with costs assumed to be 66.7% of community nurse cost[155]
Drugs and equipment	£528.59	Average drug and equipment				Cost from Brown et al. 2013, and uplifted using the PSSRU inflation indices[151, 155]
Terminal care in hospital	£4,131.52	9.66 days	£4,131.52	56%	Hospital	NHS reference costs 2017/2018 – DZ18S Respiratory Neoplasms without Interventions, with CC Score 13+. Assumed additional 0.92 excess days in line with Brown et al. 2013 using NHS reference cost weighted sum of non-elective excess days (DZ17S)[153]
Terminal care in hospice	£5,164.39	9.66 days	£5,164.39	17%	Hospice	Assumption - 1.25 x hospital stay cost[155]
Total cost						**£4573.96**

Abbreviations: CC = complication and comorbidity; GP = general practitioner; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

B.3.5.3 Adverse reaction unit costs and resource use

As outlined in section B.3.4.4 and in line with previous NICE appraisals, costs associated with AEs (of Grade ≥3 that occurred in >5% of patients in at least one treatment of interest) were included within the model.[31-33] Unit costs for each event were calculated using Healthcare Resource Group codes from previous appraisals and updated using the latest NHS reference costs (Table 58). These costs were applied as a one-off cost in the first cycle of the model.[30, 153]

Table 58. Micro-costing of adverse events

	Adverse event										
	Anaemia	**Asthenia**	**Dyspnoea**	**Fatigue**	**Febrile neutropenia**	**Hypercholesterolemia**	**Hypertriglyceridemia**	**Lipase increased**	**Neutropenia**	**Neutrophil count decreased**	**Weight increased**
Unit cost	£631.88	£0.00	£374.62	£0.00	£495.48	£336.70	£336.70	£0.00	£495.48	£0.00	£0.00
Reference	NHS reference costs (2017/18) via TA416 (2016)	TA395 (2016)	NHS reference costs (2017/18) via TA416 (2016)	TA395 (2016)	NHS reference costs (2017/18) via TA416 (2016)	NHS reference costs (2017/18) via TA500 (2018)	NHS reference costs (2017/18) via TA500 (2018)	CTCAE guidelines	NHS reference costs (2017/18) via TA416 (2016)	CTCAE guidelines	CTCAE guidelines
Description	SA01G-SA01K Acquired pure red cell aplasia or other aplastic anaemia – non-elective short stay (Weighted Average)	Assumed equal to fatigue	DZ19H-N Other respiratory disorders – non-elective short stay (weighted Average)	The cost of managing fatigue was assumed to be zero; it was assumed this will be managed by dose reductions or interruptions	SA35A-SA35E Agranulocytosis – non-elective short stay (weighted average)	The cost of all lab abnormalities was assumed to be equal to the cost of two blood tests (Directly Accessed Pathology Services, DAPS05: Haematology) and two outpatient visits (Outpatient Attendances, 370: Medical Oncology) In addition to this it was assumed that pravastatin is required for the entire duration of treatment with lorlatinib (this is applied in the patient flow)		Assumed zero cost (investigation)	SA35A-SA35E Agranulocytosis – non-elective short stay (weighted average)	Assume zero cost (investigation)	Assume zero cost (investigation)
Weighted cost (lorlatinib)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Weighted cost (PDC)	£8.60	£0.00	£17.84	£0.00	£26.96	£0.00		£0.00	£70.78	£0.00	£0.00

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; NES = non-elective short stay; NHS = National Health Service; PDC = platinum doublet chemotherapy; TA = technology appraisal

The cost of treating AEs in the model was calculated based on the frequency that each AE occurred in each treatment arm multiplied by the total cost of treating each AE. The frequencies of AEs included are reported in Section B.3.4 (Table 48). A summary of the costs associated with AEs applied within the model are presented in Table 59.

Table 59. Total one-off adverse event cost

Treatment	Total one-off adverse event cost
Lorlatinib	£168.93[a]
Pemetrexed	£124.18

Note: [a] This includes the cost of prophylactic pravastatin

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatments

The costs of subsequent treatment following disease progression and cessation of initial treatment were included within the model to reflect current practice. This was not captured within the lorlatinib trial data; therefore, assumptions had to be made. Subsequent treatment was assumed to affect cost only, and no adjustment was made to efficacy estimates for OS (and consequently the progressed disease state).

Within the atezolizumab in combination appraisal (TA584)[2], there was some consensus that 60% of patients would receive active subsequent therapy in the PDC arm. Of the 60% receiving subsequent therapy, 31% were assumed to receive atezolizumab and 69% pembrolizumab (Table 60). This aligns with clinical expert opinion that immunotherapy use would be rare and that it would be after PDC. For lorlatinib it was again assumed that 60% of patients would receive active subsequent therapy, of these 40% receive pemetrexed and 60% PDC which was consistent with clinical expert opinion.

Drug input costs, and administration costs are provided in Table 52 and Table 54, respectively. In estimating the cost of subsequent therapy, a 30% discount is assumed for both pembrolizumab and atezolizumab costs to avoid overestimating costs due to confidential discount prices.

Table 60. Subsequent treatments and duration of subsequent treatment

Subsequent treatment	Mean weeks of treatment received	Lorlatinib % experienced		PDC % experienced	
		Value	Description	Value	Description
Pemetrexed	6.30[66]	60.00%	60% receive active subsequent therapy. 40% of those receiving active therapy receive pemetrexed monotherapy. The remainder receive pemetrexed + cisplatin/carboplatin (50:50 split)	0.00%	60% receive active subsequent therapy. 31% of those receive atezolizumab and the remaining 69% receive pembrolizumab
Cisplatin	6.30[81]	18.00%		0.00%	
Carboplatin	6.30[66]	18.00%		0.00%	
Docetaxel	18.00[2]	0.00%		0.00%	
Pembrolizumab*	21.59[2]	0.00%		41.40%	
Atezolizumab*	35.80[2]	0.00%		18.60%	
BSC (no active therapy)	NA	40.00%		40.00%	
Drug cost		£2,673.23		£14,143.75	
Administration cost		£610.35		£906.73	
Total cost		£3,283.58		£15,040.49	

Abbreviations: BSC = best supportive care; NA = not applicable; PDC = platinum doublet chemotherapy
Notes: * assumes a discount of 30% of the list price

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

In line with the NICE reference case, the analyses were conducted from the NHS and PSS perspective and discounted costs and QALYs using a 3.5% discount rate. Results are presented over a lifetime (20 years) time horizon. Table 61 summarises how the base case inputs and variables were explored in scenario analyses. A full list of parameter inputs, the associated distributions and scale of uncertainty are presented in Appendix L. Parameters were explored through probabilistic and one-way sensitivity analyses.

Table 61. Summary of base case analysis inputs

Component	Parameter bundle	Tested in OWSA	Tested in PSA	Tested in scenario analysis
Model settings	Time horizon	No	No	Yes
	Discount rates	No	No	Yes
	Cycle length	No	No	No
Patient characteristics	Mean age	Yes	Yes	No
	Proportion male	Yes	Yes	No
Hazard ratios	OS	Yes	Yes	No
	PFS	Yes	Yes	No
Parametric survival parameters	OS	No	Yes	Yes
	PFS	No	Yes	Yes
	ToT	No	Yes	Yes
Adverse events	Frequencies	Yes	Yes	No
	Durations	Yes	Yes	No
	Costs	Yes	Yes	No
	Utility decrements	Yes	Yes	No
Drug costs	eMIT	Yes	Yes	No
	MIMS	No	No	No
Dosing	BSA	Yes	Yes	No
	Dose required	No	No	No
Subsequent treatment	Duration of treat treatment	Yes	Yes	No
Administration	Drug administration	Yes	Yes	Yes
Monitoring	PF	Yes	Yes	No
	PD	Yes	Yes	No
Terminal care	Terminal care	Yes	Yes	Yes
Utilities	PF	Yes	Yes	Yes
	PD	Yes	Yes	Yes

Abbreviations: BSA = body surface area; eMIT = electronic market information tool; MIMS = Monthly Index of Medical Specialities; OS = overall survival; OWSA = one-way sensitivity analysis; PD = progressed disease; PF = progression free; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; ToT = time on treatment

B.3.6.2 Assumptions

The base case analysis that used data from Study 1001 was subject to several key assumptions. These assumptions are summarised in Table 62. This table also provides a summary of the scenario analyses conducted.

Table 62. Model assumptions

Assumptions	Assumption description	Justification
Time horizon	Lifetime (20 years)	The economic model runs for 20 years to reflect the extrapolated life expectancy of the lorlatinib cohort. The impact of varying time horizon on the results was tested in sensitivity analysis
OS curves	The Generalised Gamma curve was selected for the lorlatinib base case OS	Parametric survival models were selected using guidance from TSD 14.[117] The curves selected provided good visual fits to the data and had clinical plausibility. Curves were validated by clinical experts. Alternative parametric survival models were explored for all 4 components (OS, PFS and two treatment arms) in scenario analyses
	The log-normal curve was selected for the PDC base case OS	
PFS curves	The Generalised Gamma curve was selected for the lorlatinib base case PFS	
	The Log-logistic curve was selected for the PDC base case PFS	
Target dose for cisplatin is 500mg	TA181 estimated that a target AUC of 5 would result in a dose of 500 mg, and TA347 estimated that a target AUC of 5 would result in a dose of 750mg.[128, 149] In the base case the target dose was assumed to be 500 mg	The dose of 500 mg was selected in the base case as an assumption and this results in a lower cost for cisplatin
Chemotherapy administration setting	A higher cost is applied for the administration of cisplatin (taken from NHS reference costs - assumed SB14Z: deliver complex chemotherapy – day case)[153]	This is in line with the SmPC for cisplatin which indicates that infusion should take place over a period of 6 to 8 hours.[163] This is based on assumptions made in a previous NICE technology appraisal for pemetrexed, due to the more complex administration required for cisplatin[137]
Cisplatin/ carboplatin mix in pemetrexed regimen	The proportion of patients receiving pemetrexed plus cisplatin or pemetrexed plus carboplatin in the PROFILE 1014 trial is reflective of current practice	The efficacy data for PDC were based on the pooled combination of cisplatin and carboplatin. The proportion with which these two regimens were used in the model (and the resulting impact on average therapy cost) was that observed in the PROFILE 1014 trial. These values were also in line with clinical opinion, which indicates that carboplatin/cisplatin are used equally. Scenario analysis is included which tests the carboplatin/cisplatin mix (25:75 split respectively)
Number of PDC treatment cycles	The number of PDC treatment cycles was assumed to be a maximum of six. Maintenance treatment with pemetrexed is continued	This assumption is in line with clinical practice. Scenario analyses explore capping PDC at cycle four and five
Terminal care costs	Applied as a one-off cost upon death; costs taken from Brown et al. 2013	Approach and source have been used in multiple NSCLC appraisals.[32, 82, 83, 127, 156-160] The impact of sourcing terminal care costs from Georgiou and Bardsley (2014) was tested in scenario analyses

Assumptions	Assumption description	Justification
Monitoring	Resource utilisation was assumed to be the same as that in TA406[31]	Approach and source have been used in multiple NSCLC NICE appraisals[30-33, 113, 137]
Second-line treatment	60% of patients receive active subsequent treatment	Some patients will not be well enough to receive subsequent therapy. Clinical experts, as part of this appraisal, indicated that no more than 60% of patients would be well enough to have subsequent therapy, and 60% was considered plausible in committee meetings for TA584. Therefore 60% has been applied as an upper bound on subsequent treatment[2]
Second-line treatment – lorlatinib	All patients receiving subsequent treatment receive pemetrexed. 40% received PDC (with a 50:50 split for cisplatin/carboplatin)	Given the treatment pathway, it's assumed that lorlatinib would replace pemetrexed in this line, and therefore treatment with pemetrexed and PDC would be received as a subsequent treatment. Not all patients would be able to tolerate combination therapy, hence it was assumed that 40% would receive PDC. This is supported by clinical opinion
Second-line treatment - PDC	31% of patients receiving subsequent therapy will receive atezolizumab and 69% pembrolizumab	In line with the subsequent therapies used after pemetrexed combination therapy in TA584[2]
Time on treatment	ToT for PDC used medians/PFS as a surrogate 100% of PDC patients receive pemetrexed maintenance (using PFS as a proxy for ToT)	In line with clinical opinion and UK routine practice. These assumptions were tested in scenario analysis (capping treatment at four and five cycles, and using a median ToT value to derive a ToT rather than assuming PFS as a proxy)
Utility values in progression free	Utility values were assumed to vary by treatment in the *progression free* health state	Given the safety profile of the lorlatinib versus PDC, and the difference in administration, it's reasonable to assume that HRQoL would differ across the two treatment arms
Utility values in progressed disease	Utility values were assumed equivalent by treatment arm in the *progressed* health state and applied until death	Patients would be likely to experience a lower QoL once progressed, and therefore progression free utilities may overestimate HRQoL for these patients The literature informed a lower utility for these patients using data derived from NSCLC ALK-positive EQ-5D utilities.[126] The progressed utility value is tested in scenario analysis
No additional quantified disutility due to adverse events	It was assumed that there would be no explicit decrements of disutility associated with adverse events, beyond existing on-treatment EQ-5D utility	The utility estimates included in the economic model for the lorlatinib arm were taken directly from patients on treatment in Study 1001, and so it is assumed that changes in utility caused by AEs are accounted for. The impact of including a disutility due to AEs could be deemed 'double-counting'; however, AE disutility was explored in a sensitivity analysis

Assumptions	Assumption description	Justification
Utility decreases with age	It was assumed that HRQoL in each disease state (progression free, progressed disease) would be constant irrespective of time spent in that state except for an age-adjustment.	Symptoms that impact HRQoL are directly related to the progression of disease; while a patient is in the progression free health state, they would not be expected to experience a worsening of symptoms and hence there is no expected change in HRQoL If these are time changing, this is likely to be captured in the utility value which is an average.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; AUC = area under curve; EQ-5D = EuroQol five dimensions; HRQoL = health-related quality of life; mg = milligram; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = non-small-cell lung cancer; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; SmPC = summary of product characteristics; TA = technology appraisal; ToT = time on treatment

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

Results throughout this section are presented with the incorporation of the lorlatinib PAS ([redacted]). Results of the cost-effectiveness analysis using the lorlatinib list price are presented in Appendix N. Base case results of the economic comparison between lorlatinib and PDC are presented in Table 63.

Lorlatinib was estimated to generate an additional [redacted] life years (LYs) and [redacted] QALYs in the model. This represents a substantial improvement to the length and HRQoL for patients suffering with an end-of-life disease who are otherwise in a very poor state of health. The corresponding base case ICER is £50,152 indicating that lorlatinib is a cost-effective treatment at a cost-effectiveness threshold of £50,000.

Table 63. Base case results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed	[redacted]	0.78	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,152

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Disaggregated results of the base case ICER analysis with the PAS price are presented in Appendix M.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The PSA was performed with 1,000 iterations. This analysis randomly samples parameters from within their respective distributions (see Appendix N for distribution information). The average results of this analysis are presented in Table 64. The mean incremental QALYs gained from lorlatinib across the 1,000 iterations was [redacted] with a corresponding ICER of £46,337 indicating that lorlatinib is a cost-effective treatment at a cost-effectiveness threshold of £50,000.

Table 64. Probabilistic sensitivity analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed	[redacted]	0.82	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,337

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

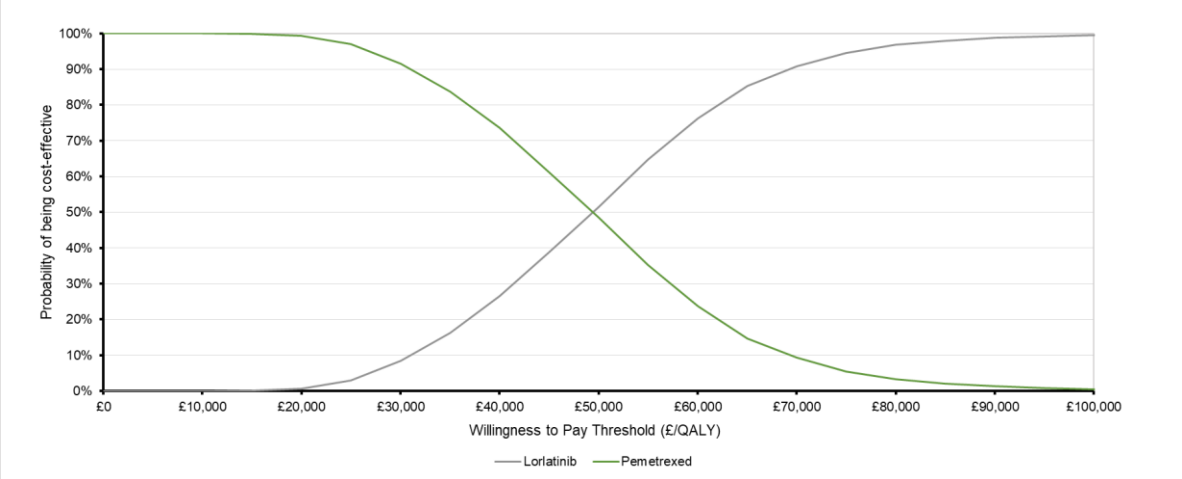
The visual results of the PSA are presented in Figure 54 which plots the incremental cost and QALY results for each PSA iteration.

Figure 54. Cost-effectiveness plane from 1,000 PSA iterations

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

From the PSA, a cost-effectiveness acceptability curve (CEAC) was constructed. The CEAC is presented in Figure 55 and shows the likelihood that lorlatinib is a cost-effectiveness option at different willingness-to-pay (WTP) thresholds. At a WTP of £50,000 the probability that lorlatinib is a cost-effective treatment option versus PDC is [redacted].

Figure 55. Incremental cost-effectiveness acceptability curve

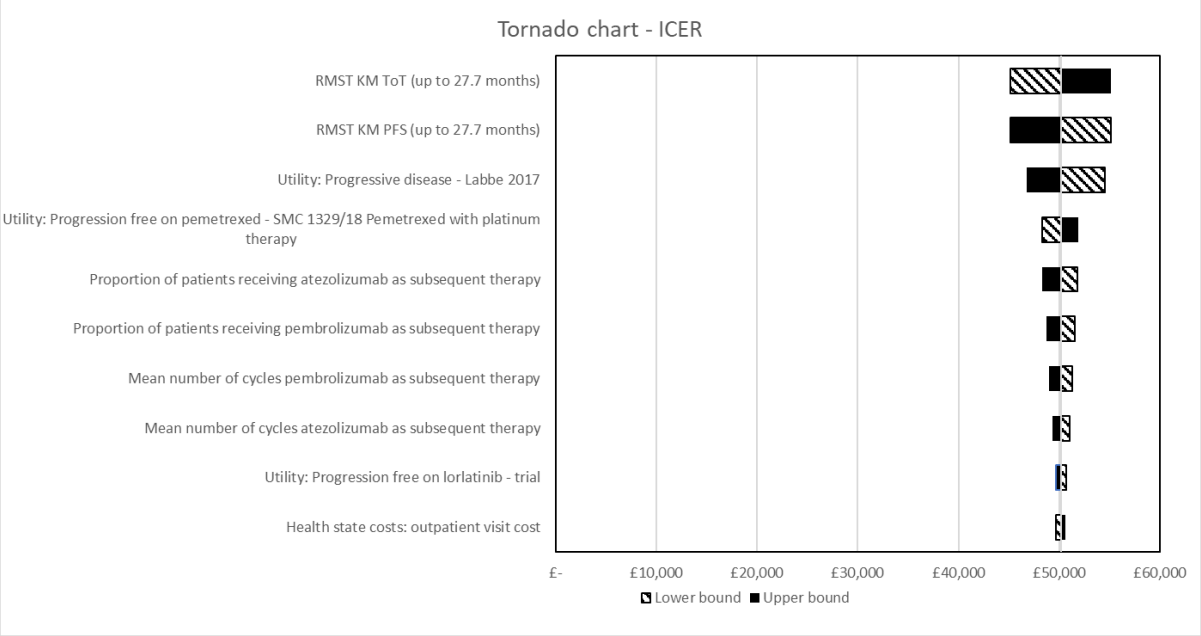


Abbreviations: QALY = quality-adjusted life year

B.3.8.2 Deterministic sensitivity analysis

Figure 56 presents a tornado diagram showing the parameters that have the greatest impact on the ICER in the base case analysis, with descending sensitivity. Four of the top 10 key drivers in the model are parameters attributed to the calculation of subsequent treatment. The parameter for progressed utility has a significant impact. The majority of parameters do not have a substantial effect on cost-effectiveness.

Figure 56. Tornado diagram displaying the 10 most influential parameters on the base case ICER



Abbreviations: ICER = incremental cost-effectiveness ratio; SMC = Scottish Medicine Consortium
Scenario analysis

Table 65 details all the parameters and assumptions that have been varied in scenario analyses, results of each scenario analysis are reported in Table 66.

Alternative PFS curves and methods for generating PDC efficacy have the largest impact on resultsMost other scenarios have minimal effect on the ICER, and do not drive the results.

Table 65. Full list of sensitivities undertaken and their respective settings

	Description	Base case setting	Sensitivity setting
1	Alternative lorlatinib OS curve	Generalised gamma	Exponential
2	Alternative lorlatinib PFS curve	Generalised gamma	Gompertz
3	Alternative PDC PFS survival option	Method 5: Independent curves & no population adjustment	Method 1: MAIC HR EXP-2:3A
4			Method 2: MAIC HR EXP-3B:5
5			Method 3: Unadjusted HR EXP-2:3A
6			Method 4: Unadjusted HR EXP-3B:5
7			Method 6: Independent curves & population adjustment
8	Alternative PDC OS survival option	Method 5: Independent curves & no population adjustment	Method 1: MAIC HR EXP-2:3A
9			Method 2: MAIC HR EXP-3B:5
10			Method 3: Unadjusted HR EXP-2:3A
11			Method 4: Unadjusted HR EXP-3B:5
12			Method 6: Independent curves & population adjustment
13	Lorlatinib: ToT	Difference between ToT and PFS RMST	Exponential
14	PDC: ToT	Yes	No cap on pemetrexed
15		6	4 cycle cap
16		6	5 cycle cap
17		Yes	No cap applied for pemetrexed and simple exponential curve derived from median ToT
18	Time horizon	20 years	10 years
19			15 years
20	Wastage	Wastage accounted	Wastage not accounted
21	Utilities	SMC 1329/18 (pemetrexed plus platinum value)	Apply Study 1001 PFS utility to pemetrexed
22		Labbe 2017	Apply Zhou utility for progressed patients (both arms)
23		Exclude	Include disutilities associated with adverse events
24		Exclude	Include disutilities associated with adverse events and applying the Study 1001 PFS utility value to pemetrexed
25	Costs & Resource use	46.15%	Cisplatin (25%) and Carboplatin (75%) split
26		Brown et al. 2013	Terminal care costs informed by Georghiou and Bardsley 2014
27		9.60	Administration cost of lorlatinib informed by NHS reference costs (SB11Z) outpatient visit for Deliver Exclusively Oral Chemotherapy (£131.61 per cycle)
28		9.60	Administration cost of lorlatinib informed by brigatinib 2019 ERG approach (£42.50 per cycle)

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; RMST = restricted mean survival time; SMC = Scottish Medicine Consortium; ToT = time on treatment

Table 66. Summary table of sensitivity analyses undertaken

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	[redacted]	£50,152
1	Alternative lorlatinib OS curve	Exponential	[redacted]	[redacted]	[redacted]	£53,064
2	Alternative lorlatinib PFS curve	Gompertz	[redacted]	[redacted]	[redacted]	£56,199
3	Alternative PDC PFS survival option	Method 1: MAIC HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£53,137
4		Method 2: MAIC HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£50,630
5		Method 3: Unadjusted HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£52,862
6		Method 4: Unadjusted HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£50,555
7		Method 6: Independent curves & population adjustment	[redacted]	[redacted]	[redacted]	£53,698
8	Alternative PDC OS survival option	Method 1: MAIC HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£44,150
9		Method 2: MAIC HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£58,118
10		Method 3: Unadjusted HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£43,022
11		Method 4: Unadjusted HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£50,072
12		Method 6: Independent curves & population adjustment	[redacted]	[redacted]	[redacted]	£42,727
13	Lorlatinib: ToT	Exponential	[redacted]	[redacted]	[redacted]	£38,701
14	PDC: ToT	No cap on pemetrexed	[redacted]	[redacted]	[redacted]	£49,897
15		4 cycle cap	[redacted]	[redacted]	[redacted]	£50,234
16		5 cycle cap	[redacted]	[redacted]	[redacted]	£50,187
17		No cap applied for pemetrexed and simple exponential curve derived from median ToT	[redacted]	[redacted]	[redacted]	£53,815
18	Time horizon	10 years	[redacted]	[redacted]	[redacted]	£48,620
19		15 years	[redacted]	[redacted]	[redacted]	£49,723
20	Wastage	Wastage not accounted	[redacted]	[redacted]	[redacted]	£51,107
21	Utilities	Apply Study 1001 PFS utility to pemetrexed	[redacted]	[redacted]	[redacted]	£51,014
22		Apply Zhou utility for progressed patients (both arms)	[redacted]	[redacted]	[redacted]	£56,119
23		Include disutilities associated with adverse events	[redacted]	[redacted]	[redacted]	£50,133
24		Include disutilities associated with adverse events and applying the Study 1001 PFS utility value to pemetrexed	[redacted]	[redacted]	[redacted]	£50,994
25		Cisplatin (25%) and Carboplatin (75%) split	[redacted]	[redacted]	[redacted]	£50,317

26	Costs & Resource use	Terminal care costs informed by Georghiou and Bardsley 2014	[redacted]	[redacted]	[redacted]	£50,001
27		Administration cost of lorlatinib informed by NHS reference costs (SB11Z) outpatient visit for Deliver Exclusively Oral Chemotherapy (£131.61 per cycle)	[redacted]	[redacted]	[redacted]	£51,991
28		Administration cost of lorlatinib informed by brigatinib 2019 ERG approach (£42.50 per cycle)	[redacted]	[redacted]	[redacted]	£50,648

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment

B.3.8.3 Summary of sensitivity analyses results

Lorlatinibs' probabilistic ICER versus the standard of care is lower than the £50,000/QALY threshold (with PAS). The results of the PSA show that Lorlatinib provided more QALYs than PDC in all iterations, and on average, lorlatinib offered [redacted] additional QALYs. There is a general consensus, that has been acknowledged across appraisals in a variety of disease areas, that when there is a divergence in ICER value the probabilistic value (£46,337) is considered the more plausible.

The one-way sensitivity analysis shows that the model is stable across inputs. Extensive scenario analyses were performed to explore structural and parameter uncertainty across a wide range of inputs. In general, the ICER remained stable with results consistently close to or below the £50,000 per QALY threshold. However, as previously discussed most of these selections can be rejected as inappropriate.

B.3.9 Subgroup analysis

There are no subgroups considered within the analysis.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis – versus data sources

Validation of the modelled outcomes versus the studies they relate to are presented in Table 67. The comparison indicates that outcomes for the model and published estimates are broadly consistent. In absolute terms modelled outcomes differ slightly from published estimates and this is proportionally larger for the PDC arm.

Table 67. Summary of model results compared with clinical data

Treatment	Average PFS (months)			Average OS (months)		
	Model result		*Median (external data source)*	Model result		*Median (external data source)*
	Median	Mean		Median	Mean	
Lorlatinib	7.9	[redacted]	6.9 (Study 1001)	21.7	[redacted]	20.4 (Study 1001)
PDC	3.0	4.2	1.6 (ALUR), 1.6 (ASCEND-5) Weighted: 1.6	6.9	9.4	5.4 months (PROFILE 1001/1005)

Abbreviations: OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival

B.3.10.2 Validation of cost-effectiveness analysis – clinical input and economic review

Several quality control measures were undertaken to validate the model findings and analysis. Details of the validation with clinical experts are provided in Table 68, alongside other modelling validation details.

Table 68. Validation details

Validation performed by	Nature of validation	Date(s)	Aspects validated
Advisory board with 7 UK clinical experts	Expert advisory board meeting	July 2018	UK treatment pathway and comparators; pre-treatment patterns and impact of efficacy; sequencing of treatment; Study 1001 results; Lorlatinib tolerability
UK clinical expert	Teleconference	Sept 2018	UK treatment pathway and comparators; pre-treatment patterns and efficacy; sequencing of treatment; subsequent treatments and efficacy; model survival curve validation
*UK clinical expert (Dr. Tim Benepal; St George's Hospital, London)	Teleconference x2	Sept 2018, Feb 2019	UK treatment pathway and comparators; subsequent treatments; model survival curve validation
*UK clinical expert (Dr Shobhit Baijal; Spire Parkway Hospital, Birmingham)	Teleconference	April 2019	UK treatment pathway and comparators; subsequent treatments; model survival curve validation; pre-treatment patterns and impact of efficacy; Pemetrexed ToT; QoL differences in PFS
BresMed health solutions	Quality control	April–May 2019	Checked input data against sources, general QC
UK clinical expert/practicing consultant medical oncologists	Meetings x4	May 2019	Pathway and place of Atezolizumab with bevacizumab, paclitaxel and Carboplatin for ALK specific patients; expected uptake and fitness of patients; opinion on Impower150 trial and EGFR majority subgroup

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; PFS = progression free survival; QC = quality check; QoL = quality of life; ToT = time on treatment; UK = United Kindom
*Note: experts are only named when they have given their explicit permission

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison of the economic evaluation with published economic literature

This is the first economic evaluation to assess the cost-effectiveness of lorlatinib versus PDC for the treatment of ALK positive advanced NSCLC.

B.3.11.2 Generalisability of the economic evaluation to the UK

The population included in the economic evaluation was consistent with the license of lorlatinib. The economic evaluation reflects the patient sample used for modelling (EXP-3B:5 cohort) from Study 1001 and clinical expert opinion suggested that the study is reasonably generalisable to England and Wales. Additionally, real world data from the compassionate use program shows that pre-treatment patterns in the EXP-3B:5 cohort reflect almost perfectly the pre-treatment patterns expected in routine practice (see Appendix R).

B.3.11.3 Strengths and weaknesses of the economic evaluation

There are some limitations of the economic evaluation. As acknowledged, Study 1001 is a single-arm trial and therefore a direct randomised comparison cannot inform efficacy in the model. Further to this, the nature of a single arm trial also limits anchored indirect methods of comparison with PDC, such as network meta-analysis.

There is also limited evidence to inform the comparator arm in the precise cohort relevant to the license population (EXP-3B:5) or the precise treatment (PDC instead of singlet chemotherapy). Although expert clinical opinion suggested that singlet chemotherapy can be used as a reasonable proxy for PDC and that outcomes following a first-generation TKI will be similar to outcomes following a second-generation TKI.

To overcome these limitations, several methodologies have been explored for generating outcome data, including MAICs, unadjusted HRs and fitted independent curves. Twelve different methods have been implemented to generate PFS and OS data for the comparator arm. The comparisons, benefits, limitations and assumptions associated with each method, are reported in detail in Section B.3.3.

Despite the limitations outlined, the cost-effectiveness analysis makes use of the best available evidence to inform the model. The model has been developed to incorporate as much IPD from Study 1001 as possible. An extensive and updated SLR was used to identify data that informs the comparison with PDC. Two studies were used in order to generate a larger evidence base to inform PFS in the PDC arm (ALUR[92] and ASCEND-5[66]) and the only study identified that reported a KM was used to inform OS in the PDC arm (PROFILE 1001/1005).[103]

The model structure is consistent with that used in almost every other NSCLC technology appraisal.[30, 31, 33, 71] Throughout the economic evaluation, the model has been aligned to prior technology appraisals, when justifiable. Extensive scenario analyses were also undertaken.

B.3.11.4 Conclusions

In conclusion, lorlatinib is an efficacious treatment for patients with advanced ALK-positive NSCLC and its use results in substantially improved clinical outcomes compared with pemetrexed plus cisplatin/carboplatin. When lorlatinib is provided with a confidential PAS, it can be considered a cost-effective treatment option for patients, with an ICER below the £50,000 WTP threshold compared with pemetrexed plus cisplatin/carboplatin. The mean ICER produced by the PSA is consistently around £46,000 and this can be considered the most plausible ICER. These results indicate that lorlatinib treatment is a cost-effective use of NHS resources.[31]

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B.5. Appendices

Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix E. Subgroup analysis

Appendix F. Adverse reactions

Appendix G. Methods of economic systematic literature reviews

Appendix H. Published cost-effectiveness studies

Appendix I. Health-related quality-of-life studies

Appendix J. Cost and healthcare resource identification, measurement and valuation

Appendix K. Features of the economic analysis and prior technology appraisals

Appendix L. Summary of parameters included within the base case economic model

Appendix M. Clinical outcomes and disaggregated results from the model

Appendix N. Cost-effectiveness results: lorlatinib (list price) versus pemetrexed in combination with cisplatin/carboplatin

Appendix O. Checklist of confidential information

Appendix P. Statistical analyses

Appendix Q. Log-cumulative hazard plots

Appendix R. Compassionate-use programme and real-world pre-treatment data

Appendix S. Comparison to atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP)

B.5.11.1 Introduction

The updated May 2019 scope from NICE listed atezolizumab with bevacizumab, paclitaxel and carboplatin ("ABCP" hereon) as a relevant comparator for patients with non-squamous disease within the ALK-positive advanced NSCLC population. Pfizer do not consider ABCP to be a relevant comparator to lorlatinib in the ALK-positive patient population based on the following: patient fitness and the high proportion with brain metastases; low expected uptake given no precedent of use in ALK-positive patients; a lack of powered clinical evidence; and consultations with practicing expert oncologists who suggested that it's use would be predominantly in EGFR patients. See sections B.1.1 and B.3.2.4 of the main submission for more information.

A simple, deterministic model comparison ("simple model" hereon) to ABCP is presented here, primarily using data from the TA584 appraisal[1] and associated committee papers. This was the appraisal for ABCP in the treatment of metastatic non-squamous NSCLC, for which the final appraisal documentation was published in May 2019. In the comparison presented within this appendix the model structure remains the same and base-case settings as close as possible to those presented in the main submission of the current appraisal. Settings for the ABCP arm of the comparison are informed by the base-case settings presented in the TA584 company submission, associated appendices, Evidence Review Group report and committee papers.

B.5.11.2 Rational for approach

The approach to this comparison was restricted by available data, which was informed by the up-to-date clinical SLRs presented in the TA584 company submission and the SLR in the main submission document of the current appraisal. The approach of an unanchored, unadjusted with population adjustment comparison between lorlatinib and ABCP was favoured for the following reasons:

- The pivotal trial in TA584 (IMpower150) contains an EGFR majority subgroup (34 EGFR, 11 ALK-positive patients) and this is the clinical data that informs the NMA, model and recommendation for the use of ABCP in EGFR and ALK-positive patients. This is the only evidence available for the use of ABCP in ALK-positive patients.
- The TA584 company submission presents an NMA to inform efficacy for the cost-effectiveness model.
    - There is no way to connect lorlatinib to this network given that Study 1001 is a single arm trial.

- This NMA must assume that EGFR and ALK-positive status are not treatment effect modifiers – the NMA contains other NSCLC patients - which is not supported by clinical expert opinion or the ERG in the TA584 appraisal.
- Even if the previous assumption were reasonable, for our purposes, a network for the combined EGFR and ALK-positive population would not be of any use. EGFR and ALK-positive NSCLC can be considered different diseases with different TKI treatments.

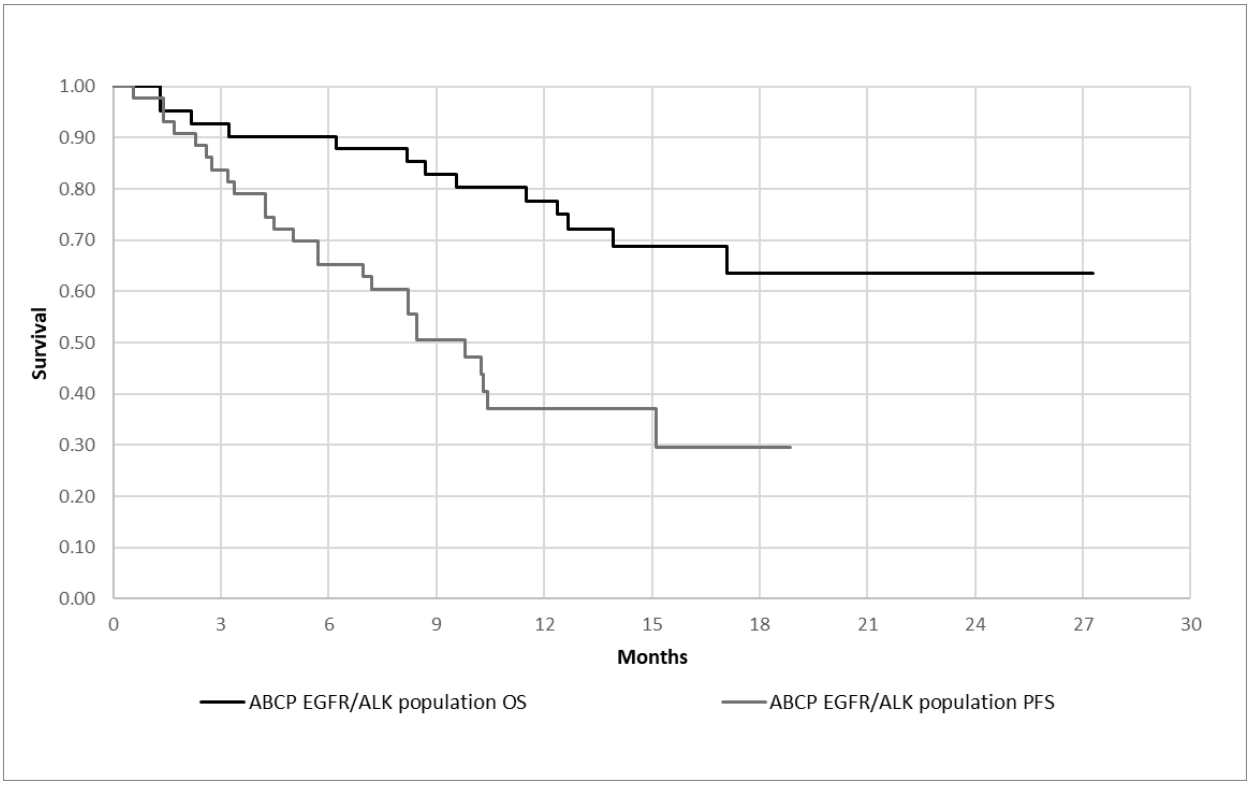
- A population adjustment – from EGFR to ALK-positive status – is not ideal, but justifiable given that the only available evidence for ABCP in ALK-positive NSCLC is a majority EGFR subgroup from the IMpower150 trial.
  - EGFR and ALK-positive NSCLC are effectively different diseases. This is evidenced by the completely different targeted TKI treatments in each disease.
  - There is evidence that ALK-positive patients experience higher rates of brain metastases[2] (around 2/3 in Study 1001) and have a less favourable prognosis[3]. This was supported by consultation with multiple clinical experts.
  - The relative efficacy of ABCP varies depending on EGFR or ALK-positive status. The reported IMpower150 HR in a recent conference presentation[4] for ABCP vs BCP for EGFR only and ALK-positive only status were different (0.60 and 0.65, respectively and both statistically insignificant). Median PFS for ABCP in EGFR and ALK-positive patients was also different (10.2 and 8.3 months, respectively).

B.5.11.3 Efficacy data to inform lorlatinib versus ABCP comparison

To generate a comparison, the IMpower150 trial was used to create an unanchored, unadjusted comparison. This study was a phase-III open label study comparing ABCP with bevacizumab, carboplatin & paclitaxel in patients with stage IV Non-Squamous Non-Small Cell Lung Cancer. The co-primary endpoints of this study were OS and PFS. Although this study was the primary study used to inform TA584, the efficacy derived is of little relevance to the EXP-3B:5 cohort in Study 1001, namely that the population is not ALK+ specific. PFS and OS were presented for this EGFR majority subgroup (n = 41 patients). Of the 41 patients, only 11 had ALK-positive status.

This is the only available evidence to inform a comparison of lorlatinib to ABCP. Figure 57 presents the PFS and OS for this majority EGFR group from IMpower150 (OS reported in TA584 Figure 30 of company submission; PFS reported in Figure S4 IMpower150 publication supplementary material[5]).

Figure 57: PFS and OS in the EGFR+/ALK+ population of IMpower150

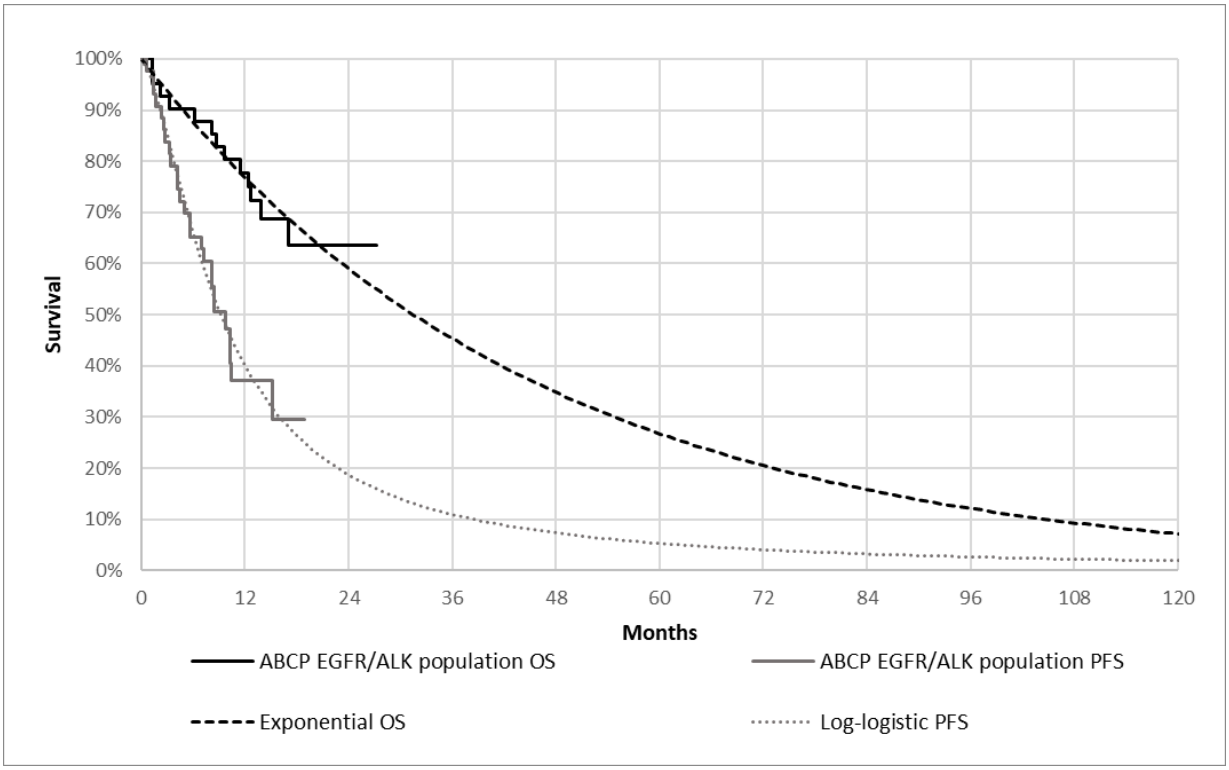


Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; ALK = anaplastic lymphoma kinase; EGFR = Epidermal Growth Factor Receptor; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival.

The observed data presented within TA584 for the subgroup were digitised. From this, pseudo-patient level data were replicated using the algorithm presented by Guyot et al. The standard six parametric survival models were fit to the replicated data for both PFS and OS: Exponential, Log-logistic, Log-normal, Weibull, Gompertz and Generalised Gamma.

Within the TA584 appraisal the exponential curve was selected as the appropriate extrapolation for OS. Therefore, the same assumption was made to inform OS in this model. The exponential curve for OS also gave the best AIC and BIC fit based on the replicated data. The TA584 company submission selected a log-normal distribution for PFS in the base-case, however the ERG preferred the log-logistic fit and so this was selected for the base-case PFS extrapolation. The log-normal gave the best AIC statistical fit, however the log-logistic was similar, and both curves provided a good visual fit to the data. Figure 58 reports the PFS and OS curves fit to the IMpower150 observed KM data.

Figure 58: Parametric survival curves fit to the Impower 150 EGFR+/ALK+ patients (OS = exponential; PFS = log-logistic)



Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; ALK = anaplastic lymphoma kinase; EGFR = Epidermal Growth Factor Receptor; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival.

In addition to fitting parametric survival models, a HR was also derived between Study 1001 (EXP-3B:5 cohort) and the ABCP arm of the IMpower150 EGFR majority subgroup. These results (Table 69) provide an alternative method of deriving the relative efficacy of lorlatinib compared with ABCP.

Table 69: Independent hazard ratio comparing lorlatinib (Study 1001) to ABCP (Impower150 EGFR majority subgroup)

	PFS	OS
Study 1001 versus IMpower 150 EGFR+/ALK+ patients	[redacted]	[redacted]

Abbreviations: ALK = Anaplastic lymphoma kinase; EGFR = Epidermal Growth Factor Receptor; OS = overall survival; PFS = progression free survival

B.5.11.4 Efficacy data to inform population adjustment

As already discussed, EGFR and ALK-positive NSCLC can be considered different diseases that result in different prognoses, with ALK+ patients typically experiencing poorer outcomes. Hence, in using the IMpower150 study, there is an inherent bias towards ABCP given that the patient population are not representative of those that would be eligible for treatment with lorlatinib (i.e. majority EGFR). To account for this bias, a population adjustment is made to estimate outcomes for ALK+ patients treated with ABCP.

To estimate a population adjustment, a HR was derived between patients receiving chemotherapy in an EGFR population and patients receiving chemotherapy in an ALK-positive setting. For ALK-positive patients the pooled Novello & Shaw data was considered the most appropriate data source for PFS[6,7]. Similarly, the Ou et al. study was considered the most appropriate data for ALK+ OS[8]. These were the sources used in the main submission. The IMPRESS study was used as the source of data for chemotherapy in EGFR patients and was a phase 3 trial that compared the continuation of gefitinib plus chemotherapy with placebo plus chemotherapy in patients with EGFR mutation-positive advanced NSCLC with progression after first-line gefitinib[9].

The HR for PFS and OS was generated using a cox-proportional hazards model, the results of which are presented in Table 70. The HRs were applied to the fitted EGFR/ALK+ curves to derive results for an ALK+ only population (i.e. population adjustment). This is a limitation, however in the absence of other data, and with such a small percentage of patients being ALK+ (11/41) in the IMpower150 subgroup, the application of this HR appeared the most appropriate way to derive a comparison of lorlatinib versus ABCP for ALK-positive patients.

Table 70: HRs for PFS and OS of EGFR+ versus ALK+ patients.

Analysis	HR
IMPRESS study chemotherapy arm: PFS versus pooled Novello et al. and Shaw et al. chemotherapy data.	[redacted]
IMPRESS study chemotherapy arm: OS versus Ou et al. chemotherapy data.	[redacted]

Abbreviations: HR = Hazard ratio; OS = Overall survival; PFS = Progression free survival;

The derived population adjustments for PFS and OS are applied in the base case comparison of lorlatinib vs ABCP and the resulting survival curves are presented in Figure 59.

Figure 59: ABCP PFS and OS base-case independent parametric curves with a population adjustment

Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; OS = Overall survival; PFS = Progression free survival.

Figure 60 presents a summary of the PFS and OS efficacy applied to inform the ABCP arm within the basic model and shows how this compares against the base case projections of survival for lorlatinib. This figure presents projections for the base-case setting of the ABCP arm: independent parametric curves fit to OS and PFS and Population adjustment to reflect an ALK-positive only population. Although the comparison has limitations due to the sparse evidence, the figure shows that lorlatinib will outperform ABCP in OS and PFS.

Figure 60: ABCP (with population adjustment) versus lorlatinib for PFS and OS.

Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; OS = Overall survival; PFS = Progression free survival.

Due to the approach taken and the limited data, there may be points at which OS is less than PFS. In any instances where this may appear, the model programming has an override function to cap PFS so that it never exceeds OS as is the standard convention in partition survival models.

B.5.11.5 Other base-case settings and data

B.5.11.5.1 Drug costs

In deriving a comparison to ABCP, dosing requirements for the combination treatment were taken from TA584 and micro-costed using latest costs. Given a treatment cycle for ABCP is 3 weeks, costs were upscaled to account for the 30-day cycle length included in the model. Drug costs and assumptions are presented within Table 71. In addition to the costs presented, Pfizer are aware that atezolizumab and bevacizumab both have a confidential patient access scheme in place. For the base-case, it has been assumed that this discount is 30%. Scenario analyses are presented applying a discount of 40% and 50% to both treatments.

Table 71: Drug costs and assumptions applied to compare lorlatinib to ABCP

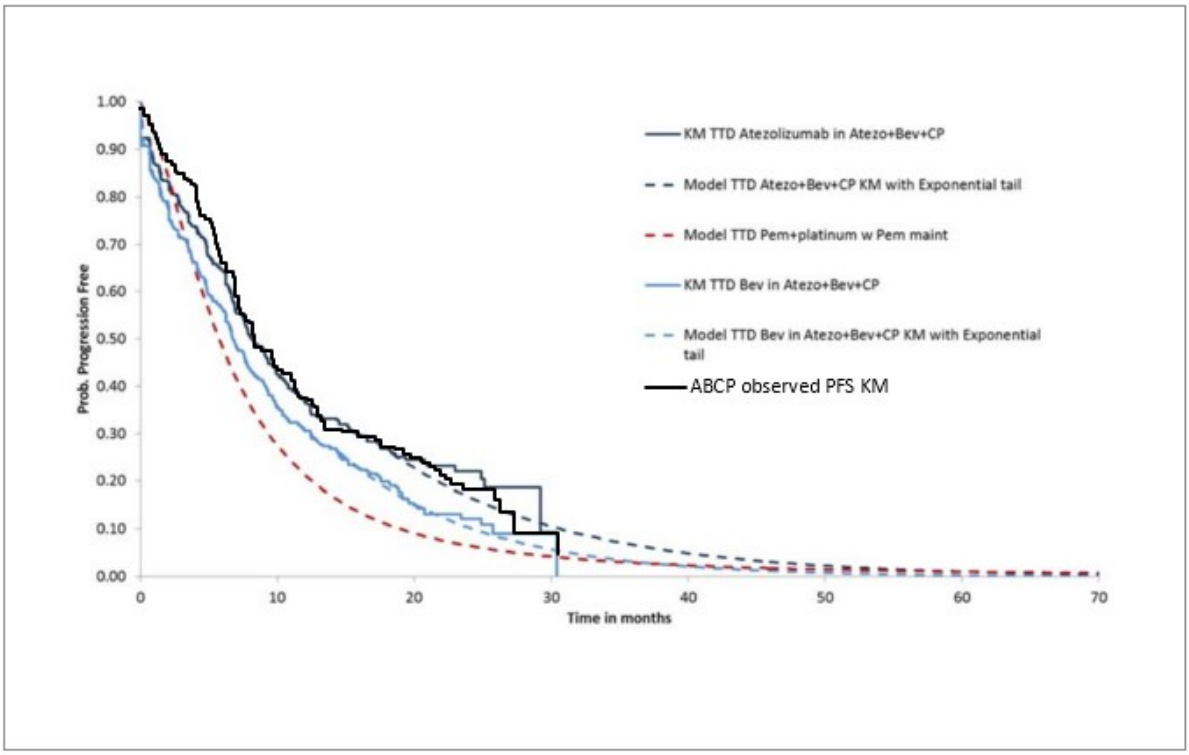
Drug	Dose per administration	Vial/tablet size	Treatment cycle length	Cost per pack	Cost per 21-day

	(taken from TA584)				treatment cycle
Atezolizumab	1200	1.2g/2ml	Every 3 weeks	£3807.69	£3,807.69
Bevacizumab	1079	100mg/4ml		£242.66	£2,576.78
		400mg/16ml		£924.40	
Carboplatin	692	50mg/5ml		£3.07	£23.68
		600mg/60ml		£17.54	
Paclitaxel	362	100mg/16.7ml		£9.49	£34.75
		300mg/50ml		£25.26	
Cost per 30-day cycle					**£7,572.28**

B.5.11.5.2 Time on treatment

A stopping rule was applied to ABCP within TA584 at 2 years. The simple model takes the same approach assuming that all patients are removed from treatment after 2 years. PFS was used as a proxy for ToT to avoid increasing model complexity. This seems an appropriate assumption to make given that ToT was relatively similar to PFS (an overlay of this is provided in Figure 61 and taken from data provided in TA584). Indeed, this is likely to be a conservative selection because the TTD curve for bevacizumab is always lower than the PFS curve for ABCP.

Figure 61: Overlay PFS with ToT



Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; KM = Kaplan Meier; PFS = TTD = Time to treatment discontinuation

For simplicity and in line with the approach taken within the main comparison, an RDI of 100% was assumed.

B.5.11.5.3 Administration costs

The company submission in TA584 applied a complex chemotherapy administration cost to ABCP. The same approach was taken but using the latest NHS reference costs. The corresponding cost per administration was £374.52 for SB14Z: Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance; day case. This is aligned to prior NSCLC appraisals and takes account of cisplatin, which has a long infusion time. Again, costs were upscaled from 21 days to 30 days to account for the differences in treatment cycle length.

B.5.11.5.4 Resource use & monitoring costs

Ongoing monitoring and management costs were incorporated into the comparison and were estimated based on health state occupation. Costs associated with management are reported in the main submission and the same approach is taken.

B.5.11.5.5 Adverse event costs

The TA584 company submission reports a total adverse event cost of £1,334.27 associated with ABCP. This is larger than the estimated adverse event costs for lorlatinib, although this is not surprising given that the ABCP combination is commonly known to cause toxicities substantial AEs. These costs were applied as a one-off in the first-cycle of the simple model, as in the main TA584 submission model.

B.5.11.5.6 Subsequent treatment costs

Within the TA584 committee papers it was reported that 60% of patients receiving treatment were assumed to go on to receive active subsequent therapy. This proportion is also cited within the main submission dossier for lorlatinib (see Section B.3.5.4.1). The TA584 committee settled on the assumption that all patients receiving active subsequent treatment beyond ABCP go on to receive docetaxel. The simple model makes the same assumption and so 60% of ABCP patients incur a subsequent therapy cost associated with 18 weeks of docetaxel treatment. The duration of subsequent treatment was also informed by TA584.

B.5.11.5.7 End of life costs

End of life costs were assumed the same as the main submission dossier with the approach taken from Brown et al. 2013.

B.5.11.5.8 Utilities

Utilities reported in the TA584 company submission were taken from IMpower150 EQ-5D values, using a time from death approach and applying disutilities associated with adverse events. The ERG within the TA584 appraisal explored a health state approach applying values of 0.71 and 0.69 respectively for PFS and PD health states, which were also derived from

IMpower150 trial data. To be aligned to the approach taken within the main submission of the current appraisal, the latter approach is adopted (i.e. applying utilities to each health state). It is reasonable to assume that this would be different for lorlatinib and chemotherapy patients due to the nature of the treatments and AEs incurred. Disutilities are not applied as they are assumed to be captured within the EQ-5D estimates for the PFS and PD health states.

For PD, the same utility value was applied for the lorlatinib and ABCP arms and was taken from the current submission (0.65) - sourced from Labbe et al (2017) and justification provided in the main submission. Scenario analyses explored adopting different utility values.

B.5.11.5.9 Summary

Table 72 presents a summary of the inputs for the ABCP arm in the simple model.

Table 72: Summary of model inputs for ABCP arm

Input component	Value	Application	Reference / Justification
Drug cost	£7.577.33	Every 30 days based on ToT	Dosing taken from TA584, with latest costs from MIMS.
Admin cost	£401.27	Every 30-days based on ToT	Approach taken from TA584 with latest cost from NHS reference costs.
Resource use: PFS	£196.84	Applied per 30-day cycle based on proportion of patients within the PD health state	Same as main submission dossier.
Resource use: PD	£197.62	Applied per 30-day cycle based on proportion of patients within the PD health state	Same as main submission dossier.
Adverse event	£1,334.27	One-off cost	Value taken from TA584.
Terminal care cost	£4,573.96	Upon entrance into progression-health state	Same as main submission dossier.
Subsequent therapy cost (drug cost and administration)	£708.17	One-off cost	Approach taken from TA584.
Utility: PFS	0.71	Health-state utility	ERG approach: TA584.
Utility: PD	0.65	Health-state utility	Same as main submission.

Abbreviations: ERG = evidence review group; PD = Progressed disease; PFS = progression-free survival; ToT = Time on treatment.

B.5.11.6 Results

B.5.11.6.1 Base case results

Table 73 presents the base case results of lorlatinib versus ABCP. Results indicate that lorlatinib offers [redacted] additional QALYs at a corresponding incremental cost of [redacted]. The resulting ICER is £27,369. The results assume that atezolizumab and bevacizumab have a PAS of 30%, and a [redacted] discount for lorlatinib is included.

Table 73: Base case results versus ABCP – lorlatinib at PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ABCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,369

Abbreviations: ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year

B.5.11.6.2 Scenario analysis results

Table 74 presents the results of scenario analyses. In all scenarios presented, lorlatinib remains a cost-effective treatment compared to ABCP at a willingness to pay threshold of £50,000 per QALY.

Table 74: Scenario analysis results versus ABCP – lorlatinib at PAS price

#	Description	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER
Base-case		[redacted]	[redacted]	[redacted]	£27,369
1	ABCP OS and PFS informed by HR versus lorlatinib and population adjustment	[redacted]	[redacted]	[redacted]	£25,360
2	ABCP utility from TA584 for PD state	[redacted]	[redacted]	[redacted]	£27,581
3	Lorlatinib utility for PFS state	[redacted]	[redacted]	[redacted]	£28,572
4	ABCP discount = 40% for atezolizumab and bevacizumab	[redacted]	[redacted]	[redacted]	£33,507
5	ABCP discount = 50% for atezolizumab and bevacizumab	[redacted]	[redacted]	[redacted]	£39,645
6	No stopping rule applied to ABCP	[redacted]	[redacted]	[redacted]	£23,722

Abbreviations: ABCP = Atezolizumab, bevacizumab, carboplatin and paclitaxel; HR = hazard ratio; LYG = life years gained; QALY = quality adjusted life year OS = overall survival, PFS = Progression free survival

B.5.11.7 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Clarification questions

[Month year]

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

[Add subheadings as needed]

A1. In the justification of comparators (Submission Document B, page 85), you say: "Due to increased use of ALK testing and increased availability of targeted treatments in UK clinical practice, a small and decreasing proportion of patients are likely to have received chemotherapy prior to an ALK TKI."

This relates to Figure 2 on page 26 of Submission Document B. Please quote data on NHS use to support your statement (e.g. from the compassionate use programme).

[Company: please enter your answer to this question here]

A2. Submission Document B, Table 1, Comparators. Based on the most recent NHS data available to the company, can the company please provide an estimate of the percentage of NHS patients potentially eligible for lorlatinib that will have had prior chemotherapy or prior immunotherapy.

[Company: please enter your answer to this question here]

A3. In appendix D.1.3, the company indicate that six RCTs and 87 non-RCTs were identified as eligible for the clinical review, but only evidence from study 1001 is a presented in the clinical effectiveness section of the submission. Can the company please clarify why none of the other identified studies have been included or discussed in clinical effectiveness section?

[Company: please enter your answer to this question here]

A4. Document B, Section B.2.4.1, page 37: Please clarify why the PRO evaluable set includes all enrolled patients and is not limited to EXP3B:5. As the different cohorts have had different prior treatment pathways, their baseline quality of life at starting lorlatinib may be different so please clarify why EXP-1 to EXP-6 can be pooled.

[Company: please enter your answer to this question here]

A5. Document B, Section B.2.5.5, page 50: Please clarify why the data cut for the patient reported outcomes is from 15 March 2017 and the efficacy data

were from 2 February 2018 (page 38). Please explain why the same data cut (i.e. February 2018) wasn't used for the PRO outcomes. Please also clarify why you were not able to use a more recent data cut in this submission.

[Company: please enter your answer to this question here]

A6. Document B, Section B.2.5.1.1, table 10, page 39: There were [redacted] treated in EXP3B:5, and in table 10, the last two rows add to [redacted] ([redacted] study discontinued, [redacted] study ongoing at data cut-off). Please explain why these two rows do not total to [redacted]. Please also clarify what is meant by study discontinued in this case and how it differs from treatment discontinuation.

[Company: please enter your answer to this question here]

A7. Appendix E, Table 29, page 86: Please provide the confidence intervals (e.g. 95%) for each of the hazard ratios presented. Please clarify how the subgroup analysis has been carried out, by providing an explanation of the models fitted. This analysis showed a difference in survival between the ECOG performance status groups, please clarify what impact this has when looking at the effect of lorlatinib.

[Company: please enter your answer to this question here]

A8. Appendix D, Section D.1.4.2.2.1, Table 21 and table 22, page 76. Please provide the confidence intervals for each hazard ratio presented.

[Company: please enter your answer to this question here]

A9. PRIORITY - Document B, Section B.2.8.3, table 24, page 57: In the table, for the ALUR study, ECOG PS 1/2 is provided as 14.3%. However, in Appendix D, section D.1.4.1.1, table 15, page 62, the second column for ALUR suggests ECOG PS = 2 is 14.3% and ECOG = 1 is 54.3%, so ECOG 1/2 should be 68.3%. Please explain why 14.3% was presented in section B.2.8.3. If it should have been 68.3% please explain what impact this would have had on the MAIC analysis and if relevant, please revise the analysis and any subsequent analysis that rely on the MAIC.

[Company: please enter your answer to this question here]

A10. Document B, Section B.2.8.3, table 24, page 57: Please provide the source file for the PROFILE study which provides the summary statistics for this study that are presented in table 24. The ERG would like to cross-check the entries and this is not possible at the moment as the reference for the data is not provided. The table footnote states 'These baseline characteristics are from the 37 patients that did not continue crizotinib but received systemic therapy and cannot be found in Ou et al 2014.

[Company: please enter your answer to this question here]

A11. Document B, Section B.2.8.3, table 24, page 57: Please provide the source reference for the summary statistics presented for the Study 1001, EXP 2 and EXP 3A cohorts.

[Company: please enter your answer to this question here]

A12. PRIORITY - Document B, Section B.2.5.1.2, table 11, page 39: Please provide a clear justification of why it is appropriate to pool data from EXP-3B, EXP-4, and EXP-5 to form the EXP-3B:5 cohort, with reference to the statistical significance of any differences in the characteristics of the individual cohorts (e.g. those identified in appendix E) and any expected differences in median survival.

[Company: please enter your answer to this question here]

A13. PRIORITY - Appendix D, Section D.1.4.2.2 pages 69-80. Please provide further detail on exactly how the MAIC methodology was implemented in the submission. Please provide statistical code that you used. Please explain why matching was carried out for the EXP2/3A cohort in addition to the relevant EXP 3B:5 cohort. Please expand on the reasoning for the four matching characteristics. Appendix D suggests ECOG and BMI should be used, but analysis doesn't highlight gender, race or brain metastases as significant predictors. Please clarify why these four were chosen and also explain why the exploratory analysis is on EXP2:5 and not just EXP 3B:5.

[Company: please enter your answer to this question here]

A14. PRIORITY - Appendix D, Section D.1.4.2.2.3, page 77 states that for each of the four matching characteristics, the percentages of patients after

matching are the same as the percentage of patients in the pooled Novello and Shaw population. Please in a single table provide the percentages for these four characteristics for each of Loratinib (original), Lorlatinib (after matching), with Novello and Shaw separately and pooled.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

B1. You have used previous STAs in ALK +ve NSCLC for resource use and utility values. Please can you clarify what values you used from those STAs?

[Company: please enter your answer to this question here]

Extrapolations of PFS, OS and ToT

B2. You fit parametric curves to available clinical data for PFS, OS and ToT in Submission Document B. In addition to graphs with the fitted curves you provide helpful statistics on predicted median and mean figures as well as rates at specific 'landmark' time points (see e.g. Table 42, page 99 for PFS). Please can you add the predicted rates at 10 years to each of these tables.

[Company: please enter your answer to this question here]

B3. In selecting which approach to use to predict PFS, OS and ToT you place emphasis on the views of clinical experts in stating what is plausible. While you state what meetings with clinical experts were held (Section B 3.10, page 151), and you report a summary of the experts' views, several points were unclear:

- **In cases where a numerical estimate of a rate was obtained, how was this done?**
- **If an expert gave a view, what was this based on – for example, had each expert used lorlatinib, in how many patients and what is the longest follow-up they have observed on a patient they initiated?**

- **Where expert views diverged, how did you handle this in reporting opinion in the submission?**

[Company: please enter your answer to this question here]

B4. Related to B1 above, if possible, please provide a summary of the questions that clinical experts were asked as part of the model validation process as well as collated responses to each question.

[Company: please enter your answer to this question here]

B5. It was not clear if you had used the previous ALK +ve NSCLC STAs to help cross validate the PFS and OS predictions of your model for 'usual care'. Can you provide that comparison, or if you have already done this make it more explicit?

[Company: please enter your answer to this question here]

B6. PRIORITY - Document B, Section B.3.3.3.1, page 91: Regarding the choice of parametric curve to derive progression free survival for lorlatinib, the submission states "When shown visual extrapolations and proportions in PFS, clinical experts favoured the generalised gamma or the Gompertz curve." Please clarify the number of clinical experts favouring each curve and their stated reasons for supporting this long-term projection.

[Company: please enter your answer to this question here]

B7. PRIORITY - Document B, Section B.3.3.3.2, page 104: Within the submission it is stated that "Clinical expert opinion suggested there would be very few patients remaining on a targeted treatment for 10 years or more." Please clarify the individual estimates of each clinical expert regarding the proportion remaining on a targeted treatment after 10 years, 5 years, and 2 years.

[Company: please enter your answer to this question here]

B8. PRIORITY - Document B, Section B.3.3.3.3, page 110: Regarding the choice of parametric curve to derive overall survival for lorlatinib, the submission states that "Even more importantly, clinical experts suggested that 10-year

survival would be closer to [redacted] than [redacted]. Therefore, the generalised gamma was selected to inform the base-case." Please detail the individual estimates of 10-year survival provided by each clinical expert, along with any further information on the stated basis for each clinician's estimate and any estimates provided at other relevant time periods, such as those referred to in Table 44 (page 109). Please also clarify whether these estimates are assumed to be equally applicable to each of the three cohorts which form EXP-3B:5 and the rationale for this assumption.

[Company: please enter your answer to this question here]

B9. PRIORITY - Document B, Section B.3.3.3.4, page 119: Regarding clinicians validating the decision to apply an independent chemotherapy curve with no population adjustment to represent progression free survival and overall survival for PDC. Please clarify the process by which clinical experts validated this selection, the number of clinicians validating the selection, the preferred approach of clinicians who did not validate this selection, and the reasons provided by clinicians for their selection.

[Company: please enter your answer to this question here]

B10. In the additional comparison with ABCP, it is stated that a population adjustment was made to account for expected differences in PFS and OS between EGFR+ and ALK+ patients treated with ABCP. The population adjustment used hazard ratios for ALK+ versus EGFR+ patients treated with chemotherapy. Please can you:

a) **Comment on the comparability of patients and potential for bias in the indirect comparison of PFS between Novello & Shaw and the IMPRESS study.**
b) **Comment on comparability of patients and potential for bias in the indirect comparison of OS between Ou et al and IMPRESS study.**
c) **Justify and provide any available evidence to support the application of these derived hazard ratios to ABCP treated patients.**

Costing assumptions and subsequent treatments

B11. In assembling data on chemotherapy (the comparator treatment) it is not always clear in Submission Document B whether this relates to the PDC regime(s) you costed in Section 3.5.1.1 (page 128). Please can you comment on whether the data used for effectiveness estimates were taken from clinical studies of pemetrexed-cisplatin or pemetrexed-carboplatin, both with 100% maintenance use. If not, please (re)state your rationale for why you believe the data can be generalised from one type of chemo to another.

B12. CS, Document B, Section B.3.5.1.1, page 131: Please clarify the method of moments approach used to estimate wastage for treatments that are administered with the use of vials. In particular, provide justification for assumptions regarding distributions employed and provide details of the sensitivity of estimates for wastage to these assumptions.

[Company: please enter your answer to this question here]

B13. In the section on subsequent treatment (Submission Document B, Section B 3.5.4.1, page 139), you make the case there are no data on what was used after lorlatinib in the main clinical study. Can you confirm no data were collected at all in the clinical study? Are there any data on what was used after lorlatinib in any other data set such as an 'early use' programme?

[Company: please enter your answer to this question here]

B14. In modelling subsequent treatment after PDC you use the data from TA 584. Given that PDC is intended to represent 'usual care' it seems strange there are no data from routine data sources or from Clinical Expert opinion. TA584 also seems an inappropriate choice given it is an immunotherapy in 1st line use. Please clarify why you selected this for the base case and consider a sensitivity analysis with NHS data instead.

[Company: please enter your answer to this question here]

B15. Considering Profile 1001 and Profile 1005 as the source of OS data for the PDC arm of the model, is it possible to comment on the subsequent treatments available to patients in the Profile trials following progression, and whether the modelled treatments are consistent with these with respect to expected impact on OS.

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1 Submission Document B, Table 3 on page 23 appears to suggest ALK positive cancers are a sub-set of adenocarcinoma, because row E comes after row D – is this correct?

[Company: please enter your answer to this question here]

C2. Submission Document B, Table 60 on page 140, in row 1 of the data, the 2nd figure across is 60, but should this be 40% of 60, i.e. 24?

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Clarification questions

August 2019

File name	Version	Contains confidential information	Date
ID1338 lorlatinib clarification letter final_PFIZER_response__AiC_CiC_Aug2019		No	9th Aug 2019

Section A: Clarification on effectiveness data

A1. In the justification of comparators (Submission Document B, page 85), you say: "Due to increased use of ALK testing and increased availability of targeted treatments in UK clinical practice, a small and decreasing proportion of patients are likely to have received chemotherapy prior to an ALK TKI."

This relates to Figure 2 on page 26 of Submission Document B. Please quote data on NHS use to support your statement (e.g. from the compassionate use programme).

The UK ALK database (Gomes et al., 2019) collected data to September 2018 and states that 45% of the group of patients in that sample had chemotherapy before ALK inhibitors. The Pfizer compassionate use program (CUP) collected data from [redacted] to [redacted] and reports that [redacted] out of [redacted] patients ([redacted]) in this cohort of patients received chemotherapy before an ALK inhibitor.

Neither provides details of the chemotherapy that was given. In the case of Pemetrexed (or pemetrexed and cisplatin/carboplatin or "PDC"), clinicians suggest that if enough time has lapsed patients can become sensitive to pemetrexed again and be retreated. Patients are more likely to respond to PDC than pemetrexed alone or docetaxel; and the former are more tolerable that docetaxel.

It is important to note that as patients die and the patient pathway changes, the pre-treatment patterns of the ALK-positive population are shifting at a fast pace. The abstract for the UK ALK database (Gomes et al., 2019) states clearly that "45% of patients received chemotherapy prior to an ALK inhibitor, *12% of which after the approval of 1st line ALK inhibitors*". This suggests that even less than 12% of the current population of patients eligible for lorlatinib will have received chemotherapy in first line.

As another illustration of how fast pre-treatment patterns are shifting in this population, the Pfizer CUP reports that [redacted] of patients received crizotinib in first line. It is widely accepted that patients treated with a 2nd generation ALK-inhibitor today would almost certainly not have received crizotinib in 1st line. Indeed, this is a key argument in the recent 2019 NICE recommendation for Brigatinib (post-crizotinib treatment):

"The committee was aware that crizotinib was no longer standard care for ALK-positive NSCLC because most people now start treatment with alectinib…Also, the committee was aware that the population eligible for brigatinib after crizotinib is small (less than 50 people) and will decrease as fewer people start treatment with crizotinib" (page 15, FAD).

The evidence above suggests that the vast majority of the ALK-positive population, that would be treated with lorlatinib if approved for use in the NHS, would not be a chemotherapy pre-treated population. As stated in the company submission, the population pre-treated with chemotherapy in first line is likely to be shrinking at least as quickly as the population pre-treated with crizotinib in first line.

A2. Submission Document B, Table 1, Comparators. Based on the most recent NHS data available to the company, can the company please provide an estimate of the percentage of NHS patients potentially eligible for lorlatinib that will have had prior chemotherapy or prior immunotherapy.

Please see our response to the above question. With respect to immunotherapies, the ALK UK database reported 6% pre-treatment with immunotherapies and the Pfizer CUP does not report any immunotherapy use in previous lines before lorlatinib use.

It is therefore reasonable to assume that virtually no patients receiving lorlatinib will have received chemotherapy or an immunotherapy in previous lines.

A3. In appendix D.1.3, the company indicate that six RCTs and 87 non-RCTs were identified as eligible for the clinical review, but only evidence from study 1001 is a presented in the clinical effectiveness section of the submission. Can the company please clarify why none of the other identified studies have been included or discussed in clinical effectiveness section?

Although six RCTs and 87 non-RCTs were identified as eligible for the clinical review, it is important to realise that the inclusion and exclusion criteria include a variety of treatments beyond lorlatinib. No other trial evidence other than Study 1001, with lorlatinib as an intervention, were identified. Hence, the Study 1001 is the only trial with lorlatinib that is relevant to the indication in this appraisal.

A4. Document B, Section B.2.4.1, page 37: Please clarify why the PRO evaluable set includes all enrolled patients and is not limited to EXP3B:5. As the different cohorts have had different prior treatment pathways, their baseline quality of life at starting lorlatinib may be different so please clarify why EXP-1 to EXP-6 can be pooled.

The PRO evaluable set is defined as all enrolled patients who received at least one dose of lorlatinib and completed a baseline and at least one post-baseline PRO assessment.

Please refer to the documents provided by Pfizer, corresponding to the PRO evaluable set for the pooled EXP-3B:5 cohort of patients only (February 2018 data cut):

- Plot of Plot of Mean Change from Baseline (+/-) SE over time for EORTC QLQ-C30 (Phase 2)
- Summary of EORTC QLQ-C30 Scales Change (Phase 2)
- Summary of EORTC QLQ-LC13 Scales Change (Phase 2).

The EXP-3B:5 data is the most appropriate pooled cohort because it is consistent with the regulatory license for lorlatinib and the population relevant to this appraisal. In addition, the following tables were provided within the submission for each of the cohorts EXP-3B, EXP-4 and EXP-5 (February 2018 data cut):

- Summary of EORTC QLQ-C30 Scales Change (Phase 2)
- Summary of EORTC QLQ-LC13 Scales Change (Phase 2).

A5. Document B, Section B.2.5.5, page 50: Please clarify why the data cut for the patient reported outcomes is from 15 March 2017 and the efficacy data were from 2 February 2018 (page 38). Please explain why the same data cut (i.e. February 2018) wasn't used for the PRO outcomes. Please also clarify why you were not able to use a more recent data cut in this submission.

The PRO data that informs the submission has been updated to the previous data cut – please see the response to A4 and the documents attached to this response.

The last available data cut and closest to the submission date for this appraisal was February 2018 cut. The next data cut is planned for the end of 2019. The next

planned data cut after this, which will be the last for the study, is currently scheduled for around September 2020.

A6. Document B, Section B.2.5.1.1, table 10, page 39: There were [redacted] treated in EXP3B:5, and in table 10, the last two rows add to [redacted] ([redacted] study discontinued, [redacted] study ongoing at data cut-off). Please explain why these two rows do not total to [redacted]. Please also clarify what is meant by study discontinued in this case and how it differs from treatment discontinuation.

Study 1001 considers two different time periods: study period and treatment period. The study period starts when a patient is enrolled in the study; then patients are treated and those who discontinue treatment may or may not remain in study for collection of additional data. Limited data collection is done after treatment discontinuation, e.g. to collect survival follow up. The row relating to “treatment discontinued” concerns only patients who started treatment; the row relating to “study discontinued” concerns patients who started the study, regardless of whether they started treatment or not.

One patient ([redacted]) enrolled into Study 1001 (EXP-4 group) and died before receiving the first dose of the study drug; the patient was not included among the 139 treated patients but was counted among the patients who discontinued the study.

A7. Appendix E, Table 29, page 86: Please provide the confidence intervals (e.g. 95%) for each of the hazard ratios presented. Please clarify how the subgroup analysis has been carried out, by providing an explanation of the models fitted. This analysis showed a difference in survival between the ECOG performance status groups, please clarify what impact this has when looking at the effect of lorlatinib.

The 95% confidence intervals have been added to Table 29 (see Table 1 below) which included the hazard ratios and p-values from univariate Cox proportional hazards models for lorlatinib patients in cohorts EXP-3B:5. For each variable (sex, age, race, ECOG PS, brain metastases, adenocarcinoma and weight) and for each outcome (OS and PFS) a separate Cox proportional hazards model was fitted including only a covariate for the variable. The coxph() function from the Survival package in R was used. From these fourteen different models, hazard ratios, confidence intervals and p-values were produced.

For the outcome of overall survival, the confidence intervals for ECOG PS do not include one and the p-values are both less than 0.05 suggesting that ECOG PS is prognostic of survival in Study 1001 (although this does not consider multiple testing). As ECOG was identified as a potential prognostic factor for outcomes it is therefore considered important to include ECOG PS in the MAIC analyses which require the identification of all prognostic factors and treatment effect modifiers.

Table 1. Updated Table 29 from Appendix E. Post-hoc subgroup analyses (EXP-3B:5)

Model	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ICR = independent central review; OS = overall survival; PFS = progression-free survival; PS = performance status
Highlighted cells indicate p<0.05

A8. Appendix D, Section D.1.4.2.2.1, Table 21 and table 22, page 76. Please provide the confidence intervals for each hazard ratio presented.

The confidence intervals are provided in the updated tables below.

Table 2. Updated Table 21 from Appendix D. HRs and p-values from univariate Cox proportional hazards models for each covariate (8 models for OS and 8 models for PFS based on independent central review) for lorlatinib patients in cohorts EXP-2 to EXP-5

Model	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other) Race (White)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (1) ECOG PS (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9) BMI (18.5-24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival
Note: p-values <0.05 are shown in bold

Table 3. Updated Table 22 from Appendix D. HRs and p-values from the two multivariate Cox proportional hazards models for lorlatinib patients in cohorts EXP-2 to EXP-5

Coefficient	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (White)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (18.5-24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival
Note: p-values <0.05 are shown in bold.

A9. PRIORITY - Document B, Section B.2.8.3, table 24, page 57: In the table, for the ALUR study, ECOG PS 1/2 is provided as 14.3%. However, in Appendix D, section D.1.4.1.1, table 15, page 62, the second column for ALUR suggests

ECOG PS = 2 is 14.3% and ECOG = 1 is 54.3%, so ECOG 1/2 should be 68.3%. Please explain why 14.3% was presented in section B.2.8.3. If it should have been 68.3% please explain what impact this would have had on the MAIC analysis and if relevant, please revise the analysis and any subsequent analysis that rely on the MAIC.

Pfizer confirms the error in Table 24 of Section B.2.8.3; the percentage of ALUR subjects with ECOG PS 1/2 should be 68.6% (24 subjects out of 35 had ECOG PS 1 or 2 at baseline) instead of 14.3%. However, as matching was performed by pooling the 35 ALUR subjects and the 116 ASCEND-5 subjects (where WHO is used as a proxy for ECOG), the pooled performance status value is influenced more heavily by the ASCEND-5 study and as such the change had a minor impact on the results. The matching percentage of ALUR/ASCEND-5 subjects with ECOG PS 1/2 was corrected from 46.4% to 58.9% and updated results are provided in the table below.

The MAIC was not used to inform the base-case and so this does not impact the base-case results submitted by the company.

Table 4. Updated Table 25. Unadjusted and adjusted HR results for progression-free survival

Weighted matching cohort (Study 1001)	Naïve		Adjusted		Adjusted (updated based on correct % of ALUR subjects with ECOG 1/2)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; EXP = expansion; HR = hazard ratio
*bootstrapped 95% CI

A10. Document B, Section B.2.8.3, table 24, page 57: Please provide the source file for the PROFILE study which provides the summary statistics for this study that are presented in table 24. The ERG would like to cross-check the entries and this is not possible at the moment as the reference for the data is not provided. The table footnote states 'These baseline characteristics are from the 37 patients that did not continue crizotinib but received systemic therapy and cannot be found in Ou et al 2014.

The data in the final row of Table 24 are the baseline characteristics corresponding to the patients in the retrospective study Ou et al., 2014 (i.e. retrospective analysis of

PROFILE 1001/1005) who did not continue crizotinib but received “systemic therapy”. These baseline characteristics cannot be found in the Ou et al., 2014 publication where baseline characteristics are only reported for the wider cohort of patients. Instead these data we’re calculated by the Pfizer global statistical team - using the raw data from this retrospective analysis - and provided to the Pfizer UK team. Therefore, there is no source for the purposes of cross-checking.

A11. Document B, Section B.2.8.3, table 24, page 57: Please provide the source reference for the summary statistics presented for the Study 1001, EXP 2 and EXP 3A cohorts.

The summary statistics presented for the Study 1001 EXP 2 and EXP 3A cohorts were not presented in the clinical study report; they have been summarised based on the patient level data available on file for PROFILE Study 1001.

A12. PRIORITY - Document B, Section B.2.5.1.2, table 11, page 39: Please provide a clear justification of why it is appropriate to pool data from EXP-3B, EXP-4, and EXP-5 to form the EXP-3B:5 cohort, with reference to the statistical significance of any differences in the characteristics of the individual cohorts (e.g. those identified in appendix E) and any expected differences in median survival.

The primary reason for pooling the EXP-3B:5 cohorts was that this collection of patients corresponds to the licence population, based on pre-treatment patterns.

Table 16 (see response to B8) presents summary statistics for each of the exploratory cohorts and shows no great variation in PFS and OS. In addition, differences in overall survival and progression-free survival outcomes split across the three cohorts were assessed and are presented below. Both the Kaplan-Meier graphs (Figure 1 and Figure 2) and hazard ratios for OS and PFS (Table 5) suggest that there are no statistically or clinically meaningful differences in overall survival and progression-free survival between the cohorts EXP-3B, EXP-4 and EXP-5.

Figure 1. Kaplan-Meier plot of overall survival for EXP-3B, EXP-4 and EXP-5

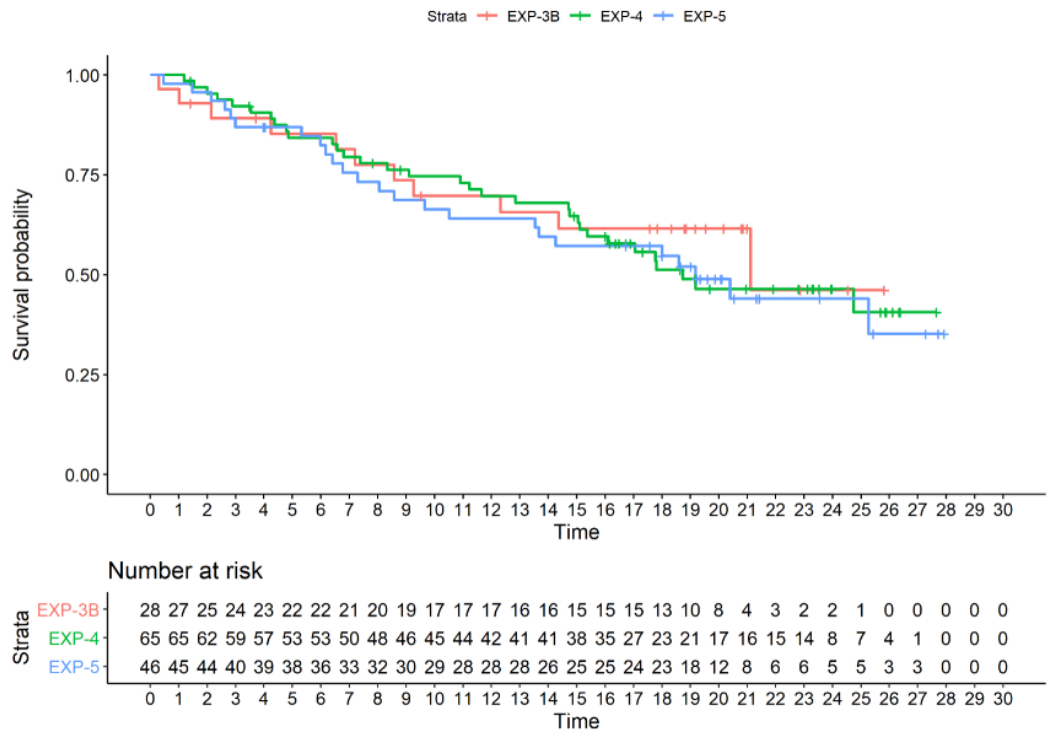

Figure 2. Kaplan-Meier plot of progression-free survival for EXP-3B, EXP-4 and EXP-5

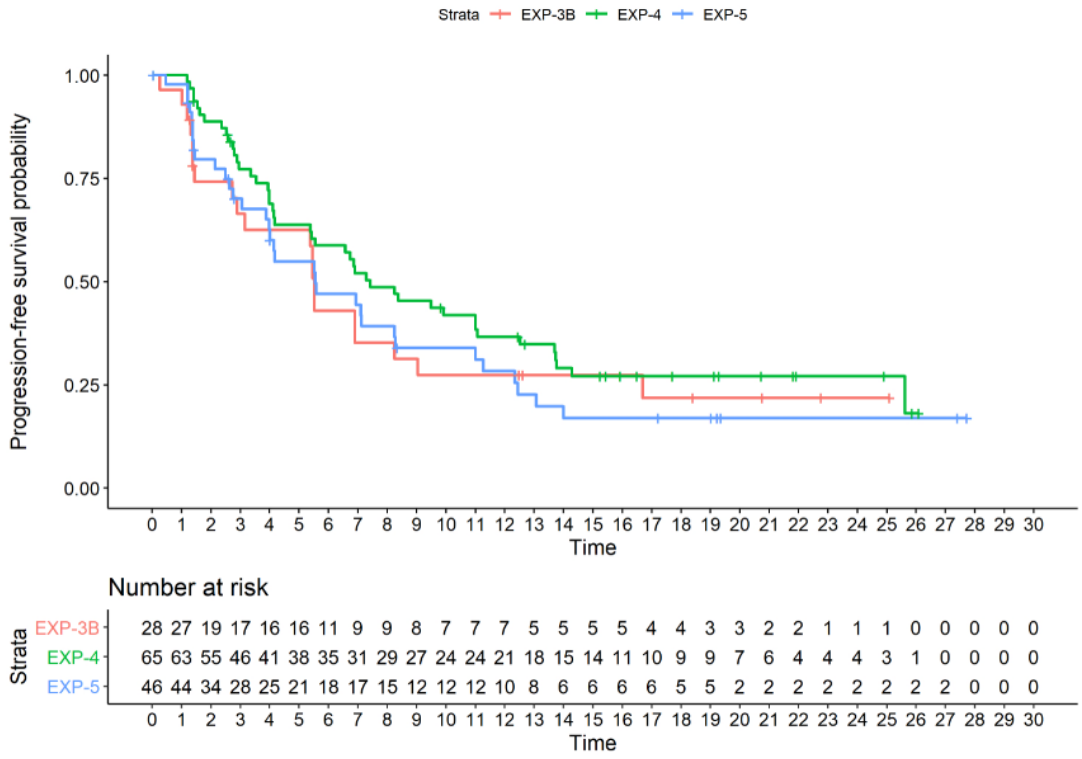

Table 5. HRs, 95% CIs and p-values from two univariate Cox proportional hazards models (one model for overall survival and one model for progression-free survival) where cohort was the only covariate included in each model

Coefficient	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
EXP-3B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival
Note: EXP-5 is the reference cohort

A13. PRIORITY - Appendix D, Section D.1.4.2.2 pages 69-80. Please provide further detail on exactly how the MAIC methodology was implemented in the submission. Please provide statistical code that you used. Please explain why matching was carried out for the EXP2/3A cohort in addition to the relevant EXP 3B:5 cohort. Please expand on the reasoning for the four matching characteristics. Appendix D suggests ECOG and BMI should be used, but analysis doesn't highlight gender, race or brain metastases as significant predictors. Please clarify why these four were chosen and also explain why the exploratory analysis is on EXP2:5 and not just EXP 3B:5.

Details of the MAIC methodology and how the MAIC results were implemented as scenario analyses is provided in Figure 21 and throughout section B.3.3 of the company submission. Results of the MAICs are provided in Table 41 of the submission dossier for PFS and Table 45 for OS.

In each analysis, the result of the MAIC was a hazard ratio (lorlatinib versus PDC). As Study 1001 provided data for lorlatinib, and PDC was the treatment we attempt to derive outcomes for, this HR was applied as a reciprocal to the lorlatinib survival curve to estimate survival for PDC.

For example, Table 41 of the company submission indicates that in Method 1 (applying the MAIC HR from the EXP-2:3A cohort), a HR of 0.20 was obtained for lorlatinib versus PDC in PFS. This suggests that lorlatinib has a higher expected PFS curve than PDC (i.e. PDC patients are more likely to experience an event). To estimate the PFS of patients receiving PDC a HR of (1/0.20 = 5) was applied as a power to the base case lorlatinib PFS curve at each individual cycle to obtain an estimate of PFS for PDC over time. The results of the MAIC methods are

summarised in Figures 32 and 49 of the company submission, for PFS and OS respectively.

The justifications for matching on both the EXP2/3A and EXP 3B:5 populations are detailed in Section B.2.8.2 of the submission:

- The majority of patients in ALUR, ASCEND-5 and PROFILE 1001/1005 studies received both chemotherapy and crizotinib previously and so arguably the most precise Study 1001 cohort for matching is EXP-3A (i.e. previous crizotinib and one or two regimens of chemotherapy given before or after crizotinib). However, a pooled EXP-3A and EXP-2 (i.e. relapse after crizotinib only) cohort was used to ensure that the sample size on which matching was conducted was not too small (effectively doubling the matching cohort). The larger the number of matching variables in proportion to the size of the Study 1001 matching sample, the more extreme the weights that are required and the lower the effective sample size for the efficacy analysis. In the extreme, the matching may not succeed in matching to all characteristics. In addition, outcomes are not expected to vary greatly with pre-treatment by crizotinib alone versus crizotinib and at least one regimen of chemotherapy, therefore matching to the pooled EXP2 and 3A cohorts is considered appropriate. This is consistent with the license indication and clinical expert opinion.

- An additional analysis was conducted that uses the pooled EXP-3B:5 as the matching cohort instead of EXP-2:3A. This analysis requires the assumption that only patient characteristics and not treatment line – i.e. pre-treatment by different ALK TKIs – affects outcomes. Each MAIC is summarised in Table 23. Unadjusted or 'naïve' results are also presented for comparison. The EXP-3B:5 cohort was less of a match to the comparator sources than the EXP-2:3A cohort, in terms of previous treatments. However, the sample size was substantially larger, and the matching cohort reflects the sample used in the cost-effectiveness model and is most relevant to the license.

The choice of the four matching characteristics was based on a combination of clinical feedback, analyses performed on the lorlatinib IPD, prognostic factors/treatment effect modifiers already identified in the disease area and the

balance of baseline characteristics between the lorlatinib patients and the comparator evidence. Further detail on the choice of the four matching characteristics can be found in Section B.2.8.3 of the submission. ECOG PS and BMI were identified as potential important effect modifiers/prognostic factors based on the lorlatinib IPD. Based on clinical feedback, the most important factors to match on were ECOG PS, brain metastases and race. Matching variables identified in literature such as Tan et al., (2016) were age, gender, race, ECOG PS, prior regimens and adenocarcinoma. Variables considered were therefore:

- ECOG PS
- BMI (not reported in the comparator studies)
- Brain metastases
- Race
- Age (considered sufficiently consistent across the lorlatinib IPD and the comparator studies)
- Gender
- Prior regimens (incorporated into the analyses by comparing to the most similar lorlatinib cohorts based on prior regimens)
- Adenocarcinoma (not reported in PROFILE 1001, but considered likely to be sufficiently consistent based on the clear comparability of the comparator studies)

The exploratory analyses were performed for EXP-2:5, as well as EXP-3B:5, to allow for a larger sample size. In addition, because the MAIC procedure was also conducted using the EXP2-3A cohort it is important to understand the impact of these characteristics in the wider population.

A14. PRIORITY - Appendix D, Section D.1.4.2.2.3, page 77 states that for each of the four matching characteristics, the percentages of patients after matching are the same as the percentage of patients in the pooled Novello and

Shaw population. Please in a single table provide the percentages for these four characteristics for each of Loratinib (original), Lorlatinib (after matching), with Novello and Shaw separately and pooled.

Tables 23 and 24 have been updated (see Table 6 and Table 7 below) with the characteristics of patients in Novello and Shaw separately and pooled. Both tables have also been updated based on the changes made and discussed in response to question A9.

Table 6. Updated Table 23. Baseline characteristics before and after matching EXP-2:3A (PFS outcome)

	N	ECOG PS 1/2 (%)	Asian (%)	Male (%)	Brain metastases (%)
ALUR chemotherapy population	35	68.6	20	48.6	74.3
ASCEND-5 chemotherapy population	116	56	33	47	59
Pooled ALUR and ASCEND-5 chemotherapy populations	151	58.94	29.80	47.68	62.91
Lorlatinib population (EXP-2 and EXP-3A) before matching	59	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib population (EXP-2 and EXP-3A) after matching with the chemotherapy population	56	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG = Eastern Cooperative Oncology Group Performance Status; EXP = expansion; N = number of patients; PFS = progression-free survival

Table 7. Updated Table 24. Baseline characteristics before and after matching EXP-3B:5 (PFS outcome)

	N	ECOG PS 1/2 (%)	Asian (%)	Male (%)	Brain metastases (%)
ALUR chemotherapy population	35	68.6	20	48.6	74.3
ASCEND-5 chemotherapy population	116	56	33	47	59
Pooled ALUR and ASCEND-5 chemotherapy populations	151	58.94	29.80	47.68	62.91
Lorlatinib population (EXP-3B:5) before matching	139	[redacted]	[redacted]	[redacted]	[redacted]
Lorlatinib population (EXP-3B:5) after matching with the chemotherapy population	134	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG = Eastern Cooperative Oncology Group Performance Status; EXP = expansion; N = number of patients; PFS = progression-free survival

Section B: Clarification on cost-effectiveness data

B1. You have used previous STAs in ALK +ve NSCLC for resource use and utility values. Please can you clarify what values you used from those STAs?

The sources of all resource use and utility inputs are summarised in

Table 8; the sources of resource use methodology from previous STAs are summarised in Table 9.

Table 8: Resource use and utility values from prior STAs

Parameter		Value	Reference in submission	Reference
Resource use				
Split of cisplatin/carboplatin		46.15% of patients receiving carboplatin	B.3.5.1.1 Acquisition costs	PROFILE 1014 (TA406)[1]
		53.85% of patients receiving cisplatin		
Docetaxel stopping rule		6 x 21-day cycles	B.3.5.1.1 Table 53: Dosing information and stopping rules	TA584[2]
Monitoring in progression free	Proportion requiring a GP visit	10%	B.3.5.2 Health-state unit costs and resource use (Table 56)	TA536, TA529, TA500, TA406, TA395, TA296.[1, 3-7]
	Proportion requiring an outpatient visit	100%		
	Proportion requiring a cancer nurse	20%		
	Proportion requiring a complete blood count	100%		
	Proportion requiring biochemistry	100%		
	Proportion requiring a CT scan	30%		
	Proportion requiring an X-ray	100%		
	Frequency of each GP visit	Monthly		
	Frequency of each outpatient visit	0.75 times per month		
	Frequency of each cancer nurse	Monthly		
	Frequency of each complete blood count	0.75 times per month		
	Frequency of biochemistry	0.75 times per month		
	Frequency of each CT scan	0.75 times per month		
	Frequency of each X-ray	0.75 times per month		

Parameter		Value	Reference in submission	Reference
Monitoring in progressed disease	Proportion requiring a GP visit	28%	B.3.5.2 Health-state unit costs and resource use (Table 56)	TA536, TA529, TA500, TA406, TA395, TA296.[1, 3-7]
	Proportion requiring an outpatient visit	100%		
	Proportion requiring a cancer nurse	10%		
	Proportion requiring a complete blood count	100%		
	Proportion requiring biochemistry	100%		
	Proportion requiring a CT scan	5%		
	Proportion requiring an X-ray	30%		
	Frequency of each GP visit	Monthly		
	Frequency of each outpatient visit	Monthly		
	Frequency of each cancer nurse	Monthly		
	Frequency of each complete blood count	Monthly		
	Frequency of biochemistry	Monthly		
	Frequency of each CT scan	0.75 times per month		
	Frequency of each X-ray	0.75 times per month		
Mean duration (weeks) of docetaxel treatment given in subsequently		18.00	B.3.5.4.1 Subsequent treatments (Table 60)	TA584[2]
Mean duration (weeks) of pembrolizumab treatment given in subsequently		21.59		
Mean duration (weeks) of atezolizumab treatment given in subsequently		35.80		
Utilities				
Alternative utility applied during progression free	Mean	0.713	Appendix I (Table 48)	TA395[8]
	SE	0.071		
	Mean	0.640		

Parameter		Value	Reference in submission	Reference
Alternative utility applied during progressed disease (LUME LUNG-1)	SE	0.010	B.3.4.3 Health-related quality of life studies	TA416, TA347. [15, 24]
Alternative utility applied during progressed disease (TA422)	Mean	0.610		TA422[9]
	SE	0.061		

Table 9: Resource use methodology from prior STAs

Parameter	Value	Reference in submission	Reference
Resource use			
Dispensing fee per administration methodology	£9.60 per administration	B.3.5.1.2 Administration costs	TA536, TA529, TA520, TA500, TA406[3, 7, 10, 11]
Alternative administration cost methodology	£42.50		TA571(Brigatinib ERG report)[12]
Methodology and frequencies of medical resources (progression free and progressed)	Table 56 within the submission dossier	B.3.5.2 Health-state unit costs and resource use (Table 56)	TA536, TA529, TA500, TA406, TA395, TA296.[1, 3-7]
Costing methodology as per Brown 2013	Table 57 within the submission dossier	B.3.5.2 Health-state unit costs and resource use (Terminal costs)	TA536, TA531, TA520, TA484, TA483, TA428, TA416, TA411, TA374. [3, 13-20]
AE inclusion methodology	Grade ≥3 that occurred in >5% of patients in at least one treatment of interest	B.3.5.3 Adverse reaction unit costs and resource use	TA536, TA406, TA395.[3, 8, 10]
AE unit cost methodology	Table 58 within the submission dossier		TA500, TA416, TA395.[8, 11, 15]
Costing methodology as per Georgiou and Bardsley 2014	Assuming a cost of £7,653 when inflated to current prices	B.3.5.2 Health-state unit costs and resource use (Terminal costs)	TA529, TA406. [21, 22]
Costing methodology of subsequent therapy	Table 60 within the submission dossier	B.3.5.4.1 Subsequent treatments (Table 60)	TA584[2]

Extrapolations of PFS, OS and ToT

B2. You fit parametric curves to available clinical data for PFS, OS and ToT in Submission Document B. In addition to graphs with the fitted curves you provide helpful statistics on predicted median and mean figures as well as

rates at specific 'landmark' time points (see e.g. Table 42, page 99 for PFS). Please can you add the predicted rates at 10 years to each of these tables.

Table 10. Updated table 40: Mean, median and landmark values and AIC and BIC statistics for lorlatinib PFS parametric survival models

Model	AIC	BIC	Mean PFS (months)	Median PFS (months)	Proportion progression-free and alive at each landmark value (%)				
					6 months	1 year	2 years	5 years	10 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = progression-free survival

Table 11. Updated Table 42: Mean, median and landmark values and AIC and BIC statistics for PDC PFS parametric survival models

Model	AIC	BIC	Mean PFS (months)	Median PFS (months)	Proportion progression-free and alive at each landmark value (%)				
					6 months	1 year	2 years	5 years	10 years
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = progression-free survival

Table 12. Updated Table 43: Mean, median and landmark values and AIC and BIC statistics for lorlatinib ToT parametric survival models

Model	AIC	BIC	Mean ToT (months)	Median ToT (months)	Proportion still on treatment at each landmark value (%)				
					6 months	1 year	2 years	5 years	10 years
Generalised gamma	[redacted]								
Exponential	[redacted]								
Weibull	[redacted]								
Log-normal	[redacted]								
Log-logistic	[redacted]								
Gompertz	[redacted]								

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; ToT = time on treatment

Table 13. Updated Table 44: Mean, median and landmark values and AIC and BIC statistics for lorlatinib OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)					
					6 months	1 year	2 years	3 years	5 years	10 years
Generalised gamma	[redacted]									
Exponential	[redacted]									
Weibull	[redacted]									
Log-normal	[redacted]									
Log-logistic	[redacted]									
Gompertz	[redacted]									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival

Table 14. Updated Table 46: Mean, median and landmark values and AIC and BIC statistics for PDC OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)					
					6 months	1 year	2 years	3 years	5 years	10 years
Generalised gamma	[redacted]									
Exponential	[redacted]									
Weibull	[redacted]									
Log-normal	[redacted]									
Log-logistic	[redacted]									
Gompertz	[redacted]									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion, OS = overall survival; PDC = platinum doublet chemotherapy

B3. In selecting which approach to use to predict PFS, OS and ToT you place emphasis on the views of clinical experts in stating what is plausible. While you state what meetings with clinical experts were held (Section B 3.10, page 151), and you report a summary of the experts' views, several points were unclear:

- **In cases where a numerical estimate of a rate was obtained, how was this done?**
- **If an expert gave a view, what was this based on – for example, had each expert used lorlatinib, in how many patients and what is the longest follow-up they have observed on a patient they initiated?**
- **Where expert views diverged, how did you handle this in reporting opinion in the submission?**

Clinical validation of overall and progression-free survival extrapolations was conducted independently with clinical experts via Webex in February 2019 and April 2019 (i.e. 2 times in total). It was incorrectly reported in the dossier that model survival curve validation also took place in the earlier Sept 2018 validation teleconference.

The KM was presented with each of the 6 survival functions overlaid (up to 240 months) with the mean and median OS reported and 6-month, 1 year, 2 year, 5 year and 10 year proportions. The following question was posed: *"Based on your experience, which curves best represent overall survival that you would expect to see in this population of patients? Are there distributions you would rule out due to unrealistic predictions?"*

Clinicians tended to focus on the proportions alive (or PFS) at each time point and the ordering of curves and this formed the basis for their preference for a curve. A summary of the notes from the 2 clinician interviews, with respect to PFS and OS curve selection (PDC and Lorlatinib arm), are provided below.

Table 15. OS and PFS curve validation notes summary

Clinician 1 (February 2019 teleconference):	• PFS for Lorlatinib: Gompertz (2nd choice: Generalised Gamma) • PFS for PDC: Exponential (2nd choice: Weibull) • OS Lorlatinib: Log-normal (2nd choice: log-logistic) • OS PDC: Weibull (2nd choice: Gompertz)
Clinician 2 (April 2019 teleconference):	• Difficult to decide between PFS and OS for PDC (curves similar) • Generalised Gamma is reasonable for PFS (lorlatinib) • Lorlatinib OS: 10% alive at 10 years (lognormal or log-logistic) more reasonable than 2% at 10 years (exponential)

Based on previous communications, the clinicians had experience with ALK-inhibitors in general. Experience with Lorlatinib among the clinicians in the validation teleconferences was as follows:

- September 2018: clinician 1 had treated 6 patients with lorlatinib, clinician 2 had treated no patients with lorlatinib
- February 2019: clinician had no experience with lorlatinib patients
- April 2019: clinician had treated 2 patients with lorlatinib.

B4. Related to B1 above, if possible, please provide a summary of the questions that clinical experts were asked as part of the model validation process as well as collated responses to each question.

Please see the collated summary notes from the advisory board and 3 clinician interviews. Note that the September 2018 teleconference was a validation for 2 medicines, with a focus on the other medicine and so the notes are relatively short for lorlatinib. A clinician validation deck is also provided.

[redacted]

B5. It was not clear if you had used the previous ALK +ve NSCLC STAs to help cross validate the PFS and OS predictions of your model for 'usual care'. Can you provide that comparison, or if you have already done this make it more explicit?

There are six prior STAs which have been conducted in the ALK+ population. Of these, three are in the 1L setting[12, 13, 31] and three are in the 2L setting[8, 11, 32]. As the indication of lorlatinib is for patients that have been previously treated with at least one prior TKI (which isn't crizotinib), the appraisals conducted in the first line setting are not relevant and should not be used to validate predictions. The remaining three appraisals were explored to try to help validate OS and PFS, however none of these were relevant (listed below).

1. TA571[32] – Brigatinib for treating ALK+ advanced NSCLC after crizotinib:

   TA571 compared brigatinib to ceritinib. Brigatinib was informed with data from the ALTA study and Study 101 which were single arm studies. ASCEND-2 and ASCEND-5 trials were used to estimate the effectiveness of the ceritinib arm within the submission. Therefore, no relevant data were identified within this STA which could be used to cross-validate the PFS and OS predictions of the 'usual care' arm of the model.

2. TA422[11] – Crizotinib for previously treated ALK+ advanced NSCLC:

   The final scope for TA422 indicated that relevant comparators for crizotinib were docetaxel, erlotinib and best-supportive care. TA422 indicated that clinical evidence for docetaxel was informed from PROFILE 1007[33], PROFILE 1005 and PROFILE 1001. However, none of these were relevant for validation:

- PROFILE 1001 was a Phase I single-arm study in ROS1 patients receiving crizotinib and therefore could not be used to validate the lorlatinib model predictions for 'usual care'.
- PROFILE 1005 – was a single-arm crizotinib study and therefore was not relevant to validate chemotherapy survival estimates.
- PROFILE 1007 was a phase-3, open-label trial comparing crizotinib with pemetrexed or docetaxel. Inclusion criteria were patients with locally advanced or metastatic ALK+ lung-cancer who had received one-prior platinum-based regimen. The chemotherapy arm of the PROFILE 1007 is therefore not a relevant comparison in this setting of lorlatinib versus PDC as the patients within PROFILE 1007 have not had prior treatment with an ALK-inhibitor.

3. TA395[8] – Ceritinib for previously treated ALK+ NSCLC:

The final scope for ceritinib for previously treated ALK+ NSCLC indicated the appropriate comparison was best-supportive care (BSC) – which was no active treatment. A systematic literature review (SLR) was conducted which identified 126 RCT and 147 non-RCT studies which may be relevant sources of clinical evidence. Of the studies found only the Ou et al publication was considered relevant. This is the same study that has been used to derive OS for the PDC arm within the current appraisal. Several limitations were acknowledged in use of the Ou et al paper, namely that only OS was presented. In the absence of any PFS data identified within the SLR, to inform PFS for BSC, a placebo arm of the phase-3 erlotinib study reported in Shepherd et al[34] was used. It was not considered appropriate to use this study to validate the 'usual care' arm for two fundamental reasons. Firstly, a placebo arm would not accurately represent active PDC treatment. Secondly, the study is in an EGFR population which the TA395 appraisal (and clinical expert opinion) has acknowledged is a distinct population to ALK+ NSCLC.[8]

Since the appraisal of ceritinib in 2015 and the SLR conducted for this appraisal, only two further studies were identified as relevant; Novello et al and Shaw et al (which present patients treated with a prior TKI). These studies provided PFS data to inform a chemotherapy arm within the model. No further OS data have been

identified since the Ou et al study. Therefore, the most relevant data has been used within this appraisal.

B6. PRIORITY - Document B, Section B.3.3.3.1, page 91: Regarding the choice of parametric curve to derive progression free survival for lorlatinib, the submission states "When shown visual extrapolations and proportions in PFS, clinical experts favoured the generalised gamma or the Gompertz curve." Please clarify the number of clinical experts favouring each curve and their stated reasons for supporting this long-term projection.

Please see the response to question B3.

B7. PRIORITY - Document B, Section B.3.3.3.2, page 104: Within the submission it is stated that "Clinical expert opinion suggested there would be very few patients remaining on a targeted treatment for 10 years or more." Please clarify the individual estimates of each clinical expert regarding the proportion remaining on a targeted treatment after 10 years, 5 years, and 2 years.

The source of this clinical validation was the 4 conversations between a Pfizer medical colleague and practicing consultant medical oncologists who treat NSCLC patients (May 2019). There was no formal curve presentation as with PFS and OS (described in the response to B3).

These conversations suggested that, anecdotally, there is great variation: some patients progress quickly on an ALK-inhibitor especially if they are heavily pre-treated; whilst there are others still on treatment for more than a year. In general, they suggested that relatively few patients would be on the same ALK-inhibitor for 10 years or more. This is consistent with the ALK UK database that reports the 95th percentile time on treatment as 14.9 months (see section B.3.3.3.2 of the company submission for a full description).

B8. PRIORITY - Document B, Section B.3.3.3.3, page 110: Regarding the choice of parametric curve to derive overall survival for lorlatinib, the submission states that "Even more importantly, clinical experts suggested that 10-year survival would be closer to [redacted] than [redacted] Therefore, the generalised gamma was selected to inform the base-case." Please detail the individual estimates

of 10-year survival provided by each clinical expert, along with any further information on the stated basis for each clinician's estimate and any estimates provided at other relevant time periods, such as those referred to in Table 44 (page 109). Please also clarify whether these estimates are assumed to be equally applicable to each of the three cohorts which form EXP-3B:5 and the rationale for this assumption.

Please see the response to question B3. EXP-3B:5 is the cohort that reflects the license and population most relevant to this appraisal and so clinical validation of PFS and OS extrapolations was only conducted for this cohort.

However, section B.2.5.4.4 of the company submission presents PFS and OS summary statistics for the combined EXP-3B:5 and each of the exploratory cohorts separately. These are presented in Table 16 and suggest there is not great variation in PFS and OS medians by exploratory cohort. For example, confidence intervals for median PFS cross for each exploratory cohort and so each cohort share a wide range of the same PFS median null hypotheses that cannot be rejected based on the trial evidence. 12 and 18-month OS probabilities also show no great variation between exploratory cohorts. Please also see the response to question A12.

Table 16. PFS and OS (Study 1001; Phase 2 ITT population)

Endpoint	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
Median (95% CI) PFS, months	5.5 (2.9, 8.2)	7.4 (5.4, 11.1)	5.6 (4.0, 8.3)	6.9 (5.4, 8.2)
Median (95% CI) OS, months	21.1 (12.3, NR)	18.7 (15.1, NR)	19.2 (10.5, NR)	20.4 (16.1, NR)
OS probability, % (95% CI)				
12 months	0.698 (0.485, 0.836)	0.696 (0.566, 0.795)	0.641 (0.482, 0.762)	0.678 (0.591, 0.750)
18 months	0.616 (0.402, 0.772)	0.512 (0.376, 0.633)	0.572 (0.414, 0.702)	0.556 (0.155, 0.306)

Abbreviations: CI = confidence interval; EXP = expansion; ITT = intention-to-treat; n = number of patients; NR = not reached; OS = overall survival; PFS = progression-free survival
Source: Pfizer Limited, 2018[95]

B9. PRIORITY - Document B, Section B.3.3.3.4, page 119: Regarding clinicians validating the decision to apply an independent chemotherapy curve with no population adjustment to represent progression free survival and overall

survival for PDC. Please clarify the process by which clinical experts validated this selection, the number of clinicians validating the selection, the preferred approach of clinicians who did not validate this selection, and the reasons provided by clinicians for their selection.

This was not explicitly validated by clinicians, but as explained in section B.3.3.3.4 was based on the suggestion by clinicians that patients receiving PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI. As reasoned in that section, this suggests that methods that do not adjust for differences in pre-treatment may not be required and so method 5 (no population adjustment) is favoured over method 6 (with population adjustment).

B10. In the additional comparison with ABCP, it is stated that a population adjustment was made to account for expected differences in PFS and OS between EGFR+ and ALK+ patients treated with ABCP. The population adjustment used hazard ratios for ALK+ versus EGFR+ patients treated with chemotherapy. Please can you:

a) **Comment on the comparability of patients and potential for bias in the indirect comparison of PFS between Novello & Shaw and the IMPRESS study.**

Patients characteristics of the studies used to derive a comparison of lorlatinib versus ABCP are presented in Table 17. To derive a HR for the population adjustment from EGFR+ to ALK+ for PFS, the Novello et al. (ALUR trial) and Shaw et al. (ASCEND-5) studies were used as the source for chemotherapy data in the ALK+ population; the Ou et al study was used as the source for OS. The IMPRESS study was used as the source of data for chemotherapy in the EGFR+ population for both PFS and OS.

The adjustment is reasonable if each population is balanced on most factors, except those factors that are consistently different between populations. This includes mutation status (ALK+ vs EGFR+) and incidence of brain metastases; the latter is expected to be significantly higher in the ALK+ population because of the way this

disease progresses – this is based on advice provided in an ad-board and multiple discussions with clinicians. The population adjustment should therefore not balance these fundamental differences between the populations.

To summarise, the use of the IMPRESS study seemed appropriate based on the following:

- There were similar patient numbers (pooled data [Novello and Shaw] vs IMPRESS)
- Both populations had received treatment with a targeted TKI treatment in the relevant mutation group (i.e. ALK and EGFR have different TKI targeted therapies): crizotinib in Shaw et al. and Novello et al., and gefitinib in IMPRESS
- See the response to B11. The Shaw et al. and Novello et al. studies can be considered reasonable proxies for platinum doublet chemotherapy (PDC) which is the chemotherapy arm in the IMPRESS trial
- Baseline characteristics were reasonably balanced:
    - The Shaw et al. study (which provides a heavier weight in the pooling of the Shaw and Novello studies given the larger sample size) has a higher proportion of patients with brain metastases than the IMPRESS study, which is expected given the ALK status of patients.
    - Age is broadly similar ranging from 54 in Shaw et al., 59 in Novello et al, and 58 years in the IMPRESS trial
    - There are some differences in the proportion of patients that are of a different race, notably there are differences in the proportion of Asian patients between Shaw et al and the IMPRESS study. This reflects the, well-established, higher prevalence of EGFR mutations in Asians[32]
    - ECOG PS 0 and 1 proportions are also similar between studies, 44% vs 40.2% and 52% vs 59.8% for Shaw et al. and the IMPRESS trial, respectively
    - The proportion male is relatively balanced and ranging from 47% in Shaw et al., 48.6% in Novello et al, and 36.4% in the IMPRESS trial

b) Comment on comparability of patients and potential for bias in the indirect comparison of OS between Ou et al and IMPRESS study.

In a similar way to PFS, a HR was derived to estimate a difference in OS for patients that are ALK+ versus those that are EGFR+. To summarise, the comparison with the IMPRESS study seemed appropriate based on the following:

- Both populations were in a similar treatment line, having been treated with a prior TKI (gefitinib in IMPRESS and crizotinib in Ou et al)
- See the response to B11 and B15. The Ou et al. study data can be considered a reasonable proxy for platinum doublet chemotherapy (PDC) which is the chemotherapy arm in the IMPRESS trial
- Baseline characteristics were reasonably balanced:
    - The proportion that were male were similar (36.4% in IMPRESS versus 40.5% in Ou et al)
    - Median age was very similar (58 in IMPRESS versus 54 in Ou et al)
    - Both Ou et al and the IMPRESS study included a majority of patients that were Asian (56.8% and 77.3% respectively), though there is some difference in the proportions
    - Patients had similar ECOG PS 1 proportions, however in general the scores suggest that patients in the Ou et al. analysis were less fit

c) Justify and provide any available evidence to support the application of these derived hazard ratios to ABCP treated patients.

Potentially relevant EGFR studies that could have been used to inform the population adjustment are limited to the IMPRESS, LUX-Lung 3 and LUX-Lung 6 studies. However, in LUX-Lung-6 a different platinum combination was assessed. LUX-Lung 3 is conducted in a treatment naïve patient population and so is not in the relevant line.

The remaining study, IMPRESS, is in the relevant line and has the correct chemotherapy arm. As such, this is considered the most appropriate data to form the comparison of EGFR+ to ALK+ patient populations.

The rationale for why a population adjustment is required is explained in the ABCP comparator appendix, but can be summarised as follows:

- EGFR and ALK-positive NSCLC are effectively different diseases. This is evidenced by the completely different targeted TKI treatments in each disease.
- There is evidence that ALK-positive patients experience higher rates of brain metastases[29] (around 2/3 in Study 1001) and have a less favourable prognosis[30]. This was supported by consultation with multiple clinical experts.
- The relative efficacy of ABCP varies depending on EGFR or ALK-positive status. The reported IMpower150 HR in a recent conference presentation[31] for ABCP vs BCP for EGFR only and ALK-positive only status were different (0.60 and 0.65, respectively and both statistically insignificant). Median PFS for ABCP in EGFR and ALK-positive patients was also different (10.2 and 8.3 months, respectively).

Table 17. Patient characteristics of studies used to inform lorlatinib versus ABCP

Study/publication	Treatment	N	Male	Average age (range)	Race	ECOG PS	Smoking	Brain metastases	Adenocarcinoma
Study 1001 (EXP 2 – EXP 5)	Lorlatinib	198	40.9%	53.7 Mean (30-85)	White: 49.0% Black: 0.5% Asian: 35.4% Other: 4.0% Unspecified: 11.1%	ECOG PS not reported by cohort in the CSR.	Not in CSR	62.1%	Not in CSR
Novello 2017	Pemetrexed	35*	48.6%	59 Median (37-80)	White: 80% Asian: 20%	ECOG PS 0: 31.4% ECOG PS 1: 54.3% ECOG PS 2: 14.3%	Current smoker: 5.7% Never smoker: 45.7% Ex-smoker: 48.6%	25.7%	100%
Shaw 2017		116*	47%	54 Median (47-64)	White: 59% Asian: 33% Other: 4% Unknown: 4%	WHO PS 0: 44% WHO PS 1: 52% WHO PS 2: 4% * WHO used as proxy for ECOG	Current smoker: 1% Never smoker: 44% Ex-smoker: 53% Missing: 3%	59%	97%
Ou et al 2014**	Systematic therapy	37	40.5%	54 Median (28-71)	Asian: 56.8% Non-Asian: 43.2%	ECOG PS 0: 21.6% ECOG PS 1: 62.2%	NA	27.0%***	100%

Study/publication	Treatment	N	Male	Average age (range)	Race	ECOG PS	Smoking	Brain metastases	Adenocarcinoma
						ECOG PS 2: 13.5% ECOG PS 3: 2.7%			
IMPRESS	Placebo (platinum doublet chemotherapy)	132	36.4%	58 Median (35-79)	White: 22% Asian: 77.3% Black or African American: 0.8%	WHO PS 0: 40.2% WHO PS 1: 59.8%	Never smoker: 68.9%	23.5%	99.2% (Adeno histology)
IMPOWER	Atezolizumab + bevacizumab + carboplatin + paclitaxel	41 (EGFR/ALK+ population)	51.2%	63.0 Median (35–76)	Asian: 31.7% Black or African American: 0% White: 63.4% Multiple: 2.4% Unknown: 2.4%	ECOG PS 0: 45.5% ECOG PS 1: 54.5%	Current smoker: 17.1% Never smoker: 56.1% Ex-smoker: 26.8%	NR	97.6%

Abbreviations: CSR = clinical study report; ECOG PS = Eastern Cooperative Oncology Group performance status; NR, not reported; WHO = World Health Organization.
Note: *Patients received either pemetrexed or docetaxel. **These baseline characteristics are for the 37 patients that did not continue crizotinib but received systemic therapy and cannot be found in the Ou et al. 2014 publication. ***Defined as progressed disease at the site of the brain at baseline

Costing assumptions and subsequent treatments

B11. In assembling data on chemotherapy (the comparator treatment) it is not always clear in Submission Document B whether this relates to the PDC regime(s) you costed in Section 3.5.1.1 (page 128). Please can you comment on whether the data used for effectiveness estimates were taken from clinical studies of pemetrexed-cisplatin or pemetrexed-carboplatin, both with 100% maintenance use. If not, please (re)state your rationale for why you believe the data can be generalised from one type of chemo to another.

A summary of the data used to inform PFS and OS for PDC within the economic model is provided within Table 18, with a description of the studies below.

Table 18: Data used to inform PFS and OS within the economic model

	Study	Label within study	Regimens	Dose	Pemetrexed maintenance therapy administered?	Justification for inclusion within the model
PFS	Novello et al	Chemotherapy	Pemetrexed (n=9)	500mg/m^2	NR	Only two studies identified in the ALK+ population where patients were pre-treated with a TKI
			Docetaxel (n=25)	75mg/m^2		
	Shaw et al	Chemotherapy	Pemetrexed (n=40)	500mg/m^2	NR	
			Docetaxel (n=73)	75mg/m^2		
OS	Ou et al	Systemic therapy	NR	NR	NR	Only study identified in the ALK+ population where patients were

						pre-treated with a TKI

Abbreviations: NR = Not reported

PFS for the PDC comparator was informed by the chemotherapy arm from Novello et al. (ALUR trial; Alectinib vs chemotherapy) and Shaw et al (ASCEND-5; Ceritinib vs chemotherapy). As reported in Table 18, patients received some mixture of pemetrexed or docetaxel singlet chemotherapy. OS for the PDC comparator was informed by Ou et al. which is a retrospective analysis of the PROFILE 1001 and PROFILE 1005 trials for patients receiving treatment post-crizotinib. This retrospective cohort of patients are likely to have been receiving some mixture of PDC and singlet chemotherapy (see response to B15).

The systematic literature review suggested that these are the only studies with a chemotherapy arm in an ALK+ population pre-treated with an ALK-inhibitor. The results of the SLR were in line with the expectations of clinicians from the July 2019 ad-board, who mentioned the ALUR and ASCEND-5 trials as sources of data. In addition, there was a consensus in the ad-board and individual clinician interviews that these studies would provide a reasonable proxy source for PDC. In the April 2019 interview, a trade-off was identified:

- Patients on singlet chemotherapy may respond less well and so these studies may underestimate PDC efficacy.
- The patients in these trials have only received one previous ALK-inhibitor whereas the population eligible for lorlatinib will be a mix of 2L+ patients (i.e. some less fit patients) and so the trials may overestimate PDC efficacy.

B12. CS, Document B, Section B.3.5.1.1, page 131: Please clarify the method of moments approach used to estimate wastage for treatments that are administered with the use of vials. In particular, provide justification for assumptions regarding distributions employed and provide details of the sensitivity of estimates for wastage to these assumptions.

For costing the intervention and comparators distributed in vial form, the ‘method of moments’ has been applied to estimate the average dose accounting for wastage.

Method of moments allows estimation of the average number of vials required per administration of a treatment where dosing is administered based upon weight or body surface area. It accounts for the distribution of a patient population's weight, as opposed to a point estimate, and fits a parametric distribution to the cumulative density of a patients' weight or body surface area.

The log-normal distribution was selected as it was considered that weight and body surface area would likely have a right skew in the tail. The variation in weight was obtained from Study 1001 IPD. The drugs for which the method of moments was used are summarised in Table 19. Where multiple vials are available with non-linear pricing, the cheapest combination is selected (e.g. if 2 x 80mg vials are cheaper than 1 x 160mg vial, then 2 x 80mg vials are costed to obtain a 160mg dose).

Table 19: Drugs utilising the Method of Moments to estimate costs

Drug	Dosing	Vial size	Vials required using Method of Moments
Pemetrexed	500mg/m^2	100mg	2.28
		500mg	1.39
Cisplatin	75mg/m^2	10mg	0.61
		50mg	2.72
		100mg	0.00
Docetaxel	75mg/m^2	20mg	0.83
		80mg	1.47
		160mg	0.00

Model options allow the inclusion and exclusion of wastage. When wastage is not incorporated into the model calculations, drug costs are calculated based on the point estimate of body surface area (the mean rather than estimating a log-normal distribution). This dose per administration is then multiplied by the cost per milligram rather than the cost per number of vials required.

B13. In the section on subsequent treatment (Submission Document B, Section B 3.5.4.1, page 139), you make the case there are no data on what was used after lorlatinib in the main clinical study. Can you confirm no data were collected at all in the clinical study? Are there any data on what was used after lorlatinib in any other data set such as an 'early use' programme?

There is no data available on treatments subsequent to lorlatinib from the compassionate use program. However, Table 20 lists all the 1st line subsequent "systemic" therapies reported by patients in the pooled EXP-3B:5 cohort (n = 139), following treatment with lorlatinib. Data was only available for 59 patients because the remaining 80 patients at the time of the data snapshot were still on lorlatinib treatment, had died and so could not report subsequent treatments, or were lost to follow-up (e.g. consent withdrawn).

Table 20 shows that the majority of the 59 patients received PDC, a 2nd generation ALK-inhibitor, immunotherapy or singlet chemotherapy. If we exclude those subsequent treatments that are not "approved" for used after lorlatinib in England and Wales (i.e. do not have NICE reimbursement in this line) – and additionally are not in line with clinical expert opinion (or opinion in TA584) - the vast majority of patients received PDC or singlet chemotherapy ([redacted]) after lorlatinib.

Table 20. Study 1001 (pooled EXP-3B:5 cohort) first line subsequent "systemic" therapy reported by patients after receiving lorlatinib

Reported Regimen	n	% of total	% of approved therapies
PDC	[redacted]	[redacted]	[redacted]
IO	[redacted]	[redacted]	[redacted]
2nd gen ALKi	[redacted]	[redacted]	[redacted]
Singlet chemo	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Total	[redacted]		

Abbreviations: PDC, pemetrexed + cisplatin/carboplatin; IO, immunotherapy; 2nd gen ALKi, 2nd generation ALK-inhibitor; singlet chemo, singlet chemotherapy

Notes: IO includes pembrolizumab, nivolumab or avelumab. Singlet chemo includes a taxane (paclitaxel, docetaxel) or a chemotherapy agent (gemcitabine, pemetrexed, bevacizumab). Other includes a mix of mainly reported combinations including taxane + chemo agent, 2nd gen ALKi + PDC, IO + 2nd gen ALKi, 2nd gen ALKi + IO and crizotinib alone (4 patients only).

Date of data Cut-off was 02 Feb 2018 and date of data Snapshot was 17 Apr 2018.

B14. In modelling subsequent treatment after PDC you use the data from TA 584. Given that PDC is intended to represent 'usual care' it seems strange there are no data from routine data sources or from Clinical Expert opinion. TA584 also seems an inappropriate choice given it is an immunotherapy in 1st line use. Please clarify why you selected this for the base case and consider a sensitivity analysis with NHS data instead.

TA584 (published 5th June 2019) was the appraisal for atezolizumab in combination (i.e. ABCP) for treating advanced non-squamous NSCLC. Two populations were considered within the final scope – people with untreated advanced, non-squamous NSCLC and people with EGFR- or ALK+ advanced non-squamous NSCLC who were previously treated with targeted therapy or who can't have targeted therapy.

Within the latter population, the company made a comparison to pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance. This population is aligned to that within the treatment setting for lorlatinib (post-targeted therapy for ALK+ advanced NSCLC, where the comparator is PDC).

As these estimates were derived from market share data, and this is the most recent technology appraisal in NSCLC (subsequent therapy for pre-treated NSCLC patients receiving PDC), selecting this appraisal to inform the choice of subsequent therapy appeared a reasonable approach. The PDC arm of TA584 was therefore used to inform subsequent therapy estimates. Pfizer are not aware of NHS data which are available to inform subsequent therapy proportions within the 'usual care' (i.e. PDC) arm of the economic model.

B15. Considering Profile 1001 and Profile 1005 as the source of OS data for the PDC arm of the model, is it possible to comment on the subsequent treatments available to patients in the Profile trials following progression, and whether the modelled treatments are consistent with these with respect to expected impact on OS.

A retrospective analysis of the crizotinib arm of the trials PROFILE 1001 and PROFILE 1005 (Ou et al. 2014) for the subgroup of patients receiving systemic therapy after progression on crizotinib was used as the source for OS data. In oncology clinical trials "systemic therapy" is usually defined as any anticancer therapies including chemotherapy regimens, immunotherapies and TKIs.

For entry to PROFILE 1005, patients had to have failed at least one line of systemic treatment as reported in Blackhall (2017), which is likely to have been some mix of PDC and singlet chemotherapy because these were the gold standard treatments

before the approval of ALK-inhibitors. PROFILE 1001 had very similar entry requirements but some patients are reported to have been treatment-naïve.

Given the lack of approved ALK-inhibitors available at the time of follow-up, it is likely that the majority of the relevant subgroup in Ou et al. would have received chemotherapy after crizotinib. Indeed, some proportion would still be sensitive to pemetrexed and so it is likely that many of these patients would have received PDC following progression on crizotinib.

To conclude, the majority of these patients after progression on crizotinib would receive some mix of PDC and singlet chemotherapy which is consistent with the pathway reported by clinical experts.

Section C: Textual clarification and additional points

C1 Submission Document B, Table 3 on page 23 appears to suggest ALK positive cancers are a sub-set of adenocarcinoma, because row E comes after row D – is this correct?

Essentially, ALK translocations are almost always of adenocarcinoma histology (e.g. 94% in the Profile 1014 study), which is why the calculation in Table 3 has been carried out in this way: the number of UK patients with an adenocarcinoma NSCLC can be calculated and then a further estimation of how many of these patients would be ALK+ based on known incidence.

C2. Submission Document B, Table 60 on page 140, in row 1 of the data, the 2nd figure across is 60, but should this be 40% of 60, i.e. 24?

Table 21 refers to the proportion of patients receiving subsequent therapy. Within the model it is assumed that 60% of patients receive active subsequent therapy whilst 40% receive best supportive care (no active therapy). Of the remaining 60%, 40% have pemetrexed monotherapy while the remaining 60% have combination (PDC). Therefore, 60% receive pemetrexed in total (as all active treatment includes pemetrexed). Table 21 shows a deconstructed approach.

Table 21: Subsequent therapy included within the model – breakdown of treatments received

Subsequent treatment / combination	Percentage in model	Assumption

Pemetrexed monotherapy	24%	60% of patients receive active treatment 40% receive pemetrexed monotherapy
Pemetrexed + cisplatin	18%	60% of patients receive active treatment 60% receive PDC 50% of PDC is pemetrexed + cisplatin
Pemetrexed +carboplatin	18%	60% of patients receive active treatment 60% receive PDC 50% of PDC is pemetrexed + cisplatin
Pemetrexed total	60%	24% + 18% + 18%
Best supportive care (no active treatment)	40%	40% of patients receive BSC (no active treatment)

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NICE National Institute for Health and Care Excellence

Patient expert statement

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Debra Montague**
2. Are you (please tick all that apply):	☐ **X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ X a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	ALK Positive UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ **X** no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **X** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ **X** I am drawing on others' experiences. Please specify how this information was gathered: We have gathered this information through our on-line support group.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	ALK-positive LC is a devastating diagnosis to receive as the majority of patients are non-smokers who were previously fit and healthy. The profile of ALK-positive LC patients is somewhat different to the stereotype of a smoker in their 70s and 80s. Almost all patients are diagnosed at stage IV in the prime of their life, as the symptoms go unnoticed until the late stage – this again has an enormous life-changing effect on patients as the current life-expectancy once diagnosed is between 2 – 3 yrs. Symptoms are generally non-specific such as a cough that lasts several weeks, fatigue (but who isn't tired working and raising a family?), back-ache or a bit breathless (but many ran races days before their diagnosis?). It is impossible to forget you have the disease as not only do you have regular monitoring but any ache, pain, cough or feeling tired raises the possibility of progression. The mental health aspects of a diagnosis of ALK-positive LC should not be under-estimated as many patients suffer depression as a result of being diagnosed. Many patients are unable to continue working due to their symptoms, so the many hospital appts can have a significant financial burden on their whole families. Experiencing side effects on treatment means further hospital investigation which incurs further costs – petrol, hospital car-parking, child-minding costs for those with young families, loss of earnings for those who are able to continue to work.

	Life changes beyond all recognition once a diagnosis has been received, not knowing how long you have to live and what quality that life will be is a dark cloud that is permanently overhead for all patients (and carers). All current treatments come with side effects, many of which are significant and impact on quality of life. The side effects can be similar to the symptoms of progression, so these add another level of anxiety into daily life. Side effects can vary from patient to patient and are a varied as weight gain, hair thinning or curling, muscle aches, frequent cramps in limbs, extreme fatigue (feeling like wading through treacle), extreme constipation requiring medical intervention and extreme sun-sensitivity even in winter (requiring factor 50 sunscreen at all times and all limbs to be covered when outside). All current treatments will ultimately fail as the cancer develops resistance to them and many patients progress a lot earlier than the clinical trials report. This means that progression through the treatment options can be swift with many patients having been prescribed 3 over a period of 18mths. Many patients have young families, who also have their lives turned upside down – going to school each day worrying if their parent will be there when they get home, watching their parents suffer with the side effects of treatment and constantly being scared they will loose their parent. Family members can become carers overnight, with all the emotional aspects of watching a loved one suffer whilst having to adapt to being a carer and the demands that has on their time. Anything that results in a hospital visit or admission is an enormous burden for carers who are required to change plans and drop all arrangements when needed. Many patients and carers are scared to go on holiday in case something happens while they are away.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel that the current targeted treatments are an enormous improvement on the traditional cancer treatment of chemotherapy. Patients can live ‘relatively normally’ without the need for weekly hospital visits and the side effects are generally much easier to tolerate than chemotherapy. Patients don’t lose their hair so feel more confident when out in public as they aren’t constantly stared at. Most patients look well for the majority of their cancer journey which helps keep life normal for their families.

	Patients learn coping mechanisms for the side effects, for example sun-sensitivity is a significant issue for many patients taking targeted therapies. 'Sun sensitivity' feels like boiling water has been poured on the skin and can occur very quickly once exposed to the sun so the majority of patients cover up in the sun, wear factor 50 sunscreen and stay in the shade to avoid this. Many patients find their initial symptoms improve vastly upon starting treatment, which means they can return to work and so continue to contribute to the UK economy. Many patients work for several years until the latter stages when they experience significant progression. Many take on new challenges to raise vital funds for further research as they clearly understand the value and need of such on-going research.
10. Is there an unmet need for patients with this condition?	We believe there is a significant unmet need for ALK-positive patients as despite there appearing to be 5 targeted treatments for patients in the UK, in reality this is not the case. Neither Crizotinib nor Ceritinib are prescribed 1st line since the availability of Alectinib. Brigatinib has been approved in England and Wales for 2nd line use only after Crizotinib which in reality means it's a choice for approx. 50 patients still being treated by Crizotinib. Once Alectinib fails there is no licensed option available currently in the UK, which would mean that all patients would move onto chemotherapy. We have several members who have fortunately received Lorlatinib through the Pfizer Compassionate Use Programme and I have captured their comments – Patient 1 – I was diagnosed June 2018 and started Alectinib at 1st line treatment. Unfortunately, by March 2019 I had a new mass which was treated with 10 rounds of radiotherapy, however the CT scan showed 2 new tumours so I needed to switch treatment. Chemo' was my only option until my Oncologist requested Lorlatinib under the CUP. So far it has stabilised my disease, benefits in addition to stability are I have significantly fewer GI side effects and I no longer need to take additional medication to manage the constipation. I am also able to go out in the sun, whereas I was extremely sun sensitive on Alectinib even in winter. The Lorlatinib tablets are easier to take as they are smaller and only once a day. I generally feel more comfortable and am 'back to normal'. I feel very passionately that Lorlatinib should be available for other patients to extend their lives with a good quality of life. Patient 2 – I was diagnosed March 2017 and given Crizotinib 1st line. After 9 mths I was switched to Brigatinib (through a CUP) as I had progression, but I progressed again on the liver and brain 24Th July

	2019 and am now taking Lorlatinib. Since transferring to Lorlatinib I have had no noticeable negative side effects to date and my previous sun sensitivity has eased. Patient 3 – I was diagnosed Dec 2018 and started on Alectinib 1st line Jan 2019. By mid April the cancer had progressed to a second site. I was switched to Lorlatinib on 22nd Mat 2019. My lungs have reopened most of the way and most of the pleural fluid has gone. Overall my quality of life is good and I very much agree that everyone should have access to Lorlatinib.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	One tablet once a day minimises impact on quality of life. Patients with a better quality of life visit their Drs less often which impacts capacity and costs in the NHS. Patients receiving targeted therapies with fewer side effects take fewer other medicines which is a cost benefit for the NHS. ● Small tablets so easy to take ● No sun sensitivity ● Improved GI effects vs Alectinib so better quality of life and reduced number of other medicines required to take. This also benefits the NHS. ● Excellent brain coverage so reduces brain metastasis without the need for expensive radiotherapy (whole brain or SRS) thus reducing the need for other NHS services
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	● Some patients experience mood swings with Lorlatinib; however, they all state they would rather this than not take it. ● Some patients have noted an increase in ‘weird and vivid dreams’
Patient population	

13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with brain metastasis may benefit more from Lorlatinib than those with progression in the body.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Previous to their diagnosis, ALK-positive LC patients led healthy lives, kept fit and didn't smoke. Their lifestyle did not contribute to their developing lung cancer.
- There are now very few treatments currently available on the NHS in England and Wales for patients progressing on their 1st line treatment, or for patients who have received 2nd and 3rd line treatments though Compassionate Use Programmes (that are now all closed). With the advent of Alectinib being the 1st line treatment of choice by clinicians across England and Wales, there are no licensed treatments once progression occurs apart from traditional chemotherapy
- The majority of patients led full lives before their diagnosis and wish to continue contributing to the UK economy as well as be alive for as long as possible to be with their families.
- Lorlatinib use in the UK is reported as 'much easier than previous targeted treatments', which all leads to patients living longer with a good/excellent quality of life.
- ALK-positive patients didn't do anything to deserve this devastating diagnosis. They are struck down with this disease in the prime of their lives and now have a significantly reduced life span.

Thank you for your time.

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Clinical expert statement

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Fiona Blackhall**
2. Name of organisation	**Royal College of Physicians, Lung Clinical Studies Group, The Christie NHS Foundation Trust**

3. Job title or position	**Professor of Thoracic Oncology and Honorary Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? **X**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X**☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is palliative with the goals of extending survival, improving symptoms, maintaining independent function and optimising quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant response is any stabilisation or regression of tumour growth in one or more metastatic sites maintained for 2 months. In the context of cancer related symptoms the response would be expected to correlate with an improvement in symptoms and quality of life.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a high unmet need for patients with ALK positive NSCLC. There is no curative treatment for metastatic disease and in excess of 50% of patients will develop brain metastases with high morbidity and mortality. The current 1st and 2nd generation ALK inhibitors available are poorly brain penetrant and associated with development of drug resistant mutations due to cancer evolution. These factors limit duration of disease control and benefit from current ALK inhibitors. For patients to have a chance of survival beyond a small number of years, and to avoid devastating functional sequelae of brain metastases effective treatment that can penetrate the brain and overcome ALK resistance mutations is required.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Current treatment options are a 3rd generation ALK inhibitor within a compassionate use programme or a clinical trial, standard of care chemotherapy with or without immunotherapy and bevacizumab, or best supportive care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE clinical guidelines for ALK positive NSCLC are in place.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not well defined once 1st/2nd generation ALK inhibitors have failed. The use of chemotherapy based regimens has a weak evidence base and in patients with brain metastases is historically ineffective. There is currently risk that patients receive ineffective treatment that carries a high risk of side effects and healthcare resource use outweighing clinical benefit.
• What impact would the technology have on the current pathway of care?	The technology would enable a more clinically effective option to be administered on progression following treatment with a 1st or 2nd generation ALK inhibitor. For the patient this would be a continuation of orally administered therapy, given as an outpatient, and without risks and side effects plus resource requirements of conventional chemotherapy based regimens.
11. Will the technology be used (or is it already used) in	The technology would be used in patients with ALK positive NSCLC who have progressive cancer on a 1st or 2nd generation ALK inhibitor. It would be given orally in the same way as current ALK inhibitors.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Healthcare resource for chemotherapy constitution and intravenous administration is not required. The treatment is oral and administered at home daily with clinical review once per cycle in the outpatient clinic setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The investment for facilities, equipment and training required is minimal since ALK inhibitors are already in use and this technology would only require a drug specific patient information sheet and the clinical team to be knowledgeable about side effect profile, administration and restricted concomitant medications.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Current care with chemotherapy based treatment regimens is ineffective for treatment of brain metastases and less effective in delaying cancer growth and spread (response rates of <30%). In patients who have previously received an ALK inhibitor lorlatinib induces higher response rates, duration of response and longer progression free survival in cancer metastases within and outside the brain than anticipated for chemotherapy based regimens from historical data. The side effect profile of lorlatinib is also favourable compared to chemotherapy based regimens.

• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Lorlatinib is a convenient, oral and well tolerated treatment. It will therefore be easier for patients and healthcare professionals than current chemotherapy based care.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Lorlatinib will be discontinued when clinical benefit is not obtained or in the case of unmanageable toxicity. Routine blood tests and vital signs monitoring will be used to guide treatment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The clinical efficacy and ease of administration plus low toxicity of lorlatinib enables patients who wish to work or maintain their role in family life such as childcare to continue.

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the chemistry of lorlatinib is innovative in its brain penetration and activity against ALK resistance mutations. These attributes account for its clinical efficacy and potential to significantly enhance quality and duration of life for patients with ALK positive NSCLC.
• Is the technology a 'step-change' in the management of the condition?	Yes in that it offers a brain penetrant active treatment in a 2nd or 3rd line setting
• Does the use of the technology address any particular unmet need of the patient population?	Yes – activity in the brain and against ALK resistance mutations
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Lorlatinib is well tolerated. The clinical efficacy against the cancer outweighs low grade side effects. The side effect profile is also favourable compared to 1st and 2nd generation ALK inhibitors in current use.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are response rate – intracranially and extracranially, side effect profile, duration of response and time to progression, health related quality of life. These endpoints were measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	N/A
22. How do data on real-world experience compare with the trial data?	Real world experience in my practice is paralleling trial data with impressive intracranial responses and improvement in quality of life/ reduction of neurological symptoms in patients who have progressed on several prior ALK inhibitors.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	ALK positive NSCLC is a rare subset of lung cancer that affects patients with a younger median age and is aetiologically not smoking related. Biologically it is a different disease to common smoking associated lung cancer. It is therefore important to consider the treatment of this type of lung cancer in its own biological context rather than extrapolating information based largely on patients with smoking related lung cancer which has a different biology and response to chemotherapy and immunotherapy.

23b. Consider whether these issues are different from issues with current care and why.	As above
Topic-specific questions	
24. • What is the standard of care for people with advanced ALK+ NSCLC that has progressed after alectinib or ceritinib as the first ALK TKI, or progressed after crizotinib as the first ALK TKI plus at least one other ALK TKI? • Please describe the uptake of atezolizumab plus bevacizumab,	A chemotherapy based regimen Or a clinical trial where possible eg of a 3rd generation ALK inhibitor Or best supportive care This is high and increasing as clinicians become familiar with the regimen despite a lack of evidence

carboplatin, paclitaxel (TA584) as a percentage of patients who progress following targeted TKI therapy.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- There is a high unmet need for effective therapies based on the biology of the disease for patients with ALK+ NSCLC
- Lorlatinib has high brain penetration and activity against the known spectrum of ALK resistance mutations
- These characteristics account for the clinical efficacy of lorlatinib in ALK + NSCLC that has progressed after initial treatment with a 1st or 2nd generation ALK inhibitor
- Lorlatinib is orally administered, well tolerated and provides a higher chance of clinical benefit than current standard of care regimens
- Current standard of care chemotherapy based regimens available for subsequent line treatment of ALK + NSCLC carry a high risk of side effects (and resource) outweighing benefit

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle upon Tyne Hospitals NHS Trust**

3. Job title or position	**Senior Lecturer and Honorary Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms (in particular those related to central nervous system disease)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in survival by 2 months. Delay in neurological symptoms impacting on independence by 3 months. A response rate of over 30% maintained for over 2 months
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes whilst responses to initial ALK inhibitor treatment with agents such as crizotinib, ceriitnib, brigatinib and alectinib can be dramatic; resistance invariably arises often within the brain. This leads to symptomatic CNS disease with very limited treatment options.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	At present patients progressing on ALK inhibitors will either receive Best Supportive Care, platinum doublet chemotherapy (potentially followed by single agent immunotherapy with pembrolizumab, nivolumab or atezolizumab) or the quadruple regimen of carboplatin paclitaxel, bevacizumab and atezolizumab (ABCP; TA584)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is poorly defined with variable access to clincial trials and compassionate access to other ALK inhibitors often being restricted to more specialist centres. Experience with using chemotherapy and the quadruple regimen ABCP will vary from centre to centre.
• What impact would the technology have on the current pathway of care?	Lorlatinib would act as an extra line of treatment with an ALK inhibitor before the patient moved to chemotherapy or chemo-immunotherapy. Most patients are now receiving 1st line alectinib and so lorlatinib would follow on from symptomatic progression on this agent.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	It will be used in the same way as present ALK inhibitors primarily in the outpatient setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No change in facilites will be required. Minimal training into the different side effect profiles compared to other ALK inhibitors will be needed.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, this provides an extra line of treatment that can result in prolonged control of symptoms; particularly for CNS symptoms which have a major impact on quality of life in this setting, and which otherwise can lead to heavy healthcare resouce use.
• Do you expect the technology to increase length of life more than current care?	Yes, although this may be diffult to formally quantify; the ability to receive an extra line of therapy should result in a longer life expextancy. Given the ability to improve CNS disease It may also allow subsequent lines of therapy such as chemo-immunotherapy which would otherwise not be possible..

• Do you expect the technology to increase health-related quality of life more than current care?	In particular for those with CNS symtoms, due to high respone rate in CNS disease
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is some controversy over whether repeat sequencing of the tumour on progression on the previous ALK inhibitor can guide the chance of subsequent response to lorlatinib. At present time in my opinion this is not suitable for routine clincial practice and remains a research tool.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No major changes from other ALK ihibitors (oral medication delivered in the out-patient setting). Clearly it uses signficiantly less medical, nursing and pharmacy time than chemotherapy or chemo-immunotherapy. Requires montoring of lipids but that is not difficult to organise, and requires no training.Some patients may require treatment with statins to manage the hypercholesterolaemia which can be associated with this medication.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required (see previous answer). Patients will be monitored clinically and with CT/MRI scans until symptomatic progression
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	No; has a major impact on CNS symptoms as described above.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Control of CNS disease on progression of previous ALK inhibitor therapy
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Mood disturbance and fatigue have been reported in clincial trials but this should be captured in the quality of life data from the trial.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free and overall survival; CNS response rate and duration of control; health related quality of life
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA584?	No
22. How do data on real-world experience compare with the trial data?	In general real world data are signfiicnantly worse than in clinical trials. This is a result of both the patient group (poorer PS and co-morbidities) and a lower standard of care (access to subsequent lines of therapies, regular brain monitoring, optimal treatment of CNS disease).
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. • What is the standard of care for people with advanced ALK+ NSCLC that has progressed after alectinib or ceritinib as the first ALK TKI, or progressed after crizotinib as the first ALK TKI plus at least one other ALK TKI? • Please describe the uptake of atezolizumab plus bevacizumab,	The standard of care would be (if fit and willing to accept side-efefcts) to consider either chemotherapy with carboplatin and pemetrexed followed by maintenance pemetrexed or the quadruple chemo-immunotherapy regimen of atezolizumab plus bevacizumab, carboplatin, paclitaxel. This would depend on patient fitness, wishes and whether they had any contraindications to the atezolizumab or bevacizumab, which may be present in a number of patients. It is relatively early to assess the uptake of ABCP for patients progressing on targeted therapy. This has varied around the country and most of the patients treated have been EGFR mutated NSCLC rather than ALK NSCLC (as these patients are rarer).

carboplatin, paclitaxel (TA584) as a percentage of patients who progress following targeted TKI therapy.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Lorlatinib has high response rates in previous ALK TKI failure
- This may be particularly important in patients with CNS disease, who have a large symptom burden
- Implementation in the NHS would be practically easy as is an oral therapy with well characterised side-effects
- This would represent an extra line of therapy for this group of patients
-

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Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Graham Scotland, Andrew Walker and Daniel Kopasker acted as health economists for this appraisal: critiqued the cost-effectiveness evidence, checked the economic model, and conducted further sensitivity analyses. Shona Fielding with help from Thenmalar Vadiveloo acted as lead statistician for this appraisal: critiqued the statistical methods presented in the submission, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence. Clare Robertson acted as systematic reviewer: critiqued the company's definition of the decision problem, the clinical effectiveness evidence and the methods used for identifying relevant studies. Paul Mason acted as information scientist: critiqued the methods used for identifying relevant studies and checked the search strategies presented in the submission. Gillian Price acted as clinical advisor: provided clinical advice and general guidance. Miriam Brazzelli led the clinical effectiveness side of the appraisal. Graham Scotland acted as project lead and led the cost-

effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ALK	Anaplastic lymphoma kinase
NSCLC	Non-small cell lung cancer
TKI	Tyrosine kinase inhibitor
QoL	Quality of life
ERG	Evidence review group
CS	Company submission
PDC	Pemetrexed with cisplatin/carboplatin
ABCP	Atezolizumab with bevacizumab, paclitaxel and carboplatin
MAIC	Matched adjusted indirect comparison
RCT	Randomised controlled trial
CRD	Centre for reviews and dissemination
ORR	Objective response rate
IC-ORR	Intercranial objective response rate
BOR	Best observed response rate
TTR	Time to tumour response
IC-TTR	Intercranial time to tumour response
DOR	Duration of response
DCR	Disease control rate
PFS	Progression free survival
OS	Overall survival
OD	Once daily
AE	Adverse event
EGFR	Epithelial growth factor receptor
ECOG	Eastern Cooperative Oncology Group
HR	Hazard ratio
CI	Confidence interval

1 Summary

1.1 Critique of the decision problem in the company submission

The population addressed in the company submission is people with advanced ALK-positive NSCLC that have progressed after treatment with one or two ALK-TKIs with or without prior chemotherapy. The intervention is lorlatinib, a selective adenosine triphosphate competitive inhibitor of ALD and c-ros oncogene 1 tyrosine kinases for the treatment of adult patients whose disease has progressed after first line alectinib or ceritinib ALK TKI therapy or crizotinib and at least one other ALK TKI. Contrary to the NICE final scope, the comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator, but at the request of NICE did provide an update which included ABCP in the economic model. The ERG considers ABCP a relevant comparator.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence for lorlatinib submitted by the company relates to a single phase two study, Study 1001[1]. This study investigates the single arm of lorlatinib for adult patients with metastatic (stage IV) ALK-positive NSCLC. The evidence presented is for the combined cohort EXP-3B:5 and consists of 139 patients. The company presented evidence that shows lorlatinib to be effective for their primary outcome, objective response rate (40.3% with 95% CI 32.1-48.9), and also showed positive results for their secondary outcomes (see section 4.2) including progression free survival of 6.9 months (95% CI 5.4-8.2).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The comparator evidence was limited to chemotherapy and the company did not consider ABCP relevant. The chemotherapy evidence was provided by three studies ALUR[2] and ASCEND5[3] (progression free survival) and PROFILE 1001/1005[4] (overall survival). The company used a matched adjusted indirect comparison to provide hazard ratios for lorlatinib versus chemotherapy for these outcomes. This

analysis showed a survival benefit (both progression free and overall) for patients treated with lorlatinib versus chemotherapy.

The ERG has reservations over the clinical effectiveness evidence submitted for the following reasons:

- evidence base for lorlatinib is from a single study, of one arm, in only 139 patients
- company indicate chemotherapy (PDC) as the only relevant comparator and did not fully consider ABCP
- evidence base for chemotherapy comes from 3 studies, which have different prior treatment pathways to the target population for lorlatinib
- there is an assumption by the company that PDC, pemetrexed monotherapy and docetaxel monotherapy are equivalent and the ERG's opinion is that PDC is superior. Pemetrexed and docetaxel were the chemotherapies used in these studies as all participants within ALUR, ASCEND5 and PROFILE 1001/1005 had previously been treated with PDC. The company offered a counter argument that patients in these trials were exposed to only one ALK TKI (crizotinib), whereas the population eligible for lorlatinib may have been exposed to two or more and so might be expected to have a worse efficacy outcome (as suggested by some clinical experts). However, the ERG remains concerned about the potential for underestimating the efficacy of PDC.
- choice of studies to inform the MAIC may not be appropriate for the reasons stated above
- the company did not use the results of the MAIC in the base case of the economic model

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a de novo cost-effectiveness model comparing lorlatinib to PDC in people with advanced ALK-positive NSCLC that have progressed after treatment with one or two ALK-TKIs. A further comparison was provided against ABCP, originally as an addendum, but later as an appendix to the CS. This later comparison was only provided as a deterministic analysis.

The company used as partitioned survival model with three health states: progression free, progressed and dead. PFS and OS for lorlatinib were informed by fitting

parametric distributions to Study 1001 efficacy data. As Study 1001 was a single arm trial, the company derived comparative effectiveness data for PDC by indirect comparison with other data sources: The chemotherapy arms of ALUR and ASCEND-5 for PFS and a retrospective analysis of the chemotherapy arms of the chemotherapy arms of PROFILE 1001/1005 for OS. The company explored six different methods for deriving comparative PFS and OS data, including the estimation of hazard ratios from MAICs and unadjusted comparisons, and independent curve fitting with and without population adjustment to account for differences in the ALK INH treatment histories between the comparator studies (post-crizotinib) and the population of relevance for lorlatinib (post-second generation ALK INH). The company ultimately selected independent curves without population adjustment (method 5) for their base case. This was due to concerns regarding the proportional hazard assumption required for the application of hazard ratios, and advice from clinical experts that PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI.

For the comparative efficacy of ABCP, the company used data from a mixed ALK+/EGFR+ subgroup from the IMPower study. Independent curves were fitted to the observed PFS and OS Kaplan Meier data, but a population adjustment was undertaken to account for poorer expected outcomes for a pure ALK+ cohort.

Treatment specific EQ-5D health state utility values (HSUVs) were applied in the progression free state of the model, and a single HSUV (0.65) was applied to the progressed state. The lorlatinib progression free HSUV ([redacted]) was derived by mapping from EORTC QLQ-C30 data collected in Study 1001. The corresponding HSUV for the PDC arm (0.72) was identified by review of the literature, and for the ABCP comparison a value of 0.71 was taken from an analysis conducted by the ERG in TA584. It was assumed that the treatment specific progression free utilities captured the impact of adverse events, but a scenario that explicitly incorporated QALY decrements associated with adverse events was also provided for the PDC comparison.

The model incorporated treatment acquisition costs, administration costs, adverse event costs, other health state costs, subsequent treatment costs, and end of life costs.

The CS recognised that treatment with lorlatinib can continue beyond progression, and so explored the use of different parametric curves for modelling time on treatment. However, due to inconsistencies with the selected PFS curve, these were rejected by the company in their base case. Instead they applied an average of [redacted] months on treatment following progression, which was the difference between restricted mean time on treatment and restricted mean PFS up to a time point of [redacted] months. For PDC it was assumed that it would be administered for a maximum of six cycles or until progression. Thereafter, 100% of those remaining progression free were assumed to proceed with pemetrexed maintenance. For ABCP, time on treatment was equated to PFS, but a stopping rule was applied at two-years (i.e. all patients removed from treatment from two years).

With respect to subsequent treatment, 60% of progressed patients were assumed to proceed with a subsequent active therapy in all arms of the model. For subsequently treated patient the distributions were: 60% PDC and 40% pemetrexed monotherapy following lorlatinib; 69% pembrolizumab and 31% atezolizumab following PCD; and 100% docetaxel following ABCP. Since the company did not have access to confidential discount prices for atezolizumab, pembrolizumab or bevacizumab, they assumed a 30% discount in their analyses to avoid overestimating costs. The ERG has rerun the company's analyses in a confidential comparator PAS appendix using the actual PAS discounts available to the NHS.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG notes the following main areas of concern with the company's economic evidence:

1. The design of Study 1001, as a non-comparative single-arm study, means there is substantial uncertainty in estimating the lifetime comparative effectiveness of lorlatinib in its licensed indication. While the company has undertaken an indirect comparison to address this, there are several issues and much uncertainty remains. Issues include:

- The selection of clinical studies to represent the PDC treatment arm, these being representative of pemetrexed or docetaxel monotherapy, or undefined systemic therapy rather than PDC.

- The selection of the method to carry out the indirect comparison, with the adjusted HRs from the MAIC being rejected in favour of independently fitted curves without adjustment.
- The source of data and approach to applying the EGFR+ to ALK+ population adjustment in the ABCP comparison:
    - The population adjustment hazard ratios were derived from unadjusted indirect comparison of study arms that differed in the type of chemotherapy received and not just the population.
    - The adjustment hazard ratios were applied to ABCP curves derived from a mixed cohort (27% ALK+) rather than a pure EGFR population.

2. The utility values selected are open to challenge:
    - The value for the progressed disease state may be on the high side compared to other available published studies.
    - There is no direct comparative evidence that pre-progression utility on lorlatinib is higher than pre-progression utility on PDC or later pemetrexed maintenance. The same point applies in the comparison with ABCP.

3. The treatment duration calculation for lorlatinib is based on the difference between the restricted mean ToT and PFS at 27.2 months in Study1001. The ERGs clinical expert advised that this might underestimate the extent by which clinicians tend to prolong treatment in routine clinical practice when there are no other effective options available.

4. The assumption that an equal proportion of patients receive subsequent therapy irrespective of previous treatment is open to question. In addition, the distribution of subsequent therapies in each arm of the model is uncertain.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Study 1001 provides a reasonable source of data for modelling expected progression-free and overall survival expectations for the relevant population of lorlatinib treated patients.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty with respect to the clinical and cost effectiveness evidence relates to the single arm study design of Study 1001, which necessitates the use of matched adjusted or unadjusted indirect comparisons. Uncertainty surrounding the comparative effectiveness of PDC and ABCP is further increased by the reliance on data that does not ideally reflect the treatment comparators and/or the population in the scope.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted several further deterministic exploratory scenario analyses, which identified the following insights:

- The ICER for lorlatinib versus PDC ranges from £43,799 (method 6) to £58,747 (method 2) when the alternative methods for estimating comparator effectiveness are applied to both OS and PFS at the same time. Method two may be a reasonable alternative to the company base case although it relies on the proportional hazards assumption.
- The ICER versus PDC rises to £55,638 if the hazard of progression and death on PDC is 40% lower than in the chemotherapy arms of the studies used inform these outcomes in the company's model.
- The ICER versus PDC is quite sensitive to the average post progression time on treatment with lorlatinib; rising to £53,938 if this is increased to [redacted] and £59,496 if this is [redacted]. An alternative approach of using the generalised gamma curve to model ToT resulted in an ICER of £56,876.
- If subsequent treatment with pembrolizumab following progression on PDC is costed at the fixed dose of 200mg every two weeks, the company base case ICER drops to £48,288.
- Changing assumptions about the proportion of patients who receive further treatment following PDC, or the distribution between PDC and pemetrexed monotherapy following lorlatinib, had little impact on the ICER.

With respect to the ABCP comparison:

- The ICER for lorlatinib was moderately sensitive to the post progression time on treatment for lorlatinib, but otherwise remained below £30,000 in the scenarios assessed by the ERG.
- Of note, when reducing the population adjustment for the increased hazard of progression and mortality in ALK+ versus EGFR+ patients, the ICER for lorlatinib dropped initially when applying a 25% reduction in the adjustment log HRs and only rose slightly when there was a 50% reduction.

Uncertainties surrounding progressed disease utility value applied in the company model also results in upward uncertainty in the ICER versus PDC and ABCP. All summarised findings above reflect analyses where drug prices are set as per the company base case. The results of the ERGs exploratory analyses are provided with current comparator PAS discounts in a confidential appendix.

2 Background

2.1 Critique of company's description of underlying health problems

The relevant health condition for this submission is anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). The company's description of ALK-positive NSCLC in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem.

Over 39,000 new cases of lung cancer were diagnosed in England and Wales in 2016[5]. NSCLC accounts for 88.5% of all lung cancer cases[5]. ALK-positive NSCLC is a subset of NSCLC, with estimated prevalence rates of between 1.6% and 5%[6-11] and is associated with advanced clinical stage and presentation[12, 13]. ALK-positive patients experience a high symptom burden, including fatigue, dyspnoea, cough, pain, weight loss, depression, shortness of breath and haemoptysis[14, 15]. The brain is a common site for progression, particularly in patients with a history of prior ALK tyrosine kinase inhibitor (TKI) treatment (45-70% of patients)[16]. Brain metastases can result in neurological dysfunction, cognitive impairment and are associated with poor prognosis[16]. ALK-positive NSCLC tend to be of younger age[12, 17] and are therefore more likely to be of working age, have dependents or be carers than those with ALK-negative disease. ALK-positive disease, therefore, has a particularly high impact on quality of life (QoL) and productivity loss.

2.2 Critique of company's overview of current service provision

The ERG considers the company's description of current service provision is accurate. ALK TKI treatments are approved as first and second line therapies. The company presents those treatments that are currently available in the UK, and the associated NICE treatment guidelines in Tables 4 and 5, Document B, of the CS and these are reproduced by the ERG below.

Table 1 ALK TKIs currently approved for the treatment of ALK-positive NSCLC in the UK

Generation	Name	Indication
First	Crizotinib (Xalkori®)	Crizotinib as monotherapy is indicated for: The first-line treatment of adults with ALK-positive advanced NSCLC The treatment of adults with previously treated ALK-positive advanced NSCLC The treatment of adults with ROS1-positive advanced NSCLC.[18]
Second	Ceritinib (Zykadia®)	Ceritinib as monotherapy is indicated for: The first-line treatment of adult patients with ALK-positive advanced NSCLC The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[19]
	Alectinib (Alecensa®)	Alectinib as monotherapy is indicated for: The first-line treatment of adult patients with ALK-positive advanced NSCLC The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[20]
	Brigatinib (Alunbrig®)	Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK-positive NSCLC previously treated with crizotinib.[21]

ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor; UK = United Kingdom

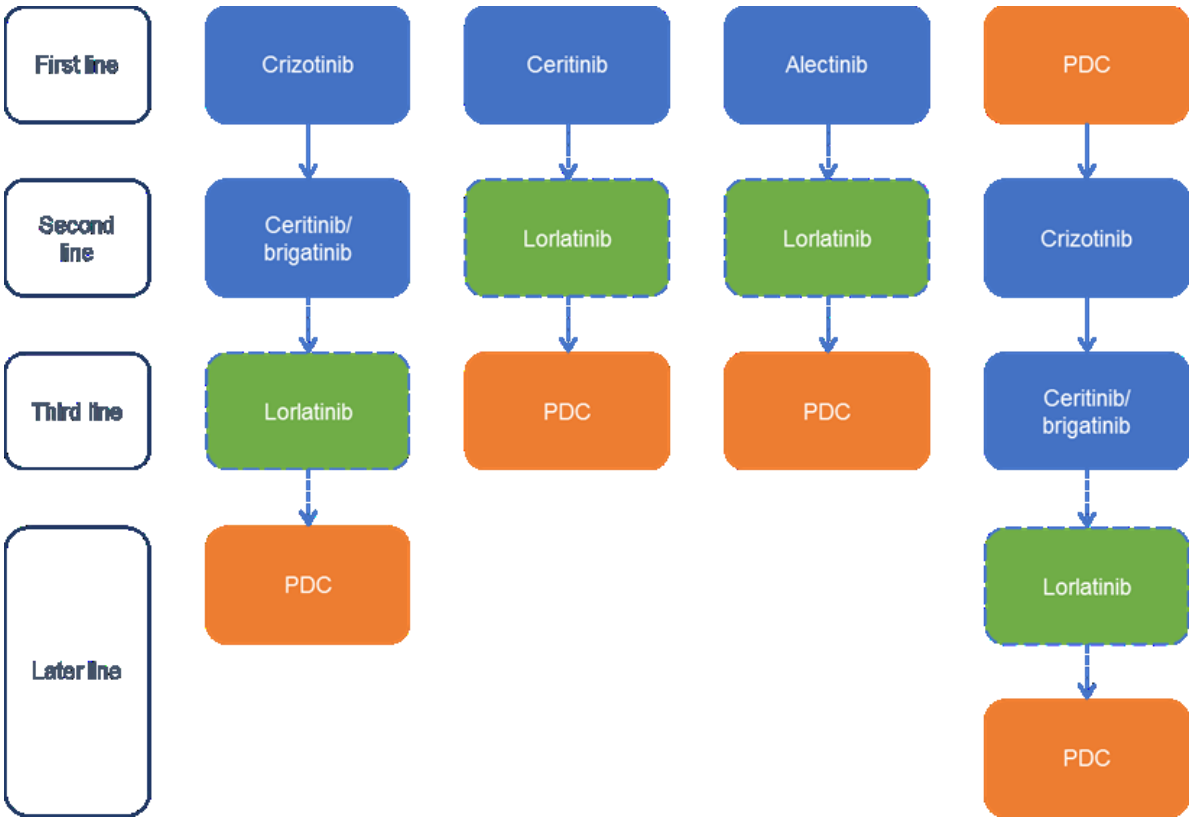
Table 2 Current NICE guidelines for the treatment of advanced ALK-positive NSCLC

Treatment line	Recommendation
First	PDC (patients with Stage III or IV NSCLC and good PS) or single-agent chemotherapy for patients who are unable to tolerate a platinum combination[22] Crizotinib[23] Ceritinib[24] Alectinib[25]
Second	Chemotherapy[22] Crizotinib[26] Ceritinib, if previously treated with crizotinib[27] Brigatinib, if previously treated with crizotinib[21]

ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PS = performance status

Crizotinib, ceritinib, alectinib and brigatinib are currently recommended for the treatment of ALK-positive NSCLC by both NICE and the European Society for Medical Oncology (ESMO)[21, 23-28]. The company notes that, while second-generation ALK TKIs offer the opportunity to sequence multiple targeted therapies, data are limited. The ERG agrees with the company that for certain lines of ALK-positive NSCLC treatment the current data are limited. The ERG clinical expert believes that all patients will have routine ALK testing at diagnosis. The ERG clinical expert agrees with the company that maximising the time patients are treated with targeted ALK TKIs to delay the need for chemotherapy is an aim of treatment and that lorlatinib will always be given after other ALK TKIs. The company state that lorlatinib will extend the possible treatment time with targeted ALK TKIs. The company present the proposed treatment pathways following the introduction of lorlatinib in Figure 2, Document B, of the CS and this is reproduced by the ERG below. It is the ERG clinical expert's opinion that alectinib is the first line treatment for most patients as it performs better that crizotinib and has a better toxicity profile compared with ceritinib. The ERG clinical expert agrees with the company's statement that clinical opinion suggests that the pathway beginning with alectinib will become the standardised pathway for up to 90% of ALK-positive NSCLC patients in the near future; and that the pathway beginning with crizotinib represents a small patient pool that is likely to shrink further. It is worth noting that the clinical pathway proposed initially by the company and reproduced here as Figure 1 does not

include atezolizumab plus bevacizumab, paclitaxel and carboplatin (ACBP), which is now recommended by NICE (TA584)[29] as an option for ALK-positive NSCLC.



ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy

Figure 1 Treatment pathways for patients with ALK-positive NSCLC, based on licensed indications and current NICE guidance, following the introduction of lorlatinib

3 Critique of company's definition of decision problem

3.1 Population

The population addressed in the NICE final scope and the CS is people with advanced ALK-positive NSCLC that have progressed after treatment with alectinib or ceritinib as the first ALK TKI or progressed after treatment with crizotinib and at least one other ALK TKI.

3.2 Intervention

The intervention in both the NICE final scope and the CS is lorlatinib. The company provides details of the technology in the draft summary of product characteristics in Appendix C of the company submission (CS) and a summary in Table 2, Document B, of the CS. Briefly, lorlatinib is a selective adenosine triphosphate competitive inhibitor of ALD and c-ros oncogene 1 tyrosine kinases and is intended as monotherapy in the treatment of adults patients whose disease has progressed after first line alectinib or ceritinib ALK TKI therapy or crizotinib and at least one other ALK TKI.[30] The recommended dose of lorlatinib is 100mg taken orally, as a tablet, once daily. Due to limited data, no dose recommendation is available for patients aged 65 years and older.[31] Lorlatinib is contraindicated or not recommended in patients who are hypersensitive to lorlatinib, or any of the excipients, taking strong CYP3A4/5 inducers, pregnant or breast-feeding during and for seven days after the last treatment dose.[31] Avoidance of pregnancy during lorlatinib treatment is advised as studies in animals have shown embryo foetal toxicity. Lorlatinib can render hormonal contraceptives ineffective. Condoms should be used either alone or in combination with hormonal contraceptives during treatment and for at least 14 weeks after the final dose. Male fertility may be compromised during treatment[31] and advice on effective fertility preservation should be sought before treatment commences. Whether lorlatinib affects female fertility is currently unknown.[31] Lorlatinib received conditional approval in the EU for the population indicated in the CS on 7th May 2019.

3.3 Comparators

The comparators in the NICE final scope are:

For people who have not had previous chemotherapy:

- Pemetrexed with cisplatin/carboplatin (adenocarcinoma or large cell carcinoma only)
    - with or without pemetrexed maintenance
- Atezolizumab with bevacizumab, paclitaxel and carboplatin (non-squamous only) [subject to NICE appraisal].

For people who have had previous chemotherapy (but not a PD-L1 immunotherapy):

- Atezolizumab (for adults with locally advanced or metastatic NSCLC who have previously received chemotherapy and targeted ALK treatment)
- Pembrolizumab (for adults with locally advanced or metastatic PD-L1-NSCLC who have had at least one chemotherapy and targeted ALK treatment)
- Best supportive care.

For people who have had previous treatment with an immunotherapy (PD-L1 inhibitor):

- Nintedanib with docetaxel (adenocarcinoma only)
- Docetaxel
- Best supportive care.

The comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company outline their rationale for differing in the choice of comparators outlined in the NICE final scope in Table 1, Document B, of the CS. The company state in their decision problem that PDC is the standard of care comparator for the vast majority of indicated patients. The company also state that they do not propose making a comparison based on whether patients have or have not received prior chemotherapy, arguing that few patients will have received chemotherapy, and these patients would not receive lorlatinib until the fourth line according to the NICE care pathway and, therefore, represent such a small fraction of the total population that does not warrant a standard of care comparison. The company further state that patients who receive chemotherapy post ALK TKI are a temporary population as no further ALK TKIs are currently available. The company

argue that recommendation of lorlatinib would render the chemotherapy post ALK TKI population obsolete. The company also suggest that lorlatinib should be considered for use after a second-generation ALK TKI in line with EMA marketing authorisation, which does not restrict lorlatinib based on prior chemotherapy status. The ERG clinical expert agrees with the company that lorlatinib will be given as second-line therapy after other ALK TKIs, unless people who have received crizotinib first-line, in which case brigatinib (instead of ceritinib) would be the more usual second-line therapy due to its more favourable safety profile.

The company state that best supportive care cannot be a comparator in this appraisal because patients receive this when they cannot tolerate or respond to ALK-inhibitors or PDC and argue that the remaining treatments, which are used conditionally based on previous immunotherapy, also cannot be comparators as very few patients have immunotherapies in any line. The company cite evidence from the UK ALK-positive database in reference to this assertion.[32]

The company state that they do not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) to be a relevant comparator for this submission based on the fitness of ALK-positive NSCLC patients and the high proportion with brain metastases, low expected uptake of ABCP in these patients due to no precedent of use and lack of powered clinical evidence and advice from expert oncologists who suggested that ABCP would predominantly be used in epidermal growth factor receptor (EGFR) patients. It is the ERG clinical expert's opinion that ABCP is a relevant comparator for lorlatinib. ALK-positive patients are likely to be generally fit compared with other NSCLC patients; however, their status is likely to deteriorate quickly following relapse on targeted therapies. ABCP use is likely to increase as standard care following targeted therapy as it allows immunotherapy to be moved up one line for those patients who are likely to benefit from this therapy. Following a request from NICE, the company incorporated ABCP as comparator in the company's economic model.

3.4 Outcomes

The outcomes stated in both the NICE final scope and CS are: overall survival (OS), progression free survival (PFS) response rates (including intercranial response), adverse events (AEs) and health-related quality of life (HRQoL).

3.5 Other relevant factors

The ERG agrees with the company that there are no known equality issues relating to the use of lorlatinib in patients with ALK-positive NSCLC.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D in the CS provides details of the searches that were undertaken to identify studies included in the reviews of efficacy and safety. The major relevant databases searched were: Embase and MEDLINE (using Embase.com), MEDLINE In-Process (using Pubmed.com) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database). No date limit was applied to the original search, which was updated in April 2019. In addition, the company searched proceedings of several relevant conferences and websites. Handsearching of bibliographies of key systematic reviews and meta-analyses were also screened.

The search strategies are documented in full in Appendix D of the CS. The company used Embase.com to search the incorporated Medline records as well as Embase content. This can lead to records being missed due to the automated conversion of MeSH terms to Emtree. However, the combination of index terms, text words, and drug identifiers in the search strategy has produced a highly sensitive search. The searches are fully reproducible and the range of sources searched is comprehensive and appropriate. The search will have identified all the relevant literature.

4.1.2 Inclusion criteria

The company provides details of the systematic review inclusion and exclusion criteria in Table 12, Appendix D, of the CS. Primary screening of titles and abstracts and secondary screening of full text articles were conducted independently by two reviewers. A third independent reviewer checked any uncertainty regarding the inclusion of studies. The ERG considers these methods comprehensive and appropriate.

The company provide the PRISMA flow diagram[33] of studies identified by their systematic review as Figure 1 in Appendix D of the CS. The company identified six RCTs, from 61 articles, and 87 non-RCT studies, from 238 articles, as eligible for inclusion in their review. Details of the included studies are presented in Table 13 in Appendix D. At clarification the company further explained that although six RCTs and 87 non-RCTs were identified as eligible, no other trial other than Study 1001[1], assessed lorlatinib as an intervention. The company state that Study 1001 is, therefore, the only trial that is relevant for this appraisal. Even though specific reasons for the exclusion of the eligible RCTs and non-RCTs were not provided by the company in their submission, the ERG agree that Study 1001 is the main source of evidence for the assessment of lorlatinib and it is unlikely that other relevant lorlatinib studies had been omitted.

4.1.3 Critique of data extraction

One reviewer conducted data extraction using a pre-agreed data extraction template. Extracted data were then independently checked for errors by a second reviewer. The ERG considers the data extraction methods used for the clinical effectiveness review robust.

4.1.4 Quality assessment

The company provide details of the quality assessment of the included RCTs and non-RCTs in Tables 27 and 28 in Appendix D of the CS. The company assessed Study 1001 using the Downs and Black checklist.[34] The ERG considers the company's quality assessment methods appropriate.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. Results are presented in Table 3.

Table 3 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The clinical effectiveness evidence for lorlatinib submitted by the company relates to a single phase two study, Study 1001[1]. This study is single arm investigating lorlatinib as a single agent in adult patients with metastatic (stage IV) ALK-positive NSCLC and consists of several cohorts of patients. The clinical effectiveness evidence is based upon the pooled EXP-3B:5 cohort (Table 4) and consists of 139 patients (data cut 2 February 2018). According to the opinion of the ERG's clinical expert, EXP-3B represents the typical cohort of patients that would receive lorlatinib in current clinical practice. However, due to the historical clinical pathway of recent years, EXP-4 and EXP-5 are also relevant, so the ERG agrees that pooling data from EXP-3B, EXP-4 and EXP-5 (EXP-3B:5) is acceptable. Patients in the EXP-2 and EXP-3A cohorts have received crizotinib as first line treatment; however, this is no longer considered a standard care pathway. So, the ERG agrees with the company that these cohorts are not relevant for this technology assessment.

Table 4 Study 1001 EXP cohorts

ALK/ROS 1 status	Cohort	Prior treatment regimen
ALK-positive	EXP-1	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI therapy)
	EXP-2	Patients relapsing after crizotinib therapy only
	EXP-3A	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Patients relapsing after one ALK TKI therapy other than crizotinib with or without any number of prior chemotherapy regimens
	EXP-4	Patients relapsing after two prior ALK TKI therapies with or without any number of prior chemotherapy regimens
	EXP-5	Patients relapsing after three or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens
ROS1-positive	EXP-6	Treatment naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

Source: Company Submission, Document B, Table 8.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The primary efficacy outcome in Study 1001 is the objective response rate (ORR) and intracranial objective response rate (IC-ORR). Secondary outcomes include time to tumour response, duration of response, disease control rate, time to tumour progression, progression free survival and overall survival. Patient reported outcomes were assessed using the EORTC QLQ-C30 and the corresponding lung cancer module QLQ-LC13.

The company present the baseline characteristics of the patients in Study 1001 in Table 11, Document B, CS, and present them separately for the cohorts EXP-3B, EXP-4, EXP-5 and well as for the pooled EXP-3B:5. In summary in the pooled cohort (n = 139), mean (SD) age was 52.5 (11.6), 43.9% male, 47.5% white, 38.1% Asian,

43.5% ECOG PS = 0 and 52.2% ECOG PS = 1, with 66.9% having brain metastases. The ERG note that the three cohorts were comparable for age, gender and ECOG PS, but EXP-3B had far fewer white participants [25% versus 49.2% (EXP-4) and 58.7% (EXP-5)] and a higher proportion of Asians (57.1% versus 35.4% and 30.4%, respectively). The proportion of patients with brain metastases at baseline was higher in EXP-5 (80.4%) than in both EXP-3B (42.9%) and EXP-4 (67.7%). The company reported that in the pooled cohort, the median duration of treatment was 10.1 months, range 0.2-27.9 months. The ERG considers the pooled EXP-3B:5 cohort appropriate and agree that the patient characteristics are broadly similar and representative of the target population.

4.2.1 Primary outcome: objective response rate (ORR) and intracranial objective response rate (IC-ORR)

Objective response rate is defined as the proportion of patients with a best overall response (BOR), defined as confirmed complete response (CR) or partial response (PR). BOR was defined as best response recorded from the start of treatment (C1D1) until progression or start of new anti-tumour therapy, whichever came first (source footnote, Table 9, Document B, CS). The company report that in the pooled cohort, lorlatinib led to ORR of 40.3% (95% CI 32.1, 48.9) with a majority achieving tumour shrinkage (full details are provided in Table 12, document B, CS). The company report that almost half (47.9% [95% CI 37.5%-58.4%]) of patients with brain metastases achieved a tumour response to lorlatinib with the majority experiencing tumour shrinkage (full details provided in Table 13, Document B, CS).

4.2.2 Secondary outcome: time to tumour response (TTR and IC-TRR)

Time to tumour response (TTR) was defined as time from C1D1 to first documentation of objective response (CR or PR). IC-TTR was defined in the same way but considered only the brain as the disease site. In the 56 (40.3%) patients that had tumour response the company report that the median TTR was 1.4 months (range 1.2-16.6), with about 75% responding within 4 months (source Table 14, Document B, CS). In those which had brain metastases, the median IC-TTR was 1.4 (range 1.2-16.2), source Table 15, Document B, CS.

4.2.3 Secondary outcome: duration of response (DOR and IC-DOR)

Duration of response (DOR) is defined as time from the first documentation of objective tumour response (CR or PR) to the first documentation of disease progression or death associated with any cause, whichever occurs first. The company report a summary of DOR in Table 16 and Figure 6 of Document B, CS. The median duration of response (95% CI) was 7.1 (5.6, 24.4) months. The ERG notes that the median DOR was longer in the EXP-4 cohort (median 12.5 months), compared with EXP-3B (5.6 months) and EXP-5 (7 months). The company report the same information for patients with brain metastases in Table 17, Figure 7, Document B, CS and show that in the pooled cohort, median IC-DOR was 14.5 months (95% CI, 11.1-not reached).

4.2.4 Secondary outcome: disease control rate (DCR and IC-DCR)

Disease control rate (DCR) has been defined by the company as the proportion of patients with disease control (CR, PR, stable disease) at 12 weeks and 24 weeks. IC-DCR is the proportion of patients with IC disease control (CR, PR, stable disease, considering only the brain as the disease site) at 12 weeks and 24 weeks. The company report the results for DCR and IC-DCR in Table 18 and Table 19 respectively of Document B, CS. In the pooled cohort, the DCR was 59.7% (95% CI 51.1-67.9) at 12 weeks and 43.2% (95% CI 34.8-51.8) at 24 weeks, with IC-DCR 73.4% (63.3-82.0) at 12 weeks and 55.3% (44.7-65.6) at 24 weeks.

4.2.5 Secondary outcome: progression free survival

Progression free survival is defined by the company as time from C1D1 to first documentation of objective disease progression or death on study due to any cause, whichever came first. The company submission, Document B, Figure 8 shows the Kaplan-Meier curve for progression free survival, and Table 20 reports that in the pooled cohort the median PFS is 6.9 months, 95% CI (5.4-8.2).

4.2.6 Secondary outcome: overall survival

Overall survival is defined as time from C1D1 to date of death due to any cause. In the pooled cohort, overall survival has median 20.4 months, 95% CI (16.1, NR). The probability of surviving to 12 months is 0.678 (95% CI 0.591-0.750) and 0.556 (0.155-0.306) to 18 months (source Table 20, Figure 9, Document B, CS).

4.2.7 Patient reported outcome: EORTC QLQ-C30/ EORTC QLQ-LC13

The company reported pooled analysis of the EORTC QLQ-C30 functioning scales for all the EXP cohorts, EXP-1:6, consisting of 255 patients, using data from the 15 March 2017 data cut. During the clarification process, the ERG expressed concern that an older data cut was used, compared to efficacy analysis (February 2018 data), and that all the cohorts were used, not just EXP-3B:5. In response (clarification question A4), the company provided updated tables for theses outcomes using the February 2018 data cut and provided the information for each of EXP-3B, EXP-4 and EXP-5 cohorts separately as well as pooled. Data presented for the later cut (Pfizer documents provided in response to clarification A4), showed similar results to the original CS and the ERG are satisfied that the data presented in the CS provide evidence that lorlatinib improves/keeps stable key patient-reported outcomes.

Using the March 2017 cut, the company reported the proportion of patients improving (≥10 points), remaining stable and worsening when compared to baseline for the global quality of life and the functional scales (Table 21, page 51, CS). The majority of patients had improved (42.4%) or remained stable (38.0%) for the global QoL score, with the majority also improving or remaining stable for each of the functioning scales (physical, role, emotional, cognitive, social). The company also report that the majority either improved or remained stable for each of the symptoms measured by QLQ-C30 and QLQ-LC13 (Table 22, Document B, CS). Key lung cancer symptoms reporting improvements were coughing (42.7%), pain in chest (29.8%) and dyspnoea (27.5%), as measured by QLQ-LC13.

4.2.8 Adverse reactions

Safety data were presented for all patients who received lorlatinib at 100 mg once daily in Study 1001, as of data cut 2 February 2018. The company state that this consists of 295 patients (17 from phase 1, 275 phase 2 and 3 from Japan lead-in cohort). In addition, the company present the safety data for the 139 patients in the EXP-3B:5 pooled cohort and it is these data which we focus on here. The median duration of lorlatinib was 16.3 months for the 100mg OD group, and 10.1 months for the pooled EXP-3B:5 cohort.

In the pooled EXP-3B:5 cohort, dose reductions and temporary discontinuations due to AEs occurred in [redacted] and [redacted] respectively. These were comparable to the 100mg OD group (Table 27, Document B, CS). Table 28, Document B, CS describes the specific AEs in both the 100mg OD group and for the EXP-3B:5 cohort. The proportions for each event type are comparable so in this ERG report, we present information on EXP-3B:5. The most common AEs were hypercholesterolemia ([redacted]), hypertriglyceridemia ([redacted]), oedema ([redacted]), peripheral neuropathy ([redacted]), with all other AEs reported in [redacted] or less of the EXP-3B:5 cohort. [redacted] of patients experienced a grade 5 AE, with [redacted] grade 3/4.

Serious adverse events occurred in [redacted] of the EXP-3B:5 cohort (full details Table 30, Document B, CS), the most common being disease progression [redacted]. Table 31, Document B, CS reported [redacted] SAEs were considered a treatment related serious adverse event, with 6 grade 3 and 4 grade 4 treatment related SAEs, none were fatal.

In the pooled EXP-3B:5 cohort, [redacted] of patients permanently discontinued lorlatinib treatment due to AEs (Table 32, Document B, CS) and this was a comparable percentage to the 100mg once daily group. Table 33, Document B, CS shows that [redacted] experienced dose reductions because of an AE, again comparable to the 100mg OD group.

The company conclude that *'safety data from Study 1001 demonstrate that lorlatinib was generally tolerable and when needed, AEs were manageable through dosing delay, dose reduction and/or standard supportive medical therapy'*. The ERG agrees with the company's conclusions.

4.2.9 Critique of evidence submitted for lorlatinib

The company present efficacy data for lorlatinib from a single phase two study of a single arm (Study 1001). No studies are presented which directly compare lorlatinib with any of the comparators specified in the NICE final scope. The company indicate that the only relevant comparator is chemotherapy. The ERG disagrees with this statement and consider ACBP a relevant comparator too. The ERG is of the opinion that the main limitation of the current assessment is that the evidence base for the

clinical effectiveness of lorlatinib relies solely on a small (n = 139) single arm study, which contains no UK based participants. The company present a MAIC to compare lorlatinib with chemotherapy (discussed in [redacted], Document B, CS); however, they do not use the MAIC results for their base case economic model.

The company present pooled data for cohorts EXP-3B, EXP-4 and EXP-5 (EXP-3B:5). The ERG agree that this best represents the current target population for lorlatinib and were happy with the decision to pool the cohorts. The ERG agree that EXP-1, EXP-2, EXP-3A were not relevant for this assessment as the prior treatment pathways do not match the target licensed population.

The ERG were initially concerned that the data cut used for efficacy date was February 2018 (nearly 18 months ago); however, at clarification the company confirmed that these are the most recent data available and that new data are not available until end of 2019, with final data ready in September 2020. The original CS presented data for quality of life outcomes based on an even earlier data cut (March 2017) but at clarification, the company provided Pfizer produced output on the more recent February 2018 data cut (see section 4.2.7 above).

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

4.3.1 Comparison with chemotherapy

The only relevant comparator considered by the company was chemotherapy, and no head to head trials were found. The evidence for the comparator of chemotherapy in ALK-positive NSCLC patients was presented for the ALUR, ASCEND5 and PROFILE 1001/1005 studies. Full details on these studies can be found in Appendix D, CS.

The ALUR trial compared alectinib (600mg twice daily) with chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 every 3 weeks), while ASCEND5 compared ceritinib (750mg per day) with chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 every 21 days). Participants in both studies had already had two lines of therapy (one line of platinum-based doublet therapy (PDC) and one of

crizotinib). The company pooled data from the chemotherapy arms of ALUR[2] and ASCEND5[3] for the PFS survival outcome within the MAIC as they reported that the baseline characteristics of the two trials were broadly similar. The ERG had concern over the use of these two studies as the evidence base for chemotherapy for the following reasons:

- all patients in ALUR/ASCEND have had PDC previously, which may not be relevant for the target population. ERG clinical opinion is use of crizotinib is falling and questioned whether these studies were the best source of comparator evidence.
- the ERG clinical expert has the opinion that while response rates on pemetrexed and docetaxel are likely to be similar, docetaxel has greater toxicity and the expert had uncertainty over their equivalence for pooling
- the ERG clinical expert did not agree with the assumption that PDC is equivalent to pemetrexed or docetaxel. The opinion is that PDC is superior to the single agents, and patients in the ALUR and ASCEND have already had the superior PDC treatment prior to study entry. The company offered a counter argument that patients in these trials were exposed to only one prior ALK TKI (crizotinib), whereas the population eligible for lorlatinib may have been exposed to two or more and so might be expected to have a worse efficacy outcome (as suggested by some clinical experts). However, the ERG remains concerned about the potential for underestimating the efficacy of PDC.

The company report that the ALUR and ASCEND5 did not provide any data for OS (page 54, Document B, CS). However, Appendix D and the publications for ALUR and ASCEND5 indicate that data for overall survival appeared to be available. It is not clear to the ERG why these data were not used by the company. Instead, the company undertook a retrospective analysis of the crizotinib arm of the PROFILE 1001 and PROFILE 1005 for the subgroup of patients receiving systemic therapy (likely chemotherapy) after progression on crizotonib. The ERG is concerned for the following reasons:

- the patient population previously treated with crizotinib were earlier dismissed by the company as being relevant to the licenced population. ERG clinical opinion is use of crizotinib is falling, and the current relevance of this population is questioned.

- the subgroup utilised here consists of only 37 patients, and the majority of patients are reported to have received PDC prior to study entry
- the subgroup here are considered 'likely' to be receiving chemotherapy but are not confirmed to be receiving chemotherapy. It is also not clear what chemotherapy they received and if they did so, given the majority were treated with PDC prior to study entry, it is likely to be one of the single agents (e.g. pemetrexed or docetaxel.

These data were then used by the company to undertake a matching-adjusted indirect comparison (MAIC) for lorlatinib versus chemotherapy for progression free survival (PFS) and overall survival (OS). A MAIC allows and indirect treatment comparison to be made when treatments are not connected by a common comparator (section 4.4).

4.3.2 Comparison to ABCP

The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator, but on request from NICE provided a short appendix to the main CS detailing the comparison. The reasons for dismissing ABCP as a relevant comparator were: patient fitness and the high proportion of brain metastases, low expected update given no precedent of use in ALK-positive patients, lack of powered clinical evidence and consultations with practicing expert oncologists who suggested ABCP use would be limited to EGFR patients. The ERG disagree with the company's position and consider ABCP a reasonable option, and it has been approved by NICE for the treatment of ALK patients.

The company present minimal efficacy data to inform the cost-effectiveness comparison of lorlatinib versus ABCP. The data for ABCP comes from a single trial (IMpower150)[29, 35, 36] which compared ABCP with bevacizumab, carboplatin and paciltaxel in patients with stage IV non-squamous NSCLC. The company note that this data is not comparable to EXP-3B:5 from Study 1001, as the IMpower150 participants are predominantly EGFR majority (n = 41) with only 11 having ALK-positive status. Further details on the ABCP comparison are found in section 5.2.4 of this report.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

4.4.1 Description/critique of the MAIC

As the evidence for lorlatinib is limited to a single arm study, the ERG agree it is not possible to undertake standard indirect comparison. NICE Technical Support Document 18[36] (TSD18) recommends that a Matching-adjusted-indirect-comparison (MAIC) can be used in this type of situation and it is an unanchored MAIC which has been implemented by the company to compare lorlatinib to chemotherapy. TSD18 provides six recommendations that all unanchored population adjustments must meet to be considered robust[36]. The ERG will present each of these in turn with an explanation as to whether they have been met by the company in their submission.

1. Unanchored population adjustment may only be considered in the absence of a connected network of randomised studies or where a single arm is involved.

The ERG agrees that recommendation one above has been met by the company as Study 1001 is a single arm study and is the only evidence available.

2. Evidence should be provided that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and present an estimate of the likely range of residual systemic error in the 'adjusted' unanchored comparison.

The company stated that clinical feedback suggested the most important prognostic variables/effect modifiers to be used in the matching were ECOG performance status (0-1 vs >1), brain metastases (yes vs no) and race (Asian vs Non-Asian). In addition, the company undertook a series of cox regression models to assess the importance of eight different variables in predicting outcome using the lorlatinib individual patient data (see section D.1.4.2.2, Appendix D, CS). The eight variables were: sex (male, female), age group (18-44, 45-64, ≥65), race (Asian, white, other), ECOG performance status (0,1,2), brain metastases (yes, no), adenocarcinoma (yes/no), weight (<66kg, ≥66kg), body mass index (BMI) (<18.5, 18.5-24.9, >24.9).

The company undertook this process on the combined data from cohorts EXP-2, EXP-3A, EXP-3B, EXP-4 and EXP-5 (EXP-2:5). Kaplan-Meier curves are available for each of these variables for each of the outcomes (OS and PFS) in Figure 2-Figure 9, section D.1.4.2.2 of Appendix D. The company provided hazard ratios for each covariate/outcome combination (Table 21 and Table 22, page 76, Appendix D). The ERG asked at clarification for 95% confidence intervals to be supplied for these estimates, which the company provided in response to clarification A8 (reproduced here as Table 5 and 6). This analysis showed that ECOG performance status and BMI were possible important predictors of outcome.

Table 5 HRs and p-values from univariate Cox proportional hazards model for each covariate for lorlatinib patients in cohorts EXP-2: EXP-5 (reproduced from company Table 2, clarification response A8 and Appendix D, table 21)

Model	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (White)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
ECOG PS (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (2)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (18.5-24.9)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival

Note: p-values <0.05 are shown in bold

[redacted]Gender was not highlighted in the above analysis, but the commented in their clarification response (A13) that gender was consider important in the literature.[37] Following this analysis and combining with clinical opinion, the company concluded that ECOG performance status (0-1 vs >1), brain metastases (yes vs no), race (Asian vs Non-Asian) and gender (male vs female) were the relevant variables for the matching process within the MAIC. The ERG agrees with this conclusion.

Table 6 HRs and p-values from multivariate Cox proportional hazards model for each covariate for lorlatinib patients in cohorts EXP-2: EXP-5 (reproduced from company Table 3, clarification response A8 and Appendix D, Table 22)

Coefficient	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (White)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (18.5-24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival

Note: p-values <0.05 are shown in bold.

3. Population adjustment methods (both propensity score weighting and outcome regression) should adjust for all effect modifiers and prognostic variables, in order to reliably predict absolute outcomes.

As discussed under recommendation two, the company adjusted for four characteristics: race, gender, ECOG and brain metastases. While the ERG agree that these variables are relevant, they cannot be sure this list is exhaustive, and that residual bias has been avoided.

4. Indirect comparisons must be carried out on the usual linear predictor scale used for the evidence synthesis of that outcome

This has been implemented the company through presentation of hazard ratios from the Cox regression models. The ERG confirm recommendation four has been met.

5. The target population for the decision problem must be explicitly stated and the population adjustment must deliver treatment effect estimates for that target population.

The company present matching (population adjustment) to both EXP-2:3A and separately EXP-3B:5 (target population). The reason behind matching on the EXP-2:3A patient population is that they are more in line with the patients within the ALUR, ASCEND5 and PROFILE 1001/1005 studies as they received both chemotherapy and crizotinib previously. The company indicate that EXP-2:3A is their primary matching cohort, but because EXP-3B:5 is the target population, they also carried out an analysis for that as well. The ERG are happy with this approach and the justification and agree recommendation five has been met.

6. Strict reporting of the assessment of covariate distributions, evidence of effect modifier status, distribution of weights and measures of uncertainty

The company present summary statistics for the relevant covariates for each of the studies, but do not provide the full covariate distribution as per the recommendations (e.g., histograms/box plots). The distribution of weights were provided by the company and the ERG agree they were acceptable. Measures of uncertainty were provided in the form of bootstrapped confidence intervals for the hazard ratio estimates. Unadjusted and adjusted estimates were provided as per recommendations. Therefore, the ERG were happy that recommendation six was met sufficiently by the company.

4.4.2 Results of the MAIC: lorlatinib vs chemotherapy

Following the matching process described in Appendix D, CS, the company presented the results in section B.2.8.4 (PFS) and B.2.8.5 (OS). The ERG noted a mistake within the MAIC for progression free survival in regard to the proportion of subjects in the ALUR study with ECOG PS 1/2. This should have been 68.6% instead of the reported 14.3%. In the clarification response (A9) the company acknowledged the error and updated the results (originally presented Table 25, CS). These updated results are presented in Table 7. This error had no impact on the cost-effectiveness as the results of the MAIC were not used in the base-case. The MAIC showed that treatment with lorlatinib provided a clear reduction in hazard, i.e. longer time to progression when compared to those treated with chemotherapy.

Table 7 Unadjusted and adjusted HR for PFS following the MAIC (reproduced from Table 4, clarification response A9)

Weighted matching cohort (Study 1001)	Naïve		Adjusted	
	HR	95% CI	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; EXP = expansion; HR = hazard ratio; *bootstrapped 95% CI

Table 8 provides the results of the MAIC for the outcome of overall survival. The company noted that the definition of brain metastases differed between Study 1001 and PROFILE, so they carried out the MAIC with and without brain metastases as one of the matching variables and obtained similar results. The results showed that lorlatinib is associated with a decreased hazard of mortality when compared to chemotherapy.

Table 8 Unadjusted and adjusted HR for OS following the MAIC (reproduced from Table 26, CS)

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases)		Adjusted (not including brain metastases)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio *bootstrapped 95% CI

4.4.3 Summary of the MAIC

In summary, the ERG considers the MAIC an acceptable method to compare the clinical effectiveness of lorlatinib to chemotherapy. If one assumes the evidence base is acceptable then the MAIC has shown clinical benefit of lorlatinib compared with chemotherapy for both PFS and OS. However, the ERG have concern over the evidence base used for chemotherapy (section 4.3.1), and therefore concern over the validity in the interpretation of the result.

The MAIC results are not used to inform the base case economic model.

4.5 Additional work on clinical effectiveness undertaken by the ERG

None.

4.6 Conclusions of the clinical effectiveness section

The company have provided evidence that lorlatinib is effective in prolonging time to progression and prolonging overall survival in patients with ALK-positive advanced NSCLC following progression from one or more previous ALK TKIs. The company provided sufficient evidence of a tolerable safety profile and evidence that lorlatinib provide stability or improvement in a number of important quality of life domains as measured by QLQ-C30 and QLQ-LC13.

The evidence for lorlatinib is limited to a single arm study, and thus a MAIC was undertaken (as recommended by NICE in these situations) and the ERG are happy the MAIC has been implemented correctly. However, as discussed above the ERG have

some have reservations over the evidence-base used for the comparator of chemotherapy.

In summary, the ERG agree with the company's conclusion on the effectiveness of lorlatinib versus chemotherapy subject to the following concerns:

- One small single arm study is the sole source of evidence for lorlatinib
- Chemotherapy is assumed by the company to be the only relevant comparator for the target population, but the ERG believe ABCP should have been considered a relevant comparator.
- ERG clinical opinion believes PDC is superior to pemetrexed and docetaxel monotherapy, but the company have made an assumption the different chemotherapy options have equal clinical benefit
- The use of PROFILE 1001/1005 to provide data for OS given the participants are 'assumed' to be on chemotherapy and not known to be. The type of chemotherapy is unknown. Overall survival data were available within ALUR/ASCEND but were not used by the company.
- the company do not use the MAIC results in the base case analysis of the economic model.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

One objective of the review was to identify previous studies of the cost-effectiveness of lorlatinib in the licensed indication. The search strategy was described in Appendix G.

The search strategy seems appropriate. While the search was conducted in August 2018 and not updated, the ERG agrees no relevant studies of cost-effectiveness of lorlatinib have been published.

The systematic review also searched for information on previous modelling, utility values and on resource use and costs; these are considered under the relevant headings of this report and only the search for previously published economic evaluations was considered here.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

The criteria are set out in Appendix G (Table 44, commencing on page 103 of the company appendices). These seemed appropriate.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies

The review identified 20 economic evaluations of medicines for ALK-positive NSCLC. None were of lorlatinib.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details

The review concluded that no published studies of lorlatinib were identified up to August 2018. The company judged that updating the review would not identify any new publications and the ERG accepts this view as far as journal articles are concerned. However:

1. The review appears to have missed TA 406[23] (crizotinib in previously untreated disease); the excluded studies are in Appendix H.1.1.3 on page 113 but does not seem to be mentioned. (TA 422[26] was a CDF review of TA 296[38], which was also not identified.)
2. It is feasible that a conference abstract could have been reported in the 12 months since the review was undertaken and ideally the company would have undertaken a search of this specific source e.g. ISPOR meetings in that period.
3. The ERG agrees there do not appear to be any reports from other HTA agencies such as ICER on lorlatinib.
4. The company review appropriately identified previous NICE TAs 395[27] and 422[26] (ceritinib after crizotinib and crizotinib after one previous treatment respectively) within ALK-positive NSCLC, but because the review was not updated it did not identify TAs 500[24] (ceritinib in previously untreated), 536[25] (alectinib in previously untreated) or 571[21] (brigatinib after one previous treatment).

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 9 NICE reference case

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Refer to NICE scope for suggested comparators in: 1) people who have not had previous chemotherapy; 2) people who have had previous chemotherapy (but not a PD-L1 immunotherapy); and 3) people who have had previous treatment with an immunotherapy (PD-L1 inhibitor)	The company has included the comparators that were listed in the scope for those who have not had previous chemotherapy or previous treatment with an immunotherapy. The company argue that first line use of chemotherapy in the ALK+ NSCLC population is rapidly diminishing, and most patients eligible for lorlatinib will not have had prior chemotherapy or immunotherapies but will have progressed primarily on alectinib as the first line treatment. The ERGs clinical expert broadly agrees with this assertion.
Patient group	People with advanced ALK-positive NSCLC that has: progressed after treatment with alectinib or ceritinib as the first ALK-tyrosine inhibitor; Or progressed after treatment with crizotinib and at least one other ALK-tyrosine kinase inhibitor.	The company submission covers the relevant patient population.

Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes. Carers not included
Form of economic evaluation	Cost-effectiveness analysis	Yes, a cost-utility analysis is performed.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, a life time perspective is taken.
Synthesis of evidence on outcomes	Systematic review	Yes, systematic reviews were carried out to inform key parameters. Uncertainties arise from the single arm design of Study 1001 and the limited availability of data to inform the comparative effectiveness of PDC and ABCP in the relevant population.
Outcome measure	QALYs	Yes
Health states for QALY	Described using a standardised and validated instrument	The health status in the model states (progression free and progressed) is based primarily on EQ-5D response data from NSCLC patients. However, the utility value applied for the pre-progression state on lorlatinib is derived by mapping from the EORTC QLQ-C30 questionnaire.
Benefit valuation	Time-trade off or standard gamble	Yes, the UK EQ-5D TTO tariff is applied.
Source of preference data for valuation of	Representative sample of the public	Yes, UK general population.

changes in HRQL		
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes, but results only presented for the company's base case comparison against PDC.
Sensitivity analysis		Covered the main sources of uncertainty, but it is the ERG's opinion that not all uncertainties were adequately addressed through sensitivity analysis.

5.2.2 Model structure

The company submission used a partitioned survival model to estimate costs and benefits. The health states were progression-free survival, post-progression survival (PPS) and dead.

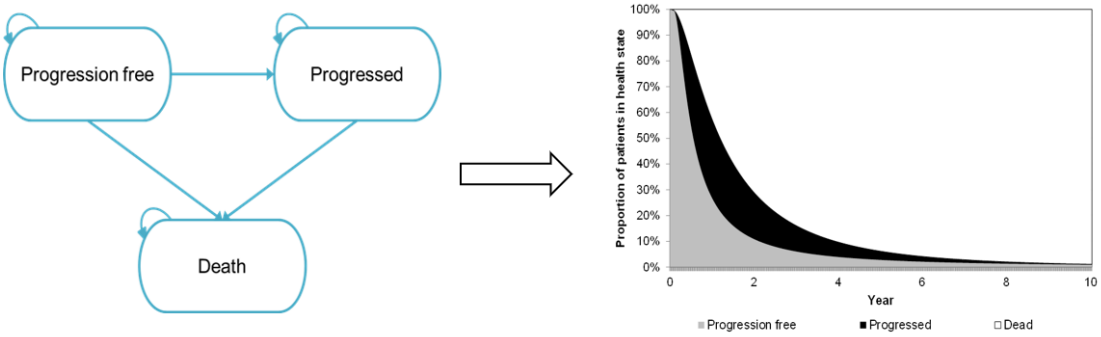


Figure 2 Company model structure (Reproduced Figure 19, Company submission, Document B, page 84)

The structure and states reflect the economic models previously used in all the NICE STAs of medicines for ALK-positive NSCLC (TAs 395[27], 406[23], 422[26], 500[24], 536[25], 571[21]). The only exception is that TA 536 divided progression into 'CNS progression' (typically metastatic disease in the brain) and non-CNS progression. This could be potentially relevant for lorlatinib if type of progression is proportionally different among those who progress on lorlatinib and PDC or ABCP.

5.2.3 Population

The patient population in the company's economic model is taken from the following table (Table 10), which describes all patients in Study 1001. The company make the case that the cohorts in the study that match the license are 3b, 4 and 5.

Table 10 Populations in Study 1001 (Source: Table 36, Company Submission, Document B, page 83)

ALK/ROS1 status	Cohort	Used in model	Prior treatment regimen
ALK-positive	EXP-1	No	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI therapy)
	EXP-2	No	Patients relapsing after crizotinib therapy only
	EXP-3A	No	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Yes	Patients relapsing after one ALK TKI therapy other than crizotinib with or without any number of prior chemotherapy regimens
	EXP-4	Yes	Patients relapsing after two prior ALK TKI therapies with or without any number of prior chemotherapy regimens
	EXP-5	Yes	Patients relapsing after three or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens
ROS1-positive	EXP-6	No	Treatment naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

Source: Company Submission, Document B, Table 36, page 83.

The population described in the Final Scope is "People with advanced ALK-positive NSCLC that have:

- progressed after treatment with alectinib or ceritinib as the first ALK-tyrosine inhibitor,

  or
- progressed after treatment with crizotinib and at least one other ALK- tyrosine kinase inhibitor."

EXP-6 is clearly not relevant because it is for NSCLC that is ROS-1 positive. EXP-1 is for treatment naïve ALK-positive patients and hence is also not relevant. EXP-2 is for relapse after crizotinib only, and the license requires the patients fail after crizotinib and at least one other TKI. EXP-3A patients failed after crizotinib and chemotherapy, not another TKI, so is also outside of the license.

The ERG therefore agrees that cohorts EXP-1, -2, -3a and -6 from Study 1001 are all outside of the final scope.

The company submission then combines all three cohorts (3B, 4, 5) into one group for the purpose of producing an estimate of effectiveness.

5.2.4 Interventions and comparators

The intervention in the company submission was lorlatinib 100mg once daily. Duration on treatment was informed by modelling of PFS and time on treatment data from Study 1001. From the EPAR SmPC[39], the recommended duration of treatment is as follows:

"Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity."

The options for comparator were specified in the final scope by whether patients have been previously treated with chemotherapy and/or a PD-L1 immunotherapy.

For those who have not had previous chemotherapy, the final scope specified:

- Pemetrexed with cisplatin/carboplatin (adenocarcinoma or large cell carcinoma only), with or without pemetrexed maintenance
- Atezolizumab with bevacizumab, paclitaxel and carboplatin (non-squamous only) [subject to NICE appraisal]

For people who have received previous chemotherapy (but not a PD-L1 immunotherapy), the final scope specified atezolizumab, pembrolizumab and 'best supportive care' (BSC) as comparators.

For people who have had previous treatment with an immunotherapy (PD-L1 inhibitor), nintedanib with docetaxel (adenocarcinoma only), docetaxel and best supportive care were listed as comparators in the final scope.

The company submission reports clinical expert views as being that for ALK+ NSCLC, targeted ALK TKIs are preferred ahead of other therapies, with the aim being to maximise the time patients are treated with these. Where available ALK TKIs are exhausted, the company note that clinicians generally favour PDC ahead of immunotherapy (with or without chemotherapy). They also note that clinical expert opinion consistently suggests that the pathway beginning with the second generation ALK-INH alectinib is quickly becoming standard care, and that the pathway beginning with chemotherapy is therefore becoming less common, representing "a small and rapidly shrinking pool of patients". The company also note that the use of the immuno-oncology medicine, atezolizumab, is likely to be low because of the limited evidence in ALK-positive disease, and 66.9% of patients in Study 1001 have brain metastases at baseline and hence are not suitable.

The company therefore conclude that chemotherapy, which they identify as pemetrexed plus carboplatin or cisplatin (PDC), is the most relevant comparator for lorlatinib in their submission. The company also submitted an addendum to their main submission which provided a comparison with the atezolizumab combination regimen (atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP)).

The ERG's clinical advice is that:

- *alectinib is probably the most widely used medicine in previously untreated patients*
- *the pathway where chemotherapy is used first is less likely as ALK testing is now routine*
- *for the diminishing population who have crizotinib as their first ALK TKI, the next line of treatment would probably be brigatinib (it may be more effective than ceritinib and has a better side-effect profile)*
- *lorlatinib will be given after other ALK-targeted treatments*

- *the atezolizumab combination regime (ABCP) is a feasible comparator for lorlatinib*
- *chemotherapy is an option in later lines but where there is a choice its use is delayed as long as possible because of side-effects*

The ERG's conclusions are that the comparison with PDC is appropriate, that other TKIs are not comparators, and that a comparison with ABCP is relevant and should be considered as part of the base-case and not as a secondary analysis.

In costing the PDC regime, the company submission specifies that this is to be followed by pemetrexed maintenance therapy for those remaining progression free after 6 cycles. The ERG note this is generally in line with recommendations from NICE TA402 (Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin)[40] and NICE TA190 (Pemetrexed for the maintenance treatment of non-small-cell lung cancer)[41]. However, NICE TA402 states that ECOG performance status should be 0 or 1 at the start of maintenance treatment[40]. Therefore, the assumption that all patients move on to maintenance pemetrexed if they remain progression free after six treatment cycles of PDC may be questionable.

The ERG also notes that nivolumab and nintedanib with docetaxel are mentioned in NICE NG122[42] as treatment options following first-line chemotherapy. Clinicians do not seem to regard these as standard treatments at this stage in the pathway and they have not been considered further in the model. Rather, atezolizumab and pembrolizumab are considered as subsequent treatments to PDC in the company model.

5.2.5 Perspective, time horizon and discounting

The perspective in the economic evaluation provided by the company was the NHS plus personal social services.

The ERG agrees this matches the NICE Reference Case.

The time horizon in the base case of the economic evaluation was 20 years. Patients in the relevant cohorts of Study 1001 were aged 52.5 on average when treatment started (from Table 11 on page 41 of Document B) so any surviving patients would be age 72.5 (52.5 plus 20) at termination of the model. However, less than 1% of the cohort are surviving in both arms of the model by this time point. Therefore, the ERG accepts the 20-year time horizon is acceptable for the base case.

The discount rate used in the company submission was 3.5% per annum (Section B.3.2.3 in Document B, page 83). This is consistent the NICE Reference Case.

5.2.6 Treatment effectiveness and ***extrapolation***

Study 1001 was non-comparative and recruited different cohorts of patients, the relevant ones for the licensed indication being distinguished by previous treatments received. It is the only source of efficacy data for lorlatinib and hence was used as the basis for estimates of effectiveness over an extended time horizon and compared to a relevant alternative.

PFS: lorlatinib

Data from the clinical study were presented in the submission in Document B, Figure 22 and Table 40 on page 94.

Standard parametric curve fits were undertaken by the company and clinical experts from the UK were asked which curve they felt was most appropriate: the company reported they favoured generalised gamma or Gompertz curves. In the base-case the generalised gamma was selected on the basis of visual and statistical fit to the observed data plus long-term plausibility (seemingly meaning the endorsement of the clinicians consulted). The generalised gamma was described as in the middle of the range of estimates for all curves (page 93, Document B).

OS: lorlatinib

OS data from the clinical study were presented in Figure 39 and Table 44 of the CS (document B, p111). The clinical data were extrapolated by fitting parametric curves. An assessment of the fit of the curves was conducted in line with NICE TSD 14[43] guidance. Following this, the opinions from two clinical experts were sought (a

description of the clinical validation process, along with issues with the process which have been identified by the ERG, is contained within Section 5.10). Upon request for clarification by the ERG, the company updated Table 44 to include the proportion alive at 10 years. This table is reproduced as Table 11 below.

Table 11 Updated Table 44: Mean, median and landmark values and AIC and BIC statistics for lorlatinib OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)					
					6 months	1 year	2 years	3 years	5 years	10 years
Generalised gamma	[redacted]									
Exponential	[redacted]									
Weibull	[redacted]									
Log-normal	[redacted]									
Log-logistic	[redacted]									
Gompertz	[redacted]									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival

From Table11, it can be seen that the exponential curve has the best statistical fit to the observed clinical data using both the AIC and BIC, although by a small margin. The company argue that selecting a parametric survival curve based primarily on information criterion is not appropriate in this case due to the limited range of information criterion values observed across the six curves. Additionally, the company argue that the information criterion values do not appear to be strongly related to landmark values of the extrapolated curves.

Rather than select a parametric OS curve based solely on information criterions, the company sought the opinions of two clinical experts. One of the clinical experts stated an expectation that 10-year OS for lorlatinib would be around [redacted], and that the [redacted] prediction of the exponential curve was overly pessimistic.

[redacted]. However, the company adopted the generalised gamma curve for extrapolating data in the base case.

The ERG recognises the difficulty of extrapolating limited clinical data substantially beyond the observed period. Although the company found a consensus amongst the two clinical experts they consulted, the ERG's clinical adviser believed that the [redacted] projected survival at 10 years for lorlatinib was optimistic given the previous treatment history and believed [redacted] to be more plausible. The ERG supports the company's decision not to adopt the most optimistic extrapolation for lorlatinib OS, despite consensus amongst the clinical experts they consulted. Based on both the ERG's clinical advice and the measures of statistical fit (AIC and BIC), the ERGs opinion is that the extrapolation based upon the exponential distribution cannot be disregarded. However, given the paucity of clinical data and substantial doubt regarding the most appropriate extrapolation, the company has adequately addressed this within their scenario analysis.

Comparative clinical effectiveness

The company made decisions about:

- Which clinical study data to use to represent the comparator arm
- Which method to use to compare lorlatinib with the 'usual care' data
- How to fit parametric curves to the data for lorlatinib and the comparator arm

Selection of clinical study data for comparator arm

The company submission included a systematic review to identify potentially relevant clinical studies. There were no studies where PDC was used in pre-treated ALK+ disease. The company's approach was to only consider studies of patients with pre-treated ALK+ disease, and the only chemotherapy treatments explicitly identified in available studies were pemetrexed monotherapy and docetaxel monotherapy. The company submission assumed that the data for these treatments would apply to PDC as well.

The selected studies were ALUR and ASCEND-5 for PFS and a retrospective analysis of PROFILE 1001/1005 for OS:

- ALUR and ASCEND-5 were RCTs in pre-treated ALK+ NSCLC patients of alectinib (ALUR) and ceritinib (ASCEND-5), both versus investigator's choice of either iv pemetrexed 500 mg/m2 or docetaxel 75 mg/m2, both every

3 weeks. Both studies were open-label, both allowed crossover and both had PFS as the primary endpoint.

- PROFILE 1001 and PROFILE 1005 were single-arm studies of crizotinib treatment, totalling 414 patients (figures from Ou 2014). The analysis was of 194 patients whose disease had progressed and was originally intended to compare patients treated with crizotinib after progression with patients who stopped crizotinib (n=120 versus n=74). The company submission argues it is the latter group who best represent the comparator arm for the lorlatinib economic evaluation because the patients have had a TKI and then get a non-TKI treatment.

ERG commentary

The ERG makes the following points about the company's choice of data of efficacy data for the comparator:

1. The ERG agree there are no studies of PDC in ALK+ patients pre-treated with ALK TKI.

2. The ERG also agree that the PFS data for pemetrexed monotherapy and docetaxel monotherapy in pre-treated patients are relevant when judging the most plausible level of effectiveness for PDC in pre-treated patients.

3. However, the ERG's clinical expert advice is that PDC would be more effective than either of the monotherapy regimes.

4. The ERG is aware of another RCT in NSCLC comparing PDC to pemetrexed monotherapy which confirmed PDC was more effective (Smit et al, JCO 2009 27 2038). There may be others, the search was not comprehensive.

5. Of the pooled sample from ALUR and ASCEND-5 (n=151), 77% were from ASCEND-5. Across the two studies, 147 patients received treatment with 98 choosing docetaxel (67%) and 49 pemetrexed. This is of concern because the published report on the ASCEND-5 RCT comments, "In previous studies, patients with ALK-rearranged non-small-cell lung cancer have been shown to be particularly responsive

to pemetrexed[44, 45]. Thus, the higher proportion of patients given docetaxel (63%) in this study than in the PROFILE 1007 study (41%) might have led to a worse overall outcome in the chemotherapy group from this study than in the PROFILE 1007 study."[3]. The preponderance of patients treated with docetaxel in the pooled sample suggests using these data to estimate the effectiveness of PDC in this population will result in an under-estimate of PFS.

6. The use of the retrospective analysis of PROFILE 1001 and 1005 to inform OS for PDC has several weaknesses:

- *The number of patients who stopped crizotinib on progression and received a subsequent systemic therapy is only 37[46] and the small sample size means there is considerable uncertainty in the interpretation of the results.*
- *The Ou paper reports these 37 patients received systemic therapy but it does not say what this was. 96% of patients were reported to have received previous platinum therapy prior to entry into the study[46] (Table 1) – assuming this to be PDC it seems unlikely PDC would be used again therefore the data are not directly relevant. As Pfizer sponsored the PROFILE studies and Ou's work it was not clear why the type of therapy received by the 37 patients was not reported.*
- *Of the 194 who progressed on crizotinib, the group who continued crizotinib after progression could be those who were the best responders to a TKI and hence the sample is skewed.*
- *Crizotinib is a 1st generation TKI and its use in England and Wales is falling. Patients potentially considered for lorlatinib are likely to have been pre-treated with a 2nd generation TKI instead which raises questions about the generalisability of the findings to modern NHS practice.*

Taken together this suggests the results could under-estimate what PDC would achieve in this setting.

7. The company submission took PFS data from one pair of studies and OS data from another pair of studies. Ou reports time to progression as well as OS; ALUR and ASCEND-5 report OS as well as PFS.

In terms of progression, Ou reports a median time of 5.7 months[46], but this is an average of patients receiving systemic therapy and BSC; only considering the former group would seem likely to have raised this figure. This is considerably above the median PFS in ALUR and ASCEND-5 which was around 1.5 months. If Ou is relevant for the OS part of the analysis, it is not clear why the data are not also relevant for the PFS analysis.

In terms of OS, the data from ALUR and ASCEND-5 were ignored, which could be argued to be because of the high rate of crossover, but an effort could have been made to adjust for this. In ASCENED-5 there were more deaths at the interim analysis on ceritinib than on chemotherapy.

8. PDC has been included in RCTs in ALK+ NSCLC but only in previously untreated patients; however, the results could still be relevant if there was evidence that the relative treatment effect between a TKI and PDC did not vary depending on treatment history. Based on a meta-analysis in 2018[47], PDC has been used in RCTs of previously untreated ALK+ patients in the following studies:

- *ASCEND-4[35] – RCT against ceritinib, HR for PFS 0.55, 95% CI 0.42 to 0.73*
- *PROFILE 1014[48] – RCT against crizotinib, HR for PFS 0.45, 95% CI 0.35 to 0.60*
- *PROFILE 1029[49, 50] – RCT against crizotinib, HR for PFS 0.42, 95% CI 0.286 to 0.565*

Of these, ASCEND-4 is more relevant because ceritinib is a 2nd generation TKI, as opposed to crizotinib which was used in the other RCTs. All of these studies would have been identified in the company's systematic review but then excluded for being in previously untreated patients. The ERG agrees that this is an issue but the hazard ratios compared to TKIs are still potentially relevant to help form a view of the plausible range for the comparative clinical effectiveness of lorlatinib, under the assumption the relative treatment effect is approximately equal irrespective of previous treatment history.

Method to compare lorlatinib to PDC

Three methods were considered to estimate PFS and OS over time with pemetrexed-plus carboplatin or cisplatin. These were:

1. Hazard ratios estimated using a matching adjusted indirect comparison (MAIC)
2. Hazard ratios estimated using an unadjusted indirect comparison (UIC)
3. Direct estimation of PFS and OS over time by fitting independent parametric models (IPMs) directly to clinical study results.

In each case, ALUR and ASCEND-5 were used for PFS, and PROFILE 1001 and 1005 for OS.

The company recognised that there was a potential issue because the studies used to provide data for PDC were better aligned to the treatment history of cohorts 2:3A in Study 1001 than to cohorts 3B:5. Therefore each of the three methods was used to provide estimates to the two lorlatinib cohorts, as described in Figure 21 from the company's submission (page 92 of Document B); reproduced as Figure 3 below.

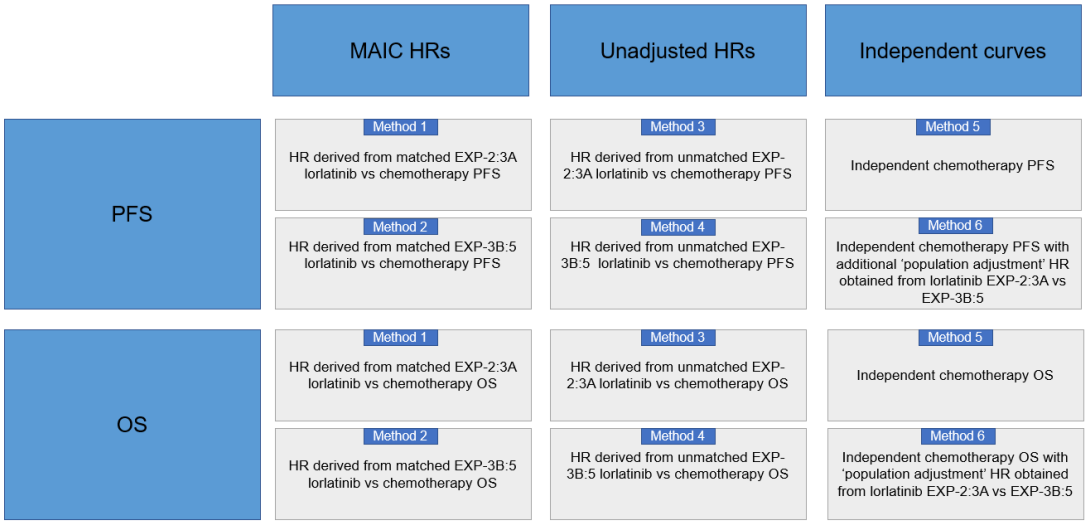


Figure 3 Summary of methods explored to derive comparator evidence (Source, Figure 21, company submission, document B, page 92)

For PFS the results of the unadjusted indirect comparison and of the MAIC were as shown in Table 12 below.

Table 12 Unadjusted and adjusted HR results for overall survival (Source: Table 25, company submission, Document B, page 62)

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases variable)		Adjusted (not including brain metastases variable)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio

*bootstrapped 95% CI

Rather than utilising the hazard ratios derived from the unadjusted comparison or MAIC, the company opted to use Method 5 (Figure 3) in their base case, using the following logic:

- The chosen methods for PFS and OS should be consistent – for example, it would be inconsistent to prefer an unadjusted comparison to 2:3A for PFS and an adjusted comparison to 3B:5 for OS.
- Proportional hazards may not hold for Methods 1 to 4
- Based on clinical opinion, PDC performance would be comparable in patients pre-treated with crizotinib vs pre-treated with a 2nd generation inhibitor.
- However, as methods 2 and 4 may have an issue with proportional hazards then method 5 is preferred.

Method 5 relied on fitting independent parametric curves to the PFS data from ALUR and ASCEND-5, and the OS data from PROFILE 1001 and 1005 for OS. The relevant published KM curves were digitised and the IPD were reconstructed, allowing alternative parametric distributions to be fitted. For PFS a log-logistic curve was selected based on having the best visual and statistical fit to the observed data (see Table 42 of the CS, document B). The ERG is satisfied that it offers the best

statistical fit based on the AIC and BIC. The same overall approach was followed for OS, and the log-normal distribution was selected based on statistical and visual fit (see Table 46 of the CS, document B). Again, the ERG is generally satisfied with the curve selection process, if not the suitability of the data upon which the fitting was based.

Whilst the final method (method 6) also utilised these independently fitted comparator curves, it included adjustments to account for the fact that the comparator sources reflected populations with fewer prior treatments than the EXP-3B:5 cohort. These adjustments were made my applying hazard ratios reflecting the difference in PFS and OS between the EXP-2:3A and EXP-3B:5 cohorts from Study 1001. However, as noted above, the company ultimately rejected this approach based on clinical advice suggesting that "*patients receiving PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI*" (P122 of CS). Thus method 5 was selected over method 6.

ERG commentary
The ERG welcomes the presentation of several methods and a number of different results as an aid to decision-making.

The ERG acknowledges the company's logic in its choice of a method; however, other logic could be applied e.g. an adjusted comparison is preferred to an unadjusted comparison and comparing to patients in cohorts 2:3A of Study 1001 is irrelevant because it is not the population covered by the license. This points to Method 2, the MAIC with comparison to cohorts 3B:5 as being the most relevant.

The methods for the two types of indirect comparisons (MAIC and UIC) were presented in Section B.2.8 of the company submission and are discussed in chapter 4 of this ERG report.

Whilst not explicitly discussed in CS, all the company's approaches for estimating comparative effectiveness give rise to a reduced hazard of death with lorlatinib in each cycle that persists throughout the model time horizon. The scenarios that relied on application of unadjusted or adjusted hazard ratios assumed proportional hazards

over entire time horizon. The company base case approach (method 5) results in a diminishing relative treatment effect over time in the model, but the hazard of mortality remains lower in the lorlatinib arm across the entire time horizon. Given the uncertainty associated with such extrapolations, the ERG explored the impact of applying more dramatic waning of the relative treatment effect, by setting the hazard of mortality in the lorlatinib arm equal to that in the PDC (or ABCP arm) from three years and five years.

5.2.7 Health related quality of life

Data collected in Study 1001

In Study 1001 the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13 were scheduled to be completed during each 21-day cycle of treatment. The completion rate for all questionnaires was [redacted] and all patients completed at least one questionnaire.

Mapping to derive the lorlatinib PFS utility value

Because the company decided not to include EQ-5D in the clinical study protocol, it was necessary to map the data that were collected to EQ-5D. A choice of algorithms was available, the company identifying five examples through a database of mapping functions collected in 2016. The five options were narrowed down to two using the following principles:

- The algorithm should map to the UK EQ-5D tariff
- The algorithm should have been derived from a sample containing some lung cancer patients
- The algorithm should be sufficiently clearly described that it can easily be applied to the current data set

The selected algorithm was that described by Longworth et al[51], which maps to EQ-5D-3L using UK tariff values, and gave an estimated utility value for PFS while on lorlatinib of [redacted].

ERG commentary

Mapping is always a second-best option compared to direct elicitation of EQ-5D in the clinical study. It introduces additional uncertainty in terms of algorithm selection, appropriateness, predictive power, etc.

The use of the 2016 mapping database to identify algorithms was a good starting point but, as a matter of good practice, the literature search should have been updated to capture any more recent studies.

Longworth et al was an NIHR-funded project to review generic and disease-specific tools for NICE decision-making and as such seems a plausible choice for the base case. However, the criteria should have included validation studies of the mapping functions (see e.g. Woodcock et al[52]). This article suggests that Longworth et al performs reasonably well, but points to possible issues with mapping worse health states.

Comparator arm (PDC): PFS

In the submission, the company could have applied the utility value for PFS from lorlatinib to time on PDC and progression-free; however, the company submission estimated a separate value instead, for two reasons:

- This is consistent with the findings of PROFILE 1007 [53]in previously treated ALK positive patients randomised to either crizotinib or chemotherapy (either docetaxel or pemetrexed monotherapy)
- The company note that within the HRQoL systematic literature review, seven out ten studies identified progression free treatment specific utilities, and four made a comparison between ALK TKIs and chemotherapy, with the difference ranging from 0.02 to 0.08).
- Lorlatinib is oral whereas chemotherapy is by iv infusion and the company assume a disutility to attending hospital.

The PFS value for PDC was based on PROFILE 1014[48] and was 0.72. The choice of PROFILE 1014 was justified because the comparator arm was PDC, it recruited ALK+ NSCLC patients, and the sample size was 171.

In sensitivity analyses values used included Zhou et al[54], TA395[27] and Blackhall et al[53] for PFS.

ERG commentary

The justification of a separate PFS value while on PDC is questionable given a lack of direct comparative evidence in the relevant population at the appropriate treatment line (following progression on second generation ALK TKI). The evidence from PROFILE 1007[53] is suggestive but there are differences, for example, chemotherapy being pemetrexed or docetaxel monotherapy rather than PDC. Also, patients in PROFILE 1007 were pre-treated with platinum-based chemotherapy and not an ALK TKI, and a relatively higher proportion were Asian in the pemetrexed group.

The second argument, that patients have higher utility on oral treatment compared to iv, should have been empirically tested.

Given the uncertainty with respect to the magnitude of any difference in utility between lorlatinib and PDC treated patients who have previously progressed on a second generation ALK TKI, and a lack of directly elicited EQ-5D data for lorlatinib at this stage, the ERG have performed further exploratory analyses whereby lorlatinib utility increments of 0.02 to 0.08 (the range reported by the company) are applied to the pre-progression PDC utility value (0.72) applied in the model.

The ERG notes the advantages stated for PROFILE 1014 as a source of utility value for PDC, but also believe the value reported by Blackhall from Study 1007 provides a plausible alternative.

PPS after progression on either treatment

The utility value for PPS was taken from the study by Labbe[55] and was 0.65. The main criterion for selecting a value was the number of ALK+ patients in the sample, or more precisely the number of confirmed ALK+ patients, because in some studies this was not separately specified. Labbe et al had 38 of 475 patients in the total sample who were ALK+.

In sensitivity analyses values used included those from TA422[26], LUME LUNG-1[56], and Zhou et al[54].

ERG commentary

The company's approach to selecting a study as a source for utility values in PPS assumes that having the ALK mutation is the most important factor, then selects the study with the most identified ALK+ patients. The ERG finds it equally plausible that for people with advanced NSCLC who have progressed after two or three lines of treatment, quality of life could be equally diminished, irrespective of genetic mutation status. Furthermore, the exact timing of the utility value applied from Labbe et al is unclear. It may reflect the health state utility of patients around the time of progression whilst still on treatment, making it less suited to representing utility across the whole time period in the progressed disease state.

From this standpoint, other sources of utility specific to the place in the treatment pathway become relevant. The study of Chouaid et al[57], cited above, reported progressive disease values of 0.59 and 0.46 specific to 2nd line and 3rd/4th line treatments of advanced NSCLC respectively. These values could both be applicable to patients in the progressed state of the company's model. In Nafees[58] 100 members of the UK public were interviewed to rate states in NSCLC using the standard gamble method; the mean value for progressed disease was 0.47.

Disutilities for adverse events

The company did not apply disutilities for adverse events in their base case analysis and assumed these would be captured in the treatment specific utilities. However, they did conduct a scenario analysis that applied disutilities. For anaemia and dyspnoea the literature search did not identify any values in NSCLC so the company used values of -0.09 and -0.048 respectively from Beusterien, et al[59] and from TA420[60].

All other disutility values were valued from Nafees et al[58] or set to zero in the base case.

Age-adjustment

All utility values were age-adjusted in the model as the patient gets older.

ERG comment

The company submission proposes utility values of [redacted] for lorlatinib until progression, 0.72 for PDC until progression and 0.65 thereafter. The ERG proposes that:

- *The progressing disease values reported by Chouaid[57] (0.59 and 0.46) may provide a better reflection of utility across time in the progressed disease state compared to the value reported by Labbe[55], since these values reflect the appropriate number of lines of treatment at entry to the state and following subsequent treatment respectively.*
- *The absolute utility value for progression free on lorlatinib is uncertain as it is based on mapping, and the difference compared to progression free on PDC is also uncertain given a lack of direct comparative evidence at this stage in the pathway.*

5.2.8 Resources and costs

Medicines costs

The license for lorlatinib states that it can be used while clinicians judge there to be a benefit from doing so. This reflects the wording of the license for ceritinib and crizotinib; for alectinib the license specified treatment to progression.

The method used to estimate treatment duration on lorlatinib was to use predicted PFS plus 2.6 months of post-progression treatment, calculated as restricted mean time on treatment minus restricted mean PFS.

The advantages stated for this method were:

- Offers best fit to PFS
- Clinically plausible, in that there are no patients who would be progression-free but 'off treatment'

- The relationship between PFS and time on treatment in Study 1001 is preserved

The company found this to be preferable to fitting parametric curves to data on time on treatment (ToT) with lorlatinib from Study 1001. While reasonable goodness-of-fit to the observed data could be achieved, the functions with better statistical fit either predicted long-term use of lorlatinib which was felt to be clinically implausible (e.g. lognormal), or did not match to the company's preferred extrapolation of PFS and OS, giving clinically implausible results such as patients discontinuing but remaining progression-free (e.g. exponential)
For PDC, the assumed treatment duration was 6 cycles or PFS.

ERG commentary
Treatment beyond progression is a feature of TKI use in ALK+ disease, especially when there are few other effective alternatives to switch to. For example, in the papers for the first meeting of the Appraisal Committee to review brigatinib in 2nd line use, the submission from NHS England states:

> *"5. NHS England also knows that treatment with brigatinib will continue after RECISTdefined disease progression in two main scenarios. The first is when there is a dimensionally small increase in an already small marker lesion: this would trigger definition of disease progression but is clinically irrelevant as the patient remains well; brigatinib would thus continue until there is clinically significant progression ie the development of symptoms. The second is when there is continued systemic response to brigatinib but disease progression in the brain which is then amenable to active treatment with radiotherapy of various types. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease. NHS England considers it likely that the marketing authorisation of brigatinib will recommend use to continue until there is loss of clinical benefit."*

The ERG has clinical advice that the situation with lorlatinib is likely to be similar. However, while it is apparent that there are problems with fitting parametric functions to observed ToT data, the rationale for the method selected is not clear.

An important criterion for ruling out some of the fitted curves was the questionable relationship with predicted PFS, but this assumes the company's preferred curve fit will be accepted. The ERG notes that whilst not providing the best statistical fit, the gamma curve for ToT suffers less from overpredicting than the lognormal, resulting in the ToT converging with PFS just after 10 years when about 3% remain progression free and on treatment. Beyond ten years the gamma ToT curve remains just below the selected PFS curve for the remainder of the model. Thus, the ERG believe it should not be ruled out as viable option.

The ERG's clinical advice is that the use of a targeted therapy may be prolonged when there is no subsequent effective therapy to use. Therefore, it believes the company estimate of [redacted] *in addition to PFS is the minimum and propose a sensitivity analysis adding* [redacted] *and* [redacted] *to PFS. In addition the ERG explores the fitted gamma curve as option for ToT with lorlatinib.*

Administration costs

In the company submission, costs of administration are set out in Table 54 on page 134 of Document B. These include £9.60 per cycle for lorlatinib (based on 12 minutes of hospital pharmacist time) and £174.40 per cycle for all other medicines, except cisplatin (with pemetrexed) which attracts a higher tariff of £374.52 for complex chemotherapy, including longer infusion time.

ERG commentary

From NHS England comment on brigatinib in 2nd line, TA595, papers for Appraisal Committee meeting 1 (page 340 of pdf file):

> *"7. NHS England notes that the drug administration cost per cycle assumed for brigatinib/ceritinib is not the correct one. These drugs are high cost chemotherapy drugs and thus the oral chemotherapy administration tariff should be used. This in 2017/18 is £120."*

In the company submission a sensitivity analysis was provided with the administration cost per cycle for lorlatinib set to £131.61, which seems to more accurately describe NHS England's view.

Subsequent treatments

The company assumed that 60% of patients in the PDC arm would receive subsequent active therapy, in line with clinical consensus reported in atezolizumab combination appraisal (TA584)[29]. With respect to the subsequent treatment distribution following PDC, the company assumed 31% receive atezolizumab and 69% receive pembrolizumab. The assumption that patients would receive one of these immunotherapies following PDC was in line with consensus reported in the FAD for atezolizumab combination (TA584).

Following progression on lorlatinib, 60% of patients were also assumed to have further treatment, with 60% receiving PDC and 40% receiving pemetrexed. This was stated by the company as being consistent with clinical expert opinion.

Finally, in the ABCP comparison provided as an addendum to the CS, the assumption was made that 60% of patients would receive docetaxel upon progression.

ERG commentary

The ERG is satisfied that the modelled subsequent therapies are appropriate and relevant to NHS routine practice. However, the following issues are noted:

1. *The FAD for the atezolizumab combination TA states[29]: "The clinical experts explained that no more than 60% of people would be well enough to have subsequent therapy". It is further noted in the FAD for TA584 that "The committee agreed that the company's revised analysis including 46.6% of people having subsequent therapy after treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was appropriate for decision making. Therefore, the 60% further treatment rate applied may represent an upper bound.*
2. *The proportional distribution of atezolizumab and pembrolizumab following PDC were taken from slide 15 of the public committee slides for TA584 (dated 02 May 2019). The ERGs own clinical expert advised that atezolizumab may be more commonly used in practice*

3. *The ERGs clinical advisor questioned the proportion of patients assumed to receive pemetrexed monotherapy following progressions rather than PDC, which is more effective. There is also a question over potential use of atezolizumab and pembrolizumab following progression on lorlatinib.*
4. *The ERGs clinical advisor questioned the percentage of patients assumed to be suitable for docetaxel following progression on ABCP. The clinicians who contributed to discussions at the committee meeting for the atezolizumab combination appraisal (TA584) seem to have expressed similar reservations: "The clinical experts noted that fewer people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance given that there would be fewer therapeutic options available. They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres".*

Taken together, these observations suggest potential for the modelling of subsequent treatments to bias cost-effectiveness in favour of lorlatinib. The ERG have carried out further exploratory analysis to assess the sensitivity of results to alternative assumptions.

Other costs

Rates of other resource use associated with health states were estimated by the company using previous STAs in ALK+ NSCLC patients. Costs associated with each resource were derived from the NHS reference costs (2017–2018)[61] and from the Personal Social Services Research Unit (2018).[62] These are summarised in Table 56 of the CS (document B, p.136). Relatively little difference is observed in the total health state costs per patient whether they are in the progression free and progressed disease state, although there are some differences in the frequency of particular elements, depending on which state the patient is in. For example, there is a higher frequency of CT scanning and X rays in the progression free state. Within the economic model the total cumulative health states costs are substantially higher for lorlatinib compared to ABCP or PDC, which is consistent with the improved patient survival.

Costs associated with adverse events were also estimated using previous STAs and NHS reference costs (2017–2018)[61]. These are summarised in Table 58 of CS (document B, p. 140), and the total is applied in the first cycle of the model. The total costs are broadly comparable for lorlatinib and PDC and contribute relatively little to overall costs and expected difference in cost. This is not the case for the ABCP comparator, which has much higher adverse event costs sourced from TA584.[29] A breakdown of this figure is not provided within the appendix to the CS.

Finally, terminal care costs were included as a single period cost in the model and were based on previous NICE appraisals in NSCLC.

The ERG generally agrees with the company's approach to costing in these categories. The source of frequency and cost data is reliable and comprehensive, and the costs have been appropriately incorporated into the economic model.

5.2.9 Cost effectiveness results

The company base case results for lorlatinib versus PDC are provided in section B3.7 of the CS. The results against ABCP were originally provided as an addendum to the CS but were later included as an appendix in an updated submission document (discussed separately below). It should be noted that atezolizumab, bevacizumab and pembrolizumab have PAS discounts in place, which the submitting company does not have access to. Atezolizumab, and bevacizumab form comparators in the ABCP comparison, and atezolizumab and pembrolizumab are included as subsequent treatments in the PDC comparison. Therefore, the company assumed a 30% discount on each of these drugs in their analyses. The ERG has reproduced the company's analyses in a confidential appendix using the actual PAS discounts currently available.

For the PDC comparison, the company provided their base case results using both deterministic and probabilistic analysis. The deterministic ICER came to £50,152 (See Table 63 of the company submission, document B), and the average probabilistic ICER was £46,337 (see Table 64 of the CS, document B). Scatter plots and acceptability curves were also provided in section B3.7 of the CS.

5.2.10 Sensitivity analyses

Further one-way deterministic sensitivity analysis of the PDC comparison revealed the 10 parameters with the greatest impact on the ICER. These included parameters underpinning the calculation of post progression lorlatinib treatment duration, the utility value for progressed disease, and parameters related to subsequent treatment (see Figure 6 of the CS, document B).

A range of further scenario analyses were also provided by the company, which included exploration of the alternative methods for estimating the comparative effectiveness (PFS and OS) of PDC.

The full list of scenarios explored by the company are provided in Table 66 of their submission (document B), and the results are presented in Table 67 of the CS (document B). Of the six methodological approaches for estimating comparative effectiveness of PDC, the ICER for lorlatinib increased most when using the HR from the MAIC of OS in the EXP-3B:5 cohort of Study1001 versus OS in the pooled PROFILE 1001/1005 cohort (method 2). Switching to method 6 for comparative OS (independent OS curve with population adjustment) produced the lowest ICER. Whilst useful for informing the individual impact of changes to the method for estimating comparative OS and PFS, the company did not show the impact of changing the method for both PFS and OS at the same time.

The ICER was also shown to be quite sensitive to the approach used to model time on treatment for lorlatinib, the PFS curve selection for lorlatinib, and the source of post-progression health state utility in the model.

Comparison with atezolizumab in combination with ABCP

In the company submission, the case was made that this comparison is not relevant, based on clinical advice and the lack of data from the Impower150 trial to support use of the ABCP regime in ALK+ patients. However, the company provided a modelled comparison, originally as an addendum to their submission, but later included as an appendix in an updated submission.

The clinical studies used were Study 1001 (cohorts 3B:5) for lorlatinib and the IMpower150 EGRF/ALK cohort for ABCP (n=41). Only 11 of the 41 were noted to be ALK+. The indirect comparison was unanchored and not adjusted for any characteristics that differed.

The same lorlatinib curves selected for the PDC comparison were retained. Published PFS and OS KM curves from the IMpower150 EGRF/ALK cohort were digitised and the IPD were reconstructed. The six standard parametric survival models were then fitted to the PFS and OS outcome data. For consistency with the ABCP appraisal (TA584), and statistical fit based on AIC and BIC, the company selected the exponential curve for OS. For PFS they selected the log-logistic curve which was the ERGs preferred curve fit in TA584. The selected curves are provided in Figure 58 of the CS, Appendix S.

In addition to the independent curve fitting, HRs for PFS and OS were also derived between Study 1001 (EXP-3B:5 cohort) and the ABCP arm of IMpower150 ALK/EGFR subgroup. These were used as an alternative method for estimating the comparative efficacy of ABCP versus lorlatinib. The HRs are presented in Table 13 below. It should be noted that these unadjusted HRs are in favour of ABCP compared to lorlatinib (i.e. higher OS and PFS in the mixed ALK/EGFR subgroup of IMPower). However, the company argue that a population adjustment is required to avoid biasing against lorlatinib.

Table 13 Independent hazard ratio comparing lorlatinib (Study 1001) to ABCP (Impower150 EGFR majority subgroup) (Source: reproduced from Table 69 of the company submission, Appendix S)

	PFS	OS
Study 1001 versus IMpower 150 EGFR+/ALK+ patients	[redacted]	[redacted]

The company apply a 'population adjustment' to reflect the fact that the majority of the relevant sub-group of IMpower150 had EGFR+ disease (n=30) rather than ALK+ disease (n=11). The submission makes the case that prognosis with ALK+ disease is poorer than for EGFR+ disease and hence a failure to adjust could bias the results. To do this, the company compared response to chemotherapy for EGFR+ patients to response to chemotherapy for ALK+ patients. Data used were from the IMPRESS study for EGFR+ patients, and ALUR/ASCEND-5 for PFS and PROFILE 1001/1005[46] for OS in ALK+ patients - in line with the PDC comparison. This gave the results presented in Table 14 below. These HRs were applied to the fitted log-logistic and exponential curves in the EGFR+/ALK+ cohort, to derive curves for an ALK= only population. The company acknowledge the limitation that ALK+ patients made up 27% of the mixed EGFR/ALK cohort, but justify their approach based on the majority being EGFR+ and a lack of alternative data sources. The population adjustments shift both PFS and OS in favour of lorlatinib.

Table 14 HRs for PFS and OS of EGFR+ versus ALK+ patients (Source: reproduced from Table 70 of the company submission, Appendix S)

Analysis	HR
IMPRESS study chemotherapy arm: PFS versus pooled Novello et al[2]. and Shaw et al[3]. chemotherapy data.	[redacted]
IMPRESS study chemotherapy arm: OS versus Ou et al[46]. chemotherapy data.	[redacted]

Other assumptions mainly reflected the comparison with PDC for lorlatinib and the economics model for ABCP used in issuing NICE TA guidance 584[29]. These included:

- Medicines costs – doses from current submission and TA584, prices updated

- Administration of medicines – updated
- Other disease costs – as for current submission
- Adverse event costs – from current submission for lorlatinib, from TA584 for ABCP
- Utility value in PFS – from Study 1001 mapped to EQ-5D in current submission ([redacted]), 0.71 for ABCP (ERG preferred figure in TA584)
- Utility value for PPS – 0.65 from current submission

The company only provided deterministic analysis for the ABCP comparison, and the base case results are reproduced in Table 15 below.

Table 15 Base case results versus ABCP – lorlatinib at PAS price (Source: reproduced from Table 73 of the CS, Appendix S)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,369

ERG commentary

The ERG believe ABCP is a relevant comparator, based on clinical advice. It may only be an option in a minority of cases at this place in the treatment pathway, but these same patients could also receive lorlatinib if it is recommended. It is licensed for ALK+ disease and accepted by NICE, so the company's point about the lack of evidence is not convincing.

The company used the correct clinical studies for the indirect comparison and the ERG agrees that the comparison cannot be anchored. However, there are two contentious aspects to the company's method for indirect comparison:

1. *The decision was not to adjust for differences in prognostic characteristics between the two patient cohorts.*
2. *A population adjustment was made for the difference between EGFR+ and ALK+ cases. The ERG agrees with TA584 that there seems to have been no rationale for the analysis of Impower150 to have combined these two*

mutations together. However, the method used is questionable since it involves comparing the effect of chemotherapy from other clinical studies of EGFR+ and ALK+ patients respectively. Chemotherapy self-evidently has a different mechanism of action to an immunotherapy and it is not clear that the results are relevant to the issue of the relative effectiveness of ABCP in EGFR+ and ALK+ patients. A more direct way would have been to split up the EGFR/ALK combined group: the results for EGFR+ patients have now been published[63].

There are other issues. For example, while it is not explicitly discussed, different utility values appear to be assumed for PFS on lorlatinib and on ABCP. The comparability of these different values is unclear.

5.2.11 Model validation and face validity check

Section B 3.10 of the CS provides details of model validation checks carried out by the company. These included checking the model's predictions of survival against published clinical data, validation by clinical experts, and input data and quality control checks performed by an external organisation.

Validation checks carried out by the company using published clinical data involved comparing the predicted median PFS and OS for lorlatinib and PDC to the observed data. Prediction for lorlatinib were compared to Study 1001. For PDC, ALUR and ASCEND-5 were used to compare PFS, and PROFILE 1001/1005 were used to compare OS. The company states that predictions and observed outcomes were broadly consistent. However, in all cases, the median PFS and OS predictions of the company's model were higher than those observed in clinical studies. For lorlatinib, the model predicted median PFS of [redacted] and median OS of [redacted]. This compared to median PFS of [redacted] and median OS of [redacted] observed in Study 1001. Within Table 67 of the CS, mean PFS and OS predictions from the company's model are also provided, but the equivalent clinical data are not provided. The model predicts an average [redacted] increase in life expectancy with lorlatinib versus PDC.

Although the magnitude of differences in median PFS and OS is not substantial when comparing model predictions to clinical data, the ERG is concerned that the consistent overprediction of survival in the company's model may indicate issues with the extrapolation of the observed data. The CS correctly states that the differences to observed data are proportionally larger in the PDC arm. As such, the overall effect on the ICER of consistently overpredicting PFS and OS for both lorlatinib and PDC cannot be predicted with certainty.

Table 68 in CS (document B, p.154) summarises the validation checks of the model which were carried out with clinical experts. These checks covered many aspects of the model structure and findings. Following submission, the company have subsequently identified an error in Table 68 and clarified that survival curve validation did not take place during the teleconference with clinical experts in September 2018.

Within the CS, validation by clinical experts is particularly emphasised when selecting parametric survival curves within the model. Clinical validation of OS and PFS extrapolations was conducted with two clinical experts in separate teleconferences. The Kaplan-Meier curve was presented to each clinical expert with six survival functions overlaid. A table was also presented which provided the proportion of patients surviving at landmark time points. The clinical experts were then asked, "Based on your experience, which curves best represent overall survival that you would expect to see in this population of patients? Are there distributions you would rule out due to unrealistic predictions?" One clinical expert, with no previous experience of treating patients with lorlatinib, provided a first and second preference for each of the four parametric survival curves (OS and PFS for PDC and lorlatinib). The second clinical expert did not state a preference for OS and PFS for PDC. For lorlatinib, the second clinical expert, who had experience of treating two patients with lorlatinib, validated the choice of a generalised gamma distribution for PFS and preferred the lognormal distribution for OS. In the latter case, the clinical expert focused on the 10-year OS rate, which they estimated to be closer to [redacted] than the [redacted] 10-year survival rate predicted by the exponential distribution. The company's base case extrapolates lorlatinib OS data using the generalised gamma distribution.

Within the company response to clarification questions, it is stated that "Clinicians tended to focus on the proportions alive (or PFS) at each time point and the ordering of curves and this formed the basis for their preference for a curve." However, the ERG notes that there was an error in the table presented to clinical experts which provided landmark values for lorlatinib OS. Specifically, 3-year OS values were erroneously presented under the heading of 5-year OS values. This error applies only to OS for lorlatinib. The correct range of values for lorlatinib 5-year OS is [redacted] rather than the range of [redacted] that was presented to clinical experts. Therefore, based on the landmark values only, the rate decline in OS for lorlatinib between 5 and 10 years appeared much higher than was predicted by each parametric curve. The ERG notes that this error did not extend to the graphical presentation of the data. Given the stated focus on landmark values and the specific focus of one clinical expert on 10-year OS for lorlatinib, it cannot be ruled out that the erroneous presentation of landmark values influenced the clinical validation process. The ERG's clinical adviser was of the opinion that it may be more reasonable to expect 10-year overall survival for lorlatinib to be closer to [redacted] than [redacted].

Table 68 of the CS also states that BresMed Health Solutions carried out checks of data inputted to the model along with general quality control checks. In addition, the ERG checked cell calculations and conducted black box checks of the model using a range of tests suggested by Tappenden and Chilcott (2014)[64]. The results of these checks are reported in Table 15. No major errors or concerns were identified which impact on the deterministic base case analysis within the CS. The ERG notes that a PSA for the ABCP comparator has not been provided by the company.

Table 16 Results of model checks conducted by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues. QALYS not equal due to different progression free utility on PDC/ABCP and lorlatinib.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None.
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None.
	Increase intervention cost	ICER is increased*	None.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None.

Model component	**Model test**	**Unequivocal criterion for verification**	**Issues identified in company model**
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested for PDC and lorlatinib. No issues. No PSA provided for ABCP comparison.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	For the ABCP comparison, it is not possible to match subsequent treatment costs since 100% of ABCP transition to progressed disease before death. This is not consistent with lorlatinib (and PDC) where a proportion of patients progress directly to death without disease progression (based on Study 1001 data).
	Amend value of each individual model parameter*	ICER is changed	No issues in the company base case.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Not tested due to time constraints.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

In addition to the scenario analyses conducted by the company, the ERG conducted some further scenario analyses to explore identified uncertainties in the modelling assumptions.

5.3.1 PDC comparison

For the comparison with PDC, these included the following:

1. Applying each of the alternative five methods for generating comparator PFS and OS curves concordantly. The company scenario analyses applied the alternative methods separately for PFS and OS, which appeared counter to the argument made in the CS that the same method should be used for PFS and OS. The five alternative methods are labelled a)-e) in Table 17
2. Applying iterative upward adjustments to PFS and OS in the PDC arm, to reflect the potential impact of underprediction of these outcomes based on the use of data that did not accurately reflect the modelled comparator; i.e. the PFS and OS data used to inform the PDC arm of the model came from patients treated with singlet chemotherapies or "systemic therapy" that may not adequately reflect the outlook for chemotherapy naïve patients treated with PDC following progression on a second generation ALK inhibitor. The analysis is justified by the ERG's clinical expert advice and reference to Zukin et al, (2013)[65] who reported hazard ratios of 0.46 (95% CI, 0.35 to 0.63) and 0.62 (95% CI, 0.46 to 0.83), for PFS and OS respectively, in a phase III RCT of pemetrexed plus carboplatin versus pemetrexed alone. This was as first-line therapy in patients with advanced NSCLC with an ECOG performance status of 2. Since the exact magnitude of any benefit of PDC over pemetrexed monotherapy is uncertain in the current setting, these exploratory scenarios utilize hazard ratios of: a) 0.9, b) 0.8, c) 0.7, and d) 0.6 to adjust the selected PDC PFS and OS curves upwards (assuming proportional hazards). Each HR is applied to PFS and OS curves simultaneously to avoid the of curves crossing.
3. Applying assumptions to reflect the possibility of treatment effect waning. The company modelling approach results in the hazard of mortality remaining lower in the lorlatinib arm over the entire duration of the model. Given the uncertainties driven by the lack of observed data to validate this assumption,

the ERG explored the impact of setting the mortality rate in the lorlatinib arm equal to that in the PDC arm from a) three years and b) five years in the model. Again, these scenarios were not informed by data, and were conducted purely to assess sensitivity of the results to the assumed ongoing treatment effects.

4. Increasing the estimated mean time on lorlatinib following progression, from [redacted] months in the company base case, to [redacted] and [redacted] to account for fact that clinicians may use the drug for longer following progression in routine practice compared to restricted mean difference observed in Study1001.
5. Exploring the impact of applying the gamma distribution to model ToT for lorlatinib. Whilst not the best statistical fit according to AIC and BIC, it provided more plausible predictions than the exponential curve which the company presented in their sensitivity analysis of this parameter. The gamma ToT curve does not cross the selected PFS curve (also gamma) until about 10 years, when ~3% remain progression free, and it remains below it thereafter.
6. Exploring alternative utility assumptions whereby increments of a) 0.02 and b) 0.08 were added to the selected progression free utility for PDC to represent progression free utility on lorlatinib (covering the range of increments reported by the company from the SLR); c) the value of 0.59 was applied for progressed disease; d) the value of 0.46 was applied for progressed disease; and e) the values in a) and d) were applied in combination (as a lower bound of what may be plausible).
7. Applying alternative assumptions with respect to subsequent treatment costs:
    a. Applying a fixed dosing regimen for pembrolizumab (200mg, every three weeks), rather than the weight-based dosing assumption of 2mg/kg every three weeks for patients who progress on PDC. This was based on advice from the ERG's clinical expert who advised that the fixed dose is more commonly applied in NHS practice.
    b. Increasing the relative proportion of subsequently treated patients who receive atezolizumab rather than pembrolizumab following progression on PDC (to [redacted] versus [redacted], rather than [redacted] versus [redacted] in the CS). This was based on advice from the ERGs clinical expert that atezolizumab may be preferred in this setting on grounds of cost.

c. Applying (a) and (b) in combination
d. Increasing the percentage of patients who progress on lorlatinib who receive PDC to 80%, rather than [redacted] in the company base case. This again was based on the ERGs own expert advice.
e. Reducing the percentage of patients receiving subsequent therapy to 50% following PDC, based on discussions reported in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer).

The results of these exploratory analyses are provided in Table 17 using the same comparator drug prices that the company applied in their analyses. In addition to the single scenarios, the ERG considered the following more conservative combination of assumptions: 2b) OS and PFS curves for PDC factored up by applying a hazard ratio of 0.8 to each; 5) gamma distribution for ToT with lorlatinib; 6c) Utility value of 0.59 for progressed disease; 7a) assumed fixed dosing of pembrolizumab at 200mg every three weeks; and 7e) 50% subsequent treatment rate following PDC to reflect diminishing treatment options. The result of this is provided as scenario 8 in Table 17 below.

However, these are not suitable for informing decision making as confidential discounts are available for pembrolizumab and atezolizumab. These analyses are therefore replicated in the confidential comparator PAS (CPAS) appendix using the actual discounts currently available to the NHS.

Table 17 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£50,152
1	Alternative PDC PFS and OS survival cure methods	a) Method 1: MAIC HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£45,921
		b) Method 2: MAIC HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£58,747
		c) Method 3: Unadjusted HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£44,104
		d) Method 4: Unadjusted HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£50,282
		e) Method 6: Independent curves & population adjustment	[redacted]	[redacted]	[redacted]	£43,799
2	Hazard ratios for upward adjustments to PFS and OS in the PDC arm	a) 0.9	[redacted]	[redacted]	[redacted]	£50,931
		b) 0.8	[redacted]	[redacted]	[redacted]	£51,943
		c) 0.7	[redacted]	[redacted]	[redacted]	£53,361
		d) 0.6	[redacted]	[redacted]	[redacted]	£55,638
3	Treatment waning	a) Hazard of death on lorlatinib equal to PCD from three years	[redacted]	[redacted]	[redacted]	£56,367
		b) Hazard of death on lorlatinib equal to PCD from five years	[redacted]	[redacted]	[redacted]	£51,600
4	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£53,938
		b) [redacted]	[redacted]	[redacted]	[redacted]	£59,496

5	Lorlatinib time on treatment	Generalised gamma	[redacted]	[redacted]	[redacted]	£56,876
6	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£52,642
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£49,382
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£51,894
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£56,119
		e) a and d combined	[redacted]	[redacted]	[redacted]	£59,256
7	Subsequent therapies	a) Fixed dose regimen for pembrolizumab	[redacted]	[redacted]	[redacted]	£48,288
		b) proportion of treated patients receiving atezolizumab and pembrolizumab following progression on PDC ([redacted] and [redacted] respectively)	[redacted]	[redacted]	[redacted]	£48,175
		c) a and b combined	[redacted]	[redacted]	[redacted]	£47,338
		d) Proportion of subsequently treated patients who receive PDC and pemetrexed alone following progression on lorlatinib (80% and 20%)	[redacted]	[redacted]	[redacted]	£50,221
		e) 50% receive subsequent therapy following PDC	[redacted]	[redacted]	[redacted]	£51,856
8	Combination	Combines 2b), 5), 6c), 7a), and 7e)	[redacted]	[redacted]	[redacted]	£61,865
		Probabilistic ICER for scenario 8	[redacted]	[redacted]	[redacted]	£59,812

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment

5.3.2 ABCP comparison

Similarly, the ERG conducted further exploratory analysis for the ABCP comparison. These included the following:

1. Reducing the magnitude of the population adjustment applied to PFS and OS curves in the ABCP arm. This is because the ALK+ versus EGFR+ population adjustments (applied to the fitted ABCP curves) were derived from unadjusted indirect comparison of ALK+ cohorts exposed to singlet chemotherapy or "systemic therapy", with a cohort of EGFR+ patients treated with cisplatin plus pemetrexed. Since the EGFR+ patients were exposed to a potentially more effective combination chemotherapy, the derived hazard ratios might overestimate the population effects. In addition, the population adjustments were applied to the fitted curves for the mixed IMPower cohort where ALK+ patients already made up 27%. Since there are no data available to better inform the need for population adjustment, the company's log hazard ratios are reduced by a) 25% and b) 50%. (i.e. to 1.33 and 1.53 for PFS and 2.01 and 2.86 for OS respectively).
2. Treatment Waning assumptions. To account for potential diminishing effectiveness over time, these analyses explored the impact of equalizing the hazard of death to that in the ABCP arm from a) year 3 and b) year 5 in the model.
3. Increasing the estimated mean time on lorlatinib following progression, from [redacted] months in the company base case, to [redacted] and [redacted] to account for fact that clinicians may use the drug for longer following progression in routine practice compared to restricted mean difference observed in Study1001.
4. Exploring the impact of applying the gamma distribution to model ToT for lorlatinib. Whilst not the best statistical fit according to AIC and BIC, it provided more plausible predictions than the exponential curve which the company presented in their sensitivity analysis of this parameter. The gamma ToT curve does not cross the selected PFS curve (also gamma) until around 10 years, when ~3% remain progression free, and it remains below it thereafter.
5. Exploring alternative utility assumptions whereby increments of a) 0.02 and b) 0.08 were added to the selected progression free utility for PDC to represent progression free utility on lorlatinib; c) the value of 0.59 was applied for

progressed disease; d) the value of 0.46 was applied for progressed disease; and e) the values in a) and d) were applied in combination (as a lower bound of what may be plausible).

6. Applying alternative assumptions with respect to subsequent treatment costs:
    a. Assuming 80% of subsequently treated patients who progress on lorlatinib receive PDC. This was based on the ERGs own expert advice.
    b. Assuming a lower percentage of patients are suitable for docetaxel following treatment with ABCP (40% rather than [redacted] assumed in the CS). This was based on the ERGs own clinical expert advice and clinical expert advice that was summarised in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer): "*The clinical experts noted that fewer people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance given that there would be fewer therapeutic options available. They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres".*

The results of these exploratory analyses are presented in Table 18. In addition, a combined scenario included a combination of: 1b) reduced population adjustment log HRs by 50%; 4) generalised gamma for ToT with lorlatinib; 5c) utility value of 0.59 for progressed disease; and 6b) 40% of patients receive subsequent treatment post ABCP. The results are presented as scenario 7 in the Table 18.

As per the PDC comparisons, these analyses are replicated in the CPAS appendix using the confidential discounted prices available to the NHS for atezolizumab and bevacizumab.

Table 18 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£27,369
1	Reducing population adjustment hazard ratios (on log scale)	a) By 25% (HR for PFS = 1.53; HR for OS = 2.86)	[redacted]	[redacted]	[redacted]	£26,857
		b) By 50% (HR for PFS = 1.33; HR for OS = 2.01)	[redacted]	[redacted]	[redacted]	£28,869
2	Treatment waning	a) Hazard of death on lorlatinib equal to ABCP from three years	[redacted]	[redacted]	[redacted]	£22,187
		b) Hazard of death on lorlatinib equal to ABCP from five years	[redacted]	[redacted]	[redacted]	£22,867
3	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£31,505
		b) [redacted]	[redacted]	[redacted]	[redacted]	£37,577
4	Lorlatinib time on treatment	Generalised gamma curve	[redacted]	[redacted]	[redacted]	£34,715
5	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£28,861
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£26,911
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£28,691
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£32,043

		e) a and d combined	[redacted]	[redacted]	[redacted]	£34,107
6	Subsequent therapies	a) 80% of subsequently treated patients who progress on lorlatinib receive PDC	[redacted]	[redacted]	[redacted]	£27,445
		b) 40% receive subsequent treatment with docetaxel following progression on ABCP	[redacted]	[redacted]	[redacted]	£27,561
7	Combination	Combines 1b), 4), 5c), and 6b),	[redacted]	[redacted]	[redacted]	£44,692

5.4 Conclusions of the cost effectiveness section

5.4.1 Summary

Based on the remaining uncertainties in the economic model, and lack of appropriate data to inform the comparative effectiveness of lorlatinib versus PDC and ABCP, the ERG finds it difficult to draw conclusions with respect to the most plausible set of assumptions to apply in the economic model. Therefore, the ERG suggests that the following issues relating to cost-effectiveness be raised in the technical report for consultation:

Issue 1

The design of Study 1001, as a non-comparative single-arm study, means there is substantial uncertainty in estimating the lifetime clinical effectiveness of lorlatinib in its licensed indication. While the company has undertaken an indirect comparison to address this, there are several issues and much of the uncertainty remains. Issues include:

- The selection of clinical studies to represent the PDC treatment arm
- The selection of the method to carry out the indirect comparison
- The most plausible projections of PFS and OS for lorlatinib
- The most plausible projections of ToT, particularly with respect to treatment post-radiographic progression treatment duration.

Issue 2

The utility values selected are open to question:

- The selected value for the progressed disease state appears high compared to other published values specific to treatment line.
- There is a lack of direct comparative evidence for the applied difference in PF utility on lorlatinib versus PF utility on PDC (the same point applies in the comparison with ABCP). The magnitude of any applied difference is therefore uncertain.

Issue 3

The treatment duration calculation for lorlatinib is broadly plausible but may underestimate the extent to which clinicians tend to prolong treatment following radiographic progression in routine practice when there are no other effective treatment options available.

Issue 4

Assumptions about proportion of patients receiving subsequent therapies following the intervention and comparator treatments, and the distribution of these subsequent therapies is uncertain and could benefit from further clinical input.

6 End of life

The company case against PDC appears consistent with the NICE criteria for consideration as an end of life treatment. Average life expectancy is well below 2 years on PDC in the company base case ([redacted]) and remains below this value across the scenarios assessed. Despite the limitations in the comparative evidence base, it is plausible to the ERG that treatment with lorlatinib will result in a gain in life expectancy of more than three months.

The same is true of the company base comparison against ABCP ([redacted]), but the average life expectancy on ABCP is dependent on the uncertain population adjustment that is applied to the fitted curve. However, it remains below 2 years as long as the log HR for the population adjustment of OS is not reduced by 55% or more (i.e. from a HR value of [redacted]). The survival gain remains above three months across all scenarios assessed.

7 Overall conclusions

The current submission focuses on adult patients with metastatic (stage IV) ALK-positive NSCLC. Overall, the company's review process for the selection and assessment of the clinical effectiveness evidence was appropriate. While the ERG agree that Study 1001 is the current best source of effectiveness evidence for lorlatinib, they are concerned about the limitation of the current evidence-base, only a small (n = 139) single arm study.

The comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator.

There is evidence to suggest lorlatinib provides a response in the target group of patients and has an impact on progression free and overall survival. The company present a matched adjusted indirect comparison to compare lorlatinib to chemotherapy, which indicates a survival benefit with lorlatinib over chemotherapy. However, as described in chapter 4, the ERG are apprehensive over the validity of the results in the MAIC due to concern over the relevance of the comparator data sources used.

The considerable uncertainties with respect to the comparative effectiveness of lorlatinib versus PDC and ABCP requires many assumptions to be made in the economic modelling and makes it difficult to establish the most plausible ICER. The ERG has conducted further scenarios analyses which lead to both upward and downward uncertainty in the ICERs versus PDC and ABCP.

The ERG is of the opinion that the evidence for lorlatinib is limited and future research should consider a head to head trial of lorlatinib against relevant comparators at the correct place in the treatment pathway.

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Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Addendum to the main ERG report

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Following submission of the ERG report for this appraisal, the NICE technical team asked the ERG to clarify where possible its preferred modelling assumptions with respect to the further exploratory scenarios it had undertaken and presented in the original report. In addition, NICE were informed by a clinical expert in ALK+ NSCLC, that for those patients who progress from lorlatinib to another active treatment (60% in the company y model), the assumption that 40% would receive pemetrexed monotherapy is incorrect. The expert stated that pemetrexed is not very relevant here, and that patients would now (since TA584) progress from lorlatinib onto either PDC (50-60%) or ABCP. Since ABCP was not included as a subsequent treatment for this population in the company model, NICE asked the ERG to conduct further sensitivity analysis which varied the percentage of progressed and subsequently treated patients who receive this combination therapy upon progression. These additional scenarios are caveated by the fact that it has only been possible to incorporate the costs of this regimen and not any potential improvement in efficacy associated with it. All analyses presented in this addendum take account of the PAS for lorlatinib but assume 30% discounts for atezolizumab, pembrolizumab, and bevacizumab. Results with the actual available discounts for atezolizumab, pembrolizumab, and bevacizumab are provided in a confidential PAS appendix to this addendum.

ERG reflection on uncertain modelling assumptions

ERG preferred modelling assumptions

Following further reflection, and at the request of NICE, the ERG clarify that they prefer the following modelling assumptions:

1. Pembrolizumab as subsequent therapy should be applied at a fixed dose of 200 mg every 3 weeks in line with clinical practice. This is on the advice of the ERGs own clinical expert, corroborated by another clinical expert consulted by NICE.
2. The utility value applied for progressed disease should be either 0.59 or 0.46, lower than the value applied in the company base case. This is because the value applied in the company base case (0.65) appears to reflect health status around the time of progression on an ALK TKI, when patients may still be on treatment (Labbe et al).[1] Thus, the ERG believe it may not be suitable for reflecting average health related quality of life throughout time spent in the progressed state where patients will continue to deteriorate over time. Therefore, the ERG tends to prefer the lower values reported by Chouaid et al. for progressive disease after 2nd line or 3rd/4th line treatment; 0.59 and 0.46 respectively.[2] On balance, 0.59 represents a reasonable compromise between the company value and the lower value of 0.46 following progression on 3rd/4th line treatments.
3. No more than 50% receive subsequent therapy following PDC. This is in line with discussion in the ACD for TA584, which suggested 60% would be the upper limit for subsequent treatment following PDC, and 50% may be more appropriate.[3] We assume 60% may still be reasonable for patients treated with lorlatinib because they will have more treatment options still available.
4. No more than 40% receive docetaxel following progression on ABCP. This is also in line with committee discussions recorded in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer).[3]

The results with these assumptions all selected are provided in Table 1 below. The combined changes have a modest effect on the company ICER.

Table 1: Cost-effectiveness results with ERG preferred assumptions selected

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
ERG base case: Lorlatinib versus PDC (progressed utility value = 0.59)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,051
ERG base case: Lorlatinib versus PDC (progressed utility value = 0.46)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,289
ERG base case: Lorlatinib versus ABCP (progressed utility value = 0.59)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,892
ERG base case: Lorlatinib versus ABCP (progressed utility value = 0.46)							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,268

<u>Assumptions that the ERG remain uncertain about</u>

1. The ERG remains concerned that the comparative efficacy (both PFS and OS) of PDC is underestimated because it is based on data from patients treated with single agent chemotherapies rather than PDC. There is evidence that PDC performs significantly better than pemetrexed monotherapy in NSCLC (see Zukin et al. 2013),[4] although not specifically in ALK+ population. Ascertaining the extent of any bias is complicated by the fact that patients in ASCEND-5, ALUR and PROFILE 1001/1005,[5-7] may have had fewer previous treatments than some in Study 1001. Patients in ASCEND-5,[5] ALUR[6] and PROFILE 1001/1005[7] had progressed after one ALK TKI (crizotinib) but had also had prior platinum-based chemotherapy. Those in Study 1001 EXP-3B:5 cohort (see company submission) had progressed following treatment with at least one second generation ALK TKI, but some had up to three or more ALK TKIs, with or without previous chemotherapy. The company claim it is possible that the single agent chemotherapy data from ALUR, ASEND-5 and PROFILE could also overestimate the comparative efficacy of PDC at the point in the pathway where lorlatinib will be used; i.e. with a previous treatment history matching that of Study1001 (EXP-3B to 5).

The trade-off between the above two arguments could benefit from wider input from clinical experts. On balance, the ERG believes that the efficacy of PDC is more likely to be underestimated than overestimated. It is of note that the PFS and OS data for single agent chemotherapy that the company used matches quite closely with PFS and OS reported by Zukin et al. for pemetrexed monotherapy as first line treatment in people with advanced NSCLC (primarily adenocarcinoma) and ECOG status 2. Further, in the RCT reported by Zukin, patients randomised to PDC had significantly improved PFS (HR = 0.46; 95%CI, 0.35-0.63) and OS (HR = 0.62; 95%CI = 0.46-0.83) compared to pemetrexed monotherapy.

2. The preferred methodological approach for comparative efficacy of PDC; independent curves with no population adjustment (due to non-proportional hazards) versus the MAIC using the EXP-3B;5 cohort. On balance the ERG prefers the company's base case approach of applying independently fitted curves (due to proportional hazards not holding), and as indicated above the ERG is more concerned about the source data used to represent PDC rather than the assumptions of the methodological approach for assessing comparative efficacy.

3. The comparative efficacy of ABCP is another major uncertainty. The company case here relies heavily on a population adjustment for ALK+ versus EGFR+ patients. However, the population adjustment hazard ratios come from comparing OS and PFS for ALK+ patients treated with single agent chemotherapy (again from ALUR, ASCEND-5 and PROFILE 1001/1005), with an EGFR+ population treated with PDC as first line treatment (IMPRESS).[8] Therefore, there is a question as to what extent the adjustment HRs reflect the inferior efficacy of the monotherapies at second or third line versus PDC at first line, rather than the different mutation status of the cohorts.

4. Time on treatment with lorlatinib, and the approach for estimating it, remain uncertain. Based on expert clinical advice, the ERG believe that patients may remain on lorlatinib for longer following progression than the average [redacted] applied in the company base case (the difference in restricted mean ToT and restricted mean PFS in Study 1001 up to [redacted] months). In the absence of more complete data to inform mean post progression ToT, the ERG tends towards favouring a fitted

parametric curve to model ToT. When considering consistency with the company's preferred lorlatinib PFS curve, the ERG further believe that the generalised gamma provides the most plausible projection of ToT out of those assessed by the company.

Taken together, the above issues lead to substantial uncertainty surrounding the cost-effectiveness of lorlatinib versus PDC and ABCP, as demonstrated through the exploratory scenario analyses in the main ERG report.

Further sensitivity analysis surrounding the comparative efficacy of PDC versus lorlatinib

In the company's base case, there is a slight problem with the selected curves for PFS (log-logistic) and OS (log-normal) in the PDC arm [redacted]. [redacted]. This is exacerbated if the curves are adjusted upwards using hazard ratios reflecting possible improved effects of PDC versus pemetrexed monotherapy (as per the scenarios in Table 17 of the main ERG report); [redacted] The proportional hazards assumption of these scenarios may also result in implausible long-term survival in the PDC arms. The problem is worse if the second-best fitting curves are selected for PFS (Gompertz) and OS (log logistic). However, if exponential curves are selected for both PFS and OS, it becomes possible to uplift these proportionally whilst generating less implausible long-term extrapolations for PDC survival. Table 2 below shows the impact of several scenarios that do this. It indicates that the potential underestimation of PDC efficacy may be less important if PFS is underestimated to a greater relative extent than OS. This is because if PFS increases by a proportionally greater amount than OS, there is a greater proportional drop in the incremental cost than the incremental QALY for lorlatinib versus PDC. This is driven by patients spending proportionally longer in the progression free state on pemetrexed maintenance therapy.

Figure 1: Fitted PFS and OS for PDC using the log-logistic and log-normal curves respectively

Figure 2: Fitted PFS and OS for PDC using the exponential curves for both

Table 2: Cost-effectiveness scenarios with upward adjustment of the fitted exponential curves for PFS and OS on PDC

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER	% surviving at 5 years
Company base case								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,152	[redacted]
Exponential curves for PFS and OS on PDC								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,440	[redacted]
Adjustment HR for PDC PFS = 0.9; Adjustment HR for PDC OS = 0.9								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,863	[redacted]
Adjustment HR for PDC PFS = 0.8; Adjustment HR for PDC OS = 0.8								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,814	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.7								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,655	[redacted]
Adjustment HR for PDC PFS = 0.8; Adjustment HR for PDC OS = 0.9								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,076	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.8								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,755	[redacted]
Adjustment HR for PDC PFS = 0.7; Adjustment HR for PDC OS = 0.9								

Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,066	[redacted]
Adjustment HR for PDC PFS = 0.46; Adjustment HR for PDC OS = 0.62 (Zukin et al. 2013)								
Pemetrexed	[redacted]	[redacted]	[redacted]					[redacted]
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,263	[redacted]

Sensitivity analysis on subsequent therapy following progression on lorlatinib

This section presents a set of exploratory sensitivity analyses that varies the percentage of subsequently treated patients who receive ABCP following progression on lorlatinib. The percentage of progressed patients who receive subsequent treatment remains at 60% throughout. In addition, at the request of NICE, and based on advice from a clinical expert, pemetrexed monotherapy is replaced with PDC in the proportional distribution of subsequent treatments.

To implement the ABCP costs, the ERG used the same drug acquisition and administration costs per treatment cycle as applied in the ABCP arm of the model and multiplied these by the proportion assumed to receive this treatment and the average number of treatment cycles. These average treatment costs are then applied as one of costs in the same manner as all other subsequent treatment costs in the company's model. This required an assumption about the mean duration of treatment with ABCP following progression on lorlatinib, and to inform this the ERG assessed the mean time on ABCP in the ABCP arm of the model [redacted]). However, since it may be reasonable to expect a shorter time on ABCP as a subsequent treatment (i.e. at a later line), the mean time on treatment applied to atezolizumab monotherapy as subsequent therapy in the PDC arm (35.8 weeks) was used instead.

These analyses are all caveated by the fact that changes are only made to the costs of subsequent treatment; i.e. the selection of subsequent treatment does not influence OS. The validity of these analyses must therefore be carefully considered in terms of whether the revised subsequent treatment distributions would be expected to affect the OS curves derived from Study 1001. This depends on the relative efficacy of the modelled subsequent treatments compared to actual subsequent treatments received in Study 1001. However, the same caveats also apply to the modelling of subsequent treatments following PDC (these also do not affect the fitted OS curves for PDC) and it is uncertain if they are consistent with subsequent treatments available to participants in PROFILE 1001/1005. Results are presented in Table 3 (PDC comparison) and Table 4 (ABCP comparison) below.

Table 3: Cost-effectiveness scenarios exploring the impact of applying costs of ABCP as a subsequent therapy following lorlatinib (lorlatinib versus PDC)

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
Company base case: 60% PDC, 40% pemetrexed in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,152
100% PDC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,290
60% PDC, 40% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,591
50% PDC, 50% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,666
40% PDC, 60% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,741
50% receive subsequent treatment with 50% PDC, 50% ABPC in subsequently treated patients							
Pemetrexed	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,555

Table 4: Cost-effectiveness scenarios exploring the impact of applying costs of ABCP as a subsequent therapy following lorlatinib (lorlatinib versus ABCP)

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER
Company base case: 60% PDC, 40% pemetrexed in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,369
100% PDC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,520
60% PDC, 40% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,588
50% PDC, 50% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,855
40% PDC, 60% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,122
50% receive subsequent treatment with 50% PDC, 50% ABPC in subsequently treated patients							
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,548

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Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Second addendum to the main ERG report

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Date completed 22 November 2019

Contains [redacted]

Following submission of the ERG report for this appraisal, the NICE technical team asked the ERG to replicate the results of the ERGs exploratory analysis (contained in Table 17 and Table 18 of the main ERG report), using list prices for comparators and subsequent treatments, rather than the company-estimated cPAS prices which the ERG used in the original tables for comparability with the company's base case results. These results are provide below as requested.

Table 17 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£46,033
1	Alternative PDC PFS and OS survival cure methods	a) Method 1: MAIC HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£42,416
		b) Method 2: MAIC HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£53,915
		c) Method 3: Unadjusted HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£40,728
		d) Method 4: Unadjusted HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£46,184
		e) Method 6: Independent curves & population adjustment	[redacted]	[redacted]	[redacted]	£40,520
2	Hazard ratios for upward adjustments to PFS and OS in the PDC arm	a) 0.9	[redacted]	[redacted]	[redacted]	£46,615
		b) 0.8	[redacted]	[redacted]	[redacted]	£47,338
		c) 0.7	[redacted]	[redacted]	[redacted]	£48,290
		d) 0.6	[redacted]	[redacted]	[redacted]	£49,710
3	Treatment waning	a) Hazard of death on lorlatinib equal to PCD from three years	[redacted]	[redacted]	[redacted]	£50,863
		b) Hazard of death on lorlatinib equal to PCD from five years	[redacted]	[redacted]	[redacted]	£46,948
4	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£49,819
		b) [redacted]	[redacted]	[redacted]	[redacted]	£55,378
5	Lorlatinib time on treatment	Generalised gamma	[redacted]	[redacted]	[redacted]	£52,758

6	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£48,319
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£45,327
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£47,633
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£51,511
		e) a and d combined	[redacted]	[redacted]	[redacted]	£54,390
7	Subsequent therapies	a) Fixed dose regimen for pembrolizumab	[redacted]	[redacted]	[redacted]	£43,371
		b) proportion of treated patients receiving atezolizumab and pembrolizumab following progression on PDC ([redacted] and [redacted] respectively)	[redacted]	[redacted]	[redacted]	£43,264
		c) a and b combined	[redacted]	[redacted]	[redacted]	£42,068
		d) Proportion of subsequently treated patients who receive PDC and pemetrexed alone following progression on lorlatinib (80% and 20%)	[redacted]	[redacted]	[redacted]	£46,102
		e) 50% receive subsequent therapy following PDC	[redacted]	[redacted]	[redacted]	£48,424
8	Combination	Combines 2b), 5), 6c), 7a), and 7e)	[redacted]	[redacted]	[redacted]	£57,114
		Probabilistic ICER for scenario 8	[redacted]	[redacted]	[redacted]	£55,057

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment

Table 18 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£8,955
1	Reducing population adjustment hazard ratios (on log scale)	a) By 25% (HR for PFS = 1.53; HR for OS = 2.86)	[redacted]	[redacted]	[redacted]	£1,197
		b) By 50% (HR for PFS = 1.33; HR for OS = 2.01)	[redacted]	[redacted]	[redacted]	Dominant
2	Treatment waning	a) Hazard of death on lorlatinib equal to ABCP from three years	[redacted]	[redacted]	[redacted]	Dominant
		b) Hazard of death on lorlatinib equal to ABCP from five years	[redacted]	[redacted]	[redacted]	Dominant
3	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£13,091
		b) [redacted]	[redacted]	[redacted]	[redacted]	£19,163
4	Lorlatinib time on treatment	Generalised gamma curve	[redacted]	[redacted]	[redacted]	£16,301
5	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£9,443
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£8,806
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£9,388
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£10,485
		e) a and d combined	[redacted]	[redacted]	[redacted]	£11,160

6	Subsequent therapies	a) 80% of subsequently treated patients who progress on lorlatinib receive PDC	[redacted]	[redacted]	[redacted]	£9,031
		b) 40% receive subsequent treatment with docetaxel following progression on ABCP	[redacted]	[redacted]	[redacted]	£9,147
7	Combination	Combines 1b), 4), 5c), and 6b),	[redacted]	[redacted]	[redacted]	£30

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 20 September 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pxii/P18/P65: The ERG only mention the rationale for why the proxy OS/PFS data for the PDC comparator may be an underestimate of efficacy.	There should be some mention of the competing rationale that the proxy OS/PFS data for PDC may be an overestimate of efficacy. See page 35 of the company response to ERG clarification questions: other things being equal, patients in a later line of therapy will have worse efficacy outcomes (as suggested by some clinical experts).	For balanced representation of this technical issue (the matter is fully acknowledged in company response to clarification questions).	The ERG does not view this as a factual inaccuracy but rather a summary of its opinion. However, we acknowledge the company's concern and for completeness we have now added mention of the company's counter argument on pages xii and 18 (see erratum). The text on page 65 merely reiterates the reason for exposing the PDC efficacy to further sensitivity analysis.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P18/P26/P42: The ERG report states that, for example, on page 18: "*The company report that the ALUR and ASCEND5 did not provide any data for OS (page 54, Document B, CS). However, Appendix D and the publications for ALUR and ASCEND5 indicate that data for overall survival*	These pages should acknowledge that Pfizer is aware of the availability of OS and PFS data (some of which is reported in the appendices of the CS). However, it should be acknowledged that the SLR did not identify additional *Kaplan-Meier* PFS and OS for PDC via the SLR, which is the data required in the methodology for producing proxy PDC data.	For balanced representation of CS and rationale for OS/PFS data sources that inform the PDC arm in the cost-effectiveness analysis.	The ERG does not view this as a factual inaccuracy but as an expression of its opinion.

appeared to be available. It is not clear to the ERG why these data were not used by the company". The submission does not mention these sources of data on page 54. However, on page 57 of document B and page 75 of the CS appendix it is explained that these are the only sources of *Kaplan-Meier* PFS and OS data via the SLR. The process by which these sources are arrived at are explained in some detail in the latter section.			

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P44/P45: The ERG report writes, respectively: "Previous lines of treatment do not influence effectiveness so the methods that do not adjusted for this, methods 2, 4 and 5, are preferred." *"However, as noted above, the company ultimately rejected this approach based on clinical advice suggesting they would not expect*	This should be restated in a more accurate way. Prior treatment history may well affect the performance of PDC (e.g. ALK-inhibitor naive vs previously treated with ALK-inhibitors); however, the CS stated that consulted clinical opinion suggested that PDC performance would be comparable in a patient *pre-treated with crizotinib vs pre-treated with a 2nd generation inhibitor*, which is a different matter.	For balanced representation of argumentation in CS and statements concerning consulted expert opinion.	The ERG acknowledges this factual inaccuracy and accepts the proposed amendment (see Erratum).

the difference between the prior treatment history of the comparator studies and the EXP-3B:5 cohort to affect the performance of PDC" But the CS does not say this – it says that "*Clinicians suggested that patients receiving PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI*" (P122 of CS). This is explained again in response to question B9 (company response to clarification questions).			

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P53: The ERG report states "*2. The evidence source for the proportional distribution of atezolizumab and pembrolizumab following PDC is unclear. The ERGs own clinical expert advised that atezolizumab may be more commonly used in practice."* These proportions (31% and 69%)	Update that these can be found in the committee papers of the TA584 appraisal and seem to have been accepted by the committee.	Correction about the reporting of data sources used in submission.	The ERG accepts this is a factual inaccuracy and has revised the phrasing to acknowledge the source of data for the proportional distribution applied by the company.

can be found on P13 of the public committee slides of 02 May 2019. And these seem to have been agreed by the committee (see page 21 of the FAD): *"At consultation, the company provided updated analyses that included only atezolizumab and pembrolizumab as subsequent therapies after pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee agreed that the company's revised analyses were more appropriate than analyses including treatment options that are not immunotherapies or not routinely commissioned in the NHS in England."*			

(please cut and paste further tables as necessary)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 21 November 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Darshan Zala
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Pfizer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Relevant comparators	
What treatments should be considered the most relevant comparators for this appraisal?	Pfizer acknowledges that Atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab ("ABCP") could be a relevant comparator in this appraisal, given that it has been approved by NICE in the same line as the main comparator platinum doublet chemotherapy ("PDC"). Other things being equal, if fitness allows, ABCP is likely to be used instead of PDC because it is more effective. This is particularly the case in patients without brain metastases, which represents around 30% of ALK+ patients in the lines relevant to the indication for lorlatinib (the EXP-3B:5 cohort in Study 1001). In the 70% of patients with brain metastases, it is less likely that ABCP will be used instead of PDC. Both regimens have low or no CNS penetration and so in this group they are likely to have similar efficacy. In addition, patients with brain metastases are more likely to be able to tolerate (i.e. be fit enough for) PDC compared with ABCP. There was some consensus in the ABCP appraisal (TA584) about this issue (ACD, p9): "*The clinical experts noted that ABCP would not be a treatment option for people with brain metastases. The committee concluded that ABCP would only be a treatment option for people who are well enough."* Once lorlatinib is available - as agreed by the clinical experts on the technical engagement call – it is likely to be the treatment of choice for 100% of patients progressing on a 2nd generation ALK inhibitor, including the 70% of patients with brain metastases. This is due to patient fitness and relative efficacy versus ABCP and PDC. Although ABCP is only formally restricted in patients with asymptomatic/controlled brain metastases, Pfizer believe that in practice a soft cap in use of 30% for ABCP is plausible.

Issue 2: Sources of evidence for comparative effectiveness	
Are ALUR/ASCEND-5 the best sources of comparator evidence for PFS?	Although the sources used to proxy PDC efficacy (PFS and OS) are not perfect, in that the patients are treated with singlet chemotherapy, they reflect the best available published sources. As noted by the ERG and technical team, the alternative is to use the pure PDC arm from the ASCEND-4 trial. However, this is a trial that compares Ceritinib and PDC in a population that has received no treatment for advanced/metastatic population ALK+ NSCLC and so reflects less advanced disease (i.e. no previous chemotherapy or ALK+ TKI). Just as with the current base-case, using this evidence source would also require an adjustment to PDC-arm efficacy but in the opposite direction (i.e. a HR applied that reduces OS and PFS). Just as any MAIC methodology cannot "weight away" possible differences in efficacy between PDC and singlet chemotherapy, it cannot adjust for this difference in population type. However**,** on balance the current sources (i.e. ALUR, ASCEND-5, Ou et al. 2014) are superior to the alternative because there is RCT and meta-analysis evidence that can be used to adjust for the relative effectiveness of doublet vs singlet chemotherapy (see below). In contrast, there cannot be randomised and controlled sources of evidence informing the relative OS/PFS projections of untreated vs later line patients with advanced/metastatic ALK+ NSCLC.
Are PROFILE 1001/1005 the best sources of comparator evidence for OS?	
Is it more plausible that the comparative efficacy of PDC has been underestimated (as suggested by the ERG), or overestimated (as suggested by the company)?	As already noted by the ERG and technical team, other things being equal, PDC is more likely to be effective than singlet chemotherapy. Pfizer has conducted a targeted literature search (see appendix A) for studies that compared the relative efficacy of doublet vs singlet chemotherapy which provides some evidence for PDC vs singlet chemotherapy. This identified another study

	and 3 SLR and meta-analyses in addition to Zukin (2013). The range for the HRs is broadly in line with the range implied by Zukin (2013) at around 0.6 to 1.
	
	There are 2 possible reasons why this adjustment should be closer to 1 than 0.6:
	
	• ALUR/ASCEND-5/Ou et al. (2014) reflect a population that has been pre-treated with chemotherapy and crizotinib, whereas the EXP-3B:5 cohort in Study 1001 is a mix with some patients in later lines of treatment and so with more advanced disease.
	  ○ EXP-3B (1 ALK +/- chemo) = 20%, EXP-4 (2 ALKs +/- chemo) = 47%, EXP-5 (3 ALKs +/- chemo) = 33%. Therefore, the majority have had > 1 previous ALK TKIs (with or without chemo).
	• Around 70% of patients in this population are expected to have brain metastases. Clinical opinion in the technical engagement call suggested that the differences in relative efficacy between PDC and singlet chemotherapy will be minimal in patients with disease progression in the brain. This is because both regimens have low or no CNS penetration.
	  ○ The results of the literature review suggest a HR of 0.6 to 1 for the relative efficacy of doublet vs singlet chemotherapy (see appendix A). However, most of this evidence is for patients with advanced/metastatic NSCLC who have received no systemic therapy (i.e. no targeted ALK TKIs but in some cases previous chemotherapy). The ASCEND-4 trial and relevant Study 1001 cohort (EXP-1) baseline characteristics suggest that a third or less of patients will have brain metastases at this early stage and so these HRs are likely to overestimate the relative efficacy of PDC vs singlet chemotherapy.
	
	Pfizer suggest that the middle of this range of HRs is a reasonable approach and so assume a HR of 0.8 in the combined scenarios presented in appendix B.

Issue 3: Selection of method for the indirect comparison used in the economic modelling	

Which method is most appropriate for use in the economic modelling and for decision making?	The main rationale for selecting independent curves in the submitted base-case was that it was unclear if OS satisfied the proportional hazards assumption, which is required for the use of methods that apply constant HRs (i.e. MAICs). Applying these when proportional hazards is violated can cause bias in long-run projections. The base-case selected method gave the 2nd highest ICER from all six methods. The ERG and technical engagement team argue that the MAIC methodology presented in the company submission was robust and therefore it can be argued that method 2 (MAIC with EXP-3B:5 matching) is just as plausible as the independent curve base-case. However, there has been no adequate justification for rejecting the method 1 MAIC presented in the company submission (MAIC with EXP-2:3A matching). That the matching is done by weighting a cohort (EXP-2:3A) that does not satisfy the license indication is not an adequate reason to reject this MAIC. The rationale for presenting this MAIC in the company submission was that it is a MAIC that attempts to adjust for the bias that may occur by comparing the Study 1001 EXP-3B:5 cohort to the earlier line PDC proxy sources (ALUR/ASCEND-5/Ou et al., 2014). This bias cannot be adjusted for by weighting via a MAIC and so using the equivalent line matching cohort means that this bias does not enter the HR applied to the lorlatinib curves in method 1. Therefore, Pfizer believe that method 1 (MAIC with EXP-2:3A matching), method 2 (MAIC with EXP-3B:5 matching) and method 5 (independent curves) give plausible ICERs.
Issue 4: The most plausible projections of PFS and OS for lorlatinib	
Which are the most plausible projections of PFS and OS for lorlatinib?	There was broad consensus between the ERG and technical team concerning the appropriate curve selection for PFS in the lorlatinib arm and so this was not discussed in the technical engagement call.

	For OS, the exponential curve had the best fit statistics but not by much, with the other curves having almost identical fit statistics. Clinical experts consulted by Pfizer suggested up to 10% alive at 10 years was plausible (Log-normal curve); a clinician consulted by the ERG suggested that 2% was also plausible (exponential curve). There was agreement from the clinical experts in the technical engagement call that 4.5% predicted alive at 10 years is a reasonable projection between the 2 clusters of curves and so the generalised-gamma base-case curve is the most appropriate selection.
Issue 5: Selection of utility values	
What is the most appropriate utility value for the progressed disease on either treatment?	A mixture of utilities for progressed disease (PD) have been accepted by previous committees: • The Ceritinib (after Crizotinib) appraisal accepted 0.46, but the comparator was BSC and not an active treatment (chemotherapy). • In first line ALK+ appraisals (ceritinib and alectinib) committees accepted higher PD utilities of around 0.56. But in recent first line EGFR appraisals, committees have accepted 0.64 (osimertinib and dacomitinib). • The recent brigatinib appraisal applied different PD utilities to account for treatment beyond progression in the brigatinib arm (for PD-on TX 0.732 and for PD-off TX 0.643). There was broad agreement in the technical engagement call that 0.46 to 0.59 is a reasonable range. To capture higher utility for treatment beyond progression in the lorlatinib arm - in-line with what was accepted in the Brigatinib appraisal – two scenarios are presented in appendix B. The Labbe (2017) utility of 0.65 is thought to be reflective of progressed patients following treatment with a TKI and so this is applied in the lorlatinib arm for newly progressed patients for the number of

	months for which they receive lorlatinib beyond progression. 0.59 and 0.46 is then applied in both arms as the progressed off-TX utility: • Method 1: 0.65 for lorlatinib patients in progression and on treatment and 0.59 for progressed and off treatment in both arms. • Method 2: 0.65 for lorlatinib patients in progression and on treatment and 0.46 for progressed and off treatment in both arms.
Is it appropriate to use a higher PFS utility value for lorlatinib compared with PDC or ABCP?	There was consensus that the PFS utility for lorlatinib will be higher compared with chemotherapy or chemotherapy and immunotherapy regimens (PDC or ABCP) and so this was not discussed during the technical engagement call. Generally, the utility increment for lorlatinib ([redacted]) vs PDC (0.72) is comparable or smaller than in other appraisals. The increment is smaller than found in the PROFILE 1007 trial (crizotinib = 0.82, PDC = 0.73). The lorlatinib value is also lower than the value accepted for Brigatinib in the recent appraisal (0.793).
Issue 6: Treatment duration on lorlatinib	
What is the most plausible time on treatment for lorlatinib?	There was consensus among the clinical experts on the technical engagement call that 3 to 3.5 months of treatment beyond progression with lorlatinib is clinically plausible. This is supportive of an additional scenario that uses UK real world data to estimate a time on treatment beyond progression. As reported in section B.3.3.3.2 of the company submission, the UK database of ALK patients reported 14.9 months as the 95th percentile for duration of treatment on ALK+ TKIs. Treating this as an effective upper bound and differencing with the calculated restricted mean PFS gives 4.3 months (14.9 – 10.6 = 4.3). The value of 4.3 can be seen as an effective upper bound on treatment months beyond progression and so taking the mid-point

	between the base-case treatment beyond progression months ([redacted]) and 4.3 gives 3.5 months. Therefore 3.5 months is included in the scenarios in appendix B.
Issue 7: Assumptions about subsequent therapies	
Are the assumed proportion of patients receiving subsequent therapies and the distribution of these subsequent therapies appropriate for decision making?	There was consensus among clinicians on the technical engagement call about the proportion and types of subsequent treatments. Based on these comments, the following subsequent treatment assumptions are included in the scenarios presented in appendix B: • Lorlatinib: 45% receive subsequent treatments with the remaining 55% receiving BSC. Of the 45%, 66% now receive ABCP and 33% receive PDC. • PDC: 45% receive subsequent treatments with the remaining 55% receiving BSC. The 45% receive immunotherapies in the proportions from the original company submission (69% atezolizumab, 31% bevacizumab based on TA584). • ABCP: 75% receive docetaxel and 25% BSC. The assumption that pembrolizumab is given as a fixed dose is also included because clinical experts had previously suggested this is standard practice in the NHS.
Issue 8: Cancer Drugs Fund	
Does lorlatinib meet the criteria for inclusion in the Cancer Drugs Fund (CDF)?	The evidence supporting this submission is derived from a Single arm, open-label, multicentre Phase 1/2 study. This is the only study that currently provides data for lorlatinib. As such, the

	degree of uncertainty due to limitations in the evidence-base suggests that lorlatinib can potentially be a suitable candidate to the Cancer Drugs Fund (CDF). Despite the uncertainties raised by the ERG and the NICE Technical Team, Pfizer believe the economics case presented is robust and indicates that lorlatinib satisfies the criteria for routine commissioning. Further, it is unclear whether any uncertainties with regards the cost-effectiveness of lorlatinib could be addressed with further data collection. This is also the view of the NICE Technical Team. Pfizer welcomes the Committee's views on this matter at the forthcoming Appraisal Committee Meeting.

Appendix A: Relative efficacy of doublet vs singlet chemotherapy

A targeted literature review was undertaken with the aim of understanding the relationship between doublet and single-agent chemotherapy in NSCLC. The databases and websites searched were Google, PubMed, Clinicaltrials.gov and NICE. The keywords used in the search were NSCLC, ALK, Single, Single-agent, Doublet, Chemotherapy and Pemetrexed.

Table 1 presents the results of this targeted literature review - 2 RCTs and 3 meta-analyses were identified. Only Zuchin et al (2013) compared pemetrexed with carboplatin/cisplatin vs pemetrexed; however, the Sun et al. (2014) meta-analysis compared pemetrexed based doublet chemotherapy with pemetrexed alone which may be a reasonable proxy. The remaining studies compared doublet vs singlet chemotherapy regimens in general. No studies specified any mutation type including ALK+. No studies reported the proportion of brain metastases at baseline, but this is expected to be relatively low given the early line advanced NSCLC population of each study.

In general, the reported HRs range from around 0.6 to 1 (no statistically significant difference) which is consistent with the range presented across the company submission, ERG report and technical team report scenarios.

Table 1. Results of targeted literature review

Identified study	Study type	Population	Comparison	Sample size	Inclusion of brain metastases	HR and 95% CI (doublet vs singlet)
Zuchin et al. (2013)	RCT phase 3	1L patients with advanced NSCLC, ECOG PS of 2, no prior chemotherapy. No ALK+ specified.	PDC vs Pemetrexed	205	Patients with brain metastases were eligible if neurologically stable and no longer receiving corticosteroids after appropriate therapy. No baseline statistics.	**0.62 (0.46-0.83)** for OS and **0.46 (0.35-0.63)** for PFS.
Quoix et al. (2011)	RCT phase 3	1L locally advanced or metastatic NSCLC, aged 79-89 years. No ALK+ specified.	carboplatin plus paclitaxel vs vinorelbine or gemcitabine monotherapy	451	Only patients with asymptomatic brain metastases eligible. No baseline statistics.	**0.64 (0.52-0.78)** for OS and **0.51 (0.42-0.62)** for PFS.
Luo et al (2015)	Meta-analysis	1L treatment of advanced NSCLC with performance status (PS) 2, and of the six trials, the lowest median age reported was 65. No ALK+ specified.	Five treatment comparisons were assessed across the studies including: Gemcitabine + vinorelbine vs vinorelbine; paclitaxel + carboplatin vs paclitaxel; gemcitabine + carboplatin vs gemcitabine; paclitaxel + gemcitabine vs paclitaxel; pemetrexed + carboplatin vs pemetrexed.	Six trials with 386 participants in the single-agent group and 389 participants in the doublet group were	Not specified.	**0.72 (0.61–0.84)** for OS for all studies combined. Only Zuchin et al. (2013) was pemetrexed based RCT.

				included in this review.		
Sun et al. (2014)	Meta-analysis	Randomized controlled trials which compared pemetrexed-based doublet with single-agent pemetrexed in patients as second-line treatment NSCLC. No ALK+ specified.	Pemetrexed-based doublet compared with pemetrexed alone.	Four eligible randomized clinical trials including 1,084 patients were selected	Not specified.	**0.88 (0.74-1.04)** for OS and **0.91 (0.73-1.15)** for PFS. **Statistically insignificant.**
Des Guetz et al. (2012)	Meta-analysis	1L Advanced non-small cell lung cancer (NSCLC) aged more than 70 years. No ALK+ specified.	Third generation agents (gemcitabine, vinorelbine, paclitaxel, docetaxel) alone or in combination with platinum or none platinum containing therapy (i.e. doublet therapy).	10 trials including 2,605 patients.	Not specified.	**0.92 (0.82–1.03)** for OS. **Statistically insignificant.**

Appendix B: Cumulative impact of unresolved uncertainty (including updated lorlatinib PAS)

Table 2 and Table 3 contains the results reflecting the updated confidential PAS for lorlatinib (■) and the spread of ICERs with the remaining unresolved uncertainty following the technical engagement meeting. The following settings apply in the presented results:

- Issue 1: ABCP remains a comparator.
- Issue 2: given the clinical expert comments the range of efficacy adjustment for the PDC proxy sources has been set at the middle of the 0.6-1 range (i.e. 0.8).
- Issue 3: this issue is unresolved and so the ICER range reflects method 1, method 2 and method 5.
- Issue 4: given the clinical expert comments the generalised gamma curve for lorlatinib OS is selected.
- Issue 5: this uncertainty is unresolved and the ICER range reflects the fixed PD utility value of 0.59 and the two additional methods (described above).
- Issue 6: given clinical expert comments and the new calculation presented by Pfizer, 3.5 months of additional lorlatinib has been inputted.
- Issue 7: the new subsequent treatment patterns for each arm now fully reflect those given by the clinical experts, including adding ABCP as a subsequent treatment to lorlatinib and setting pembrolizumab as a fixed dose when given as a subsequent treatment to PDC.

Therefore issue 3 and issue 5 are the main unresolved issues and determine the range of ICERs presented below.

As in the submitted base-case, the PSA mean ICER vs PDC (Table 2) is consistently around £4k less than the deterministic ICER and this can be taken as the more plausible. Therefore, the range of plausible ICERs is from £47,061 to £60,334, with 6 of the 9 scenarios giving ICERs below £50k.

Table 2. ICER vs. PDC range with unresolved uncertainty (including updated lorlatinib PAS and assumed subsequent treatment discounts)

#	Scenario	Description	ICER change from original base-case	Deterministic ICER	Probabilistic ICER
1	Base-case vs. PDC	Company submitted base-case settings with updated lorlatinib PAS and assumed subsequent treatment PAS	-	£42,877	£39,595
2	Base-case but updated with resolved issues	Scenario 1 but with inputs updated for resolved issues 2, 4, 6 and 7.	+£6,738	£49,615	£45,709
3a	Updated base-case with method 5 (independent curves) and different PD utilities	Independent curves base-case (method 5) and 0.59 PD utility	+£8,566	£51,443	£47,742
3b		Independent curves base-case (method 5) and utility method 1	+£7,874	£50,751	£47,061
3c		Independent curves base-case (method 5) and utility method 2	+£10,521	£53,398	£49,902
4a	Updated base-case with method 2 (EXP-3B:5 MAIC) and different PD utilities	Method 2 MAIC and 0.59 PD utility	+£21,661	£64,538	£60,334
4b		Method 2 MAIC and utility method 1	+£20,609	£63,486	£60,059
4c		Method 2 MAIC and utility method 2	+£20,448	£63,325	£60,311

5a	Updated base-case with method 1 (EXP-2:3A MAIC) and different PD utilities	Method 1 MAIC and 0.59 PD utility	+£3,934	£46,811	£44,756
5b		Method 1 MAIC and utility method 1	+£3,437	£46,314	£43,857
5c		Method 2 MAIC and utility method 2	+£6,144	£49,021	£47,171
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and assume a PAS discount of [redacted] on Atezolizumab and Bevacizumab (ABCP subsequent treatments for lorlatinib) and Pembrolizumab and Atezolizumab (subsequent treatments for PDC). See above for the definitions of utility method 1 and method 2.					

Table 3 presents the results for the comparison with ABCP with unresolved uncertainty relating to progressed disease utilities driving the range of ICERs. The results show that even with this unresolved uncertainty, lorlatinib is cost-effective in all scenarios.

Table 3. ICER vs. ABCP range with unresolved uncertainty (including updated lorlatinib PAS and assumed subsequent treatment discounts)

#	Scenario	Description	ICER change from original base-case	ICER
1	Base-case vs. PDC	Company submitted base-case settings with updated lorlatinib PAS and assumed subsequent treatment and comparator PAS	-	£35,192
2	Base-case but updated with resolved issues	Scenario 1 but with inputs updated for resolved issues 4, 6 and 7	+£4,835	£40,027
3a	Updated base-case with different PD utilities	0.59 PD utility	+£6,768	£41,960
3b		Utility method 1	+£6,213	£41,405
3c		Utility method 2	+£9,549	£44,741
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and assume a PAS discount of [redacted] on Atezolizumab and Bevacizumab (ABCP comparator and subsequent treatment for lorlatinib)				

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

ERG comment on the company response to the technical engagement report

Produced by Aberdeen HTA Group

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Date completed **Revised version updated on the 6 Dec 2019**

Contains [redacted]

In their response to the technical engagement report the company addressed each of the issues and provided an updated base case economic analysis and further scenario analyses to address these. The revised set of analyses included an updated PAS for lorlatinib. This addendum to the ERG report provides a commentary on the company's response to technical engagement and revised modelling and highlights any outstanding areas of uncertainty that may need to be considered by the committee. It should be read in conjunction with the company's response document dated 22 Nov 2019. Upon request by the NICE technical team, the ERG have replicated the company's revised analysis using list prices for all comparator treatments and subsequent therapies. A set of results using the actual PAS discounts for comparators and subsequent treatments is provided as a confidential appendix.

This Document is a revised version of the original which was updated following identification of an apparent bug in the company's revised model. This related to the calculation of ABCP costs as subsequent treatment following progression on lorlatinib. The company estimated that patients would receive ABCP for an average of 8.23 model cycles following progression. However, the weighted calculation of subsequent treatment costs in the company revised model was picking up the number of docetaxel treatment cycles (6) for ABCP, rather than the 8.23 mentioned above. This applied to both the calculation of drug acquisition costs and administration costs. Further, the administration cost calculation for ABPC following lorlatinib was picking up the docetaxel administration cost (£174 per treatment cycle), rather than the ABCP administration costs per model cycle as applied in the ABCP treatment arm of the model. Finally, the ERG identified what it believes to be an error in the calculation of ABCP admin costs per cycle, resulting in these being applied on four-week schedule rather than the appropriate three-week schedule. The ERG has assessed the impact of correcting these issues in the company's revised analyses and incorporates these changes in the results presented throughout this revised document.

ERG commentary on the company's response to technical engagement

Below the ERG comment on the company's responses to the seven key areas of uncertainty raised in the technical engagement report.

Issue 1: ABCP remains a comparator.

The company acknowledge that the ABPC regimen (atezolizumab, bevacizumab, paclitaxel, carboplatin), when used in line with TA584 could be a comparator for lorlatinib.

However, they make the case ABCP is more likely to replace of PDC in patients without evidence of brain metastases when treatment commences, since both regimens have low or no CNS penetration and so are likely to have similar efficacy in those with brain metastasis. They state NICE TA 584 supports this and quote the ACD for that guidance (NICE TA584).

ERG comment on company response:

The logic of the company's comment is that the licensed indication for lorlatinib could be considered as two distinct subgroups of patients, one without evidence of brain metastases at baseline and one with evidence of brain metastases. This would then involve separate ICERs because the comparators and clinical evidence would be different between the two groups. It is true the company provided ICERs against ABCP and PDC separately in the submission document and this could be said to correspond to the groups without brain metastases and with brain metastases. However, these ICERs were not based on clinical evidence specific to the absence or presence of brain metastases, but for all patients combined. By the company's own logic, this seems inappropriate.

Given the possibility the ICERs for the two groups could be quite different, the committee may be minded to request ICERs from the company to assist with decision-making.

Issue 2: given the clinical expert comments the range of efficacy adjustment for the PDC proxy sources has been set at the middle of the 0.6-1 range (i.e. 0.8)

In the company submission, ALUR and ASCEND-5 (Shaw et al. 2017; Novello et al. 2017) were used for PFS and PROFILE 1001/1005 for OS (Ou et al. 2014). In the ERG report, the criticism was that neither used PDC and involved an estimate of effectiveness from monotherapy. There is an RCT arm in ALK-positive disease that used PDC (ASCEND-4)(Soria et al. 2017) and while it was acknowledged that this was in previously untreated

patients, a case could be made for using an estimate based on the observed data but adjusting for the difference between different positions in the treatment pathway.

In the technical engagement response comment, the company say (to paraphrase a little) that in deriving an estimate of the effectiveness of PDC in the licensed indication for lorlatinib they faced a choice between 'right line, wrong treatment' or 'wrong line, right treatment'. They argue for the former because there is evidence from RCTs to adjust for the relative effectiveness of doublet vs singlet chemotherapy.

To inform this adjustment the company have conducted a targeted review of studies comparing PDC vs singlet chemotherapy, which identified hazard ratios ranging from 0.6 (40% reduction in hazards) to 1 (no reduction in hazards). The argue this should be closer to 1 rather than 0.6 in the for the current indication and treatment line, because: 1) the relevant cohort from Study1001 is at a later line of treatment with more advanced disease compared to the studies suggesting benefit for PDC versus singlet chemotherapy; and 2) around 70% of patients in this population are expected to have brain metastases, with clinical opinion in the technical engagement call suggesting that the differences in relative efficacy between PDC and singlet chemotherapy will be minimal in such patients. The company therefore apply the middle value of 0.8 in their new scenarios presented for consideration.

ERG note on ABCP comparison: Whilst ERG is generally satisfied with the company's approach to dealing with the uncertainty regarding the comparative efficacy of PDC, it believes there is greater remaining uncertainty surrounding the comparison with ABCP. The comparison with ABCP also suffers from a lack of comparative data, and indeed any available data on the efficacy of ABCP in an ALK+ cohort following progression on a second generation ALK TKI. Therefore, the company used PFS and OS data for ABCP from a primarily EGFR+ cohort (Impower150) (Reck et al. 2019), and then adjusted these curves for an ALK+ cohort. However, the population adjustment hazard ratios were derived by comparing OS and PFS for ALK+ patients treated with single agent chemotherapy (from ALUR, ASCEND-5 and PROFILE 1001/1005), with an EGFR+ cohort treated with PDC as first line treatment (IMPRESS trial) (Mok et al. 2017). Therefore, there is a question regarding to what extent the adjustment HRs reflect the inferior efficacy of the monotherapies at second or third line versus PDC at first line, rather than the different mutation status of the cohorts. Further, in amending the comparative efficacy of PDC in their updated base case (scenario 2 in the company response), but leaving ABCP efficacy unchanged, the

company model [redacted]. *This seems to lack clinical plausibility, particularly if ABCP is more likely to be used in patients without brain metastasis because it is more effective than PDC. Therefore, the ERG believe it is necessary to explore the impact of reducing the population adjustments applied to ABCP efficacy. This is done by applying a proportional reduction of 25% to the log hazard ratios for population adjustment. For example, the population adjustment HR (ALK+ versus EGFR+) for OS in the company model is* [redacted]. *This is reduced to* [redacted] *in the ERG exploratory analysis. Figures 1 and 2 below illustrate the impact that this has on the adjusted OS curve for ABCP, relative to the lorlatinib and the adjusted PDC OS curves in the company updated base case.*

Figure 1 OS curves applied in the company's revised base case, with adjustment to the PDC curve to reflect superior efficacy compared to single agent chemotherapy, and the company's full population adjustment (for ALK+ versus EGFR+) applied to ABCP.

Figure 2 OS curves applied in ERG exploratory ABCP comparison, with a proportionally reduced population adjustment (for ALK+ versus EGFR+) applied to ABCP.

Issue 3: Approach for comparative efficacy of PDC - this issue is unresolved and so the ICER range reflects method 1, method 2 and method 5

The company submission presented six different ways to make the comparison between the single-arm clinical study for lorlatinib and the evidence for PDC from ALUR, ASCEND-5 and the PROFILE 1001/1005, including:

- *HRs from MAICs comparing the chemotherapy cohorts to the less heavily treated EXP-2:3A cohort of Study1001 (method 1)*
- *HRs from MAICs comparing the chemotherapy cohort to the more heavily treated EXP-3B:5 cohort of Study1001 (method 2)*
- *Unadjusted HRs from cox models comparing the chemotherapy cohorts with the less heavily treated EXP-2:3A cohort of Study1001 (method 3)*
- *Unadjusted HRs from cox models comparing the chemotherapy cohorts with the more heavily treated EXP-3B:5 cohort of Study1001 (method 4)*
- *Directly fitted curves without adjustment for prior treatment (method 5).*
- *Directly fitted curves with adjustment to PDC for prior treatment (method 6).*

Based on clinical opinion suggesting PDC would be expected to perform equally poorly following treatment with crizotinib (as per the available data sources) or a second generation ALK-TKI (in line with the license for lorlatinib), the company appeared to narrow the choice in their original submission to those methods that did not adjust the PDC curves for prior treatment (methods 2, 4 and 5) (section B3.3.3.4, company submission, document B). They ultimately preferred method 5 because it was unclear if the proportional hazards assumption required for methods 2 and 4 were satisfied for OS.

In its report the ERG accepted method 5 as reasonable but also argued, based on the company's reasoning of not needing to account for prior treatment in the PDC curves, that the MAICs versus the Study 1001 EXP-3B:5 cohort could be equally relevant. This is because: adjustments for potential confounders may be preferred over no adjustment when combining evidence from single arm studies; the EXP-3:B5 cohort is in line with the license for lorlatinib; and clinical experts consulted by the company did not appear to suggest that PDC would perform differently after progression on crizotinib or a second-generation ALK TKI.

In their response to the Technical Engagement question, the company acknowledge Method 2 is plausible but argue that Method 1 is equally plausible. Method 1 was the MAIC using cohort EXP-2:3A of the lorlatinib clinical study which includes patients outside of the lorlatinib license. However, the evidence for the comparator arm (ALUR/ASCEND-5) also comes from earlier lines of therapy, so this provides an element that cannot be adjusted for in the MAIC.

The ERG still believes that methods 2 and 5 are more in line with the clinical rationale outlined in the company's original submission, but accept that method 1 cannot be rejected since it is possible that PDC could perform more poorly if used at the line corresponding to the EXP-3B:5 cohort of Study 1001.

The ERG's proposal to the committee is that ICERs based on Methods 1, 2 and 5 be considered, but note the company's original clinical advice which seemed to suggest that the methods that did not adjust for differences in treatment history were most valid.

Issue 4: given the clinical expert comments the generalised gamma curve for lorlatinib OS is selected

The clinical experts originally consulted by the company suggested that up to 10% alive at 10 years was plausible (Log-normal curve), but the ERGs clinical expert felt that 2% was more plausible (exponential curve).

The company note that there was agreement between the clinical experts present on the technical engagement call that 4.5% overall survival at 10 years for lorlatinib was a reasonable projection, sitting between the two clusters. The ERG is satisfied that the generalised gamma provides a suitable base case on this basis. However, extrapolations are always subject to uncertainty, and so it would seem reasonable to expect that the exponential curve should also be tested in scenario analysis under the company's revised model specification – to assess upward uncertainty in the ICERs.

Issue 5: this uncertainty is unresolved and the ICER range reflects the fixed PD utility value of 0.59 and two additional methods

The company have offered three additional scenarios on top of their original utility assumptions for progressed disease (0.65 across time in the PD state). The first utilises 0.59 across the entire time in state. The second and third methods assume a value of 0.65 for the additional time on lorlatinib treatment following progression. This is justified by the company based on Labbe et al (2017), who reported a value of 0.65 around the time of progression on an ALK TKI. The company combine this with the values of either 0.59 or 0.46 reported by Chouaid et al. (2013) for progressive disease after 2nd line or 3rd/4th line treatment. The ERG preferred these lower values in the original submission on the grounds that the 0.65 may not reflect the average health related quality of life across the time spent in the progressed state where patients will deteriorate over time.

Of the three options presented by the company in their response to the technical engagement, the ERG on balance believe that the 0.59 may represent a reasonable average, reflecting the fact that patients may start at a higher level of utility in the PD state, but will deteriorate to below 0.59 over time. Since clinical experts also indicate that patients may continue to derive benefit from remaining on lorlatinib compared to other available treatments following disease progression, the company's assumption to apply the higher value of 0.65 to this extended time on treatment may also be reasonable. This would point to company method 1

(scenario 3b) as being a reasonable analysis. However, the rate of deterioration in the PD state is also uncertain and so too is the average utility across the time in state, so it is also useful that the company have assessed the impact of assuming the lower 0.46 value following the extended time on lorlatinib treatment (company scenario 3c).

Issue 6: given clinical expert comments and a new calculation presented by the company, 3.5 months of additional lorlatinib treatment after progression has been assumed.
The company note that the clinical experts consulted on the technical engagement call suggested that 3 to 3.5 months of treatment beyond progression with lorlatinib is clinically plausible, slightly higher than the [redacted] months applied in the company's original base case.

To further inform this uncertainty, the company refer to the UK database of ALK patients, which reported 14.9 months as the 95th percentile for duration of treatment with an ALK TKI (Gomes et al. 2019). They then subtract the restricted mean PFS of 10.6 months (from Study 1001) to estimate an upper bound on the treatment months beyond progression (4.3 months). Taking the average of the value applied in their original base case and the 4.3 months, gives 3.5 months which is in line with the clinical experts on the TE call. Thus 3.5 is applied in the company's revised base case.

The ERG is reasonably satisfied with the revision. However, it should be noted that the 14.9 months referred to by the company is the upper 95% confidence limit for an estimated median time on treatment (brigatinib) (Gomes et al), and the [redacted] represents the restricted mean PFS for lorlatinib at [redacted] months in study 1001. Thus, the calculation has its limitations for confirming the 3.5 months suggested by clinical experts.

Issue 7: the new subsequent treatment patterns for each arm now fully reflect those given by the clinical experts, including adding ABCP as a subsequent treatment to lorlatinib and setting pembrolizumab as a fixed dose when given as a subsequent treatment to PDC
The company have revised their assumptions about subsequent treatments in line with clinical experts present on the technical engagement call.

The ERG is generally satisfied that the changes are in in line with experts consulted, with 45% now assumed to receive further active treatment following progression on lorlatinib and PDC, with most treated patients receiving ABCP (66%) following progression on lorlatinib.

However, the ERG is uncertain about the justification for assuming a greater proportion (75%) receive further treatment with docetaxel following progression on ABCP. The ERG feel it may therefore be justified to assess the impact of reducing the proportion subsequently treated patients to 45% following progression on ABCP. It can be noted that this parameter has a small impact on the ICER.

ERG check of the company's revised modelling submitted in response to technical engagement

The company submitted the revised model that was used for their revised base case and scenarios as described in their response document. The ERG has checked this and confirms it is consistent with the previous model; i.e. it is possible to follow through all changes from the original company base case to the revised company base and further scenarios. Tables 1 and 2 below present all the company's analyses using the updated PAS discount for lorlatinib, but list prices for comparators and subsequent treatments. The impacts of the ERGs revisions are also shown in scenarios 2b and 2c, and these are also incorporated in the scenarios 3-5. Table 3 and 4 below show the results of the few additional scenarios conducted by the ERG, using the updated company base case with ERG corrections as the reference.

Table 1 ICERs vs. PDC range with unresolved uncertainty (including updated lorlatinib PAS and list prices on subsequent treatments)

#	Scenario	Description	ICER change from original base-case	Deterministic ICER	Probabilistic ICER
1	Base-case vs. PDC	Company submitted base-case settings with updated lorlatinib PAS and **list prices on** subsequent treatments	-	£34,091	£31,318
2a	Base-case but updated with resolved issues	Scenario 1 but with inputs updated for resolved issues 2, 4, 6 and 7.	+14,467	£48,558	£44,325
2b		(2a) with ERG correction of post lorlatinib ABCP costs	+£19,506	£53,597	£48,752
2c		(2b) With ERG correction of ABCP admin costs	+£19,749	£53,840	£49,022
3a	Updated base-case (2c) with method 5 (independent curves) and different PD utilities	Independent curves base-case (method 5) and 0.59 PD utility	+£21,732	£55,823	£50,898
3b		Independent curves base-case (method 5) and utility method 1	+£20,981	£55,072	£50,767
3c		Independent curves base-case (method 5) and utility method 2	+£23,854	£57,945	£54,668

4a	Updated base-case (2c) with method 2 (EXP-3B:5 MAIC) and different PD utilities	Method 2 MAIC and 0.59 PD utility	+£35,718	£69,809	£66,115
4b		Method 2 MAIC and utility method 1	+£34,580	£68,671	£65,372
4c		Method 2 MAIC and utility method 2	+£34,405	£68,496	£65,999
5a	Updated base-case (2c) with method 1 (EXP-2:3A MAIC) and different PD utilities	Method 1 MAIC and 0.59 PD utility	+£16,103	£50,194	£47,966
5b		Method 1 MAIC and utility method 1	+£15,571	£49,662	£47,487
5c		Method 2 MAIC and utility method 2	+£18,473	£52,564	£50,294
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and apply list prices for Atezolizumab and Bevacizumab (ABCP subsequent treatments for lorlatinib) and Pembrolizumab and Atezolizumab (subsequent treatments for PDC). See above for the definitions of utility method 1 and method 2.					

Table 2 ICER vs. ABCP range with unresolved uncertainty (including updated lorlatinib PAS and list prices on subsequent treatments)

#	Scenario	Description	ICER change from original base-case	ICER
1	Base-case vs. PDC	Company submitted base-case settings with updated lorlatinib PAS and list prices on comparators and subsequent treatments	-	Dominant
2	Base-case but updated with resolved issues	Scenario 1 but with inputs updated for resolved issues 2, 4, 6 and 7	-	£8,269
2b		2 with ERG correction of post lorlatinib ABCP costs	-	£13,169
2c		2b With ERG correction of ABCP admin costs	-	£12,505
3a	Updated base-case (2c) with different PD utilities	0.59 PD utility	-	£13,109
3b		Utility method 1	-	£12,935
3c		Utility method 2	-	£13,978
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and apply list prices for Atezolizumab and Bevacizumab (ABCP comparator and subsequent treatment for lorlatinib)				

Table 3 ERG further exploratory analysis for PDC comparison using the company's revised base case with ERG corrections for reference (scenario 2 in Table 1)

#	Scenario	Description	ICER	Probabilistic ICER
1	Base-case but updated with resolved issues (Scenario 2c)	Company scenario 1 but with inputs updated for resolved issues 2, 4, 6 and 7, and ERG revisions.	£53,840	£49,022
2	Updated base case (2c) with alternative extrapolation of lorlatinib OS	Exponential rather than generalised gamma for lorlatinib OS	£58,763	£61,128
Notes: All scenarios include the updated confidential PAS for lorlatinib [redacted] and apply list prices for Atezolizumab and Bevacizumab (ABCP subsequent treatments for lorlatinib) and Pembrolizumab and Atezolizumab (subsequent treatments for PDC). See above for the definitions of utility method 1 and method 2.				

Table 4 ERG exploratory analysis for ABCP comparison using the company's revised base case with ERG corrections for reference (scenario 2 in Table 1)

#	Scenario	Description	ICER
1	Base-case but updated with resolved issues and ERG corrections (Scenario 2c)	Company scenario 1 but with inputs updated for resolved issues 2, 4, 6 and 7, and ERG revisions.	£12,505
2	Updated base case (2c) with alternative extrapolation of lorlatinib OS	Exponential rather than generalised gamma for lorlatinib OS	£10,576
3	Updated base case (2c) with reduced population adjustment for ABCP curves	25% reduction applied to log HRs for population adjustment of ABCP curves	£5,514
4a	ERG scenario 3 applied with the company's different PD utilities	0.59 PD utility	£5,759
4b		Utility method 1	£5,665
4c		Utility method 2	£6,021
5	Updated base case (2c) with reduced proportion of patients receiving subsequent treatment following ABCP	45% receive docetaxel after ABPC, rather than 60%.	£12,793
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and apply list prices for Atezolizumab and Bevacizumab (ABCP comparator and subsequent treatment for lorlatinib)			

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final technical report

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

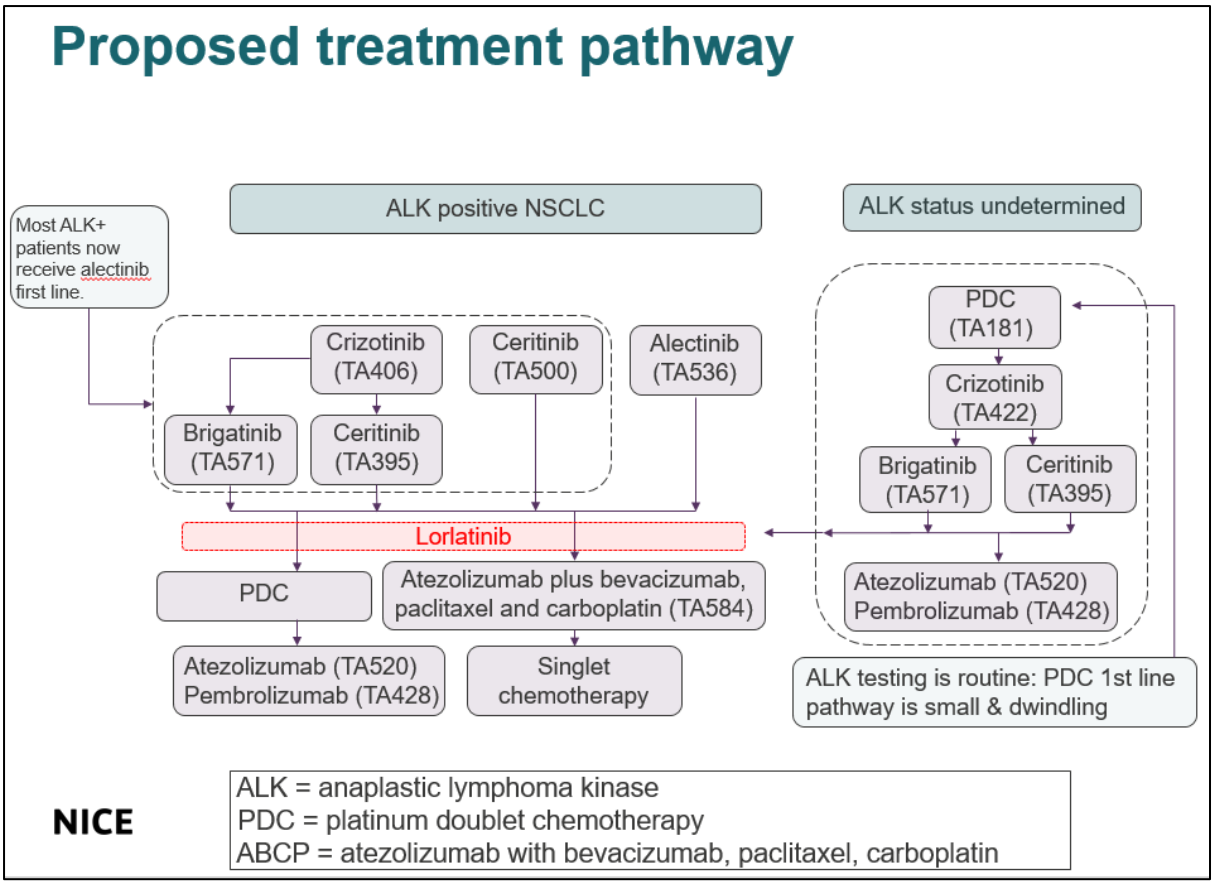
Issue date: December 2019

1. Topic background

1.1 Disease background: ALK+ 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)
- NSCLC can be squamous - squamous cell carcinoma or non-squamous - adenocarcinoma (most non-squamous cancers) and large-cell carcinoma.
- In 2016 approximately 32,533 people were diagnosed with NSCLC in England, of whom 53% had stage IV disease.
- Prognosis is often poor due to late diagnosis.
- ALK is a rare mutation with an estimated prevalence rate of between 1.6% and 5% in NSCLC, almost exclusively in adenocarcinoma NSCLCs.
- ALK testing is a standard part of the diagnostic work-up in NSCLC.
- ALK mutations are more common in younger people who are non-smokers.
- Brain metastases are a frequent complication, occurring in ~30% of ALK+ NSCLC.

1.2 Proposed treatment pathway



1.3 The technology

Marketing authorisation	Lorlatinib received conditional approval in the EU for the indication in this submission on 7 May 2019.
Mechanism	Lorlatinib is a macrocyclic, selective, adenosine triphosphate-competitive, brain penetrant, small molecule tyrosine kinase inhibitor (TKI).
Indications	Lorlatinib as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after: • Alectinib or ceritinib as the first ALK TKI therapy • Crizotinib and at least one other ALK TKI.
Administration	The recommended dose of lorlatinib is 100mg taken orally, once daily. Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.

Conditional MA:
In order to further confirm the efficacy and safety of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study CROWN (1006) comparing lorlatinib versus crizotinib for the first-line treatment of advanced ALK-positive NSCLC (by Dec 2021). In order to further confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK TKI therapy, the MAH should conduct a prospective single arm study investigating patients in that same setting (by June 2024).

1.4 Clinical evidence: key trial

Study	B7461001 (NCT01970865; Study 1001; data cut Feb 2018)
Study design	Single arm, open-label, multicentre Phase 1/2 study
Population	Adult patients with metastatic ALK-positive or ROS1-positive NSCLC
Location (number of centres in which patients were randomised to lorlatinib)	Australia (2), Canada (1), France (4), Germany (1), Hong Kong (1), Italy (4), Japan (10), Korea (1), Singapore (2), Spain (4), Switzerland (2), Taiwan (1), US (11)
Intervention(s)	Lorlatinib
Comparator(s)	N/A
Supports MA	Yes
Used in the model	Yes
Rationale for use/non-use in the model	Efficacy data for lorlatinib is used in the model because this is the only study that currently provides data for lorlatinib in the population and line of relevance to this submission.

1.5 Clinical evidence: baseline characteristics

		EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
Mean (SD) age, years		55.0 (11.6)	52.2 (11.8)	51.5 (11.2)	52.5 (11.6)
Gender, n (%)	Female	16 (57.1)	37 (57.0)	25 (54.3)	78 (56.1)
	Male	12 (42.9)	28 (43.1)	21 (45.7)	61 (43.9)
Race, n (%)	White	7 (25.0)	32 (49.2)	27 (58.7)	66 (47.5)
	Black	1 (3.6)	0 (0.0)	0 (0.0)	1 (0.7)
	Asian	16 (57.1)	23 (35.4)	14 (30.4)	53 (38.1)
	Other	1 (3.6)	3 (4.6)	2 (4.3)	6 (4.3)
	Unspecified	3 (10.7)	7 (10.8)	3 (6.5)	13 (9.4)
ECOG PS, n (%)	0	14 (51.9)	25 (38.5)	21 (45.7)	60 (43.5)
	1	13 (48.1)	37 (56.9)	22 (47.8)	72 (52.2)
	2	0 (0.0)	3 (4.6)	3 (6.5)	6 (4.3)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Brain metastases, n (%)		12 (42.9)	44 (67.7)	37 (80.4)	93 (66.9)
Prior cancer treatment, n (%)	Surgery	16 (57.1)	33 (50.8)	29 (63.0)	78 (56.1)
	Radiotherapy	12 (42.9)	49 (75.4)	34 (73.9)	95 (68.3)
	Systemic therapies	28 (100.0)	65 (100.0)	46 (100.0)	139 (100.0)

1.6 Key trial results: PFS & OS from Study 1001

Endpoint	EXP-3B (n=28)	EXP-4 (n=65)	EXP-5 (n=46)	EXP-3B:5 (n=139)
Median (95% CI) PFS, months	5.5 (2.9, 8.2)	7.4 (5.4, 11.1)	5.6 (4.0, 8.3)	6.9 (5.4, 8.2)
Median (95% CI) OS, months	21.1 (12.3, NR)	18.7 (15.1, NR)	19.2 (10.5, NR)	20.4 (16.1, NR)
OS probability, % (95% CI)				
12 months	0.698 (0.485, 0.836)	0.696 (0.566, 0.795)	0.641 (0.482, 0.762)	0.678 (0.591, 0.750)
18 months	0.616 (0.402, 0.772)	0.512 (0.376, 0.633)	0.572 (0.414, 0.702)	0.556 (0.155, 0.306)

1.7 Indirect evidence

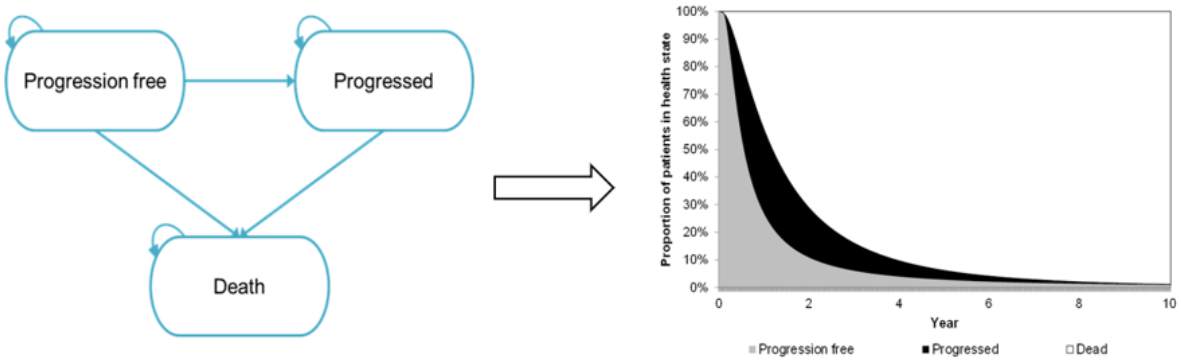
Weighted matching cohort (Study 1001)	Naïve		Adjusted		Adjusted (updated based on correct % of ALUR subjects with ECOG 1/2)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases)		Adjusted (not including brain metastases)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio *bootstrapped 95% CI

1.8 **Model structure**

- Partitioned survival model with 3 health states: *progression-free, progressed disease* and *death.*
- A lifetime horizon of 20 years applied in the model base case.
- 30-day cycle length (aligns with pack size), with a half-cycle correction applied.
- NHS and Personal Social Services (PSS) perspective
- An annual discount rate of 3.5% for costs and benefits



2. Summary of the draft technical report

2.1 After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below. In summary, the technical team considered the following:

Issue 1 **Resolved at technical engagement - ABCP is a relevant comparator.** The company indicated in its submission that the only relevant comparator should be platinum doublet chemotherapy (PDC), whereas the NICE scope and ERG consider that atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) is also a relevant comparator as it was recommended in TA584 (June 2019) and should therefore now be considered established practice in the NHS in England. The company's submission focuses on the comparison with PDC as

its base case and has included a comparison with ABCP in an appendix.

Issue 2 **Resolved at technical engagement - a HR of 0.8 is accepted as a reasonable estimation of the comparative efficacy between PDC and singlet chemotherapy.** The company has undertaken an indirect comparison for lorlatinib and PDC to address the limitations of the non-comparative single-arm Study 1001, but there is uncertainty concerning the selection of clinical studies to represent the PDC treatment arm. PFS data was estimated from the ALUR and ASCEND-5 trials and OS data was estimated from an unrelated retrospective analysis of the PROFILE 1001/1005 trials. The majority of patients in these trials had been previously treated with PDC and crizotinib and were being treated with single agent chemotherapies. These patients most closely match the 2:3A cohort from Study 1001 which previously received crizotinib, rather than cohort 3B:5 which previously received one or more ALK TKI and is the focus of the company submission. In addition, use of these data as a proxy for PDC outcomes assumes that single agent chemotherapy agents are equivalent to PDC.
For the comparison with ABCP, the company provided an unanchored indirect comparison which was not adjusted for any differing characteristics.

Issue 3 **For committee consideration.** There is uncertainty surrounding the selection of the method to carry out the indirect comparison. The company used 3 techniques for comparing the single arm data for lorlatinib to PDC:
i) hazard ratios (HRs) estimated using a matching adjusted indirect comparison (MAIC),
ii) HRs estimated using an unadjusted indirect comparison, and
iii) direct estimation of PFS and OS by fitting parametric curves to chemotherapy data from the clinical studies.

Ultimately the MAIC approaches conducted by the company, which were considered robust by the ERG, were rejected in favour of fitting independent curves to the chemotherapy data .

Issue 4 **Resolved at technical engagement - the generalised gamma curve is the most appropriate for lorlatinib OS in the base case.** The company's projections of PFS and OS for lorlatinib are uncertain due to the difficulty of extrapolating limited clinical data substantially beyond the observed period, and a lack of clinical expert consensus. The ERG agrees with the company's choice of the generalised gamma curve for PFS, but the choice of the generalised gamma curve for OS is contradicted by the company's own experts and also the ERG's clinical expert advice.

Issue 5 **For committee consideration.** The utility values selected are open to question:

- the selected value for the progressed disease state appears high compared to other published values specific to treatment line.
- there is a lack of direct comparative evidence for the applied difference in progression free (PF) utility values for lorlatinib compared with PF utility values for PDC (the same point applies in the comparison with ABCP). The magnitude of any applied difference is therefore uncertain.

Issue 6 **Resolved at technical engagement - 3.5 months treatment with lorlatinib beyond progression is appropriate for decision making.** The treatment duration estimate for lorlatinib is broadly plausible but may underestimate the extent to which clinicians tend to provide treatment following radiographic progression in routine practice when there are no other effective treatment options available.

Issue 7 **Resolved at technical engagement - revised assumptions for proportion and type of subsequent treatment are appropriate for decision making.** Assumptions about proportion of patients receiving subsequent therapies following the intervention and comparator treatments, and the proportion of patients on each treatment is uncertain and could benefit from further clinical input.

Issue 8 **Resolved at technical engagement - lorlatinib is not a suitable candidate for the CDF.** The company has not made a case to apply for funding through the CDF. If lorlatinib is not recommended for routine commissioning, the committee will need to consider if it could be recommended for use within CDF.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is based on a non-comparative single-arm study with a subgroup of only 139 patients. No direct comparative evidence is available.

2.3 The cost-effectiveness results include a confidential patient access scheme discount for lorlatinib. Results including all confidential discounts prepared by the ERG will be discussed by the committee.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £56,345 per QALY gained for PDC (see table 1a), and £13,716 per QALY gained for ABCP (see table 1b). For the comparison with PDC, the ICER is most sensitive to changes to the hazard of progression and death on PDC, the choice of method of indirect comparison, and the choice of average post-progression time on treatment. For the comparison with ABCP, the ICER is most sensitive to the post-progression time on treatment for lorlatinib. These estimates do not include the commercial

arrangements for ABCP, because these are confidential and cannot be reported here. When all the commercial arrangements for lorlatinib and atezolizumab and bevacizumab are taken into account, the resulting ICER is higher than the ICER calculated using the list prices atezolizumab and bevacizumab.

2.5 Lorlatinib appears to meet both criteria to be considered a life-extending, end-of-life treatment when compared with both PDC and ABCP. For PDC, average life expectancy is well below 2 years on PDC in the company base case ([redacted]) and remains below this value across the scenarios assessed. Despite the limitations in the comparative evidence base, it is plausible to the ERG that treatment with lorlatinib will result in a gain in life expectancy of more than three months. The average life expectancy for treatment with ABCP was [redacted] although there is some uncertainty around this value due to the population adjustment that was applied to the fitted curve by the company. However, life expectancy with ABCP remains below 2 years as long as the log HR for the population adjustment of overall survival is not reduced by 55% or more (i.e. from a HR value of [redacted] to [redacted]). The survival gains remain above 3 months across all scenarios assessed.

2.6 In terms of innovation and unmet need, the company have stated that lorlatinib is a third generation ALK TKI that allows central nervous system penetration and retention in the intracranial space, thereby addressing the unmet need for additional treatment options for patients who develop brain metastases. It was specifically designed to inhibit resistant ALK mutations, including the ALKG1202R mutation that increases significantly after treatment with second-generation agents.

2.7 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Relevant comparators

Questions for engagement	What treatments should be considered the most relevant comparators for this appraisal?
Background/description of issue	The company has indicated in its submission that the only relevant comparator should be PDC, whereas the NICE scope and the ERG consider that ABCP is also a relevant comparator as it was available to patients through interim Cancer Drugs Fund funding before being recommended in TA584 (June 2019). It should therefore now be considered established practice in the NHS in England. **The company** Although ABCP has recently been recommended for the treatment of metastatic, non-squamous NSCLC (TA584), it does not believe there is any evidence to suggest that ABCP constitutes a 'standard of care' comparator in the specific ALK-positive population for the following reasons: • The uptake of ABCP in the ALK-positive population is expected to be small. ABCP was approved by MHRA in December 2018 for the early access to medicines scheme (EAMS) with an indication including ALK-positive patients. However, there is no precedent for use in the ALK-positive population via EAMS or any other free access programme. Data from the lorlatinib compassionate use programme show that no included patients (enrolled up to April 2019) had the combination in any reported lines (i.e. lines 1 to 5). The UK ALK database also shows no evidence of use in any line. Lack of previous patient and clinician use suggests low uptake. • The company consulted an additional four clinical experts on the inclusion of this combination as a comparator. These experts suggested that the combination is more

	relevant for EGFR patients and that based on ALK patient fitness and high levels of brain metastases (and low ABCP penetration into the brain), uptake is expected to be low. • The only available clinical evidence for ABCP efficacy in ALK-positive patients is a subgroup from the IMpower150 trial (41 patients, only 11 of which ALK-positive). • Experts in the TA584 committee meeting also expected eligible patients in the ALK-positive population to be small particularly because of the levels of brain metastases (around 70% in Study 1001) **The ERG** It is the ERG clinical expert's opinion that ABCP is a relevant comparator for lorlatinib. ALK-positive patients are likely to be generally fit compared with other NSCLC patients; however, their status is likely to deteriorate quickly following relapse on targeted therapies. ABCP use is likely to increase as standard care following targeted therapy as it allows immunotherapy to be moved up one line for those patients who are likely to benefit from this therapy.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of lorlatinib, it is important to establish the relevant comparators.
Technical team preliminary judgement and rationale	The technical team are aware that treatment for ALK+NSCLC has been advancing at a rapid pace, and that treatment pathways are subject to regular changes which will potentially take hold in clinical practice at different rates in different clinical centres. There is some uncertainty regarding the extent to which ABCP will be used in ALK+ patients following targeted treatment with ALK TKIs. Although statistics show that it has not yet been widely used in this population, some clinical experts believe that following TA584 uptake will start to increase because of the lack of other targeted treatments in the pathway, and because patients are likely to be willing to use ABCP rather than chemotherapy. The technical team agrees with the ERG that ABCP is a comparator and believe that expected use following targeted ALK TKIs might be as much as 50% of those who progress onto further active treatment. Given that ABCP has been recommended in this population as a treatment option for ALK+ NSCLC, the technical team considers that ABCP should be regarded as a comparator in this appraisal.
Summary of comments	**Comments from the company:** Pfizer acknowledges that ABCP could be a relevant comparator, particularly as it is likely to be used in those patients without brain metastases as it is more effective than PDC (approximately 30% of

	patients in the lines relevant to the indication for lorlatinib). Neither ABCP nor PDC have CNS penetration, so are both likely to have similar efficacy in people with brain metastases. ABCP will only be a treatment option for those who are well enough. Once lorlatinib is available it is likely to be the treatment of choice for all patients progressing on a 2nd generation ALK TKI, including the 70% with brain metastases. **Comments from the clinical experts:** Uptake of ABCP will be variable, but there is no evidence for the efficacy of PDC followed by single agent immunotherapy in this ALK+ population, so the preference will often be for ABCP in those who are well enough. It is estimated that of those progressing after current ALK TKI treatment, approximately 60% would be expected to be fit enough for ABCP, and 40% would progress onto PDC. Agreement with the company concerning the preference for using lorlatinib over ABCP for all patients when it becomes available, due to CNS activity.
Technical team judgement after engagement	The inclusion of ABCP as a comparator in the appraisal is appropriate.

Issue 2 – Sources of evidence for comparative effectiveness

Questions for engagement	2a. Are ALUR/ASCEND-5 the best sources of comparator evidence for PFS? 2b. Are PROFILE 1001/1005 the best sources of comparator evidence for OS? 2c. Is it more plausible that the comparative efficacy of PDC has been underestimated (as suggested by the ERG), or overestimated (as suggested by the company)?
Background/description of issue	The systematic literature review conducted by the company identified the ALUR and ASCEND-5 studies as the most relevant sources of chemotherapy PFS data in ALK-positive NSCLC patients. A published retrospective analysis of PROFILE 1001(unrelated to Study 1001) and PROFILE 1005 studies were selected as the best sources for OS data. **The Company** The ALUR and ASCEND-5 trials were used to provide PDC arm PFS data for ALK-positive NSCLC patients after they had progressed on crizotinib and previous chemotherapy. These 2 sources had

	similar baseline characteristics and were pooled for the purposes of the MAIC. A retrospective analysis of the crizotinib arm of the PROFILE 1001 and PROFILE 1005 trials for the subgroup of patients receiving systemic therapy (unconfirmed, but likely to be single agent chemotherapy) after progression on crizotinib was used as the source for PDC arm OS data. The majority of patients in ALUR, ASCEND-5, and PROFILE 1001/1005 studies had received both PDC and crizotinib previously, and so arguably the most relevant matching subgroup in Study 1001 is EXP-3A, but a pooled EXP-3A and EXP-2 cohort was used in order to double the matching cohort size and ensure that the sample size was not too small for the MAIC. An additional analysis was conducted that used the pooled EXP-3B:5 cohort (patients who had one or more ALK-TKI previously) for matching instead of EXP-2:3A. This latter analysis assumes that it is only patient characteristics and not treatment line (e.g. pre-treatment by different ALK TKIs) that affects outcomes. **The ERG** The ERG raises several concerns regarding the comparison of lorlatinib with chemotherapy. Participants in both the ALUR and ASCEND-5 trials had previously been treated with PDC and crizotinib prior to the intervention (alectinib and ceritinib, respectively). The company pooled data from the chemotherapy arms of these trials for the PFS survival outcome within the MAIC. Because these patients had been previously treated with PDC and also crizotinib, the use of which is falling due to the emergence of second-generation targeted treatments, the ERG question whether these patients are relevant to the target population. In addition, the chemotherapy arm of these trials comprised single agents (pemetrexed, docetaxel) rather than PDC (which eligible patients had already been treated with) and this implies an assumption of equivalence between these singlet chemotherapies and PDC which is disputed by the ERG's clinical expert. The ERG therefore question whether ALUR and ASCEND-5 are the best sources of comparator PFS evidence for this appraisal. ASCEND-4 was an RCT that included PDC against ceritinib, a 2nd generation ALK TKI (as opposed to crizotinib used in ALUR/ASCEND-5). This was identified by the company but disregarded because it was a previously untreated population. But the ERG believe that the HRs are still potentially relevant to help form a more accurate view of the plausible range for the comparative clinical effectiveness of lorlatinib, under the assumption that relative treatment effect is approximately equal irrespective of treatment history.

	Similarly, the ERG raises concerns regarding the retrospective analysis of the crizotinib arms of the PROFILE 1001/1005 with a subgroup of patients who received systemic therapy (likely chemotherapy) after progression on crizotinib. As with the ALUR and ASCEND-5 trial populations, the patient population previously treated with crizotinib are considered to be an increasingly marginal subgroup of the licensed population for lorlatinib, and so the relevance of the populations in PROFILE 1001/1005 are questionable. The small subgroup of 37 patients, the majority of whom received PDC prior to study entry, are assumed to be on singlet chemotherapy (pemetrexed or docetaxel), but it is not clear what these patients received and the proportion on chemotherapy is unconfirmed. Taken together, these factors suggest that the results could underestimate what PDC would achieve in this setting, though the extent of this bias is difficult to determine. The ERG points to evidence from Zukin et al (2013) that provides evidence of PDC performing significantly better than pemetrexed monotherapy in NSCLC, though not specifically ALK+ patients. The company offer a counter argument that patients in these trials were exposed to only one ALK TKI (crizotinib), whereas the population eligible for lorlatinib may have been exposed to two or more and so might be expected to have a worse efficacy outcome (as suggested by some clinical experts). The trade-off between the above two arguments would benefit from further clinical input. However, on balance, the ERG remains concerned about the potential for underestimating the efficacy of PDC. The ERG provides iterative upward adjustments to PFS and OS in the PDC arm as part of the sensitivity analysis. **Comparison with ABCP** The ERG also remain uncertain about the comparative efficacy of ABCP for similar reasons. For this comparison, the company relies heavily on a population adjustment for ALK+ versus EGFR+ patients. However, the population adjustment HRs comes from comparing OS and PFS for ALK+ patients treated with single agent chemo (again from ALUR, ASCEND-5 and PROFILE 1001/1005), with an EGFR population treated with PDC (from IMPOWER). So there remains considerable uncertainty regarding extent to which the adjustment HRs actually reflect the inferior efficacy of the monotherapies versus PDC, rather than the different mutation status. Other differences between the populations and treatment histories also contribute to this uncertainty.

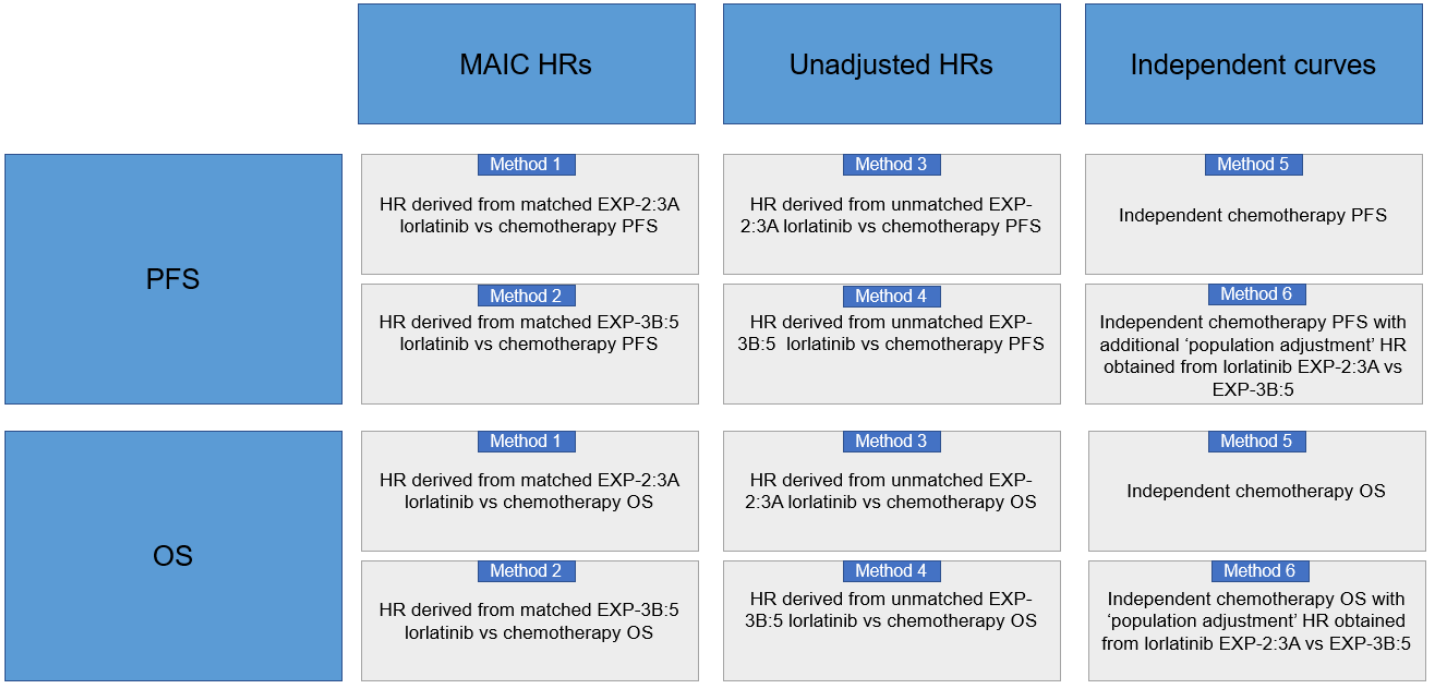
Why this issue is important	A lack of direct evidence adds uncertainty regarding the true comparative efficacy of lorlatinib. To be able to assess the clinical- and cost-effectiveness of lorlatinib, it is important to establish what comparative data is the most relevant to this appraisal.
Technical team preliminary judgement and rationale	The trial data for the PDC arm (estimated from ALUR/ASCEND-5 for PFS and from PROFILE 1001/1005 for OS) are problematic due to the fact that the patients in these trials are dissimilar from the 3B:5 cohort of patients from Study 1001 that is the focus of the company submission. But no other sources of PDC data exist that match this population, and so it becomes necessary to determine the extent of any bias for or against lorlatinib that arises through the trade-off between patients who are being actively treated with single agent chemotherapy but have been exposed to fewer lines of treatment (PDC and crizotinib), compared with patients who would be treated with PDC following at least one, and up to three or more ALK TKIs, with or without prior chemotherapy (cohort 3B:5 from Study 1001). The technical team shares the ERG's concern that the efficacy of PDC is underestimated rather than overestimated. Additional clinical expert advice will be important to establishing whether the assumptions made by the company in its comparisons are plausible considering the limitations in the evidence base. There is also a question over the appropriateness of assuming that relative treatment effect is approximately equal irrespective of treatment history, as suggested by the ERG.
Summary of comments	**Comments from the company:** Although the sources used to proxy PDC efficacy (PFS and OS) are not perfect, in that patients are treated with singlet chemotherapy, they reflect the best available published sources. The alternative is to use the PDC arm from the ASCEND-4 trial, but this would also require an opposite adjustment to the PDC-arm efficacy to account for the fact that the population in this trial has less advanced disease. All things being equal, PDC is more likely to be effective than singlet chemotherapy. A targeted literature search has provided a range of HRs for the comparative efficacy of PDC vs singlet chemotherapy that are broadly in line with the range implied by Zukin (2013) of 0.6 to 1. Pfizer suggest that the middle of this range, 0.8, is a reasonable approach to this uncertainty. **Comments from the clinical experts:** Sequencing is very important. In a previously chemotherapy-naïve population, you would expect PDC to be better than singlet chemotherapy, but only extra-cranially rather than intra-cranially. The efficacy of the chemotherapy arms across ALK+ trials has been very consistent. We know that PDC is better than singlet chemotherapy, but this is from trials earlier in the pathway and there is no evidence at this later stage when brain metastases are increasingly prevalent in this ALK+

	population. On balance, the conflicting factors in the trials mean that the relative efficacy of PDC is likely neither under- nor over-estimated to any great extent.
Technical team judgement after engagement	The technical team accepts a HR of 0.8 as a reasonable estimation of the comparative efficacy between PDC and singlet chemotherapy.

Issue 3 – Selection of method for the indirect comparison used in the economic modelling

Questions for engagement	Which method is most appropriate for use in the economic modelling and for decision making?
Background/description of issue	The company compared 3 different techniques for comparing the single arm data for lorlatinib to PDC: i) hazard ratios (HRs) estimated using a matching adjusted indirect comparison (MAIC) ii) HRs estimated using an unadjusted indirect comparison, and iii) direct estimation of PFS and OS by fitting parametric curves to chemotherapy data from the clinical studies. Ultimately the MAIC approaches conducted by the company were rejected in favour of fitting independent curves to the chemotherapy data. **The company** Three techniques were used to compare the single-arm data for lorlatinib with that of PDC: • MAICs used to obtain a HR to represent the difference between lorlatinib and chemotherapy for both PFS (pooled ALUR and ASCEND-5) and OS (PROFILE 1001/1005). HRs were derived using a weighted Cox proportional hazards model using individual patient data for the relevant lorlatinib cohorts, and corresponding weights for the PDC arm. • Unadjusted HRs derived from the differences between the pooled ALUR and ASCEND-5 studies compared to Study 1001 for PFS, and a retrospective analysis of PROFILE 1001/1005 compared to Study 1001 for OS.

- Independent parametric models fitted directly to evidence sourced from the literature for the chemotherapy arm (ALUR/ASCEND-5 for PFS, PROFILE 1001/1005 for OS). By fitting independent curves to the chemotherapy data, the assumption that proportional hazards holds across the two treatments has been avoided.



	The company rejected the results of the MAIC and unadjusted HRs in favour of method 5 that fitted an independent curve to the chemotherapy data from ALUR/ASCEND-5 for PFS and PROFILE 1001/1005 for OS, based on the following justifications: a. The chosen methods for PFS and OS should be consistent – for example, it would be inconsistent to prefer an unadjusted comparison to 2:3A for PFS and an adjusted comparison to 3B:5 for OS. b. Methods 1 to 4 assume proportional hazards (PH) over time. The PH assumption is likely to hold for adjusted and non-adjusted PFS irrespective of matching cohort, but it is unclear whether the PH assumption is satisfied for OS, particularly with the EXP-3B:5 cohort. Therefore, the company considered that methods 2 and 4 may not be appropriate for the OS outcome. c. Clinical advice received by the company suggested that previous lines of treatment do not influence effectiveness, so the methods that do not adjust for this, methods 2, 4 and 5, are preferred. d. However, as methods 2 and 4 may have an issue with proportional hazards then method 5 is preferred. **The ERG** The company recognised that there was a potential problem in that the studies used to provide data for PDC were better aligned to the treatment history cohorts 2:3A from Study 1001, than to cohorts 3B:5 that were used as the base case population for the company submission. Therefore, all three of the above methods were used to provide estimates for the 2 lorlatinib cohort groups (2:3A and 3B:5). But rather than using the hazard ratios derived from the unadjusted comparison or MAIC, the company chose to use Method 5 in their base case. Method 5 relied on fitting independent parametric curves to the PFS data from ALUR and ASCEND-5, and the OS data from PROFILE 1001 and 1005 for OS. For PFS a log-logistic curve was selected based on having the best visual and statistical fit to the observed data. The same process was used to select the log-normal distribution for OS. The ERG are satisfied with the curve selection process, but have concerns about the suitability of the data upon which the fitting was based. While the ERG acknowledges the company's logic in its choice of a method, an opposing logical argument could be made that an adjusted comparison is preferred to an unadjusted comparison and that making a comparison using patients in cohorts 2:3A of Study 1001 is irrelevant because it is not the population covered by the license. This argument would point to Method 2, the MAIC with comparison to cohorts 3B:5, as being the most relevant. On balance the ERG prefers the company's base case approach of applying the independently fitted curves,

<table>
<tr><td></td><td>and as indicated above the ERG is more concerned about the source data to represent PDC rather than the assumptions of the methodological approach for assessing comparative efficacy.

All the company's approaches for estimating comparative effectiveness give rise to a reduced hazard of death with lorlatinib in each cycle that persists throughout the model time horizon. The scenarios that relied on application of unadjusted or adjusted hazard ratios assumed proportional hazards over entire time horizon. The company base case approach (method 5) results in a diminishing relative treatment effect over time in the model, but the hazard of mortality remains lower in the lorlatinib arm across the entire time horizon. Given the uncertainty associated with such extrapolations, the ERG explored the impact of applying more dramatic waning of the relative treatment effect, by setting the hazard of mortality in the lorlatinib arm equal to that in the PDC (or ABCP arm) from three years and five years.</td></tr>
<tr><td>Why this issue is important</td><td>There is uncertainty regarding the selection of the method used to compare relative efficacy. The ERG's sensitivity analysis shows that the choice of method has an impact on the ICER (using original PAS price for lorlatinib against list price for comparators and subsequent treatments).
<table>
<tr><th colspan="3">Description</th><th>Incremental costs</th><th>Incremental LYs</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="3">Company Base-case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£46,033</td></tr>
<tr><td rowspan="5">1</td><td rowspan="5">Alternative PDC PFS and OS survival cure methods</td><td>a) Method 1: MAIC HR EXP-2:3A</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£42,416</td></tr>
<tr><td>b) Method 2: MAIC HR EXP-3B:5</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£53,915</td></tr>
<tr><td>c) Method 3: Unadjusted HR EXP-2:3A</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£40,728</td></tr>
<tr><td>d) Method 4: Unadjusted HR EXP-3B:5</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£46,184</td></tr>
<tr><td>e) Method 6: Independent curves & population adjustment</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£40,520</td></tr>
</table></td></tr>
</table>

Technical team preliminary judgement and rationale	The technical team notes that there are logical arguments to support and counter the company choice of method used to compare relative efficacy. The technical team also acknowledges that the ERG is less concerned with the choice of method to compare relative efficacy than the robustness of the underlying trial data used to estimate the comparative efficacy of PDC. The company's implementation of the MAIC was considered robust by the ERG, therefore, the company's decision to reject the MAIC results in favour of fitting independent curves to the chemotherapy data seems an unusual choice. The technical team agrees with the ERG's suggestion that method 2 (HR derived from MAIC with cohort 3B:5) would be equally appropriate, and it is worth noting that this option has a considerable upward impact on the ICER.
Summary of comments	**Comments from the company:** The main rationale for selecting independent curves in the submitted base case was that it is unclear if OS satisfied the proportional hazards assumption, which is required for the use of methods that apply constant HRs (i.e. MAICs). Applying these when proportional hazards is violated can cause bias in long-run projections. The ERG and technical engagement team argue that the MAIC methodology presented in the company submission is robust, and that method 2 MAIC is plausible, but no adequate justification is given for the rejection of the method 1 MAIC. Pfizer therefore believes that methods 1 (MAIC with EXP-2:3A matching), 2 (MAIC with EXP-3B:5 matching) and 5 (independent curves) all give plausible ICERs. **Comments from the ERG:** the ERG acknowledges the company's logic in its choice of a method. While accepting the plausibility of methods 1 and 2, on balance, the ERG prefers the choice of independently fitted curves for the base case.
Technical team judgement after engagement	All 3 methods will be considered during the appraisal.

Issue 4 – The most plausible projections of PFS and OS for lorlatinib

Questions for engagement	Which are the most plausible projections of PFS and OS for lorlatinib?

Background/description of issue	The company's projections of PFS and OS for lorlatinib are uncertain due to the difficulty of extrapolating limited clinical data substantially beyond the observed period, and a lack of consensus between clinical experts consulted by the company and ERG. **The company** In the base case analysis, the Study 1001 trial was used to derive PFS for lorlatinib. All parametric curves were fitted to the lorlatinib PFS data, which were taken from the EXP-3B:5 cohort of patients in Study 1001. While all curves had a similar visual fit, the generalised gamma curve was selected for the base case. This was based on the visual fit to the observed data, statistical fit (lowest AIC and second lowest BIC), and long-term plausibility. When shown visual extrapolations and proportions in PFS, clinical experts favoured the generalised gamma or the Gompertz curve. The estimate of PFS provided by the generalised gamma curve was also in the middle of the range of estimates provided by all curves. To derive long-term OS for lorlatinib, parametric curves were fitted to the lorlatinib OS data taken from the EXP-3B:5 cohort of Study 1001. Although the exponential curve had the best fit statistics, the generalised gamma curve was deemed to be the most appropriate selection. Fit statistics in this case are not a useful criterion for curve selection because the range of fit statistics between curves was not large and the ordering on long-term extrapolations do not conform with ordering on fit statistics. Therefore, an overemphasis on fit statistics can lead to spurious conclusions. Even more importantly, clinical experts suggested that 10-year survival would be closer to [redacted] than [redacted].

	Therefore, the generalised gamma was selected to inform the base-case, being a compromise between the exponential curve and the log-normal preference of the clinical experts. OS parametric curves – lorlatinib:  **The ERG** The ERG acknowledges the difficulty of extrapolating limited clinical data substantially beyond the observed period. Although the company found a consensus amongst the two clinical experts they consulted, the ERG's clinical adviser believed that the [redacted] projected survival at 10 years for lorlatinib was optimistic given the previous treatment history and believed [redacted] to be more plausible. The ERG supports the company's decision not to adopt the most optimistic extrapolation for lorlatinib OS, despite consensus amongst the clinical experts they consulted (the first preference of both clinical experts was the log-normal curve).

	Based on both the ERG's clinical advice and the measures of statistical fit (AIC and BIC), the ERGs opinion is that the extrapolation based upon the exponential distribution cannot be disregarded. However, given the paucity of clinical data and substantial doubt regarding the most appropriate extrapolation, the ERG believes the company has adequately addressed this within their scenario analysis.
Why this issue is important	The choice of extrapolation is likely to drive costs and QALYs in the model.
Technical team preliminary judgement and rationale	The technical team note the consensus regarding the choice of the generalised gamma curve for the extrapolation of PFS, but also the wide range of views on the choice of curve for OS. The company opted to contradict the views of its clinical experts whose views were markedly different to those of the clinical expert consulted by the ERG. The technical team therefore feel strongly that further clinical expert opinion is required to reduce uncertainty about the most plausible extrapolation of OS for lorlatinib.
Summary of comments	**Comments from the company:** There was broad consensus between the ERG and technical team concerning the appropriate curve selection for PFS in lorlatinib. For OS, the exponential curve had the best fit statistics by a small margin, with the other curves having almost identical fit statistics. Clinical experts consulted by Pfizer suggested up to [redacted] alive at 10 years was plausible (Log-normal curve); a clinician consulted by the ERG suggested that [redacted] was also plausible (exponential curve). **Comments from the clinical experts:** Within the proviso that there isn't sufficient evidence concerning 10-year survival in this patient population, there was general agreement from the clinical experts that 4.5% predicted alive at 10 years is a reasonable projection between the 2 clusters of curves and so the generalised gamma base case curve is the most appropriate selection.
Technical team judgement after engagement	The technical team accepts the generalised gamma curve is the most appropriate for lorlatinib OS in the base case.

Issue 5 – Selection of utility values

Questions for engagement	5a. What is the most appropriate utility value for the progressed disease on either treatment? 5b. Is it appropriate to use a higher PFS utility value for lorlatinib compared with PDC or ABCP?
Background/description of issue	The selected value for the progressed disease state appears high compared with other published values specific to treatment line. Also, there is no direct comparative evidence that pre-progression utility estimates on lorlatinib is higher than pre-progression utility estimates on either PDC or ABCP. **The company** To inform the utility estimates used in the model, a SLR was performed to identify published utility values associated with advanced/metastatic ALK-positive NSCLC. Labbe at al. (2017), identified as an update to an earlier study (Labbe et al. 2016), evaluated EQ-5D derived health state utility scores using a longitudinal cohort of Canadian outpatients diagnosed with metastatic lung cancer (including ALK-positive) across various disease states. Utility values for the ALK-positive population using IUK preference weights (for those receiving ALK TKIs) in the progression-free and progressed disease states were 0.73 and 0.65, respectively. This study represents the largest source of NSCLC ALK-positive EQ-5D utility values and is therefore the closest that aligns with the decision problem. For progression-free utilities, it was considered appropriate to apply treatment-specific utilities given that patients receiving chemotherapy are likely to have a poorer HRQoL than patients on ALK TKIs. This difference was supported by other studies, such as PROFILE 1007, where utilities for the ALK TKI crizotinib (0.82, 95% CI: 0.79-0.85) were significantly greater ($p<0.05$) than for PDC (0.73, 95% CI: 0.70-0.79). Additionally, within the HRQoL SLR, seven out of the ten studies identified had progression-free treatment-specific utilities. Applying such treatment-specific utility values within the submission for lorlatinib also accounts for the decrement due to the method of administration of PDC (intravenous infusion v oral). In the submission, the PFS for lorlatinib was mapped from the EORTC QLQ-C30 to the EQ-5D-3L to give a utility value of [redacted]. The PFS utility value of 0.72 for PDC was taken from the PROFILE 1014 study. For progressed disease, the utility value of 0.65 was taken from Labbe 2017 for both lorlatinib and PDC. **The ERG**

	The main criteria used to justify this utility value for progressed disease is the number of confirmed ALK-positive patients in the study sample (because some studies did not separately specify by mutation status). This justification assumes that the ALK mutation is the most important factor in determining the most appropriate utility value, but the ERG finds it equally plausible that for people with advanced NSCLC who have progressed after two or three lines of treatment, quality of life could be equally diminished irrespective of any genetic mutation status. The ERG believes that the utility value applied for progressed disease should be either 0.59 or 0.46, lower than the value applied in the company base case. This is because the value applied in the company base case (0.65) appears to reflect health status around the time of progression on an ALK TKI, when patients may still be on treatment (Labbe et al). Thus, the ERG believe it may not be suitable for reflecting average health related quality of life throughout time spent in the progressed state where patients will deteriorate over time. Therefore, the ERG prefers the lower values reported by Chouaid (2013) for progressive disease after 2nd line or 3rd/4th line treatment; 0.59 and 0.46 respectively. In support of this, Nafees et al (2008) interviewed 100 people in the UK to rate health states in NSCLC using the standard gamble and found the mean value for progressed disease to be 0.47. There is no direct comparative evidence that pre-progression utility on lorlatinib is higher than pre-progression utility on either PDC or ABCP, and so further clinical advice is required to determine whether this utility decrement is appropriate to reflect the experienced HRQoL differences between these treatments.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of lorlatinib, it is important to identify the most appropriate utilities for PFS and PPS states.
Technical team preliminary judgement and rationale	The technical team share the ERG's concerns about the choice of 0.65 for progressed disease. The utility values provided by Chouaid (2013) and Nafees et al (2008) are highly suggestive that a lower utility value between 0.46 and 0.59 would be more clinically plausible. The technical team support a post-progression utility value that would be in line with previous appraisals of ALK TKIs used in the same point in the pathway. In the appraisal for ceritinib where people were previously treated with crizotinib (TA395) the committee accepted a progressed disease utility value of 0.46, and 0.59 was later accepted in the appraisal of brigatinib (TA571). It is worth noting that the progressed disease

	utility values accepted in the appraisals of ceritinib (TA500) and alectinib (TA536) for untreated ALK+ populations were 0.56 and 0.565/0.52 (the latter two utility values representing Non-CNS and CNS progression respectively). The technical team therefore agree that the most plausible progressed disease utility value is between the range of 0.46 and 0.59. With respect to the difference in treatment-specific PFS utility values, the technical team are not concerned that there is no empirical evidence to validate this assertion by the company. In discussion with both clinical experts and patients, it was generally agreed that quality of life was expected to be higher on lorlatinib than on PDC, primarily due to the difference in commonly experienced adverse events between the two treatments. The company did not apply disutilities for adverse events in their base case analysis and assumed these would be captured in the treatment-specific utilities. However, they did conduct a scenario analysis that applied disutilities.
Summary of comments	**Comments from the company:** There was broad agreement in the technical engagement call that 0.46 to 0.59 is a reasonable range for the post progression health state. To capture the higher utility for treatment beyond progression in the lorlatinib arm, in-line with what was accepted in the Brigatinib appraisal, two plausible scenarios are presented for consideration: • Method 1: 0.65 for lorlatinib patients in progression and on treatment and 0.59 for progressed and off treatment in both arms. • Method 2: 0.65 for lorlatinib patients in progression and on treatment and 0.46 for progressed and off treatment in both arms. **Comments from the clinical experts:** Patients with brain metastases typically deteriorate very quickly and have significant morbidity, so a value appropriate to a population with brain metastases would be most appropriate. Lorlatinib is highly effective intra-cranially and has an associated effect on quality of life for patients. The PFS utility difference between lorlatinib and comparators is appropriate.
Technical team judgement after engagement	The technical team feel that it is appropriate to consider post-progression utility values that take account of whether patients are being actively treated with lorlatinib, in line with the approach

	accepted for the appraisal of brigatinib. Both methods proposed by the company will be considered in the appraisal.

Issue 6 – Treatment duration on lorlatinib

Questions for engagement	What is the most plausible time on treatment (ToT) for lorlatinib?
Background/description of issue	The wording of the licence for lorlatinib states that it can be used while clinicians judge there to be a benefit from doing so, rather than until progression. The treatment duration calculation is plausible but may underestimate the extent to which clinicians tend to prolong treatment following radiographic progression in routine practice in situations where there are no other targeted treatment options available. **The company** Treatment beyond progression was permitted for lorlatinib in Study 1001. Different extrapolations of Study 1001 data were explored for goodness of fit and tested against clinical expert opinion for validity. Constraints associated with all of the parametric curve extrapolations, such as producing clinically implausible results or conflicting with the company's preferred extrapolations of PFS and OS, motivated the company to implement an alternative approach to estimate the time on treatment for lorlatinib. In the base case, ToT was equated to PFS but newly progressed patients in each cycle accrued the treatment costs associated with [redacted] months of lorlatinib to account for treatment beyond progression. This was calculated as the difference between the restricted mean time on treatment minus the restricted mean PFS. The advantages of this method include: • The most plausible parametric curve is fitted to PFS • The relationship between PFS and ToT is clinically plausible, and no patients remain off treatment and progression free, and • The costs of treatment in progression are accounted for in a way that preserves the relationship between PFS and ToT that was observed during Study 1001

	The ERG Treatment beyond progression is a feature of TKI use in ALK-positive disease, especially where there is a lack of effective alternatives to switch to. This was accepted in the NICE appraisal for brigatinib (TA571), where clinicians continue treatment until there is perceived to be a loss of clinical benefit. Clinical expert advice to the ERG suggests that the situation is likely to be the same for lorlatinib. While the ERG accept that there are issues around the fitting of curves to observed ToT data from Study 1001, the rationale proposed in support of the method selected by the company is not clear. The criterion for rejecting some of the fitted curves was that they did not fit well with the company's preferred curve for PFS, but this assumes that this is the PFS curve that will be accepted by the committee. The ERG notes that the gamma curve for ToT suffers less from overpredicting than the lognormal, resulting in the ToT converging with PFS just after 10 years when about 3% remain progression free and on treatment. Beyond this the curve remains just below PFS for the remainder of the model, and so the ERG believe it should not be ruled out as a viable option. The ERG, based on clinical expert advice, believes that the company estimate of [redacted] months in addition to PFS should be considered a minimum. In the absence of more complete data to inform mean post progression ToT, the ERG tends towards favouring a fitted parametric curve to model ToT. When considering consistency with the fitted lorlatinib PFS curve, the ERG further believe that the generalised gamma provides the most plausible projections of those assessed by the company. The ERG explores ToT by adding [redacted] and [redacted] months to PFS in sensitivity analysis.
Why this issue is important	The time on treatment estimate is likely to drive the incremental costs and the ICER.
Technical team preliminary judgement and rationale	The technical team share the ERG's concerns regarding the potential for patients to remain on lorlatinib for longer than has been estimated in the company model. The ERG has conducted a sensitivity analysis where an additional [redacted] and [redacted] was added to ToT based on clinical expert opinion. The technical team's own engagement with clinical experts suggests that actual ToT post-progression might not be as long as these estimates due to recent availability of subsequent treatments other than chemotherapy. Since the publishing of TA584, ABCP is now available as a treatment option for some patients, and so it is possible that the motivation to remain on ALK TKIs post progression has been somewhat reduced.

Summary of comments	**Comments from the company:** There was consensus among the clinical experts on the technical engagement call that 3 to 4 months of treatment beyond progression with lorlatinib is clinically plausible. As reported in section B.3.3.3.2 of the company submission, the UK database of ALK patients reported 14.9 months as the 95th percentile for duration of treatment on ALK+ TKIs. Treating this as an effective upper bound and differencing with the calculated restricted mean PFS gives 4.3 months. Taking the mid-point between the base-case treatment beyond progression months ([redacted]) and 4.3 gives 3.5 months. **Comments from the clinical experts:** It is becoming increasingly necessary to distinguish between brain and other sites of progression, because the length of treatment beyond progression will largely depend on the site of progression. Some extra-cranial sites of progression can now be controlled with radiotherapy, allowing for ongoing treatment with the ALK TKI. So [redacted], [redacted] and [redacted] months are all clinically plausible, but of those [redacted] is probably the most plausible. The average is about 3 months, but it may be slightly longer when going from a TKI to chemotherapy rather than to another TKI (and taking into account that clinical trials do not always accurately reflect real clinical practice).
Technical team judgement after engagement	The technical team consider that 3.5 months treatment beyond progression with lorlatinib is appropriate for decision making.

Issue 7 – Assumptions about subsequent therapies

Questions for engagement	Are the assumed proportion of patients receiving subsequent therapies and the distribution of these subsequent therapies appropriate for decision making?
Background/description of issue	Assumptions about the proportion of patients receiving subsequent therapies following the intervention and comparator treatments, and the distribution of these subsequent therapies is uncertain and could benefit from further clinical input. **The company** Within the ABCP appraisal (TA584) there was some consensus that up to 60% of patients would receive active subsequent therapy in the PDC arm. Of the 60% receiving subsequent therapy, 31%

	were assumed to receive atezolizumab and 69% pembrolizumab. For lorlatinib, it was again assumed that 60% would receive subsequent therapy, and of these 40% would receive pemetrexed and 60% would receive PDC. **The ERG** The ERG is satisfied that the modelled subsequent therapies are appropriate and relevant to routine NHS practice. However, the ERG note the following reservations: • That the 60% further treatment rate may represent an upper bound because the committee for TA584 ultimately accepted a revised analysis of 46.6% of patients receiving active subsequent therapy in both the ABCP and PDC arms • That the ERG's clinical expert adviser questioned the proportion of patients assumed to receive pemetrexed following progression rather than the more effective PDC, and also the proportions receiving atezolizumab and pembrolizumab following lorlatinib • The ERG's clinical expert adviser also questioned the percentage of patients assumed to be suitable for docetaxel following progression on ABCP, reservations that seem to be echoed by clinical expert discussion in the committee meeting for the atezolizumab combination appraisal (TA584). Taken together, these observations suggest some potential for the modelling of subsequent treatments to bias cost-effectiveness in favour of lorlatinib.
Why this issue is important	Changes to the subsequent treatments received has some limited impact on the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	The technical team share the ERG's view that some of the subsequent treatment assumptions in the company submission could be incorrect in the light of rapidly changing or variable clinical practice. Further clinical input is required to determine the most plausible estimates.
Summary of comments	**Comments from the company:** There was consensus among clinicians on the technical engagement call about the proportion and types of subsequent treatments. Based on these comments, the following subsequent treatment assumptions are proposed:

	• Lorlatinib: 45% receive subsequent treatments with the remaining 55% receiving BSC. Of the 45%, 66% now receive ABCP and 33% receive PDC. • PDC: 45% receive subsequent treatments with the remaining 55% receiving BSC. The 45% receive immunotherapies in the proportions from the original company submission (69% atezolizumab, 31% bevacizumab based on TA584). • ABCP: 75% receive docetaxel and 25% BSC. **Comments from the clinical experts:** Comments on the proportion and type of subsequent treatments are reflected in the revised assumptions detailed above.
Technical team judgement after engagement	The revised assumptions for proportion and type of subsequent treatment are appropriate for decision making.

Issue 8 – Cancer Drugs Fund

Questions for engagement	Does lorlatinib meet the criteria for inclusion in the Cancer Drugs Fund (CDF)? • Does lorlatinib has plausible potential to be cost-effective? • Could data collection reduce the outstanding uncertainty identified in this report? • What data would be most useful to collect to address the outstanding uncertainties?
Background/description of issue	Generally, technologies that receive conditional marketing authorisations and which have a high degree of clinical uncertainty due to limitations in the evidence base can potentially be candidates for the CDF. In this case, lorlatinib has a conditional marketing authorisation and the clinical trial evidence is based on a non-comparative single-arm study with a subgroup of only 139 patients, and no direct comparative evidence is available. **The company** The company has not made a case to apply for funding through the CDF.

	The ERG The ERG have made no comment on the suitability of lorlatinib for funding through the CDF as the company have not expressed any intention to pursue it. The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but would require information on its effectiveness before it can be considered for routine commissioning (when the guidance is reviewed). The arrangements for the CDF agreed by NICE and NHS England in 2016 are specified in NICE's Cancer Drugs Fund methods guide (addendum).
Why this issue is important	If lorlatinib is not recommended for routine commissioning, the committee will need to consider if it could be recommended for use within the CDF.
Technical team preliminary judgement and rationale	The technical team considers that lorlatinib does not meet the criteria for inclusion in the CDF: • It considers that lorlatinib has plausible potential to be cost-effective, taking into account end-of-life criteria. • However, it considers that there is clinical uncertainty that cannot be reduced through data collection. According to the specific obligations of the conditional marketing authorisation for lorlatinib: • the company should submit the clinical study report for the phase III trial (CROWN 1006) comparing lorlatinib with crizotinib for the first line treatment of advanced ALK-positive NSCLC by December 2021 in order to confirm the efficacy and safety of lorlatinib. ○ As this evidence is for the first line treatment of previously untreated patients, it is not relevant to the indication being appraised (indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after: i) alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or ii) crizotinib and at least one other ALK TKI.

	• the company should conduct a prospective single arm study investigating patients who progressed after alectinib or ceritinib as the first ALK TKI therapy in order to further confirm the efficacy of lorlatinib in patients by June 2024.
	  ○ As this is a single-arm trial, it will not reduce the lack of comparative evidence.
	• Treatments that are funded through the CDF are automatically enrolled in the Systemic Anti-Cancer Treatment (SACT) dataset which collects information on the use of systemic-anti cancer therapies across all NHS England trusts.
	  ○ Although SACT data could potentially provide some evidence on the effect of lorlatinib in NHSE patients such as addressing some of the generalisability issues regarding the evidence being based on studies conducted in Asian patients, this is not a key uncertainty that needs to be resolved. In past appraisals with similar clinical trial populations, such as TA595, the committee has judged that the evidence was suitable for decision-making.
	The technical team does not consider that lorlatinib is a suitable candidate for the CDF, as it does not meet the criteria necessary for reducing the outstanding uncertainty in the evidence base.

Summary of comments	No comments received.
Technical team judgement after engagement	The technical team is satisfied that lorlatinib is not a suitable candidate for the CDF.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions

	Pre-TE technical team assumptions	Issue	Post-TE agreed assumptions
Weight-based dosing for pembrolizumab of 2mg/kg every three weeks for patients who progress on PDC	Clinical experts agree that a fixed dose regimen for pembrolizumab (200mg every 3 weeks) is now standard practice in the NHS	-	**Accepted**
PFS and OS data used to inform the PDC arm of the model may have underestimated its effectiveness	ERG conducted iterative upward adjustments to PFS and OS in the PDC arm using HRs of 0.9, 0.8, 0.7 and 0.6	Issue 2	**HR of 0.8 accepted**
Method 5 for comparing lorlatinib to PDC (independent curves)	Method 1 (MAIC HR EXP:2:3A) and Method 2 (MAIC HR EXP-3B:5) are equally plausible	Issue 3	**For committee deliberation**
Generalised gamma curve selected for lorlatinib OS	Log-normal and exponential curves were also considered plausible	Issue 4	**Generalised gamma accepted**
PD utility is 0.65	The value proposed by the company is high compared with published values. 0.59 and 0.46 are more plausible, as is a separate value for PD while still on treatment with lorlatinib	Issue 5	**For committee deliberation**
Time on treatment following progression is [redacted] months	Time on treatment following progression is plausibly 3.5 months, [redacted] months, [redacted] months, or generalised gamma curve	Issue 6	**3.5 months accepted**
60% receive subsequent therapy following PDC	50% or 45% receive subsequent therapy following PDC, in line with TA584	Issue 7	**45% accepted**

Following technical engagement, Issues 3 and 5 remain as unresolved and are to be deliberated by the committee. Issues 2, 4 and 6 have been resolved as summarised in Table 1 above. Issue 7 has been resolved following discussion with 2 clinical experts at technical engagement, and the proportion and types of subsequent treatment have been accepted as described in Issue 7, above.

Following technical engagement, additional options were presented by the company for progressed disease utility values that take into account the possibility that utility is higher in the period following progression on lorlatinib while remaining ion treatment (Method 1 and Method 2, described in Issue 5, above). In addition, the ERG identified several minor errors in the company's revised model, which were corrected in the following analyses.

The tables below show the impact on the cost-effectiveness estimate for lorlatinib compared with PDC (1a) and ABCP (1b) using the updated confidential PAS discount for lorlatinib and the list price for comparators and subsequent treatments. Table 1a provides ICERs for the different options within Issues 3 and 5 simultaneously.

Table 1a: Impact of unresolved issues (3 and 5) on the cost-effectiveness estimate for lorlatinib compared with PDC using the updated confidential PAS discount for lorlatinib and list price for comparators and subsequent treatments

Scenario	Description	ICER change from original base-case	Deterministic ICER	Probabilistic ICER
Base-case vs. PDC	Post-TE agreed base-case settings with updated lorlatinib PAS and list prices on subsequent treatments	-	£34,091	£31,318
Base-case + resolved issues	As above but with inputs updated for resolved issues 2, 4, 6 and 7, and model errors corrected.	+£19,749	£53,840	£49,022
Updated base-case + independent curves (method 5)	0.59 PD utility	+£21,732	£55,823	£50,898
	Utility method 1	+£20,981	£55,072	£50,767
	Utility method 2	+£23,854	£57,945	£54,668
Updated base-case + EXP-3B:5 MAIC (method 2)	0.59 PD utility	+£35,718	£69,809	£66,115
	Utility method 1	+£34,580	£68,671	£65,372
	Utility method 2	+£34,405	£68,496	£65,999
Updated base-case with EXP-2:3A MAIC (method 1)	0.59 PD utility	+£16,103	£50,194	£47,966
	Utility method 1	+£15,571	£49,662	£47,487
	Utility method 2	+£18,473	£52,564	£50,294
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and apply list prices for Atezolizumab and Bevacizumab (ABCP subsequent treatments for lorlatinib) and Pembrolizumab and Atezolizumab (subsequent treatments for PDC). Method 1: 0.65 for lorlatinib patients in progression and on treatment and 0.59 for progressed and off treatment in both arms. Method 2: 0.65 for lorlatinib patients in progression and on treatment and 0.46 for progressed and off treatment in both arms.				

Table 1b: Impact of unresolved issue (5) on the cost-effectiveness estimate for lorlatinib compared with ABCP using the updated confidential PAS discount for lorlatinib and list price for comparators and subsequent treatments

Scenario	Description	ICER change from original base-case	ICER
Base-case vs. PDC	Post-TE agreed base-case settings with updated lorlatinib PAS and list prices on comparators and subsequent treatments	-	Dominant
Base-case updated with resolved issues	As above but with inputs updated for resolved issues 4, 6 and 7, and model errors corrected.	-	£12,505
Updated base-case with different PD utilities	0.59 PD utility	-	£13,109
	Utility method 1	-	£12,935
	Utility method 2	-	£13,978
Notes: All scenarios include the updated confidential PAS for lorlatinib ([redacted]) and apply list prices for Atezolizumab and Bevacizumab (ABCP comparator and subsequent treatment for lorlatinib) Method 1: 0.65 for lorlatinib patients in progression and on treatment and 0.59 for progressed and off treatment in both arms. Method 2: 0.65 for lorlatinib patients in progression and on treatment and 0.46 for progressed and off treatment in both arms.			

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate

Table 3: Other issues for information

Issue	Comments
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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