NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Contents:

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

NICE National Institute for Health and Care Excellence

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346)

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviations

AE	Adverse event
CDF	Cancer Drugs Fund
CNS	Central nervous system
CS	Company submission
CSR	Clinical study report
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
ERG	Evidence review group
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health-related quality of life
IRC	Independent review committee
KM	Kaplan Meier
NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
PRO	Patient-reported outcome
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SST	Subsequent systemic therapy
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TTF	Time to treatment failure

Key issues – clinical effectiveness

- Are the results from ARCHER 1050 generalisable to clinical practice?
  - The trial included no UK centres and only XXX of participants were from European countries
  - The trial included people with EGFR positive NSCLC specifically with exon 19 deletion (del19) and exon 21 L858 substitutions (L858R) only and ECOG performance score 0 or 1 and excluded people with brain metastases
  - The trial has a high proportion of people with an Asian family origin
- Is the ARCHER 1050 bias in favour of dacomitinib because the dacomitinib treatment arm had more females, and ECOG performance score of 0?
- Is the company's fractional polynomial (FP) model appropriate for decision making?
  - Are the patients in ARCHER 1050 and LUX-lung 7 similar?
  - The ERG considers that the transitivity assumption may be violated
  - The company does not present results of the indirect comparison between dacomitinib and afatinib
  - The ERG had concerns over the use of the FP analysis with respect to the extrapolations for the survival outcomes.
- Is it reasonable to assume equal efficacy between erlotinib and gefitinib?

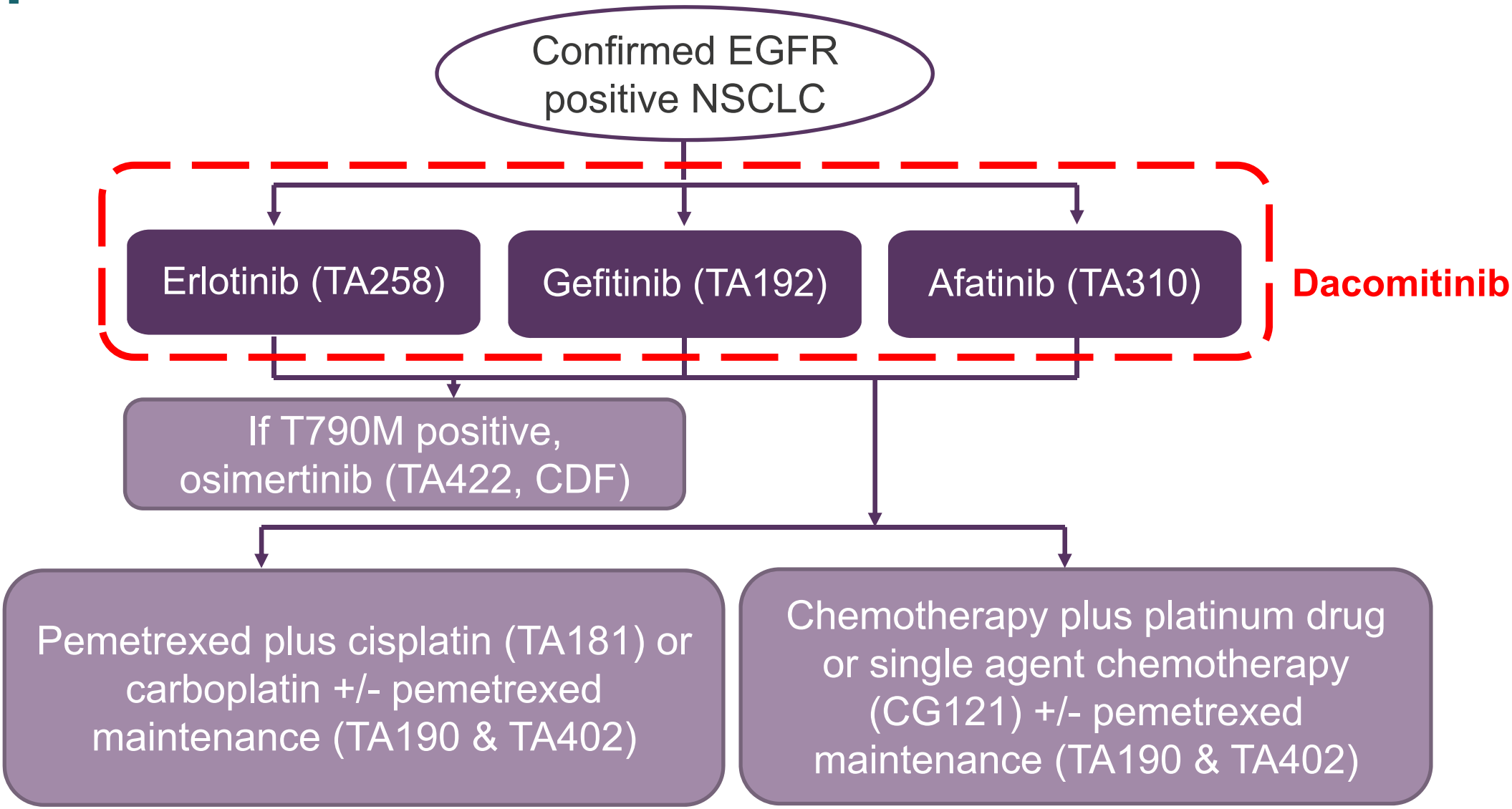
Key issues – cost effectiveness

- Does the generalised gamma (company) or log-normal (ERG) parametric curve for gefitinib give more clinically plausible PFS estimates?
- Does the generalised gamma (company) or log-logistic (ERG) parametric curve for gefitinib give more clinically plausible OS estimates?
- Is it reasonable to assume equal efficacy between dacomitinib and the comparators from month 36 onwards for OS?
- Is it clinically plausible that dacomitinib provides both pre- and post-progression benefit?
- Is the utility value of 0.64 from literature (company) or XXX from ARCHER 1050 (ERG) a more clinically plausible post-progression utility value?
- Is it reasonable to include disutilities associated with adverse events?
- Does the modelling of the proportion of patients receiving subsequent therapy after a first line TKI and the subsequent therapies received reflect clinical practice?
- Should the cost for rebiopsy for osimertinib (currently the CDF) be included in the model?

Background
Non-small-cell lung cancer (NSCLC)

- Lung cancer → more than 45,000 people were diagnosed in England in 2016
- Mostly diagnosed at an advanced stage → cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV)
- NSCLC = estimated up to 85 to 90% of lung cancer cases
- In 2016, approximately 32,500 people were diagnosed with NSCLC in England, and around 61% had stage IIIB or stage IV disease
- 1-year survival for stage III NSCLC is 42.5%, for stage IV it is 15.5%
- Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma
- Approximately 5–50% of NSCLC cases are characterised by del19 and L858R EGFR alterations, depending on ethnicity, sex, smoking status and histological subtype
- Prognosis for people with EGFR positive NSCLC is slightly better than general NSCLC → outcomes are still poor

Treatment pathway in the UK: EGFR positive NSCLC



Dacomitinib

Mechanism of action	Second generation tyrosine kinase inhibitor (TKI) → selective and irreversible TKI that has activity against 3 members of the ErbB family of proteins (EGFR/HER-1, HER2 and HER4)
CHMP positive opinion	Dacomitinib as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR-activating mutations
Administration & dosage	One oral 45mg dose daily (available in three dose strengths – 45mg, 30mg and 15mg) until disease progression or unacceptable toxicity
Cost (list price)	List price: XXXX for 30 x 15mg or 30 x 30mg or 30 x 45mg capsules
Average cost of treatment course (list price)	Based on the mean treatment duration of XXX months in the economic model, the average cost of treatment is XXXX list price and XXXX (with PAS)
Patient access scheme (PAS)	PAS application has been approved by NHS England for dacomitinib. This provides a simple discount to the list price

Decision problem

	Final Scope	Company	
Population	People with untreated locally advanced or metastatic NSCLC with EGFR activating mutation(s)	✓ - only included del19 and L858R EGFR mutations	
Intervention	Dacomitinib	✓	
Outcomes	Overall survival Progression-free survival Overall response rate Duration of response Adverse events of treatment, Health-related quality-of-life	✓	
Comparators	Afatinib, erlotinib, gefitinib	✓	
Subgroups	None	✓	

ERG comment: Trial population is narrower than the scope. Approx. 90% of EGFR+ mutations are del19 & L858R.

Clinical expert perspective

- There is an unmet need → comparators can control the disease but progression occurs on average within 12 months
- Repeat biopsy is taken on progression → receive osimertinib if tumour is T790M positive. If not T790M positive, receive platinum doublet chemotherapy or continue initial therapy beyond progression
- People are reluctant to change to chemotherapy in this setting
- Dacomitinib is the 1st EGFR inhibitor to show survival benefit → improved OS and PFS over the 1st and 2nd generation EGFR inhibitors in use in current clinical practice
- Toxicity profile similar to afatinib → diarrhoea and skin toxicity can impact on a patient quality of life but shouldn't cause too many problems if managed appropriately
- Dacomitinib requires dose adjustments in a number of patients, as does afatinib → gefitinib and erlotinib do not
- Real world data from EGFR inhibitors matches relatively well to trial data except people with poorer ECOG performance status and active bran metastases do worse than trial population
- Third generation TKIs such as osimertinib now have data available → improved safety profile compared with dacomitinib → likely use 3rd generation TKIs instead of 2nd generation

Patient expert perspective

Submission received from Roy Castle Lung Foundation

- There is an need for treatments with better outcomes than currently available
- People with EGFR positive NSCLC tend to be younger, female and have never smoked when compared with the overall NSCLC population
- People tend to have a poor outlook on disease progression → impacting family and carers
- Life extension is of paramount importance to people with EGFR positive NSCLC and their families
- Side effects are similar to other TKIs → rashes and diarrhoea most common grade 3 to 4 adverse events but anecdotal experience reports that dacomitinib relatively well tolerated
- Easy administration as dacomitinib is an oral therapy

Professional organisation perspective

Submission received from British Thoracic Oncology Group

- The second generation drug dacomitinib adds a further first line alternative treatment for untreated EGFR positive NSCLC
- The ARCHER 1050 trial demonstrated a PFS, and importantly OS, advantage over current standard of care, gefitinib
- People with brain metastases were excluded from the ARCHER 1050 trial → outcomes in the real world may differ from the trial evidence
- Longer-term impact of dacomitinib may be limited as 3rd generation TKIs (e.g. osimertinib) may replace its use if they are approved

Clinical effectiveness

Summary of sources of evidence

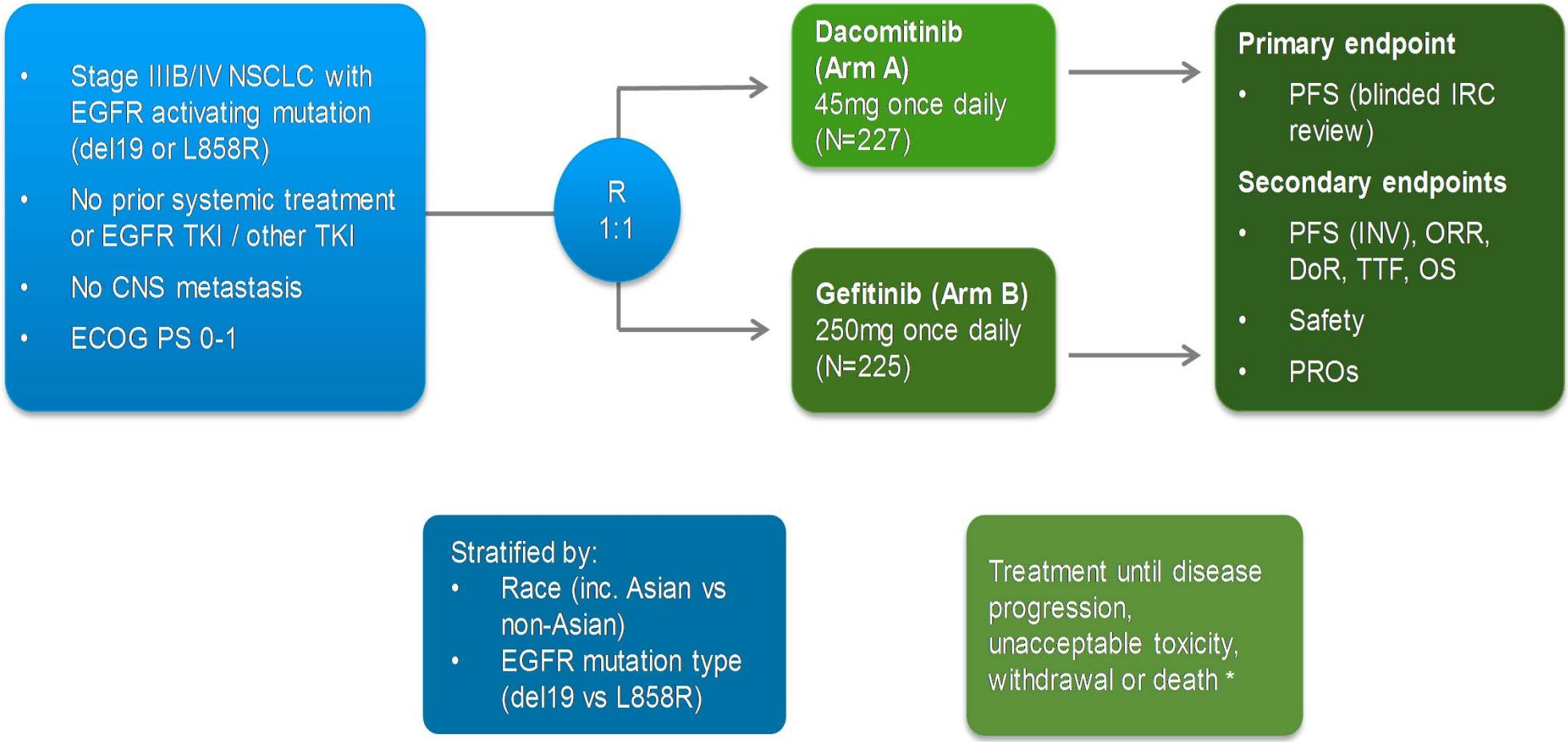
Evidence type	Comparison	Source of evidence
RCT	Dacomitinib compared with gefitinib	ARCHER 1050
NMA	Dacomitinib compared with afatinib	LUX-Lung 7 ARCHER 1050
Assumption	Assumed equal clinical efficacy between erlotinib and gefitinib	Based on committee conclusion in NICE appraisal of afatinib TA310

Company's main clinical evidence: ARCHER 1050

Design	Phase III, randomised, multicentre, open-label study
Population	• People with locally advanced or metastatic newly diagnosed, treatment-naïve NSCLC or with recurrent NSCLC • All eligible patients had tumours that tested positive for at least one EGFR-activating mutation (either the del19 or L858R)
Intervention, dose	Dacomitinib (n=227), 45 mg orally, once daily
Comparator, dose	Gefitinib (n=224), 250 mg orally, once daily
1◦ outcome	PFS (IRC assessment)
2◦ outcomes	PFS (investigator assessment), OS, ORR, DoR, AEs of treatment, TTF (IRC and investigator assessment), HRQoL
Pre-specified subgroups	• Age (<65 years vs >65 years) • Sex • ECOG PS (0 vs 1) • Race (Asian vs non-Asian) • Smoking history (never vs former or current) • EGFR mutation (del19 vs L858R)

PFS = progression-free survival, OS = overall survival, ORR = objective response rate, DoR = duration of response, AE = adverse event, TTF = time-to-treatment failure, IRC = independent review committee, ECOG PS = Eastern Cooperative Oncology Group performance status, HRQoL = Health-related quality of life

ARCHER 1050 study design



People received treatment for a maximum of 48 months

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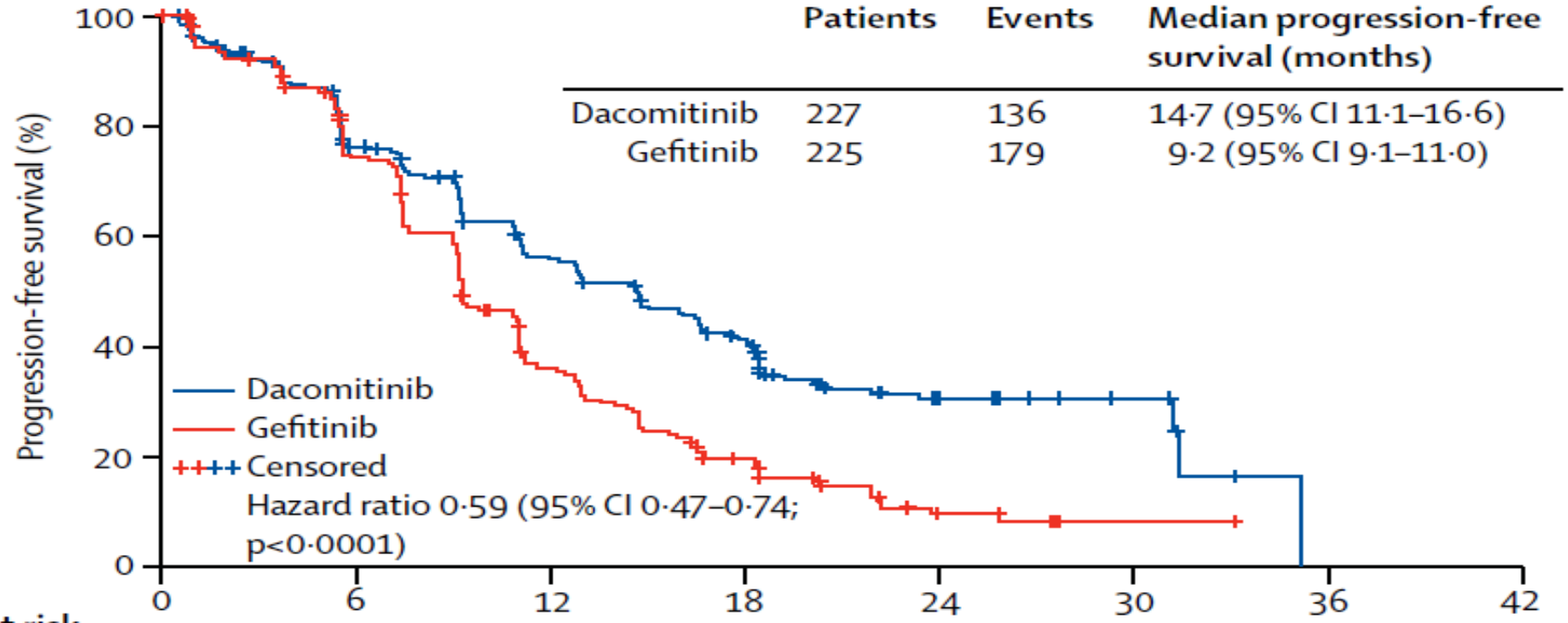
Archer 1050: Baseline characteristics

Population		Dacomitinib N=227	Gefitinib N=225
Sex, n (%)	Male	81 (35.7)	100 (44.4)
Family origin, n (%)	White	56 (24.7)	49 (21.8)
	Black	1 (0.4)	0
	Asian	170 (74.9)	176 (78.2)
Smoking status, n (%)	Never smoked	147 (64.8)	144 (64.0)
	Ex-smoker	65 (28.6)	62 (27.6)
	Smoker	15 (6.6)	19 (8.4)
ECOG performance status n, (%)	0	75 (33)	62 (28)
	1	152 (67)	163 (72)
Disease stage at screening, n (%)	Stage IIIB	18 (8)	16 (7)
	Stage IV	184 (81)	183 (81)
	Unknown	25 (11)	26 (12)
Mutation type, n (%)	del19	134 (59)	133 (59)
	L858R	93 (41)	92 (41)

ERG comment: Trial imbalance with sex, and ECOG PS → all potentially favouring the reported effectiveness of dacomitinib. High proportion of Asians and people with brain metastases excluded → may impact generalisability

ARCHER 1050: Dacomitinib significantly improves PFS compared with gefitinib

- Improvement of 5.5 months in median PFS compared with gefitinib
- Reduction of 41% in the risk of progression compared with gefitinib
- Investigator-assessed PFS was consistent with the blinded IRC analysis



	Patients	Events	Median progression-free survival (months)
Dacomitinib	227	136	14·7 (95% CI 11·1–16·6)
Gefitinib	225	179	9·2 (95% CI 9·1–11·0)

Number at risk (number censored)								
Dacomitinib	227 (0)	154 (23)	106 (31)	73 (36)	20 (74)	6 (88)	0 (91)	0 (91)
Gefitinib	225 (0)	155 (15)	69 (23)	34 (27)	7 (40)	1 (45)	0 (46)	0 (46)

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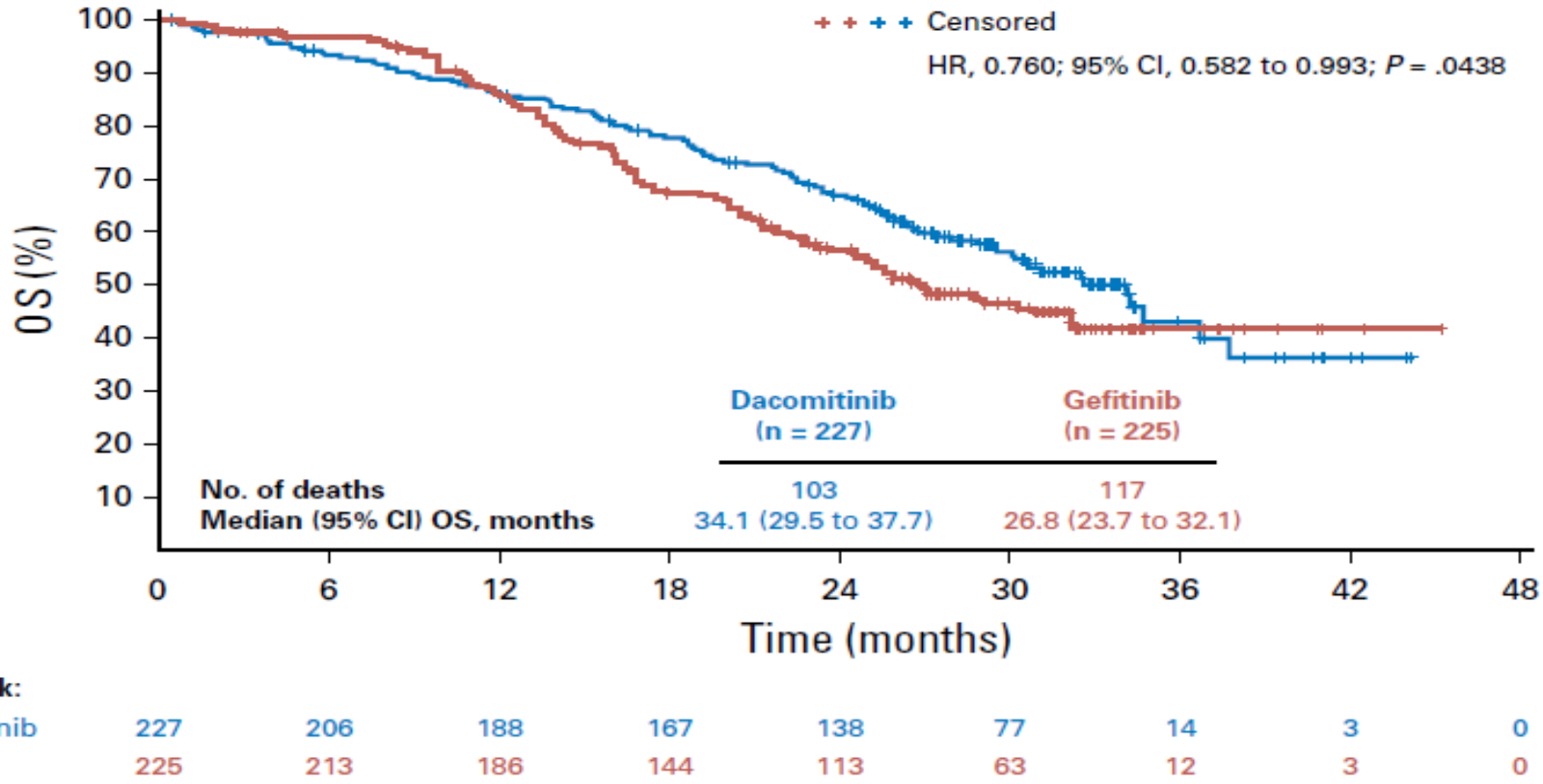
ARCHER 1050: Dacomitinib significantly improves OS compared with gefitinib

- Improvement of 7.3 months in median OS compared with gefitinib
- Reduction of 24% in the risk of death compared with gefitinib



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ARCHER 1050 : Subsequent systemic therapies (SST, from CSR)

	Dacomitinib (N=227) n (%)	Gefitinib (N=224) n (%)
Any SST	XXXX	XXXX
Number (%) of patients with SST; 2 or more patients in dacomitinib treatment arm		
pemetrexed	XXXX	XXXX
carboplatin	XXXX	XXXX
cisplatin	XXXX	XXXX
osimertinib	XXXX	XXXX
gefitinib	XXXX	XXXX
docetaxel	XXXX	XXXX
gemcitabine	XXXX	XXXX
erlotinib	XXXX	XXXX
paclitaxel	XXXX	XXXX
Others	XXXX	XXXX

ARCHER 1050: Health Related Quality of Life

EQ-5D-3L absolute score (PRO population)

	Dacomitinib (n=224)	Gefitinib (n=221)	Difference
VAS	Baseline: 73.1 (SD 19.6) End of study[a]: [redacted]	Baseline: 74.7 (SD 17.6) End of study[a]: [redacted]	Baseline: -1.6 End of study[a]: [redacted]
Utility index	Baseline: [redacted] End of study[a]: [redacted]	Baseline: [redacted] End of study[a]: [redacted]	Baseline: [redacted] End of study[a]: [redacted]

EQ-5D = European Quality of Life-5 Dimensions; PRO = patient-reported outcome; VAS = visual analogue scale; [a]Assumed by ERG.

ARCHER 1050: Dose reductions were higher with dacomitinib than gefitinib

- Dose reductions were required in 66.1% and 8.0% of patients in the dacomitinib and gefitinib treatment arms, respectively.

Dose reductions (for 2% or more of patients in either treatment arm (safety population)

AE category	Dacomitinib N=227	Gefitinib N=224
Any AEs, n (%)	150 (66.1)	18 (8.0)
Gastrointestinal disorders, n (%)	27 (11.9)	3 (1.3)
Skin and subcutaneous tissue disorders, n (%)	91 (40.1)	4 (1.8)
Infections and infestations, n (%)	53 (23.3)	2 (0.9)
Investigations, n (%)	4 (1.8)	7 (3.1)

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ARCHER 1050: Treatment-emergent AEs leading to permanent discontinuation were similar for both treatment arms

- Although more patients in the dacomitinib arm than gefitinib arm discontinued treatment temporarily due to AEs, rates of permanent discontinuations due to treatment-related AEs were similar between the treatment arms (XXXX versus XXXX, respectively)

AE, n (%)	Dacomitinib N=227	Gefitinib N=224
All causality AEs		
Any AEs	XXXXXX	XXXXXX
Treatment-related AEs		
Any AEs	XXXXXX	XXXXXX

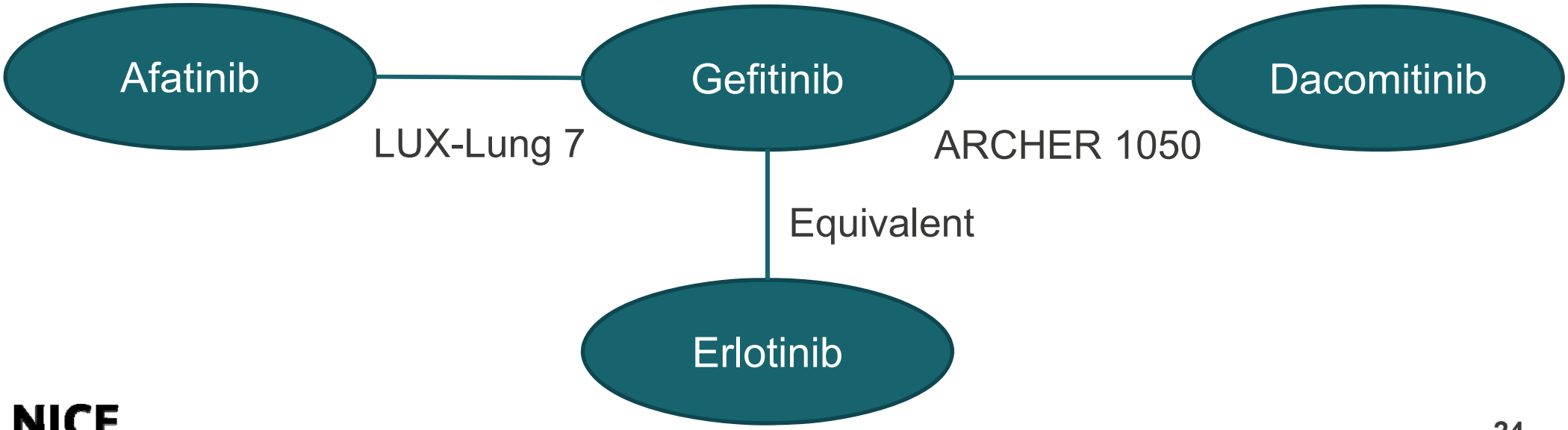
Clinical trials of EGFR-TKIs: dacomitinib and afatinib have a higher incidence of common AEs than other TKIs

Drug	Diarrhoea	Stomatitis / Mucositis	Paronychia	Dermatitis acneiform
Dacomitinib	85%	41%	62%	49%
Gefitinib (TA192)	34 to 54%	15 to 40%	14 to 32%	15 to 66%
Erlotinib (TA258)	25 to 57%	13%	4%	NR
Afatinib (TA310)	88 to 95%	52 to 72%	33 to 57%	81 to 89%

- Data from first-line clinical trials of EGFR-TKIs in patients with advanced NSCLC

Company's network meta-analysis comparing dacomitinib with afatinib and erlotinib

- No direct evidence comparing dacomitinib to UK standard of care therapies, other than gefitinib
- Systematic literature review conducted to identify relevant studies
- Gefitinib & erlotinib assumed to be clinically equivalent → based on committee conclusion for NICE appraisal of afatinib (TA310)
- NMA included two studies: LUX-Lung 7 and ARCHER 1050



Comparison of key baseline characteristics in ARCHER 1050 and LUX-LUNG 7

Trial Name	ARCHER 1050		LUX-Lung 7	
Arm	Dacomitinb	Gefitinib	Afatinib	Gefitinib
N	227	225	160	159
Median Age, years	62	61	63	63
Males, %	36	44	43	33
Asian, %	75	78	59	55
ECOG 0, %	33	28	32	30
ECOG 1, %	67	72	68	70
Brain Metastases, %	0	0	16	15
Stage IV, %	81[a]	81[a]	95	98
Never smoker, %	65	64	66	67
Del 19, %	59	59	58	58
L858R, %	41	41	42	42

[a] Proportion at screening; in addition, 11% of dacomitinib and 12% of gefitinib were classified as 'unknown' but were newly diagnosed with stage IV a time of study entry.

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Company conducted a fractional polynomial analysis as proportional hazards do not hold

- Proportional hazards assumption tested and found to not hold for PFS and OS
- Fractional polynomial model used to allow for time-varying hazards to be incorporated into the analysis
- Traditional indirect treatment comparison was explored in scenario analysis
- First and second order fractional polynomial models were explored
- Models were applied to the base-case survival functions for gefitinib then analysed for clinical plausibility

How the company selected the models

- DIC was used to compare the goodness-of-fit of different fixed effect models with first- and second-order FPs of different powers P1 and P2. The model with the lowest deviance information criteria (DIC) was considered as the model providing the ‘best’ fit to the observed data.

- The final model was selected after also considering the clinical plausibility of the curves

- For PFS, the lowest DIC model (second-order, P1=1, P2=1.5) overfitted the tail of the KM curve, and the next lowest (P1=0.5, P2=1.5) was considered more clinically plausible

- For OS, the lowest DIC model (P1=1, P2=1.5) similarly overfitted the tail of the KM. None of the second-order FP models were clinically plausible and so the first-order model P1=0 was selected, with P=0.5 applied in scenario analysis

Fractional polynomial results for PFS and OS (months): Means & medians compared with observed data

PFS (IRC)						
Model	Geftinib/Erlotinib		Dacomitinib		Afatinib	
	Median	Mean	Median	Mean	Median	Mean
P1=0.5; P2=1.5* (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5; P2=1* (company scenario analysis)			[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	9.23	-	14.65	-	-	-

OS						
Model	Geftinib/Erlotinib		Dacomitinib		Afatinib	
	Median	Mean	Median	Mean	Median	Mean
P1=-0.5* (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0* (company scenario analysis)			[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	26.84	-	34.07	-	-	-

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*Generated with 'base' gefitinib generalised gamma curve

ERG comments on fractional polynomial NMA

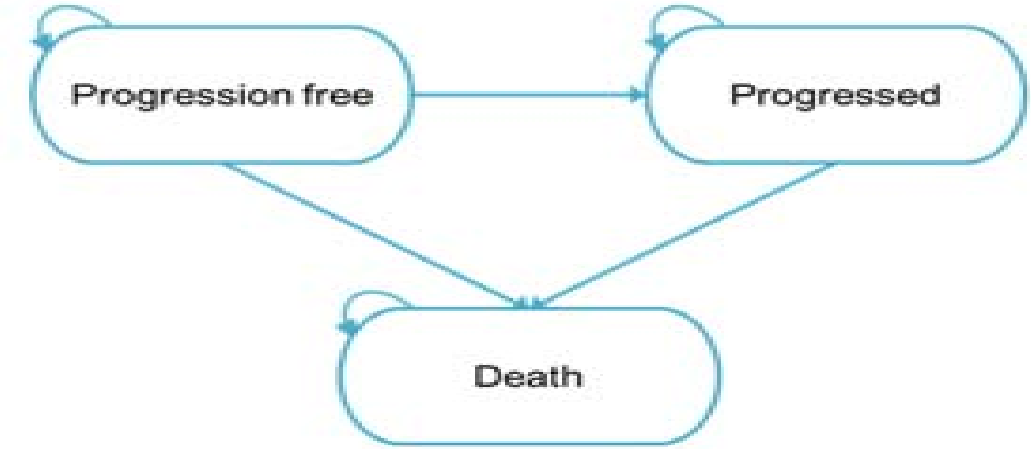
- It is unclear whether the company has concluded that there is a statistically significant difference between any of the comparators or not based on this analysis.
- Whilst they appear to be implemented correctly, fractional polynomials ay not be suitable for extrapolating because of their tendency to over-fit, as well as to be influenced by tail data. This is supported by the large number of models that the company was forced to exclude due to the implausible hazard ratios estimated.
- It is unclear whether the fractional polynomial analysis is suitable for extrapolation of PFS and OS in this appraisal.
- Given differences in baseline characteristics of included RCTs, the ERG considers that there is the potential that transitivity assumption is violated.

Additional analyses conducted by ERG

- Company does not present the results of the indirect treatment comparison between dacomitinib and afatinib, so the ERG conducted a fixed-effect NMA using surface under the cumulative ranking curve (SUCRA) to rank interventions
- For PFS: analyses based on SUCRA values suggest higher probability that dacomitinib is superior to afatinib but there is no significant difference between the two drugs (PFS HR 0.80; 95% CI 0.57-1.12).
- For OS: analyses based on SUCRA values suggest higher probability that dacomitinib is superior to afatinib but there is no significant difference between the two drugs (OS HR 0.88; 95% CI 0.61-1.29).
- Caution required because of potential transitivity assumption violation and proportional hazard assumption violation, so results are exploratory

Cost effectiveness

Company's 3 state partitioned survival model



Time horizon	15 years
Cycle length	28 days
Half cycle correction	Yes
Duration of treatment effect	Continued across model time horizon
Discount rate	3.5% per year
Perspective	NHS and Personal social services

ERG comment: The model does not capture survival following second and third-line treatment directly or separately. Instead, time in post-progression survival was derived using the area under the curve approach; the difference in the survival between overall and progression-free survival

Company used generalised gamma to extrapolate the gefitinib curve from ARCHER 1050 for PFS

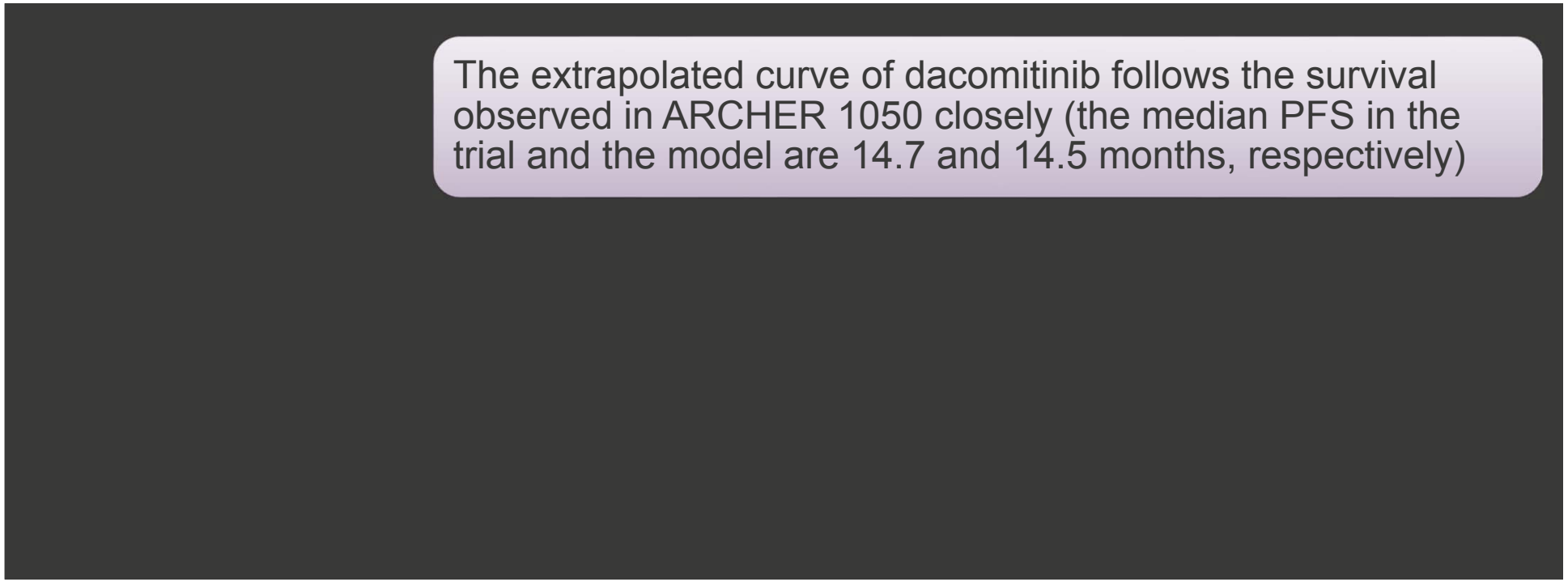
[redacted]

Distribution	Proportion PF at		
	2 years	3 years	5 years
Exponential	XXXX	XXXX	XXXX
Weibull	XXXX	XXXX	XXXX
Gompertz	XXXX	XXXX	XXXX
Log-logistic	XXXX	XXXX	XXXX
Log-normal	XXXX	XXXX	XXXX
Generalised gamma	XXXX	XXXX	XXXX

[redacted]

ERG comment: Extrapolation with generalised gamma may be too pessimistic beyond two years. ERG considered the log-normal and log-logistic models, and alternatively using a two-phase piecewise model (e.g. KM data followed by a parametric extrapolation), in later analyses.

Company generated PFS curves for dacomitinib, afatinib & erlotinib by applying time-varying hazard ratios to gefitinib curve



Company used generalised gamma to extrapolate the gefitinib curve from ARCHER 1050 for OS

[redacted]

Distribution	Proportion alive at		
	3 years	5 years	10 years
Exponential	XXXX	XXXX	XXXX
Weibull	XXXX	XXXX	XXXX
Gompertz	XXXX	XXXX	XXXX
Log-logistic	XXXX	XXXX	XXXX
Log-normal	XXXX	XXXX	XXXX
Generalised gamma	XXXX	XXXX	XXXX

ERG comment: Extrapolation with generalised gamma may be too pessimistic beyond two years. ERG considered the log-normal and log-logistic models, and alternatively using a two-phase piecewise model (e.g. KM data followed by a parametric extrapolation), in later analyses.

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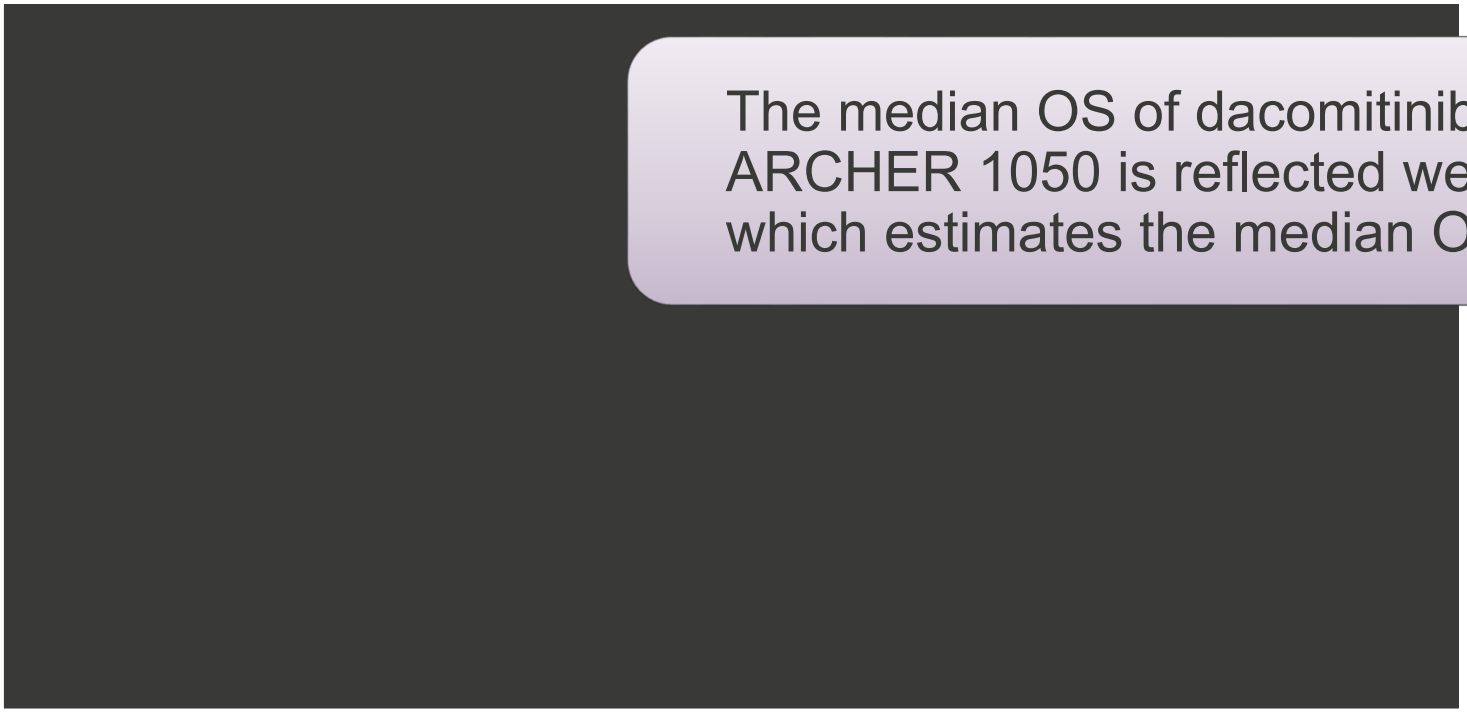

The median OS of dacomitinib of 34 months in ARCHER 1050 is reflected well in the extrapolation which estimates the median OS of 33.0 months

The company took a similar approach in their modelling of OS. They fitted a range of parametric models to the observed OS data from the gefitinib arm of ARCHER 1050 and selected a model based on the statistical goodness-of-fit, clinical plausibility and visual fit.

ERG's approach to extrapolating PFS

- The ERG considered company's approach to PFS pessimistic for all considered first-line treatments
- The ERG chose a different parametric curve (log-normal) for gefitinib that predicts more patients to be progression-free at 5 years than under the company's assumptions.
- The ERG chose a different fractional polynomial (P1=0.5, P2= 1) which improved the dacomitinib PFS extrapolation, but may still be pessimistic in the tail.
- The afatinib extrapolation remained implausible, and so the ERG resorted to modelling the proportion of progression-free afatinib patients as the mean of the proportions from the dacomitinib and gefitinib progression-free populations.

ERG's approach to extrapolating OS

- The company's OS modelling was thought to be too pessimistic for all interventions. ERG preferred not to rely on the fractional polynomial NMA extrapolation, and instead assumed a HR=1 from 36 months for OS across all comparators.
- The company's base-case assumptions suggests both pre-progression and post-progression benefit for dacomitinib. The ERG considered this unlikely to be plausible
- With the ERG's preferred PFS and OS assumptions, dacomitinib provides an OS and PFS benefit over the comparators, but has a shorter post-progression survival time

Company included subsequent therapies as a one-off cost in their base case

Subsequent treatment	Proportion of people receiving second- and third-line treatment	
	Second-line (%)[a]	Third-line (%)[b]
Osimertinib	56%	-
Platinum doublet chemotherapy	44%	56%
Docetaxel	-	44%

[a] model assumed that 71% of people who progressed received second-line treatment
[b] model assumed that 48% of original cohort received third-line treatment

- Included as the lowest cost per mg of any vial and complete vial sharing was assumed

ERG comment: ERG considered that the subsequent treatments following first-line treatment are appropriate. However, it was not clear what strategy/methods that were used to identify the EGFR-T790M mutation to guide subsequent treatment decisions (cost of biopsy not included)

Company inputs: utility values

	Mean utility (95% CI)	Source
Progression-free		
Dacomitinib	XXX XXXXXX	EQ-5D from ARCHER 1050
Gefitinib	XXX XXXXXX	EQ-5D from ARCHER 1050
Afatinib	XXX XXXXXX	Assumed equal to dacomitinib based on similarity of safety profile
Erlotinib	XXX XXXXXX	Assumed equal to gefitinib based on similarity of safety profile
Progressed disease		
All treatments	0.64	Based on the results of the SLR the study by Labbé provided the most appropriate values for this analysis

- Non-treatment specific PF values from ARCHER 1050 XXX and one-off disutility for adverse events explored in sensitivity analysis

ERG included disutilities for AEs and age

- The company didn't include disutilities for AEs or for aging
- The ERG did not accept that the inclusion of disutility decrements in the base-case would constitute ‘double counting’ because EQ-5D data only collected on one day of 28-day cycle so a large proportion of AEs would not have been captured
- The ERG supported the use of progression free utility value data from the trial, but felt that the progressed disease utility values should also be from the trial rather than the literature
- The ERG used all values from the trial and included disutility for aging and AEs

Resource use omissions

The ERG had concerns relating to costs that might have been excluded from the analysis:

- resource use and costs associated with unscheduled hospital admissions
- MRI scans for suspected brain metastases or cord compression
- costs associated with the diagnosis of T790M

The ERG considered that the costs included in the model are likely to be an underestimate of the true costs associated with managing/treating NSCLC.

Cost effectiveness results

Available cost-effectiveness results

Analysis	Results	Document or slide(s) in PMB
Company base case & scenario analyses	Dacomitinib **with confidential PAS discount** versus comparators (erlotinib, afatinib and gefitinib) **with PAS discounts** assumed by the company	PMB slides 45-48
Additional analyses from company	Dacomitinib and comparators (erlotinib, afatinib and gefitinib) **all at list prices**	Appendix M in appendix to the company submission
ERG base case & scenario analyses	Dacomitinib (**with PAS discount**) versus comparators (**at list prices**)	PMB slides 52-59
Additional analyses, applying ERG's suggested changes to company's base case	Dacomitinib **with confidential PAS discount** versus comparators (erlotinib, afatinib and gefitinib) **with PAS discounts** assumed by the company	PMB slides 50-51
Additional analyses, applying ERG's suggested changes to company's additional analyses	Dacomitinib and comparators (erlotinib, afatinib and gefitinib) **all at list prices**	ERG report, Section 6.1.2, Tables 59 to 61, pages 136 to 138

Company's deterministic results: dacomitinib (with PAS) versus comparators (with company assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Definitions: dominated: both more expensive and results in the same or poorer outcomes than the comparator; extendedly dominated: a treatment that is not cost-effective because another available treatment provides more units of benefit at a lower cost per unit benefit

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Company's probabilistic results: dacomitinib (with PAS) versus comparators (with company assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Definitions: dominated: both more expensive and results in the same or poorer outcomes than the comparator; extendedly dominated: a treatment that is not cost-effective because another available treatment provides more units of benefit at a lower cost per unit benefit

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Company's scenario analyses

Parameter	Company base case	Company scenario analysis
Progression free survival for gefitinib	• Curve for gefitinib: Generalised gamma • Survival for the other comparators from the FP NMA (P1=0.5; P2=1.5)	• Curve for gefitinib: Log-normal • Treatment effect based on conventional NMA
Overall survival for gefitinib	• Curve for gefitinib: Generalised gamma • Survival for the other comparators from the FP NMA (P1=0.5; P2=1.5)	• Curve for gefitinib: Log-logistic • Treatment effect based on conventional NMA
Progression-free survival utility value (1)	Treatment specific utility based on ARCHER 1050 and assumption ([redacted])	Non-treatment specific PFS utility value ([redacted]) based on ARCHER 1050. Progressed disease (0.64) from Labbé with AE disutilities
Progression-free survival utility value (2)	Treatment specific utility based on ARCHER 1050 and assumption ([redacted])	Non-treatment specific PFS utility value (0.77) based on Labbé. Progressed disease (0.64) from Labbé with AE disutilities.
Treatment beyond disease progression	No	Including treatment beyond disease progression

Company's scenario analysis results: dacomitinib (with PAS) versus comparators (with company assumed PAS)

Scenario	versus gefitinib		versus erlotinib		versus afatinib	
	ICER	% change	ICER	% change	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG's preferred base case assumptions

Parameter	Company base case	ERG base case
Progression free survival for gefitinib	• Curve for gefitinib: Generalised gamma • Survival for the other comparators from the FP NMA (P1=0.5; P2=1.5)	• Curve for gefitinib: Log-normal • Survival for the other comparators from the FP NMA (P1=0.5; P2=1) • Assumed PFS equal to mean PFS for dacomitinib and gefitinib from 36 months
Overall survival for gefitinib	• Curve for gefitinib: Generalised gamma • Survival for the other comparators from the FP NMA (P1=0.5; P2=1.5)	• Curve for gefitinib: Log-logistic • Survival for the other comparators from the FP NMA (P1=0.5;P2=1) • Assumed equal efficacy, on the hazard scale, from 36 months onwards
Post-progression utility value	0.64 from Labbé et al	Weighted-mean utility value from the ARCHER 1050 trial = XXX
Disutilities due to adverse events	Not included in the model	• Diarrhoea: -0.15 • Fatigue: -0.18 • ALT increased: 0 • Paronychia: -0.20 • Rash: -0.20
Age-related disutilities	No age-adjustment applied	Included from the study published by Ara and colleagues
Gefitinib PAS discount	Applied in Cycle 2	Applied in Cycle 3

Impact of ERG's preferred assumptions on company's base case (1): dacomitinib (with PAS) versus comparators (with company assumed PAS)

Scenario	versus gefitinib		versus erlotinib		versus afatinib	
	ICER	% change	ICER	% change	ICER	% change
Base-case	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib survival projection (PFS) using log-normal	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib survival projection (OS) using log-logistic	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

Impact of ERG's preferred assumptions on company's base case (2): dacomitinib (with PAS) versus comparators (with company assumed PAS)

Scenario	versus gefitinib		versus erlotinib		versus afatinib	
	ICER	% change	ICER	% change	ICER	% change
Disutilities associated with AEs	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Post-progression utility from ARCHER 1050	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Age-related disutilities	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Correction of the PAS applied to gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

Company's deterministic base-case results (run by ERG): dacomitinib (with PAS) versus comparators (list price)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	XXXX	XXXX	XXXX	XXXX	XXXX
Dacomitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Afatinib	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's deterministic base-case results: dacomitinib (with PAS) versus comparators (list price)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	XXXX	XXXX	XXXX	XXXX	XXXX
Dacomitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Afatinib	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's probabilistic base-case results: dacomitinib (with PAS) versus comparators (list price)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	XXXX	XXXX	XXXX	XXXX	XXXX
Dacomitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Afatinib	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's additional scenario analyses

Parameter	ERG base case	ERG scenario analysis
Progression free survival	• Curve for gefitinib: Log-normal • Survival for the other comparators from the FP NMA (P1=0.5; P2=1) • Assumed afatinib PFS equal to mean PFS for dacomitinib and gefitinib from **36 months**	Assumed afatinib PFS equal to mean PFS for dacomitinib and gefitinib from **55 months**
Overall survival	• Curve for gefitinib: Log-logistic • Survival for the other comparators from the FP NMA (P1=-0.5) • Assumed equal efficacy, on the hazard scale, from 36 months onwards	Assumed dacomitinib OS equal to that of afatinib
Post-progression utility value	Weighted-mean utility value from the ARCHER 1050 trial = XXX	0.64 from Labbé et al
NMA method for OS	Company's FP NMA, including: • Curve for gefitinib: Log-logistic • Survival for the other comparators from the FP NMA (P1=-0.5) • Assumed equal efficacy, on the hazard scale, from 36 months onwards	Company's traditional proportional hazards NMA

ERG's scenario analysis results (1): dacomitinib (with PAS) versus comparators (list price)

- **Log-normal** parametric curve for progression-free survival for gefitinib and equal efficacy assumed **from month 55**

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's scenario analysis results (2): dacomitinib (with PAS) versus comparators (list price)

- **Log-logistic** parametric curve for progression-free survival for gefitinib and equal efficacy assumed **from month 55**

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's scenario analysis results (3): dacomitinib (with PAS) versus comparators (list price)

- **Using utility values from Labbe et al.**

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	XXXX	XXXX	XXXX	XXXX	XXXX
Dacomitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Afatinib	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG's scenario analysis results (4): dacomitinib (with PAS) versus comparators (list price)

- Using results from the NMA for overall survival (HR constant)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	XXXX	XXXX	XXXX	XXXX	XXXX
Dacomitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Gefitinib	XXXX	XXXX	XXXX	XXXX	XXXX
Afatinib	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

End of life

- Company have not presented a case that dacomitinib meets the end of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current approved options are already associated with >24 month survival outcomes. In ARCHER 1050, the median OS for gefitinib was 26.8 months (95% CI: 23.7, 32.1).
There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment	As detailed in Section B.2.6.3.2, dacomitinib demonstrated a 7.3 month improvement in median OS and a 24% reduction in the risk of death compared with gefitinib in EGFR+ NSCLC. The median OS was 34.1 months (95% CI: 29.5, 37.7) in the dacomitinib arm compared with 26.8 months (95% CI: 23.7, 32.1) for gefitinib (HR: 0.760; 95% CI: 0.582, 0.993; 2-sided p-value=0.0438; stratified analysis).[34,40]

ERG comment: ERG considers that dacomitinib does not meet the end of life criteria

Equality & innovation

Equality

- The company, experts & professional organisation identified no equality issues

Innovation

- Company claim that dacomitinib is innovative → improves survival compared with gefitinib with a longer duration of effect with indirect treatment comparison further supporting survival improvement compared with other TKIs

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346)

Document B

Company evidence submission

7th December 2018

File name	Version	Contains confidential information	Date
ID1346_Dacomitinib_EGFR_NSCLC_ DocumentB_07DEC18.docx	**Final**	**No**	**7th December 2018**

Contents

Figures

Tables

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[1]

	Final scope issued by the NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated locally advanced or metastatic NSCLC with EGFR activating mutation(s).	As per final scope	Not applicable
Intervention	Dacomitinib	As per final scope	Not applicable
Comparator(s)	Afatinib, Erlotinib, Gefitinib	As per final scope	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Overall response rate • Duration of response • Adverse events of treatment, • Health-related quality-of-life	As per final scope	Not applicable
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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	The economic analysis does not include the cost of testing for EGFR status.	EGFR testing is standard UK clinical practice and all comparators require EGFR testing. Therefore, testing would

	Final scope issued by the NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 patient access schemes for the intervention or comparator technologies will be taken into account. The use of dacomitinib is conditional on the presence of EGFR mutation status. The economic modelling should include the costs associated with diagnostic testing for EGFR-TK mutation in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		continue irrespective of the outcome of this appraisal, and as it is required for all treatments in the decision problem, including the testing cost would not have any impact on the incremental results.
Subgroups to be considered	None	As per final scope	Not applicable
Special considerations including issues related to equity or equality	None	As per final scope	Not applicable

Abbreviations: AE = adverse event; del19 = exon 19 deletion; DoR = duration of response; EGFR = epidermal growth factor receptor; EGFR-TK = epidermal growth factor receptor tyrosine kinase; HRQoL = health-related quality of life; L858R = exon 21 Leu858Arg substitution; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year.

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with dacomitinib for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive advanced non-small-cell lung cancer (NSCLC) is presented in Table 2. The summary of product characteristics (SmPC) and European public assessment report for dacomitinib are presented in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Dacomitinib (Vizimpro®, Pfizer)
Mechanism of action	Dacomitinib is a second generation, selective and irreversible TKI that has activity against three members of the ErbB family of proteins (EGFR/HER-1, HER2 and HER4), providing improved efficacy compared with reversible first-generation TKIs.[2] Similar to first-generation TKIs, dacomitinib competes with ATP in the kinase domain of EGFR; however, dacomitinib covalently binds at the edge of the ATP binding site on Cys773 of EGFR via the Michael mechanism (addition of nucleophile to an α, β unsaturated carbonyl).[3] This results in dacomitinib irreversibly blocking ATP from binding to the kinase, rendering it inactive (thereby irreversibly inhibiting HER tyrosine kinase activity).[3] Dacomitinib is active against mutated EGFR, including the activating mutations in the kinase domain of EGFR that increase its activity. The two most common EGFR mutations are del19 and L858R substitution,[4] which account for approximately 85% of all EGFR mutations. Additionally, these EGFR mutations have been identified in approximately 5–50% of NSCLC cases, with marked variation in frequency depending on smoking history, gender, ethnicity and histological subtype.[2,5-9] Their presence can make the NSCLC cells more dependent on EGFR for growth and more sensitive to TKIs, and as a result, dacomitinib has demonstrated potent inhibitory activity in cell lines harbouring both of these.[3,4,10]
Marketing authorisation/CE mark status	A marketing authorisation submission to the European Medicines Agency was conducted in February 2018, for "[redacted]". The expected decision date from the Committee for Human Medicinal Products is [redacted].
Indications and	Dacomitinib (Vizimpro®) is expected to be indicated

UK approved name and brand name	Dacomitinib (Vizimpro®, Pfizer)
any restriction(s) as described in the SmPC	"[redacted]", aligned with the indication in this appraisal.
Method of administration and dosage	Dacomitinib has a convenient once-daily oral 45mg dose and is recommended until disease progression or unacceptable toxicity occurs. The tablets should be swallowed whole with water and can be taken with or without food at approximately the same time every day. Dacomitinib is available in three dose strengths – 45mg, 30mg and 15mg – making dose modifications to individualise treatment straightforward.
Additional tests or investigations	For the indication currently under consideration, patients need to be routinely tested for the presence of EGFR mutations. At present, EGFR testing is standard practice in England and Wales when making decisions about the first-line treatment of locally advanced or metastatic NSCLC.[11]
List price and average cost of a course of treatment	**List price:** [redacted] for 30 x 15mg or 30 x 30mg or 30 x 45mg capsules **Average cost of a course of treatment:** Based on the mean treatment duration of [redacted] months in the economic model the average cost of treatment is [redacted] at list price and [redacted] with the PAS applied.
Patient access scheme (if applicable)	A simple discount of [redacted] on the list price has been submitted to NHS England.

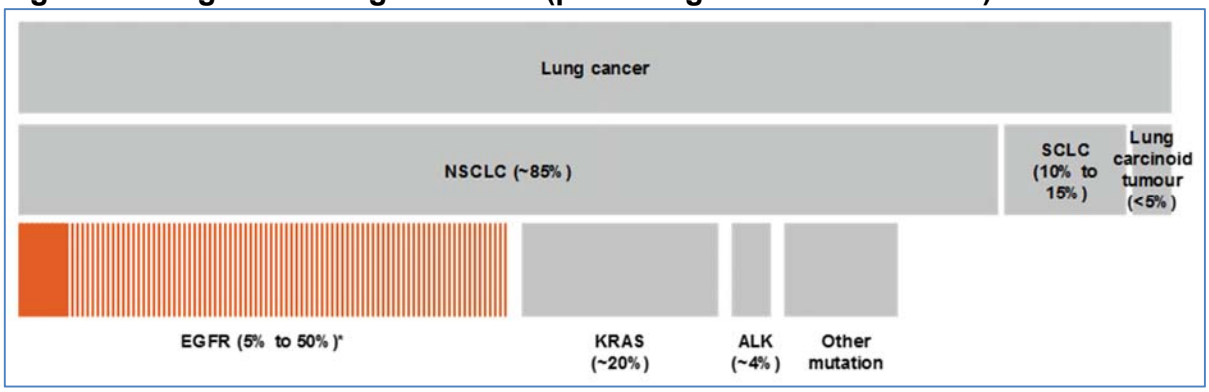
Abbreviations: ATP = adenosine triphosphate; del19 = exon 19 deletion; EGFR = epidermal growth factor receptor; HER = human EGFR related; L858R = exon 21 Leu858Arg substitution; NHS = National Health Service; NSCLC = non-small-cell lung cancer;
SmPC = summary of product characteristics; TKI = tyrosine kinase inhibitor; UK = United Kingdom.

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

B.1.3.1 Disease background

Lung cancer is the leading cause of cancer death worldwide and is responsible for over 35,000 deaths annually in the UK (2016).[12] Lung cancer is divided into two main groups: small-cell lung cancer (SCLC) and NSCLC, with the latter comprising approximately 85% of all lung cancer cases (Figure 1).[13] There are three main subtypes on NSCLC, including squamous cell carcinoma (25% of lung cancers), adenocarcinoma (40% of lung cancers), and large cell carcinoma (10% of lung cancers).[14]

Figure 1. Lung cancer segmentation (percentage of incident cases)[5-8]



*Variation in the rate of mutation reflects differences in smoking history, ethnicity, gender and histological subtype of the study population.
ALK = ALK receptor tyrosine kinase; EGFR = epidermal growth factor receptor; KRAS = KRAS proto-oncogene; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer.

Despite advances in the care of patients with advanced lung cancer, survival rates are poor. Patients diagnosed with lung cancer in England and Wales between 2010–2011 had one-year survival rates of 32.1% and five-year survival rates of 9.5%.[12] According to the 2017 National Lung Cancer Audit annual report from the Royal College of Physicians, patients with stage IV NSCLC, the 1-year survival rate for patients with distant metastatic disease (i.e. stage IV) in England and Wales was 15.5% compared with 81.7% for stage I.[15] Furthermore, despite advances in early detection, approximately 75% of patients with NSCLC still present with advanced disease at the time of diagnosis (stage III or IV).[16] Thereby, making extension of overall survival in these patients a key goal of current treatments.

The burden of symptoms among patients with advanced lung cancer is also considerable, with patients commonly experiencing disease-related symptoms at diagnosis such as cough, dyspnoea, pain, weight loss and night sweats.[17] Among patients with NSCLC, the symptomatic burden results in poor quality of life that deteriorates with disease progression.[18] Moreover, treatment with chemotherapy also has a negative impact on quality of life in this patients group, and is associated with an increase in symptoms such as neutropenia, fatigue, nausea and vomiting, appetite loss and constipation.[19] This highlights the importance of delaying disease progression for as long as possible in order to relieve symptoms, delay the use of chemotherapy and maintain quality of life.

The identification of mutations in lung cancer has led to the development of molecularly targeted therapy in order to improve survival outcomes in patients with advanced disease.[14] For example, a subgroup of patients with NSCLC have specific mutations in the epidermal growth factor receptor (EGFR) gene. Approximately 5–50% of NSCLC cases being characterised by EGFR alterations, depending on ethnicity, gender, smoking status and histological subtype (Figure 1),[5-8,20] with the highest rates of EGFR mutations observed in patients of Asian descent, female gender, non-smokers and patients with adenocarcinoma.[5,7]

Reported prevalence of EGFR mutations in adenocarcinoma (the most common lung cancer subtype), based on ethnicity, have ranged from approximately 11% in a study of French patients to 50% in a study of Japanese patients.[21,22] Based on a study of European patients, EGFR mutations were identified in approximately 14.1% of NSCLC cancer patients.[23] Prognosis for patients diagnosed with EGFR+ NSCLC is slightly better than general NSCLC, however outcomes are still extremely poor with a five-year survival rate of approximately 15% among patients with stage IV disease. [24]

The most common EGFR mutations are exon 19 deletion (del19) and exon 21 L858R substitutions (L858R), with these comprising 45–82% and 30% of EGFR mutations, respectively. Commonly referred to as ‘sensitising mutations’ as they confer sensitivity to TKIs.[25] These two mutations alone constitute approximately 80–90% of EGFR

mutations in adenocarcinomas. As a result of these mutations causing structural changes in the adenosine triphosphate (ATP) binding site of the intracellular domain of EGFR, TKIs such as dacomitinib have increased affinity to EGFRs.[25,26]

B.1.3.2 Clinical pathway and current guidelines

The most significant paradigm change of the past decade for NSCLC management was signalled by the use of TKIs in the first-line treatment of patients with targetable EGFR mutations.[27]

B.1.3.2.1 First-line therapy

In adult patients diagnosed with Stage III/IV NSCLC who test positive for EGFR mutation, NICE currently recommends the TKIs afatinib, erlotinib and gefitinib as first-line treatment options (Figure 2) according to technology appraisal (TA) guidance 192 (gefitinib), 258 (erlotinib), and 310 (afatinib).[11,28,29] Due to delayed confirmation of their EGFR status, patients diagnosed with Stage III/IV NSCLC may also receive non-targeted chemotherapy in the form of platinum-based doublet chemotherapy (this is comprised of a single, third-generation drug [docetaxel, gemcitabine, paclitaxel or vinorelbine], plus a platinum drug [either carboplatin or cisplatin]).[30] Furthermore, NICE recommends pemetrexed in combination with cisplatin as an option for the first-line treatment if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.[31]

B.1.3.2.2 Second-line therapy

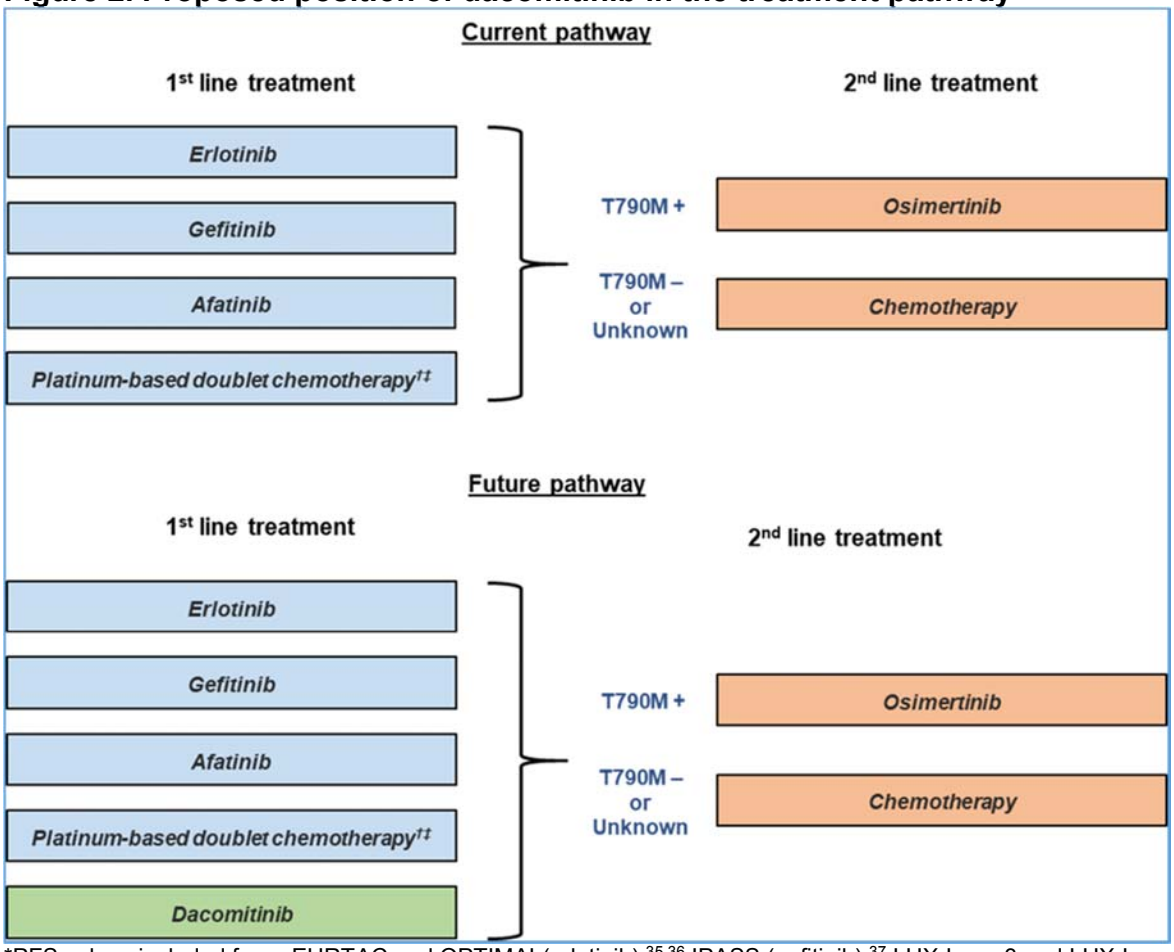
In adult patients diagnosed with Stage III/IV NSCLC with EGFR mutations, osimertinib is recommended by NICE as an option for use within the Cancer Drugs Fund in those whose disease has progressed after first-line treatment with a TKI and are T790M mutation-positive (Figure 2).[32] Patients that progress on TKIs but do not develop a T790M mutation may receive chemotherapy in the second-line (pemetrexed in combination with either cisplatin or carboplatin, or single agent chemotherapy [docetaxel, gemcitabine, paclitaxel or vinorelbine]; Figure 2).

B.1.3.3 Position of technology in the clinical pathway

The current licensed therapies for the first-line treatment of EGFR+ NSCLC are limited to first-generation TKIs erlotinib and gefitinib, and the second-generation TKI afatinib. As a new second-generation TKI, dacomitinib provides an important alternative to currently available therapies for first-line treatment of patients with EGFR+ NSCLC (Figure 2) and contributes to maintaining innovation in EGFR+ NSCLC to improve outcomes for patients. In particular, dacomitinib offers a new treatment option that improves efficacy and has a longer duration of effect versus gefitinib.[33,34] Additionally, network meta-analysis (NMA) results indicate that dacomitinib exhibits a consistent trend toward improved time to disease progression and survival when compared with current standard-of-care TKIs. Dacomitinib may therefore be a more suitable choice versus current standard-of-care TKIs for prolonging time on targeted treatment in first-line and delaying progression to second-line treatments such as chemotherapy or osimertinib.

Besides extending the armamentarium available for the first-line treatment of EGFR+ NSCLC beyond gefitinib, afatinib and erlotinib, NICE approval of dacomitinib in first-line setting is expected to not restrict treatment options in subsequent lines (Figure 2).

Figure 2. Proposed position of dacomitinib in the treatment pathway



*PFS values included from: EURTAC and OPTIMAL(erlotinib);[35,36] IPASS (gefitinib);[37] LUX-Lung 3 and LUX-Lung 6 (afatinib);[38,39]
platinum-based doublet chemotherapy (EURTAC);[35] dacomitinib (ARCHER 1050).[33]
†Patients with delayed confirmation of their EGFR-TK mutation-positive status may receive a platinum based doublet chemotherapy regimen in the first-line.
‡Chemotherapy treatment with pemetrexed in combination with either cisplatin or carboplatin is commonly used in clinical practice. For those people for whom treatment with a platinum drug is not appropriate, NICE clinical guidelines recommend single agent therapy with either docetaxel, gemcitabine, paclitaxel or vinorelbine.
Abbreviations: PFS = progression-free survival; T790M = secondary point mutation at amino acid position 790 that substitutes methionine for threonine.

B.1.4 Equality considerations

There are no known equality issues relating to the use of dacomitinib in patients with EGFR+ NSCLC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

B.2.1.1 Search strategy

A de novo systematic literature review (SLR) was conducted in October 2017, with an update conducted in August of 2018, to identify all relevant clinical data from the published literature regarding the clinical effectiveness of first-line treatments in EGFR+ NSCLC. The SLR was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care" and is described in Appendix D.1.

B.2.1.2 Study selection

The SLR search was originally conducted from a global perspective with interventions wider that those in the scope of this appraisal. The total number of included studies was then refined to the subset relevant to the decision problem of this appraisal.

B.2.2 List of relevant clinical effectiveness evidence

The SLR for clinical evidence identified two full peer-reviewed publications and three conference proceedings, from one randomised controlled trial (RCT) of dacomitinib in the population relevant to the decision problem, ARCHER 1050 (NCT01774721). ARCHER 1050 studied adult patients with EGFR mutation-positive advanced NSCLC that had not been previously treated. A summary of the clinical effectiveness data from ARCHER 1050 is presented in Table 3. A summary of the other studies identified by the SLR is presented in Appendix D.1.

Table 3. Clinical effectiveness evidence for ARCHER 1050

Study	ARCHER 1050 (2017)				
Study design	Phase III, randomised, multicentre, open-label, efficacy and safety study.				
Population	Subjects with locally advanced or metastatic newly diagnosed, treatment-naïve NSCLC or with recurrent NSCLC. All eligible patients had tumours that tested positive for at least one EGFR-activating mutation (either the del19 or L858R).				
Intervention(s)	Dacomitinib (N=227)				
Comparator(s)	Gefitinib (N=224)				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in model	ARCHER 1050 is the pivotal trial for dacomitinib as a first line treatment for advanced EGFR+ NSCLC. It therefore provides the most appropriate evidence which can be used in the model.				
Reported outcomes specified in the decision problem	**Primary outcome** • PFS (IRC assessment) **Secondary outcomes** • PFS (investigator assessment) • OS • ORR • DoR • AEs of treatment • TTF (IRC and investigator assessment) **Patient reported outcomes** • EQ-5D-3L • EORTC QLQ-C30 • EORTC QLQ-LC13				
All other reported outcomes specified in the scope	Not applicable				

Abbreviations: del19 = exon 19 deletion; DoR = duration of response; EGFR = epidermal growth factor receptor; EGFR+ = epidermal growth factor receptor mutation positive; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D-3L = European Quality of Life-5 Dimensions 3-level; IRC= Independent Review Committee; L858R = EGFR-TK mutation with an amino acid substitution at position 858 from a Leucine to an Arginine; NSCLC = non-small-cell Lung Cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST= Response Evaluation Criteria in Solid Tumours; TTF = time-to-treatment failure.

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

The pivotal trial ARCHER 1050 compared the efficacy and safety of first-line treatment with dacomitinib versus gefitinib in patients with newly diagnosed advanced or recurrent

(minimum of 12 months disease-free interval between completion of systemic therapy and recurrence of NSCLC required; patients with recurrent NSCLC must have only completed neoadjuvant/adjuvant therapy previously) EGFR+ NSCLC.[33,34,40] It is the only phase III head-to-head study to compare a second-generation TKI with a standard-of-care first-generation TKI in this disease indication in the first-line setting. In the pivotal phase III trials of other currently licensed TKIs, chemotherapy was the comparator in the first-line setting.[9,35,36,38,39,41-45] Results from ARCHER 1050 have been reported for the primary endpoint, PFS, key secondary endpoints, OS, overall response rate (ORR) and duration of response (DoR), patient-reported outcomes (PRO) and safety.[33,34] The sections below provide a detailed description of the study design and methodology of the pivotal trial ARCHER 1050 (see Table 4 for overview).

Table 4. ARCHER 1050 trial overview[33,34,40]

Trial number (acronym)	NCT01774721, DP312804 (ARCHER 1050)
Trial design	Randomised, open-label, head-to-head, phase III trial
Method of randomisation	Patients were randomised 1:1 to either dacomitinib or gefitinib according to a computer-generated code assigned by an interactive web response system. The randomisation procedure was stratified by race and EGFR mutation status.
Eligibility criteria	**Inclusion criteria:** • ≥18 years old (≥20 years in Japan and South Korea) • Newly diagnosed Stage IIIB/IV or recurrent NSCLC • Presence of EGFR mutation (del19 or L858R mutation), with or without concurrent T790M mutation • ECOG PS of 0-1 • EGFR mutation status testing prior to randomisation • Adequate renal, hepatic, and haematological function **Exclusion criteria:** • Mixed histology that included elements of small cell or carcinoid lung cancer • Mutation status other than del19 or L858R, with or without T790M mutation • History of brain metastases or leptomeningeal metastases • History of, or currently suspected, diffuse non-infectious pneumonitis or interstitial lung disease • Prior anti-cancer systemic treatment of early, locally advanced, or metastatic NSCLC • Uncontrolled medical conditions
Settings and locations where the data were	Multicentre (71 sites worldwide)

Trial number (acronym)	NCT01774721, DP312804 (ARCHER 1050)
collected	
Trial drugs and concomitant medications	**Trial drugs** • Dacomitinib 45 mg orally, once daily* • Gefitinib 250 mg orally, once daily **Concomitant medications** • CYP2D6 substrates • Strong amines • P-glycoprotein • Supportive care **Disallowed medications** • Drugs with a narrow therapeutic index and dependent on CYP2D6 metabolism • Previous anti-cancer systemic treatment of locally advanced, or metastatic NSCLC • Surgery
Outcomes used in the economic model or specified in the scope, including primary outcome	**Primary outcome** • PFS (IRC assessment) **Secondary outcomes** • PFS (investigator assessment) • OS • ORR • DoR • AEs of treatment
Pre-specified subgroup analyses	• Age (<65 years vs >65 years) • Sex • ECOG PS (0 vs 1) • Race (Asian vs non-Asian) • Smoking history (never vs former or current) • EGFR mutation (exon 19 deletion vs Leu858Arg)

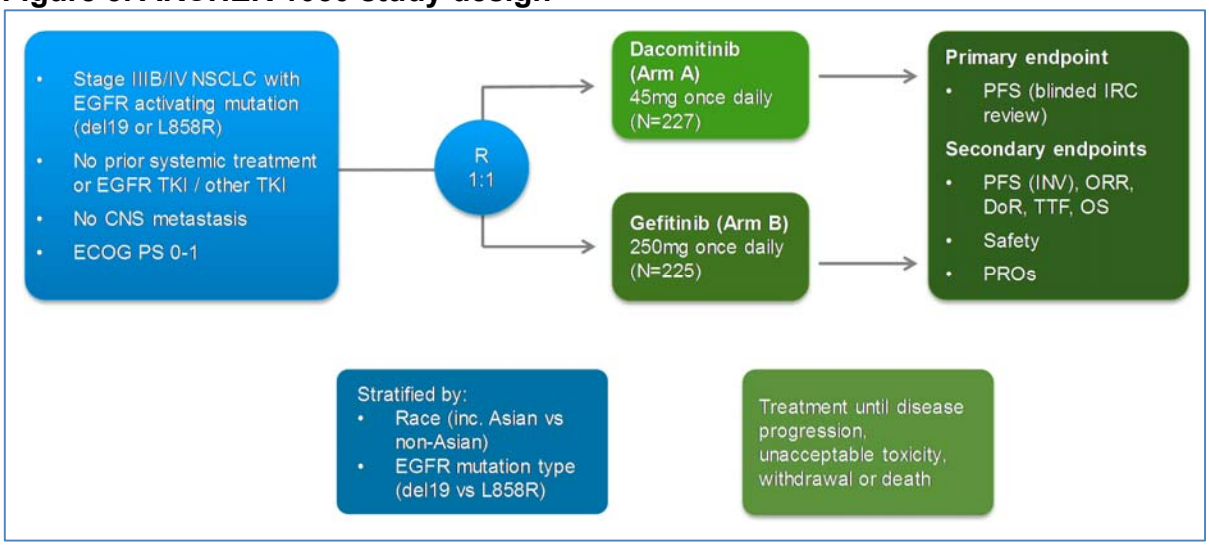
*Dose modifications were allowed to manage treatment-related toxicity that was not controlled by optimal supportive care, or not tolerated due to symptoms or interference with normal daily activities, regardless of severity.
Abbreviations: AE = adverse event; del19 = exon 19 deletion; CYP2D6 = cytochrome P450 2D6; DoR= duration of response; EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; L858R = exon 21 Leu858Arg substitution; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PS = performance status; T790M = secondary point mutation at amino acid position 790 that substitutes methionine for threonine.

B.2.3.1 Trial design

ARCHER 1050 was an international, randomised, phase III, open-label, multicentre study comparing the efficacy and safety of first-line treatment with dacomitinib versus gefitinib in patients with newly diagnosed advanced or recurrent EGFR+ NSCLC.[33,34,40] It is the only phase III head-to-head study that compared a second-generation TKI (dacomitinib) with a standard-of-care first-generation TKI (gefitinib) for first-line

treatment in this disease indication. An overview of the study design is provided in Figure 3.

Figure 3. ARCHER 1050 study design



Abbreviations: del19 = exon 19 deletion; DoR = duration of response; ECOG PS 0-1 = Eastern Cooperative Oncology Group Performance Status 0 or 1; EGFR = epidermal growth factor receptor; INV = investigator assessment; IRC = independent review committee; L858R = exon 21 Leu858Arg substitution; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = ratio; TKI = tyrosine kinase inhibitor; TTF = time to treatment failure.

Patients were randomised 1:1 to either dacomitinib or gefitinib and were treated up to a maximum duration of 48 months until disease progression, intolerable toxicities, withdrawal, death, or investigator decision dictated by protocol compliance, whichever occurred first. The randomisation procedure was stratified by race (Japanese versus mainland Chinese versus other East Asian versus non-Asian) and EGFR mutation status (del19 versus the L858R). A central Interactive Web Response System (IWRS) was used for patient enrolment at the time of informed consent and randomisation, as well as for drug management. Once patient eligibility was confirmed, patients were randomised by the IWRS according to a computer-generated random code to ensure that approximately an equal number of patients would be assigned to each treatment arm in the stratification categories of race and EGFR mutation status, based on their values as determined at randomisation.

B.2.3.2 Eligibility criteria

The ARCHER 1050 eligibility criteria are summarised in Table 5.

Table 5. ARCHER 1050 eligibility criteria

Inclusion criteria	Exclusion criteria
1. Patient consent 2. ≥18 years in age (≥20 years in Japan and Korea) 3. Presence of EGFR mutation (del19 or L858R) +/- concomitant T790M mutation 4. Newly diagnosed Stage IIIB/IV* or recurrent† NSCLC of adenocarcinoma histopathology and/or cytopathology or its variants 5. ECOG PS of 0 or 1 6. No prior treatment with systemic therapy for locally advanced or metastatic NSCLC 7. Radiologically measurable disease (RECIST version 1.1 criteria) 8. Adequate organ function, including: a. Estimated creatinine clearance ≥30 mL/min b. Urinary protein <3+ by urine dipstick c. Absolute neutrophil count ≥1500 cells/mm^3 d. Platelets ≥100,000 cells/mm^3 e. Haemoglobin ≥10.0 g/dL f. Bilirubin ≤1.5 x ULN g. AST and ALT ≤2.5 x ULN (≤5.0 x ULN if hepatic metastases) 9. Patients must have fulfilled one of the following (where applicable): a. Postmenopausal b. They or their partners were surgically sterile	1. Evidence of mixed histology and/or cytology that included elements of small cell or carcinoid lung cancer. Diagnosis of "NSCLC not otherwise specified", squamous, or mixed adeno-squamous lung carcinomas 2. Any other mutation other than del19 or L858R (presence of both concurrently was exclusionary) 3. History or evidence of brain metastases or leptomeningeal metastases 4. Any previous anti-cancer systemic treatment of locally advanced, or metastatic NSCLC (including EGFR-TKI or other TKIs)‡ 5. Any surgery (not including minor procedures), palliative radiotherapy, or pleurodesis ≤2 weeks of baseline 6. Any clinically significant gastrointestinal abnormalities that may have impaired intake, transit, or absorption of the study drug 7. Current enrolment in another therapeutic clinical study 8. Any psychiatric or cognitive disorder that would have limited the understanding or rendering of informed consent and/or compromise compliance with study requirements; or known drug abuse/alcohol abuse 9. History of, or currently suspected, diffuse non-infectious pneumonitis or ILD 10. Any history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption 11. Uncontrolled or significant cardiovascular disease

Inclusion criteria	Exclusion criteria
c. Agreed to use effective contraception d. Those with reproductive potential must have had a negative pregnancy test prior to starting study treatment 10. Willing and able to comply with study scheduled visits, treatment plans, laboratory tests, and other study procedures	12. Severely impaired (defined as Child-Pugh class C) hepatic dysfunction 13. Prior malignancy or evidence of another concurrent malignancy 14. Other severe acute or chronic medical condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results 15. Use of narrow therapeutic index drugs that were CYP2D6 substrates or a product with known effects on PK of gefitinib in reference to package insert from screening to randomisation.

*Based on Union for International Cancer Control staging system version 7 and the WHO/IASCLHistologic Classification of Lung Cancer Criteria.
†Minimum of 12 months disease-free interval between completion of systemic therapy and recurrence of NSCLC required.
‡Exceptions included: palliative radiotherapy to lesions that were not followed for tumour assessment on this study (i.e. non-target lesions); completed neoadjuvant/adjuvant chemotherapy and/or combined modality chemotherapy/radiation therapy where there was ≥12-month disease-free interval between completion of systemic therapy and recurrence of NSCLC.
Abbreviations: ALT = alanine aminotransferase. AST = aspartate aminotransferase; CYP2D6 = cytochrome P450 2D6; del19 = exon 19 deletion; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IASCL = International Association of Study of Lung Cancer; ILD = interstitial lung disease; L858R = exon 21 Leu858Arg substitution; NSCLC = non-small-cell lung cancer; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumours; T790M = secondary point mutation at amino acid position 790 that substitutes methionine for threonine; ULN= upper limit of normal; WHO = World Health Organisation.

B.2.3.3 Settings and locations where the data were collected

The study was conducted at 71 study sites worldwide.[33] Countries with study sites that randomised patients into the study were China (21 sites), Hong Kong (2 sites), Italy (13 sites), Japan (10 sites), Poland (3 sites), Republic of Korea (5 sites), and Spain (17 sites).

B.2.3.4 Trial drugs and concomitant medications

B.2.3.2.1 Treatments administered

Patients received open-label study treatment and were randomized in a 1:1 ratio to one of the following two treatment arms:

- Investigational treatment: dacomitinib 45 mg orally once daily
- Comparator treatment: gefitinib 250 mg orally once daily.

Randomised patients received continuous daily oral dosing of study treatment for up to 48 months from the date of first dosing or until one of the following criteria was met (whichever occurred first):

- Disease progression
- Initiation of a new anti-cancer therapy
- Unacceptable toxicities
- Global deterioration of health-related symptoms
- Pregnancy
- Withdrawal of consent
- Loss to follow-up

- Death
- Investigator decision dictated by protocol compliance
- Study termination or patient completion of 48 months from first dosing date.

B.2.3.2.2 Dose modifications

Dacomitinib dose reductions could take place to manage treatment-related toxicity that was not controlled by optimal supportive care, or not tolerated due to symptoms or interference with normal daily activities, regardless of severity. Three dosage strengths were available to accommodate two levels of dose reduction (Table 6).

If, after a dose reduction, a patient subsequently tolerated treatment well at that level in the judgment of the investigator, the dose could be increased to the next dose level. If a patient could not tolerate treatment after dose reduction to 15 mg, treatment was discontinued.

Table 6. Dacomitinib dose reduction levels

Dose Level	Dose (once daily)
Recommended starting dose	45 mg
First dose reduction	30 mg
Second dose reduction	15 mg

For patients in either treatment arm, study treatment could be interrupted for Grade 3, Grade 4, or intolerable Grade 2 toxicity (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Upon recovery to Grade 2 or baseline, and in the clinical judgment of the investigator with the agreement of the patient, the treatment could be resumed as in Table 7.

Table 7 Approach to resuming dacomitinib or gefitinib treatment after dose interruption

Medication	Dose modifications
Dacomitinib	• For interruption due to Grade 3 or intolerable Grade 2 toxicity, treatment could be resumed at the same dose level or reduced per protocol. • For episodes of Grade 4 toxicity, reduction to the next dose level was mandated.
Gefitinib	• For interruption due to Grade 3, Grade 4, or intolerable Grade 2

Medication	Dose modifications
	toxicity, treatment could be resumed with daily or every other day dosing. • If gefitinib dosing was resumed with every other day dosing after interruption, all attempts were made to return the patient to once-daily dosing, if possible. • If dose was interrupted due to treatment-related toxicity, the dosing could be resumed at a temporarily reduced frequency (i.e. every other day dosing rather than daily dosing). If the patient was tolerating gefitinib at the every other day dosing, the investigator could determine whether to re-escalate the dosing back to daily dosing.

For patients whose study treatment (in either arm) had been interrupted due to treatment-related toxicity as described above, treatment was permanently discontinued if they failed to recover within 2 weeks of dose interruption, unless it was agreed with the sponsor that the patient could resume treatment after a lapse of >2 weeks.

B.2.3.2.3 Prior and concomitant medications

Table 8 provides an overview of the procedures undertaken for prior and concomitant medications.

Table 8. Prior and concomitant medications and procedures

Medication	Procedure description
CYP2D6 substrates	For the dacomitinib arm, the use of concomitant medications that were highly dependent on CYP2D6 for metabolism required consideration of both the therapeutic index and the degree of CYP2D6 metabolism (list not exhaustive): • For drugs highly dependent on CYP2D6 metabolism, dose reduction was based on substrate sensitivity to CYP2D6 metabolism. • For drugs partly dependent on CYP2D6-mediated metabolism, with a high likelihood of supratherapeutic exposure (i.e. exposure levels greater than would be used in actual treatment of a medical condition) in combination with dacomitinib; clinical monitoring was required and dose-reduction was necessary. • Prodrugs, or drugs with highly active metabolites were replaced by an alternative within the therapeutic class which produces metabolites with lower or no activity.
Lidocaine	Lidocaine exposures could significantly increase in the presence of strong amines, such as dacomitinib. Lidocaine could be used systemically, but clinical monitoring (including telemetry) was recommended.
P-glycoprotein	Concurrent administration of drugs that were P-glycoprotein substrates (e.g. digoxin) and had a narrow therapeutic index were monitored for exaggerated effect and/or toxicities.

Medication	Procedure description
Acid-reducing agents	Concomitant use of proton pump inhibitors and H_2 antagonists with dacomitinib were avoided, if possible. The use of short-acting antacids was permitted.
Supportive care	Subjects who were receiving bisphosphonates to control pain/bone metastases as recommended in current guidelines for bone-targeted therapy could continue while on the study. • However, initiation of bisphosphonate therapy after randomisation was considered progression of disease unless otherwise previously agreed. Palliative radiotherapy for painful bony lesions was permitted providing that: • Lesions were known to be present at the time of study entry. • Clear indication that palliative radiotherapy was needed for better palliation than alternative analgesic options and not due to disease progression.

Abbreviations: CYP2D6 = cytochrome P450 2D6; H_2 = Histamine 2.

B.2.3.2.4 Disallowed medications

Subjects who previously received any of the following treatments were not included in the trial:

- Drugs dependent on cytochrome P450 2D6 (CYP2D6) metabolism with narrow therapeutic index including:
    - Procainamide
    - Pimozide
    - Thioridazine.
- Any previous anti-cancer systemic treatment of locally advanced, or metastatic NSCLC were not allowed (including EGFR-TKI or other TKIs). Exceptions included:
    - Palliative radiotherapy to lesions that were not followed for tumour assessment on this study (i.e. non-target lesions).

- Completed neoadjuvant/adjuvant chemotherapy and/or combined modality chemotherapy/radiation therapy where there was ≥12-month disease-free interval between completion of systemic therapy and recurrence of NSCLC.

- Any surgery (not including minor procedures e.g. lymph node biopsy), palliative radiotherapy or pleurodesis within 2 weeks of baseline assessments.

B.2.3.5 Outcomes used in the economic model or specified in the scope

Table 9 provides an overview of all the outcomes used in the economic model and/or specified in the scope of this submission.

Table 9. Outcomes included in the economic model or specified in the submission scope

Outcome	Definition
Primary outcome	
PFS (IRC)	Time from randomisation to the date of disease progression (per RECIST version 1.1 criteria) as determined by blinded IRC review or death due to any cause, whichever occurred first. The length of PFS was calculated as follows: • PFS (months) = [(progression/death date [censor date] – randomization date) + 1] /30.4375 Documentation of progression must have been by objective disease assessment. Objective disease assessments were based on RECIST version 1.1 guidelines.
Secondary outcomes	
PFS (IA)	Defined in the same way as the primary endpoint, except that the objective disease assessment was based on investigator assessment.
OS	Time from randomisation to the date of death from any cause. The length of OS was calculated as follows: • OS (month) = [death date or last known alive date – randomisation date + 1]/30.4375.
ORR	ORR was defined as the proportion of patients with a BOR* characterised as either a CR or PR (per RECIST version 1.1 criteria) relative to the total number of patients. ORR analysis was conducted by both blinded, IRC analysis and investigator assessment.
DoR	Time from the first documentation of objective response (CR or PR, whichever occurred first) to the date of disease progression or death from any cause, whichever occurred first. DoR was calculated for the subgroup of patients with an objective tumour response. DoR analysis was conducted by both blinded, IRC analysis and investigator assessment. DoR was calculated as follows: • DoR (months) = [progression/death date (censor date) – date of first documentation of CR or PR + 1]/30.4375.
PRO outcomes	
EORTC QLQ-C30 and EORTC QLQ-LC13	Evaluated using the EORTC QLQ-C30† questionnaire and its corresponding module for lung cancer, EORTC QLQ-LC13‡. For the EORTC QLQ-C30, higher scores for the five functional scales and the global QoL scale indicated higher level of functioning or global QoL, whereas for symptom scales/single items, a higher score indicated a higher level of symptoms or problems. The EORTC QLQ-C30 was scored according to its scoring manual. The scoring approach for the EORTC QLQ-LC13 was identical to that for the symptom scales/single items of the QLQ-C30.[46] Each scale of the EORTC QLQ-C30 and the EORTC QLQ-LC13 were transformed so that scale scores ranged

Outcome	Definition
	from 0 to 100. Patients were classified as “improved,” “stable,” or “deteriorated” according to a 10-point change (threshold perceived as being clinically meaningful).
EQ-5D	Assessed using the EQ-5D questionnaire which was collected day 1 of cycle 1 which provided the baseline assessment of PROs, days 8 and 15 of cycle 1 and at the beginning of each cycle afterwards (up to a total of 41 cycles), at the end of treatment and at a single post-progression follow-up.. The EQ-5D instrument consists of the following: • *EQ-5D descriptive system:* measures a subject’s health state on five dimensions which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions is scored by the patient on a 3-level scale (1=no problem, 2=some problem, and 3=extreme problem). • *EQ-VAS:* assesses the respondent’s self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D was scored according to its scoring manual. Each dimension of the health state profiles included the proportion of patients reporting each of the levels noted above. A health utility index score was calculated using the standard algorithm provided in the manual.
Time to deterioration	Time to deterioration was a composite endpoint defined as the time from randomisation to the first time the subject’s score shows a 10 point or higher increase in several symptoms based on assessment by the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments. These included: • Pain in chest; arm/shoulder (EORTC QLQ-LC13) • Dyspnoea (EORTC QLQ C30) • Dyspnea sub-scale (EORTC QLQ-LC13) • Fatigue (EORTC QLQ-C30) • Cough (EORTC QLQ-LC13). Symptom deterioration was defined as a score increase of 10 points or higher (threshold that subjects perceive as being clinically significant) held for at least two consecutive cycles.
Safety outcomes	
AEs	Characterised by type, frequency, severity (as graded by NCI CTCAE version 4.0 criteria), timing and relationship to treatment on each arm, laboratory abnormalities observed, and left ventricular imaging observed. AEs were coded and classified using the MedDRA version 19.1 classification system.
TEAE	An AE was considered treatment-emergent if: • The event occurred after the start of study treatment and <28 days after final dose of study treatment and was not seen prior to the start of treatment. • The event was seen prior to the start of treatment but increased in NCI CTCAE version 4.0 grade after the

Outcome	Definition
	start of treatment but <28 days after final dose of study treatment. Disease progression was not considered a TEAE unless the subject died of disease <28 days after discontinuation of treatment.
Treatment-related AEs	Treatment-related AEs were defined as TEAE with cause possibly, probably or definitely related to treatment as judged by the investigator.

*BOR per RECIST version 1.1 was defined as the best response recorded from the time of randomisation until disease progression.
†The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global health status/quality of life, disease/treatment-related symptoms (fatigue, pain, nausea/vomiting, dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease.
‡The EORTC QLQ-LC13 module includes questions specific to the disease associated symptoms (dyspnea, cough, haemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy, and alopecia), and analgesic use of lung cancer subjects.
Abbreviation: AE = adverse event; BOR = best overall response; CR = complete response; DoR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D = European Quality of Life-5 Dimensions; EQ-VAS = European Quality of Life visual analogue scale; HRQoL = health-related quality of life; IRC = independent review committee; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours; TEAE = treatment-emergent adverse event; TTF = time to treatment failure.

B.2.3.6 Summary of the baseline characteristics of trial participants

Demographic and baseline clinical characteristics are summarized for all patients in the intent-to-treat (ITT) population in Table 10. Demographic characteristics and baseline clinical characteristics were generally well balanced between the treatment groups in the ITT population.

Although there was some differences in gender (females comprised 64.3% and 55.6% of the dacomitinib and gefitinib arms, respectively), this was not unexpected as EGFR mutations in NSCLC are more common among females.[5] Additionally, the study population were predominantly patients of Asian ethnicity; the proportion of non-Asian patients in the dacomitinib and gefitinib arms was 25.1% and 21.8%, respectively. The high Asian component in ARCHER 1050 is partly due to Asian populations having a higher incidence of EGFR mutations and thus having more eligible trial participants.[5,8] Therefore, it is common for all or a high proportion of patient to be of Asian decent in studies conducted in this setting.[47].

Table 10. Baseline characteristics of participants in the ARCHER 1050 trial (ITT Population)

Baseline characteristic	Dacomitinib N=227	Gefitinib N=225
Gender		
Male, n (%)	81 (35.7)	100 (44.4)
Female, n (%)	146 (64.3)	125 (55.6)
Age (years)		
Median	62.0	61.0
Mean (standard deviation)	61.2 (11.26)	60.9 (10.17)
Range	28-87	33-86
<65, n (%)	133 (58.6)	140 (62.2)
≥65, n (%)	94 (41.4)	85 (37.8)
≥65–<75, n (%)	[redacted]	[redacted]
<75, n (%)	[redacted]	[redacted]
≥75, n (%)	[redacted]	[redacted]
Race		
White, n (%)	56 (24.7)	49 (21.8)
Black, n (%)	1 (0.4)	0
Asian, n (%)	170 (74.9)	176 (78.2)
Japanese, n (%)	40 (17.6)	41 (18.2)

Baseline characteristic	Dacomitinib N=227	Gefitinib N=225
Mainland Chinese, n (%)	114 (50.2)	117 (52.0)
Other East Asian, n (%)	16 (7.0)	18 (8.0)
Weight (kg)		
Median	59.50	60.00
Mean (standard deviation)	60.13 (12.841)	61.20 (10.784)
Range	30.0-130.0	36.9-93.5
Smoking status		
Never smoked, n (%)	147 (64.8)	144 (64.0)
Ex-smoker, n (%)	65 (28.6)	62 (27.6)
Smoker, n (%)	15 (6.6)	19 (8.4)
ECOG performance status		
0, n (%)	75 (33)	62 (28)
1, n (%)	152 (67)	163 (72)
Disease stage at screening		
Stage IIIB, n (%)	18 (8)	16 (7)
Stage IV, n (%)	184 (81)	183 (81)
Unknown*, n (%)	25 (11)	26 (12)
EGFR mutation†		
del19‡, n (%)	134 (59)	133 (59)
L858R§, n (%)	93 (41)	92 (41)

*Newly diagnosed with Stage IV at time of study entry.
†EGFR mutations (at randomisation) were identified from tumour specimens.
‡At randomisation, two patients in the gefitinib group (and none in the dacomitinib group) had the Thr790Met mutation.
§At randomisation, two patients in the dacomitinib group (and none in the gefitinib group) had the Thr790Met mutation.
Abbreviations: del19 = exon 19 deletion; ECOG = Eastern Cooperative Oncology Group; L858R = exon 21 Leu858Arg substitution.

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

B.2.4.1 Objective, sample size and analysis sets

Table 11. Primary objective, sample size and analysis sets of the ARCHER 1050 trial[40]

	Objective / hypothesis	Sample size	Analysis sets
ARCHER 1050	The primary objective of the ARCHER 1050 trial was to demonstrate that dacomitinib is superior to gefitinib with respect to PFS (determined by blinded IRC review), in patients with EGFR+ advanced NSCLC.	The primary endpoint of the study was PFS as determined by blinded IRC review. It was estimated that approximately 440 randomised patients and ≥256 PFS events would be required to achieve a 90% power to detect a ≥50% improvement in PFS (i.e. improvement in median PFS from 9.5 to at ≥14.3 months) in patients randomised to receive dacomitinib versus those randomised to receive gefitinib (i.e. HR ≤0.667, 1-sided stratified log-rank test α=0.025; 1:1 randomization; and censoring rate ~42%). At the end of the study, the primary analysis tested the HR (dacomitinib/gefitinib) ≥1 versus <1 using a 1-sided stratified log-rank test. The study was considered a positive study if at the time of the final PFS the 1-sided stratified log-rank test was significant at the 0.025 level. Final OS analysis was pre-specified to occur after ≥201 deaths.[34]	**ITT Population** Treatment assignment designated according to initial randomisation, regardless of whether patients received study treatment or received a different treatment from that to which they were randomised. Primary population for evaluating efficacy endpoints and patient characteristics. **AT and Safety Population** All patients who received ≥1 dose of study treatment. Patients were analysed in the treatment group according to study treatment received. Primary population for evaluating treatment administration and safety. **PRO Analysis Set** Patients from the AT Population who started treatment, completed a baseline PRO assessment, and completed ≥1 post-baseline PRO assessment after the first dose.

Abbreviations: AT = as-treated; EGFR+ = epidermal growth factor receptor mutation positive; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; PRO = patient-reported outcome; OS = overall survival.

B.2.4.2 Censorship and missing data management

The censorship methodology for the primary and secondary outcomes of ARCHER 1050 are summarised in Table 12.

Table 12. Censorship for primary and secondary outcomes in the ARCHER 1050 trial[48]

Outcome	Censorship description
Primary outcomes	
PFS (IRC)	Patients last known to be alive, progression-free, and who had a baseline and ≥1 on-study disease assessment were censored to new (non-protocol) anti-cancer treatment status as follows: • Did not start a new anti-cancer treatment: censored at the date of the last objective disease assessment that verified lack of disease progression. • Started new anti-cancer treatment: censored at the date of the last objective disease assessment documenting no progression prior to the start of the new treatment. Patients with inadequate baseline disease assessment were censored at the date of randomisation. Patients with no on-study disease assessments were censored at the date of randomisation unless death occurred prior to the first planned assessment. Patients who progressed after starting a new anti-cancer treatment were censored at the date of the last objective disease assessment documenting no progression prior to the start of the new treatment. Patients with documentation of progression or death after an unacceptably long interval (>16 weeks, usually ≥2 missed or indeterminate assessments) since the last tumour assessment were censored at the time of the last objective assessment documenting no progression.
Secondary outcomes	
OS	In the absence of confirmation of death, survival time was censored at the last date the subject was known to be alive. Subjects who lacked data beyond enrolment had their survival times censored at randomisation.
PFS (IA)	Approach to censorship was the same as outlined for primary endpoint.
DoR	Approach to censorship was the same as outlined for primary endpoint.
TTF	Patients last known not to have failed treatment were censored at the date of the last objective disease assessment documenting no progression. Patients last known not to have failed treatment and with no on-study disease assessments were censored at the date of randomisation.
PRO outcomes	For time to deterioration in PRO symptoms, subjects were censored at the last time when they completed an assessment for pain, dyspnoea, fatigue or cough if they have not deteriorated.

Abbreviations: AT = as-treated; EGFR+ = epidermal growth factor receptor mutation positive; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome.

The approach to managing missing data is summarised in Table 13.

Table 13. Missing data management overview

Category	Missing data management
Missing data in efficacy endpoints	
Baseline tumour assessment	If baseline tumour assessment was inadequate the subject was unable to be assessed for RECIST response. If there were no assessments after dosing, response was indeterminate unless progression was documented or determined by blinded IRC review or investigator assessment ≤12 weeks. Inadequate baseline assessment included: • Not all required baseline assessments were done. • Assessments were done outside the required window. • Measurements were not provided for one or more target lesions. • One or more lesions designated as targeted were not measurable.
Objective status at each tumour assessment	If measurements for ≥1 target lesions were missing and disease did not qualify as progression or symptomatic deterioration, the objective status for that evaluation was indeterminate. If non-target disease was not assessed, then a subject who qualified for an objective status of CR based on target disease was classified as PR. Otherwise, missing non-target disease assessments generally did not affect response determination, subject to review by blinded IRC review or investigator assessment. If a target lesion was documented as too small to measure without unequivocal complete disappearance of the lesion, a default value of 5mm was assigned and the objective status was assigned accordingly.
BOR/ORR	Subjects without a response in whom treatment failed (death, symptomatic deterioration, discontinuation of treatment for other reason) prior to objective progression were assumed to be non-responders. An exception was made for subjects who discontinued treatment with objective stable disease and, subsequently, had assessment documenting response prior to starting a new treatment. These subjects were classified as responders. Subjects with unknown best response (all objective statuses prior to progression were indeterminate and progression >12 weeks after randomisation) were assumed to be non-responders. For subjects with indeterminate objective status prior to progression, but progression occurred ≥12 weeks after randomisation, best response was “progressive disease”.
Time-to-event endpoints	For time-to-event endpoints, missing dates were handled as described in the “Missing data in dates” section of this table. Subjects who did not experience the event of interest were censored.
PRO outcomes	Subjects with missing baseline scores or with baseline scores, but with no follow-up scores, were not assessable for change from baseline and time to deterioration analyses. For the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D assessments, in cases where two answers were given to one item, the more severe answer was counted.

Category	Missing data management
	If less than half of the constituent items on the EORTC QLQ-C30 and EORTC QLQ-LC13 were answered for a multi-item subscale, that subscale was considered missing. Single item subscales were considered missing if the constituent item was incomplete. On the EQ-5D, questions not answered were considered as missing items, and were neither imputed nor utilised.
Missing data in safety endpoints	
Safety endpoints	The percentage of subjects with an AE were calculated using the number of AT subjects as the denominator. Therefore, no subjects in the AT population were excluded from AE displays. The denominator for summary tables for each laboratory parameter were all subjects in the AT population with at least one evaluable cycle for that parameter. Different laboratory parameters had different denominators, depending on the number of evaluable subjects for each parameter. An evaluable cycle was any cycle with at least one assessment of that parameter. Therefore, subjects with no assessments of a particular laboratory parameter were not included in the analysis of that parameter.
Missing data in dates	
Efficacy analyses	The following conventions for partial dates was applied for efficacy analyses: • If the day of the month was missing for any date used in a calculation, the first day of the month was used to replace the missing date unless the calculation resulted in a negative time duration (e.g. date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration was used. • If the day of the month and the month was missing for any date used in a calculation, the 1st of January was used to replace the missing data. • For OS and PFS, if these conventions produced a date that resulted in a negative time to event, then the time to event was re-set to 1 day.
AEs	Missing dates in AEs were inputted using the following approach: • For the start date, if the day of the month was missing, the first day of the month was used to replace the missing date. If both day and month were missing, the 1st of January of the non-missing year was used. • For the stop date, if the day of the month was missing, the last day of the month was used to replace the missing date. If both day and month were missing, December 31 of the non-missing year was used. If the start date was missing for an AE, the AE was considered to be treatment-emergent unless the collection date was prior to the treatment start date.

Abbreviations: AE = adverse event; AT = as-treated; BOR = best overall response; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D = European Quality of Life-5 Dimensions; IRC = independent review committee; ORR = objective response rate; OS = overall survival; PFS= progression-free survival; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours.

B.2.4.3 Statistical analysis

B.2.4.3.1 Primary outcome

PFS based on blinded, IRC review were summarised in the ITT population. Estimates of the PFS curves obtained from the Kaplan-Meier method were displayed graphically. The median (and other quartiles) event time and corresponding 2-sided 95% CI for the median were provided for each treatment arm. Probability of PFS at clinical meaningful time points were estimated and presented with 95% CI based on the Greenwood method.

Differences in PFS between treatment arms were analysed by the Cox Regression (i.e. for estimated HR and its 95% CI) and log rank test (1-sided, α=0.025) for 1-sided p-value, both stratified by race and EGFR mutation status based on their values at randomisation.

HRs and p-values for PFS in subgroups were estimated from the unstratified Cox regression model and the unstratified log-rank test, respectively. The proportions of patients achieving objective responses were compared between groups using Pearson's χ^2 test.

B.2.4.3.2 Secondary outcomes

A log-rank test, stratified by EGFR mutation status at randomisation and race, was used to assess PFS based on investigator assessment, OS, TTF, and DoR. A Cox proportional hazards model, stratified by EGFR mutation status and race as used in the log-rank test, was used to calculate HRs and 95% CI for OS and TTF in the ITT population and DoR among the objective responders in the ITT population. P-values were determined by the log-rank test with adjustment for the same stratification factors. All p values were 2-sided.

ORR was summarised along with the corresponding exact 2-sided 95% CI using a method based on the Binomial distribution. The Cochran-Mantel-Haenszel test stratified by race and EGFR mutation status were used to compare ORR between the 2 treatment arms. The relative risk ratio estimator were used to contrast the

treatment effects on response rates. A point estimate and a 2-sided 95% CI were calculated using the normal approximation.

B.2.4.3.3 Patient-reported outcomes

Repeated measures mixed-effects modelling was used to compare the two treatment groups with respect to the overall change from baseline scores on the EORTC QLQ-C30 and EORTC QLQ-LC13 scales using two-sided tests that were not adjusted for multiple testing.

The Kaplan-Meier method was used to estimate the time-to-deterioration of symptoms and compared between treatment groups using the Hochberg-adjusted log-rank test. A sensitivity analysis was conducted without the condition of two consecutive cycles of deterioration, using the same methods and summary statistics.

B.2.4.3.4 Final and interim analyses

The final analysis of primary endpoint, PFS, was performed after the maturity of the primary endpoint, and after all subject data had been submitted and cleaned. At the time of final analysis of the primary endpoint, a gate-keeping procedure was used for hypotheses testing in a hierarchical approach to control the family-wise error rate for the analyses of primary endpoint, and secondary endpoints of ORR based on blinded IRC review and OS.

An interim analysis was not planned or performed for the primary endpoint (PFS per IRC review). However, an interim analysis for OS was performed at the same time as the final analysis for PFS (i.e. taking into account the time required for PFS per IRC review to be completed, available and cleaned in the database).

The final analyses were also based on the p-values or Z scales outlined in Table 14 for decision-making.

Table 14. Stopping boundary for overall survival expressed as hazard ratios, Z scales, and p-values

OS analysis	Population	Number of OS events	Boundary	HR	Z scale	p-value
Interim analysis	ITT	101	Futility	0.8933	0.5672	0.2853
			Efficacy*	0.2404	7.1635	0
Final	ITT	201	Efficacy	0.7583	1.96	0.025

OS analysis	Population	Number of OS events	Boundary	HR	Z scale	p-value
analysis						

* The interim analysis is for futility only; the trial was not stopped for efficacy based on comparison of OS at the interim analysis.
Abbreviations: HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

B.2.4.5 Patient withdrawals

All patients who received at ≥1 dose of study drug were included in the safety analysis. Patients could withdraw from treatment at any time at their own request or could be withdrawn at any time for safety, behavioural, or administrative reasons. Reasons for withdrawal are outlined in section B.2.3.2.1.

Patients who withdrew from the study and also withdrew consent for disclosure of future information had no further evaluations, and no additional data were collected (see Appendix D for patient disposition details).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included clinical trial (ARCHER 1050) was conducted using the NICE Quality Appraisal Checklist for quantitative intervention studies (Table 15).[49] A summary of the quality assessment is presented below in Table 15, while the complete quality assessment is available in Appendix D (**Error! Reference source not found.**).

Table 15. Summary of ARCHER 1050 quality appraisal

Assessment criteria	ARCHER 1050
Was the method used to generate random allocations adequate?	Yes
Was allocation adequately concealed?	Not applicable (open label study)
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not applicable (open label study)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Were the statistical analyses undertaken appropriate?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

Clinical efficacy summary
• First-line treatment with dacomitinib resulted in a statistically and clinically meaningful improvement in PFS compared with gefitinib in patients with EGFR+ NSCLC (Section 2.6.2 and Section 2.6.3.1). • First-line treatment with dacomitinib resulted in a significant improvement in OS compared with gefitinib in patients with EGFR+ NSCLC (Section 2.6.3.2). • First-line treatment with dacomitinib was associated with a high ORR comparable to gefitinib in patients with EGFR+ NSCLC (Section 2.6.3.3). • First-line treatment with dacomitinib resulted in significant improvements in DoR (Section 2.6.3.4) and TTF (Section 2.6.3.5) compared with gefitinib in patients with EGFR+ NSCLC. • Dacomitinib helps patients with EGFR-mutation positive NSCLC reduce key disease-related symptoms and maintain overall HRQoL (Section 2.6.4).

Abbreviations: DoR = duration of response; EGFR+ = epidermal growth factor receptor mutation positive; HRQoL = health-related quality of life; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; TTF = time to treatment failure.

B.2.6.1 Overview of clinical effectiveness results

Table 16 presents an overview of the clinical effectiveness results from ARCHER 1050.

Table 16. Summary of clinical effectiveness results in the ARCHER 1050 trial (ITT Population)[33,34,40]

Outcome	Dacomitinib N=227	Gefitinib N=225
PFS (based on blinded IRC)		
Patients with PFS event, n (%)	136 (59.9)	179 (79.6)
Median PFS, months (95% CI)*	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)†	0.589 (0.469, 0.739)	
P-value (1-sided)†	<0.0001	
PFS (based on investigator assessment)		
Patients with PFS event, n (%)	140 (61.7)	177 (78.7)
Median PFS, months (95% CI)*	16.6 (12.9, 18.4)	11.0 (9.4, 12.1)
HR (95% CI)†	0.622 (0.497, 0.779)	
P-value (1-sided)†	<0.0001	
OS		
Deaths, n (%)‡	103 (45.4)	117 (52.0)
Median months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)†	0.760 (0.582, 0.993)	
P-value (2-sided)†	0.0438	
BOR (based on blinded IRC)		
Complete response, n (%)	12 (5.3)	4 (1.8)
Partial response, n (%)	158 (69.6)	157 (69.8)
Stable, n (%)	30 (13.2)	27 (12.0)
Progressive disease, n (%)	12 (5.3)	15 (6.7)

Outcome	Dacomitinib N=227	Gefitinib N=225
Intermediate, n (%)	15 (6.6)	22 (9.8)
Objective response rate (CR plus PR), n (%)	170 (74.9)	161 (71.6)
95% exact CI[§]	(68.7, 80.4)	(65.2, 77.4)
BOR (based on investigator assessment)		
Complete response, n (%)	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]
Stable, n (%)	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]
Intermediate, n (%)	[redacted]	[redacted]
Objective response rate (CR plus PR), n (%)	[redacted]	[redacted]
95% exact CI[§]	[redacted]	[redacted]
DoR (based on blinded IRC)		
Number with a response (CR or PR), n (%)	170 (74.9)	161 (71.6)
Median duration of response, months (95% CI)[Ŧ]	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)
Descriptive summary of response duration (months), n	170	161
Mean (standard deviation)	12.78 (7.681)	9.17 (5.549)
Median	12.02	8.11
Range	0.0-34.3	0.0-32.2
DoR in responders (based on investigator assessment)		
Number with a response (CR or PR), n (%)	[redacted]	[redacted]
Median duration of response, months (95% CI)[Ŧ]	[redacted]	[redacted]
Descriptive summary of response duration (months), n	[redacted]	[redacted]
Mean (standard deviation)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

*Kaplan-Meier estimates of time to event (months) 50% quartile (95% CI). Based on the Brookmeyer-Crowley Method.
[†]This is based on stratified analysis.
[‡]Per the statistical analysis plan, the final OS analysis was to occur after a pre-specified minimum of 201 deaths. Data cut-off on February 17, 2017, with 220 deaths observed.
[§]Using exact method based on binomial distribution.
[Ŧ]Kaplan-Meier estimates of response duration (months) quartiles (95% CI); Based on the Brookmeyer-Crowley method.
Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DoR = duration of response; HR = hazard ratio; INV = investigator assessment; IRC = independent review committee; ITT = intent-to-treat; PFS = progression-free survival; PR = partial response.

B.2.6.2 Primary endpoint

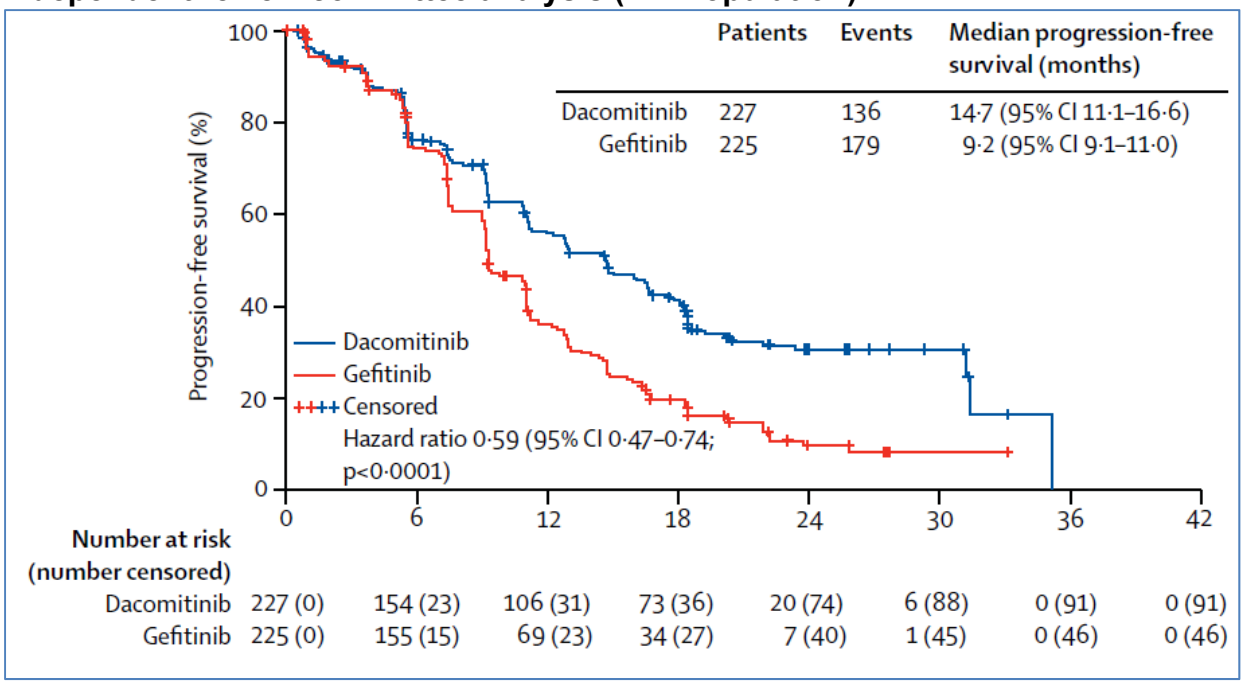
First-line treatment with dacomitinib resulted in a statistically and clinically meaningful improvement in PFS compared with gefitinib in patients with EGFR+ NSCLC. The ARCHER 1050 trial met its primary objective by demonstrating that dacomitinib was superior to gefitinib in prolonging PFS as determined by blinded IRC review.[33,40]

Overall, a total of 315 patients (69.7%) in ARCHER 1050 had a PFS event as of the data cut-off date, after application of all the censoring rules. Of the 315 PFS events, 136 patients (59.9%) were from the dacomitinib arm and 179 patients (79.6%) from

the gefitinib arm. Dacomitinib demonstrated a 5.5 month improvement in median PFS and a 41% reduction in the risk of progression compared with gefitinib; median PFS was 14.7 months (95% CI: 11.1, 16.6) for dacomitinib versus 9.2 months (95% CI: 9.1, 11.0) for gefitinib (HR: 0.589; 95% CI: 0.469, 0.739; 1-sided p-value<0.0001; unstratified log-rank test).[33,40]

The Kaplan-Meier plot for PFS based on blinded IRC review is shown in Figure 4. The median duration of PFS follow-up using reverse Kaplan-Meier method in the ITT population was 22.1 months. The probability of being event-free at 12 months was 55.7% (95% CI: 48.5, 62.3) for the dacomitinib arm versus 35.9 (95% CI: 29.3, 42.4) for the gefitinib arm. At 24 months, the probability of being event-free was 30.6% (95% CI: 23.8, 37.5) versus 9.6% (95% CI: 5.6, 15.0), respectively.[33,40]

Figure 4. Kaplan-Meier plot of progression-free survival based on blinded, independent review committee analysis (ITT Population)*[33]



*Stratified HR and its CI were obtained from the stratified Cox Regression and stratified p-value was based on the stratified log-rank test with race (Japanese vs mainland Chinese and other East Asian versus non-Asian) and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = Intent-to-treat.

B.2.6.3 Secondary endpoints

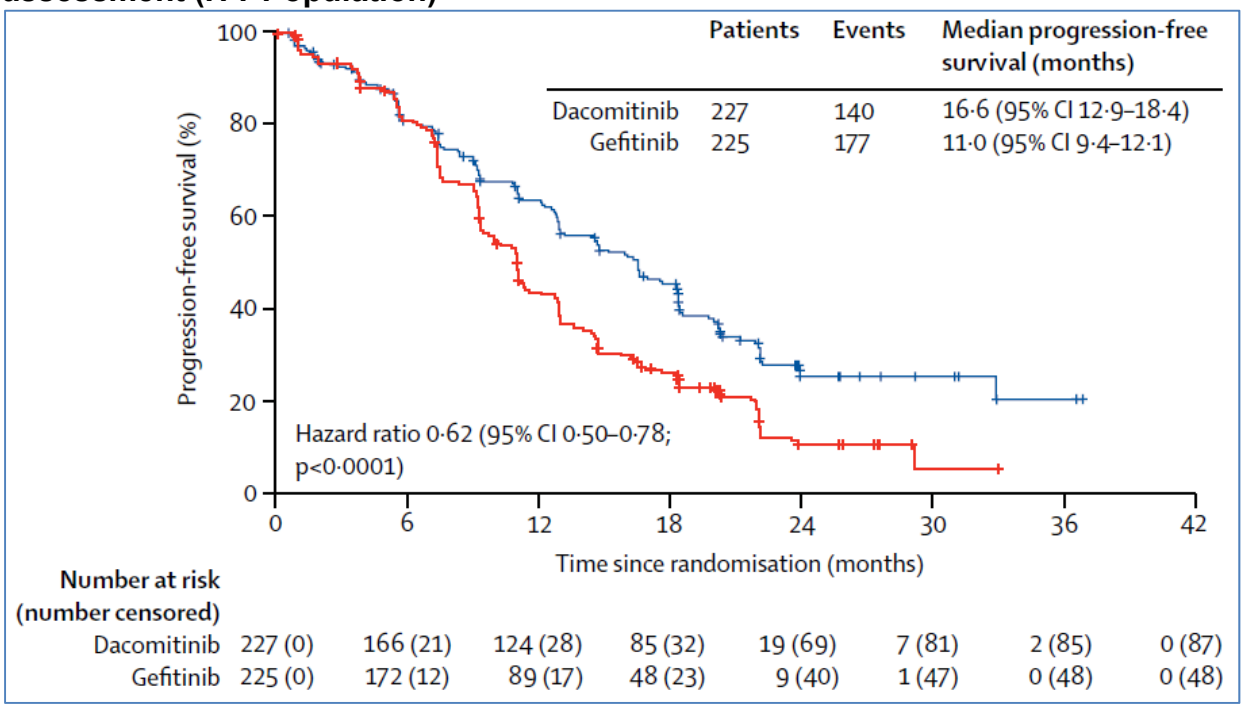
B.2.6.3.1 Progression-free survival based on investigator assessment

Investigator-assessed PFS was consistent with the blinded IRC analysis and also showed significantly prolonged PFS in the dacomitinib arm compared to gefitinib.

Median PFS was 16.6 months (95% CI: 12.9, 18.4) in patients treated with dacomitinib compared with 11.0 months (95% CI: 9.4, 12.1) for the gefitinib treatment arm (HR: 0.625; 95% CI: 0.500, 0.782; 1-sided p-value<0.0001; unstratified log-rank test). The difference in median PFS between treatment arms was 5.6 months, consistent to that determined by blinded IRC analysis (5.5 months).[33,40]

The Kaplan-Meier plot for PFS based on investigator assessment is shown in Figure 5. The median duration of PFS follow-up using reverse Kaplan-Meier method in the ITT population was 23.9 months. The probability of being event-free at 12 months was 63.8 (95% CI: 56.8, 69.9) for the dacomitinib arm versus 43.7 (95% CI: 36.9, 50.3) for the gefitinib arm. At 24 months, the probability of being event-free was 25.4 (95% CI: 18.7, 32.6) versus 9.6% 10.5 (95% CI: 6.3, 16.1), respectively.[33,40]

Figure 5. Kaplan-Meier plot of progression-free survival based on investigator assessment (ITT Population)*[33]



*HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and Wilcoxon test with Race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat.

B.2.6.3.2 Overall survival

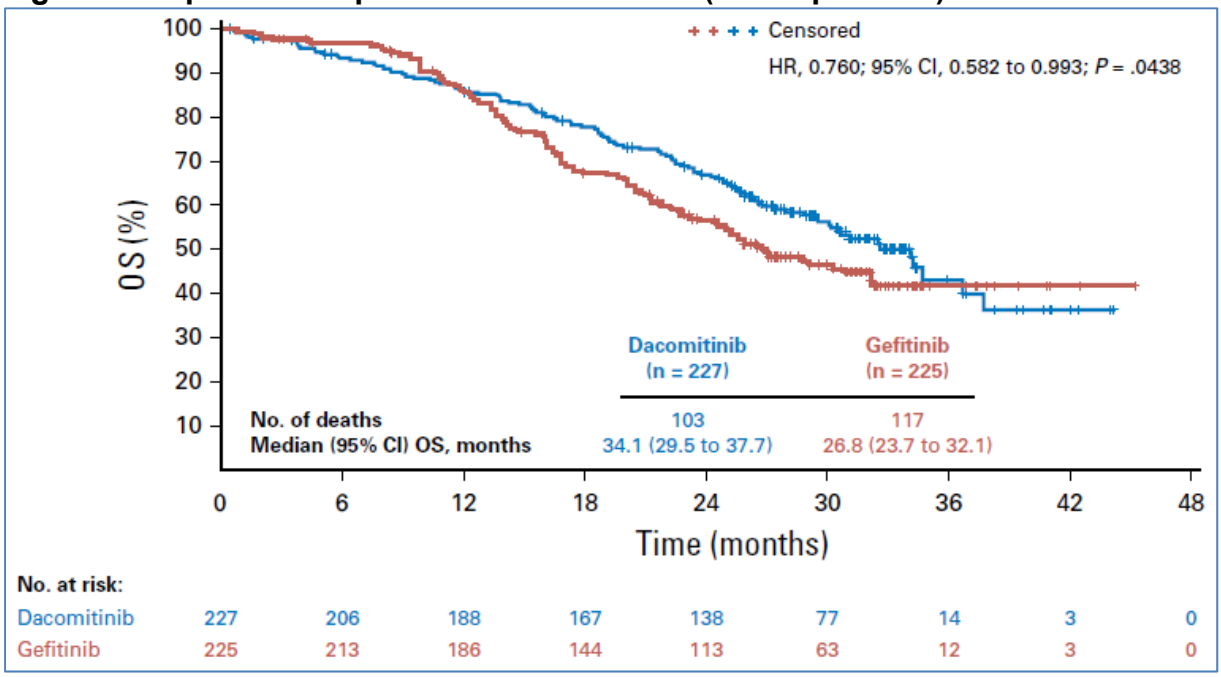
Dacomitinib is the first TKI to show an OS benefit in a phase III study (ARCHER 1050) against an active comparator in patients with locally advanced or metastatic EGFR+ NSCLC.[34,40]

In ARCHER 1050, dacomitinib demonstrated a 7.3 month improvement in median OS and a 24% reduction in the risk of death compared with gefitinib in EGFR+ NSCLC. The median OS was 34.1 months (95% CI: 29.5, 37.7) in the dacomitinib arm compared with 26.8 months (95% CI: 23.7, 32.1) for gefitinib (HR: 0.760; 95% CI: 0.582, 0.993; 2-sided p-value=0.0438; stratified analysis).[34,40]

The final overall survival analysis was planned to occur after ≥201 deaths. 220 deaths were observed at the data-off date on February 17, 2017 (103 [45.4%] and 117 [52%] in the dacomitinib and gefitinib arms, respectively). Median follow-up for OS for the whole study population was 31.3 months, with median follow-up at 31.1

and 31.4 months in the dacomitinib and gefitinib arms, respectively. The Kaplan-Meier plot for OS is shown in Figure 6.[34,40]

Figure 6. Kaplan-Meier plot of overall survival (ITT Population)[34]



Abbreviations: CI = confidence interval; CNS = central nervous system; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

B.2.6.3.3 Objective response rate

In ARCHER 1050, treatment with dacomitinib was associated with a high response rate comparable to gefitinib.[33] The objective response rate (ORR; complete response [CR] and partial response [PR]) for ITT patients in the dacomitinib and gefitinib arms was 74.9% (95% CI: 68.7, 80.4 and 71.6% (95% CI: 65.2, 77.4), respectively; 1-sided p-value=0.1942 based on the Cochran-Mantel-Haenszel test, stratified by EGFR mutation status and race.[33,40]

Response rates based on blinded IRC review are summarised in Table 17. Of the 227 patients randomised to the dacomitinib arm, 158 patients (69.6%) achieved PR and 12 patients (5.3%) achieved CR. A similar number of patients achieved PR (n=157; 69.8%) in the gefitinib arm; however, a smaller proportion of patients reported CR (n=4; 1.8%).[33,40]

Table 17. Summary of response rates based on independent review committee analysis (ITT population)[33,40]

Response outcomes	Dacomitinib N=227	Gefitinib N=225

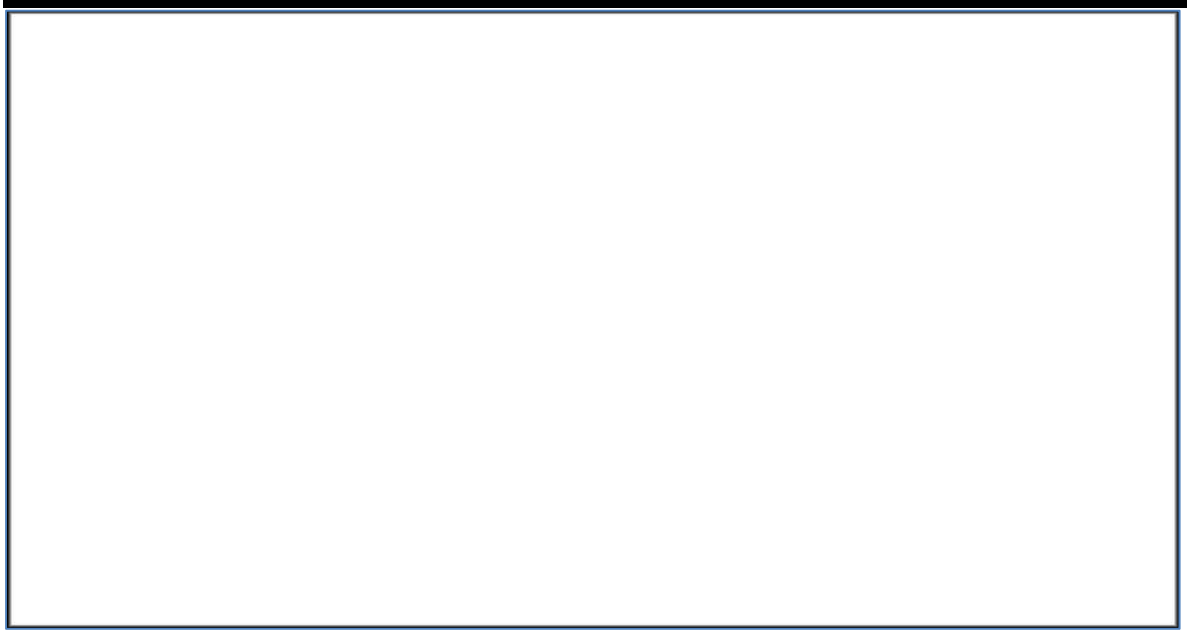
Response outcomes	Dacomitinib N=227	Gefitinib N=225
Responses		
CR, n (%)	12 (5.3)	4 (1.8)
PR, n (%)	158 (69.6)	157 (69.8)
Stable disease, n (%)	30 (13.2)	27 (12.0)
Progressive disease, n (%)	12 (5.3)	15 (6.7)
Indeterminate, n (%)	15 (6.6)	22 (9.8)
ORR (CR plus PR), n (%)	170 (74.9)	161 (71.6)
95% exact CI*	(68.7, 80.4)	(65.2, 77.4)
P-value versus gefitinib		
1-sided p-value (stratified)†	0.1942	NA
1-sided p-value (unstratified)‡	0.2117	NA

*Using exact method based on binomial distribution.
†p-value is from the Cochran-Mantel-Haenszel test stratified by EGFR mutation status (exon 19 deletion vs the L 858R mutation in exon 21) based on their values at randomization and by race (Japanese vs mainland Chinese and other East Asian vs non-Asian).
‡p-value is from a Pearson χ^2 test. When the number in at least one cell is too small (<5), an exact test was used.
Abbreviations: χ^2 = chi-square; CI = confidence interval; CR = complete response; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; L858R = EGFR-TK mutation with an amino acid substitution at position 858 from a Leucine to an Arginine; N = number of patients; n = number of patients meeting pre-specified criteria; ORR = objective response rate; PR = partial response.

B.2.6.3.4 Duration of response

Treatment with dacomitinib resulted in significant improvements in DoR compared with gefitinib in patients with EGFR+ NSCLC. The median DoR based on blinded IRC review for the dacomitinib arm was 14.8 months (95% CI: 12.0, 17.4) versus 8.3 months (95% CI: 7.4, 9.2) in those who received gefitinib (HR: 0.40; 95% CI: 0.31, 0.53; 2-sided p-value<0.0001; stratified Cochran-Mantel-Haenszel test). This corresponds to a 6.5 month improvement in patients who received dacomitinib versus gefitinib. The Kaplan-Meir plot of DoR based on blinded IRC review is presented in XXXXXXX7.[33,40]

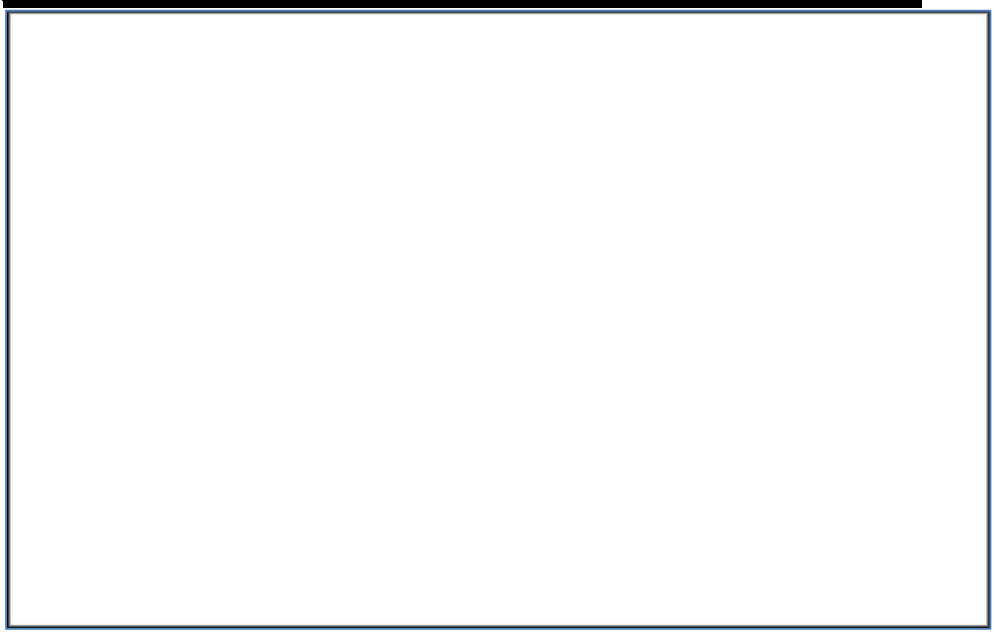
[redacted]7



*HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and Wilcoxon test with Race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = independent review committee; N = total number.

The median DoR based on investigator assessment for the dacomitinib arm was 15.9 months (95% CI: 13.8, 17.6) versus 9.2 months (95% CI: 8.2, 11.0) in the gefitinib arm (HR: 0.55; 95% CI: 0.42, 0.71; 2 sided p-value<0.0001; stratified Cochran-Mantel-Haenszel test). This corresponds to a 6.7 month improvement in patients who received dacomitinib versus gefitinib, similar to 6.5 month improvement determined by the blinded IRC review. The Kaplan-Meir plot of DoR based on investigator assessment is presented in XXXXXXX8.[33,40]

8



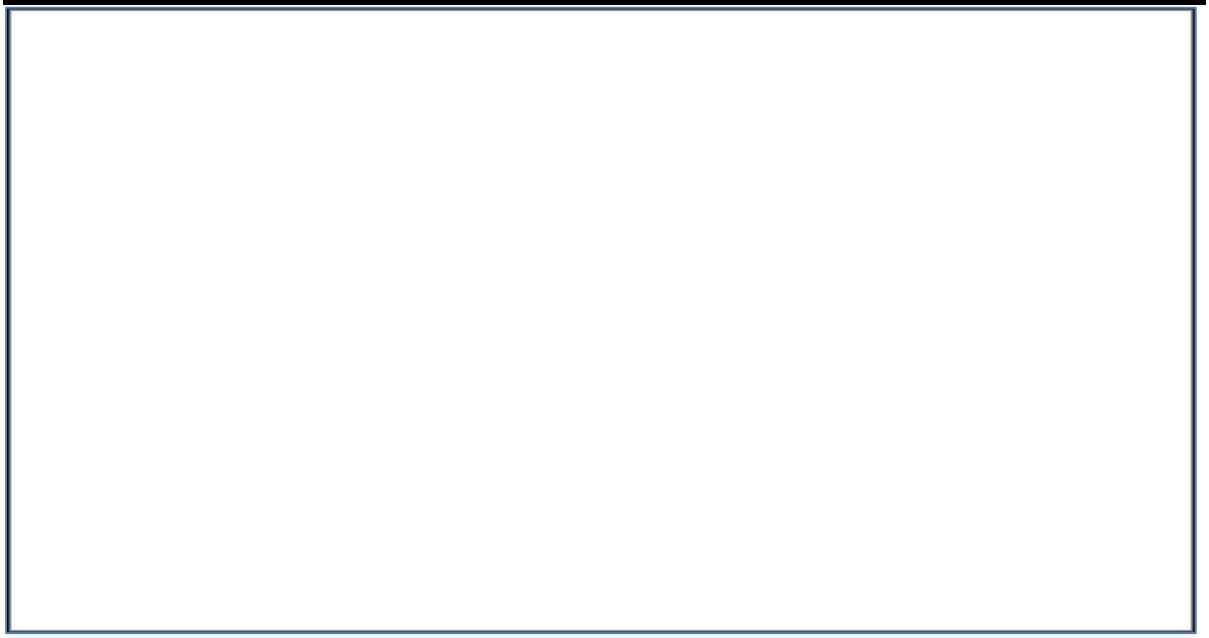
*HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and Wilcoxon test with race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat.

B.2.6.3.5 Time-to-treatment failure

In addition to the significantly longer DoR, treatment with dacomitinib is also associated with a significantly longer TTF compared to gefitinib.[33,40]

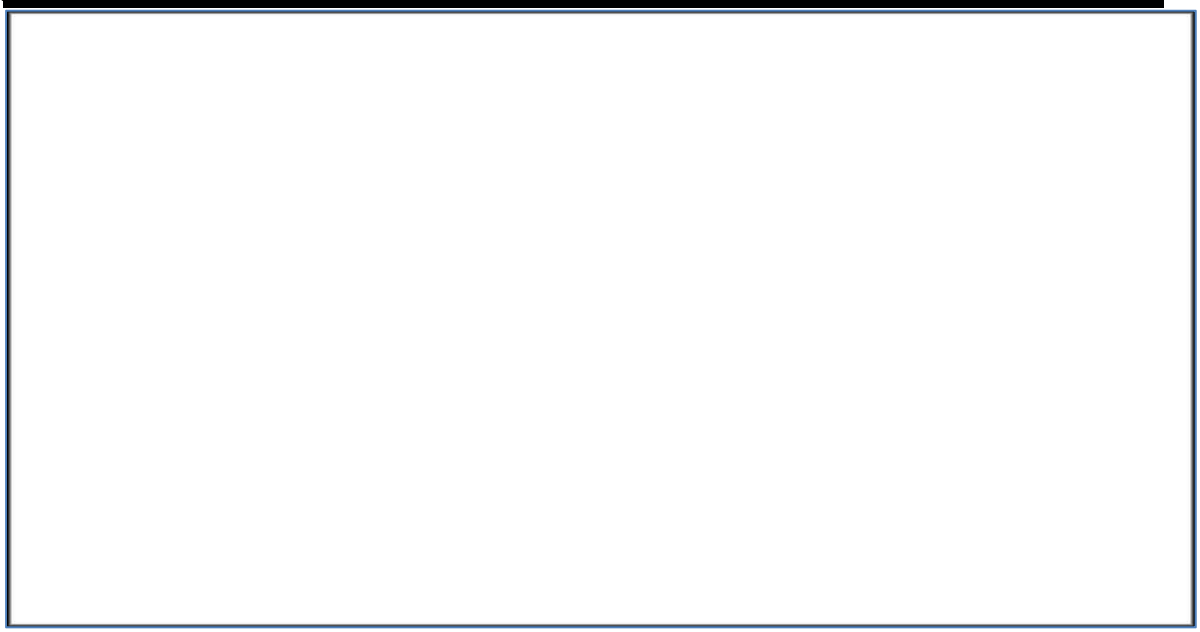
In total, 168 (74.0%) patients in the dacomitinib treatment arm and 197 (87.6%) patients in the gefitinib arm had a treatment failure event. The median TTF based on blinded IRC review was 11.1 months (95% CI: 9.2, 14.6) and 9.2 months (95% CI: 7.6, 9.4) in patients treated with dacomitinib versus gefitinib, respectively (HR: 0.67; 95% CI: 0.54, 0.83; 1-sided p-value<0.0001; stratified analysis). The Kaplan-Meir plot for TTF based on blinded IRC review is presented in XXXXXXX9.[33,40]

9



*HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and Wilcoxon test with race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat.

Investigator-assessed TTF results were consistent with the blinded IRC analysis. Median TTF based on investigator assessment was 13.0 months (95% CI: 11.1, 16.6) for patients treated with dacomitinib compared to 11.0 months (95 CI: 9.3, 11.1) for patients treated with gefitinib (HR: 0.70; 95% CI: 0·56, 0·86; 1-sided p-value=0.0003; stratified log-rank test). The Kaplan-Meir plot for TTF based on investigator assessment is presented in XXXXXXX10.[33,40]



*HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and Wilcoxon test with race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomisation as the stratification factors.
Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; INV = investigators assessment; ITT = intent-to-treat.

Additionally, dacomitinib was associated with a longer treatment duration; median treatment duration was 66.6 weeks (range: 0.3, 162.7) with dacomitinib and 52.1 weeks (range: 0.3, 148.3) with gefitinib.[40]

B.2.6.4 Patient-reported outcomes and health-related quality-of-life

In ARCHER 1050, PRO measures for both dacomitinib and gefitinib treatment groups had high completion rates, with >90% completion for the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires for most treatment cycles.

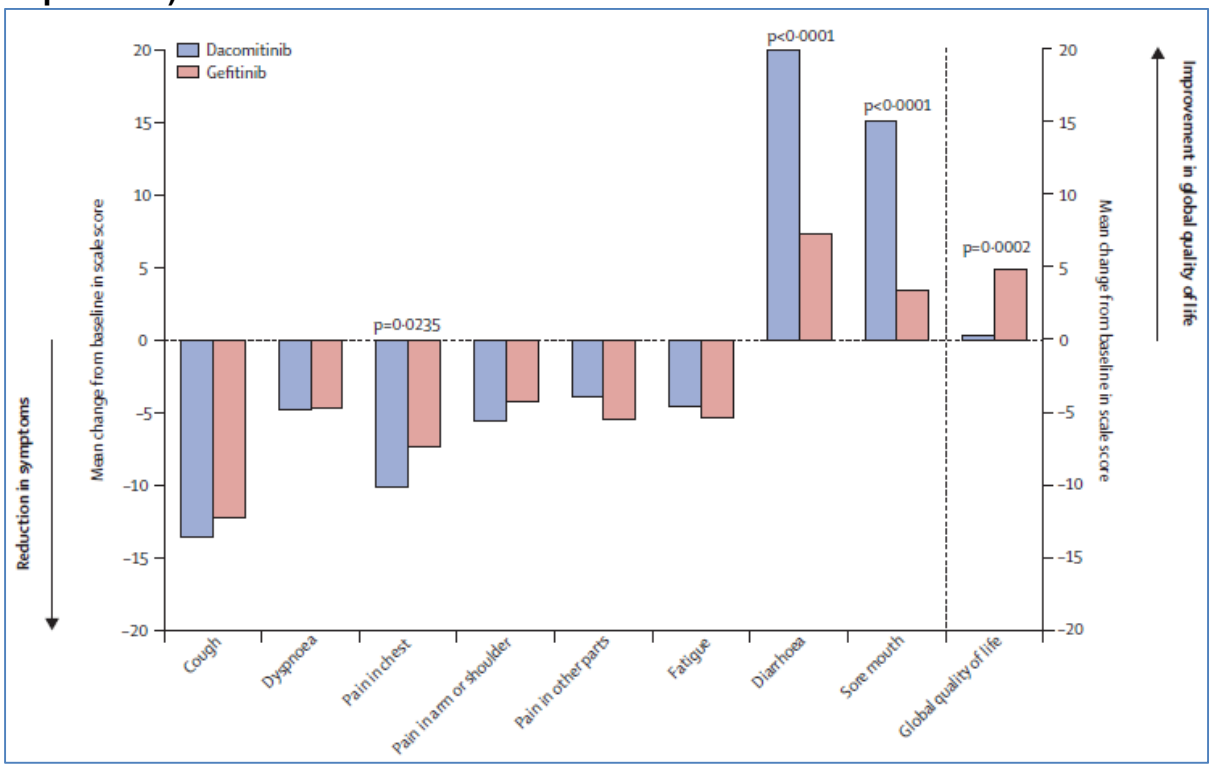
B.2.6.4.1 EORTC QLQ-C30 and EORTC QLQ-LC13

In ARCHER 1050, disease-related (i.e. cough, dyspnoea, pain in chest, pain in arm or shoulder, pain in other parts, fatigue) and treatment-related (i.e. diarrhoea and sore mouth) symptoms were assessed using EORTC QLQ-C30 and EORTC QLQ-

LC13. Additionally, a global quality-of-life (QoL) assessment was conducted using EORTC QLQ-C30.

Treatment with dacomitinib or gefitinib was associated with improvements in disease-related symptoms.[33] The repeated-measures mixed model analysis of disease-related symptoms showed that improvement from baseline in the key lung cancer symptoms of cough, dyspnoea, pain in arm or shoulder and fatigue was similar in both treatment groups. The same was observed in the majority of treatment cycles in both the dacomitinib and gefitinib arms (**Error! Reference source not found.** in Appendix D). Dacomitinib treatment was associated with significantly greater and clinically meaningful overall improvement from baseline in pain in chest versus gefitinib (mean improvement: -10.24 versus -7.44 for dacomitinib and gefitinib, respectively; p=0.0235; Figure 11).[33]

Figure 11. Mean change from baseline in disease-related symptoms, treatment-related symptoms and global quality-of-life in participants from the ARCHER 1050 trial (as assessed by EORTC-QLQ-C30 and EORTC-QLQ-LC13; PRO Population)[33]



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; PRO = patient-reported outcome.

Although clinically meaningful improvements (≥10 point change in score from baseline) were observed in cough for both patients with dacomitinib (-13.61) and patients treated with gefitinib (-12.28),[33] these improvements were maintained for longer for both cough and pain in chest symptoms in the dacomitinib arm (28/30 cycles and 23/30 cycles, respectively) compared with the gefitinib treatment arm (cough: 22/30 and pain in chest: 12/30; **Error! Reference source not found.** in Appendix D).[50] In addition, these scores were worse on average at the end of treatment and post discontinuation follow-ups, further demonstrating the important of prolonged time on treatment in reducing symptom burden (**Error! Reference source not found.** in Appendix D).

With regards to treatment-related symptoms, the repeated-measures mixed effect model showed that dacomitinib was associated with clinically meaningful worsening in diarrhoea and sore mouth and the worsening was significantly greater compared with gefitinib (Figure 11).[33] However, the difference between treatment groups in treatment-related symptoms generally occurred early, and declined over the course of treatment, with the mean score reported in the range of [redacted] (EORTC QLQ-C30 and EORTC QLQ-LC13 score of [redacted]; **Error! Reference source not found.** in Appendix D).[40]

Additionally, despite an increase from baseline in the treatment-related symptoms of diarrhoea and sore mouth in the dacomitinib treatment arm, global QoL was maintained (Figure 11) with dacomitinib.[33] There was a non-clinically meaningful improvement in global QoL for gefitinib and although the difference from baseline compared with dacomitinib was statistically in favour of gefitinib, the difference between groups was small (improvement from baseline: 0.20 for dacomitinib versus 4.94 for gefitinib; p=0.0002). The improvement from baseline in global QoL for patients treated with dacomitinib was not statistically significant.

B.2.6.4.2 Time-to-deterioration

Time-to-deterioration was used to assess the change in patient-reported symptoms (defined as time from randomisation to the first time a patient's score showed a ≥10 point increase from baseline). An increase of ≥10 points was considered a clinically

significant deterioration in the symptom and the primary assesmement required that the deterioration occurred for at least two consecutive cycles.[33] There was no statistically significant difference between treatment groups in time-to-deterioration in the composite endpoint of pain (chest, arm/shoulder), dyspnoea, fatigue and cough, or in the individual symptom items. The HR for the composite endpoint favoured gefitinib (HR: 1.17; 95% CI: 0.93, 1.48; Hochberg-adjusted p-value=0.5327) and was driven primarily by fatigue. The HRs for pain, dyspnoea and cough were in favour of dacomitinib.

B.2.6.4.3 EQ-5D

EQ-5D-3L assessments were made at the following time points as per the ARCHER 1050 trial protocol: day 1 – cycle 1 which provided the baseline assessment of PROs, days 8 and 15 of cycle 1 and at the beginning of each cycle afterwards (up to a total of 41 cycles), at the end of treatment and at a single post progression follow-up. Changes from baseline in the EQ-5D visual analogue scale (VAS) were small and not clinically meaningful in either treatment group, although gefitinib was associated with a significantly greater change from baseline than dacomitinib in VAS and utility index scores (Table 18)[40] Further details of the EQ-5D results are presented in section B.3.4.

Table 18. Absolute scores in EQ-5D (PRO Population)[40]

	Dacomitinib	Gefitinib	Difference
Absolute score			
VAS	[redacted]	[redacted]	[redacted]
Utility index	[redacted]	[redacted]	[redacted]

*p<0.05.
Abbreviations: EQ-5D = European Quality of Life-5 Dimensions; PRO = patient-reported outcome; VAS = visual analogue scale.

B.2.7 Subgroup analysis

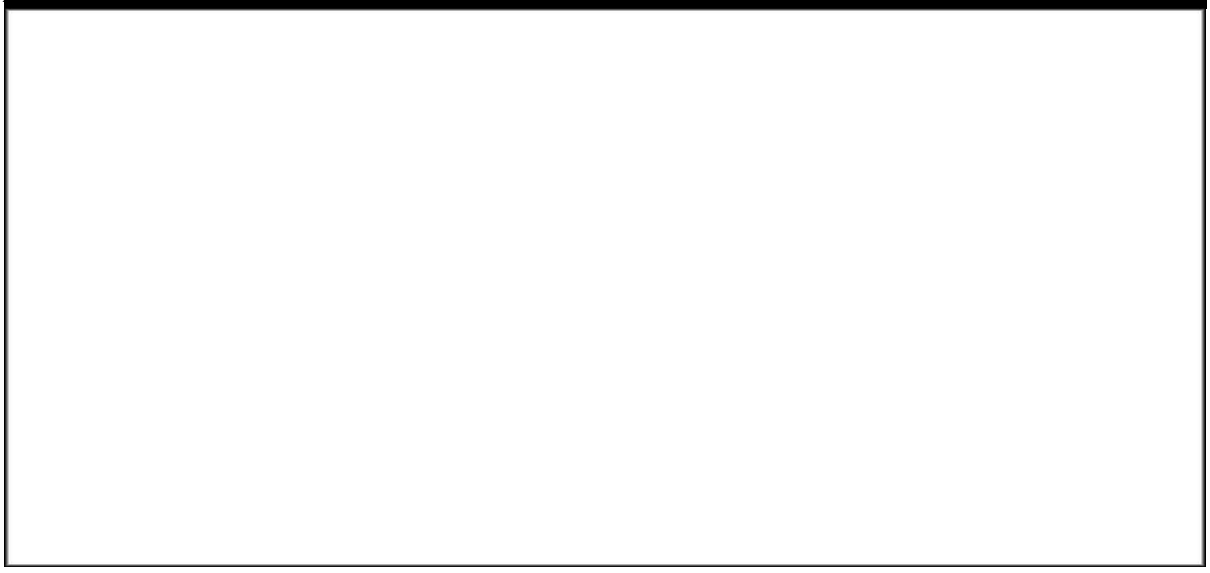
B.2.7.1 Progression-free survival

Several subgroup analyses based on pre-specified patient baseline characteristics were conducted. Overall, the subgroup analyses for PFS based on blinded IRC review were largely consistent with the results of the primary analysis with HR<1. An exception to this was seen in the ≥75 age group where the HR=1.137 (CI: 0.586,

2.207). . However, the sample size consisted of only 28 and 21 patients for the dacomitinib and gefitinib arms, respectively. A forest plot presenting the pre-specified subgroup analyses for PFS based on blinded IRC review is presented in XXXXXXX12.

[redacted] 12

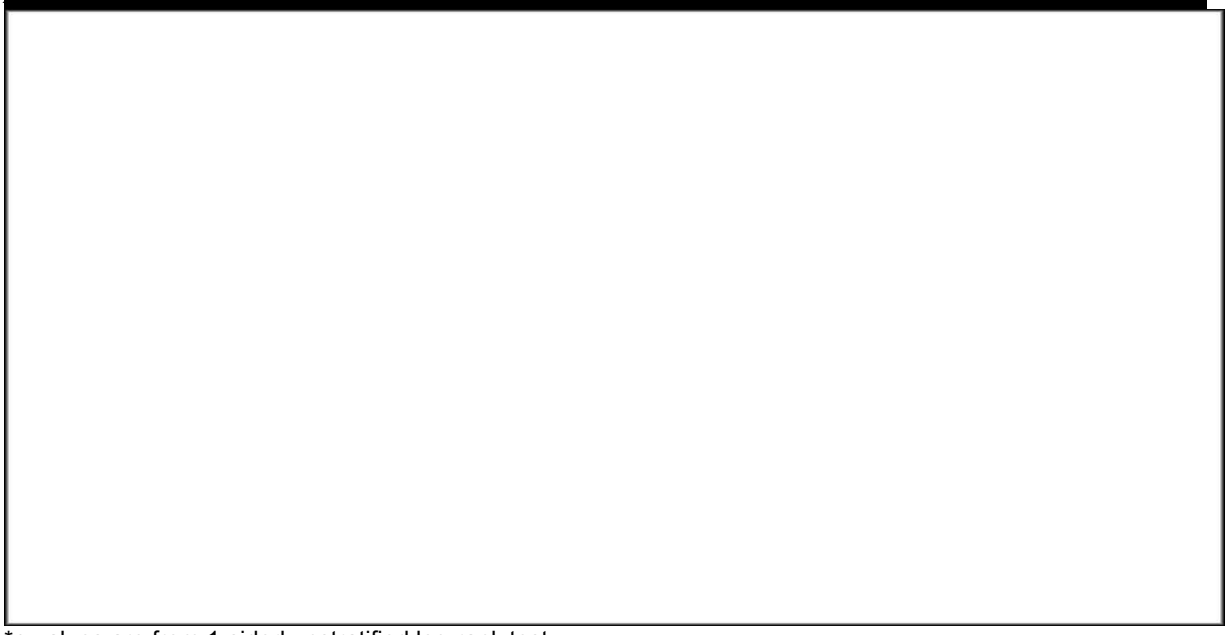
[redacted]



*p-values are from 1-sided unstratified log-rank test.
Abbreviations: +/- = with/without/unknown T790M mutation; - = without T790M mutation; CI = confidence interval; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; L858R = EGFR-TK mutation with an amino acid substitution at position 858 from a leucine to an arginine; N = number of patients; PS = performance status; T790M = secondary point mutation at amino acid position 790 that substitutes methionine for threonine.

Subgroup analyses for PFS based on investigator assessment also demonstrated a reduced risk of progression in the majority of categories, consistent with the results of the blinded IRC review. As with the blinded IRC review, [redacted]). A forest plot of subgroup of these analyses for PFS based on investigator assessment is presented in XXXXXXX13.

13

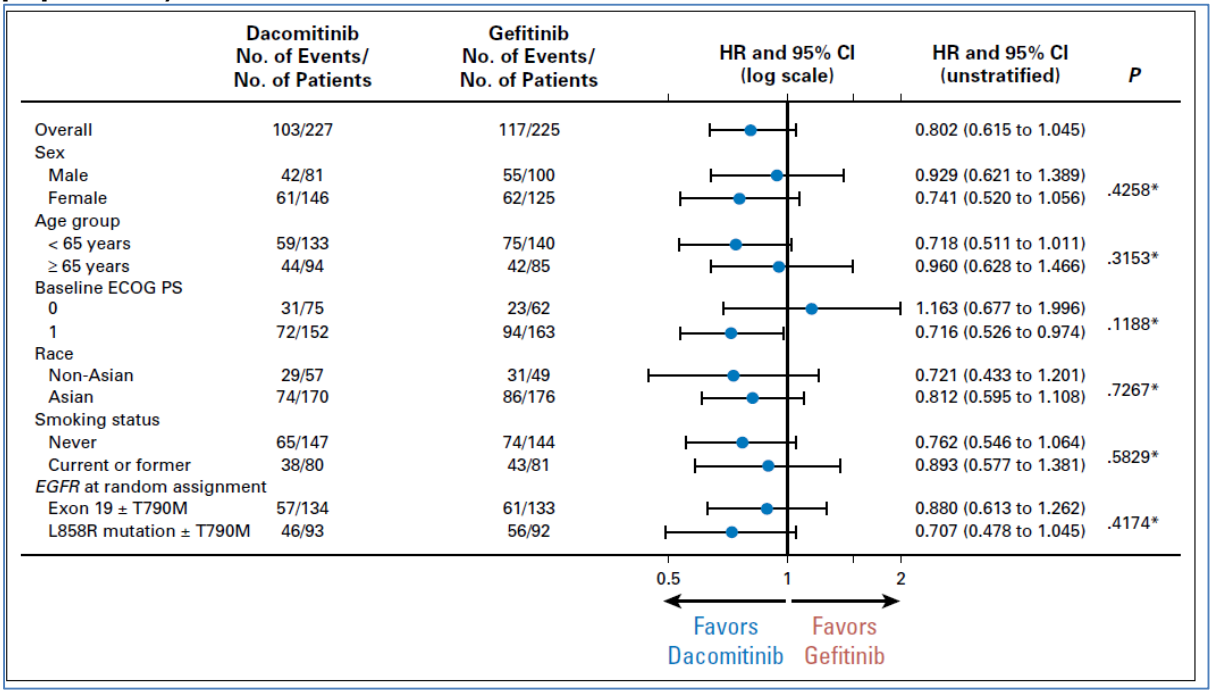


*p-values are from 1-sided unstratified log-rank test.
Abbreviations: +/-, with/without/unknown T790M mutation; -, without T790M mutation; CI, confidence interval; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intent-to-treat; L858R, EGFR-TK mutation with an amino acid substitution at position 858 from a leucine to an arginine; N, number of patients; PS, performance status; T790M, secondary point mutation at amino acid position 790 that substitutes methionine for threonine.

B.2.7.2 Overall survival

Dacomitinib is the first drug to show an OS benefit in a phase III study against an active comparator in a NSCLC patient population that included patients with EGFR del19 or L858R substitution.[34] A forest plot of subgroup of these analyses for OS is presented in Figure 14.

Figure 14. Forest plot of overall survival (stratified by subgroups; ITT population)*



*P interaction.
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; HR = hazard ratio; L858R = EGFR-TK mutation with an amino acid substitution at position 858 from a Leucine to an Arginine; T790M = secondary point mutation at amino acid position 790 that substitutes methionine for threonine.

Treatment with dacomitinib was shown to improve OS in patients in the del19 mutation subgroup and L858R substitution. Additionally, in the OS analyses pertaining to the ethnicity, dacomitinib demonstrated OS benefits compared with gefitinib in both the non-Asian and Asian subgroups. Although, the ARCHER 1050 trial was not powered for subgroup analyses, the results were all aligned and numerically in favour of dacomitinib (with the exception of ECOG PS 0).

B.2.8 Meta-analysis

This section is not applicable for the current submission as no meta-analysis was conducted. ARCHER 1050 is the only clinical trial available for dacomitinib for the first-line treatment of EGFR+ NSCLC.

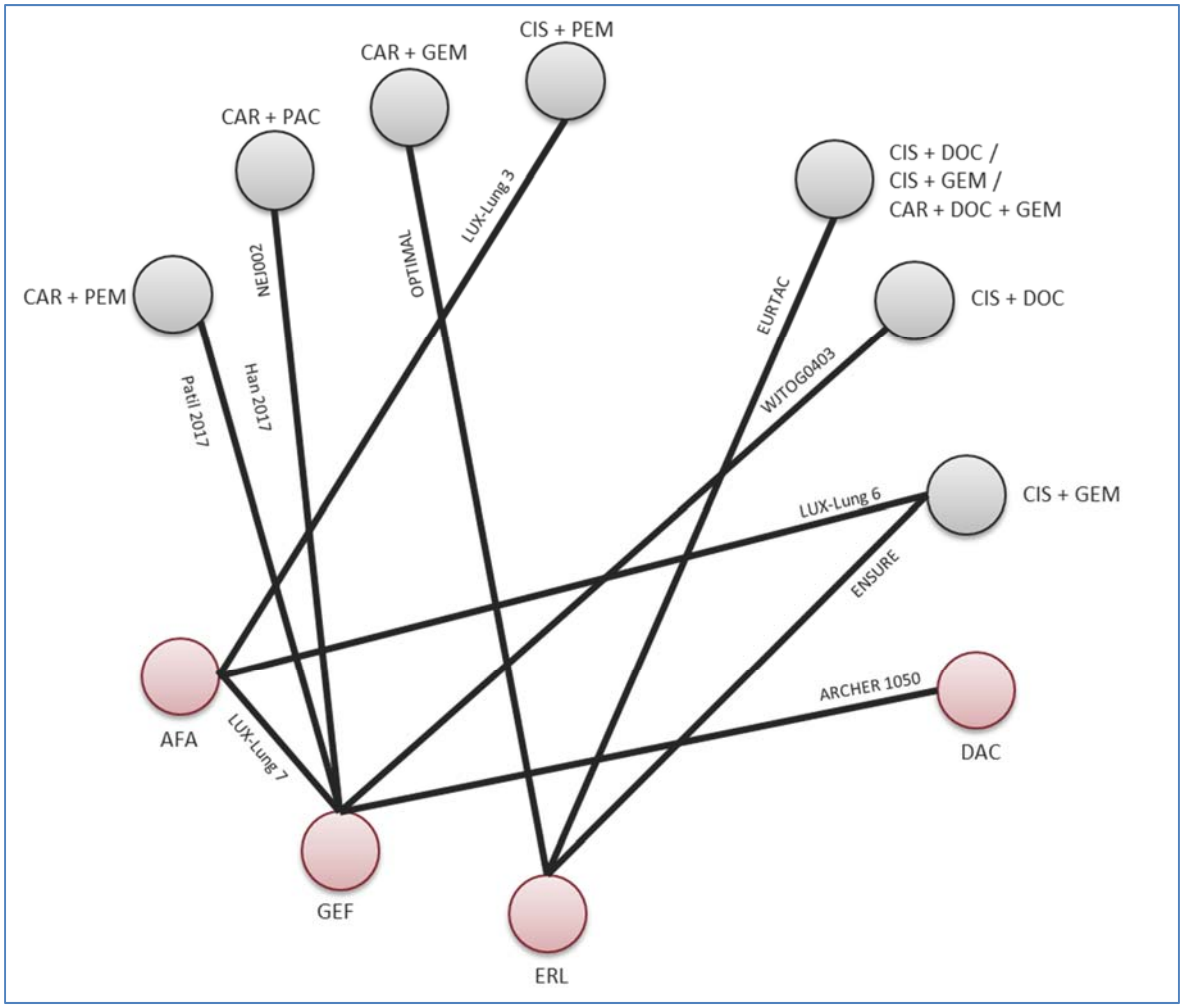
B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Systematic literature review and trial network

A SLR was conducted (as described in section B.2.1 and Appendix D.1) to identify relevant studies providing evidence for the efficacy and safety of interventions relevant to the decision problem of this appraisal.

The full set of 11 RCTs included in the refined SLR formed a network with several loose ends (i.e. connections between TKIs and chemotherapies that did not connect back into the network), presented in Figure 15.[9,33,35,36,38,39,41,42,44,45,51]

Figure 15. Feasibility assessment network diagram of the 11 trails included in the network



Abbreviations: AFA = afatinib; CAR = carboplatin; CIS = cisplatin; DAC = dacomitinib; DOC = docetaxel; ERL = erlotinib; GEF = gefitinib; GEM = gemcitabine; PAC = paclitaxel; PEM = pemetrexed.

In the NICE appraisal of afatinib for untreated EGFR+ NSCLC the committee concluded that gefitinib and erlotinib had equal clinical benefit:[52]

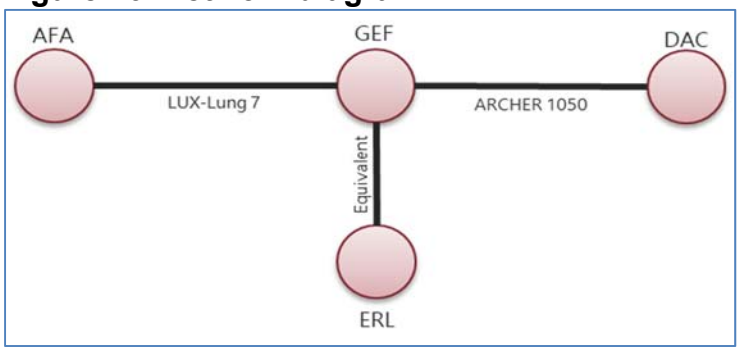
'The Appraisal Committee noted the advice provided by clinical experts, that erlotinib and gefitinib were similar treatments with similar efficacy and levels of adverse reactions, and concluded that an assumption of equal clinical benefit for erlotinib and gefitinib was appropriate.'

This assumption was also accepted by the SMC during the appraisal of gefitinib (SMC 615/10) where a cost-minimisation analysis was submitted which assumed equal efficacy between EGFR TKIs.[53]

Following these appraisals, further evidence of equivalence has been demonstrated in a phase III RCT (CTONG 0901) comparing erlotinib versus gefitinib in first- and second-line EGFR+ NSCLC.[54] The study did not include treatment line as a stratification factor and was therefore not included in the NMA. Nonetheless, the study presented a first-line subgroup analysis (gefitinib n=84; erlotinib n=81) which reported the following: PFS HR=0.96 (95% CI: 0.69, 1.35; p=0.827) and OS HR=0.98 (95% CI: 0.67, 1.42; p=0.902). Although this did not represent fully randomised data, it was the best available evidence for erlotinib versus gefitinib in untreated EGFR+ NSCLC and demonstrated that the assumption of equivalence holds in practice.

In line with previous NICE and SMC committee conclusions and the supporting data from the recent RCT subgroup analysis, it was assumed that erlotinib was equivalent to gefitinib in this NMA. This assumption was also reflected in discussions with UK clinical experts.[55] Therefore, the network included two studies, ARCHER 1050 and LUX-Lung 7, presented in Figure 16.

Figure 16. Network diagram



Abbreviations: AFA = afatinib; DAC = dacomitinib; ERL = erlotinib; GEF = gefitinib.

Further details of the two studies in the final network are presented in Appendix D.1.8, including patient characteristics, follow-up time, treatment effect modification, treatment schedules and risk of bias.

B.2.9.2 Proportional hazards assumption

Traditional indirect treatment comparison (ITC) techniques rely on the assumption of constant HRs and, if violated, can produce results that are not robust. In cost-effectiveness evaluations based on comparisons of expected survival where the tail of the survival function can have an impact on the expected survival, violations of the constant hazard ratio can lead to biased estimates.[56]

The proportional hazards assumption was assessed through the use of log cumulative hazard plots (parallel line suggested proportional hazards held) and Schoenfeld residual (flat line with no systematic trend suggested proportional hazards held) in ARCHER 1050 and LUX-Lung 7 to determine the most appropriate approach for the NMA. In ARCHER 1050 there was some crossing of the curves in the log cumulative hazard plots for OS whilst there was a systematic downward trend in the Schoenfeld residuals for PFS. Therefore, it was concluded there was insufficient evidence that proportional hazards was not violated in ARCHER 1050 for both PFS and OS. In LUX-Lung 7 there was no clear violation of proportional hazards in OS given that the log cumulative hazard plot showed reasonably parallel line and the Schoenfeld residuals were flat. However, the Schoenfeld residuals for PFS showed an increasing trend, demonstrating a potential violation of proportional hazards assumption for PFS. **Error! Reference source not found.** to **Error!**

Reference source not found. in Appendix D.5 present log cumulative hazards and Schoenfeld residuals plots for both PFS and OS.

Given the potential violations of proportional hazard for PFS and OS in at least one of the trials included in the network, a fractional polynomial (FP) analysis was conducted based on Jansen (2011) and Dias (2018) which allowed time-varying hazards to be incorporated into the analysis.[56,57] A traditional ITC akin to the Bucher method was also explored in scenario analysis (Appendix D.7) to demonstrate the impact of the assumption.[58]

B.2.9.3 Fractional polynomial analysis

The FP analysis was conducted for the overall population using KM curves for PFS (based on blinded IRC review) and OS from the relevant trials included in the network. Only a fixed-effects analysis was considered due to the lack of multiple trials for each comparison within the network resulting in between trial heterogeneity not being applicable.

For the FP analysis, the number of patients at risk and the number of events were calculated for a pre-defined number of time intervals. For PFS (IRC) and OS, time intervals of 0.5 month and 1 month were used, respectively.

FP models of first- and second-order were explored in the analysis. The application of the fractional polynomial model included the following steps:

1. The first step included fitting a large number of first- (9 models) and second-order (45 models) models

2. The “best fitting models” based on the deviance information criteria (DIC) were then plotted for further consideration

3. These model were then applied to estimated survival functions and were compared graphically for clinical plausibility. If no plausible model was identified the “best fitting model” criteria was expanded.

D.2.9.3.1 Model specification

The FP model analysis was performed under a Bayesian framework. Uninformative priors were used for the d and μ parameters: normal distribution with mean 0 and variance 9^2 and 10^2 respectively. The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method and implemented in the R and JAGS 4.0 software. Furthermore, each FP model fitting used:

- Four chains
- 400,000 iterations as 'burn-in'
- A total of 800,000 iterations (including burn-in) for final estimates

The convergence of the chains was assessed by the Gelman-Rubin statistic. A Gelman-Rubin statistics less than 1.1 implies convergence of the parameter. In addition, other model diagnostics (n.eff and MCMC trace-plots) were investigated to ensure proper convergence.

See Appendix D.6.1 for further details on the FP analysis specification.

D.2.9.3.2 Model selection

DIC was used to compare the goodness-of-fit of different fixed effect models with first- and second-order FPs of different powers P1 and P2. The model with the lowest DIC was considered as the model providing the 'best' fit to the observed data. To ensure a sufficient number of models were explored whilst still remaining practical, all models with DIC<+5 of the best fitting model were included for further consideration. The final model was selected after also considering the clinical plausibility of the curves.

Progression-free survival

The model fit statistics for PFS (IRC) are presented in Table 19, where the lowest DIC (1173.2) was a second-order fractional polynomial *P1=1, P2=1.5*. All models with DIC less than 1778 (Table 3) were plotted to assess the clinical plausibility.

Table 19. Goodness-of-fit estimates for fractional polynomial models of different powers p1 and p2 – PFS (IRC)

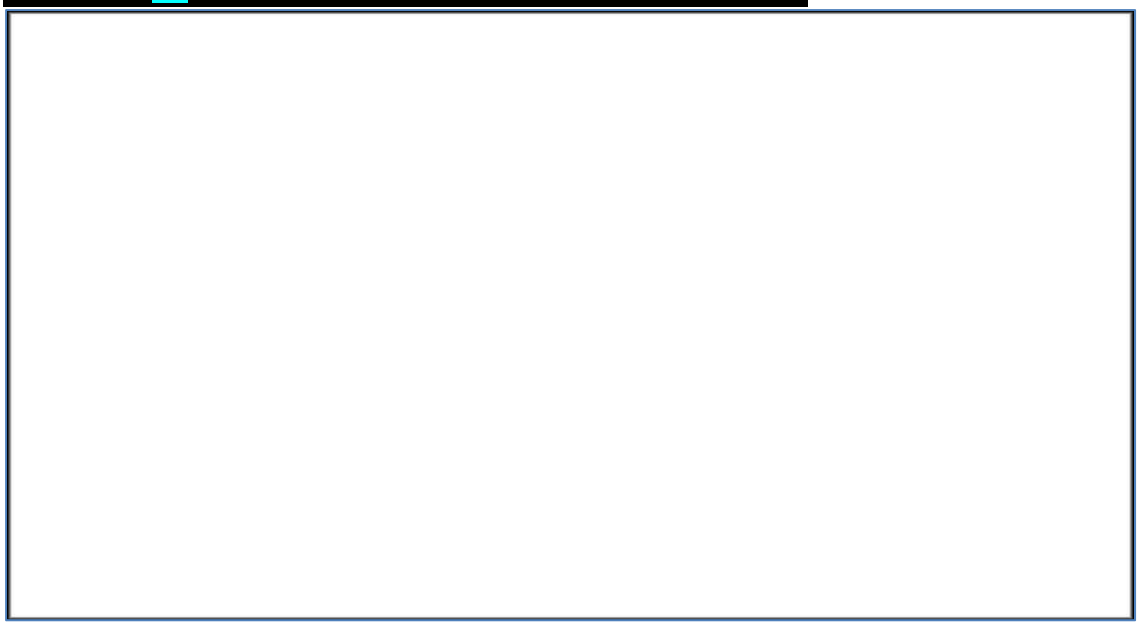
Power P1	Power P2	Dbar	Dhat	pD	DIC
1	1.5	1161.67	1150.11	11.56	1173.23
0.5	1.5	1162.91	1151.60	11.31	1174.21
1	1	1162.49	1150.57	11.92	1174.41
0.5	2	1163.15	1151.59	11.56	1174.71
1.5	1.5	1163.34	1151.43	11.91	1175.26
0.5	1	1165.12	1153.39	11.73	1176.86
1.5	2	1165.73	1154.55	11.18	1176.92

Abbreviations: DIC = Deviance information criterion.

All these FP models were explored for the most plausible baseline (geftinib) parametric model (generalised gamma) as determined in section B.3.3.1.2 (presented in Appendix D.6.3.1).

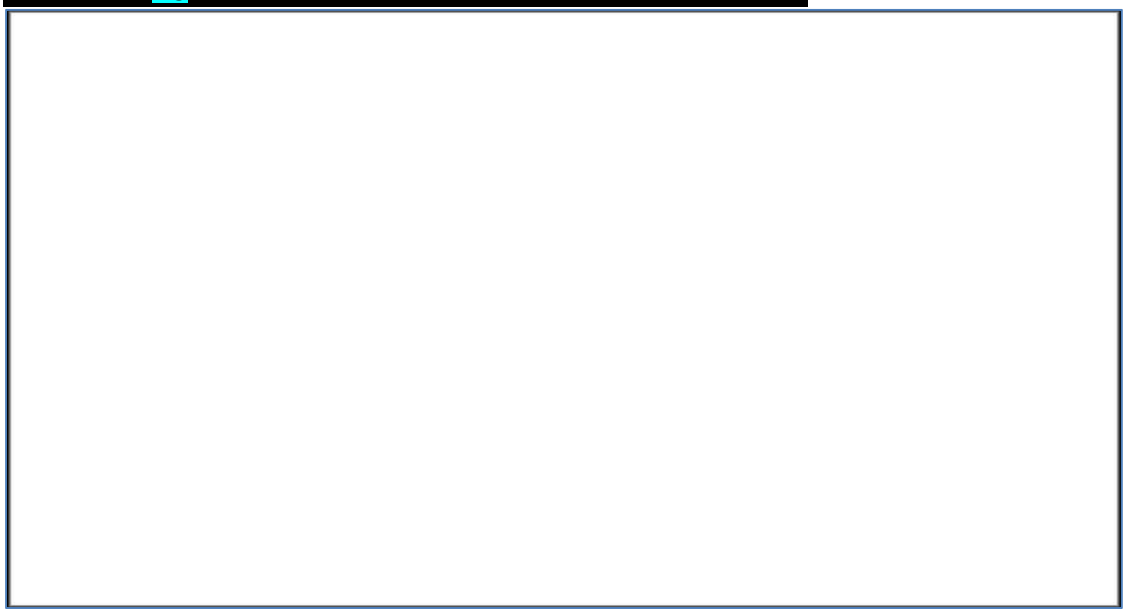
Despite *p1=1, p2=1.5* providing the lowest DIC value, the model over fitted the tail of the dacomitinib KM curve ([redacted]), which therefore resulted in clinically implausible extrapolations due to dacomitinib crossing all other comparators (XXXXXXX17). There was no clinical rational to suggest why there would be a significant higher rate of progression for dacomitinib compared to comparators beyond 2-years (**Error! Reference source not found.**).

[redacted]17[redacted]



Abbreviations: KM = Kaplan-Meier.

[redacted]18



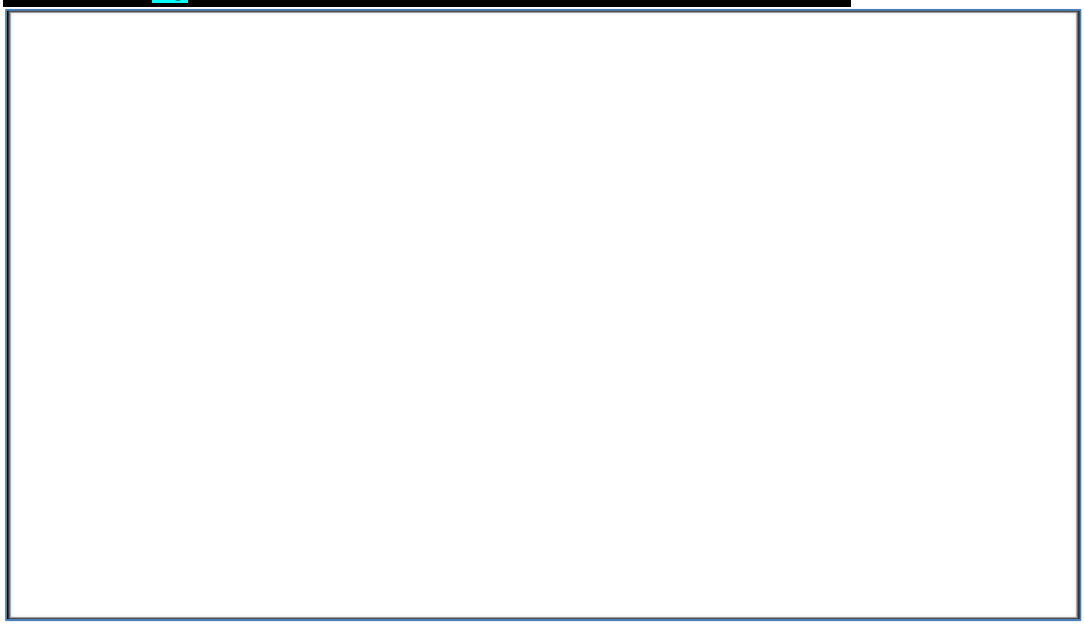
The next best fitting second-order model provided a plausible estimate which was in line with the observed data (XXXXXXX19) and provided more clinical plausible instantaneous HRs between dacomitinib and gefitinib up to around 50 months (XXXXXXX20). Therefore, in the base-case analysis, the second-order *P1=0.5, P2=1.5*, was applied, with the other most clinically plausible model within DIC<+5 applied in sensitivity analysis (*P1=0.5, P2=1,* [see **Error! Reference source not found.**; Appendix D.6.3.1]). The projected means for the base-case and scenario analysis are presented in Table 21 along with the medians compared to the observed data from ARCHER 1050, which demonstrate the face validity of the dacomitinib projection.

Table 20. Means and medians from fractional polynomial models compared to observed data – PFS(IRC)

Model	Geftinib/Erlotinib		Dacomitinib		Afatinib	
	Median	Mean	Median	Mean	Median	Mean
P1=0.5; P2=1.5*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5; P2=1*			[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	9.23	-	14.65	-	-	-

*Generated with 'base' gefitinib generalised gamma curve

[redacted] 19



Abbreviations: KM = Kaplan-Meier.

[redacted] 20

Overall survival

The model fit statistics for OS are presented in Table 21, where the lowest DIC (603.1) was a second-order fractional polynomial *P1=1, P2=1.5*. All models with DIC less than 608 were then plotted to assess the clinical plausibility.

Table 21. Goodness-of-fit estimates for fractional polynomial models of different powers p1 and p2 – OS

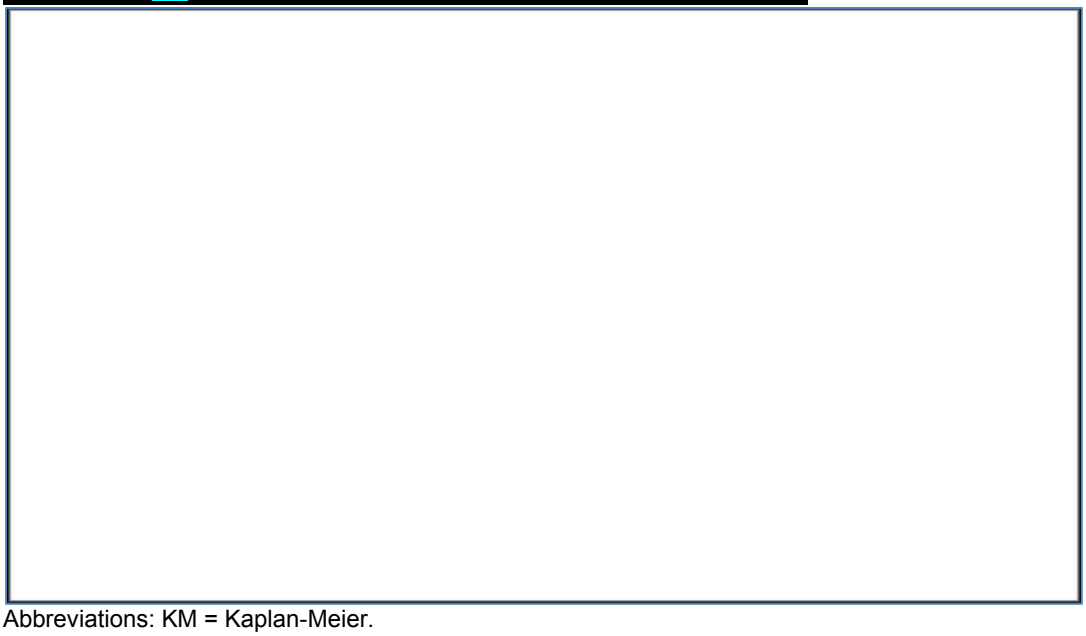
Power P1	Power P2	Dbar	Dhat	pD	DIC

Power P1	Power P2	Dbar	Dhat	pD	DIC
1	1.5	591.37	579.66	11.72	603.09
1	1	591.23	578.79	12.44	603.67
0.5	1.5	591.80	579.29	12.51	604.31
0	1.5	593.81	581.32	12.49	606.31
0.5	1	594.15	580.04	14.10	608.25
0	1	595.93	583.07	12.86	608.78
0	0.5	597.91	585.48	12.43	610.34
-0.5	-	603.39	595.91	7.48	610.87
1.5	1.5	600.06	588.51	11.55	611.61
0	-	604.15	596.25	7.91	612.06
-0.5	0	602.98	593.28	9.70	612.68

Abbreviations: DIC = Deviance information criterion.

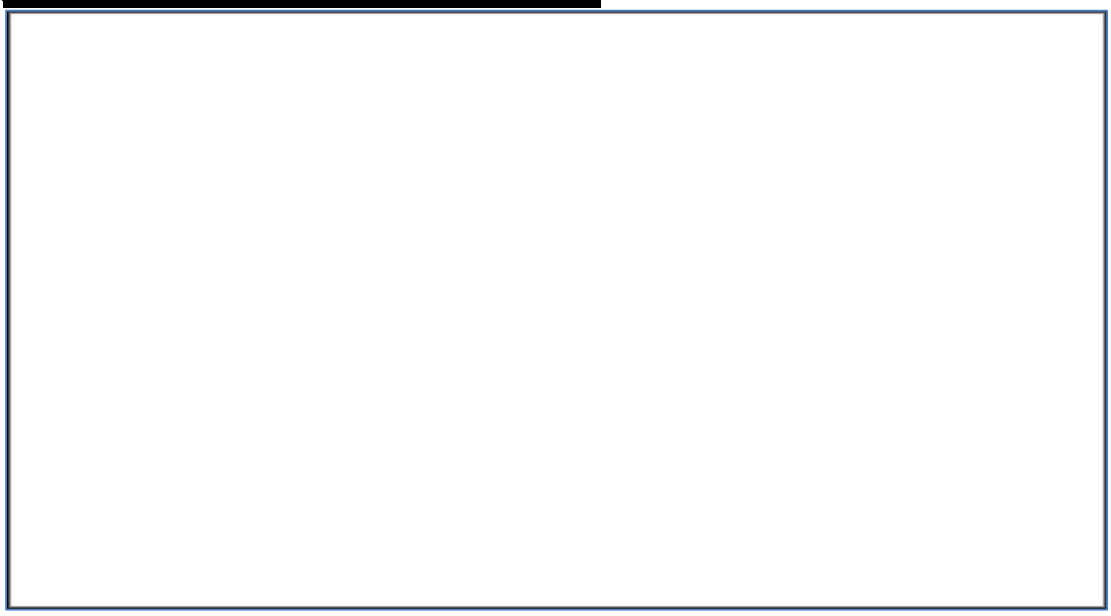
The second-order model *p1=1, p2=1.5* provided the lowest DIC value, however the model did not provide clinically plausible extrapolations as the additional flexibility of the second-order model lead to significant over fitting of the tail of the KM, which was subject to censoring and thus associated with greater uncertainty. This trend was observed in all models with DIC<+5 (see models presented with baseline generalised gamma in Appendix 6.3.2). Therefore, models with less accurate fit to the observed data were explored (DIC<+10).

[redacted] 21



Abbreviations: KM = Kaplan-Meier.

[redacted]22[redacted]



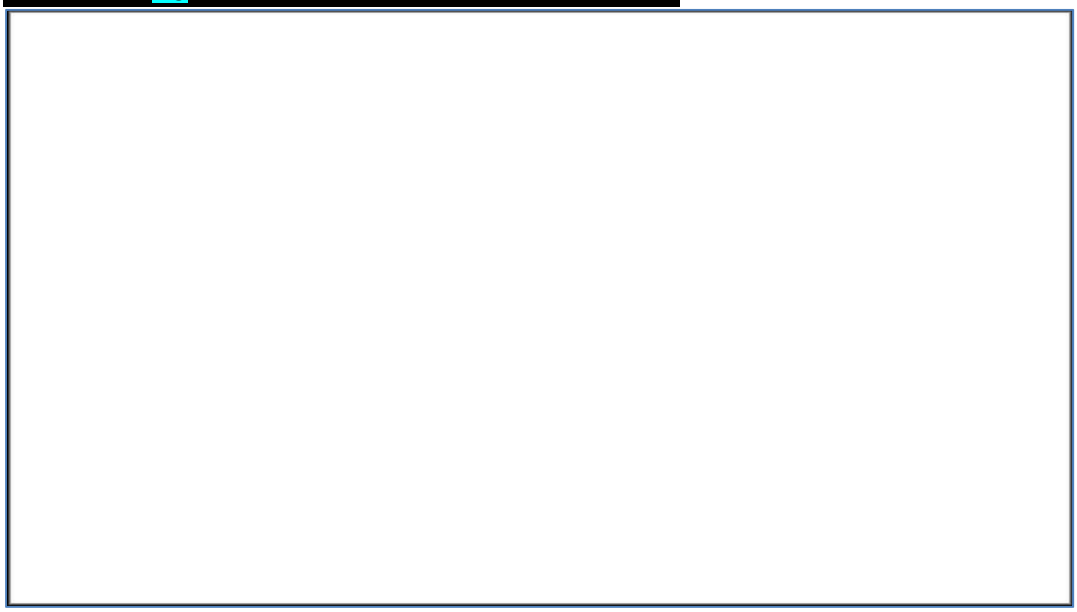
The same pattern was observed with all the additional second-order models. However, the first-order models provided plausible estimates (XXXXXXX23) and instantaneous hazards over time (XXXXXXX24) which were in line with the observed data. Therefore, in the base-case analysis, the best fitting first order *P1=-0.5* was applied with *P1=0* (**Error! Reference source not found.**, Appendix D.6.3.2) applied in scenario analysis. The projected means for the base-case and scenario analysis are presented in Table 22 along with the medians compared to the observed data from ARCHER 1050, which provide face validity for the applied FP model.

Table 22. Means and medians from fractional polynomial models compared to observed data – OS

Model	Geftinib/Erlotinib		Dacomitinib		Afatinib	
	Median	Mean	Median	Mean	Median	Mean
P1=-0.5*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0*			[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	26.84	-	34.07	-	-	-

*Generated with 'base' gefitinib generalised gamma curve

[redacted] 23



Abbreviations: KM = Kaplan-Meier.

[redacted] 24

B.2.10 Adverse reactions

B.2.10.1 Overall adverse events

Overall safety data from ARCHER 1050 are summarised in Table 23. Most patients experienced an all-cause AE, with proportions comparable between dacomitinib and gefitinib (99.6% and 98.2%, respectively).[33,40] A higher number of patients in the dacomitinib arm reported Grade 3 AEs (any cause) versus those who received

gefitinib ([redacted] versus [redacted], respectively); however, the number of patients with Grade 4 events was low and comparable between treatment arms ([redacted] versus [redacted] for dacomitinib and gefitinib, respectively).[40] More patients required a dose reduction due to an AE (any cause) with dacomitinib than with gefitinib (66.1% versus 8.0%, respectively).[33] However, dose reductions are not recommended in the approved license for gefitinib[59] therefore every other day dosing was classed as a dose reduction. The frequency of all causality serious adverse events (SAEs) was similar in both treatment groups (27.3% versus 22.3%, respectively).[40]

The overall frequency of treatment-related AEs was comparable between the two treatment arms ([redacted] versus [redacted] for dacomitinib and gefitinib, respectively), whereas the frequency of SAEs attributed to treatment was low, occurring in just [redacted] ([redacted]) patients treated with dacomitinib and [redacted] ([redacted]) patients treated with gefitinib.[33] Discontinuation rates due to treatment-related AEs were also low in both dacomitinib- and gefitinib-treated patients ([redacted] and [redacted] of patients, respectively).[33]

Table 23. Summary of adverse events in the ARCHER 1050 trial (Safety Population)*[40]

Adverse event	Dacomitinib N=227	Gefitinib N=224
All-causality AEs		
Patients with any AE, n (%)	226 (99.6)	220 (98.2)
Patients with any SAE, n (%)	62 (27.3)	50 (22.3)
Patients with any AE Grade 3/4, n (%)	[redacted]	[redacted]
Patients with any AE Grade 3, n (%)	[redacted]	[redacted]
Patients with any AE Grade 4, n (%)	[redacted]	[redacted]
Patients with any AE leading to dose reduction,† n (%)	150 (66.1)	18 (8.0)
Patients with any AE leading to temporary discontinuation, n (%)	[redacted]	[redacted]
Treatment-related AEs		
Treatment-related AEs, n (%)	[redacted]	[redacted]
Treatment-related SAE, n (%)	[redacted]	[redacted]
Treatment-related AE Grade 3/4, n (%)	[redacted]	[redacted]
Treatment-related AE Grade 3, n (%)	[redacted]	[redacted]
Treatment-related AE Grade 4, n (%)	[redacted]	[redacted]
Treatment-related AE Grade 5, n (%)	[redacted]	[redacted]
Treatment-related fatal AE, n (%)	[redacted]	[redacted]
Treatment-related AEs leading to discontinuation, n (%)	[redacted]	[redacted]

*MedDRA (version 19.1) coding dictionary applied.
†Dose reduction to manage toxicity due to AE(s) is described in the protocol as every other day dosing for gefitinib.

‡Dacomitinib: two (one related to untreated diarrhoea, one related to untreated cholelithiasis/liver disease).
§Gefitinib: one (related to sigmoid colon diverticulitis/rupture complicated by pneumonia).
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

B.2.10.2 Common adverse events

AEs (any cause) reported by ≥10% of patients in either treatment arm by treatment arm are summarised in Table 24. Although the pattern of AEs showed some differences between the treatment arms, overall, the majority of AEs in patients treated with dacomitinib or gefitinib were mild or moderate in severity (classed as Grades 1 or 2, respectively).[33]

In the dacomitinib arm, the most common (reported in ≥30% of patients) Grade 1/2 AEs from any cause were diarrhoea (78%), paronychia (54%), stomatitis (40%) and dermatitis acneiform (35%), while the most common Grade 3 AEs were dermatitis acneiform (14%), diarrhoea (8%) and paronychia (7%)[33] In comparison, the most common AEs in patient treated with gefitinib were diarrhoea (56%), and those associated with liver toxicity, including an increase in alanine transaminase (ALT; 39%) and aspartate transaminase (AST; 36%).[33] The most common grade 3 AEs were raised ALT levels (8%), AST increase (4%) and dyspnoea (2%).[33] The rate of Grade 4 AEs was low, (2% for both treatment groups).[33]

Table 24. Most common AEs (≥10% in any group) from any cause in participants from the ARCHER 1050 trial (Safety Population)*[33]

Adverse event	Dacomitinib N=227				Gefitinib N=224			
	Grade(s)				Grade(s)			
	1–2	3	4	5	1–2	3	4	5
Any adverse event, n (%)	83 (37)	116 (51)	5 (2)	22 (10)	128 (57)	67 (30)	5 (2)	20 (9)
Diarrhoea, n (%)	178 (78)	19 (8)	0	1 (<1%)	123 (55)	2 (1)	0	0
Paronychia, n (%)	123 (54)	17 (7)	0	0	42 (19)	3 (1)	0	0
Dermatitis acneiform, n (%)	80 (35)	31 (14)	0	0	64 (29)	0	0	0
Stomatitis, n (%)	91 (40)	8 (4)	0	0	39 (17)	1 (<1)	0	0
Decreased appetite, n (%)	63 (28)	7 (3)	0	0	54 (24)	1 (<1)	0	0
Dry skin, n (%)	60 (26)	3 (1)	0	0	38 (17)	0	0	0
Weight decreased, n (%)	53 (23)	5 (2)	0	0	36 (16)	1 (<1)	0	0
Alopecia, n (%)	52 (23)	1 (<1)	0	0	28 (13)	0	0	0
Cough, n (%)	48 (21)	0	0	0	41 (18)	1 (<1)	0	0
Pruritus, n (%)	44 (19)	1 (<1)	0	0	28 (13)	3 (1)	0	0
ALT increased, n (%)	42 (19)	2 (1)	0	0	69 (31)	19 (8)	0	0
Conjunctivitis, n (%)	43 (19)	0	0	0	9 (4)	0	0	0
Nausea, n (%)	40 (18)	3 (1)	0	0	48 (21)	1 (<1)	0	0
AST increased, n (%)	42 (19)	0	0	0	72 (32)	9 (4)	0	0
Rash, n (%)	30 (13)	10 (4)	0	0	24 (11)	0	0	0
Palmar-plantar erythrodysesthesia syndrome, n (%)	31 (14)	2 (1)	0	0	7 (3%)	0	0	0
Pain in extremity, n (%)	31 (14)	0	0	0	26 (12)	0	0	0
Dyspnoea, n (%)	25 (11)	4 (2)	1 (<1)	0	24 (11)	4 (2)	0	2 (1)
Asthenia, n (%)	24 (11)	5 (2)	0	0	25 (11)	3 (1)	0	0
Constipation, n (%)	29 (13)	0	0	0	31 (14)	0	0	0
Mouth ulceration, n (%)	28 (12)	0	0	0	13 (6)	0	0	0
Maculopapular rash, n (%)	18 (8)	10 (4)	0	0	26 (12)	1 (<1)	0	0
Upper respiratory tract infection, n (%)	25 (11)	3 (1)	0	0	28 (13)	0	0	0
Musculoskeletal pain, n (%)	24 (11)	2 (1)	0	0	28 (13)	0	0	0
Dermatitis, n (%)	21 (9)	4 (2)	0	0	8 (4)	1 (<1)	0	0
Insomnia, n (%)	23 (10)	1 (<1)	0	0	33 (15)	0	0	0
Anaemia, n (%)	20 (9)	2 (1)	0	0	11 (5)	5 (2)	0	0

Adverse event	Dacomitinib N=227				Gefitinib N=224			
	Grade(s)				Grade(s)			
	1–2	3	4	5	1–2	3	4	5
Chest pain, n (%)	22 (10)	0	0	0	32 (14)	0	0	0
Hypokalaemia, n (%)	11 (5)	9 (4)	2 (1)	0	9 (4)	4 (2)	0	0
Vomiting, n (%)	18 (8)	2 (1)	0	0	29 (13)	0	0	0
Back pain, n (%)	18 (8)	0	0	0	34 (15)	1 (<1)	0	0
Pustular rash, n (%)	6 (3)	8 (4)	0	0	3 (1)	0	0	0
Hypertension, n (%)	10 (4)	3 (1)	0	0	6 (3)	4 (2)	0	0
Disease progression, n (%)	0	0	0	8 (4)	0	0	0	11 (5)
Pleural effusion, n (%)	1 (<1)	5 (2)	0	0	4 (2)	1 (<1)	0	1 (<1)
Lymphocyte count decreased, n (%)	0	5 (2)	0	0	2 (1)	0	0	0
Abnormal hepatic function, n (%)	2 (1)	0	0	0	3 (1)	4 (2)	0	0

*The table lists all-cause, maximum grade adverse events reported in at least 10% of patients in either treatment group at grades 1–2, and adverse events reported at grade 3–5 in at least 2% of patients in either treatment group.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase. AST = aspartate aminotransferase.

Common treatment-related AEs that that were reported in [redacted] of patients in both treatment arms included diarrhoea (dacomitinib: [redacted]; gefitinib: [redacted]), dermatitis acneiform (dacomitinib: [redacted]; gefitinib: [redacted]) and paronychia (dacomitinib: [redacted]; gefitinib: [redacted]).[33,40] In addition, stomatitis, dry skin, decreased appetite and alopecia were reported in [redacted] patients treated with dacomitinib, while increased ALT and AST levels were commonly reported in the gefitinib treatment arm (Table 25).[33,40] The majority of treatment-related AEs were mild or moderate in severity.[33]

Table 25: Most common treatment-related adverse events occurring in [redacted] of patients from the ARCHER 1050 trial (Safety Population)[40]

Adverse event*	Dacomitinib N=227				Gefitinib N=224			
	Grade(s)				Grade(s)			
	1–2	3	4	5	1–2	3	4	5
Diarrhoea, n (%)	[redacted]							
Paronychia, n (%)	[redacted]							
Dermatitis acneiform, n (%)	[redacted]							
Stomatitis, n (%)	[redacted]							
Decreased appetite, n (%)	[redacted]							
Dry skin, n (%)	[redacted]							
Alopecia, n (%)	[redacted]							
ALT increased, n (%)	[redacted]							
AST increased, n (%)	[redacted]							

*Arranged in descending order of frequency in the dacomitinib treatment group.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported.

B.2.10.3 Exposure to study drug and dose adjustments due to adverse events

The median duration of treatment in ARCHER 1050 was longer in the dacomitinib treatment arm ([redacted] weeks; range: [redacted]) versus the gefitinib arm ([redacted] weeks; range: [redacted]).[40] However, frequency of AE data were not adjusted for the

increased length of exposure in patients treated with dacomitinib, indicating that comparative assessment may be biased against dacomitinib.[40]

Dose reductions were required in 66.1% and 8.0% of patients in the dacomitinib and gefitinib treatment arms, respectively.[40] For dacomitinib-treated patients, the median time-to-dose reduction was 2.8 months (IQR: 1.3–4.2 months) and the median duration of the dose reduction was 11.3 months (IQR: 4.8–18.9 months).[33] Overall, 38.3% (87/227) of patients required a dose reduction to 30mg daily, while 27.8% (63/227) of patients required a dose reduction to 15mg daily.[33] Gefitinib dose reductions (every other day dosing) occurred in 8% (18/224) of patients. Among gefitinib-treated patients, the median time to dose reduction was 3.3 months (IQR: 2.4–4.2 months) and the median duration of the dose reduction was 5.2 months (IQR: 2.5–7.9 months).[33] Table 26 provides a summary for AEs that resulted in a dose reduction in ≥2% of patients.[40]

Table 26: Adverse events (all-cause) resulting dose reductions (reported for ≥2% of patients in any treatment arm) in the ARCHER 1050 trial (Safety Population)*[33,40]

AE category†	Dacomitinib N=227	Gefitinib N=224
Any AEs, n (%)	150 (66.1)	18 (8.0)
Gastrointestinal disorders, n (%)	27 (11.9)	3 (1.3)
Diarrhoea, n (%)	19 (8.4)	3 (1.3)
Stomatitis, n (%)	6 (2.6)	0
Skin and subcutaneous tissue disorders, n (%)	91 (40.1)	4 (1.8)
Dermatitis acneiform, n (%)	46 (20.3)	3 (1.3)
Rash maculo-papular, n (%)	11 (4.8)	0
Rash, n (%)	10 (4.4)	0
Dermatitis, n (%)	7 (3.1)	0
Dry skin, n (%)	7 (3.1)	0
Palmar-plantar erythrodysaesthesia syndrome, n (%)	5 (2.2)	0
Infections and infestations, n (%)	53 (23.3)	2 (0.9)
Paronychia, n (%)	38 (16.7)	2 (0.9)
Rash pustular, n (%)	9 (4.0)	0
Investigations, n (%)	4 (1.8)	7 (3.1)
ALT increased, n (%)	0	6 (2.7)
AST increased, n (%)	0	5 (2.2)

*Dacomitinib was managed by dose reductions of the daily dose whereas gefitinib was managed by dosing every other day. Patient 04802003 had an AE (Acne of skin of arms) that was not coded as per MedDRA and therefore was not reported in this table.
†AEs are sorted by descending frequency in the dacomitinib arm.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

More patients in the dacomitinib arm than the gefitinib arm discontinued treatment temporarily due to AEs ([redacted] versus [redacted], respectively; Table 27).[40] Most AEs leading to temporary treatment discontinuation were considered related to the study treatment and therefore the frequencies of treatment-related AEs associated with temporary discontinuations are very similar to the all causality AEs.[40]

Table 27: Adverse events (all-cause) that resulted in temporary discontinuations reported for ≥2% of patients in any treatment arm of the ARCHER 1050 trial (Safety Population)[40]

AE category*	Dacomitinib† N=227	Gefitinib N=224
Any AEs, n (%)	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]
Dermatitis acneiform, n (%)	[redacted]	[redacted]
Rash, n (%)	[redacted]	[redacted]
Rash maculo-papular, n (%)	[redacted]	[redacted]
Dermatitis, n (%)	[redacted]	[redacted]
Pruritus, n (%)	[redacted]	[redacted]
Dry skin, n (%)	[redacted]	[redacted]
Acne, n (%)	[redacted]	[redacted]
Infections and infestations , n (%)	[redacted]	[redacted]
Paronychia, n (%)	[redacted]	[redacted]
Rash pustular, n (%)	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]
Stomatitis, n (%)	[redacted]	[redacted]
Vomiting, n (%)	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]
Asthenia, n (%)	[redacted]	[redacted]
Mucosal inflammation, n (%)	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]
Decreased appetite, n (%)	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]
ALT increased, n (%)	[redacted]	[redacted]
AST increased, n (%)	[redacted]	[redacted]
Hepatobiliary disorders, n (%)	[redacted]	[redacted]
Hepatic function abnormal, n (%)	[redacted]	[redacted]

*AEs are sorted by descending frequency in the dacomitinib arm.
†Dacomitinib was managed by dose reductions of the daily dose whereas gefitinib was managed by dosing every other day. Patient 04802003 had an AE (Acne of skin of arms) that was not coded as per MedDRA and therefore was not reported in this table.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Although more patients in the dacomitinib arm than gefitinib arm discontinued treatment temporarily due to AEs, rates of permanent discontinuations due to treatment-related AEs were similar between the treatment arms (versus , respectively; Table 28).[40]

Table 28: Treatment-emergent adverse events leading to permanent discontinuation of treatment in patients from the ARCHER 1050 trial (Safety Population)[40]

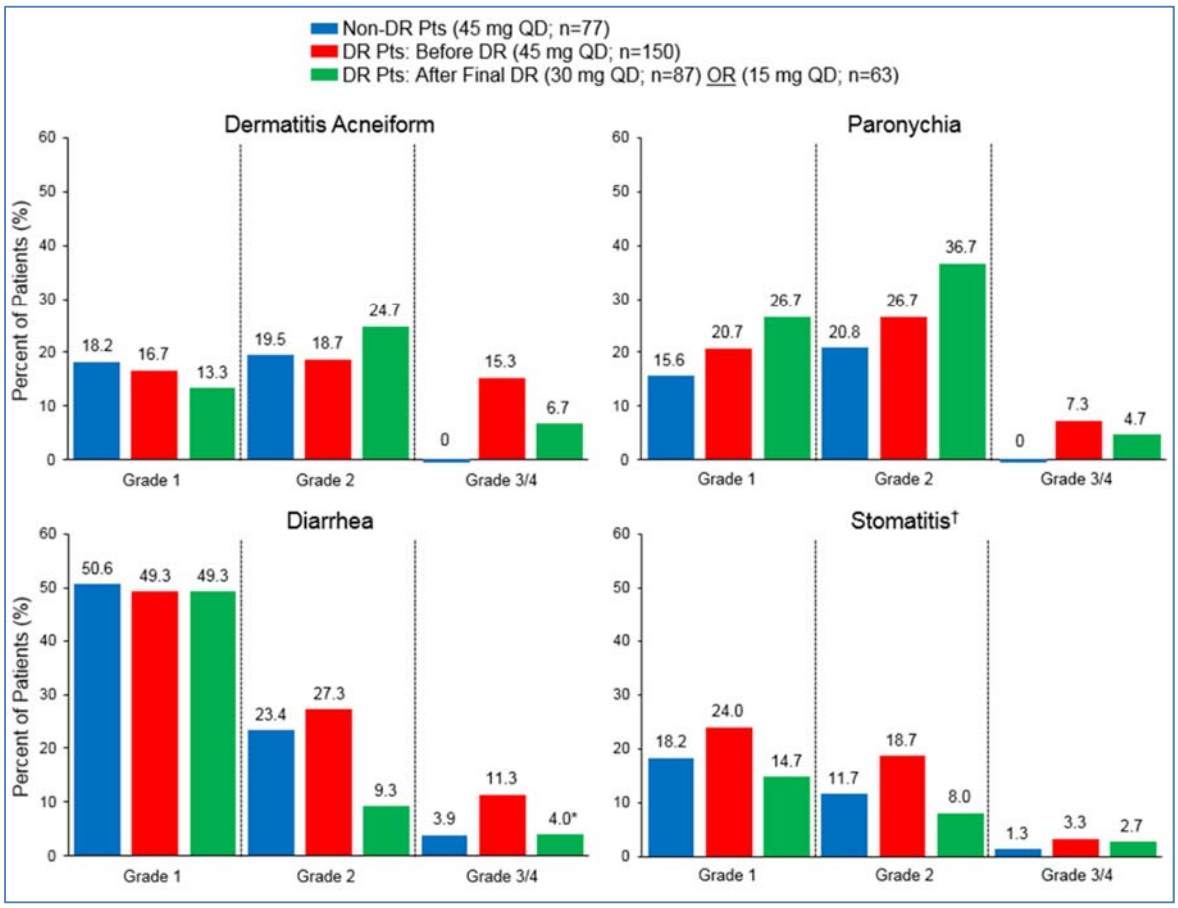
TEAE, n (%)	Dacomitinib N=227			Gefitinib N=224		
All causality TEAEs						
Any TEAEs						
Pneumonia						
Disease progression						
Dermatitis acneiform						
Alanine aminotransferase increased						
Treatment-related TEAEs						
Any TEAEs						
Dermatitis acneiform						
Diarrhoea						
Alanine aminotransferase increased						

Abbreviations: TEAE = treatment-emergent adverse event.

B.2.10.3.1 Effect of dose adjustments on safety and efficacy outcomes

In the ARCHER 1050 trial, patients who started treatment with dacomitinib 45 mg once daily and required dose reductions (to either 30 mg or 15 mg once daily) experienced lower incidences of adverse events with no impact on efficacy. For instance, grade 3 and 4 events of dermatitis acneiform, paronychia, diarrhoea and stomatitis were substantially decreased following dose reductions (Figure 25). The most pronounced reductions occurred for dermatitis acneiform and diarrhoea, where the number of patients with grade 3 and 4 events decreased from 15.3% to 6.7% and 11.3% to 4.0%, respectively.[60]

Figure 25. Incidence of common adverse events in the ARCHER 1050 trial before and after dacomitinib dose reductions[60]



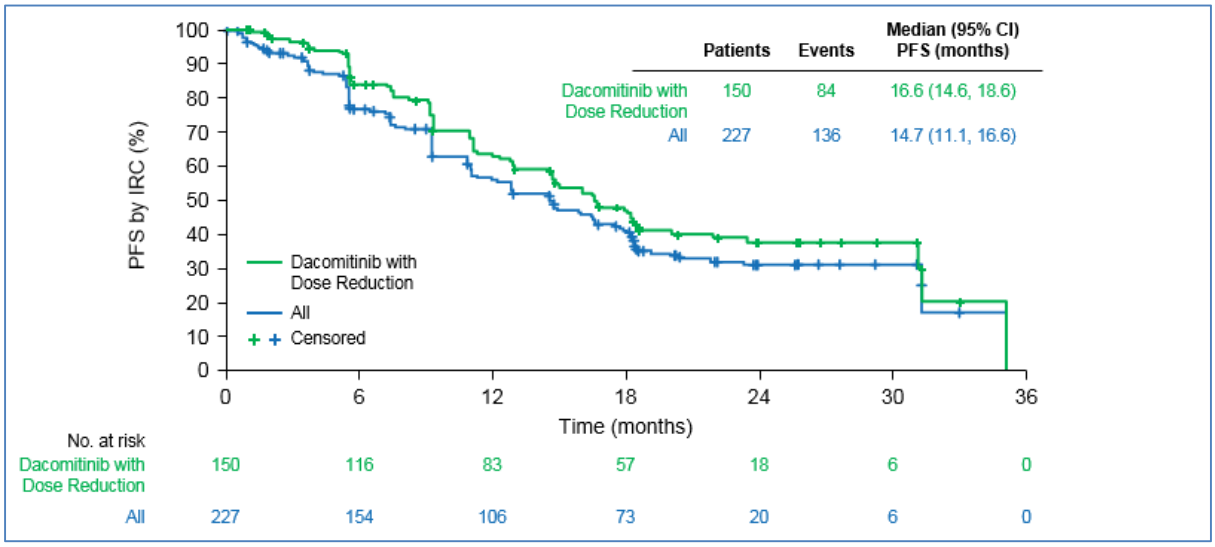
*One Grade 5 event occurred after dose reduction, and is not included in this percentage.

†One non-stomatitis Grade 4 event resulted in a dose reduction.

Abbreviations: DR = dose reduction; QD = once daily;

Despite these dose reductions, the PFS benefit was maintained and was similar between patients with dacomitinib dose reductions and the overall dacomitinib treatment arm population (16.6 months [95% CI: 14.6, 18.6] versus 14.7 months [11.1, 16.6]; Figure 26).

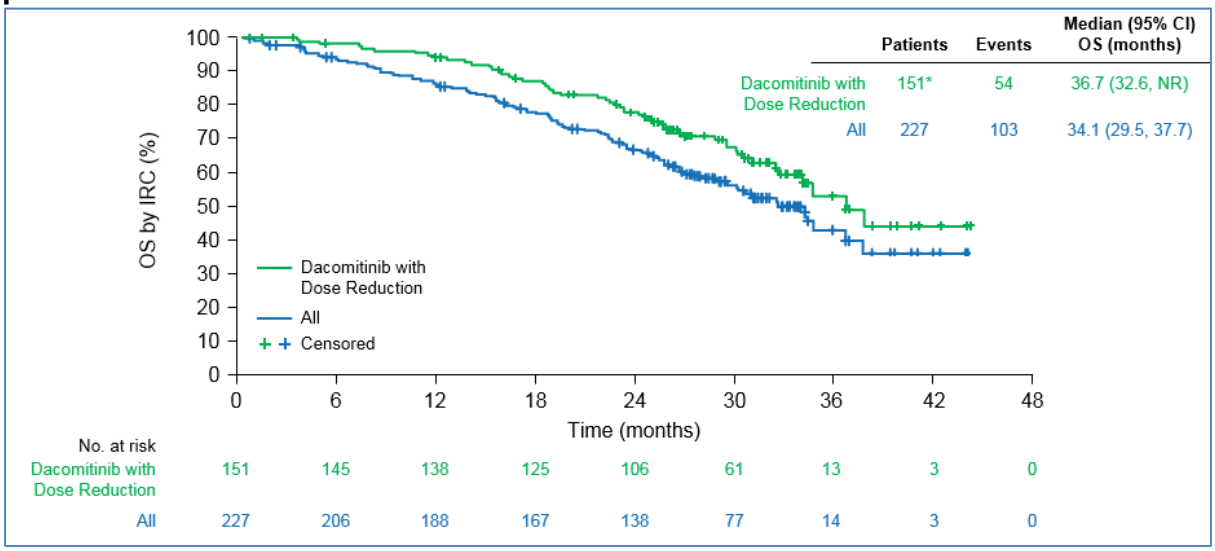
Figure 26. Median progression-free survival per blinded independent review committee analysis for dacomitinib in all patients versus with patients with dose reduction[60]



Abbreviations: CI = confidence interval; IRC = independent review committee; PFS = progression-free survival.

Similar to PFS, the OS benefit was also maintained in patients with dacomitinib dose reductions compared to the overall dacomitinib treatment arm population: 36.7 months (95% CI: 32.6, NR) versus 34.1 months (29.5, 37.7; Figure 27).[60]

Figure 27. Median overall survival for dacomitinib in all patients versus patients with dose reduction[60]



Abbreviations: CI = confidence interval; IRC = independent review committee; NR = not reported; OS = overall survival.

B.2.10.4 Safety of dacomitinib in relation to the decision problem

The incidence of AEs reported for dacomitinib in the ARCHER 1050 trial was consistent with other clinical studies of dacomitinib, with no new safety signals identified.[33]

As indicated in previous sections, the most common AEs experience during treatment with dacomitinib were diarrhoea, paronychia, stomatitis and dermatitis acneiform.[33] According to a consensus meeting of UK-based multidisciplinary panel of medical and clinical oncologists, these AEs are typical of treatment with EGFR-TKIs and vary widely from first- to second-generation TKIs.[61] Based on naïve comparisons, dacomitinib appears to have a safety profile consistent with currently licensed TKIs in the UK, particularly afatinib (however, with numerically lower rates of diarrhoea, stomatitis and dermatitis acneiform; Table 29). Given that the most common AEs associated with dacomitinib are also typical of the TKI treatment class (e.g. diarrhoea, stomatitis, paronychia and dermatitis), its approval is unlikely to change current clinical practice as clinicians may be already familiar with managing these AEs.[33,61]

Table 29. Incidence of common AEs reported in first-line clinical trials of EGFR-TKIs in patients with advanced NSCLC*[33,61]

Drug	Diarrhoea	Stomatitis / Mucositis	Paronychia	Dermatitis acneiform‡
Dacomitinib	85%	41%	61.7%	48.9%
Gefitinib†	34.2–54%	15.2–40.2%	13.5–32%	15.2–66.2%
Erlotinib	25–57%	13%	4%	NR
Afatinib	88.3–95%	51.9–72.1%	32.6–56.8%	80.8–89.1%

*Incidence ranges reported for treatments with data available from multiple trials: IPASS,[37] First-SIGNAL,[62] NEJ002[42,43] and WJTOG3405[44] (gefitinib); OPTIMAL[36] and EURTAC[35] (erlotinib); LUX-Lung 3[38], LUX-Lung 6[39] and LUX-Lung 7[63](afatinib); ARCHER 1050[33] (dacomitinib).
†Includes data from ARCHER 1050; some studies also enrolled patients with EGFR wild-type tumours.
‡Reported as "acneiform rash" for gefitinib and afatinib.
Abbreviations: AE = adverse event; EGFR = epidermal growth factor receptor; NR = not reported; NSCLC = non-small-cell lung cancer; TKI = tyrosine kinase inhibitor.

In ARCHER 1050, although more patients in the dacomitinib treatment arm required a dose reduction versus the gefitinib arm (66.1% versus 8.0%, respectively),[40] efficacy outcomes for dacomitinib-treated patients were consistently improved compared with the gefitinib treatment arm. Dacomitinib is available in three dose strengths – 45 mg, 30 mg and 15 mg – making dose modifications to individualise treatment straightforward (while also maintaining efficacy). Dacomitinib offers an

advantage over gefitinib as dose reductions are not recommended in the approved license for the latter; this would therefore be expected to impact the dose reductions, discontinuations and AE profile achieved in real-world clinical practice with gefitinib.[59] Additionally, despite a higher number of dacomitinib patients requiring dose reductions, a similar proportion of patients in both the dacomitinib and gefitinib arms experienced a treatment-related AE leading to treatment discontinuation (22 [10%] and 15 [7%] patients in the dacomitinib and gefitinib arms, respectively).[33]

B.2.11 Ongoing studies

There are no additional, ongoing Phase III trials in the public domain for dacomitinib for the first-line treatment of EGFR-positive NSCLC.

B.2.12 Innovation

Dacomitinib is a second generation, selective and irreversible EGFR-TKI that has activity against all three members of the ErbB family (EGFR/HER1, HER2 and HER4), providing improved efficacy compared with reversible first-generation TKIs. Irreversible binding of an agent is believed to help extend its efficacy and delay the development of resistance, whereas targeting more than one family member of the ErbB family may improve efficacy and overcome redundancy associated with receptor crosstalk.

As a second-generation TKI, dacomitinib also offers a new and important alternative for treatment of patients with EGFR+ NSCLC in first-line treatment setting alongside afatinib.

In patients with EGFR+ advanced NSCLC, dacomitinib is the first and only EGFR-TKI to show significant OS benefit in a phase III randomised trial (ARCHER 1050) against an active comparator. The median OS was 34.1 months (95% CI: 29.5, 37.7) with dacomitinib versus 26.8 months (95% CI: 23.7, 32.1) with gefitinib ((HR, 0.760).[34]

Additionally, of the current approved treatments for EGFR+ NSCLC, dacomitinib has the numerically longest PFS data. Median PFS based on blinded IRC analysis was 14.7 months (95% CI: 11.1, 16.6) in the dacomitinib arm and 9.2 months (95% CI:

9.1, 11.0) in the gefitinib arm (HR 0.59). Investigator-assessed median PFS was 16.6 months (95% CI: 12.9, 18.4) in the dacomitinib arm and 11 months (95% CI: 9.4, 12.1) in the gefitinib arm (HR 0.62).[33]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of clinical evidence

In the ARCHER 1050 trial, treatment with dacomitinib was associated with a significant improvement in the primary endpoint, PFS based on blinded IRC analysis, when compared to gefitinib.[33,40] Patients who received dacomitinib were associated with a median PFS of 14.7 months (95% CI: 11.1, 16.6) compared to 9.2 months (95% CI: 9.1, 11.0) in patients treated with gefitinib.[33,40] This translated to a 5.5 month median improvement in PFS and, based on a HR of 0.589, indicated a 41% reduction in the risk of progression ($p<0.0001$).[33,40] These findings were further supported by the results of the PFS based on investigator assessment, where dacomitinib was associated with a median PFS of 16.6 months [95% CI: 12.9, 18.4] compared to 11.0 months [95% CI: 9.4, 12.1] with gefitinib (HR: 0.62; 95% CI: 0.50, 0.78; $p<0.0001$). Given the detrimental effect of symptoms associated with EGFR+ NSCLC (as outlined in section B.1.3.1), the PFS improvements of dacomitinib relative to gefitinib may have a positive impact on patients by delaying disease progression and potentially reducing the burden of symptoms, such as cough, dyspnoea and pain.

Treatment with dacomitinib demonstrated significant improvements in OS, a key secondary outcome. Patients treated with dacomitinib reported median OS of 34.1 months (95% CI: 29.5, 37.7) compared to 26.8 months (95% CI: 23.7, 32.1) with gefitinib (HR: 0.760; 95% CI: 0.582, 0.993; 2-sided p-value=0.0438; stratified analysis).[34,40] This translated into a 7.3 month improvement in median OS and 24% reduction in the risk of death compared with gefitinib.

The significant improvements in PFS and OS associated with dacomitinib are further supported by results from the NMA, which indicated that dacomitinib is associated with superior PFS and OS when compared to both erlotinib and afatinib.

First-line treatment with dacomitinib resulted in significant improvements versus gefitinib in the secondary endpoints of DoR (median 14.8 months versus 8.3 months for dacomitinib and gefitinib, respectively; p<0.0001) and TTF (median 11.1 months versus 9.2 months, respectively; p=0.0001).[33,40] These clinically meaningful[64] improvements in PFS, DoR and TTF compared to gefitinib further highlight the potential role of dacomitinib in delaying the use of subsequent treatments thereby increasing the total time on active therapy in currently available treatment sequences.[19]

Treatment with dacomitinib was also shown to significantly reduce key disease-related symptoms based on a self-reported QoL assessment with the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. In particular, clinically meaningful improvements (≥10 point change in score from baseline)[64] were observed in more treatment cycles for cough and chest pain symptoms in patients treated with dacomitinib arm (28/30 and 23/30 treatment cycles, respectively) compared with the gefitinib arm (22/30 and 12/30 treatment cycles, respectively).[33,50] Additionally, chest pain was significantly improved in patients treated with dacomitinib compared with gefitinib (mean improvement: -10.24 versus -7.44; p=0.0235).[33] Given the significant burden of symptoms among patients with NSCLC,[17] this indicates the importance of dacomitinib maintaining global QoL in NSCLC patients, which is subsequently maintained for longer than gefitinib given the difference in TTF.

Most patients in the ARCHER 1050 trial experienced an all-causality AE, with proportions comparable between dacomitinib and gefitinib (99.6% and 98.2%, respectively).[33,40] Although, a higher number of patients in the dacomitinib arm reported Grade 3 AEs of any cause versus those who received gefitinib ([redacted] versus [redacted], respectively), the number of patients with Grade 4 events was low and comparable between treatment arms ([redacted] versus [redacted]).[40] In patients treated with dacomitinib in ARCHER 1050, the most common all-cause AEs (of any grade) were diarrhoea (87.2%), paronychia (61.7%), dermatitis acneiform (48.9%) and stomatitis (43.6% of patients), whereas for gefitinib the most common all-cause AEs were diarrhoea (55.8%), increase in ALT (39.3%), increase in AST (36.2%) and dermatitis acneiform (28.6%). The safety profile of dacomitinib appears consistent with that of other TKIs. Additionally, the majority of treatment-related AEs associated

with dacomitinib were mild to moderate in severity[33] and managed using dose interruption, dose reduction and/or supportive measures, without compromising efficacy.[60] As such, dacomitinib is expected to provide an important alternative treatment option to EGFR+ NSCLC patients without impacting the current treatment paradigm in the UK. Given that currently licensed TKIs have been available for several years, it is anticipated that clinical practitioners may be familiar with the adverse events associated with this therapy class. For instance, the most common AEs associated with dacomitinib were those typically associated with TKI treatment (e.g. diarrhoea, stomatitis, paronychia and dermatitis),[33,61] which may already be readily managed within the UK clinical setting. Dacomitinib is therefore unlikely to change current clinical practice as clinicians may be familiar to the typical AEs associated with current standard-of-care treatments. Discontinuation rates due to treatment-related AEs were also low in both dacomitinib- and gefitinib-treated patients (9.7% and 6.7% of patients, respectively).[33]

B.2.13.2 Strengths and limitations of clinical evidence

B.2.13.2.1 Strengths of the evidence

The ARCHER 1050 trial is the only phase III head-to-head study to compare a second-generation TKI with a standard-of-care first-generation TKI in patients with locally advanced or metastatic EGFR+ NSCLC in the first-line setting.

When compared using to evidence from a NMA, ARCHER 1050's head-to-head design provides a clearer indication of dacomitinib's clinical benefits compared with other TKIs, in addition to having increased certainty in its results. Furthermore, TKIs are the standard of care for EGFR+ NSCLC in the first-line in the current UK treatment pathway. As such, the head-to-head design of the ARCHER 1050 trial directly comparing dacomitinib against an approved TKI in first-line is more reflective of the current treatment pathway than trials comparing a TKI against chemotherapy. Comparators in the phase III trials of afatinib, gefitinib and erlotinib were limited to chemotherapy (although afatinib was more recently compared with gefitinib in LUX-Lung 7, this was a phase II study).

The efficacy outcomes assessed in the ARCHER 1050 trial are relevant to UK clinical practice and are consistent with those reported in previous EGFR+ NSCLC submissions (i.e. afatinib, gefitinib, erlotinib and osimertinib).[65-68] Although ARCHER 1050 was an open-label trial, in addition to investigator assessments, it used a third-party blinded IRC review which comprised of ≥2 independent radiologic experts and a third radiologic expert acting as an adjudicator. Trials which utilise open-label designs and IRC review of efficacy outcomes are well-established in NSCLC and have been used for other TKIs already assessed in other submissions (afatinib – LUX-Lung 3 and LUX-Lung 6; erlotinib – EURTAC and OPTIMAL).[35,36,39,69,70]

The ARCHER 1050 trial also included assessments of the effect of treatment on patients' health-related quality-of-life (HRQoL), disease/treatment-related symptoms and general health status through various PRO instruments. In addition to the widely-used generic cancer instrument EORTC QLQ-C30, patient symptoms were also assessed using the lung cancer-specific EORTC QLQ-LC13. The EQ-5D was also used in the ARCHER 1050 trial, the instrument preferred by NICE, for eliciting utility values for economic modelling. PRO assessments were conducted regularly (every 28 days) and the rates of completion were high for the majority of cycles (>90% of patients answered all questions).

Additionally, the ARCHER 1050 trial was prospectively powered to show a difference on a single primary endpoint. It was estimated that 440 randomised patients with a minimum of 256 observed PFS events would be required to achieve a 90% power to detect a ≥50% improvement in PFS in the dacomitinib group versus the gefitinib group in the ITT population (i.e. HR: ≤0.667).[33] This is in contrast to other head-to-head studies of TKIs, such as LUX-Lung 7, which had no specific statistical power for its three co-primary endpoints.[9] The improvement in PFS with dacomitinib versus gefitinib in the ARCHER 1050 trial (5.5 months) was numerically greater than that with afatinib versus gefitinib in LUX-Lung 7 (0.1 months).[33] Additionally, the estimated PFS at 24 months with dacomitinib (30.6%) in ARCHER 1050 was also numerically higher than that with afatinib (17.6%) in LUX-Lung 7.[9,33]

B.2.13.2.2 Limitations of the evidence

As mentioned previously, one limitation of the ARCHER 1050 trial was that the study consisted of an open-label design, where investigators and patients were not masked to treatment assignment. However, the results for PFS, objective responses, and DoR by investigator assessment were consistent with those based on blinded IRC analysis, thereby supporting the validity of these findings.[33]

The dacomitinib group had a higher proportion of female patients and proportions of patients with an ECOG performance status of 0 than the gefitinib group. These artefacts of randomisation were not considered limitations to the study or the results because gender is not considered a prognostic factor of PFS in patients with EGFR+ NSCLC and generally there is no difference in outcomes between ECOG performance status of 0 and 1.[33] This was also evident for OS where non-significant interaction terms were observed for both gender and ECOG performance status (Figure 14).

An additional limitation pertaining to baseline characteristics revolves around the exclusion of patients with brain metastases from the study as the extent of CNS penetration of dacomitinib was not known at the time of the study design. This may have limited the full extent to which the activity of dacomitinib was investigated. However, given the lack of adequate CNS penetration (1% rate) associated with gefitinib,[71] the efficacy results are unlikely to have been affected by the exclusion of this patient population.

The trial network did not contain a ‘closed loop’ of evidence, meaning that comparison between dacomitinib and afatinib was entirely dependent on the gefitinib arm of each study, thereby increasing uncertainty. This was a result of sparse evidence, which paradoxically highlights the importance of ARCHER 1050 trial design and the inclusion of a clinically active and relevant comparator to tackle the lack of head-to-head evidence in trials comparing TKIs.

B.2.13.3 Relevance of the evidence base to the decision problem

ARCHER 1050 is relevant to the decision problem in regards to the patient population, comparators and outcomes considered.

ARCHER 1050 consisted of patients with confirmed locally advanced or metastatic EGFR+ NSCLC, the population defined within the decision problem. Patient demographic and baseline characteristics were representative of the intended patient population for dacomitinib in the first-line setting. All patients enrolled in ARCHER 1050 had tumours of adenocarcinoma histology with the vast majority of patients having stage IIIb or IV disease, which is consistent with the disease profile of patients with EGFR+ NSCLC treated in the NHS.

ARCHER 1050 shared similar baseline characteristics to the studies utilised in the most recent previous EGFR appraisal[68] (AURA extension, AURA2 and IMPRESS). In the appraisal 'experts highlighted that these trials were more generalisable than most other lung cancer trials because people with EGFR mutation-positive NSCLC tended to be diagnosed at a younger age, were fitter and not necessarily smokers compared with other types of lung cancer' and therefore, the committee concluded that the trials used 'were broadly generalisable to clinical practice'. Therefore, the patient population in ARCHER 1050 can be considered generalisable to UK clinical practice.

The ethnic mix typically treated in the NHS would differ to that of ARCHER 1050, where approximately 25% of patients were described as non-Asian and 75% were described as Asian. As indicated previously, there is a high focus on Asian populations in clinical trials within this disease indication,[47] and previous submissions for TKIs in the treatment of EGFR+ NSCLC included trials which comprised a major Asian component. Although members of the Appraisal Committee have acknowledged the association between Asian patients and increased response to lung cancer treatment,[72,73], current evidence around the impact of ethnicity is not definitive. Furthermore, clinical expert opinion suggested that studies with a predominately Asian population tend to mirror what is seen in Caucasian patients.

With regards to currently approved therapies in the UK, the decision problem also highlights the limited treatment options available for patients with EGFR+ NSCLC, whereby only three TKIs (afatinib, erlotinib, gefitinib) are currently approved in the first-line setting. There may therefore be an unmet need for new treatments that can

provide prolonged PFS and survival, improve disease symptoms and maintain patient QoL.

B.2.13.4 End-of-life-criteria

Dacomitinib provides an extension to life in excess of 3 months; however patients on current standard-of-care have life expectancies that exceed 24 months. Therefore, dacomitinib does not meet the end-of-life criteria (Table 30).

Table 30. Summary of end-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current approved options are already associated with >24 month survival outcomes. In ARCHER 1050, the median OS for gefitinib was 26.8 months (95% CI: 23.7, 32.1).
There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment	As detailed in Section B.2.6.3.2, dacomitinib demonstrated a 7.3 month improvement in median OS and a 24% reduction in the risk of death compared with gefitinib in EGFR+ NSCLC. The median OS was 34.1 months (95% CI: 29.5, 37.7) in the dacomitinib arm compared with 26.8 months (95% CI: 23.7, 32.1) for gefitinib (HR: 0.760; 95% CI: 0.582, 0.993; 2-sided p-value=0.0438; stratified analysis).[34,40]

Abbreviations: CI = confidence interval; EGFR+ = epidermal growth factor receptor mutation positive; HR = hazard ratio; NHS = National Health Service; NSCLC = non-small-cell lung cancer; OS = overall survival.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to inform the present submission. A detailed description of the search, its methods, and results (including the relevant results of the previous SLR) are provided in Appendix G.

B.3.1.1 Summary of identified studies and results

No previously published cost-effectiveness studies of dacomitinib were identified.

The systematic review identified 31 unique publications from 28 studies that met the inclusion criteria for the broader set of comparators, none of which were economic evaluations relevant to decision making in the UK. However, six HTA appraisals were identified; three were conducted by NICE (TA192, TA258 and TA310) and three were conducted by the SMC (ID 920/13, ID 615/10, and ID 749/11). These are summarised in Appendix G.

B.3.2 Economic analysis

Given that no published cost effectiveness studies relevant to the technology appraisal were identified in the SLR, a *de novo* economic evaluation was included in the submission.

B.3.2.1 Patient population

The population considered in the economic evaluation is identical to the trial population recruited in the ARCHER 1050 phase III clinical study [redacted], i.e. treatment-naïve patients with advanced NSCLC and activating mutations in EGFR (see Section B.2.3).[33]Inclusion and exclusion criteria for ARCHER 1050 are described in Section B.2.3.2.[33]

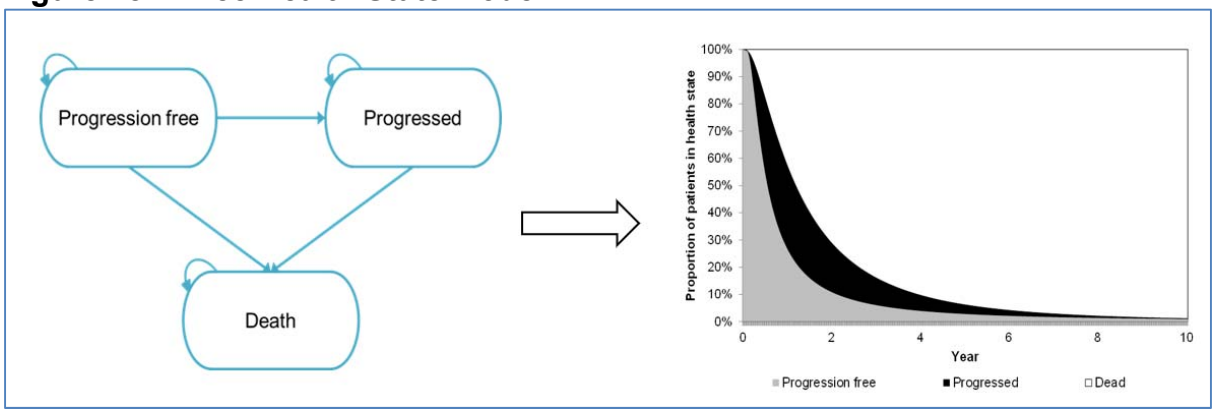
B.3.2.2 Model structure

The cost-effectiveness (cost-utility) model was developed in Microsoft Excel® using an area under the curve (partitioned survival analysis [PartSa]) model structure.

The model structure (depicted in Figure 28), comprised three health states; progression-free (PF), progressed disease (PD) and death. All patients enter the model in the PF state and are at risk of progression or death. Upon progression patients enter the PD state where they remain until *death*. Death is an absorbing state.

The PFS curve dictated the proportion of patients remaining in the PF state; the OS curve informed the percentage of patients that were alive, and the remaining patients (alive minus progression-free) were in the PD state.

Figure 28. Three Health State Model



The three-state model structure was chosen for several reasons:

- The structure captures two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life;
- The data requirement for the model (PFS and OS) are aligned with the endpoints of ARCHER 1050;
- The model structure and health states are common for metastatic oncology models, and have been used in previous National Institute for Health and Care Excellence (NICE) NSCLC appraisals.[67,74-77]

The cost of second- and third-line subsequent treatments were applied as one-off costs upon discontinuation of first- and second-line treatment, respectively. The model design did not explicitly capture the efficacy of subsequent treatment after progression from the initial therapy. The clinical impact of the subsequent treatments on survival received by patients in the trial was captured between PFS and OS and

was thereby inherently captured under the PartSA framework. Therefore, varying the composition of subsequent treatments only alters costs and not survival.

B.3.2.2.1 Features of the economic analysis

The analysis was constructed from the perspective of the NHS and the personal social services (PSS) in England and Wales. Costs were based on 2016/2017 prices (which are 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.[78]

A lifetime time horizon of 15 years was applied in the base-case given that it was aligned with the maximum life expectancy of the cohort predicted by the base-case parametric survival analysis (<1% alive at 15 years). Therefore, this was considered long enough to capture the long-term clinical and economic impacts of advanced NSCLC, an incurable disease requiring treatment until end of life.

The model cycle-length was 28-days which was believed short enough to capture the granularity of disease progression and matched the assessment schedule of ARCHER 1050. Aligned with previous appraisals in NSCLC, costs and outcomes were half-cycle corrected by averaging the number of patients at the start and end of each cycle, with the exception of drug acquisition costs in the PF state in which it was assumed that administration would occur at the beginning of the cycle, eliminating the need for half cycle correction.[29,65,66]

A summary of the model features is presented in Table 31, alongside a comparison with models included in previous NICE appraisals of treatments for newly diagnosed advanced NSCLC.

Table 31. Features of the economic analysis

Factor	Previous appraisals			Current appraisal	Justification
	TA258 (erlotinib)[66]	TA310 (afatinib)[29]	TA192 (gefitinib)[65]		
Summary of analytic methods	Semi-Markov method*	Partitioned survival method	Markov state transition model	Partitioned survival method	Allows best use of available data (PFS/OS) - primary and secondary outcomes of ARCHER 1050. Captures two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life. Commonly used in previous oncology NICE appraisals, including NSCLC.
Patient population	EGFR+ aNSCLC	EGFR+ aNSCLC	EGFR+ aNSCLC	EGFR+ aNSCLC	Population aligned with the ARCHER 1050 population, the final scope and the expected EMA marketing authorisation.
Time horizon	10 years	10 years	5 years	15 years	Aligned with the maximum life expectancy of the cohort predicted by the base-case parametric survival analysis (<1% alive at 15 years).
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	Aligns with the NICE reference case[78]
Discount	3.5% health benefits and costs	3.5% health benefits and costs	3.5% health benefits and costs	3.5% health benefits and costs	Aligns with the NICE reference case[78]
Cycle length	1 month	1 month	21-day	Four-week (28-day)	Aligns with the schedule of the ARCHER 1050 trial
Half-cycle correction	Yes – Where appropriate (i.e. not	Yes	Yes	Yes – Where appropriate (i.e.	N/A

Factor	Previous appraisals			Current appraisal	Justification
	TA258 (erlotinib)[66]	TA310 (afatinib)[29]	TA192 (gefitinib)[65]		
	when assessing the cost of an oral therapy)			not when assessing the cost of an oral therapy)	
Treatment waning effect?	No	No	No	No	N/A
Source of utilities	Nafees et al 2008	LUX-Lung trial, Chouaid et al. 2012, Nafees et al. 2008	Nafees et al. 2008	ARCHER 1050 (EQ-5D-3L; UK tariff); LUME-Lung 1 (TA347)	Value from ARCHER 1050 aligned with NICE reference case.[78] LUME-Lung 1 accepted by ERG in TA347 and recommended by ERG in TA416.[68,79]
Source of costs	BNF PSSRU	BNF NHS Reference costs PSSRU	BNF NHS Reference costs	BNF eMIT NHS Reference costs PSSRU	N/A

*An extrapolated area under the curve approach was used in order to determine the proportion of patients in PFS at each month of the model. All other transitions in the model were estimated using a Markov framework

Abbreviations: aNSCLC = advanced non-small-cell lung cancer; BNF = British National Formulary; EGFR+ = epidermal growth factor receptor mutation positive; eMit = Drugs and pharmaceutical electronic market information tool; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; PSSRU = Personal Social Services Research Unit.

B.3.2.2.2 Intervention technology and comparators

The intervention, dacomitinib, was implemented within the model as per its expected marketing authorisation, and according to the recommended dosing regimen, i.e. 45mg/day. The comparative treatments were also implemented as per their respective marketing authorisations and licensed dosing regimens.

Aligned with the NICE scope for first-line EGFR+ patients, the following comparators were included in the base-case:

- Gefitinib
- Afatinib
- Erlotinib

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

The primary data source for the model was ARCHER 1050. ARCHER 1050 was a randomised, head-to-head trial comparing dacomitinib versus gefitinib (see Section B.2.2 and B.2.3 for further details). However, as discussed in Section 2.9.1, a NMA was required to allow comparison against afatinib, and erlotinib was assumed equivalent to gefitinib following previous committee conclusions and observed clinical data.[29] Due to the potential violations of the proportional hazards assumption, which was assessed in Section 2.9.2 prior to conducting the NMA, a FP NMA was used to allow hazard ratios to vary over time.

Fractional polynomials are an alternative to regular polynomials that provide flexible parameterization for continuous variables.[80]The entirety of the available KM data are used to indirectly compare interventions. Following the selection of the most appropriate FP model, comparator curves are then constructed in the model using the gefitinib curve as a reference by applying the time dependent hazard ratios (i.e., non-proportional hazards). As such, the FP framework removes the need for separate parameterisation for each comparator.

The following sections provide justification for the selected extrapolations for the time-to-event data (PFS and OS) for the reference treatment in the network (geftinib from ARHCER 1050).

The PFS and OS curves were calculated in ARCHER 1050 using the KM estimation method. PFS assessed by the IRC was included in the base-case analysis given that it was the primary outcome of ARCHER 1050. Six parametric distributions were considered following guidance from the NICE Decision Support Unit (DSU): the exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma.[81] This was conducted using the *streg* procedure in STATA.

For each endpoint, the distributions for the base-case and scenario analyses reference arm were selected following the guidance inform the NICE DSU .[81] The model selection process included the following considerations:

- Ranking distributions based on statistical goodness-of-fit to the observed data according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
- A visual inspection consisting of an analysis of the “Observed vs Predicted” plot. The KM and parametric survival curves were plotted to assess the fit during the trial period, and the long-term extrapolation.
- Comparison of predicted median values and higher quantiles of the distributions
- Consultation with clinical experts to assess the plausibility of the extrapolations
- Comparison of fitted curves to external data

B.3.3.2 Progression-free survival

B.3.3.2.1 Gefitinib

In the network gefitinib was the ‘base’ curve against which comparative estimates for the other treatments in the analysis (dacomitinib, afatinib and erlotinib) were generated.

AIC and BIC values (Table 32) showed the best fit for PFS was the log-logistic for gefitinib closely followed by the Weibull and generalised gamma. The relatively higher AIC/BIC for the log-normal, Gompertz and exponential suggest these are less preferable.

Table 32. Goodness-of-Fit Statistics (PFS) - Gefitinib

Distribution	AIC	BIC	Mean	Median	Proportion PF at		
					2 years	3 years	5 years
Exponential	550.92	554.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	514.46	521.29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	532.35	539.18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	513.38	520.21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	529.33	536.16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	514.65	524.90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	9.23	9.6%	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free.

All distributions provided similar visual fits to the observed KM data (XXXXXXX29) with predicted medians close to the observed data, with the exception of the exponential which substantially underestimated the observed data for approximately the first 8 months. However, beyond the end of the observed data the logarithmic distributions (log-logistic and log-normal) produced much higher tails than the other distributions which questioned their suitability.

Clinical expert feedback indicated that the distributions with higher tails (the exponential, log-logistic and log-normal) predicted long-term (5-year) PFS estimates that were appropriate. However, the 3-year rates were considered slightly high for these distributions, although the predictions from the Weibull and generalised gamma distributions were considered to potentially underestimate survival at 3 years. Clinicians suggested they would expect the true survival to fall somewhere between the upper and lower models (indicating the highest and lowest distributions could be excluded as too extreme) but noted several of the projected curves were relatively similar to one another (see XXXXXXX29).

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Abbreviations: KM = Kaplan-Meier.

Given the low number of patient at risk beyond 24 months (7 patients), external data was considered to provide further evidence for the most appropriate extrapolation. Two studies identified in the SLR reported median follow-up greater than ARCHER 1050. Two-year and three-year rates of 5% and 1-2% were observed for gefitinib, respectively in LUX-Lung 7 in contrast to 12% and 6% in WJTOG 3405.[63,82] One additional study was identified in a targeted literature search.[24] It was a single arm observational study from one centre so was potentially subject to bias and only included 67% first line patients. However, it required a minimum follow-up of 5 years if patients were alive at the time of analysis. Therefore, it provided the only fully complete gefitinib/erlotinib EGFR+ NSCLC KM data up to 5 years. The three-, four- and five-year PFS rates were 8%, 3% and 0% respectively. Therefore, considering the data from LUX-Lung 7 which was the most relevant study as it was included in the NMA the generalised gamma was the most appropriate distibution. This was also reinforced by the Lin study.[24] Nonetheless, the WJTOG 3405 study demonstrated that a very small proportion of patients can experience prolonged PFS, which provided some evidence that the long tails of the log-logistic and log-normal were potentially plausible.[82]

Based on the above considerations, the generalised gamma was applied in the base-case analysis as it had one of the best statistical fits; it had a good visual fit to the observed data; it produced a mean PFS in the middle of the range of the distributions, aligning with clinician feedback and it predicted three, four and five year landmark rates aligned with the best available external literature (relevance to the decision problem and lack of censoring). The log-normal was considered in scenario analysis, as it provided the lowest mean of the logarithmic distribution which had plausible visual fits to the observed data and predicted 5 year rates in line with clinician opinion and one of the external studies.

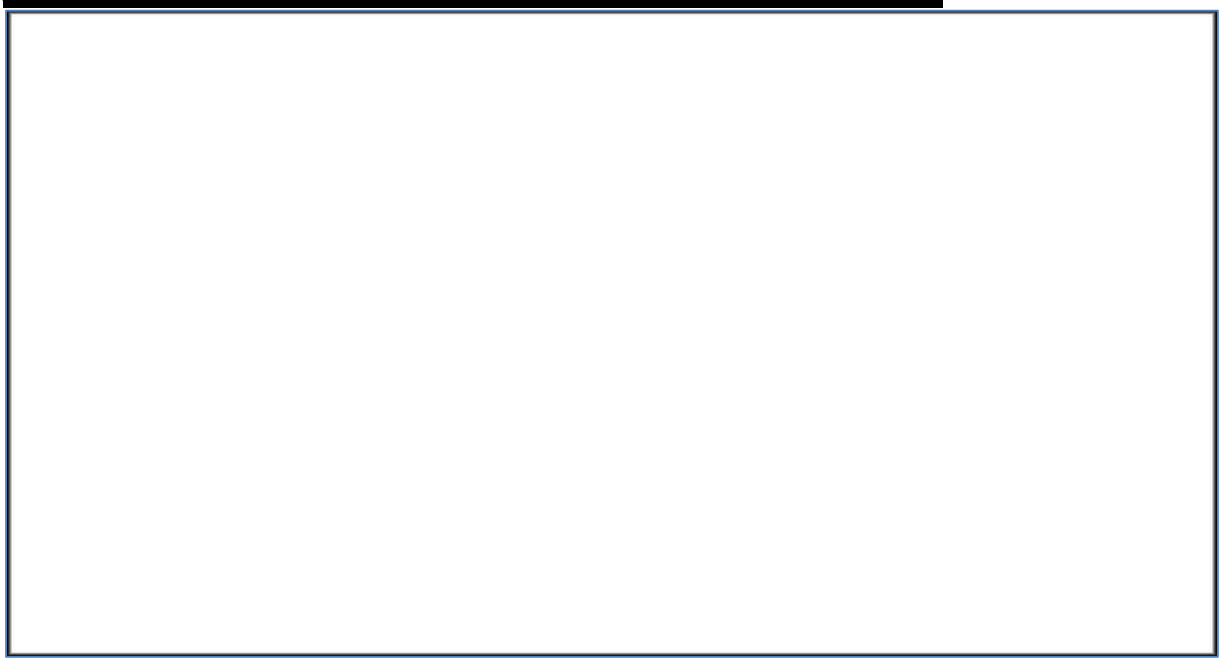
The remaining four distributions were considered to provide inferior predictions for the following reasons:

- Weibull: very similar prediction to the generalised gamma, however, it had a slightly lower mean which was not reflective of the clinician feedback
- Log-logistic: despite providing the best statistical fit to the observed data it was not included as it predicted a higher mean than the log-normal
- Gompertz: second worst statistical fit and predicted the lowest mean
- Exponential: worst statistical fit and very poor visual fit

B.3.3.2.2 Comparators (dacomitinib, afatinib, erlotinib)

As previously discussed, curves for dacomitinib, afatinib and erlotinib were generated by taking the gefitinib extrapolation and applying the time-varying hazard ratios estimated from the FP model. These comparative curves are presented against the base-case gefitinib curve in XXXXXXX30. A scenario analysis is also presented against the log-normal curve fitted to gefitinib (XXXXXXX30). Details of the FP approach are provided in Section B.2.9 and Appendix D.

[redacted]



Abbreviations: KM = Kaplan-Meier.

The extrapolated curve of dacomitinib follows the survival observed in ARCHER 1050 closely (the median PFS in the trial and the model are 14.7 and 14.5 months, respectively).

B.3.3.3 Overall Survival

B.3.3.3.1 Gefitinib

The steps taken to identify the preferred distribution for PFS (Section B.3.3.1.2) were repeated for OS. As with PFS, distributions were fitted to gefitinib as the 'base' curve, against which comparative estimates for the other treatments were generated.

The AIC/BIC (Table 33) indicated the log-logistic and generalised gamma provided the best fits the observed data. However, given the maturity of the observed OS data, the statistical fit may not be as informative as it was for PFS, noting it may be more reliable to judge best fit based on the clinical plausibility of the extrapolation.

Table 33. Goodness-of-Fit Statistics (OS)

Distribution	AIC	BIC	Mean	Median	Proportion PF at		
					2 years	3 years	5 years
Exponential	488.64	492.06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	461.29	468.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	474.30	481.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	455.76	462.59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	463.23	470.06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	460.69	470.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	26.84	41.7%	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

All distributions provided similar visual fits to the observed KM data (XXXXXXX31) with predicted medians close to the observed data, with the exception of the exponential which substantially underestimated the observed data for approximately the first 18 months. Beyond the end of the observed data both the exponential and logarithmic distributions (log-logistic and log-normal) produced much higher tails than the other distributions.

Clinical expert opinion suggested that long-term predictions generated by the log-logistic, log-normal, and exponential distributions were implausibly high. In contrast, predictions with Weibull and Gompertz distributions were thought to underestimate long-term survival. All the consulted clinical expert opinion centred on the generalised gamma as providing the most plausible estimates, noting that only a small proportion are expected to be alive beyond 10 years.

[redacted]

Abbreviations: KM = Kaplan-Meier.

As with PFS, external data was also considered in the selection of the most plausible model. LUX-Lung 7 only had 7 patients at risk beyond 45 months therefore; WJTOG 3405 and Lin 2016 provided the only long-term data for validation.[24,63,82] Their respective three-year rates of ~39% and ~48% were aligned with those observed in ARCHER 1050 (42%). Five-year rates were ~21% and ~15% for WJTOG 3405 and Lin 2016, respectively, suggesting the generalised gamma, log-logistic and log-normal provided plausible five-year rates. The six- and seven-year rates were identical 11% and 7% between the two studies and only Lin 2016 reported up to 8 years (0%). Therefore, the generalised gamma was deemed the most closely aligned to the long-term external data.

Consequently, the generalised gamma was applied in the base-case analysis as it had one of the best statistical fits; it had a good visual fit to the observed data; consulted clinical expert opinion centred on the distribution and it predicted five to eight rates aligned with the available external literature. The log-logistic was considered in scenario analysis, as it provided the lowest mean of the logarithmic distributions which had plausible visual fits to the observed data and predicted 5 year rates in line with the external studies.

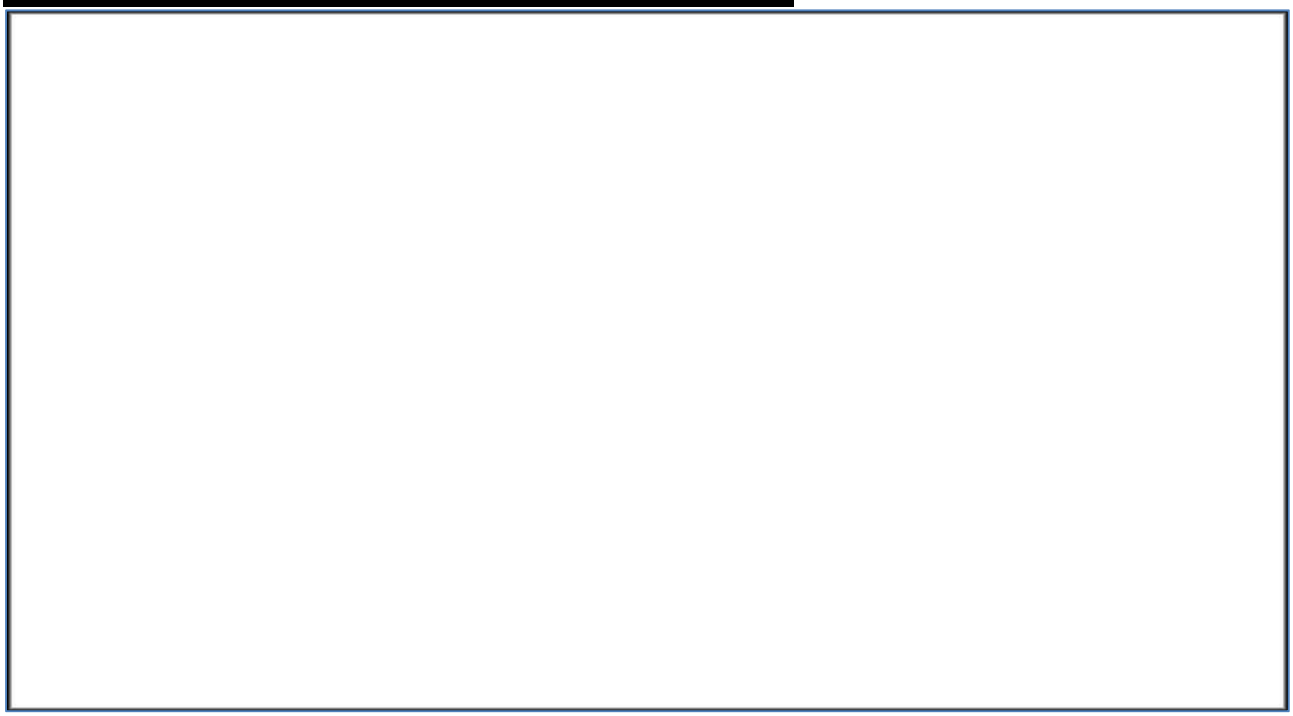
The remaining four distributions were considered to provide inferior predictions for the following reasons:

- Weibull: despite providing the best statistical fit it had a lower mean than the generalised gamma which was not reflective of the external literature and clinician feedback
- Log-normal: it was not included as it predicted a higher mean than the log-logistic
- Gompertz: second worst statistical fit and predicted the lowest mean which was considered implausible during clinician feedback
- Exponential: worst statistical fit and very poor visual fit

B.3.3.3.2 Comparators (dacomitinib, afatinib, erlotinib)

As with PFS, comparator curves were generated using the gefitinib extrapolation for OS (the generalised gamma) and applying the time-varying hazard ratios estimated from the base-case FP model. These are presented for the base-case against the observed dacomitinib and gefitinib from ARCHER 1050 in XXXXXXX32. As with PFS, the efficacy of erlotinib was assumed to be equal to the efficacy of gefitinib (see section B.2.9).

[redacted]32



Abbreviations: KM = Kaplan-Meier.

The median OS of dacomitinib of 34 months in ARCHER 1050 is reflected well in the extrapolation which estimates the median OS of 33.0 months.

B.3.3.4 Treatment Discontinuation

Despite data being available from ARCHER 1050, time to treatment discontinuation (TTD) was not used to determine treatment duration because it was not available for all the other comparators. In order to address this inconsistency, all patients were assumed to be treated until progression, with PFS being used as a proxy for treatment duration. This assumption was supported by the minimal difference observed in the 24 month restricted means between TTD and PFS (IRC) of [redacted]

months for dacomitinib. In contrast, the restricted mean of TTD for gefitinib was [redacted] months greater than PFS (IRC); therefore it was conservative to assume that PFS was a proxy for TTD. Despite the limitations associated with medians as a proxy for the average, a scenario analysis was used to explore the impact of this assumption which incorporated the difference between median PFS and TTD from ARCHER 1050 and LUX-Lung 7[9] as a one-off cost upon progression.

B.3.4 Measurement and valuation of health effects

Utility values were applied to both health states in the model (PFS, PD) to capture patient QoL associated with treatment and disease outcomes. The recent NICE position statement prefers utility values to be derived from EuroQoL Five-Dimension Three Level (EQ-5D-3L)[83] which is consistent with the measurement tool used in the ARCHER 1050 trial; hence no mapping or cross-walk was required. Trial data were preferred as a source of utility inputs given that this allowed utility and efficacy data to be derived from the same population.

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

EQ-5D-3L assessments were made at the following time points as per the ARCHER 1050 trial protocol: day 1 – cycle 1 which provided the baseline assessment of PROs, days 8 and 15 of cycle 1 and at the beginning of each cycle afterwards (up to a total of 41 cycles), at the end of treatment and at a single post progression follow-up. Treatment specific utilities were calculated using UK utility population weights.[84]

To account for the autocorrelation between repeated measures from individuals, a repeated measures mixed-effects model was applied to the utility scores. The model had an intercept term, a linear time trend term, a term for treatment group, a term for baseline covariate and a term for treatment-by-time interaction. The intercept and slope terms for time were random effects with an assumed unstructured variance/covariance matrix. In addition, each observation was assumed to be measured with error and the error terms are independent of each other. A sandwich estimator was used to estimate the variance of the fixed effects terms. The Kenward-Roger procedure was used to adjust for the degrees of freedom. All parameter estimates were obtained using restricted maximum likelihood estimation.

The rates of completion were high with >90% answering all questions for almost all cycles for the EQ-5D questionnaire in both the dacomitinib and gefitinib arms.

The PF utility values generated from ARCHER 1050 were aligned with the NICE reference case and are presented in Table 34.[78]

Table 34. EQ-5D-3L PFS utility values by treatment from ARCHER 1050

Treatment	Mean	95% CI
Dacomitinib	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]

Abbreviations: CI = confidence interval

B.3.4.2 Mapping

Mapping was not conducted as EQ-5D-3L was collected in ARCHER 1050.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant quality of life evidence for use in the cost-effectiveness analysis. This search updated a previous SLR conducted in March 2017 to inform the submission for TA529,[74] which was a search for cost-effectiveness in advanced NSCLC. The TA529 SLR was itself an update of SLRs conducted to inform three previous NICE NSCLC submissions, TA406,[85] TA296[86] and TA258.[66]

A detailed description of the search, its methods, and results (including the relevant results of the previous SLRs) are provided in Appendix H.

B.3.4.3.1 Summary of identified studies and results

The search for TA529 identified a total of 33 publications on 22 unique studies were ultimately eligible for inclusion. In this updated search a total of 3 publications covering 3 unique studies and 3 HTA submissions were identified for inclusion. One study (Labbé 2017) specifically in the EGFR mutation-positive population was identified.[87] The remaining included studies reported utility values from within a broader NSCLC population. Nafees et al. 2008 reported utility values in the broader population but was discussed in later sections so is also summarised below. Summary details from all included studies and HTA submissions are provided in Appendix H.

Nafees et al. 2008[88] aimed to elicit UK-based societal utility values for various stages of NSCLC and grade III-IV toxicities associated with treatment. The base questionnaire was adapted from a previously existing metastatic breast cancer health state questionnaire; revised to describe metastatic NSCLC patients receiving second-line treatment and was validated by clinical experts. Standard gamble interviews were used to derive health state utility scores in a sample of 100 members of the general UK public. Utility values were associated with stable disease and no side effects: 0.653; and with progressive disease: 0.473.

Labbé et al. 2017[87] aimed to evaluate EuroQol five dimensions (three level version; EQ-5D-3L)-derived health state utility scores using a longitudinal cohort of Canadian outpatients diagnosed with metastatic lung cancer across various disease states (EGFR, anaplastic lymphoma kinase [ALK], SCLC, wild-type NSCLC). Follow-up among patients varied, with a median of 12 months (range: 0-201 months) post-diagnosis. Utility values for the EGFR population using UK preference weights were: stable on most appropriate treatment (TKI): 0.77±0.02; progressive disease: 0.64±0.03.

B.3.4.4 Adverse reactions

In line with previous submissions, the impact on costs and HRQoL associated with treatment-related AEs (of Grade 3 or higher that occurred in >5% of patients in at least one treatment of interest) were considered in the model.[77,85,89] It was assumed that Grade 1/2 AEs had negligible impact on costs and HRQoL; these were therefore excluded. The probability of incurring an AE for dacomitinib and geftinib (and erlotinib) was taken from ARCHER 1050. For afatinib, the incidences of AEs were taken from LUX-Lung 7.[63] Table 35 includes the final list of AEs that meet the criteria used and are applied in the model.

Table 35. List of adverse events included in the model

Adverse event	Dacomitinib (n=227)[40]	Gefitinib (n=224)[40]	Afatinib (n=160)[63]	Erlotinib*
ALT increased	2 (0.9%)	18 (8.0%)	0 (0.0%)	18 (8.0%)
Diarrhoea	18 (7.9%)	1 (0.4%)	21 (13.1%)	1 (0.4%)
Fatigue	0 (0.0%)	0 (0.0%)	9 (5.6%)	0 (0.0%)
Paronychia	17 (7.5%)	3 (1.3%)	3 (1.9%)	3 (1.3%)
Rash (grouped term)	55 (24.2%)	1 (0.4%)	15 (9.4%)	1 (0.4%)

*Erlotinib assumed equivalent to gefitinib (see Section B.2.9.1)

Within the base-case, AE disutility's were not included to avoid double counting as the treatment specific PF values were assumed to already capture the effect of any AEs as these were informed by the trial data. A scenario analysis was included to explore the impact of including a one-off utility decrement which was calculated 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 in the first cycle of the model. A summary of these inputs is provided in Table 36.

Table 36. Adverse event utility decrements and durations

Adverse event	Utility decrement (SE)	Source/assumption	Duration (days [range])	Source/ assumption
ALT increased	0	Assumed zero; laboratory findings only with no hospitalisation or symptoms indicated[90]	-	-
Diarrhoea	-0.147 (0.045)	Derived from EQ-5D with UK values set from LUX-Lung 3[29]	6.6 (5.95-7.25)	Derived from LUX-Lung 3[29]
Fatigue	-0.179 (0.053)	Derived from EQ-5D with UK values set from LUX-Lung 1[29]	32.0 (27.76-36.24)	Derived from LUX-Lung 1[29]
Paronychia	-0.202 (0.028)	Assumed equal to rash	12.3 (11,51-13.09)	Assumed equal to rash
Rash (grouped term)	-0.202 (0.028)	Derived from EQ-5D with UK values set from LUX-Lung 3[29]	12.3 (11,51-13.09)	Derived from LUX-Lung 3[29]

Abbreviations: EQ-5D = European Quality of Life-5 Dimensions; SE = standard error.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The PF utilities applied in the base-case model were from ARCHER 1050 given that it conformed to the NICE reference case. There was a statistically significant difference observed in EQ-5D between the dacomitinib and the gefitinib arms; however the utility difference observed in ARCHER 1050 was smaller than minimally important differences in EQ-5D reported in previous studies in oncology.[40,91,92] Despite the insignificant clinical difference, treatment specific utilities were considered in the analysis to avoid omitting the observed statistical difference and therefore bias the results in favor of dacomitinib.

Given that treatment specific values have not been applied frequently in previous NSCLC appraisals, a scenario was included which applied the non-treatment specific PF values from ARCHER 1050 ([redacted]) with one-off disutility's for adverse events applied.

Values derived from ARCHER 1050 were slightly higher than those observed in LUX-Lung 7 (0.77 afatinib and 0.80 gefitinib) and LUX-Lung 3 (0.784) which represents the only identified EQ-5D values derived in RCTs of EGFR+ NSCLC patients.[9,29] These values were also aligned with the only real world EGFR+ NSCLC value identified in the SLR (Labbé et al. 2017 [0.77]), therefore this value was applied in scenario analysis.

Assumptions were made for the utility value for the other comparators given that they were not included in ARCHER 1050. The afatinib PF utility was assumed to be equal to dacomitinib based on their similar safety profiles, while erlotinib was set to be equal to the utility observed with gefitinib, given the assumption of equivalent efficacy and safety (see Section B.2.9.1).

Given that EQ-5D was not collected beyond progression in ARCHER 1050, the PD utility was sourced from the literature. Labbé et al. identified in the SLR (see section B.3.4.3.1 for further detail) reported a PD utility value of 0.64 and was applied in the base-case analysis. This value was also aligned with the PD value from the LUME-Lung 1 study applied in TA347 and subsequently recommended by the ERG in

TA416.[79,93] Although the LUME-Lung 1 study was not in EGFR+ NSCLC, it collected EQ-5D in a RCT with NSCLC patients and derived the values with the UK utility weights. Therefore, 0.64 was considered the most appropriate values for the PD state. The Evidence Review Group (ERG) in TA416 also suggested the value from Nafees [88](see section B.3.4.3.1 for further details). This study did not meet the NICE reference case as it did not use EQ-5D or derive values from patients, so was not considered a robust source. In addition, a recent repeated of this study by Nafees et al.[94] that was identified in the SLR, reported a PF value of 0.883 and PD of 0.166, which further demonstrates the unreliability of the original Nafees study.

Table 37. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Progression-free – Dacomitinib	[redacted]	[redacted]	B.3.4.1	Pre-progression utilities were sources from the pivotal trial in line with the NICE reference case. For comparators values were assumed equal based on the similarity of safety profiles.
Progression-free – Gefitinib	[redacted]	[redacted]		
Progression-free – Afatinib	[redacted]	[redacted]		
Progression free – Erlotinib	[redacted]	[redacted]		
Progressed disease	0.64 (0.03)	NR	B.3.4.3.1	Based on the results of the SLR (see section B.3.4.3) the study by Labbé provided the most appropriate values for this analysis.

Abbreviations: NICE = National Institute for Health and Care Excellence; NR = not reported; SLR = systematic literature review.

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

The following cost categories were included in the model:

- First line treatment costs consisting of drug acquisition, drug administration, and AE costs. All primary treatments were administrated orally; therefore, the monthly treatment cost was based on unit price (per mg) and recommended dosing regimen (mg), in addition to the associated administration cost.

Treatment related AE costs were included based on the impact of treatment-related Grade 3 or higher AEs.

- Subsequent treatment costs were applied upon progression and were calculated assuming a basket of treatments. Akin to first line treatment costs, they included drug acquisition costs and administration costs. However, treatment-related AE costs were not included for subsequent treatments.

- Disease management costs were equivalent across treatments and were health state specific (PF and PD).

- Terminal care costs were applied as a one-off cost upon death.

A relevant SLR was previously conducted in March 2017 to inform the submission for TA529 which was to search for general costs and resource use from a UK NHS perspective associated with advanced NSCLC. This update was conducted to identify new relevant literature published since the last search (17 March 2017) on 01 August 2018, refer to Appendix I for more details.

B.3.5.1 Intervention and comparators' costs and resource use

A summary of dosing information used to inform intervention and comparator costs is presented in Table 38. Dosing information was derived from the respective SmPC for each comparator.[33,59,95,96]

Drug acquisition costs in the base-case have been calculated assuming list prices for all drugs (see Table 38 below).

Table 38. Unit costs of interventions and comparators

Treatment	Dosing Schedule	Strength	Pack size	Package Price (£)	Cost per model cycle (£)
Dacomitinib	45 mg once daily, orally[33]	45 mg	30	[redacted]	[redacted]
Gefitinib	250 mg once daily, orally[59]	250 mg	30	£2,167.71	£2,023.20
Afatinib	40 mg once daily, orally[95]	40 mg	28	£2,023.28	£2,023.28
Erlotinib	150 mg once daily, orally[96]	150 mg	30	£1,631.53	£1,522.76

Source: BNF. Access date: Jun 20, 2018
Abbreviations: BNF = British National Formulary.

Dose intensity was not applied in the model as all first-line treatments in the model were oral therapies, therefore missed doses would be unlikely to result in cost savings. In addition, dose intensity data for comparator treatments were not available.

All primary treatments were oral therapies and did not require hospital administration. Therefore, administration costs consisted of a dispensing fee only. A dispensing fee of £9.40 per administration was applied to each treatment which included 12 minutes of hospital pharmacist time (Hospital pharmacist [Band 6]; radiographer cost per working hour [£47]) in line with previous NSCLC appraisals.[74,75,77,85,97,98]

B.3.5.2 Subsequent treatment costs

The cost of second- and third-line treatments was applied upon progression. The composition of subsequent treatments was informed by clinical expert opinion[99] and Sequist 2017.[100] In the second-line it was assumed that approximately 60% of patients would develop the T790M mutation when treated with first- or second-generation TKIs.[101] The majority of these patients would receive osimertinib; however, a small proportion of patients would not be diagnosed as T790M positive due to false negative tests or difficulties with obtaining a sample for biopsy. All other patients would receive platinum doublet chemotherapy (PDC). For patients that received third-line treatment, those that received osimertinib second-line would go on to receive PDC and those that had PDC in the second-line would subsequently have docetaxel. Given that some patients would be unable or unwilling to receive subsequent therapy it was assumed that 71% and 48% of patients received second-

and third-line treatment, respectively.[100] The second- and third-line treatment proportions are presented in Table 39.

Table 39. Second- and third-line treatment basket compositions

Second-line treatments	Share of patients	Third-line treatments	Share of patients
Osimertinib	56%	PDC	56%
PDC	44%	Docetaxel	44%
Docetaxel	0%	-	-
Proportion receiving second-line treatment	71%	Proportion receiving third-line treatment	48%

Abbreviations: PDC = platinum doublet chemotherapy.

The average duration of subsequent second- and third-line treatments was converted to reflect the 28-day model cycle (reported in cycles, in Table 40). The reported median duration of time on treatment for second-line treatment of PDC was sourced from Sequist 2017 and the duration of osimertinib was derived from the larger and more recent AURA3 trial.[100,102] Third-line therapy durations for PDC and docetaxel were sourced from Sequist 2017.[100]

Table 40 Median duration in cycles of second-line and third-line treatment

Treatments	Duration (months)	Duration (# of model cycles)	Source
Second-line treatment			
Osimertinib	8.1	8.81	Mok 2017[102]
Platinum based CT	2.90	3.15	Sequist 2017[100]
Single agent CT	1.40	1.52	Sequist 2017[100]
Third-line treatment			
Platinum based CT	2.50*	2.72	Sequist 2017[100]
Single agent CT	2.50	2.72	Sequist 2017[100]

*Assumed the same as single agent CT.
Abbreviations: CT = chemotherapy.

The acquisition costs for subsequent treatments are presented in Table 41. Dosing regimens were source from their respective SmPCs.[103-105] Dose calculations for PDC and docetaxel assumed a body surface area (BSA) of 1.75m^2 (weighted average by gender [from ARCHER 1050 40%/60%[40]] of males 1.89m^2 and females 1.65m^2 from Sacco[106] which was previously recommended by an ERG[68]). PDC consisted of a combination of pemetrexed plus cisplatin or pemetrexed plus carboplatin. Cisplatin was assumed to be given to 54% of the patients in combination with pemetrexed while the remainder would receive carboplatin and pemetrexed.[107]

Osimertinib was administered orally; therefore the administration cost consisted of a dispensing fee only. Administration costs for IV therapies were include in line with infusion time from their respective SmPCs and are presented in Table 42. [103-105]

Table 41 Acquisition cost of subsequent therapies

Treatment	Dosing Schedule	Strength	Package size	Package Price (£)	Cost per model cycle (£)
Osimertinib	80 mg once daily	80 mg	30	£5,770.00[108]	£5,385.33
Pemetrexed	500 mg/m^2 every 21 days	500 mg	1 vial	£800.00[109]	£1,866.67
Carboplatin	400 mg/m^2 every 21 days	450 mg/45 ml	1 vial	£18.73[109]	£38.85
Cisplatin	75 mg/m^2 every 21 days	50 mg/50 ml	1 vial	£4.48[109]	£15.68
Docetaxel	75 mg/m^2 every 21 days	80 mg/4 ml	1 vial	£14.74[109]	£32.34

Table 42 Administration cost of subsequent therapies

Treatment		Administration method	IV infusion time	Cost per administration	Source
Osimertinib		Oral	-	£9.40	PSSRU 2017[97]
PDC	Pemetrexed with carboplatin	IV	15-60 minutes	£241.07	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance[110]
	Pemetrexed with cisplatin	IV	160 minutes	£355.54	SB14Z; Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[110]
Docetaxel		IV	60 minutes	£241.07	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance[110]

Abbreviations: IV = intravenous

B.3.5.3 Health-state unit costs and resource use

Resource usage for the disease management costs in the PF and PD states were based on values from TA296[86] (now TA422[111]) which used values from TA162[112] and TA258[66] (Table 43). These estimates were viewed as the best available

estimates in the literature as they were informed by expert opinion (5 top UK clinicians specialising in the treatment of NSCLC), have been subject to review by NICE ERGs and appraisal committees on an additional four occasions[74,85,89,98]. Unit costs were derived from the National Schedule of Reference Costs for 2016/2017 and PSSRU 2017.[97,110]

A one-off cost of £4,593 for terminal care was incurred at death to account for the additional resource usage in the months prior to death. This cost was based on resource usage from Brown et al. 2013[113] (calculations are presented in Table 44), which has been utilised during eight previous NSCLC appraisals[68,70,75,76,114-117].

Table 43. List of health states and associated costs in the economic model

Items	Use in model	Unit cost[97,110]	Progression-free survival		Progressed disease	
			Frequency	Frequency per model cycle	Frequency per cycle	% of patients
Outpatient visit	Medical Oncology - Non-Admitted Face-to-Face Attendance, Follow-up	£172.67	0.75 visits per month	0.69	1 visit per month	0.92
GP visit	GP per surgery consultation lasting 9.22 minutes	£38.00	10% patients; 1 per month	0.09	28% patients 1 per month	0.26
Cancer nurse	N10AF: Specialist Nursing, Cancer Related, Adult, Face to face	£82.09	20% of patients; receive 1 per month	0.18	10% patients 1 per month	0.09
Complete Blood Count	DAPS05: Haematology	£3.06	0.75 per month	0.69	1 per month	0.92
Biochemistry	DAPS04: Clinical Biochemistry	£1.13	0.75 per month	0.69	1 per month	0.92
CT scan (other)	RD26Z: Computerised Tomography Scan of Three Areas, with Contrast (outpatient)	£122.51	30% patients; 0.75 per month	0.21	5% patients 0.75 per month	0.03
Chest X-ray	DAPF: Direct Access Plain Film	£29.78	0.75 per month	0.69	30% patients 0.75 per month	0.21
Total cost per 28 day cycle			**£186.53**		**£190.43**	

Abbreviations: CT = computerised tomography; GP = general practitioner.

Table 44. Details of terminal care cost calculation

Setting	% of patients in each care setting	Resource	Unit cost	Consumption of resource	Cost	Assumptions/references
Home	27.3%	Community nurse visit	£67.00	28 hours	£5,285.96	PSSRU 2017: Cost per hour Band 8a[97]
		GP Home visit	£93.60	7.00 visits		PSSRU 2017: GP per minute of patient time £4.00;[97]PSSRU 2015: 11.4 minutes home visit and 12 minutes travel time per visit[118]
		Macmillan nurse visit	£44.69	50 hours		Cost assumed to be 66.7% of community nurse cost.[113]
		Drugs and equipment	£520.31	Average drug and equipment		Cost from Brown et al. and uplifted using the PSSRU inflation indices.[97,113]
Hospital	55.80%		£4,094.43	9.66 days	£4,094.43	NHS reference costs 2016/2017 – non-elective long-stay weighted sum of HRG code DZ17S 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)[110]
Hospice	16.90%		£5,118.04		£5,118.04	Assumption - 1.25 x hospital stay cost.[113]
Total cost per event					**£4,592.71**	

Abbreviations: PSSRU = Personal Social Services Research Unit.

B.3.5.4 Adverse reaction unit costs and resource use

In line with previous submissions, 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 (Table 35; Section B.3.4.4).[77,85,89] These costs are applied as a one-off cost in the first cycle of the model. Unit costs for each event were calculated using HRG codes from previous appraisals and updated using the latest NHS reference costs (Table 45).[110] The total cost of AEs for each treatment is presented in Table 46.

Table 45. Cost of treating adverse events

Adverse event	Cost per event	Details/source
ALT increased	£0	Assumed zero; laboratory findings only with no hospitalisation or symptoms indicated in CTCAE v4.03 guidelines[90]
Diarrhoea	£462.08	FD01F-J Gastrointestinal Infections without Interventions, with CC Score 0-8+ (Non-elective, short stay [weighted average])
Fatigue	£592.48	SA01G-K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-8+ (Non-elective, short stay [weighted average])
Paronychia	£436.17	Assumed same as rash
Rash (grouped term)	£436.17	JD07E-K Skin Disorders without Interventions, with CC Score 0-19+ (Non-elective, short stay [weighted average])

Table 46. Total cost of treating adverse events by treatment

Treatments	Management Cost
Dacomitinib	£175
Gefitinib	£10
Afatinib	£143
Erlotinib	£10

B.3.5.5 Miscellaneous unit costs and resource use

No additional costs were included in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

All model inputs applied in the base-case and sensitivity analyses are summarised in **Error! Reference source not found.** (Appendix L).

B.3.6.2 Assumptions

A summary of key assumptions is provided in Table 47.

Table 47. Summary of assumptions applied in the economic model

Area	Assumption	Justification
Model		
Time horizon	15 years	Aligned with the maximum life expectancy of the cohort predicted by the base-case parametric survival analysis (<1% alive at 15 years) (see section B.3.3.1.3)
Population	EGFR+ NSCLC	Population identical to the ARCHER 1050 phase III clinical study, in line with the scope of the current appraisal and with the expected EMA marketing authorisation.
Comparators	Afatinib, erlotinib, gefitinib	In line with the NICE scope
Model Structure	Partitioned survival	Captures the chronic nature of the condition and two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life. Commonly used in previous oncology NICE appraisals, including NSCLC
Cycle length	Four-week (28-day)	Aligns with the schedule of the ARCHER 1050 trial, captures differences in dosing on a monthly basis.
Half cycle correction	Acquisition and administration costs of oral treatments are not half-cycle corrected	Oral treatments were assumed to be dispensed at the beginning of the cycle

Survival		
Erlotinib equivalent to gefitinib	Erlotinib was assumed to have equal efficacy (PFS and OS) and safety to geftinib	In line with previous NICE and SMC committee conclusions and the supporting data from the recent RCT subgroup analysis,.
Proportional hazards assumption	Proportional hazards was assumed to be potentially violated for PFS and OS	Given potential violation in at least one trial in the network (tested using log cumulative hazard plots and Schoenfeld residuals) a FP NMA was utilised to allow hazards to vary over time in the base-case analysis. A traditional ITC was also explored in a sensitivity analysis.
Utility		
Progression-free health state utility value	PF utility values were assumed to be treatment specific	ARCHER 1050 collected EQ-5D aligned with the NICE reference case. There was a statistically significant difference observed between dacomitinib and gefitinib in EQ-5D, however it did not exceed a minimally important difference. Therefore, a conservative assumption was made to apply treatment specific utilities in the base-case and a single non-treatment value was explored in scenario analysis.
Disutility due to adverse events	Disutility due to adverse events was not included in the base-case model	Given that treatment specific values were applied in the base-case that are elicited from the EQ-5D on treatment (thus capturing disutilities on treatment), it was considered that including separate disutilities for adverse events would be double counting. A one-off disutility was explored in scenario analysis.
Costs		
Duration of treatment	PFS was assumed a suitable proxy for TTD	Despite a post hoc analysis of TTD being available from ARCHER 1050, it was not available for all the other comparators. This was a conservative assumption given that TTD was observed to closely follow PFS for dacomitinib in

		ARCHER 1050, in contrast to gefitinib, where TTD was observed to exceed PFS by a few months on average.
Relative dose intensity	RDI was not included in the model	Given that all primary treatments were administered orally, RDI was not considered relevant.
Vial sharing	Complete vial sharing was assumed	Only subsequent treatments were administered intravenously. Therefore, for simplicity these therapies were estimated using the lowest cost per mg of any vial.
Cost of adverse events	The cost of adverse events are applied as a one-off cost at the start of treatment	The majority of adverse events will occur within the first year of treatment and any adverse events occurred beyond the first year will only have a minimal difference due to discounting.
Cisplatin/ carboplatin mix in PDC regimen	The proportion of patients receiving cisplatin or carboplatin in PDC was assumed from PROFILE 1014	These values have been applied in a previous NSCLC appraisal and are therefore considering representative of UK clinical practice.

Abbreviations: EMA = European Medicines Agency; FP = fractional polynomial; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NSCLC = non-small cell lung cancer; OS = overall survival; PDC = platinum doublet chemotherapy; PF = progression-free; RCT = randomised controlled trial; RDI = relative dose intensity; SMC = Scottish Medicines Consortium; TTD = time-to-treatment discontinuation

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base-case results are presented in Table 48. Gefitinib was the first EGFR TKI to be appraised by NICE. The manufacturer offered a complex PAS (a cost of £12,200 applied on receipt of the third monthly pack) which was considered in our base-case. The manufacturers of erlotinib and afatinib offered simple PASs, which are confidential. As such, the base-case assumes the PAS for each in order to present the committee with a set of results more relevant to decision making than at list price. Given the conclusion of the committee in the appraisal of afatinib with respect to erlotinib's assumed equivalence to gefitinib (Document B.2.9.1), parity

costing was assumed between gefitinib and erlotinib; therefore, given the treatment duration of gefitinib/erlotinib, a simple discount of [redacted] from the erlotinib list price of £1,631 was assumed to achieve cost parity. For afatinib, given its slight benefit versus the first generation TKIs, a PAS of [redacted] on the list price of £2,023 was assumed. The results without PAS for all comparators are reported in Appendix L.

Table 48. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/ QALY)	ICER incremental (£/QALY)
Gefitinib	[redacted]	[redacted]	[redacted]	--	--	--	--	--
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,038	Extendedly dominated
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,305	£29,305

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

The modelled outcomes are aligned with the clinical inputs which show dacomitinib has a longer survival than the three current TKIs. Dacomitinib was associated with higher total LYs ([redacted]) versus all comparators ([redacted]) and QALYs ([redacted] versus [redacted]). Dacomitinib was also associated with higher cost.

In the fully incremental analysis, and dacomitinib was associated with an ICER of £29,305 versus gefitinib. These results indicate that dacomitinib is a cost-effective treatment option to manage EGFR mutation-positive NSCLC patients.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

In order to o explore and quantify uncertainty in the outcomes of the analysis, a probabilistic sensitivity analysis (PSA) was undertaken using 10,000 iterations of the model, with values for key parameters sampled stochastically from assigned

distributions to each parameter. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in Appendix L.

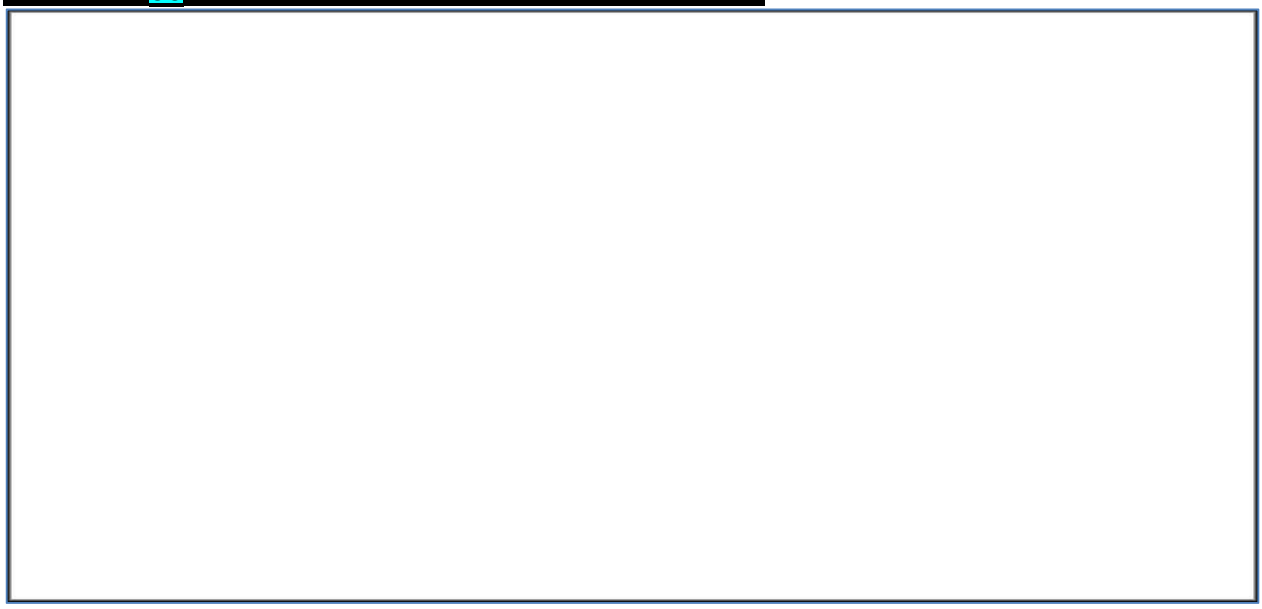
Probabilistic results are presented in Table 49 and the corresponding scatter plot and cost-effectiveness acceptability curve are represented in XXXXXXX33 and Figure 34, respectively.

Table 49. Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/ QALY)	ICER incremental (£/QALY)
Gefitinib	[redacted]	[redacted]	[redacted]	--	--	--	--	--
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,015	Extendedly dominated
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,381	£29,381

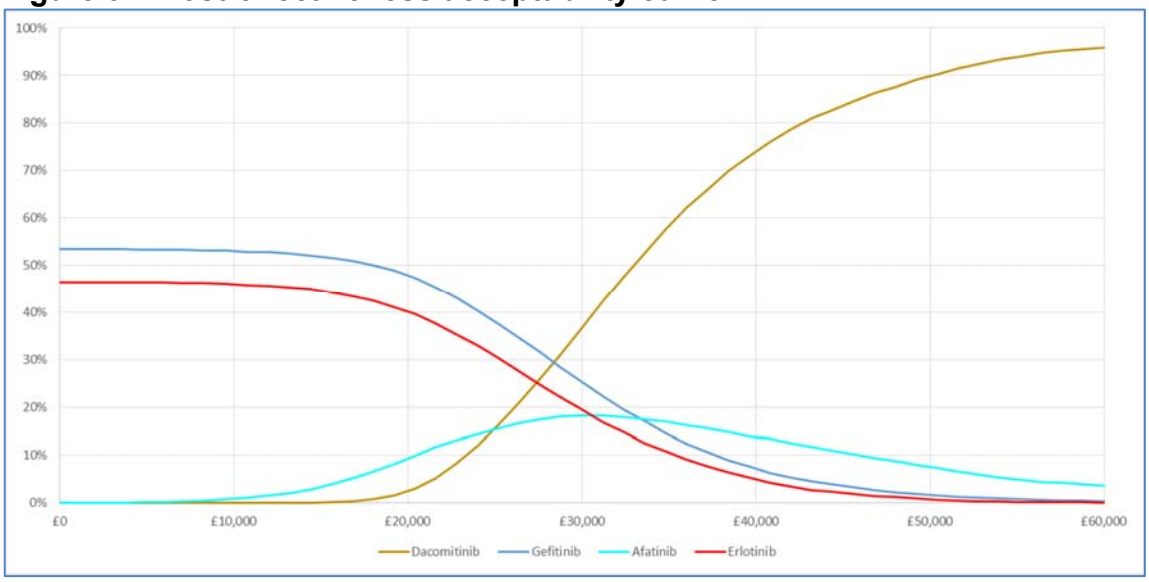
Abbreviations: ICER = incremental cost-effectiveness ratio; Incr = incremental; LYG: life years gained; QALYs: quality-adjusted life years

[redacted] 33 [redacted]



Abbreviations: QALY: quality-adjusted life year

Figure 34. Cost-effectiveness acceptability curve



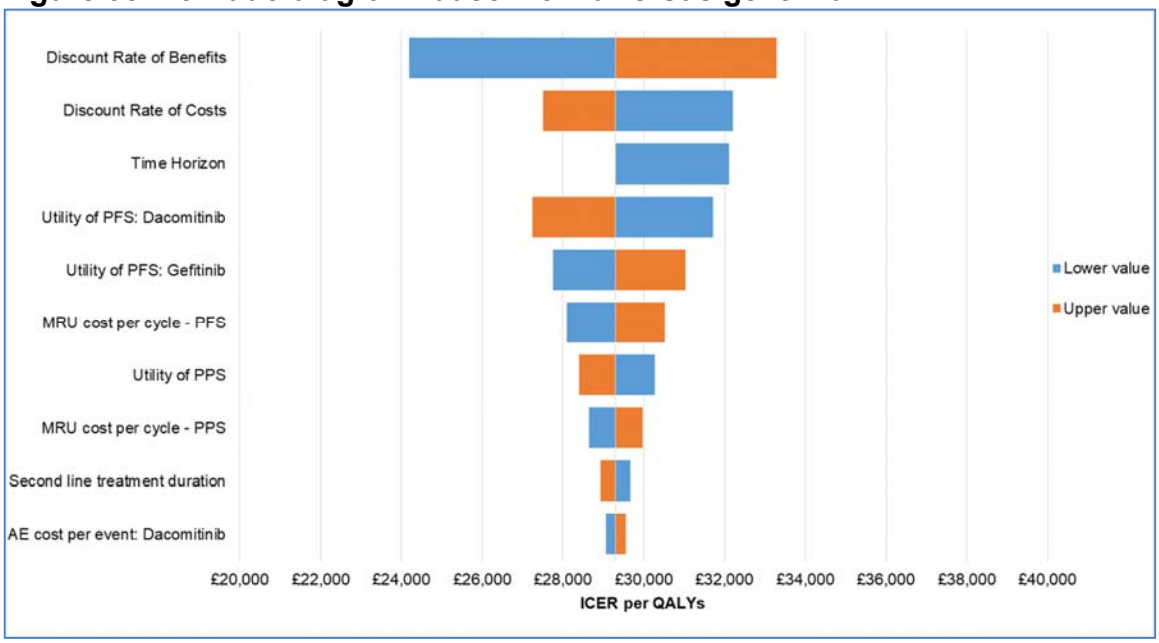
The same pattern was observed in the probabilistic analysis. Dacomitinib resulted in higher LYs, QALYs, and costs compared to all comparators and was cost-effective at a £30,000 per QALY threshold. The cost-effectiveness acceptability curve shows that there is an approximately 37% chance of dacomitinib being cost-effective compare to all comparators at the £30,000 per QALY threshold.

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted for all key variables in the model. The mean values and ranges applied are detailed in Appendix L.

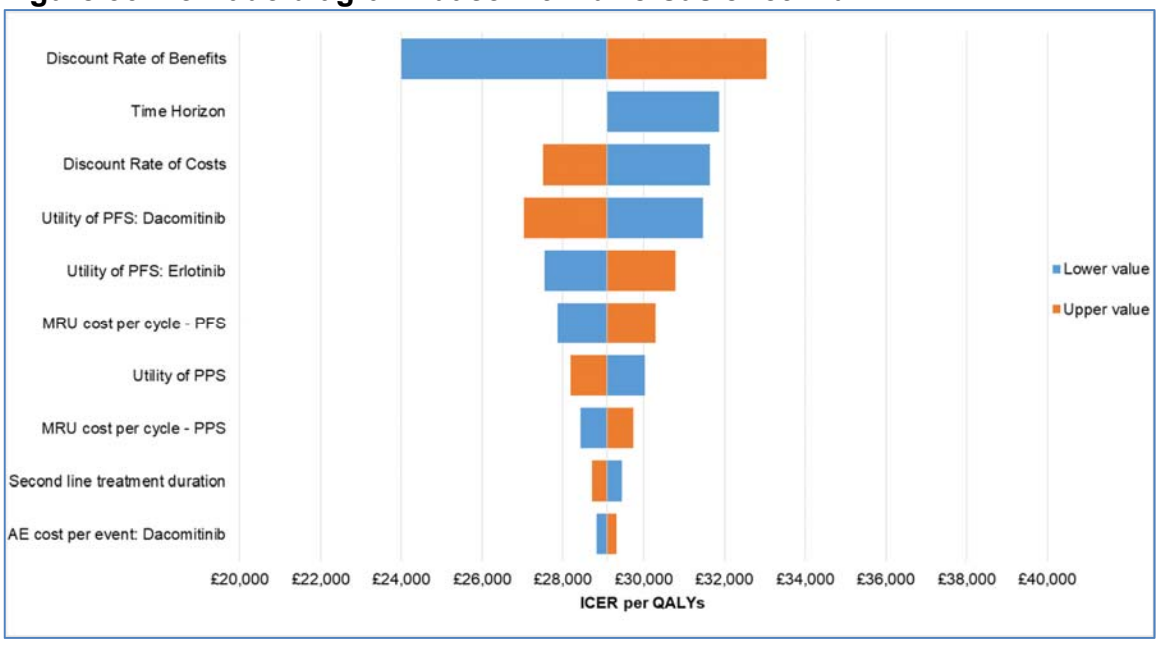
The tornado diagrams showing the key drivers of cost-effectiveness versus gefitinib, erlotinib and afatinib are presented in Figure 35, Figure 36 and Figure 37, respectively.

Figure 35. Tornado diagram: dacomitinib versus gefitinib



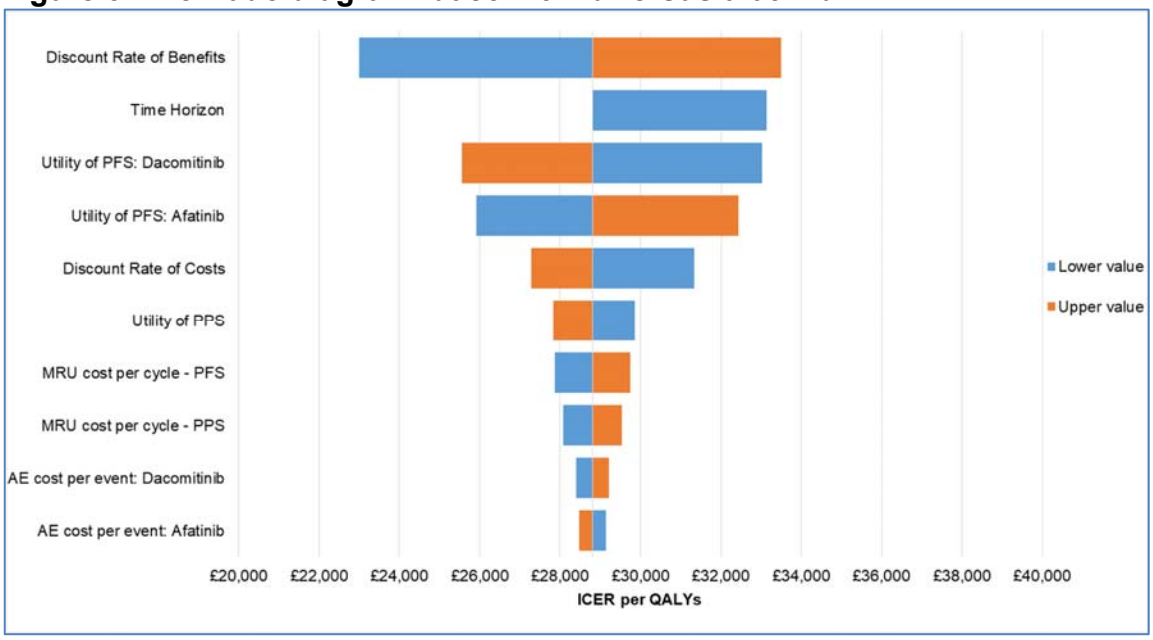
Abbreviations: ICER = incremental cost-effectiveness ratio

Figure 36. Tornado diagram: dacomitinib versus erlotinib



Abbreviations: ICER = incremental cost-effectiveness ratio

Figure 37. Tornado diagram: dacomitinib versus afatinib



Abbreviations: ICER = incremental cost-effectiveness ratio

B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess the sensitivity of the model to various assumptions. Details of each scenario are presented in Table 50. The results of the scenario analyses are presented versus gefitinib, erlotinib and afatinib in Table 51, Table 52 and Table 53, respectively.

Table 50. Details of scenario analyses

Scenario	Base-case	Scenario description	Reference to section in submission
Gefitinib survival projection (PFS)	Generalised gamma	Log-normal	B.3.3.1.2
Gefitinib survival projection (OS)	Generalised gamma	Log-logistic	B.3.3.1.3
FP model (PFS)	FP model P1=0.5 and P2=1.5	FP model P1=0.5 P2=1	B.2.9.3.2
FP model (OS)	FP model P1=-0.5	FP model P1=0	B.2.9.3.2
NMA methodology (PFS and OS)	FP NMA	Traditional proportional hazards NMA	B.2.9.3.2
Utility (PF) with AEs	Treatment specific utility based on ARCHER 1050 and assumption ([redacted])	Non-treatment specific utility based on ARCHER 1050 ([redacted]) with AE disutility's	B.3.4.5
Utility (PF) with AEs	Treatment specific utility based on ARCHER 1050 and assumption ([redacted])	Non-treatment specific utility based on Labbé (0.77) with AE disutility's	B.3.4.5
Treatment beyond progression	Discontinue treatment upon progression	Dacomitinib [redacted] months (PFS 14.7 vs TTD [redacted]) Gefitinib/erlotinib [redacted] months (PFS 9.2 vs TTD [redacted]) Afatinib +2.7 month (PFS 11.0 vs TTD 13.7)	B.3.3.4

Abbreviations: FP = fractional polynomial; NMA = network meta-analysis; OS = overall survival; PD= progressed disease; PF= progression-free; PFS = progression-free survival; PD= progressed disease; TTD = time to treatment discontinuation

Table 51. Results of base-case scenario analysis versus gefitinib

Scenario	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,305**	**-**
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,882	22%
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,344	-24%
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,170	6%
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,711	-5%
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,659	5%
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,195	-14%
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,108	-11%
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,444	11%

Abbreviations: OS = overall survival; PD= progressed disease; PF = progression-free; PFS= progression-free survival

Table 52. Results of base-case scenario analysis versus erlotinib

Scenario	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,084**	**-**
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,013	10%
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,180	-24%
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,954	6%
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,503	-5%
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,451	5%
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,004	-14%
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,911	-11%
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,677	-15%

Abbreviations: OS = overall survival; PD= progressed disease; PF = progression-free; PFS= progression-free survival

Table 53. Results of base-case scenario analysis versus afatinib

Scenario	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,808**	**-**
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,035	8%
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,371	-26%
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,391	9%
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,441	-12%
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,319	16%
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,188	-2%
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,089	1%
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,735	-28%

Abbreviations: OS = overall survival; PD= progressed disease; PF = progression-free; PFS= progression-free survival

B.3.8.4 Summary of sensitivity analyses results

The probability of dacomitinib being the most cost-effective treatment at a threshold of £30,000 per QALY is 37%.

One-way sensitivity analysis showed that the inputs that most affect the ICERs were those related to the discount rates for costs and outcomes and time horizon, none of which are inputs considered to be uncertain. Following these was the PF utilities which had a moderate effect as they were varied indvidually by treatment and thus was not as plausible as the utility scenarios explored where all PFS values were varied simultaneously. The model was relatively insensitive to the PD utility value as the model predicted similar mean duration in PD for all treatments.

Scenarios looking at different OS projection, the cost of continuing treatment beyond progression and applying non treatment specific utility values with AE disutility's resulted in significant changes in the cost-effectiveness estimates. All other scenario resulted in marginal changes with the exception of the log-normal PFS which was considered to slightly overestimate long-term PFS. Also of note, was the insensitivity of the model to the use of the proportional hazards ITC.

In summary, the model is relatively insensitive to assumptions and dacomitinib remained a cost-effective strategy when clincailly plausible scenarios were considered.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Comparison of clinical inputs to previous clinical studies

As discussed in Section 3.3.1.2-3 previous EGFR studies with median follow-up greater than ARCHER 1050 were used to justify the base-case parametric models.

Table 54 and Table 55 demonstrate that the PFS and OS base-case models provided good fits to the observed data from ARHCER 1050 and the long-term extrapolation were aligned with the external studies. For more detail refer to Section 3.3.1.2-3.

Table 54. Comparison of gefitinib outcomes against previous studies (PFS)

	Median	Proportion PF at			
		1 year	2 years	3 years	5 years
Base-case (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUX-Lung 7	10.9	39.5%	5.6%	1.5%	-
Lin 2016	12.1	54%	16.2%	8.4%	0.0%
WJTOG 3405	9.6	41.6%	12.4%	6.2%	-

Abbreviations: PF= progression-free; PFS = progression-free survival

Table 55. Comparison of gefitinib outcomes against previous studies (OS)

	Median	Proportion alive at						
		1 year	2 years	3 years	5 years	6 years	7 years	8 years
Base-case (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUX-Lung 7	24.5	84.6%	50.9%	32.7%	-			
Lin 2016	30.9	89.9%	66.3%	39.3%	14.6%	10.5%	6.6%	0.0%
WJTOG 3405	34.8	85.1%	64.3%	47.5%	21.0%	10.9%	6.8%	-

Abbreviations: OS = overall survival

Comparison of model outcomes to previous analyses

Comparison could not be drawn against previous EGFR appraisals given the numerous limitations and lack of final base-case outcomes reported.

Therefore, cost-effectiveness studies identified in the SLR (see Appendix G) were utilised to validate the model outcomes. Two studies were identified which reported LYs and utilised similar methodologies and clinical data:

- [redacted]
- [redacted]

Clinical expert opinion

Two UK clinician experts provided validation in separate one-to-one meetings on key inputs in the cost-effectiveness analysis. For further details please see Section 3.3 (survival data) and Section 3.5 (subsequent treatments).

B.3.10.2 Quality control

Internal quality control of the economic model was undertaken by the developers of the model on behalf of the manufacturer.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison with published economic literature

To our knowledge this is the first economic evaluation comparing dacomitinib with approved EGFR TKIs in patients with EGFR-positive NSCLC.

B.3.11.2 Relevance of the economic analysis to all patients who could potentially use the technology in the decision problem

This evaluation considers all patients identified in the decision problem.

B.3.11.3 Generalisability of the analysis

ARCHER 1050 shared similar baseline characteristics to the studies utilised in the most recent previous EGFR appraisal[68] (AURA extension, AURA2 and IMRESS). In the appraisal '*experts highlighted that these trials were more generalisable than most other lung cancer trials because people with EGFR mutation-positive NSCLC tended to be diagnosed at a younger age, were fitter and not necessarily smokers compared with other types of lung cancer*' and therefore, the committee concluded that the trials used '*were broadly generalisable to clinical practice'*. Furthermore, clinical expert opinion suggested that studies with a predominately Asian population tend to mirror what is seen in Caucasian patients. Therefore, the patient population in ARCHER 1050 applied in the economic analysis can also be considered generalisable to UK clinical practice.

The model was developed using costs and resource usage from UK based sources and from previous technology appraisals presented to NICE. Where UK resource usage was not available (subsequent treatments) these were validated with UK clinical experts.

In summary, all steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of dacomitinib reflective of UK clinical practice.

B.3.11.4 Strength of the economic analysis

The economic analysis has number of key strengths:

- The PartSA model structure was simple and has been applied in numerous previous NSCLC appraisals, utilises the available data from the pivotal trial and comparator trial and captures the key outcomes of interest in NSCLC.

- The relatively novel FP approach utilised in the NMA, is being increasingly utilised in NICE appraisals. The FP method integrated time vary hazard ratios which meant it did not rely on the arbitrary assumption of a constant and maintained treatment effect, which has been a key criticism in previous NICE appraisals.

- EQ-5D was collected in the ARCHER 1050 study. This allowed the PF utility to be aligned with the NICE reference case (EQ-5D; measured directly from patients; valued using UK general population tariff). In addition, a repeated measures mixed-effects model was used to calculate utility values which accounted for the correlated between repeated measures, which avoided patients with longer term follow-up biasing the estimated values.

- All resource usage and costs (administration, PF and PD disease management and terminal care costs) have been validated and accepted in multiple previous NSCLC appraisals, providing an element of certainty in these values.

- DSA and scenario analysis demonstrated that the results are insensitive to a large number of parameters and assumptions.

B.3.11.5 Limitation of the economic analysis

A limitation of the analysis was that both PFS and OS data had to be extrapolated as neither were complete (i.e. not all patients had experienced the corresponding event) from ARCHER 1050. Despite this, by extrapolating based on the observed data in ARCHER 1050, the best available evidence has been taken into account. The modelled curves varied in their extrapolations, indicating that there was uncertainty in the long-term outcomes for these patients. However, any uncertainty around the long-term extrapolation was mitigated by the use of:

- Long-term data from previous EGFR NSCLC studies with median follow-up greater than ARCHER 1050 to provide expected land mark rates
- UK clinical expert opinion on the most appropriate curves
- Sensitivity analysis to demonstrate the impact of assuming alternative curves

A minor limitation was that EQ-5D was only collected prior to progression in ARCHER 1050. Therefore, data from external literature was required to inform the utility value for the PD state. However, the source identified in the SLR was aligned with the NICE reference case directly in the population of interest and the value was aligned with a previous ERG recommended value in NSCLC.

B.3.11.6 Conclusions

Dacomitinib is a novel, innovative treatment which is associated with improvements in key outcomes for EGFR mutation-positive NSCLC patients. Dacomitinib is the first TKI to show an increase to life expectancy in its phase III study against an active comparator in patients with locally advanced or metastatic EGFR+ NSCLC (Document B.2.6.3.2). In addition, dacomitinib has the longest PFS data (Document B.2.6.2) compared to current approved treatments for EGFR+ NSCLC, which both delays the onset of greater symptom burden and delay the use of subsequent treatments thereby increasing the total time on active therapy in currently available treatment sequences. It is expected that, as a result of improvements in efficacy,

dacomitinib's position in the clinical pathway alongside the three current standard-of-care TKIs is an important step forward in improving patient outcomes.

The base-case analysis showed dacomitinib is a cost-effective treatment with ICERs of dacomitinib versus gefitnib, erlotinib and afatinib of £29,305, £29,084 and £28,808, respectively with the assumed PASs. The economic analysis had a number of strengths, including a simple well accepted structure, an indirect comparison that allowed for the exploration of non-proportional hazards assumption on survival, utilities that were derived directly from patients and resource usage that had been extensively utilised and accepted in previous appraisals. Minor limitations associated with survival extrapolations and utilities were mitigated through the use of the best available external data and clinical expert opinion. Sensitivity analyses demonstrated minimal variation in cost-effectiveness outcomes when these key areas of uncertainty were explored. In addition, the model projections were consistent with the clinical data and previous economic analysis.

In summary, dacomitinib, a novel second-generation TKI, is a step forward for the first-line management of EGFR+ NSCLC patients in England and Wales and demonstrates value for money for the NHS.

B.4 References

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B.5 Appendices

[redacted]

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Base-case analysis inputs

Appendix M: Base-case results

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Single technology appraisal

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Dear [Insert name],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on the 7th of December from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter). The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on the **23rd of January 2019**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Luke Cowie, Technical Lead (Luke.Cowie@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Technology Appraisals, on behalf of
Linda Landells
Associate Director – Technology Appraisals
Centre for Health Technology Evaluation

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Single technology appraisal

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Clarification questions

March 2019

File name	Version	Contains confidential information	Date
		Yes/no	

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Notes for company

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Section A: Clarification on effectiveness data

Literature searching

A1. Four publications from three studies initially included in the broad review are excluded for this company submission (CS). Citations (reference numbers 124-126) related to three of these publications are provided in the text (CS Appendix page 195). Please provide citation details and a PDF of the publication that is not cited.

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

A2. Please provide citation details for all of the 339 + 40 publications excluded at full-text review, as not all of them are listed in the CS Appendices (Sections 1.7.2.1-1.7.2.3., page 209-234)

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

A3. Please provide the record of the search in Clinicaltrials.gov.

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

A4. Please provide references and underlying evidence in support of the statement *"These two mutations alone constitute approximately 80–90% of EGFR mutations in adenocarcinomas."* (CS Document B, page19).

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

A5. In the update of the systematic reviews used to identify records reporting health-related quality of life, and publications reporting information related to resource use and costs, it appears that 64 records (Figure 65, CS Appendix, page.310) and 27

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records (Figure 70, CS Appendix, page.350) were excluded, respectively. Please provide a list of the excluded records with the reasons for exclusion.

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

ARCHER 1050 trial

A6. Priority question: In the CS, it is stated that *"clinical expert opinion suggested that studies with a predominately Asian population tend to mirror what is seen in Caucasian patients"* (CS Document B, page92). Please elaborate on this claim and explain whether these views are specific to non-small-cell lung cancer (NSCLC), especially in light of evidence to the contrary in other NSCLC treatments?

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

A7. Priority question: In the CS, it is stated that *"Patient demographic and baseline characteristics [of ARCHER 1050 participants] were representative of the intended patient population for dacomitinib in the first-line setting."* (CS Document B, page 92). Please provide a simple comparison highlighting similarities and differences in patient demographic characteristics, including race/ethnicity, between ARCHER 1050 participants and the intended patient population for dacomitinib in England.

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

A8. Priority question: Please provide Kaplan Meier (KM) plots of overall survival (OS) and progression-free survival (PFS) for the Asian and non-Asian populations in the ARCHER 1050 trial by treatment arm.

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

A9. Priority question: Figure 14 (CS Document B, page 63) presents the forest plot of OS (stratified by subgroups; intention-to-treat (ITT) population). Please provide the equivalent forest plot and information (i.e. HR and 95% CI, p-values for interactions) for PFS.

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A10. The NICE scope for this appraisal is for people with 'EGFR activating mutations'. The ARCHER 1050 trial included only people with del19 or L858R mutation and people with both of these mutations were excluded, (CS Document B Table 5, page 28). Please explain why these people were excluded from the trial**.**

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

A11. For the ARCHER 1050 trial, please provide details on how many participants were randomised in European sites (Italy, Spain, Poland).

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

A12. Please clarify how the blinded Independent Review Committee (IRC) review of PFS was carried out in ARCHER 1050.

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

A13. Please provide the definition for *"global deterioration of health"* (CS Appendix, Section D.2, Figure 39), which is used as a reason for discontinuation.

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

A14. Please provide the definition for *"adequate renal, hepatic and haematological function"* (CS Document B, Table 4), which is used as an inclusion criterion in ARCHER 1050.

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

A15. Table 8 (CS Document B, page 32) lists prior and concomitant medications used during the ARCHER 1050 trial. Please provide details of concomitant medications given by study treatment arm.

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

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A16. In the CS Document B (page 92), it is stated that the *"vast majority"* of participants had stage IIIb or IV disease. Please clarify if the remaining participants are those with disease stage 'unknown' at study screening and stage IV at study entry (CS Table 10).

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

A17. Please clarify how ARCHER 1050 trial participants were diagnosed with the T790M mutation and describe the treatment pathway for these patients.

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

A18. Figure 13 (CS Document B, page 62) gives forest plots for PFS, stratified by subgroups. In the non-Asian population, median PFSl appears to be [redacted] months in the dacomitinib group and [redacted] months in the gefitinib group (HR [redacted] [95%CI[redacted], [redacted]]; p=[redacted]). Please:

i) justify why one-sided p-values were used in this analysis and confirm whether the p-value ([redacted]) above is correct.

ii) confirm the significance threshold for Figures 12 and 13 is 0.025 (from the statistical analysis plan), and explain why this is not included in the figures.

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

Section B: Clarification on cost-effectiveness data

Literature searching

B1. In the PRISMA diagram in Figure 64 (CS Appendix, page. 288), it is indicated that 169 records were excluded at full-text stage. Please provide a list of the excluded studies with the reasons for exclusion.

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

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ARCHER 1050 trial

B2. Priority question: Please provide a comparison of the gefitinib and dacomitinib smoothed-hazard and cumulative hazard plots, with the company base case gen-gamma and FP models overlaid. Please present these as two figures.

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

B3. Priority question: Please provide an updated economic model that allows:

i) a comparison between both treatment arms of the ARCHER 1050 trial to be made with both treatment arms being modelled by independent parametric models (i.e. no proportionality assumption and not using results from the fractional polynomial (FP) network meta-analysis (NMA));

ii) the cost-effectiveness analysis to be undertaken separately for the ITT, Asian and non-Asian population.

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

B4. **Priority question:** Please provide hazard and cumulative hazard plots against time:

i) for both the gefitinib and dacomitinib treatment arms of ARCHER 1050 overlaid with the fits of each parametric model (i.e. without using FP). Please present these as four figures.

ii) with the parametric curves for both gefitinib and dacomitinib in the Asian and non-Asian populations.

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

B5. Priority question: Please clarify how the parametric models fitted to the gefitinib treatment arm of ARCHER 1050 were combined with the FP analysis. Were the hazard ratios from the FP analysis applied to the parametric model? If so, please clarify

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why the gefitinib treatment arm was modelled using the parametric fit to the ARCHER 1050 trial data, rather than the FP model alone.

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

B6. Priority question: Figure 32 (CS Document B, page 108) presents the OS curves, along with the company's choice of the fully-fitted parametric curves applied to the observed data. Data beyond 30 months are immature, with the KM curves appearing to overlap at approximately 36 months. Please add an option to the economic model that allows entering a hazard ratio of 1 for OS across all comparators after 36 months (e.g. a waning effect).

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

B7. Priority question: In Figures 5 and 6 (CS Document B, page 52-53), the KM plots for PFS and OS appear to overlap and cross. Please:

i) provide a justification for not applying a two-phase piecewise (KM plus parametric) modelling approach to model survival outcomes used in the economic model;

ii) add an option that allows implementing a two-phase piecewise model, using KM data until 8 months for PFS and 12 months for OS, after which parametric models are fitted and used to extrapolate.

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

B8. Priority question: Figure 14 (CS Document B, page.64) presents the forest plot of OS (stratified by subgroups; ITT population). Please provide the equivalent forest plot and information (i.e. HR and 95% CI, p-values for interactions) for PFS (IRC).

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

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B9. A table ('Adverse Events' worksheet; cells 'E7:J14') in the company's economic model reports the frequency of Adverse Events (AEs) by treatment. Please:

i) clarify whether these values represent the proportion of people who experienced each of the listed AE or reflects the number of AEs that people experienced (i.e. it captures recurrent events);

ii) provide a full list of incidences (first, second, and subsequent) of grade 3-5 AEs, by treatment.

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

B10. In the economic model, the progression-free states is assigned utility values obtained from the ARCHER 1050 trial, while utility values for progressed disease are taken from the study by Labbé and colleagues. Given that the ARCHER 1050 trial methodology states that *"Patient reported outcomes were assessed at days 1 (baseline), 8, and 15 of cycle one, on day 1 of subsequent cycles, at the end-of-treatment visit, and at the posttreatment follow up visit"* (Wu et al., 2017 p. 1456), please provide summary statistics for the EQ-5D data collected at the end-of-treatment/post treatment follow-up visits by trial treatment arm.

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

B11. In the CS (Document B, page 107) it is stated that time-to-treatment discontinuation was not available for all the comparators. Please give information on treatment duration for those comparators (afatinib and erlotinib) where such information is available.

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

B12. Please provide the standard errors for the mean progression-free utility values reported in Table 37 (CS, Document B, page113).

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

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B13. Please reproduce the FP NMA for the Asian and non-Asian populations.

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

B14. Please provide the digitised graph and resulting generated data for the FP NMA.

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

B15. Please provide the FP NMA code and data.

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

B16. There appears to be a discrepancy between the cost per cycle values in CS Document B (Table 38, page116) and the equivalent values in the economic model (sheet 'Medical Costs, Drugs', cells F26:F29). Please clarify whether the values in cells F26:F29 are incorrect and confirm that these values have not been used in the calculations underpinning any of the results presented in the submission.

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

B17. Please confirm whether monetary values related to health care use taken from past analyses and literature (e.g. cost of terminal care) are appropriately adjusted for differential timing.

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

B18. In CS Document B, page112, it is stated that "these values were also aligned with the only real world EGFR+ NSCLC value identified in the SLR (Labbé et al. 2017 [0.77]), therefore this value was applied in scenario analysis." Please clarify the meaning of the expression 'real world values' in this particular context.

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

B19. Please confirm whether utility values used in the economic model calculations have been adjusted over the time horizon to reflect the modelled patients' age-related decline in health-related quality of life.

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

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Section C: Textual clarification and additional points

C1. Please define the footnotes for adverse events in Figure 39 (CS Appendix D.2, page 256).

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

C2. In CS Document A, page 20, the Incremental Cost Effectiveness Ratio (ICER) for dacomitinib is reported to be £[redacted] per QALY gained. This result is not consistent with the ICER value for dacomitinib reported in Table 6, page 20. Please confirm whether £[redacted] is a typographical error.

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

C3. Please provide all 134 references (related to CS Document B and Appendix) as either a RIS. file or an archived EndNote library.

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

C4. Please provide a PDF for reference 55 'Pfizer. Data on file. 2017', cited at the end of page 65 (CS Document B, section B.2.9.1)

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

C5. Please provide a PDF for reference 99. 'Pfizer. Pfizer One-to-one interviews with UK clinical experts; Pfizer Data on File. 2018', cited on page115 (CS Document B, section B.3.5.2)

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

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Single technology appraisal

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
ID1346_Dacomitinib_EGFR_NSCLC_Clarification_Response_23JAN19.docx	Final	Yes	23rd January 2019

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Dear Linda,

Pfizer would like to thank Warwick Evidence and the NICE technical team for the clarification questions and opportunity to provide further detail to aid the evaluation of our evidence submission. Please find below Pfizer's response to the questions. Please note that additional programming is being conducted for question B9 which is not included in this current document.

We noted that in question A8 we are requested to provide KM plots of OS and PFS for the Asian and non-Asian populations. Pfizer believes the ITT is the appropriate population for decision making. There are significant limitations with using the non-Asian subgroup from ARCHER 1050 because of the relatively small proportion of patients (23% of ITT), the imbalance of older patients between treatment arms in this subgroup, and the fact the study was not powered to show statistically significant differences between treatments in this subgroup (more details are provided in A8).

The ERG have also requested additional scenarios that explore survival extrapolations. However, Pfizer would like to highlight that it feels these could only be considered exploratory given the evidence base and the recommendations in NICE DSU guidelines. One such assumption is that the observed survival benefit dissipates at 36 months. This is based on censored data (small numbers of patients at risks) and is misaligned to the previously observed trends. Furthermore, such an approach is not recommended in the NICE DSU guidelines.

Despite the limitations with these scenarios, Pfizer has responded to the ERG's requests and has provided an updated economic model along with related files containing additional source data. Should the ERG require additional clarity we welcome further opportunity to engage.

Sincerely,

[redacted]

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Section A: Clarification on effectiveness data

Literature searching

A1. Four publications from three studies initially included in the broad review are excluded for this company submission (CS). Citations (reference numbers 124-126) related to three of these publications are provided in the text (CS Appendix page 195). Please provide citation details and a PDF of the publication that is not cited.

In addition to the primary publications included in the CS, please see the following companion PDF publications attached with the response:

- CONVINCE
  - **Shi 2017** (abstract only available online http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9041)
  - **Shi 2016** *First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy in lung adenocarcinoma patients with EGFR mutation (CONVINCE)* Annals of Oncology 27 (Supplement 6): vi416–vi454
- JO25567
  - **Zhang 2016** *Efficacy and safety of bevacizumab plus erlotinib versus bevacizumab or erlotinib alone in the treatment of non-small-cell lung cancer: a systematic review and meta-analysis* BMJ Open 2016;6:e011714.
  - **Kato 2018** *Erlotinib Plus Bevacizumab Phase II Study in Patients with Advanced Non-small-Cell Lung Cancer (JO25567): Updated Safety Results* Drug Saf. 41(2):229-23

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A2. Please provide citation details for all of the 339 + 40 publications excluded at full-text review, as not all of them are listed in the CS Appendices (Sections 1.7.2.1-1.7.2.3., page 209-234)

Please see list of citation for those missing from CS in Appendix A (97 studies that did not include intervention of interest and the 21 studies that were unavailable).

A3. Please provide the record of the search in Clinicaltrials.gov.

Please see details of the search strategy applied in Clinicaltrails.gov in Table 1 and the respective data extraction excel file attached with the response (Clinicaltrials.gov.xlsx).

Table 1: Clinicaltrials.gov search strategy for RCT/non-RCT SLR

Field	Search term
Condition or disease	Non Small Cell Lung Cancer
Study type	All studies
Study Results	Studies with Results
Age Group	Adult (18-64); Older Adult (65+)
Sex	All

A4. Please provide references and underlying evidence in support of the statement *"These two mutations alone constitute approximately 80–90% of EGFR mutations in adenocarcinomas."* (CS Document B, page19).

The relevant reference is Reference 25 from the CS:

- Juan O, Popat S. Treatment choice in epidermal growth factor receptor mutation-positive non-small cell lung carcinoma: latest evidence and clinical implications. Therapeutic advances in medical oncology. 2017;9(3):201-216

There is also underlying evidence in the following publications:

- Allan L, Dhananjay C, Gregory R, William P, Vincent M, Maureen Z, Valerie R, Mark K, and Marc L. *EGFR Mutations in Lung Adenocarcinomas: Clinical Testing Experience and Relationship to EGFR Gene Copy Number and Immunohistochemical Expression*. J Mol Diagn. 2008 May; 10(3): 242–248.

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'The two most common EGFR mutations are short in-frame deletions of exon 19 and a point mutation (CTG to CGG) in exon 21 at nucleotide 2573, which results in substitution of leucine by arginine at codon 858 (L858R). Together, these two mutations account for ~90% of all EGFR mutations in non-small cell lung cancer (NSCLC)' (page 242)

'Seventy-eight (23%) of these tumors had an EGFR mutation, with 55 (71%) exon 19 deletions and 23 (29%) exon 21 L858R mutations.' (page 242)

- *Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, Shimizu N, Fujisawa T, Feng Z, Roth JA, Herz J, Minna JD, Gazdar AF. Clinical and Biological Features Associated With Epidermal Growth Factor Receptor Gene Mutations in Lung Cancers. J Natl Cancer Inst. 2005 Mar 2;97(5):339-46*

'Three types of mutations constituted 94% of the mutations that we detected: deletions in exon 19, duplications and/or insertions in exon 20, and a single-point mutation in exon 21.'

Of this 94%, Exon 19 was observed in 46% and Exon 21 L858R in 39% (Table 2).

A5. In the update of the systematic reviews used to identify records reporting health-related quality of life, and publications reporting information related to resource use and costs, it appears that 64 records (Figure 65, CS Appendix, page.310) and 27 records (Figure 70, CS Appendix, page.350) were excluded, respectively. Please provide a list of the excluded records with the reasons for exclusion.

Please see lists of citation for excluded health-related quality-of-life studies in Appendix B and resource usage and cost studies in Appendix C.

ARCHER 1050 trial

A6. Priority question: In the CS, it is stated that *"clinical expert opinion suggested that studies with a predominately Asian population tend to mirror what is seen in*

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Caucasian patients" (CS Document B, page92). Please elaborate on this claim and explain whether these views are specific to non-small-cell lung cancer (NSCLC), especially in light of evidence to the contrary in other NSCLC treatments?

This initial statement was informed by various discussions with UK clinicians. Following this clarification request, we have reached out again to UK clinical experts for additional advice. Feedback is that there is no common consensus as to whether ethnicity plays a role; advice suggests prognosis is more usually driven by mutation type, age and performance status however, as opposed to geographic differences.

A number of the afatinib studies included Asian and non-Asian subgroups (LUX-Lung 3, LUX-Lung 7) however, given the higher prevalence of EGFR mutations in Asian populations both these trials had predominantly Asian cohorts, therefore leading to a lack of power in the non-Asian subgroup to detect significance. These studies have however, demonstrated there is no common direction for the relative efficacy between Asian versus non-Asian patient.

Table 2. Summary of progression-free survival results in Asian and Non-Asian patients

Trial	Intervention	Comparator	N	Asian	Asian HR	Non-Asian HR
LUX-Lung 3	Afatinib	Chemotherapy	345	72%	0.54 (0.38, 0.76)	0.68 (0.39, 1.19)
LUX-Lung 7	Afatinib	Geftinib	319	60%	0.76 (0.54, 1.06)	0.72 (0.49, 1.06)

Abbreviation: HR = hazard ratio

A7. Priority question: In the CS, it is stated that *"Patient demographic and baseline characteristics [of ARCHER 1050 participants] were representative of the intended patient population for dacomitinib in the first-line setting."* (CS Document B, page 92). Please provide a simple comparison highlighting similarities and differences in patient

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demographic characteristics, including race/ethnicity, between ARCHER 1050 participants and the intended patient population for dacomitinib in England.

No UK specific demographic information for EGFR NSCLC patients was identified in the CS and the company has not been made aware of UK EGFR demographic data during clinical expert consultation.

It should be noted that, as discussed in CS Document B page 137, ARCHER 1050 shared similar baseline characteristics to the studies utilised in the most recent EGFR appraisals (Table 3) where the committee acknowledged that these studies were broadly generalisable to clinical practice.

Table 3. Summary of progression-free survival results in Asian and Non-Asian patients

Baseline characteristic		ARCHER 1050		AURA pooled	IMPRESS
		Dacomitinib	Gefitinib	Osimertinib	Platinum doublet chemotherapy
Age	Mean	62.0	61.0	62.2	57.0
	Median	61.2	60.9	63.0	58.0
Gender	Male	36%	44%	32%	36%
	Female	64%	56%	68%	64%
EGFR	Exon 19 deletion	59%	59%	68%	65%
	L858R	41%	41%	29%	32%
ECOG	0	33%	28%	37%	40%
	1	67%	72%	63%	60%
Smoking status	Never	65%	64%	69%	69%
	Ever	29%	28%	28%	NR
	Current	7%	8%	2%	NR

Abbreviations: NR = Not reported.
Source: TA416 Osimertinib NICE STA Submission – February 2016 Table 4.7 page 76

A8. Priority question: Please provide Kaplan Meier (KM) plots of overall survival (OS) and progression-free survival (PFS) for the Asian and non-Asian populations in the ARCHER 1050 trial by treatment arm.

Progression-free survival - Asian

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Overall, a total of [redacted] patients ([redacted]) in the Asian population from ARCHER 1050 had a PFS event as of the data cut-off date, after application of all the censoring rules. Of the [redacted] PFS events, [redacted] patients ([redacted]%; n=170) were from the dacomitinib arm and [redacted] patients ([redacted]%; n=176) from the gefitinib arm. Dacomitinib demonstrated a [redacted] month improvement in median PFS; median PFS was xx.x months (95% CI: [redacted]) for dacomitinib versus [redacted] months (95% CI: [redacted]) for gefitinib (HR: [redacted]; 95% CI: [redacted]; 1-sided p-value<0.0001; unstratified log-rank test).

The Kaplan-Meier plot for PFS based on blinded IRC review for the Asian population is shown in XXXXXXX1. The probability of being event-free at 12 months was [redacted]% (95% CI: [redacted]) for the dacomitinib arm versus [redacted]% (95% CI: [redacted]) for the gefitinib arm. At 24 months, the probability of being event-free was [redacted]% (95% CI: [redacted]) versus [redacted]% (95% CI: [redacted]), respectively.

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Overall survival - Asian

In the Asian population, a total of [redacted] deaths were observed at the data-off date on February 17, 2017 ([redacted] [redacted%] and [redacted] [redacted%] in the dacomitinib and gefitinib arms, respectively). The Kaplan-Meier plot for OS is shown in XXXXXXX2.

Dacomitinib demonstrated a [redacted] month improvement in median OS in the Asian population. The median OS was [redacted] months (95% CI: [redacted]) in the dacomitinib arm compared with [redacted] months (95% CI: [redacted]) for gefitinib (HR: [redacted]; 95% CI: [redacted]).

[redacted]2[redacted]

[redacted]

Progression-free survival – non-Asian

Overall, a total of [redacted] patients ([redacted%]) in the non-Asian population from ARCHER 1050 had a PFS event as of the data cut-off date, after application of all the censoring rules. Of the [redacted] PFS events, [redacted] patients ([redacted%]; n=57) were from the dacomitinib arm and [redacted] patients ([redacted%]; n=49) from the gefitinib arm. Dacomitinib demonstrated a [redacted] month improvement in median PFS; median PFS was [redacted]

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months (95% CI: [redacted]) for dacomitinib versus [redacted] months (95% CI: [redacted]) for gefitinib (HR: [redacted]; 95% CI: [redacted]).

The Kaplan-Meier plot for PFS based on blinded IRC review for the non-Asian population is shown in XXXXXXX3. The probability of being event-free at 12 months was [redacted]% (95% CI: [redacted]) for the dacomitinib arm versus [redacted]% (95% CI: [redacted]) for the gefitinib arm. At 24 months, the probability of being event-free was [redacted]% (95% CI: [redacted]) versus [redacted]% (95% CI: [redacted]), respectively.

[redacted]3[redacted]

[redacted]

Overall survival – non-Asian

In the non-Asian population, a total of [redacted] deaths were observed at the data-off date on February 17, 2017 ([redacted] [redacted]%] and [redacted] [redacted]%] in the dacomitinib and gefitinib arms, respectively). The Kaplan-Meier plot for OS is shown in XXXXXXX2.

Dacomitinib demonstrated an [redacted] month improvement in median OS in the non-Asian population. The median OS was [redacted] months (95% CI: [redacted]) in the

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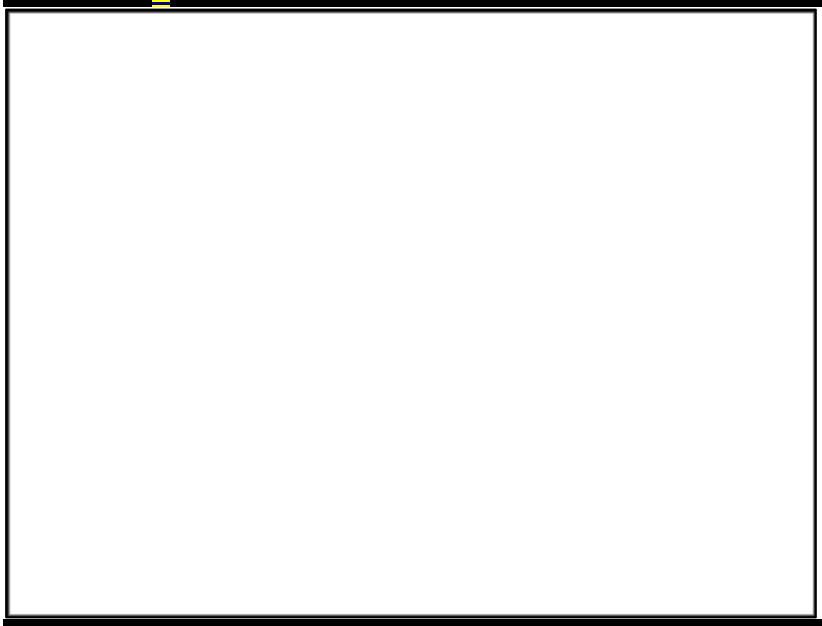
dacomitinib arm compared with [redacted] months (95% CI: [redacted]) for gefitinib (HR: [redacted]; 95% CI: [redacted]).

[redacted]4



[redacted]

In Study 1050, the results from both the PFS and final OS analyses indicated a clinical benefit of dacomitinib over gefitinib in both the non-Asian and Asian subgroups:

- PFS results in the non-Asian and Asian subgroups were consistent with the primary results analysed in the ITT population, which showed that dacomitinib treatment resulted in an improvement in PFS versus gefitinib (HR=0.589 with 1-sided p<0.0001).

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The pre-specified final analysis of OS demonstrated a significant improvement in OS for dacomitinib versus gefitinib (HR=0.760 with 1-sided p=0.0219) in the ITT population, representing a 24.0% lower risk of death in favour of dacomitinib compared with gefitinib.

[redacted]

The data summarised above provide evidence that subgroup analyses of both PFS and OS in non-Asian patients should be interpreted with caution, taking into account how random chance could influence the results in a relatively small subgroup of patients. Study 1050 was not powered to show a statistically significant difference between the treatment arms of the non-Asian and Asian subgroups. However, the positive trend (HR<1) in both PFS and OS in favour of dacomitinib seen in the non-Asian subgroup, which was consistent with overall results in the ITT population, provides reassurance of a positive clinical benefit in this population.

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A9. Priority question: Figure 14 (CS Document B, page 63) presents the forest plot of OS (stratified by subgroups; intention-to-treat (ITT) population). Please provide the equivalent forest plot and information (i.e. HR and 95% CI, p-values for interactions) for PFS.

Please see Figure 12 (CS document B, page 61) for the forest plot for PFS IRC for the ITT. The p-values for the interactions between subgroups were not included in Figure 12 however, so are presented below in Table 4. PFS analyses by baseline characteristic subgroups were generally consistent with the primary analysis of PFS. It should be noted that the ARCHER 1050 study was not designed to have sufficient power to test subgroup interactions.

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Table 4. P-value interaction terms for forest plots of progression-free based on blinded independent review committee analysis

Subgroup	P-value interaction
Gender (male vs. female)	[redacted]
Age group (<65 vs. ≥65)	[redacted]
ECOG (0 vs. 1)	[redacted]
Race (Asian vs. Non-Asian)	[redacted]
Smoking status (never vs. ever)	[redacted]
EGFR at randomisation (Exon 19 vs. L858R mutation)	[redacted]

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; L858R = EGFR-TK mutation with an amino acid substitution at position 858 from a leucine to an arginine.

A10. The NICE scope for this appraisal is for people with 'EGFR activating mutations'. The ARCHER 1050 trial included only people with del19 or L858R mutation and people with both of these mutations were excluded, (CS Document B Table 5, page 28). Please explain why these people were excluded from the trial**.**

At the time that the A7471050 study was being designed, established activating mutations were EGFR exon 19 deletion and EGFR L858R mutation in exon 21 and thus the study eligibility criteria were written based on the known knowledge at that time (Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361(10):947-57). It is extremely rare for a patient to have both exon 19 deletion and the L858R mutation in exon 21 (indeed a previous study reporting these mutually exclusive, Matsuo 2016). At the time of study start, the potential implication of such EGFR double mutation on clinical outcomes was not defined. Based on external expert discussion and the estimated very limited incidence for patients presenting both mutations at the same time in this first-line setting, it was decided from a clinical perspective to follow a conservative approach to keep such patients excluded to ensure clear defined study population.

CITATION: Matsuo et al. Association of EGFR Exon 19 Deletion and EGFR-TKI Treatment Duration with Frequency of T790M Mutation in EGFR-Mutant Lung Cancer Patients. Sci Rep. 2016; 6: 36458.

A11. For the ARCHER 1050 trial, please provide details on how many participants were randomised in European sites ([redacted]).

The summary of participants across European sites is listed in Table 5.

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Table 5. Summary of Patient Accrual by Country ([redacted]**)**

Country, n (%)	Dacomitinib (n=227)	Gefitinib (n=225)	Total (n=452)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A12. Please clarify how the blinded Independent Review Committee (IRC) review of PFS was carried out in ARCHER 1050.

Digitization and blinding of image data

All electronic header information (e.g., subject identifiers) was blinded within the digital data set. Data fidelity was fully maintained. As with every step in the process of preparing imaging data for the read, a visual QC review of the overall quality of the digital images was performed.

When saving data, a unique, subject-traceable file name was created for each masked image file (regardless of imaging modality) using a specific coding system. Utilizing this file name, all images were saved on a network. During the read process, descriptive information about the images was allowed to be annotated in the file/window title bar. The display of this information was needed to track the blinded data; it was also be used in the displaying of images for the reader within the read system.

Independent Review

A read session was defined as a read application code module that corresponds to specific events within the review cycle (i.e., baseline assessment and follow-up assessment). A radiologist must have committed to an assessment within a read session before moving onto the next read session.

Two primary board-certified radiologists and a board-certified adjudicating radiologist (all selected from a pool of radiologists) performed an independent review of response and disease progression for each subject. The review comprised an assessment of

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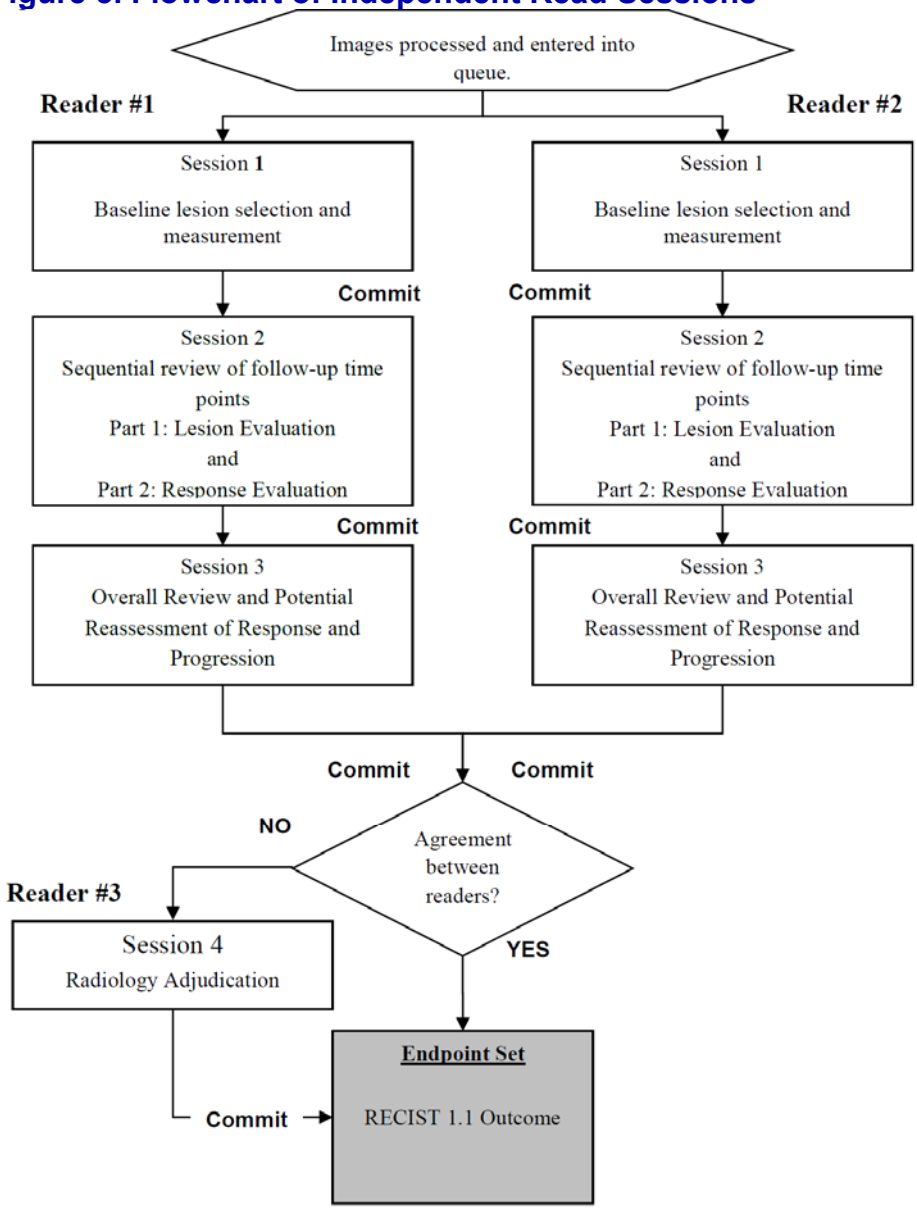
radiographic images acquired during the study. The determination of response and progression was based on RECIST 1.1 as specifically modified for this study. The review process consisted of the steps in Figure 5.

Figure 5. Flowchart of Independent Read Sessions



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The results from these reviews were used to generate the primary endpoint of PFS and derive other tumour control endpoints.

A13. Please provide the definition for *"global deterioration of health"* (CS Appendix, Section D.2, Figure 39), which is used as a reason for discontinuation.

Global deterioration of health was defined as clinical progression causing discontinuation of treatment without objective evidence of disease progression which is not associated to an adverse event.

A14. Please provide the definition for *"adequate renal, hepatic and haematological function"* (CS Document B, Table 4), which is used as an inclusion criterion in ARCHER 1050.

Adequate organ function includes the following criteria:

a. Estimated creatinine clearance ≥30 mL/min (as determined by Cockcroft-Gault formula or the study site's standard formula);

b. Urinary protein <3+ by urine dipstick. If urine protein by dipstick is ≥3+, then a urine protein/creatinine ratio (UPC) should be obtained. The patient may enter only if UPC is <2.0;

c. Absolute neutrophil count (ANC) ≥1500 cells/mm3;

d. Platelets ≥100,000 cells/mm3;

e. Hemoglobin ≥10.0 g/dL;

f. Bilirubin ≤1.5 x upper limit of normal (ULN);

g. Aspartate aminotransferase (AST; also known as SGOT) and Alanine aminotransferase (ALT; also known as SGPT) ≤2.5 x ULN (≤5.0 x ULN if hepatic metastases).

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A15. Table 8 (CS Document B, page 32) lists prior and concomitant medications used during the ARCHER 1050 trial. Please provide details of concomitant medications given by study treatment arm.

On-study concomitant drug treatments are reported in Table 14.4.2.4.1 (Pfizer 2017 *ARCHER 1050 CSR CONFIDENTIAL* page 14252 provided in reference pack). [redacted]

A16. In the CS Document B (page 92), it is stated that the *"vast majority"* of participants had stage IIIb or IV disease. Please clarify if the remaining participants are those with disease stage 'unknown' at study screening and stage IV at study entry (CS Table 10).

Table 10 in the CS Document B where it is presented that 89% of patients have either Stage IIIB or Stage IV disease at the time of screening, with the remaining 11% classed as 'unknown'. All patients with 'unknown' current disease stage were newly diagnosed stage IV at the time of study entry (<2 months interval from initial disease stage) and were confirmed after the database snapshot (see footnote of Table 10 Pfizer 2017 *ARCHER 1050 CSR CONFIDENTIAL* page 134). The phrase "vast majority" is used in the text in reference to these data and so reflects the known stage of disease at study entry.

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A17. Please clarify how ARCHER 1050 trial participants were diagnosed with the T790M mutation and describe the treatment pathway for these patients.

In ARCHER 1050, there was no pre-specified T790M test upon progression given that the trial was initiated in 2013. Therefore, no information was available in the clinical database for this study and thus, it can only be assumed that since [redacted] patients received osimertinib post-progression ([redacted] patients in the dacomitinib arm and [redacted] patients in the gefitinib group as subsequent therapy) T790M testing was performed given that use of osimertinib requires that a patient had a T790M mutation.

Of note, patients who agreed to an optional research aspect of the study, whole blood samples (10 mL; to be processed for plasma according to the Study Manual) were collected at the end of treatment visit for a retrospective analysis for the presence of circulating EGFR mutations including exon 20 T790M. This was only collected for a small number of patients and was not centrally tested; therefore, it was not possible to conduct a post hoc analysis of treatment pathways.

A18. Figure 13 (CS Document B, page 62) gives forest plots for PFS, stratified by subgroups. In the non-Asian population, median PFSI appears to be [redacted] months in the dacomitinib group and [redacted] months in the gefitinib group ([redacted]; p=[redacted]). Please:

i) justify why one-sided p-values were used in this analysis and confirm whether the p-value ([redacted]) above is correct.

One-sided p-values were used for consistency with the testing applied for the ITT primary endpoint analysis.

The p-value in the figure was incorrect and should be [redacted] rather than [redacted].

ii) confirm the significance threshold for Figures 12 and 13 is 0.025 (from the statistical analysis plan), and explain why this is not included in the figures.

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The significance threshold of 0.025 in SAP refers to the analyses on the overall population rather than subgroup analyses. For the subgroup analyses on the primary endpoint or subgroup analyses on secondary endpoints, there were no formal testing procedures or multiplicity adjustments associated with them; hence, there was no significance threshold included in the figures.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. In the PRISMA diagram in Figure 64 (CS Appendix, page. 288), it is indicated that 169 records were excluded at full-text stage. Please provide a list of the excluded studies with the reasons for exclusion.

Please see lists of citations for excluded economic evaluation studies in Appendix D.

ARCHER 1050 trial

B2. Priority question: Please provide a comparison of the gefitinib and dacomitinib smoothed-hazard and cumulative hazard plots, with the company base case gen-gamma and FP models overlaid. Please present these as two figures.

The smoothed hazard and cumulative hazard plots for PFS are presented in XXXXXXX6 and XXXXXXX7, respectively, and for OS in XXXXXXX8 and XXXXXXX9, respectively. All plots demonstrate that the base-case generalised gamma curves for gefitinib provide good fits to the observed data and the FP models applied to the baseline generalised gamma models for dacomitinib provide good fits to the observed data up until there are low number of patients at risk.

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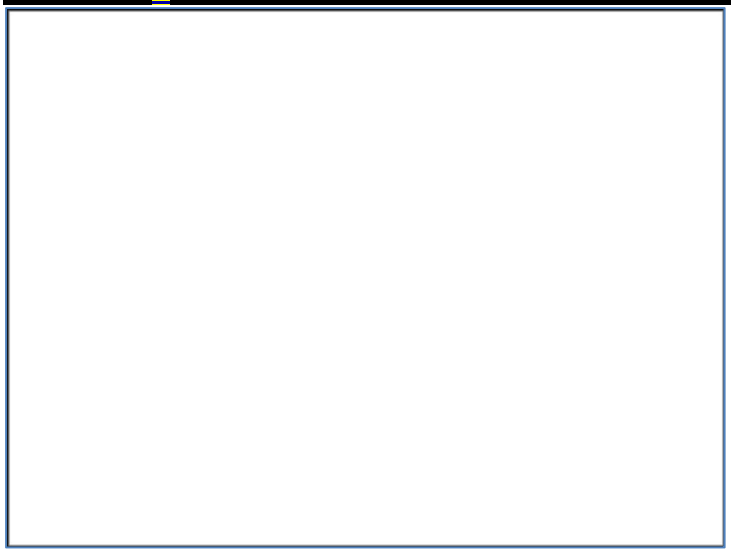
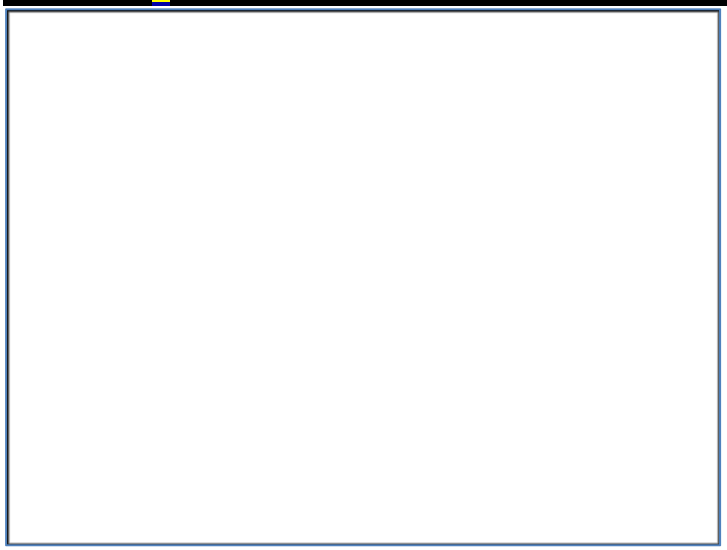


Abbreviations: FP = fractional polynomial; KM = Kaplan-Meier.
Smoothing factor =0.85

[redacted] 7



Abbreviations: FP = fractional polynomial; KM = Kaplan-Meier.

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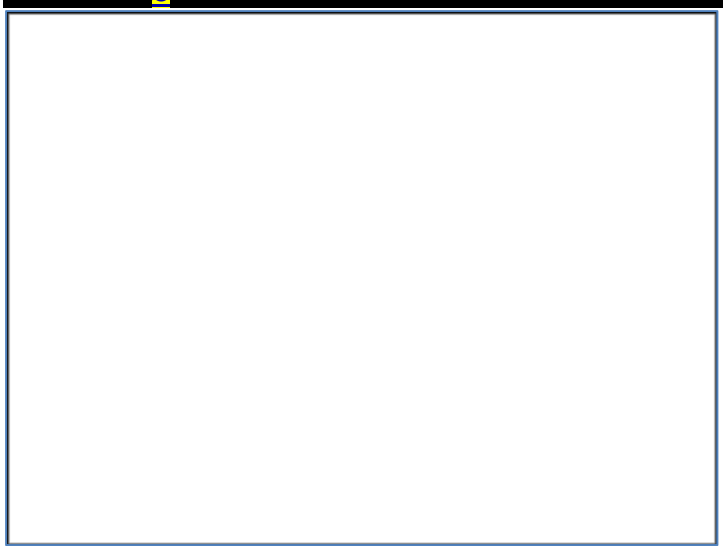

Abbreviations: FP = fractional polynomial; KM = Kaplan-Meier.
Smoothing factor =0.75

[redacted] 9

Abbreviations: FP = fractional polynomial; KM = Kaplan-Meier.

B3. Priority question: Please provide an updated economic model that allows:

i) a comparison between both treatment arms of the ARCHER 1050 trial to be made with both treatment arms being modelled by independent parametric models (i.e. no proportionality assumption and not using results from the fractional polynomial (FP) network meta-analysis (NMA));

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This analysis was not included in the original model as it does not allow afatinib to be included within the cost-effectiveness estimates. Therefore, in the CS the 'best' fitting model was only discussed for the base curve, gefitinib, from which the other treatment curves were estimated using the FP estimates. The fit of independent parametric models to dacomitinib's PFS and OS are presented below.

Progression-free survival

AIC and BIC values (Table 6) showed the best fit for PFS was the log-logistic for dacomitinib closely followed by the Weibull and generalised gamma. The relatively higher AIC/BIC for the log-normal, Gompertz and exponential suggest these are less preferable.

Table 6. Goodness-of-Fit Statistics (PFS) - Dacomitinib

Distribution	AIC	BIC	Mean	Median	Proportion PF at		
					2 years	3 years	5 years
Exponential	550.00	553.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	545.20	552.04	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	549.48	556.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	543.52	550.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	547.18	554.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	545.26	555.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	14.7	30.1%	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free.

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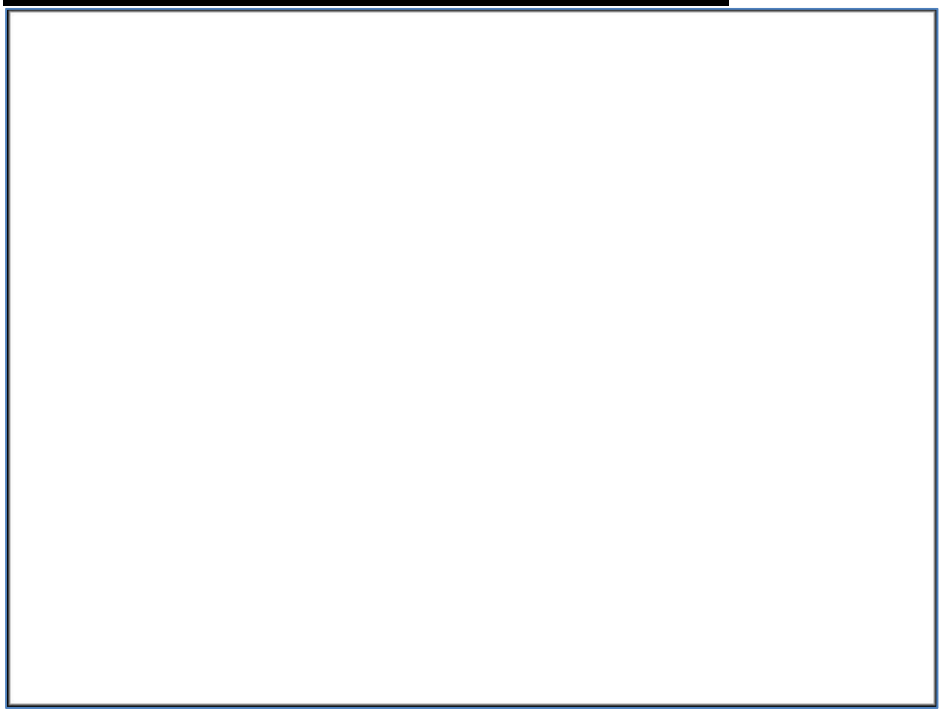

Abbreviations: KM = Kaplan-Meier.

As with the gefitinib distributions, all distributions provided similar visual fits to the observed data and beyond the observed period the two logarithmic distributions, exponential and generalised gamma produced much higher tails (XXXXXXX10). Due to the minimal difference in means between the remaining two distributions (Weibull, Gompertz) either could be considered appropriate.

Given the guidance in NICE DSU TSD 14 that the same distribution should be fitted unless there is 'substantial justification' otherwise (Latimer et al 2013, page 18), both the Weibull and Gompertz are the plausible distributions in a scenario where independent curves are fit, given these all have similar fits for gefitinib. However, the use of independent models is not well aligned with the observed data; the CS base-case uses a flexible time varying hazard to estimate the dacomitinib and afatinib curves and is thus expectedly produces a model which better represents and extrapolates the observed data.

Overall survival

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The AIC/BIC (Table 7) indicated the Gompertz and Weibull provide the best fits to the observed data. However, given the maturity of the observed OS data, the statistical fit may not be as informative as it was for PFS, hence it may be more reliable to judge best fit based on the clinical plausibility of the extrapolation.

Table 7. Goodness-of-Fit Statistics (OS) - Dacomitinib

Distribution	AIC	BIC	Mean	Median	Proportion alive at		
					3 years	5 years	10 years
Exponential	478.01	481.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	465.03	471.88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	463.00	469.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	469.40	476.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	480.04	486.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	465.06	475.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	34.1	43.0%	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

[redacted] 11

Abbreviations: KM = Kaplan-Meier.

All distributions provided similar visual fits to the observed KM data (XXXXXXX11) with predicted medians close to the observed data, with the exception of the exponential (which substantially underestimated the observed data for approximately the first 18 months). Beyond the end of the observed data both the exponential and

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logarithmic distributions (log-logistic and log-normal) produced higher tails than the other distributions. In contrast, the Gompertz and generalised gamma produced conservatively implausible extrapolations with almost all patients dead after 7 years.

Therefore, the most plausible extrapolation is the Weibull, although the 10 year survival rate compared to the 5 year survival rate could be considered slightly lower than may be expected given clinician feedback suggesting the use of the generalised gamma for gefitinib. In addition, as discussed for PFS, there is no clear rationale to apply independent parametric distributions between treatment arms, therefore, aligned with the preferred Weibull for dacomitinib, the Weibull should also be applied for gefitinib. However, the use of the Weibull was dismissed due to clinician feedback and external data discussed in CS Document B page 106. Therefore, the use of independent models for OS is not clinically plausible.
As noted above for PFS, the CS base-case uses a flexible time varying hazard to estimate the dacomitinib and afatinib curves and is thus expectedly produces a model which better represents and extrapolates the observed data.

For completeness this functionality has been added, please exclude afatinib and erlotinib from the model by selecting 'No' in 'Settings' cells G26 and G27 and the user can then select 'Independent models' in cell G4 and G5 on the 'Clinical Inputs' sheet. Coefficients for the new models are added on the Parameters PFS and Parameters OS sheets.

ii) the cost-effectiveness analysis to be undertaken separately for the ITT, Asian and non-Asian population.

Analyses of the non-Asian subgroup patients should be interpreted with caution noting size of the sample (57 in the dacomitinib arm and 49 in the gefitinib arm) and the fact that ARCHER 1050 was not powered to show statistically significant differences between the treatment arms in the non-Asian and Asian subgroups. As noted in the response to question A8,

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Despite the limitations listed above, in response to the request parametric models were fitted, to PFS and OS data for the Asian and Non-Asian subgroups and included in the cost-effectiveness model (the subgroup can be selected in 'Settings' G20). Details of AIC/BIC are presented in Table 8 and Table 9 for PFS and OS, respectively. Coefficients for the new models are added on the Parameters PFS and Parameters OS sheets.

Table 8. Goodness-of-Fit Statistics - PFS

Distribution	Dacomitinib Asian		Gefitinib Asian		Dacomitinib Non-Asian		Gefitinib Non-Asian	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	405.76	408.90	430.46	433.63	138.61	140.65	122.38	124.27
Weibull	402.51	408.78	403.35	409.69	137.08	141.17	114.73	118.52
Gompertz	405.23	411.50	414.92	421.26	139.15	143.24	121.09	124.88
Log-logistic	402.17	408.44	406.25	412.59	136.83	140.92	110.32	114.10
Log-normal	405.80	412.07	418.02	424.36	137.46	141.55	114.70	118.48
Generalised gamma	403.83	413.23	404.77	414.28	138.32	144.45	114.78	120.45

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 9. Goodness-of-Fit Statistics - OS

Distribution	Dacomitinib Asian		Gefitinib Asian		Dacomitinib Non-Asian		Gefitinib Non-Asian	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	341.57	344.71	372.80	375.97	135.91	137.96	114.05	115.94
Weibull	326.17	332.44	354.22	360.56	136.95	141.04	105.01	108.80
Gompertz	326.37	332.64	364.05	370.39	136.22	140.31	107.66	111.44
Log-logistic	328.22	334.49	350.06	356.40	138.47	142.56	104.60	108.38
Log-normal	338.99	345.26	351.59	357.93	138.70	142.79	111.59	115.37
Generalised gamma	327.58	336.99	352.82	362.33	137.80	143.93	107.01	112.68

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

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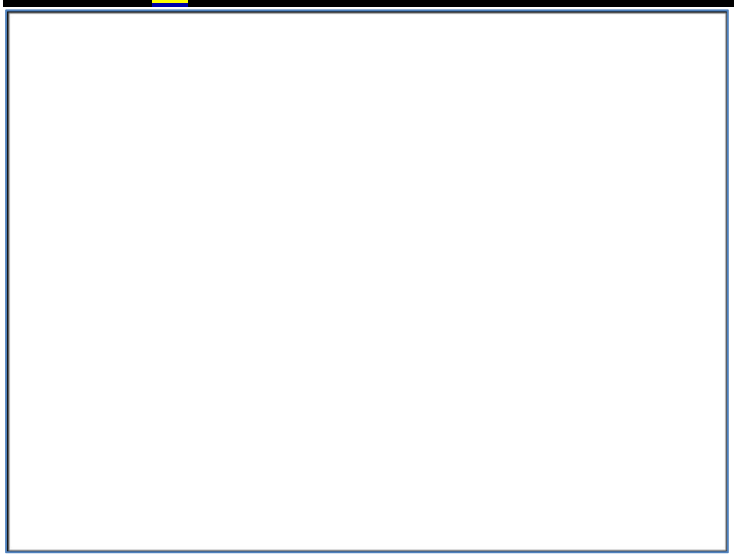
B4. **Priority question:** Please provide hazard and cumulative hazard plots against time:

i) for both the gefitinib and dacomitinib treatment arms of ARCHER 1050 overlaid with the fits of each parametric model (i.e. without using FP). Please present these as four figures.

Please see PFS and OS hazard and cumulative hazard plots against time for dacomitinib and gefitinib for the ITT population in XXXXXXX12 to XXXXXXX19.

XXXXXXX12 and XXXXXXX13 reflect the conclusions in CS Document B page 102, that the generalised gamma provides a good fit to the observed data (hazards and cumulative hazards) up to 24 months, beyond which hazards continue to steadily increase up to 30 months which is reflective of the external data and clinician opinion.

[redacted] 12



Abbreviations: KM = Kaplan-Meier.

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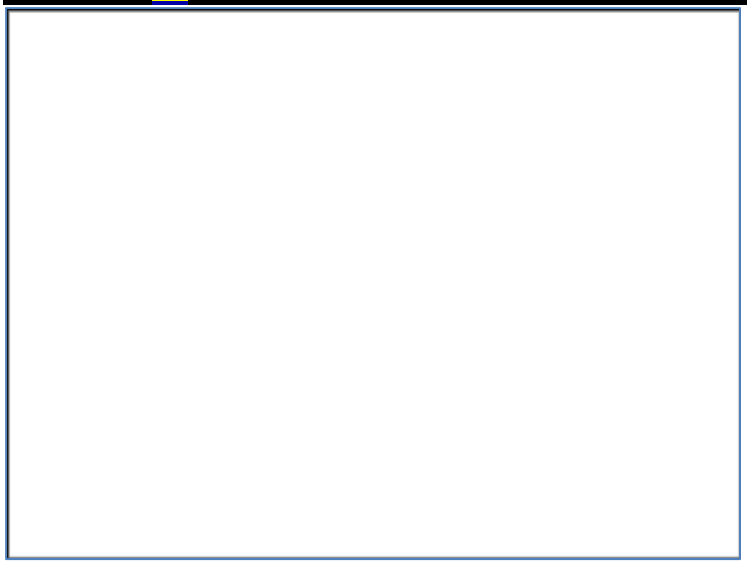
[redacted] 13



Abbreviations: KM = Kaplan-Meier.

XXXXXXX14 and XXXXXXX15 show that all distributions provide good fits to the observed data for the first 20 months, in line with the conclusion in B3. Beyond 20 months the gompertz and Weibull demonstrate increasing hazards, in contrast to the others which plateau or decrease. This is aligned with the conclusion in B3 that either Weibull or gompertz are appropriate distributions for the observed data.

[redacted] 14

Abbreviations: KM = Kaplan-Meier.

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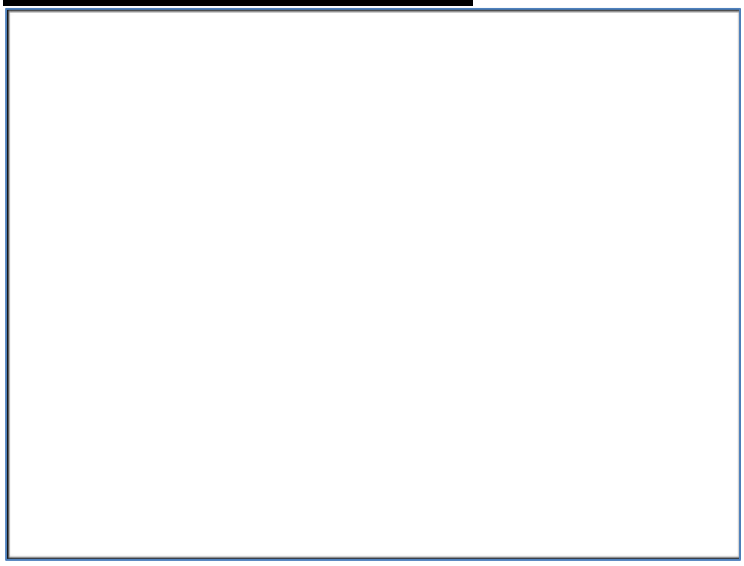
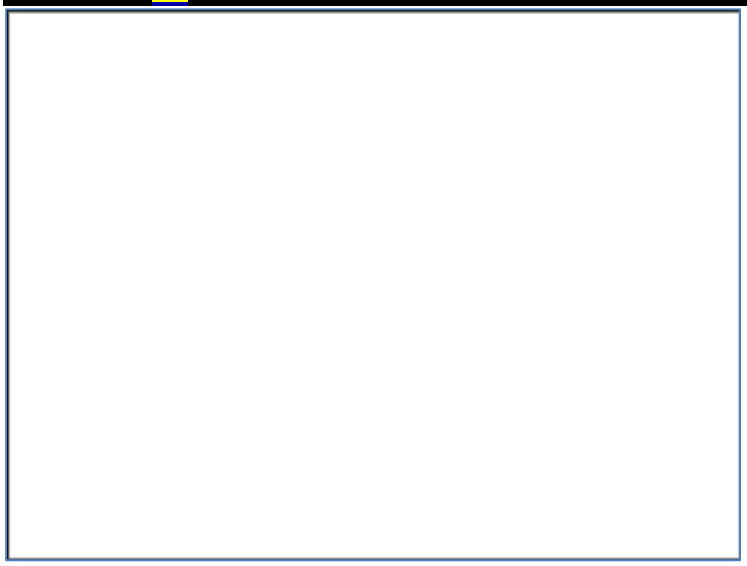
15 [redacted]



Abbreviations: KM = Kaplan-Meier.

XXXXXXX16 and XXXXXXX17 reflect the conclusions in CS Document B page 105 to 106, that the generalised gamma provides a good fit to the observed data (hazards and cumulative hazards) up to 34 months, beyond which hazards continue to steadily increase up to 40 months which is reflective of the external data and clinician opinion.

16 [redacted]



Abbreviations: KM = Kaplan-Meier.

17 [redacted]

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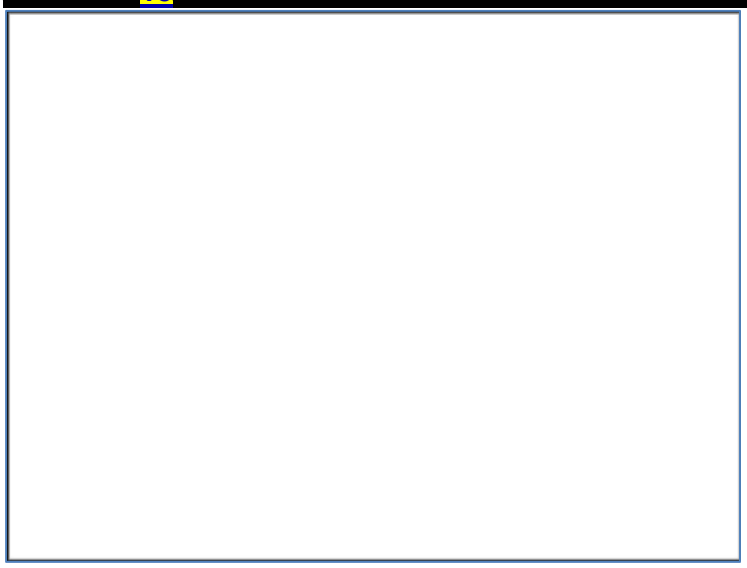
Abbreviations: KM = Kaplan-Meier.

XXXXXXX18 and XXXXXXX19 show that all distributions provide good fits to the observed data with the exception of the exponential, in line with the conclusions in B3. Beyond 30 months only the Weibull demonstrates increasing hazards, in contrast to the others which plateau or decrease. This is aligned with the conclusion in B3 that the Weibull is the appropriate distribution for the observed data.

[redacted]18



Abbreviations: KM = Kaplan-Meier.

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[redacted] 19

Abbreviations: KM = Kaplan-Meier.

ii) with the parametric curves for both gefitinib and dacomitinib in the Asian and non-Asian populations.

Please see the hazard and cumulative hazard plots for Asian and Non-Asian subgroups in XXXXXXX20 to XXXXXXX35. As discussed in A8 and B3ii), the Asian/Non-Asian subgroup analysis should be interpreted with caution due to small sample sizes and as ARCHER 1050 was not powered to show a statistically significant differences between the treatment arms in the non-Asian and Asian subgroups.

[redacted] 20

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Abbreviations: KM = Kaplan-Meier.

21 [redacted]

Abbreviations: KM = Kaplan-Meier.

22 [redacted]

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Abbreviations: KM = Kaplan-Meier.

[redacted]

Abbreviations: KM = Kaplan-Meier.

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Abbreviations: KM = Kaplan-Meier.

[redacted] 25 [redacted]

Abbreviations: KM = Kaplan-Meier.

[redacted] 26 [redacted]

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Abbreviations: KM = Kaplan-Meier.

27 [redacted]

Abbreviations: KM = Kaplan-Meier.

28 [redacted]

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Abbreviations: KM = Kaplan-Meier.

29 [redacted]

Abbreviations: KM = Kaplan-Meier.

30 [redacted]

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Abbreviations: KM = Kaplan-Meier.

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Abbreviations: KM = Kaplan-Meier.

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Abbreviations: KM = Kaplan-Meier.

[redacted] 35

Abbreviations: KM = Kaplan-Meier.

B5. Priority question: Please clarify how the parametric models fitted to the gefitinib treatment arm of ARCHER 1050 were combined with the FP analysis. Were the hazard ratios from the FP analysis applied to the parametric model? If so, please clarify

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why the gefitinib treatment arm was modelled using the parametric fit to the ARCHER 1050 trial data, rather than the FP model alone.

Yes, the time varying hazard ratios for dacomitinib and afatinib were applied directly to the base line (gefitinib) parametric model.

The FP analysis was not coded to provide gefitinib as a FP model. The approach taken was to fit a wide range of first- and second- order models with varying powers (54 models in total) to explore the full range of possible alternatives. It was not practical to consider the fit to the observed data and the extrapolation of each individual FP models to all comparators simultaneously. Instead, the six standard parametric distributions were explored to provide an anchor for the time varying hazard ratios to be applied. The resulting base-case generalised gamma provided a good representation of the observed data and the extrapolation reflected clinical expert opinion and was validated through external data.

The approach was acceptable once the base-case FP model was applied, as it provided plausible fits for dacomitinib (CS Document Figure 30 page 104 and Figure 32 page 107). This is further demonstrated in the hazards plots request for B2.

B6. Priority question: Figure 32 (CS Document B, page 108) presents the OS curves, along with the company's choice of the fully-fitted parametric curves applied to the observed data. Data beyond 30 months are immature, with the KM curves appearing to overlap at approximately 36 months. Please add an option to the economic model that allows entering a hazard ratio of 1 for OS across all comparators after 36 months (e.g. a waning effect).

The OS data from ARCHER 1050 are mature as medians are available. In the observed data, there are approximately 10% more patients alive in the dacomitinib arm versus the gefitinib arm at 24 and 30 months (66.9% versus 56.4% and 56.2% versus 46.3%, respectively). The base-case uses the observed data, which demonstrates dacomitinib's superior efficacy, and extrapolates these data in line with NICE DSU TSD 14. Beyond 30 months the data the data is subject to censoring and

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the numbers at risk at 36 months are very small (14 in the dacomitinib arm and 12 in the gefitinib arm).

The assumption that the observed survival benefit disappears beyond 36 months can be considered arbitrary and not evidence based given:

- it is based on censored data that is driven by small patient numbers.
- it disregards the trend seen in the observed data prior to this point.
- it abandons the parametric curve fits that have been modelled in line with DSU guidelines

Despite limitations with the plausibility of this analysis, the functionality has been added to the cost-effectiveness model, please see switch in 'Clinical Inputs' J16. The source for the time varying HRs up to 36 months, followed by HR=1 after, are included in the model on the FP NMA HR sheet in columns K and L.

When the HR=1 is applied at 36 months in the model, the incremental survival for dacomitinib versus comparators is reduced because the post-progression period for dacomitinib becomes shorter; mean post-progression survival is [redacted] years for dacomitinib versus [redacted] for other comparators. There is no known clinical rational to suggest that upon progression patients would have a worse prognosis with dacomitinib, hence the analysis is not considered to have external validity. The validity of this analysis is further brought into question when considering ARCHER 1050 shows dacomitinib is associated with a statistically significant median gain in OS of 7.3 months versus gefitinib, whereas under the waning effect assumption the modelled mean LY gain is considerably underestimated to 2.9 months.

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B7. Priority question: In Figures 5 and 6 (CS Document B, page 52-53), the KM plots for PFS and OS appear to overlap and cross. Please:

i) provide a justification for not applying a two-phase piecewise (KM plus parametric) modelling approach to model survival outcomes used in the economic model;

The NICE DSU TSD14 (Latimer et al. 2013) was used to inform the company's modelling approach. During model selection, the DSU suggests that piecewise modelling is only required when inadequate fits are provided by standard parametric functional forms. The use of piecewise models can however be assessed primarily through log-cumulative hazard plots which:

'show where significant changes in the observed hazard occur, which can be useful when considering the use of different parametric models for different time periods in a piecewise modelling approach.' (Latimer et al. 2013 pg. 20)

The log-cumulative hazard plots for OS from both ARCHER 1050 and LUX-Lung 7 show that there are no single time points where significant changes are observed in the hazards (CS Appendix Figure 42 page 261 & Figure 46 page 263). The PFS plots show a significant change in the hazards, however in both trials this occurs around log time 0 (i.e. in the first month) so cannot be considered informative (CS Appendix Figure 44 page 262 & Figure 48 page 264). From these plots it is evident that the crossing of the curves was due to gradual fluctuations in the hazards. Therefore, piecewise modelling was not considered for this dataset as the log-cumulative hazard plots do not support it.

The current base-case was validated with the fitted curves providing good fits to the observed data (CS Document B Figure 30 page 104 & Figure 32 page 107) with the exception of the tail for OS. However, as mentioned in question B6, these are subject to censoring and therefore not particularly informative for the extrapolation. There will inherently be slight variations in the hazards, but such are not sufficient to suggest piecewise models. However, to account for such small variations, the base-case uses the flexible 3-parameter generalised gamma model. Further, this was

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applied with the additional of flexible first- and second- order fractional polynomial models allowing time-varying hazards to estimate treatment curves.

ii) add an option that allows implementing a two-phase piecewise model, using KM data until 8 months for PFS and 12 months for OS, after which parametric models are fitted and used to extrapolate.

As noted above, there was no clear rational to conduct the analyses as a preferred approach as there were no significant changes observed in the hazards. In addition, removing 8/12 months of data reduces the sample size and creates additional uncertainty in the extrapolations. However, as requested, the functionality has been added to the model; please exclude afatinib and erlotinib from the model by selecting 'No' in 'Settings' cells G26 and G27 and the user can then select 'KM plus extrapolation' in cell G4 and G5 on the 'Clinical Inputs' sheet. Coefficients for the new models are added on the Parameters PFS and Parameters OS sheets.

Progression-free survival

There was no meaningful difference in statistical fit (Table 10) between the parametric models fitted from 8 month and all distributions provided similar visual fits to the observed KM data (XXXXXXX36). Beyond the observed period, the exponential and the Weibull provided fits were aligned with the previously received clinical expert feedback and external data, as discussed in CS Document B page 101. All the other distributions (Gompertz, log-logistic, log-normal and generalised gamma) provided 3- and 5-year rates that were considered high when compared to clinician opinion and external data (LUX-Lung 7 and Lin).

Table 10. Goodness-of-Fit Statistics (PFS) - Gefitinib

Distribution	AIC*	BIC*	Mean	Median	Proportion PF at		
					2 years	3 years	5 years
Exponential	376.43	379.26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	378.34	383.99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	376.11	381.77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	371.68	377.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Log-normal	366.34	372.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	365.59	374.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	9.2	[redacted]	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free
*AIC/BIC for parametric model fitted from 8.28 months (nearest model cycle to 8 months)

[redacted] 36

Abbreviations: KM = Kaplan-Meier.

As with gefitinib, there was no meaningful difference in statistical fit (Table 11) between the parametric models fitted from 8 months and all distributions provided similar visual fits to the observed dacomitinib KM data (XXXXXXX37). Beyond the observed data, the Gompertz, log-logistic, log-normal and generalised gamma all predicted high 5 year rates. The tails of the exponential and Weibull could also be considered high but are the most plausible of these models.

Table 11. Goodness-of-Fit Statistics (PFS) - Dacomitinib

Distribution	AIC	BIC	Mean	Median	Proportion PF at		
					2 years	3 years	5 years
Exponential	363.25	366.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	365.21	371.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	364.75	370.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Log-logistic	363.68	369.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	361.09	366.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	362.92	371.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	14.7	[redacted]	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free
*AIC/BIC for parametric model fitted from 8.28 months (nearest model cycle to 8 months)

[redacted] 37

Abbreviations: KM = Kaplan-Meier.

In conclusion, the exponential or Weibull for PFS are the most appropriate models in this scenario, however the visual fit of the models are not superior to the standard parametric gefitinib models. Further, the dacomitinib models are similar to the independent dacomitinib parametric models which have long tails and do not reflect the observed data as discuss in B3. This, coupled with the lack of change in hazard discussed in B7i), does not support the use of a piecewise analysis for PFS.

Overall survival

As with PFS there was no meaningful difference in statistical fit (Table 12) between the parametric models fitted from 12 months and all distributions provided similar visual fits to the observed KM data (XXXXXXX38). In line with the clinician opinion and

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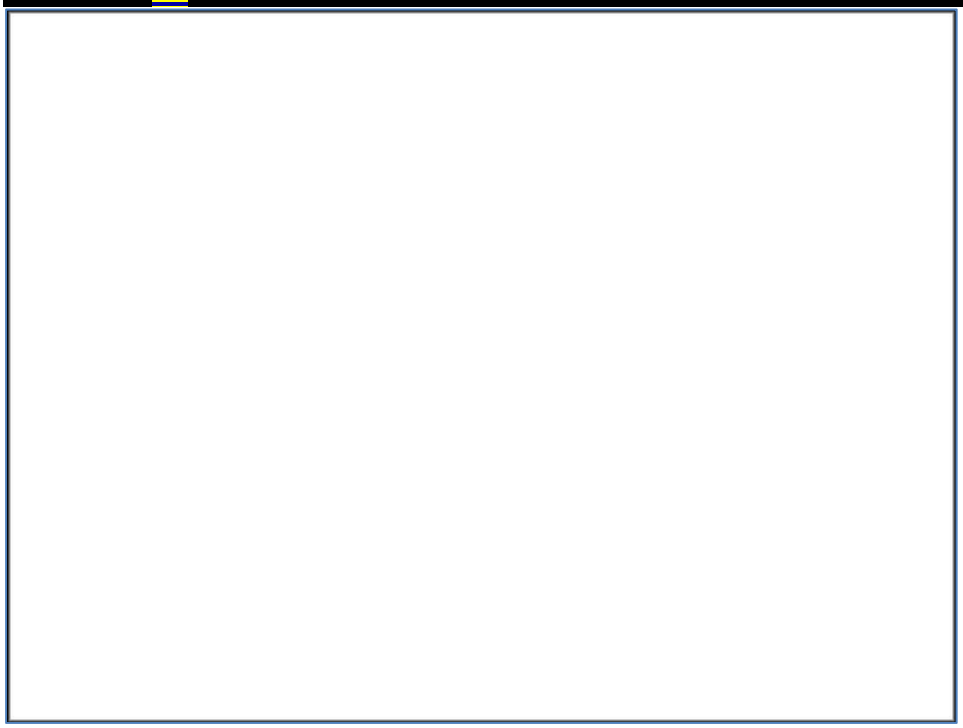
external data from CS Document B page 105-106, only the exponential and Weibull provide plausible extrapolation.

Table 12. Goodness-of-Fit Statistics (OS) - Gefitinib

Distribution	AIC	BIC	Mean	Median	Proportion alive at		
					3 years	5 years	10 years
Exponential	459.82	463.04	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	461.52	467.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	460.04	466.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	459.49	465.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	459.22	465.67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	460.97	470.65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	26.8	[redacted]	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free
*AIC/BIC for parametric model fitted from 11.96 months (nearest model cycle to 12 months)

[redacted] 38



Abbreviations: KM = Kaplan-Meier.

Again, statistical fit (Table 13) was not informative and all distributions fitted the observed data well (XXXXXXX39). All distributions apart from the exponential predict lower mean survival for dacomitinib compared to gefitinib which is counter to the observed data (considering the median PFS and OS are greater for dacomitinib than

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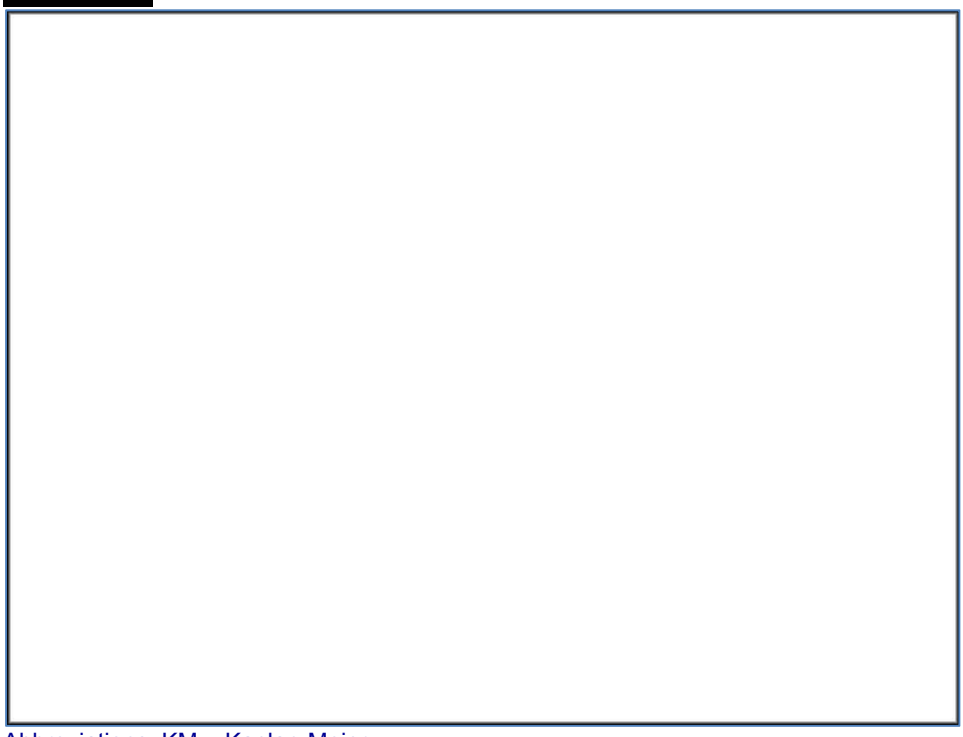
gefitinib) and implausible given no known clinical justification as to why; therefore the exponential presents the only plausible piecewise model for OS.

Table 13. Goodness-of-Fit Statistics (OS) - Dacomitinib

Distribution	AIC	BIC	Mean	Median	Proportion alive at		
					3 years	5 years	10 years
Exponential	359.24	362.48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	352.09	358.57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	355.05	361.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	352.10	358.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	353.31	359.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	353.78	363.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	34.1	[redacted]	-	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free
*AIC/BIC for parametric model fitted from 11.96 months (nearest model cycle to 12 months)

[redacted] 39



Abbreviations: KM = Kaplan-Meier.

In conclusion, the piecewise exponential models provides a plausible scenario given the lack of a viable independent model for OS, as discussed in B3.

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B8. Priority question: Figure 14 (CS Document B, page.64) presents the forest plot of OS (stratified by subgroups; ITT population). Please provide the equivalent forest plot and information (i.e. HR and 95% CI, p-values for interactions) for PFS (IRC).

Please see response to A9 which addresses this question.

B9. A table ('Adverse Events' worksheet; cells 'E7:J14') in the company's economic model reports the frequency of Adverse Events (AEs) by treatment. Please:

i) clarify whether these values represent the proportion of people who experienced each of the listed AE or reflects the number of AEs that people experienced (i.e. it captures recurrent events);

These values represent the proportion of people who experienced each of the listed AEs.

ii) provide a full list of incidences (first, second, and subsequent) of grade 3-5 AEs, by treatment.

Typically, grade 3-5 adverse event (AE) incidences are reported by the number of patients who have experienced an event as opposed to the number of individual grade 3-5 events. Indeed, the ARCHER 1050 data and LUX-LUNG 7 data both report AE incidences as the number of patients experiencing an event. Providing data on the number of events (grade 3-5) in order to look at AE recurrence cannot be done for LUX-LUNG 7 as this is not the company's trial; hence, bias would be introduced into any comparative analysis.

The company have not provided a full list of grade 3-5 event incidences that reflects recurrence of adverse events because of complexities in how this is defined appropriately given the potential for the short term change in the grade of an AE. As a single event can occur across sequential days, it can fluctuate up and down between multiple grades during this time, recording the number of times an AE becomes grade 3 may not accurately reflect the number of independent events.

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However, in order to provide additional data to the ERG that allows a deeper interpretation of grade 3-5 AEs beyond the currently reported patient incidences, the company are re-analysing patient level data in ARCHER 1050 to provide a list of patient incidences for grade 3-5 AEs by individual cycle. Although these data are not event incidences but patient incidences, an examination on a cycle-by-cycle level will allow insight into the recurrence of AEs. The economic model uses a cut off of >5% but these data will be provided for AEs in which the grade 3 frequency is >2%.

B10. In the economic model, the progression-free states is assigned utility values obtained from the ARCHER 1050 trial, while utility values for progressed disease are taken from the study by Labbé and colleagues. Given that the ARCHER 1050 trial methodology states that *"Patient reported outcomes were assessed at days 1 (baseline), 8, and 15 of cycle one, on day 1 of subsequent cycles, at the end-of-treatment visit, and at the posttreatment follow up visit"* (Wu et al., 2017 p. 1456), please provide summary statistics for the EQ-5D data collected at the end-of-treatment/post treatment follow-up visits by trial treatment arm.

Please see summary statistics for EQ-5D collected at end-of-life/post-treatment in Table 14.

Table 14. Summary of mean EQ-5D health index score

Time point	Dacomitinib				Gefitinib			
	Median	Mean	95% CI	n	Median	Mean	95% CI	n
End of treatment	[redacted]	[redacted]	[redacted]	121	[redacted]	[redacted]	[redacted]	145
Post-treatment	[redacted]	[redacted]	[redacted]	75	[redacted]	[redacted]	[redacted]	107

Abbreviations: CI = confidence interval.

B11. In the CS (Document B, page 107) it is stated that time-to-treatment discontinuation was not available for all the comparators. Please give information on

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treatment duration for those comparators (afatinib and erlotinib) where such information is available.

Time-to-treatment discontinuation (TTD) was not available for afatinib. However, in the most recent publication of LUX-Lung 7 (Paz-Ares 2017) time-to-treatment failure (TTF) was presented. We are not aware of other data for afatinib. In the model, erlotinib was assumed equivalent to gefitinib so the treatment duration is assumed the same.

In the model, treatment duration is currently assumed equivalent to PFS for all comparators. In ARCHER 1050 there is minimal difference between TTD and PFS (IRC) for dacomitinib in a naïve restricted means analysis at 24 months ([redacted]); this demonstrates that dacomitinib's average treatment duration would not be expected to exceed progression. In contrast however, both gefitinib and afatinib are associated with treatment duration greater than progression; the restricted mean of TTD at 24 months for gefitinib shows it was [redacted] months greater than PFS (IRC) and the median difference observed in afatinib's PFS (11.0 months) and its TTF (13.7 months) suggest treatment duration (and related cost) several months longer than PFS (Paz-Ares 2017).

B12. Please provide the standard errors for the mean progression-free utility values reported in Table 37 (CS, Document B, page113).

Please see standard error below in Table 15.

Table 15. Standard errors for the mean PFS utilities

State	Utility mean	Standard error*
Progression-free – Dacomitinib	[redacted]	[redacted]
Progression-free – Gefitinib	[redacted]	[redacted]
Progression-free – Afatinib	[redacted]	[redacted]
Progression free – Erlotinib	[redacted]	[redacted]

*Calculated from confidence intervals

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B13. Please reproduce the FP NMA for the Asian and non-Asian populations.

It is not possible to conduct the FP analysis for the Asian and non-Asian populations as a network cannot be formed. The FP analysis is dependent on Kaplan-Meier plots being available as these are used as input data in the analysis, and for LUX-LUNG 7 Kaplan-Meier plots are not available for Asian and non-Asian subgroups.

B14. Please provide the digitised graph and resulting generated data for the FP NMA.

Please see PFS (LUXLung7_PFS IRC.png) and OS (LUXLung7_OS.png) graphs attached with the response along with the generated data (LUXLung7_Data.xlsx).

B15. Please provide the FP NMA code and data.

Please see code and data in NMA_FP_Data_Analysis_Code.zip attached in the response.

B16. There appears to be a discrepancy between the cost per cycle values in CS Document B (Table 38, page116) and the equivalent values in the economic model (sheet 'Medical Costs, Drugs', cells F26:F29). Please clarify whether the values in cells F26:F29 are incorrect and confirm that these values have not been used in the calculations underpinning any of the results presented in the submission.

The hidden values on 'Medical Costs_Drugs' cells F26:F29 are not included in the base case; this model functionality was included to allow a cost per cycle to be entered directly into the model, should it be wished. These values are hardcoded (as noted in cell I28) and are only applied when 'Yes' is selected in cell G5. This cell is set to 'No',

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therefore the values have not been used in any of the results presented in the CS submission.

B17. Please confirm whether monetary values related to health care use taken from past analyses and literature (e.g. cost of terminal care) are appropriately adjusted for differential timing.

All unit cost (administration, disease management, terminal care and adverse events) have been sourced from the National Schedule of Reference Costs for 2016/2017 and PSSRU 2017 which were the most recent available at the time of submission (these have not been inflated), with the exception of 'Drug and equipment' in the terminal care cost, which was inflated to 2017 using the inflation indices from the PSSRU.

B18. In CS Document B, page112, it is stated that "these values were also aligned with the only real world EGFR+ NSCLC value identified in the SLR (Labbé et al. 2017 [0.77]), therefore this value was applied in scenario analysis." Please clarify the meaning of the expression 'real world values' in this particular context.

The term "real world" is used in the CS in line with the title of the study from which utilities were taken: *"Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy" (Labbe 2017).* This is a longitudinal cohort study at Princess Margaret Cancer Centre in Toronto evaluated EQ-5D-3L-derived health state utilities in 475 outpatients between 2014 and 2016 with metastatic lung cancer across various disease states, including 183 EGFR-positive patients. As these utilities are taken from a real-world setting as opposed to a solely pre-license clinical trial setting, they are titled "real world" by the study authors and have also been so in the CS.

B19. Please confirm whether utility values used in the economic model calculations have been adjusted over the time horizon to reflect the modelled patients' age-related decline in health-related quality of life.

No, the estimates have not been adjusted over time.

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Section C: Textual clarification and additional points

C1. Please define the footnotes for adverse events in Figure 39 (CS Appendix D.2, page 256).

Please see detail of footnote below:

**22 treatment-emergent adverse events related to study drug, 18 treatment-emergent adverse events not related to study drug, and one non-treatment-emergent adverse event. †15 treatment-emergent adverse events related to study drug and 12 treatment-emergent adverse events not related to study drug.* (Reference 33: Wu et al. 2017)

C2. In CS Document A, page 20, the Incremental Cost Effectiveness Ratio (ICER) for dacomitinib is reported to be £[redacted] per QALY gained. This result is not consistent with the ICER value for dacomitinib reported in Table 6, page 20. Please confirm whether £[redacted] is a typographical error.

Yes; the values should read £[redacted] in line with the table above the text.

C3. Please provide all 134 references (related to CS Document B and Appendix) as either a RIS. file or an archived EndNote library.

Please see .RIS file attached with response.

C4. Please provide a PDF for reference 55 'Pfizer. Data on file. 2017', cited at the end of page 65 (CS Document B, section B.2.9.1)

The reference for this statement should read '99' rather than '55' (i.e. the same source as cited in the below question C5. This is a reference to direct one-to-one clinical expert consultation which have been conducted in order to seek advice around the disease area, treatment pathway, and expected clinical benefit of treatments.

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C5. Please provide a PDF for reference 99. 'Pfizer. Pfizer One-to-one interviews with UK clinical experts; Pfizer Data on File. 2018', cited on page115 (CS Document B, section B.3.5.2)

One-to-one interviews with UK clinical experts is reference to direct telephone or face to face consultations with clinical experts such as lung oncologists which have been conducted in order to seek advice around the disease area, treatment pathway, and expected clinical benefit of treatments. These consultations are not held in formal advisory board settings and as such there is no internal report that can be provided.

Appendices

Appendix A

Reason for Exclusion: Interventions/ Comparators

- Epidermal growth factor receptor mutation analysis in advanced non-small cell lung cancer: review of economic evaluations and framework for economic analyses. Health Technology Assessment Database, 2010. http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011001150/frame.html (accessed.
  - *This study compares EGFR testing strategy vs non-testing strategy.*
- Ahn MJ, Tsai CM, Hsia TC, et al. Cost-effectiveness of bevacizumab-based therapy versus cisplatin plus pemetrexed for the first-line treatment of advanced non-squamous NSCLC in Korea and Taiwan. Asia Pac J Clin Oncol, 2011. http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22011000969/frame.html (accessed.
  - *Examined bevacizumab (not in combination with erlotinib) in comparison to cisplatin and pemetrexed*
- Alimujiang S, Zhang T, Han ZG, et al. Epidermal growth factor receptor tyrosine kinase inhibitor versus placebo as maintenance therapy for advanced non- small-cell lung cancer: a meta-analysis of randomized controlled trials. Asian Pacific Journal of Cancer Prevention, 2013.
  - *Maintenance therapy with EGFR-TKIs vs. Placebo*
- Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors--a meta-analysis and systematic review. PLoS ONE 2013; 8(1): e51780.

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- *Examined bevacizumab combination therapy vs chemotherapy*

- An C, Zhang J, Chu H, et al. Study of Gefitinib and Pemetrexed as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer Harboring EGFR Mutation. Pathol Oncol Res 2016; 22(4): 763-8.

  - *Examined gefitinib + pemetrexed vs gefitinib+ placebo*

- Arrieta O, Anaya P, Morales-Oyarvide V, Ramirez-Tirado LA, Polanco AC. Cost-effectiveness analysis of EGFR mutation testing in patients with non-small cell lung cancer (NSCLC) with gefitinib or carboplatin-paclitaxel. Eur J Health Econ 2016; 17(7): 855-63.

  - *Examined EGFR testing with gefitinib, vs no testing with standard chemotherapy*

- Banz K, Bischoff H, Brunner M, et al. Comparison of treatment costs of grade 3/4 adverse events associated with erlotinib or pemetrexed maintenance therapy for patients with advanced non-small-cell lung cancer (NSCLC) in Germany, France, Italy, and Spain. Lung Cancer 2011; 74(3): 529-34.

  - *Examined erlotinib or pemetrexed maintenance therapy*

- Barlesi F, Pujol JL. Combination of chemotherapy without platinum compounds in the treatment of advanced non-small cell lung cancer: a systematic review of phase III trials. Lung Cancer, 2005. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12005001167/frame.html (accessed.

  - *Examined cisplatin, carboplatin, ifosfamide, gemcitabine, and vinorelbine*

- Bischoff, Hg,Ruckert, A,Reinmuth, N,Grohe, C,Bohnet, S,Zum, Buschenfelde Cm. Osimertinib (OSI) vs Standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFRm advanced NSCLC: FLAURA. Oncology research and treatment. Conference: 33. Deutscher krebskongress, DKK. Germany. 2018. 41:187

  - *Osimertinib used as intervention*

- Bongers ML, Coupe VMH, Jansma EP, Smit EF, Uyl-de Groot CA. Cost effectiveness of treatment with new agents in advanced non-small-cell lung cancer: a systematic review. Pharmacoeconomics 2012; 30(1): 17-34.

  - *Systematic review*
  - *Examined first-line therapy trials with (gemcitabine+cisplatin) or (gemcitabine+ docetaxel) versus other platinum-based regimens (paclitaxel, docetaxel and vinorelbine).*

- Botrel TEA, Clark O, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis. Lung Cancer 2011; 74(1): 89-97.

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- *Examined bevacizumab (not in combination with erlotinib) in combination with other agents*

- Carlson JJ, Veenstra DL, Ramsey SD. Pharmacoeconomic evaluations in the treatment of non-small cell lung cancer. Drugs 2008; 68(8): 1105-13.
  - *Examined chemotherapy, surgery, RT, best supportive care (no studies with TKIs)*

- Chang JWC, Hou M-M, Hsieh J-J, et al. Early radiographic response to epidermal growth factor receptor-tyrosine kinase inhibitor in non-small cell lung cancer patients with epidermal growth factor receptor mutations: A prospective study. Biomedical Journal 2015; 38(3): 221-8.
  - *Examined erlotinib and gefitinib*
  - *Results for erlotinib and gefitinib are compiled and presented as "TKI therapy"*

- Chen J, Wu X, Shi T, Kang M. Efficacy of targeted agents in the treatment of elderly patients with advanced non-small-cell lung cancer: A systematic review and meta-analysis. Onco Targets Ther 2016; 9: 4797-803.
  - *Examined different chemotherapies with or without Targeted therapies (no trial with interventions of interest was included).*

- Chen Y, Yang J, Li X, et al. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. Cancer Sci 2016; 107(12): 1800-5.
  - *Compared TKIs (erlotinib or gefitinib as one group) vs RT*

- Chen YJ, Chen LX, Han MX, Zhang TS, Zhou ZR, Zhong DS. The efficacy and safety of chemotherapy in patients with nonsmall cell lung cancer and interstitial lung disease: A PRISMA-compliant Bayesian meta-analysis and systematic review. Medicine (United States) 2015; 94 (36) (no pagination)(e1451).
  - *Examined carboplatin, docetaxel, gemcitabine, pemetrexed, cisplatin, vinorelbine, paclitaxel, bevacizumab (not in combination with erlotinib), carboplatin, and etoposide*

- Chien CR, Shih YCT. Economic evaluation of bevacizumab in the treatment of non-small cell lung cancer (NSCLC). ClinicoEconomics and Outcomes Research 2012; 4(1): 201-8.
  - *Bevacizumab containing regimens (not in combination with erlotinib)*

- Chouaid C, Atsou K, Hejblum G, Vergnenegre A. Economics of treatments for non-small cell lung cancer. Pharmacoeconomics 2009; 27(2): 113-25.
  - *Different regimens of chemotherapy, radiotherapy and best supportive care were compared with gefitinib and erlotinib in >1st line therapy trials*

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- Chouaid C, Le Caer H, Corre R, et al. Cost analysis of erlotinib versus chemotherapy for first-line treatment of non-small-cell lung cancer in frail elderly patients participating in a prospective phase 2 study (GFPC 0505). Clin Lung Cancer 2013; 14(2): 103-7.
  - *Examined erlotinib followed by chemotherapy*
- Chouaid C, Le Caer H, Locher C, et al. Cost effectiveness of erlotinib versus chemotherapy for first-line treatment of non-small cell lung cancer (NSCLC) in fit elderly patients participating in a prospective phase 2 study (GFPC 0504). BMC Cancer 2012; 12: 301.
  - *Examined docetaxel/gemcitabine followed by erlotinib after progression vs erlotinib followed by docetaxel/gemcitabine after progression*
- Dae HL, Han JY, Heung TK, et al. Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first: Result of a randomized pilot study. Cancer 2008; 113(1): 143-9.
  - *Examined gemcitabine and vinorelbine + radiotherapy*
- de Haas S, Delmar P, Bansal AT, et al. Genetic variability of VEGF pathway genes in six randomized phase III trials assessing the addition of bevacizumab to standard therapy. Angiogenesis 2014; 17(4): 909-20.
  - *Examined bevacizumab vs placebo*
- Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005; **23**(25): 5900-9.
  - *Examined carboplatin and paclitaxel + erlotinib vs carboplatin and paclitaxel+ placebo*
- Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol* 2007; **25**(12): 1545-52.
  - *Examined erlotinib + cisplatin and gemcitabine vs placebo + cisplatin and gemcitabine*
- Gerber NK, Yamada Y, Rimner A, et al. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. *International Journal of Radiation Oncology Biology Physics* 2014; **89**(2): 322-9.
  - *Examined erlotinib either alone or in combination with cytotoxic chemotherapy vs WBRT, with or without the addition of erlotinib after completion of radiation vs stereotactic radiosurgery*

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- Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. *J Clin Oncol* 2004; **22**(5): 777-84.
  - *Examined gefitinib in combination with gemcitabine and cisplatin*

- Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. *J Med Econ* 2016; **19**(6): 630-44.
  - *This study is a CUA of nivolumab vs docetaxel and erlotinib as second-line therapy only.*

- Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based C. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review. *Journal of Thoracic Oncology* 2010; **5**(2): 260-74.
  - *Examined erlotinib + chemo (no trial with TKI monotherapy arm was included in the SLR)*

- Gray, J.,Okamoto, I.,Sriuranpong, V.,Vansteenkiste, J.,Imamura, F.,Lee, J. S.,Pang, Y.,Cobo, M.,Kasahara, K.,Hodge, R.,Lentrichia, B.,Dearden, S.,Ramalingam, S.. Osimertinib vs SoC EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC (FLAURA): plasma ctDNA analysis. Journal of thoracic oncology. 2017. Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12:S1754-S1755
  - *Examined osimertinib as intervention*

- Greer JA, Pirl WF, Jackson VA, et al. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol*, 2012. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/141/CN-00831141/frame.html (accessed.
  - *Palliative care integrated with standard oncology care or standard oncology care alone*
  - *Only 6/151 patients received TKI as standard care, and drug was unspecified.*

- Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. *Ann Pharmacother* 2009; **43**(3): 490-501.
  - *Examined bevacizumab in combination with other agents (not with erlotinib)*

- Gridelli C, Ciardiello F, Gallo C, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J Clin Oncol* 2012; **30**(24): 3002-11.

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- *Compared first- line erlotinib + second-line (cisplatin + gemcitabine) vs first- line (cisplatin+gemcitabine) + second-line erlotinib*

- Gridelli C, Morgillo F, Favaretto A, et al. Sorafenib in combination with erlotinib or with gemcitabine in elderly patients with advanced non-small-cell lung cancer: a randomized phase II study. *Ann Oncol* 2011; **22**(7): 1528-34.
  - *Compared (sorafenib + gemcitabine) vs (sorafenib + erlotinib)*

- Hapani S, Sher A, Chu D, Wu S. Increased risk of serious haemorrhage with bevacizumab in cancer patients: a meta-analysis. *Oncology* 2010; **79**(1-2): 27-38.
  - *Examined bevacizumab only (not in combination with erlotinib)*

- Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. *J Clin Oncol* 2004; **22**(5): 785-94.
  - *Examined gefitinib in combination with paclitaxel and carboplatin*

- Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005; **23**(25): 5892-9.
  - *Examined carboplatin and paclitaxel + erlotinib vs carboplatin and paclitaxel+ placebo*

- Hirsch FR, Kabbinavar F, Eisen T, et al. A randomized, phase II, biomarker-selected study comparing erlotinib to erlotinib intercalated with chemotherapy in first-line therapy for advanced non-small-cell lung cancer.[Erratum appears in J Clin Oncol. 2011 Oct 10;29(29):3948 Note: Camidge, Ross [corrected to Camidge, D Ross]]. *J Clin Oncol* 2011; **29**(26): 3567-73.
  - *Examined erlotinib vs erlotinib + chemo (paclitaxel+carboplatin)*

- Huang H, Zheng Y, Zhu J, Zhang J, Chen H, Chen X. An updated meta-analysis of fatal adverse events caused by bevacizumab therapy in cancer patients. *PLoS ONE* 2014; **9**(3): e89960.
  - *Examined bevacizumab only (not in combination with erlotinib)*

- Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012; 30(17): 2063-9.
  - *Erlotinib/carboplatin/paclitaxel not a valid comparator*

- Jiang T, Min W, Li Y, Yue Z, Wu C, Zhou C. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. *Cancer Med* 2016; **5**(6): 1055-65.

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- *Radiotherapy + TKIs vs radiotherapy alone or radiotherapy + chemotherapy.*

- Kanarkiewicz M, Zaganczyk M, Zurawski B, Tujakowski J, Windorbska W, Krysinski J. Cost-effectiveness analysis of advanced stage non-small cell lung cancer treatment with cisplatin-vinorelbine and carboplatin-gemcytabine combination regimens. *Nowotwory* 2014; **64**(3): 217-23.

  - *Examined cisplatin + vinorelbine vs carboplatin + gemcitabine*

- Kato T, Seto T, Nishio M, et al. Erlotinib Plus Bevacizumab Phase Ⅱ Study in Patients with Advanced Non-small-Cell Lung Cancer (JO25567): Updated Safety Results. Drug Saf 2018; 41(2): 229-37.

  - *Examined erlotinib plus bevacizumab versus erlotinib*

- Kim YH, Sumiyoshi S, Hashimoto S, et al. Expressions of insulin-like growth factor receptor-1 and insulin-like growth factor binding protein 3 in advanced non-small-cell lung cancer. *Clin Lung Cancer* 2012; **13**(5): 385-90.

  - *Examined immunohistochemical expression of IGF receptors and response to chemotherapy (cytotoxic or TKIs as a single group) in NSCLC*

- Kimura H, Matsui Y, Ishikawa A, Nakajima T, Yoshino M, Sakairi Y. Randomized controlled phase III trial of adjuvant chemo-immunotherapy with activated killer T cells and dendritic cells in patients with resected primary lung cancer. *Cancer Immunol Immunother* 2015; **64**(1): 51-9.

  - *Examined adjuvant chemo-immunotherapy with activated killer T cells and dendritic cells vs chemotherapy*

- Koeppen H, Yu W, Zha J, et al. Biomarker analyses from a placebo-controlled phase II study evaluating erlotinib+/-onartuzumab in advanced non-small cell lung cancer: MET expression levels are predictive of patient benefit. *Clin Cancer Res* 2014; **20**(17): 4488-98.

  - *Onartuzumab + erlotinib vs placebo + erlotinib*

- Kumar G, Woods B, Hess LM, et al. Cost-effectiveness of first-line induction and maintenance treatment sequences in non-squamous non-small cell lung cancer (NSCLC) in the U.S. *Lung Cancer* 2015; **89**(3): 294-300.

  - *Erlotinib was considered maintenance therapy and wasn't included in the first line or induction therapy groups: (different chemotherapy regimens)*

- La Salvia A, Rossi A, Galetta D, et al. Intercalated Chemotherapy and Epidermal Growth Factor Receptor Inhibitors for Patients With Advanced Non-Small-cell Lung Cancer: A Systematic Review and Meta-analysis. *Clin Lung Cancer* 2017; **18**(1): 23-33.e1.

  - *Examined chemotherapy intercalated with an EGFR-TKI versus chemotherapy*

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- Lacouture ME, Keefe DM, Sonis S, et al. A phase II study (ARCHER 1042) to evaluate prophylactic treatment of dacomitinib-induced dermatologic and gastrointestinal adverse events in advanced non-small-cell lung cancer. *Ann Oncol* 2016; **27**(9): 1712-8.
  - *Prophylactic treatment of GI and skin adverse events in dacomitinib therapy*

- Lai XX, Xu RA, Li YP, Yang H. Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. *Onco Targets Ther* 2016; **9**: 2421-8.
  - *Examined treatment with or without bevacizumab + concurrent chemotherapy and/or biological agent (no trial with TKI monotherapy vs erlotinib + bevacizumab was included)*

- LeCaer H, Barlesi F, Corre R, et al. A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study). *Br J Cancer* 2011; **105**(8): 1123-30.
  - *Examined (docetaxel/gemcitabine followed by erlotinib after progression) vs erlotinib followed by (docetaxel/gemcitabine after progression)*

- Lee SM, Lewanski CR, Counsell N, et al. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. *J Natl Cancer Inst* 2014; **106**(7).
  - *Examined whole brain RT+ placebo vs whole brain RT + erlotinib*

- Leighl NB, Rizvi NA, de Lima LG, Jr., et al. Phase 2 Study of Erlotinib in Combination With Linsitinib (OSI-906) or Placebo in Chemotherapy-Naive Patients With Non-Small-Cell Lung Cancer and Activating Epidermal Growth Factor Receptor Mutations. *Clin Lung Cancer* 2017; **18**(1): 34-42.e2.
  - *Examined linsitinib + erlotinib vs erlotinib + placebo*

- Lester-Coll NH, Rutter CE, Bledsoe TJ, Goldberg SB, Decker RH, Yu JB. Cost-Effectiveness of Surgery, Stereotactic Body Radiation Therapy, and Systemic Therapy for Pulmonary Oligometastases. *Int J Radiat Oncol Biol Phys* 2016; **95**(2): 663-72.
  - *Erlotinib was compared with RT and surgery*

- Li T, Piperdi B, Walsh WV, et al. Randomized Phase 2 Trial of Pharmacodynamic Separation of Pemetrexed and Intercalated Erlotinib Versus Pemetrexed Alone for Advanced Nonsquamous, Non-small-cell Lung Cancer. *Clin Lung Cancer* 2017; **18**(1): 60-7.
  - *Pemetrexed/ Erlotinib not a valid comparator*

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- Liang W, Wu X, Hong S, et al. Multi-targeted antiangiogenic tyrosine kinase inhibitors in advanced non-small cell lung cancer: Meta-analyses of 20 randomized controlled trials and subgroup analyses. *PLoS ONE* 2014; **9 (10) (no pagination)**(e109757).
  - *Examined vandetanib, sunitinib, cediranib, sorafenib, motesanib and nintedanib containing regimens against other non-MATKI regimens (no subset analysis for study TKIs as controls).*
- Lister J, Stanisic S, Kaier K, Hagist C, Gultyaev D, Walzer S. Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain. *ClinicoEconomics and Outcomes Research* 2012; **4**(1): 299-305.
  - *Compared bevacizumab-based chemotherapy vs standard chemotherapy*
- Luo S, Chen L, Chen X, Xie X. Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases. *Oncotarget* 2015; **6**(18): 16725-34.
  - *Examined radiotherapy without TKIs vs TKIs + radiotherapy*
- Miller VA, Johnson DH, Krug LM, et al. Pilot trial of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib plus carboplatin and paclitaxel in patients with stage IIIB or IV non-small-cell lung cancer. *J Clin Oncol*, 2003. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/903/CN-00437903/frame.html (accessed.
  - *Examined gefitinib in combination with carboplatin and paclitaxel*
- Mok T, Wu Y-L, Lee JS, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. *Clin Cancer Res* 2015; **21**(14): 3196-203.
  - *Interventions were gemcitabine/platinum plus sequential erlotinib or placebo*
- Mok TSK, Geater SL, Su WC, et al. A randomized phase 2 study comparing the combination of ficlatuzumab and gefitinib with gefitinib alone in asian patients with advanced stage pulmonary adenocarcinoma. *Journal of Thoracic Oncology* 2016; **11**(10): 1736-44.
  - *Ficlatuzumab + gefitinib vs gefitinib*
- Mok TSK, Wu Y-L, Yu C-J, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2009; **27**(30): 5080-7.
  - *Examined erlotinib + gemcitabine + carboplatin/cisplatin vs placebo+ gemcitabine +carboplatin/cisplatin*

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- Morth C, Valachis A. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies. *Lung Cancer*, 2014. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12014025131/frame.html (accessed.

  - *Examined gemcitabine, carboplatin, cisplatin, pemetrexed, paclitaxel, vinorelbine, docetaxel*

- Nadeem H, Jayakrishnan TT, Rajeev R, Johnston FM, Gamblin TC, Turaga KK. Cost differential of chemotherapy for solid tumors. *Journal of Oncology Practice* 2016; **12**(3): e299-e307.

  - *Examined cisplatin-based chemotherapies.*

- Neubauer MA, Hoverman JR, Kolodziej M, et al. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *Journal of Oncology Practice*, 2010. http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22010000855/frame.html (accessed.

  - *Examined chemotherapy regimens*

- Ohe, Y.,Ramalingam, S.,Reungwetwattana, T.,Chewaskulyong, B.,Dechaphunkul, A.,Lee, K. H.,Imamura, F.,Nogami, N.,Cheng, Y.,Cho, B. C.,Cho, E. K.,Vansteenkiste, J.,Voon, P. J.,Zhou, C.,Gray, J.,Hodge, R.,Rukazenkov, Y.,Soria, J. C.. Osimertinib vs standard of care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA. Annals of oncology. 2017. Conference: 3rd european society for medical oncology asia congress, ESMO. 2017. Singapore 28:x125

  - *Examined osimertinib as intervention*

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- Soo RA, Loh M, Mok TS, et al. Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer: Results of a meta-analysis of randomized controlled trials. *Journal of Thoracic Oncology* 2011; **6**(6): 1030-8.

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- Stanisic S, Bischoff HG, Heigener DF, et al. Societal cost savings through bevacizumab-based treatment in non-small cell lung cancer (NSCLC). *Lung Cancer* 2010; **69 Suppl 1**: S24-30.

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- Wang J, Xia T-Y, Wang Y-J, et al. Prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**(3): e59-65.

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  - *Examined high dose patritumab+ erlotinib vs low dose patritumab+ erlotinib vs erlotinib + placebo*

- Yu H, Zhang A. Gefitinib and docetaxel for the treatment of non-small cell lung cancer: A meta-analysis. *Int J Clin Exp Med* 2016; **9**(11): 21057-65.

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- *Examined pemetrexed + cisplatin or carboplatin + gefitinib vs pemetrexed–platinum*

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- Zhang L, Cao F, Wang Y, Wang S, Zhong D. Antiangiogenic agents combined with chemotherapy in the first-line treatment of advanced non-small-cell lung cancer: overall and histology subgroup-specific meta-analysis. *Oncol Res Treat* 2014; **37**(12): 710-8.

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  - *Erlotinib as first-line therapy + docetaxel and cisplatin as second-line therapy vs docetaxel and cisplatin as first-line therapy plus erlotinib as second-line therapy*

- Zheng M-h, Sun H-t, Xu J-g, et al. Combining Whole-Brain Radiotherapy with Gefitinib/Erlotinib for Brain Metastases from Non-Small-Cell Lung Cancer: A Meta-Analysis. *Biomed Res Int* 2016; **2016**: 5807346.

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- Zhou J-G, Tian X, Wang X, et al. Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials. *Med Oncol* 2015; **32**(2): 471.

  - *Examined erlotinib + platinum-based chemotherapy vs platinum-based chemotherapy*

- Zhuang H, Yuan Z, Wang J, Zhao L, Pang Q, Wang P. Phase ii study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. *Drug Design, Development and Therapy* 2013; **7**: 1179-86.

  - *Examined WBRT vs WBRT + erlotinib*

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- Shi J, Zhu J. Health Resource Utilization in Patients with Advanced Non-Small Cell Lung Cancer Receiving Chemotherapy in China. Clin Drug Invest 2016; 36(1): 77-86.
- Sun J, WuH X, Gu Y, Shu Y, Liu L. Clinical study of icotinib in treatment of advanced non-small cell lung cancer. China J Mod Dr 2014; 52: 116–9.
- Wei F, Wang J, Zou Q, Z T. Effect of icotinib hydrochloride targeted therapy on non small cell lung cancer. J Haerbin Med Univ 2015; 49: 364–6.

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- Zeng X, Li M, ZX Pu D. Efficacy of icotinib for advanced lung adenocarcinoma. Sichuan J Cancer Control 2013; 26: 12-5.

Appendix B

Reason for Exclusion: Population

- Milbury, K.,Malliah, S.,Liao, Z.,Yang, C.,Shannon, V.,Cohen, L. (2017). Randomized controlled trial of a dyadic yoga program for lung cancer patients undergoing radiotherapy and their family caregivers Psycho-Oncology, 26 (Supplement 3)(#issue#), 8
- Tan, O.,Shrestha, R.,Schofield, D. (2017). Review of the utility and the costeffectiveness of next-generation sequencing technology in cancer care Twin Research and Human Genetics, 20 (5)(#issue#), 479-480
- Vicente Conesa, M. A.,Zafra Poves, M.,Ivars, M. A.,Ballester, I.,Carmona-Bayonas, A.,Ayala De La Pena, F. (2017). Health related quality of life and utility weights of medical oncology inpatients Annals of Oncology, 28 (Supplement 5)(#issue#), v397

Reason for Exclusion: Did not report relevant outcomes

- Brahmer, J. R.,Rodriguez-Abreu, D.,Robinson, A. G.,Hui, R.,Csoszi, T.,Fulop, A.,Gottfried, M.,Peled, N.,Tafreshi, A.,Cuffe, S.,O'Brien, M.,Rao, S.,Hotta, K.,Zhang, J.,Lubiniecki, G. M.,Deitz, A. C.,Rangwala, R.,Reck, M. (2017). Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial Lancet Oncology, 18(12), 1600-1609
- Capaldi, D. P.,Sheikh, K.,Di Cesare, R.,Palma, D. A.,Parraga, G. (2017). Is ventilation heterogeneity related to quality of life scores post-radiation therapy in non-small cell lung cancer patients? American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 195(no pagination), #Pages#
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- Gajra, A.,Karim, N. A.,Mulford, D. A.,Villaruz, L. C.,Matrana, M. R.,Ali, H. Y.,Santos, E. S.,Ong, T. J.,Sanford, A.,Amiri, K.,Spigel, D. R. (2017). Safety and efficacy of nab-paclitaxel (nab-P)-based therapy in patients (pts) with non-small cell lung cancer (NSCLC) and performance status (PS) 2: Results from ABOUND.PS2 Journal of Clinical Oncology. Conference, 35(15 Supplement 1), #Pages#
- Kourkoulas, N.,Kyriopoulos, D.,Athanasakis, K. (2017). Cost-effectiveness analysis of atezolizumab compared to the standard of care for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in Greece Value in Health, 20 (9)(#issue#), A439

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- Langer, C. J.,Anderson, E.,Jotte, R.,Goldman, J.,Haggstrom, D.,Modiano, M.,Socoteanu, M.,Smith, D.,Dahkil, C.,Konduri, K.,Kim, E.,Sanford, A.,Amiri, K.,Weiss, J. (2017). Quality of life (QoL) in elderly NSCLC patients (pts) treated with nabpaclitaxel/ carboplatin (nab-P/C) in the ABOUND.701 trial Annals of Oncology, 28 (Supplement 5)(#issue#), v488-v489
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Clarification question B9ii

B9. A table ('Adverse Events' worksheet; cells 'E7:J14') in the company's economic model reports the frequency of Adverse Events (AEs) by treatment. Please:

ii) provide a full list of incidences (first, second, and subsequent) of grade 3-5 AEs, by treatment.

Following on from the response to clarification question B9ii, the company have completed the additional analysis. Please see the full list of incidences for grade 3-5 treatment-related AEs occurring at a frequency of >2% in either treatment arm in the PDF attached with this response (Table 14.3.1.4.1.8 CONFIDENTIAL.pdf). As previously discussed, the company have not provided a full list of grade 3-5 event incidences because of complexities in how this is defined appropriately given the potential for the short term change in the grade of an AE, however an examination on a cycle-by-cycle level allows insight into the recurrence of AEs.

For all AEs included in this additional analysis, the incidences were similar to the number of patients experiencing the events, demonstrating that there was a low rate of reoccurrence. This was expected given the ability to dose reduce and appropriate management of the conditions.

[redacted]

LUX-Lung 7 PFS data updated CE model

In response to the more recent data-cut for Progression Free Survival (PFS) in the comparator trial LUX-Lung 7 that Pfizer identified, please see the model attached with the updated fractional polynomial (FP) analysis (*ID1346_Dacomitinib_EGFR_NSCLC_CEmodel_04FEB19(ACiC).xlsb*). The following updates have been applied to the most recent CE model previously provided in responses to clarification question on 23 January 2019:

- *FP NMA HR Y7:Y13* – named range updated
- FP NMA HR rows 121 to 161 – PFS FP model parameters updated

The base-case PFS model (second-order *P1=0.5, P2=1.5)* remained in the DIC+5 criterion (CS Document B.2.9.3.2 page 68) and provided the most plausible fit of the models. An update to CS Document B Table 19 page 68-69 is provided below.

Table 19. Goodness-of-fit estimates for fractional polynomial models of different powers p1 and p2 – PFS (IRC)

Power P1	Power P2	Dbar	Dhat	pD	DIC
1	1.5	1234.62	1223.22	11.40	1246.02
1	1	1235.36	1223.60	11.75	1247.11
1.5	1.5	1236.49	1225.18	11.31	1247.81
0.5	**1.5**	**1236.73**	**1224.81**	**11.92**	**1248.65**
1	2	1237.37	1225.60	11.77	1249.15

Abbreviations: DIC = Deviance information criterion.

As discussed in CS Document B page 70 the second-order *P1=0.5, P2=1 was* included in sensitivity analysis, but in the updated FP analysis it did not meet the DIC+5 criterion. However, it was included in the updated model to allow this scenario to be explored as it still provided a plausible fit.

The updated csv data file for FP PFS analysis is also attached (*Data_RBase_NMA_PFS_updated.csv).*

NICE National Institute for Health and Care Excellence

Patient organisation submission – Roy Castle Lung Cancer Foundation

Dacomitinib for untreated, EGFR positive non-small-cell lung cancer [ID1346]

Thank you for agreeing to give us your organisation's 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 submission

- 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	[redacted]

2. Name of organisation	ROY CASTLE LUNG CANCER FOUNDATION
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of EGFR positive Non Small Cell Lung Cancer (NSCLC).
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and	The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, patient/carer panel, online forums and its Lung Cancer Information Helpline.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of advanced NSCLC is devastating. Recent years have seen the emergence of target therapies, for segmented populations, including EGFR. These have provided hope for patients, significantly extending survival, as compared with traditional chemotherapy. To date, however, it would appear that such therapies, although providing significant benefit to these patients, are not curative and the cancer progresses. As such, there is a need for improved treatment options. Characteristics of EGFR positive lung cancer is that patients tend to be younger, more are female and more are never smokers, than we see in NSCLC overall – as such, patients tend to present late, having more advanced disease at diagnosis. As with other NSCLC patients, this group of patients, on disease progression will have a poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Target therapies (Gefitinib, Erlotinib and Afatinib) have brought obvious benefit to this patient group. However, these therapies are not 'curative' and patients progress, despite these treatments. As such, there is a need for therapies with better outcomes than currently available.

8. Is there an unmet need for patients with this condition?	Most definitely.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	From the ARCHER 1050 study, benefit is seen by patients in the improvement over Gefiitinib. The overall survival was 34.1 months for Dacomitinib and 26.8 months for Gefitinib. Median Progression Free Survival was 14.7 months and 9,2 months in the Dacomitinib arm and Gefitinib arm respectively. The potential for extensions in life, is of paramount importance to this patient population and their families.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects of the treatment. Side effects are similar to those with other TKIs. However, in the ARCHER 1050 study, more treatment- related serious adverse events were reported in the Dacomitinib arm (9%) than in the Gefitinib arm (4%). Rashes and diarrhoea are the most common grade 3-4 side effects seen with Dacomitinib. In the anecdotal experience reported to us, it appears to be relatively well tolerated. Dacomitinib is also an oral therapy – meaning ease of administration.

Patient population	
11. 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.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Despite the benefits of first generation TKIs , there remains unmet need in this EGFR patient population
- Dacomitinib is a second generation, irreversible EGFR TKI and it has shown improvement in overall survival and progression free survival, as compared with a first generation, reversible TKIs (Gefitinib)
- Therapy is oral and relatively well tolerated
-
-

Thank you for your time.

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Professional organisation submission

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Thank you for agreeing to give us your organisation's 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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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group**
3. Job title or position	[redacted]

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):
5a. Brief description of the organisation (including who funds it).	**BTOG is a self-funded group of healthcare professionals involved in the multidisciplinary care of patients with lung and other thoracic malignancies.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms; to delay progression of symptoms; to improve survival

7. 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.)	30% reduction
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is debatable. There are several drugs already available, but based on the results of the ARCHER 1050 trial dacomitinib offers clinically meaningful improvement compared with first generation drugs (Wu et al. Lancet Oncology (2017) 18:1454, Mok et al J Clin Oncol (2018) 36:2244). However, a third generation drug has now shown very significant superiority in PFS compared to first generation drug in the FLAURA trial (Soria et al. New Engl J Med (2017)), and this is likely to replace the current standard of care.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	First line therpy with gefitinib, erlotinib or afatinib. Followed by osimertinib on progression, in the 50% of patients who have a T790M somatic mutation as resistance mechanism
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE; ESMO; ASCO; NCCN

• 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.)	It is well defined, although there is little data to support the choice of one of the other from current standards gefitinib, erlotinib & afatinib
• What impact would the technology have on the current pathway of care?	It would provide an additional alternative drug. The results of the ARCHER 1050 trial suggest that dacomitinib may be associated with a clinically significant improvement in OS compared with the current standard of care
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	No
• In what clinical setting should the technology be used? (For example,	Specialist thoracic oncology clinics

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as above
• Do you expect the technology to increase length of life more than current care?	Yes, as above
• Do you expect the technology to increase health-related quality of life more than current care?	No

12. 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	
13. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference in ease of use compared with standard of care

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – standard response assessment with CT scans
15. 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
16. 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	This is an incremental improvement over current standard of care

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?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the ARCHER 1050 trial the burden of toxicity was in general a little greater with dacomitinib than for gefitinib
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the control arm treatment of the ARCHER 1050 trial (gefitinib) is a standard of care in first line treatment of EGFR+ NSCLC

• 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?	PFS; OS. Yes, reported in the Wu et al. and Mok et al. trials referenced above
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	The ARCHER 1050 trial excluded patients with brain metastases (a common finding in NSCLC). Therefore, depending on relative CNS penetration of the experimental and control arm drugs, the difference in outcomes for these 2 drugs may not be exactly the same in the real world as those reported in the trial
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- The second generation drug dacomitinib adds a further first line alternative for EGFR-mutated NSCLC
- The ARCHER 1050 trial demonstrated a PFS, and importantly OS, advantage over current standard of care
- This trial evidence differs from the real-world population in that patients with disease metastatic to brain were excluded
- The expected approval in the first line setting of osimertinib, a third generation drug in this class, may supplant first and second line drugs, so the longer-term impact of dacomitinib may be limited

Thank you for your time.

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Clinical expert statement

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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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 University**

3. Job title or position	**Senior Lecturer**
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.)	Palliate cancer related symptoms, shrink down cancer on radiological imaging and prevent progression as long as possible and extend survival.
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 Progression free survival of more than 3 months, an improvement in radiological response rates by 10 % or a reduction in the development of central nervous metastases by 5%, an improvement in overall survival by more than 6 weeks.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) can control the cancer but progression occurs on average within 12 months.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	With 1st/ 2nd EGFR inhibitors as 1st line treatment. In patients who progress on these a repeat biopsy is taken. If this shows the cancer has become resistant due to a 2nd mutation in EGFR (T790M) the patient will change therapy to osimertinib. In the absence of a biopsy or the demonstration of T790M on the biopsy the options are to continue the 1st line therapy beyond progression or switch to platinum doublet chemotherapy. In practice many patients are reluctant to change to chemotherapy in this setting and will continue their initial therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. ESMO clinical guidelines as to management of metastatic lung cancer Planchard et al. ESMO NSCLC Guidelines 2018 Ann Oncol (2018) 29 (suppl 4): iv192–iv237. NICE technology appraisals TA192, TA258, TA310,TA416 NICE guideline CG121 (being updated)
• 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.)	Yes. It is recommended that all patients with lung cancer with a sensitising mutation in EGFR receive a 1st and 2nd generation EGFR inhibitors (gefitinib, erlotinib and afatinib) as 1st line of therapy. There is variation across the country and between clinicians as to which of these are used as preferred therapy.
• What impact would the technology have on the current pathway of care?	Dacomitinib would be another option that clinicians could use when choosing 1st line therapy
11. Will the technology be used (or is it already used) in	Yes. Dacomitinib would be given as an oral therapy in oncology clinics to patients at 1st presentation with local advanced or metastatic lung cancer with a sensitising EGFR mutation

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There would not be any major differences except the longer time on therapy with dacomitinib compared to the other 1st/2nd generation EGFR inhibitors.
• 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.)	Minimal; doctors and nurses already well trained in the management of EGFR side-efefcts and they are very similar to afatinib which is in common practice
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	Yes, The Archer study showed a significant improvement in survival compared to one of the current 1st generation EGFR inhibitors (gefitinib which is in common use) of approximately 6 months.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Dacomitinib is associated with longer disease control. In lung cancer the main driver of health related quality of life is cancer symptoms. These will be reduced with dacomitinib treatment and the length of disease control should off-set the toxicity seen with this agent in most patients
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 example, any concomitant	Likely to be similar. Dacomiitnib does require dose adjustments in a number of patients. This is also the case with afatinib although not with gefitinib and erlotinib. Likely to be the concurrent medications to manage skin and gastro-intestinal toxicity such as topical antibiotics and lopermaide but will be similar to afatinib.

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?	No additional testing will be required; EGFR testing at 1st diagnosis is already well embedded in the NHS. Patients will be monitored as previously with oncologist/ specialist nurse review to ensure clinical benefit and tolerability with regular CT scans to document formal response to treatment as with present care.
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	No. It is clear that dacomiitnib is an improvement in terms of PFS and OS over the 1st and 2nd generation EGFR inhibitors in present use. However the emerging data in the 1st line setting with 3rd generation TKI

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?	inhibitors such as osimertinib is likely to supplant dacomitinib, particularly as it has an improved safety profile.
• Is the technology a 'step-change' in the management of the condition?	No; see above.
• Does the use of the technology address any particular unmet need of the patient population?	No
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?	Diarrhoea and skin toxicity can impact on a patient quality of life but shouldn't cause too many problems if managed appropriately with dose reductions and supportive measures.
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?	Overall survival Progression Free Survival Health Related quality of life Toxicity Development of CNS disease Rates of subsequent treatment
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

• 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. How do data on real-world experience compare with the trial data?	We have yet to generate real world data with dacomiitnib. In general real world data from EGFR inhibitors matches relatively well on trial data except that patients with poorer PS and active brain disease do worse than the trial population
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Dacomitinib is the 1st EGFR inhibitor to show survival benefit
- The toxicity profile and method of use are similar to afatinib
- It represents and advance on present UK standard of Care
- Its use is likely to be supplanted by the emerging data with 1st line 3rd generation EGFR inhibitors
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

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	**Carol A Davies**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ ✓ other (please specify): Macmillan Lung Cancer Nurse Specialist and NLCFN committee member
3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ ✓ 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 ☐ ✓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
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: ☐ ✓ I am drawing on others' experiences. Please specify how this information was gathered: I work with Patients (and carers) with lung cancer and keep myself up to date with relevant trial results
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?	An incurable lung cancer diagnosis comes with a variety of debilitating symptoms. These include breathlessness, fatigue, (both can impact on mobility) pain, loss of appetite & psychological concerns. Carers often feel helpless

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Always hoping for new innovative treatments; in this patient group that will shrink the cancer (as cure is not possible),that will extend one's life (but with minimal side effects) that preserve or improve performance status, and improve one's quality of life.
10. Is there an unmet need for patients with this condition?	Definitely
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	No experience of this technology as such unable to answer this question
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	**No experience of this technology as such unable to answer this question**
Patient population	
13. Are there any groups of patients who might benefit	Good PS patients with untreated EGFR-positive NSCLC.

more or less from the technology than others? If so, please describe them and explain why.	Trial data identifies that Dacomitinib comes with significant side effects as such not suitable for large proportion of patients who are diagnosed with PS 2 or 3
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not to my knowledge
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For	

example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Trial data suggests overall survival benefit when compared to Gefitinib.
- A lung cancer treatment for this group of patients with a proven (trial data) overall survival benefit is a positive result for lung cancer patients

- Careful patient selection is essential – as comes with significant side effects. Careful monitoring of and prompt treatment of side effects essential
- Likely not suitable for large proportion of untreated EGFR- positive NSCLC patients as many present PS 2 or 3
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NHS England submission for the 1st meeting of the NICE appraisal of dacomitinib in the treatment of locally advanced/metastatic activating EGFR mutation positive non small cell lung cancer

Indicates commercial in confidence

1. There are 3 NICE-recommended monotherapy options for the 1st line treatment of activating EGFR positive non small cell lung cancer (NSCLC): erlotinib, gefitinib and afatinib. The greatest use in England of these 3 drugs is with afatinib although significant market share remains with both erlotinib and gefitinib. Afatinib has the best pedigree in relation to clinical evidence as it was compared at the time of the clinical trial with optimal chemotherapy for NSCLC and also has since been shown to be superior (in progression free survival) to gefitinib. Afatinib has the most side-effects of these 3 agents and in NHS practice is probably offered to patients at the fitter end of the spectrum of performance status.
2. Although trials of EGFR-TKIs have generally been performed in patients of ECOG performance status of 0 or 1, clinical use has extended to patients of lower performance status, at least for gefitinib and erlotinib. The reason for this is that responses to EGFR-TKIs can be quick and thus patients can rapidly improve their performance status and quality of life. The chronic side-effects of EGFR-TKIs are very important to patients, hence the need for a balance to be achieved between the efficacy of therapy and the side-effects of treatment.
3. The most valid clinical comparator for dacomitinib is currently afatinib especially given the considerable side-effect profile of dacomitinib as its use is more likely to be in the patients fit enough to receive afatinib. Erlotinib and gefitinib remain appropriate comparators in theory but less so in practice as erlotinib and gefitinib have fewer side-effects and so are more likely to be given to patients who are less fit. NHS England.
4. NHS England notes that 76% of the ARCHER 1050 study were Asian. The intention to treat (ITT) progression free survival (PFS) analysis showed a significant benefit with dacomitinib over gefitinib (14.7 vs 9.2 months). Pre-specified analyses showed that the PFS difference for Asian patients was 18.2 vs 10.9 months (n=259) whereas for non-Asian patients was 10.9 vs 9.1 months (n=72). Whilst the number of non-Asian patients was small and NHS England is fully aware of the dangers of subgroup analysis, NHS England has uncertainties as to whether the ITT benefit of dacomitinib would be fully translated into outcomes for patients in England.
5. NHS England notes with concern the difference in side-effects between dacomitinib and gefitinib in ARCHER 1050 with dacomitinib associated with much higher rates of diarrhoea and cutaneous toxicity. Dose reductions from the initial starting dose were necessary in 66% of dacomitinib patients versus 8% for gefitinib patients. Of the dacominitib dose reductions, 38% of all patients reduced to two thirds of the starting dose and 28% of all patients reduced to one third of the starting dose of dacomitinib. Dacomitinib is a drug with very significant toxicity.

6. The dacomitinib phase III trial included patients of ECOG performance status of 0 or 1 only. The much higher rates of dose reductions/interruptions seen with dacomitinib vs gefitinib were in a fit population of patients and hence NHS England is concerned as the toxicities of dacomitinib likely to be seen in practice in England.
7. Adverse toxicities for a chronic treatment such as dacomitinib are very important and side-effects of grades 1 and 2 are still significant daily issues for patients. NHS England would therefore wish the effect of these chronic toxicities to be included in the utility values employed in the cost effectiveness modelling.
8. NHS England notes that patients with brain metastases were excluded from ARCHER 1050 unlike Lux-Lung 7 (afatinib vs gefitinib) in which 16% of patients had brain secondaries. The proportions of Asian patients were also different (75% ARCHER 1050 vs 57% in Lux-Lung-7). The indirect comparison of dacomitinib vs afatinib therefore has significant uncertainties.
9. NHS England observes that in the ARCHER 1050 trial, patients were treated for a maximum of 4 years. If NICE recommends the use of dacomitinib, NHS England would with the Appraisal Committee to address the issue as to whether this cap in treatment duration would apply or not in its recommendations.
10. NHS England notes the subsequent treatments received so far by patients after progression on dacomitinib/gefitinib in the ARCHER 1050 study. Osimertinib has been used less than would be expected in England (8-13%) and yet the company has modelled a 2nd line treatment rate with osimertinib of 56% which is too high. NHS England observes that 12-13% in ARCHER 1050 received a further line of treatment with erlotinib or gefitinib and neither of these are commissioned in England after failure of initial EGFR-TKI therapy. The company indicates that the 2nd line systemic treatment rate in EGFR-mutated NSCLC is 71% and the 3rd line treatment rate is 48%. Both these figures are too high, the likely figures in NHS practice being 50-60% and 25-30%.
11. Given the toxicity of dacomitinib and that the NHS has to provide and pay for all the monitoring of a drug such as dacomitinib plus the resources to treat and mitigate the drug's side-effects, NHS England is surprised that Pfizer plans to charge the same amount for a 45mg dose of dacomitinib as it does for a 15mg dose.
12. Whilst there is immaturity as to overall survival data in the ARCHER 1050 study, NHS England does not view the Cancer Drugs Fund as being a worthwhile use of CDF resources for a NICE recommendation to the CDF for treatment with dacomitinib. There are already 3 NICE-recommended drugs in this position in the treatment pathway, all of which would be trumped by a NICE recommendation for 1st line osimertinib.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

March 2019

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346). Main Evidence Review Group Report.

Produced by: **Warwick Evidence**, University of Warwick, Coventry, CV4 7AL

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Date completed: 20 February 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 127889.

Declared competing interests:

PA, EL, DG, MJ, RC, JP, JK, XA, JC, JG, JM and LA declare no competing interests.

LA declares a honorarium received from Pfizer for participation in a panel set up to provide expert opinion on aspects of an unrelated submission to NICE (Tofacitinib for moderately to severely active ulcerative colitis [TA574]).

Acknowledgements:

The ERG team are grateful to Dr John Green (BSc MBChB DM FRCPE FRCP) who acted as an expert clinical advisor throughout the course of this appraisal.

Rider on responsibility for report:

This report should be referenced as follows:

Auguste P., Loveman E., Gallacher, D., Jordan M., Court R, Patterson J., Kaur J., Green J., Colquit J., Armoiry X., Mason J and Andronis L. *Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346): A Single Technology Appraisal.* Warwick Evidence, University of Warwick, February 2019.

Contributions of authors

Lazaros Andronis (Senior Research Fellow) led and co-ordinated the project; **Peter Auguste** (Research Fellow) co-ordinated and conducted the appraisal of the economic evidence; **Emma Loveman** (Senior Researcher) co-ordinated and conducted the appraisal of clinical effectiveness evidence; **Daniel Gallacher** (Research Fellow) conducted the appraisal of statistical elements in the submission; **Mary Jordan** (Research Associate) contributed to the appraisal of the economic evidence; **Rachel Court** (Information Specialist) conducted ERG searches and the critique of the company searches; **Jacoby Patterson** (Clinical Fellow) contributed to the appraisal of the clinical effectiveness evidence; **Jatinder Kaur** (Academic F2 Doctor) contributed to the appraisal of the clinical effectiveness evidence; **John Green** (Consultant in Oncology) contributed to the appraisal of the clinical effectiveness evidence; **Jill Colquitt** (Senior Researcher) contributed to the appraisal of the clinical effectiveness evidence; **Xavier Armoiry** (Professor of Pharmacology) contributed to the appraisal of statistical elements (Network Meta Analysis); **James Mason** (Professor of Health Economics) contributed to the appraisal of the economic evidence. All listed authors contributed to writing sections of the report, and reviewed and commented on the final version of the report.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse Event
AIC	Akaike Information Criterion
AT	As Treated
BIC	Bayesian Information Criterion
BNF	British National Formulary
CE plane	Cost-Effectiveness plane
CEAC	Cost-Effectiveness Acceptability Curve
CR	Complete Response
CS	Company Submission
CSR	Clinical Study Report
DIC	Deviance Information Criterion
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions Questionnaire
ER	Oestrogen Receptor
ERG	Evidence Review Group
FDA	Food and Drug Administration
GP	General Practitioner
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
IRC	Independent Review Committee
ITT	Intention-To-Treat
KM	Kaplan-Meier
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis

NR	Not Reported
NSCLC	Non Small Cell Lung Cancer
OS	Overall Survival
ORR	Objective response rate
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PH	Proportional Hazards
PPS	Post-progression survival
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Risk Ratio
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SLR	Systematic Literature Review
TKIs	Tyrosine Kinase Inhibitors
TTF	Time to Treatment Failure
UK	United Kingdom
WTP	Willingness-To-Pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's decision problem is consistent with the NICE scope. However, the evidence obtained from the ARCHER 1050 trial presents some deviations from the decision problem and the ARCHER 1050 trial population is not wholly representative of the UK population.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence for the clinical effectiveness of dacomitinib comes from a large multi-centre RCT which has an active comparator with a tyrosine kinase inhibitor (TKI) (gefitinib), the ARCHER 1050 trial. Median follow-up was 22.1 months (dacomitinib) and 23.0 months (gefitinib) for progression-free survival (PFS) based on blinded Independent Review Committee (IRC), and 31.1 months and 31.4 months, respectively, for overall survival (OS). A statistically significant improvement was found in PFS assessed by blinded IRC (the primary outcome) with dacomitinib compared with gefitinib: median 14.7 months vs 9.2 months, HR 0.59 (95% CI 0.47, 0.74), p<0.0001.

Median survival improved significantly with dacomitinib compared with gefitinib: median 34.1 months vs 26.8 months, hazard ratio (HR) 0.76 (95% CI 0.58, 0.99), p=0.044. There was no statistically significant difference in the objective response rate (complete response + partial response) for dacomitinib (74.9%, 95% CI 68.7, 80.4) compared with gefitinib (71.6%, 95% CI 65.2, 77.4) assessed by blinded IRC, p=0.194. The median duration of response by blinded IRC review was significantly longer in the dacomitinib arm compared with gefitinib [Kaplan-Meier estimates of response duration quartiles 14.8 months vs 8.3 months, HR 0.40 (95% CI 0.31, 0.53), p<0.0001].

Disease-related symptoms assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13 (cough, dyspnoea, pain in chest, pain in arm or shoulder, pain in other parts, fatigue) reduced in both groups; only the reduction in chest pain was significantly greater with dacomitinib than gefitinib (-10.24 vs -7.44, p=0.024).

Treatment-related symptoms were assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13. Both diarrhoea and sore mouth, worsened significantly more with dacomitinib compared with

gefitinib, and these changes were considered clinically meaningful (mean scores diarrhoea: 19.88 vs 7.32, p<0.0001; sore mouth: 15.09 vs 3.51, p<0.0001).

Statistically significant differences in the EQ-5D absolute VAS score and utility index were observed in favour of gefitinib.

Rates of any all-cause and treatment-related adverse events were similar between dacomitinib and gefitinib. There were slightly higher rates of any all-cause and any treatment-related grade 3 adverse event and serious adverse events with dacomitinib (based on observation of the proportions only), and dose reductions or temporary discontinuations were more frequently observed with dacomitinib.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS systematic review of clinical effectiveness was generally well executed. Two studies that the CS excluded from the broader review may have been eligible, however, these omissions would not have affected the results seen. Overall the ERG considered there to be a low chance of systematic error in the findings of the review.

The main clinical evidence for dacomitinib was drawn from the ARCHER 1050 trial which was a multi-centre study comparison with gefitinib. The trial had a high risk of performance bias (owing to the open-label design) but low risks of detection and attrition bias.

The ARCHER 1050 trial presents a number of potential issues in terms of representativeness to the population of England and Wales. There were no UK sites participating in the trial and only [redacted] of sites were from European countries. There was a high proportion of Asian participants, the population was limited to two epidermal growth factor receptor (EGFR) mutations only (albeit the most common ones), and the trial excluded people with brain metastases. In addition, there are imbalances in potential prognostic factors between arms.

The ERG have no concerns about the analysis sets used in the ARCHER 1050 trial or with the censorship and management of missing data used. The outcome measures appear appropriate. With regard to the trial statistics, the CS did not justify why a one-sided p-value was used for PFS and a two-sided p-value for OS and it is unclear to the ERG why there were different data time cut-off points for these two key analyses. The company did not provide significance thresholds alongside p-values presented throughout their submission, and it was unclear to the ERG whether formal

hypotheses were being tested or whether conclusions should be drawn, particularly for the sub-group analyses. The ERG considers that caution is required in the interpretation of the analysis of OS, as the proportional hazards assumption was violated. For patient reported outcomes, there was no adjustment for multiple comparisons.

The CS undertook a network meta-analysis (NMA) comparing dacomitinib with afatinib. The ERG agrees that other than the LUX-Lung 7 trial of afatinib versus gefitinib, there were no other relevant trials for the comparison. The CS adequately described the methods of their NMA approaches and provides a reasonable justification for using the fractional polynomial (FP) analysis. Despite this, the ERG has concerns over the use of the FP analysis with respect to the extrapolations for the survival outcomes but also because there are no detailed results or interpretation of the findings of the FP analysis.

In addition, the CS does not adequately assess the included study populations for transitivity and the ERG considers that the transitivity assumption may be violated. Finally, the CS does not present results of the indirect comparison between dacomitinib and afatinib. Although caution is recommended in the interpretation of the ERG analyses, these show no significant differences between the two respective treatments for PFS or OS.

1.4 Summary of cost-effectiveness evidence submitted by the company

The CS included a systematic review of economic evidence, a review of evidence on resource use and costs, a separate review to identify studies that measure health-related quality of life (HRQoL) in people with non-small-cell lung cancer (NSCLC) patients, and an electronic partitioned survival model built in a widely available spreadsheet application (Microsoft Excel ®).

The search for cost-effectiveness studies comparing the use of dacomitinib against other treatments did not identify any relevant references. The majority of the studies identified evaluated the cost-effectiveness of other treatments. Few elevant studies reporting resource use and costs were identified.

The company constructed a partitioned survival model to trace a cohort of treatment naïve patients with locally advanced or metastatic EGFR-positive NSCLC who may undergo treatment with dacomitinib compared to gefitinib, erlotinib or afatinib. Partitioned survival modelling considers the PFS and the OS curve directly, with the time in post-progression calculated using the difference

in area between the two curves. The company's model comprised three health states: progression-free, post-progression (progressed disease) (PD) and dead.

The model started from a hypothetical cohort of people reflective of the participants in the ARCHER 1050 trial,[1] all of whom began in the progression-free (PF) health state. Over time, people were at risk of progression or death. Transitions between health states was unidirectional and occurred at the end of each 28-day cycle, where people remained in the same health state or progressed. In each cycle, people incurred costs and accrued benefits depending on the health state they occupied. A half-cycle correction was applied in the base-case and the model concluded at a 15-year time horizon.

The company modelled PFS for gefitinib and erlotinib using a generalised gamma curve fitted to the gefitinib arm of ARCHER 1050. They then performed a FP NMA to obtain time-varying hazard ratios for afatinib and dacomitinib and apply these to the gefitinib extrapolation. The ERG found the company's predictions to be pessimistic and preferred a log-normal extrapolation and alternative adjustments for the comparators.

Similarly, for OS the company used a generalised gamma curve for gefitinib and applied HR obtained from FP NMA for the dacomitinib and afatinib. The ERG argues for a log-logistic extrapolation for gefitinib and suggests assuming a HR of 1 from 3 years onwards for the comparators.

Health-related quality of life values for the pre-progression health states were derived from the EQ-5D collected from the ARCHER 1050 study,[1] while utility values for the post-progression health state were obtained from the literature.[2] On clarification, the company provided utility values collected from participants in ARCHER 1050 trial[1] who were in the post-progression health state. The ERG preferred the use of these utility values; hence they were included in the ERG's base-case. The impact of treatment related adverse events was not accounted for directly in the company's base-case analysis, as it was assumed that these would have been captured by EQ-5D data collected in the trial. However, the ERG argues that it is unlikely that quality of life decrements associated with treatment related AEs are captured by the EQ-5D, unless it is arranged for the instrument to be administered at the same time of these events. Utility decrements (disutilities) were included in the ERG's base-case for treatment related adverse events.

Total cost estimated in the model comprised of cost of treatments (drug acquisition and drug administration), subsequent treatment and administration costs, resource use and costs associated with each health state, treatment related to adverse events and terminal care costs. The company's base-case analysis (presented in the main CS report) was based on a proposed price discount in the form of a PAS for dacomitinib and speculations on the PAS discounts for the comparators. The costs included in the model were in line with the NHS and PSS perspective, were appropriately discounted and were reported in current prices. Though there were no discrepancies in the costs included in the analysis, there were concerns relating to costs that might have been excluded from the analysis. Notably, resource use and costs associated with unscheduled hospital admissions, magnetic resonance imaging scans for suspected brain metastases or cord compression and costs associated with the diagnosis of T790M mutation (personal communication with clinical expert). Excluding these costs may potentially lead to an underestimate of the true costs associated with managing/treating people with NSCLC.

The company presented results for two comparisons: (i) dacomitinib with PAS discount versus comparators with PAS discount calculated/assumed by the company (in the main CS document); (ii) dacomitinib at list price versus comparators at list price (in the CS Appendix).

In relation to comparison (i), the company's base-case deterministic results suggests that dacomitinib was the most costly and most effective treatment option, with an incremental cost-effectiveness ratio (ICER) of approximately [redacted] per quality-adjusted life year (QALY). Results from the PSA indicated that at a willingness to pay (WTP) threshold of £30,000 per QALY dacomitinib has a [redacted] probability of being cost-effective. The company's sensitivity analysis results showed that the monthly discount rate applied to costs and benefits were the key drivers of the cost-effectiveness analysis. With regards to comparison (ii) above, the ICER for the comparison between dacomitinib versus erlotinib was approximately [redacted] per QALY gained, with a probability of dacomitinib being cost-effective at £30,000 per QALY being [redacted].

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG did not identify any major errors in the company's model. The results reported in the company submission (CS) reflected those in the model submitted. However, the following concerns and uncertainties were noted:

- The modelling of PFS and OS of gefitinib was pessimistic, potentially underestimating the number of QALYs and costs for all comparators.

- The extrapolation of dacomitinib and afatinib was reliant on results from the FP NMA, the majority of which were not considered plausible by the ERG.

- We noted that there were some resource use and costs that have been excluded from the analysis: unscheduled hospital admissions, MRI scans for suspected brain metastases or spinal cord compression and costs associated with the diagnosis of T790M mutation.

- Utility values obtained from the EQ-5D-3L instrument administered to ARCHER 1050 trial participants were appropriate for use in the model although the company only used these for the PF state. Progressive disease (PD) values from the best alternative sources found in the literature were used. However, as ARCHER 1050 trial utility data were available for PD, the ERG considered these data more appropriate to use within the company's base-case, an approach that is more aligned with NICE DSU recommendations.[3]

- HRQoL reductions associated with AEs and ageing were not incorporated in the model for the base-case analysis which the ERG believe is an important omission. The ERG believes that it is appropriate to include these adjustments in the model. as well as using the utility values obtained from the trial.

Errors and concerns were addressed in the ERG's preferred base-case analysis, and uncertainties were explored in various scenario analyses.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company conducted a systematic review of clinical effectiveness evidence, which is deemed to be generally methodologically sound and is likely to have captured the evidence base adequately. A single RCT was included that compared dacomitinib with an active comparator (gefitinib) of relevance to the NICE scope. The trial was of reasonable size and quality and assessed key clinical and safety outcomes and was appropriately summarised in the CS.

The company's model is logical, in line with other models for this condition, and depicts the clinical pathways for treating people with EGFR+ advance/metastatic NSCLC fairly accurately. In general, the process of identifying and justifying the choice of key model inputs was transparent and congruent with established methods. The economic analysis conforms to the NICE reference case in that the perspective, discount and the lifetime horizon is considered to be long enough to capture the costs and benefits of dacomitinib, gefitinib, erlotinib and afatinib. The majority of the assumptions made in order to have a workable model appear to be appropriate. Finally, the results presented in the CS report are consistent with the the results and graph outputs generated in the company's spreadsheet model.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness

There was no direct evidence for dacomitinib compared to the other scoped comparators erlotinib or afatinib. The CS assumed equivalence for gefitinib and erlotinib which the ERG considers reasonable given evidence seen but an indirect comparison was required to compare dacomitinib with afatinib. This indirect comparison has a number of areas of uncertainty:

- The CS does not adequately assess the included study populations for transitivity and the ERG considers that the transitivity assumption may be violated.
- A FP analysis is used in the CS as the main analysis and while this appears reasonable there are no detailed results or interpretation of the findings of the analysis.
- Outcomes were restricted to OS and PFS and no comparison was made on adverse events.
- The CS does not present results of the indirect comparison between dacomitinib and afatinib.
- The ERG has concerns over the use of the FP analysis with respect to the extrapolations for the survival outcomes.

The evidence presented in the CS may not be wholly applicable to the population in England and Wales for a number of reasons. The population was limited to the two most common EGFR mutations and excluded people with brain metastases and there is consequently an evidence gap

about the effects of dacomitinib in these groups. There was also high proportion of Asian participants compared to European participants. Asian populations have higher rates of EGFR mutations and while there is no consistent evidence for the influence of ethnicity on outcomes in EGFR mutation positive NSCLC, including from the companies own sub-group analyses, the ERG note uncertainty around the degree of generalisability in the evidence to the population seen in clinical practice in the NHS.

Cost-effectiveness

The following weaknesses and limitations, which directly or indirectly feed into the economic analysis, were identified by the ERG:

- The parametric models used to extrapolate progression-free and overall survival for gefitinib were considered to be too pessimistic, thus underestimating the expected number of QALYs and costs incurred for all treatments
- The extrapolations for dacomitinib and afatinib were reliant on the results from the FP NMA.
- The negative impact on HRQoL (expressed in the form of disutilities) associated with AEs have been under-represented in the base-case as specific decrements have not been included and the rationale that trial data would have captured disutility is unfounded.
- No adjustment for age-related disutilities in the company's base-case analysis.
- Resource use and costs may have potentially been underestimated.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.7.1 Exploratory analyses related to clinical effectiveness

The ERG has undertaken an exploratory indirect comparison of dacomitinib and afatinib via a traditional network meta-analysis (NMA). Although caution is required in the interpretation of this analysis (potential transitivity assumption violation and proportional hazards assumption violation) the ERG undertook this analysis as no comparison was presented by the CS. The ERG undertook a fixed-effect NMA using a frequentist framework and generated the surface under the cumulative ranking curve (SUCRA) to rank each intervention. There were no statistically significant

differences between dacomitinib and afatinib for OS or PFS, although there were greater SUCRA values for dacomitinib.

The ERG has also tabulated data for key adverse events for afatinib from the LUX-Lung 7 trial which compared afatinib with gefitinib. The ERG considers that on balance there is no clear distinction between the adverse event profiles for dacomitinib and afatinib.

1.7.2 Exploratory analyses related to cost-effectiveness

The critique of submitted evidence focuses on analyses presented in the CS submission, namely (i) dacomitinib with PAS discount versus comparators with PAS discount calculated/assumed by the company (in the main CS document); (ii) dacomitinib at list price versus comparators at list price (in the CS Appendix). During communication with the NICE Technical Team overlooking this appraisal, it was suggested that a further comparison should be carried out between dacomitinib (applying the company's PAS discount) versus the gefitinib, erlotinib and afatinib (at list prices).

The ERG undertook this comparison, which formed the basis for applying the ERG preferred values and assumptions. These were:

- For PFS, used the log-normal parametric curve for gefitinib with the results from the FP NMA to derive the survival for the other comparators (P=0.5, P2=1). Assumed afatinib PFS to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards
- For OS, used the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assumed equal efficacy, on the hazard scale, from 36 months onwards
- Included disutilities associated with adverse events
- Used the post-progression utility value from the ARCHER 1050 trial
- Included age-related disutilities from the study published by Ara and colleagues[4]
- Correction made to how the PAS for gefitinib had been applied

Under these assumptions, dacomitinib dominated gefitinib and afatinib. When compared to erlotinib, dacomitinib had an ICER of approximately [redacted] per QALY. At a willingness-to-pay threshold of £30,000 per QALY, dacomitinib had a [redacted] probability of being cost-effective.

Results from the ERG's scenario analysis showed that using the results from the traditional NMA for survival had the greatest impact to the ERG's base-case ICER.

The company's base-case deterministic results reported in the CS inevitably differ to those estimated by the ERG in their base case analysis, given the fact that the ERG's base-case results relate to the comparison between dacomitinib with PAS discount versus prices for the comparators.

The ERG has also produced a Confidential Appendix comparing dacomitinib (with PAS discount suggested in the CS) against erlotinib, gefitinib and afatinib (with confidential PAS discounts ascertained by NICE).

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

The CS presents evidence on the clinical effectiveness and cost-effectiveness of dacomitinib for untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations. The CS states EGFR mutations are prevalent in 5-50% of NSCLC cases with rates depending on factors including ethnicity, gender and smoking status; the ERG clinical advisor believes the upper limit would be 40%. The highest rates of EGFR mutations are seen in people of Asian descent, female gender, non-smokers and with adenocarcinoma histological subtype. The ERG clinical advisor notes that despite accumulating data it is difficult to assess the precise contribution of these four factors and, with different methods for the assessment of EGFR mutation status used, this is why there are wide estimates of prevalence. In Caucasian populations rates are in the region of 10-20%. The ERG agrees that the most common EGFR mutations are exon 19 deletion (del19) and exon 21 L858R substitutions (L858R). The CS says these comprise 45-82% and 30% of EGFR mutations respectively (although the latter correctly ranged from 29%-39% in clarification response A4) and that between them these two mutations constituted approximately 80-90% of EGFR mutations in adenocarcinomas[5](additional references were provided in response to clarification A4[6, 7]). Evidence identified by the ERG suggests this rate may possibly be higher.[8]

The ERG has identified no concerns regarding the description of the prognosis of those with advanced lung cancer or the description of the burden of symptoms and the impact on quality of life of people with lung cancer. Prognosis in EGFR-positive NSCLC is slightly better than for general NSCLC and this is in part due to factors such as differences in natural history and characteristics of patients such as a younger age in this population.

2.2 Critique of company's overview of current service provision

The CS briefly summarises the treatment pathway for people with EGFR mutation positive locally advanced or metastatic NSCLC, discussing first line and subsequent lines of therapy. Dacomitinib is being positioned as a first line treatment option and the ERG clinical expert agrees that the summary in the CS is accurate. Currently NICE recommends the tyrosine kinase inhibitors (TKIs) afatinib, erlotinib and gefitinib as first line treatment options, and these are relevant comparators in the CS decision problem (see Section 1.1). In some instances when confirmation of EGFR mutation

status is delayed a platinum-based doublet chemotherapy is used. Figure 1 (cropped from CS Figure 2) illustrates the proposed position of dacomitinib in the treatment pathway. The ERG clinical advisor confirmed that there is individual preference for which of the current TKIs to use in clinical practice, but that erlotinib is still favoured in the UK by many clinicians and that afatinib is more commonly used in Europe. Dacomitinib and afatinib are second-generation TKIs. The CS states that as a second-generation TKI with irreversible binding to the receptor, dacomitinib has a longer duration of effect than the first generation TKIs. It must be noted that, although osimertinib (Tagrisso ®, AstraZeneca) is not a relevant comparator in the present appraisal, the ERG believes that is potentially an alternative treatment option as it is also indicated as first line therapy in EGFR-positive NSCLC patients.

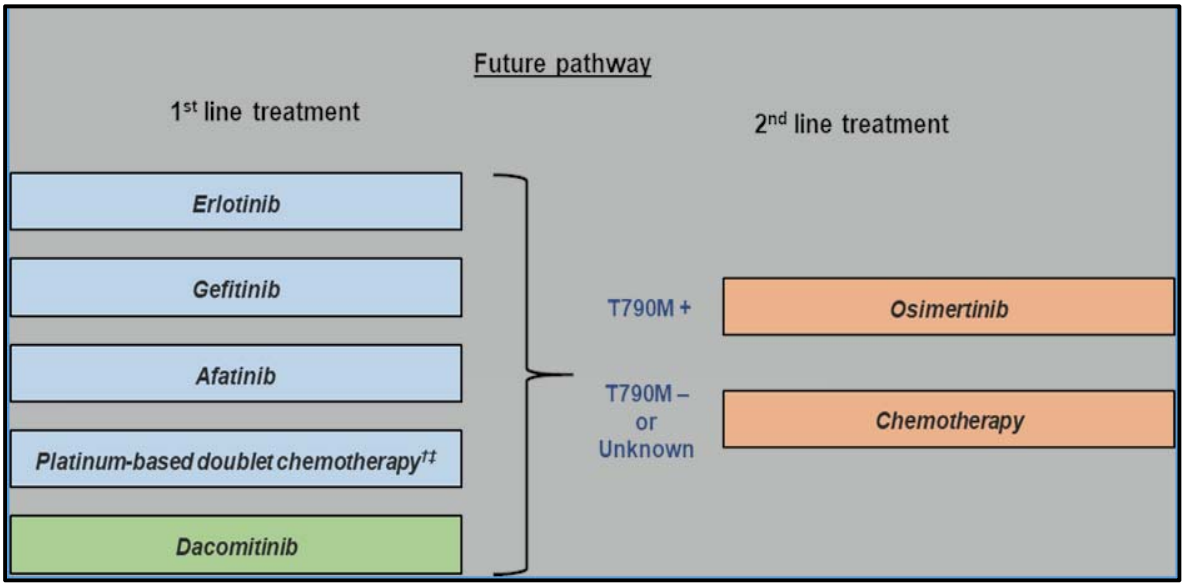


Figure 1: Proposed future position of dacomitinib in the treatment pathway of advanced EGFR+ NSCLC.

†Patients with delayed confirmation of their EGFR-TK mutation-positive status may receive a platinum based doublet chemotherapy regimen in the first-line.
‡Chemotherapy treatment with pemetrexed in combination with either cisplatin or carboplatin is commonly used in clinical practice. For those people for whom treatment with a platinum drug is not appropriate, NICE clinical guidelines recommend single agent therapy with either docetaxel, gemcitabine, paclitaxel or vinorelbine.

3 Critique of company's definition of decision problem

3.1 Decision problem

The company's decision problem is as follows:

- **Population**: People with untreated locally advanced or metastatic NSCLC with EGFR activating mutation(s).
- **Intervention**: dacomitinib
- **Comparators**: afatinib, erlotinib, gefitinib
- **Outcomes**: overall survival (OS); progression-free survival (PFS); overall response rate (ORR); duration of response (DoR); adverse events (AE); health-related quality-of-life (HRQoL).

There are no subgroups in the NICE scope or in the company decision problem, and there are no special considerations. The company's decision problem is consistent with the NICE scope. The evidence presented from the ARCHER 1050 trial has some deviations from the decision problem as summarised in Table 1.

Table 1: Differences between the decision problem and the evidence provided in the CS.

Issue	ERG comments
Population	
The ARCHER 1050 trial population have either exon 19 deletion (del19) or exon 21 L858R (L858R) substitutions.	This is a narrower population than all EGFR mutations as covered in the scope. Clarification A10 confirms that these were the established activating mutations at the time of design of the ARCHER 1050 trial. The ERG clinical advisor states this has been a common eligibility criteria in clinical trials. These two mutations make up approximately 90% of EGFR mutations (clarification response A4) but it is possible that the other mutations have less favourable responses to treatment. The European Medicines Agency (EMA) have published a positive opinion in January 2018 for dacomininib monotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR activating mutations.[9] The ERG notes that the FDA approval for dacomitinib is in EGFR del19 or L858R substitutions specifically.[10]

The ARCHER 1050 trial excluded people with brain metastases.	Estimates vary but clinical advice to the ERG suggests that approximately 15% of NSCLC EGFR mutation positive cases may have been excluded from the trial because they had brain metastases. Brain metastases can adversely affect prognosis and the exclusion of these people may limit the generalisability of the results of the trial to the population of England and Wales. However, trials in other TKIs have also excluded participants with brain metastases and these treatments are still used in some clinical situations in people with brain metastases. The ERG clinical advisor considers that this exclusion was reasonable; however as 20-30% of patients have clinical or radiological evidence of central nervous system disease the ERG notes this limitation in current evidence.
The ARCHER 1050 trial population included a large proportion of Asian participants (77% of the total).	Results may not be wholly applicable to the population in England and Wales. Asian populations have higher rates of EGFR mutations. There is no consistent evidence for the influence of ethnicity on outcomes in EGFR mutation positive NSCLC. This issue is discussed in more detail below.
Comparators	
There is no direct comparison with afatinib or erlotinib. Comparison with afatinib is via an indirect comparison using gefitinib as the common comparator. Comparison with erlotinib is made on the basis of the assumption of similarity between gefitinib and erlotinib.	Based on the known evidence the ERG considers the assumption of equivalence to be reasonable for efficacy (case made by the CS and see Section 4.4) and adverse events (ERG clinical advisor notes that there are differences in profile but severity overall is similar).

The ERG considers the question over the generalisability of the population in the ARCHER 1050 trial to the population of England and Wales to be a central question. The difference in the ethnic mix between the ARCHER 1050 trial and the likely NHS population was acknowledged in the CS (CS B.2.13.3). The CS stated in B.2.7.2 that for OS results were 'numerically' in favour of dacomitinib in both the Asian and non-Asian subgroups of ARCHER 1050, although the ERG notes

(see Section 4.2.3 for more details) that there were no statistically significant effects in either of these subgroups. For PFS on the other hand, the effect was statistically significant in the Asian subgroup but not the non-Asian subgroup. The CS acknowledged that these data were from small and likely underpowered subgroup analyses.

The ERG asked a number of points of clarification with regard to this issue and in particular to assess whether dacomitinib does have a different effect in Asian and non-Asian populations. This was to allow the ERG to consider whether the non-Asian population (23% of the ARCHER 1050 population) would be more relevant to represent the population in England and Wales than the predominantly Asian population in the trial.

The CS section B.2.13.3 states that "clinical expert opinion suggested that studies with a predominately Asian population tend to mirror what is seen in Caucasian patients". In response to clarification question A6, the company qualified this statement by further discussion with UK clinicians which clarified that there is no consensus as to whether ethnicity has a role in prognosis, a view that is shared with the ERG clinical advisor. The company also summarised sub-group analyses of PFS from two clinical trials of afatinib in which there was no clear direction of effect in Asian and non-Asian subgroups.

To explore the sub-group analyses presented by the CS in more detail the ERG requested Kaplan-Meier (KM) plots of OS and PFS in the Asian and non-Asian populations in ARCHER 1050. The company provided these plots and the related median survival estimates and hazard ratios in clarification response A8. These HRs concur with those in the CS Figures 12 and 14 respectively. In both analyses there was a clinical benefit favouring dacomitinib but there was a larger point estimate of HR (indicating less benefit) in non-Asian participants than Asian participants for PFS and a larger point estimate in Asian participants than non-Asian participants for OS. Due to the small patient numbers in these subgroups, the ERG concur with the company that the data should therefore be interpreted with caution. However due to the ongoing debate of ethnicity and treatment efficacy, the ERG notes that there is uncertainty as to whether the observed effectiveness of dacomitinib compared to gefitinib could be expected to be repeated in the UK population.

The ERG reiterates that the population of the ARCHER 1050 trial lack generalisability to the population included in the NICE scope, however, that there is no compelling evidence to suggest that the non-Asian population subgroup data should be used instead of the entire trial population.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS includes a systematic review undertaken to identify published literature on the clinical effectiveness of all first-line treatments in EGFR+ NSCLC (B.2.1.1 and appendix D.1).

4.1.1 Searches

Broad searches were undertaken in relevant databases and other appropriate sources, such as reference lists of identified systematic reviews, relevant conferences and a trial register. No record of the search of the trial register, Clinicaltrials.gov, was included, but this and a list of results prior to selection was provided in response to clarification question A3, although no search date is given. The CS (B.2.1.1) states that searches were undertaken on Oct 2017 and updated in Aug 2018. There appears to be a very slight discrepancy in reporting search dates as the tables in Appendix D give a date of 22 September 2017 for the original searches and no dates for the 2018 update searches. Both the original and update searches were limited to documents published from 2004 onwards and in the English language. Searches included appropriate search terms for the intervention and comparators in the NICE scope (and other comparators), and for NSCLC. In the CS appendix, in table 57 (Search strategy for MEDLINE (Ovid)), there appears to be a small error in reporting relating to exactly which line numbers were combined at steps 26 to 29 (for example, line 27 says '23 not 27', rather than '23 not 26') and a line number is missing between steps 5 and 6. Other tables do not include this reporting error. The use of the filter 'Studies with Results' and to a lesser extent the condition term 'Non Small Cell Lung Cancer' in the search strategy for ClinicalTrials.gov was not appropriate. The ERG undertook an independent targeted search of ClinicalTrials.gov and checked the reference list of a recent NMA.[11]

ClinicalTrials.gov, searched by the ERG 7th February 2019

130 Studies found for: (EGFR) AND (dacomitinib OR gefitinib OR erlotinib OR afatinib) AND (random OR randomized OR randomised) | Active, not recruiting, Completed, Suspended, Terminated, Withdrawn, Unknown status Studies | Lung Cancer OR NSCLC

The ERG identified four studies that should have been identified by the company's searches but were not listed in the submission (Lilenbaum,[12] Chen,[13] Xing,[14] Soria[15]). Two of these would not

have met the company's inclusion criteria, but two were eligible for the feasibility assessment network. However, the absence of these studies does not impact on the results of the CS as they would not connect back to the network and would not have been included in the final NMA. These were:

- Xing 2017 (RECEL trial), erlotinib versus etoposide plus cisplatin with concurrent radiotherapy.
- Soria 2018 (FLAURA) osimertinib versus gefinitib.

The ERG also identified a recent NMA of relevant interventions (Lin 2018),[11] which was excluded by the CS (study design NMA). The ERG checked the included studies for any additional references. The company feasibility network and the Lin 2018 NMA included similar studies, with the following exceptions:

- The CS additionally included Patil 2017 and Han 2017 (both gefinitib vs chemotherapy)
- Lin 2018 additionally included Soria 2018 (FLAURA trial, ostimertinib vs SOC) and Yang 2017 (1st line subgroup gefitib versus erlotinib)

As noted above, the Soria 2018 publication of the FLAURA trial was not identified by the company's searches but is relevant to the broader SLR. The company identified the Yang 2017 study but excluded it as there was no stratification for line of therapy and it was considered a post hoc subgroup. Although the ERG is unclear whether this was fully justified the inclusion of the study would not have affected the NMA as the comparison was between erlotinib and gefitinib (see Section 4.3 [equivalence studies])

4.1.2 Inclusion criteria

CS section B.2.1.2 notes that the systematic literature review (SLR) was originally undertaken from a global perspective (wider range of interventions) and then refined to reflect the decision problem.

Further details of the eligibility criteria for the SLR are presented in Appendix D.1. These include eligibility criteria for the potential comparator studies for the network meta-analysis. The refined eligibility criteria in CS Table 64 (Appendix D.1) cover the treatments included in the decision problem, either as interventions or comparators. The eligibility criteria also state that chemotherapy, best supportive care or placebo and radiotherapy (if in combination with one of the

included interventions) were potential comparators. These are not scoped comparators but were included to permit possible links within the evidence network.

Studies in adults with locally advanced or metastatic EGFR-positive NSCLC that had not previously been treated were included. In CS Appendix D.1.8.1 it states that EGFR was required to have been molecularly selected prior to randomisation. This resulted in exclusions of two relevant trials, IPASS and First-SIGNAL, which reported post-hoc EGFR mutation positive subgroup data. The ERG agrees with these exclusions: IPASS compared gefitinib with carboplatin plus paclitaxel and First-SIGNAL compared gefitinib with gemcitabine plus cisplatin and the EGFR-positive groups were subgroups in both studies. In addition, these studies would not have connected to the network for the comparison of dacomitinib versus gefitinib, erlotinib or afatanib. One relevant trial of dacomitinib versus gefitinib, ARCHER 1050, was included.[1]

As discussed in Section 4.1.1 the ERG notes that one study excluded by the company for intervention (Zhao 2017: erlotinib as first-line therapy + docetaxel and cisplatin as second-line therapy vs docetaxel and cisplatin as first-line therapy plus erlotinib as second-line therapy)[16] actually reported overall response rates after first-line therapy. This would therefore have been eligible for the broader SLR and feasibility assessment. In addition, the CS also excluded a study comparing gefitinib with erlotinib (Yang 2017[17]) because data for first line therapy was from a post-hoc subgroup only. This subgroup may also have been of relevance in the broader SLR but the ERG does not consider this omission will have affected the results or conclusions of the company network meta-analysis (NMA).

Ten comparator trials were included to form a network (presented in CS Figure 15), although most did not connect dacomitinib to the three other treatments of relevance to the decision problem. These trials were summarised in CS Table 65 (Appendix D.1) and were:

- Three trials (ENSURE, EURTAC and OPTIMAL[18-20]) of erlotinib vs. chemotherapy;
- Four trials (Han 2017, NEJ002, Patil 2017 and WJTOG3405[21-24]) of gefinitinb vs. chemotherapy;
- Two trials (LUX-Lung 3 and LUX-Lung 6[25, 26]) of afatinib vs. chemotherapy
- One trial (LUX-Lung 7[27, 28]) of afatinib vs. gefitinib.

CS Table 66 (Appendix D.1) provides summary details of these trials, although their respective population characteristics are not presented.

However, of these potential comparator studies only one study was actually used in the comparison because there were no links between the other studies in the network (discussed in Section 4.3). This study, the LUX-Lung 7 trial[27, 28] included participants who would match the decision problem of the current appraisal (previously untreated adults with stage IIIB or IV NSCLC and EGFR mutation positive). Appendix D.1.7 lists reference details for included studies and excluded studies with reasons.

A PRISMA style flow-diagram with numbers is presented. Not all excluded studies were available in the original CS, but these were subsequently provided in response to clarification request A2. A two-stage study selection process was undertaken (titles and abstract screening, full paper screening) by two independent reviewers with arbitration from a third reviewer if necessary, for the main SLR. The CS does not state how studies were screened out of the network but the exclusions appear appropriate.

4.1.3 Critique of data extraction

The approach to the data extraction is appropriate (data extraction was by two independent blinded reviewers and after reconciling differences a third reviewer could be included to reach consensus for any remaining discrepancies, data were extracted in to a pre-specified extraction form).

4.1.4 Quality assessment

The company assessed the quality of the ARCHER 1050 RCT using NICE recommended criteria (CS Table 15) and the Cochrane risk of bias tool (CS Appendix Table 75). There were some differences in the company's responses between these tools, which are summarised in Table 2. The ERG generally agrees with the company's judgements, and notes the potential performance bias (systematic differences in care or in exposure to other factors) that may arise from the open-label design. The risk of detection bias was considered to be low due to blinded IRC review of PFS and ORR (details of how blinding was achieved was provided in clarification response A12).

There was a higher proportion of women (64.3% vs 55.6%) and people with ECOG PS 0 (33% vs 28%) in the dacomitinib arm compared with the gefitinib arm (Section 4.2). The reason for these imbalances is unclear and could be due to selection bias (despite appropriate procedures in place) or could be due to chance. The CS states that the difference in gender was not unexpected given the higher frequency of EGFR mutations among females than males. However, this does not explain

the imbalance since EGFR mutations were required for inclusion and randomisation should have ensured an even distribution between arms. Gender is a potential prognostic factor (see Section 4.2.1). The CS states that generally there is no difference in outcomes between ECOG PS 0 and 1, citing ARCHER 1050 as evidence. The ERG's clinical advisor noted that PS 0 and 1 are usually grouped together in trials, however there is evidence overall that ECOG PS may be an independent prognostic factor (see Section 4.2). The risk of selection bias is therefore uncertain.

The company gives the trial an overall judgement of high risk of bias due to the open-label design. The ERG agrees with this as the trial has a high risk of performance bias (differences between groups in care provided or in exposure to other factors), but notes that the risk of detection bias and attrition bias is low.

Table 2: Risk of bias assessment of ARCHER 1050.

Assessment criteria	Company response		ERG response (Cochrane tool)
	NICE criteria (CS Table 15)	Cochrane tool (CS Appendix Table 7)	
Method used to generate random allocations adequate?	Yes	Low risk	Low risk
Allocation adequately concealed?	Not applicable[a] Open label study	Low risk	Low risk
Groups similar at the outset of the study in terms of prognostic factors?	Yes	Low risk	Imbalance in gender and PS[b]
Care providers and participants blind to treatment allocation?	Not applicable Open label study	High risk	High risk
Outcome assessors blind to treatment allocation?		Low risk	Low risk
Unexpected imbalances in drop-outs between groups?	No	Low risk [d]	Low risk [d] Differences explained
Were the statistical analyses undertaken appropriate? [c]	Yes		
Evidence to suggest authors measured more outcomes than they reported?	No	Low risk	Low risk
Other bias	NR	Unclear Sponsored by pharmaceutical company	Low risk No other bias apparent
Overall judgement	NR	High risk Open-label	High risk

NR, not reported. [a]The company's response is referring to masking of treatment, rather than concealment of the allocation sequence, which the ERG considered appropriate as a central interactive web response system was used. [b] Potential prognostic factors (although not an item on the Cochrane tool). [c]Question as worded in CS Table 15; the full question should be 'Did the analysis include an intention to treat analysis? If so, was this appropriate and were

appropriate methods used to account for missing data?' [d]Cochrane risk of bias criterion: Attrition bias due to amount, nature or handling of incomplete outcome data.

4.1.5 Overall quality of the CS SR

The ERG's appraisal of the CS systematic review of clinical effectiveness is summarised in Table 3. The systematic review processes were well documented and appear reasonable. Although the evidence presented deviates from the CS decision problem (Section 3), there is a low chance of systematic error in the systematic review.

Table 3: ERG QA of the CS SR.

CRD Quality Item; score Yes/No/Uncertain with comments	ERG response
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Eligibility criteria are presented and appear appropriate.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes. Searches were reasonably comprehensive
3. Is the validity of included studies adequately assessed?	Yes. The ERG generally agrees with the company's judgements
4. Is sufficient detail of the individual studies presented?	Yes. The CS presents sufficient detail.
5. Are the primary studies summarised appropriately?	The CS summarises key characteristics of the relevant trials and the results adequately.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The evidence for dacomitinib is provided by a single pivotal RCT. ARCHER 1050 (NCT01774721) is a company-sponsored phase III, multicentre, open-label RCT comparing dacomitinib with gefitinib. Summary details of the trial are provided in CS section B2.3 to B2.5 and appendices D2 to D4. The trial is reported in two full publications (Wu 2017,[1] Mok 2018[29]) and the outcomes are consistent with the NICE scope. The data cut-off for for PFS was July 2016 and for overall survival was February 2017. It is not clear to the ERG why the PFS data cut was not updated at the time of the OS analysis (see Section 5.2.6 for further details).

The trial was conducted across 71 sites in seven countries, but these did not include the UK (China, Spain, Italy, Japan, Republic of Korea, Poland, Hong Kong). The proportion of participants from European sites was provided in clarification response A11 ([redacted]). Over three-quarters of the trial participants were of Asian ethnicity and therefore the trial was not representative

of the UK population in this regard (see Section 3, and clarification response A7). The prevalence of EGFR mutations is influenced by ethnicity, with higher rates in Asian populations; the implications of this are discussed further in Section 4.6.

The population included in the trial was people with locally advanced or metastatic newly diagnosed, treatment-naïve NSCLC or with recurrent NSCLC. Those with recurrent disease were required to have a minimum of 12 months disease-free interval between completion of systemic therapy and recurrence of NSCLC and must have only completed neoadjuvant/adjuvant therapy previously (prior anti-cancer systemic treatment of early, locally advanced, or metastatic NSCLC, was a reason for exclusion). The trial clinical study report (CSR) shows that [redacted] had recurrent disease in each arm ([redacted]).

Previous radiotherapy for non-target lesions and systemic therapy completed with at least 12 months disease-free interval prior to recurrence was allowed.

Inclusion was limited to people with the del19 *or* L858R EGFR-activating mutations. People with both mutations or with other EGFR mutations were excluded because the implication of double mutation on clinical outcomes was not clear at the time the trial commenced (detail provided in clarification response A10). Although these account for 80-90% of mutations (see Section 2.1), that leaves a proportion of EGFR mutations for which there is no evidence on the effectiveness of dacomitinib. Clinical expert advice to the ERG noted that these other mutations have variable response to different TKIs in preclinical studies, and that del19 mutations have better outcomes and possibly a better response to TKIs. Participants could have concurrent T790M mutations, although this isn't expected to influence outcomes as the proportion would likely be small (likely around 1% at first line).

Other key eligibility criteria are reported in CS Table 5. People with history or evidence of brain metastases were excluded. ERG expert opinion is that this was reasonable and in line with some other trials of TKIs (however, see discussion in Section 3). The ERG clinical advisor also notes that a significant number of patients in clinical practice have a performance status of 2, some 5-15% have mutations other than del19 and L858R, and some have comorbidities such as chronic obstructive pulmonary disaese or cardiac disease, all of which would not have been included in the

ARCHER 1050 trial. However, our clinical advisor notes that these are common exclusions in clinical trials.

Participants were randomised to dacomitinib 45mg orally once daily or gefitinib 250mg orally once daily in a 1:1 ratio. Treatment continued for a maximum of 48 months or until disease progression, intolerable toxicities, withdrawal, death or investigator decision. Dose modifications for dacomitinib to manage treatment-related toxicity were described in CS B.2.3.2.2.

The comparator, gefitinib, is a first-generation TKI and was recommended by NICE in TA192 for first-line treatment of locally advanced or metastatic NSCLC in people with EGFR mutation. The CS notes that this is the first trial to compare TKIs; chemotherapy was the comparator in the pivotal trials of other licensed TKIs (gefitinib, erlotinib and afatinib).

A flow chart of participant numbers was provided in CS Appendix D2. Of 720 patients assessed for eligibility, 63% did not meet inclusion criteria (no further details provided). A total of 452 people were randomised, of these one participant in the gefitinib arm withdrew consent and did not receive treatment. The ITT population included all randomised participants (Section 4.2.2). Overall, a lower proportion of the dacomitinib arm discontinued treatment (71% vs 83% gefitinib) and the study (40.1% vs 46.7% gefinitib). A higher proportion of the dacomitinib arm discontinued treatment due to adverse events (18.1% vs 12.1% see clarification response C1 for details of adverse event by relation to study drug), but a lower proportion discontinued dacomitinib due to progression or relapse (34.8% vs 50.4% gefitinib) or global deterioration of health (defined in clarification A13, 11.5% vs 14.7% gefitinib). The most common reasons for discontinuing the study were death (dacomitinib 33.5% vs gefitinib 40.4%) and refusing further follow-up (dacomitinib 6.2% vs gefitinib 4.4%).

4.2.1 Baseline characteristics of participants of ARCHER 1050 trial.

Table 4 shows the key baseline characteristics of the trial participants. The CS (B.2.3.6) states that the demographic and clinical characteristics were generally similar between the arms of the trial. When comparing the data presented in the trial publication and the CS, there are no errors or differences noted. The ERG has noted that the groups are indeed well-balanced in terms of disease stage at screening and EGFR mutation but note some imbalance in the following characteristics.

Table 4: Baseline characteristics in ARCHER 1050

Baseline characteristic	Dacomitinib N=227	Gefitinib N=225
Male, n (%)	81 (35.7)	100 (44.4)
Female, n (%)	146 (64.3)	125 (55.6)
Age, years, median (range)	62 (28-87)	61 (33-86)
Age, years, mean (SD)	61.2 (11.26)	60.9 (10.17)
White, n (%)	56 (24.7)	49 (21.8)
Black, n (%)	1 (0.4)	0
Asian, n (%)	170 (74.9)	176 (78.2)
Japanese, n (%)	40 (17.6)	41 (18.2)
Mainland Chinese, n (%)	114 (50.2)	117 (52.0)
Other East Asian, n (%)	16 (7.0)	18 (8.0)
Never smoked, n (%)	147 (64.8)	144 (64.0)
Ex-smoker, n (%)	65 (28.6)	62 (27.6)
Smoker, n (%)	15 (6.6)	19 (8.4)
ECOG performance status 0, n (%)	75 (33)	62 (28)
ECOG performance status 1, n (%)	152 (67)	163 (72)
Stage IIIB at screening, n (%)		16 (7)
Stage IV at screening, n (%)	184 (81)	183 (81)
Unknown at screening [a], n (%)	25 (11)	26 (12)
del19, n (%)	134 (59)	133 (59)
L858R, n (%)	93 (41)	92 (41)
[a] Newly diagnosed with stage IV a time of study entry.		

There are more female compared with male participants in both treatment groups. The company has referred to this in their summary and have stated that this was to be expected, given the higher proportion of ECFR mutations in NSCLC occurring in females. Nonetheless, 64.3% are female in the dacomitinib group compared with 55.6% in the gefitinib group. The CS states in section B.2.13.2.2 that gender is not a prognostic factor for PFS in EGFR+ NSCLC, citing the ARCHER 1050 trial as evidence. The ERG has identified evidence which suggests that female gender may be an independent prognostic factor for NSCLC, including in those with EGFR-mutation positive NSCLC, summarised below.[30-33] In addition, evidence suggests that females respond better to

treatment with EGFR TKIs, although the ERG clinical advisor notes the evidence is not clear that female sex is a predictive factor.[34]

All participants were classified as either stage 0 or 1 in terms of ECOG performance status (PS). More participants in the dacomitinib arm (33% vs 28%) were classified as better in terms of performance status (PS 0) compared with the gefitinib group. Although the CS states in section B.2.13.2.2 that ECOG PS is not a prognostic factor, citing the ARCHER 1050 trial, other evidence suggests that the difference between ECOG PS 0 and 1 is significant in terms of patients' overall survival.[33, 35]

A reasonable quality NMA[30] meta-analysed 39 studies that compared overall survival data for women versus men with NSCLC. The populations were very heterogeneous and some studies used univariate analysis whilst others used multivariate. An overall survival advantage was found for women even after allowing for advanced stage disease, proportion with adenocarcinoma and smoking status.

A second meta-analysis[34] also found improved overall survival in women with NSCLC compared with men when combining trials reporting multivariate analysis of overall survival. Moreover, the meta-analysis of PFS from six EGFR TKIs trials found that women had an additional 10% reduction in risk of progression, whereas the analysis of ALK inhibitor trials (n=4) found the benefit was similar for men and women. In contrast, no PFS benefit from Anti-PD1 inhibitors was found in women (5 trials). However, the analyses did not consider ethnicity or smoking status and it is unclear whether all relevant studies were included.

Two primary studies from Taiwan that investigated the effect of gender were also identified by the ERG.[31, 32] Ethnicity was not reported by the studies but having an Asian population they could be considered comparable to ARCHER 1050 and LUX-Lung 7 in this respect. Hsu and colleagues compared stage, age, smoking history and histology between men and women in a prospective cohort study of 695 patients with NSCLC. The study was 4 years duration but median follow-up was not reported. In univariate analyses, younger patients, never-smokers and females had better overall survival. However, in multivariate analysis only age and stage were independent prognostic factors; the female survival advantage in the previous analysis could be attributed to younger age and fewer smokers. Tseng and colleagues conducted a retrospective database review of 11,678 patients with adenocarcinoma to assess the impact of smoking. They found than female gender was

an independent prognostic factor in multivariate analysis in both EGFR-mutant and EGFR-wild type groups.

A retrospective database analysis in Japan [33] included 26,957 NSCLC patients; 21,856 of these had PS 0 or 1 and had a median follow-up of 13.6 years and 9.0 years, respectively. A significant difference in median survival was found between PS 0 and 1 after adjusting for gender, age, smoking status, histology, stage, period of diagnosis, use of radiotherapy, and chemotherapy. Never smoker, early stage, female gender, squamous cell carcinoma histology, and treatment were all independent favourable prognostic factors.

A retrospective case series[35] in Turkey analysed 122 patients with T4 N0-3 M0 (nodule in different lobes, no distant organ metastasis) local advanced NSCLC, 96 of which had PS 0 (n=10) or 1 (n=86). In multivariate analysis, ECOG PS at diagnosis was had a significant impact on overall survival (but not event-free survival), as did age, stage and primary treatment.

Overall, the dacomitinib arm has a higher proportion of potentially favourable prognostic factors in terms of gender and, to a lesser extent, ECOG PS. This could bias the trial in favour of dacomitinib.

ERG summary

The clinical effectiveness evidence for dacomitinib comes from a large multi-centre RCT which has an active comparator with a TKI (gefitinib). There are some potential issues with regard to the generalisability of the trial participants including having no UK sites, a high proportion of Asian participants, limited to two EGFR mutations only (albeit the most common) and the exclusion of people with brain metastases. In addition, there are imbalances in potential prognostic factors between arms.

4.2.2 Trial analysis sets, outcomes and statistics.

The analysis sets in ARCHER 1050 were an Intent-to-treat (ITT) population (dacomitinib N=227; gefitinib N=225); an As-treated (AT) population and Safety Population (dacomitinib N=227; gefitinib N=224) and the Patient-reported outcome (PRO) population (patients from the AT population who started treatment, completed a baseline PRO assessment, and completed ≥1 post-baseline PRO assessment after the first dose; dacomitinib N=226 gefitinib N=222 for baseline

completion of PRO questionnaire; >90% of patients answered all questions for almost all cycles in both treatment groups).

The outcome measures considered were overall survival (OS), progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), adverse events (AE) of treatment and health-related quality-of-life (HRQoL). Definitions were provided for each of these and the ERG does not have any concerns about these outcomes.

The censorship methodology for the primary and secondary outcomes of ARCHER 1050 and the approach to managing missing data were also presented. In terms of the trial statistics, the primary outcome was PFS based on blinded IRC review in the ITT population. Estimates of the PFS curves obtained from the Kaplan-Meier method were displayed graphically. The median (and other quartiles) event time and corresponding 2-sided 95% CI for the median were provided for each treatment arm. Probability of PFS at clinical meaningful time points were estimated and presented with 95% CI based on the Greenwood method. Differences in PFS between treatment arms were analysed by the Cox Regression (i.e. for estimated HR and its 95% CI) and log rank test (1-sided, α=0.025) for 1-sided p-value, both stratified by race and EGFR mutation status based on their values at randomisation. HRs and p-values for PFS in subgroups were estimated from the unstratified Cox regression model and the unstratified log-rank test, respectively. The proportions of patients achieving objective responses were compared between groups using Pearson's χ^2 test.

For the secondary outcomes, a log-rank test, stratified by EGFR mutation status at randomisation and race, was used to assess PFS based on investigator assessment, OS, TTF, and DoR. A Cox proportional hazards model, stratified by EGFR mutation status and race as used in the log-rank test, was used to calculate HRs and 95% CI for OS and TTF in the ITT population and DoR among the objective responders in the ITT population. P-values were determined by the log-rank test with adjustment for the same stratification factors. ORR was summarised along with the corresponding exact 2-sided 95% CI using a method based on the Binomial distribution. The Cochran-Mantel-Haenszel test stratified by race and EGFR mutation status were used to compare ORR between the 2 treatment arms. The relative risk ratio estimator were used to contrast the treatment effects on response rates. A point estimate and a 2-sided 95% CI were calculated using the normal approximation.

The ERG have identified no concerns about the analysis sets; with censorship and management of missing data or the outcome measures used. With regard to the trial statistics, the CS did not justify

why a one-sided p-value was used for PFS and a two-sided p-values for OS and it is unclear to the ERG why there were different data cut-offs for PFS and OS analyses..

For the patient-reported outcomes, repeated measures mixed-effects modelling was used to compare the two treatment groups with respect to the overall change from baseline scores on the EORTC QLQ-C30 and EORTC QLQ-LC13 scales using two-sided tests that were not adjusted for multiple testing. The Kaplan-Meier method was used to estimate the time-to-deterioration of symptoms and compared between treatment groups using the Hochberg-adjusted log-rank test. A sensitivity analysis was conducted without the condition of two consecutive cycles of deterioration, using the same methods and summary statistics.

It is unclear why the results of the PROs were not adjusted for multiple testing (the result of not adjusting for multiple testing could be an increased likelihood of finding "significant" results which are actually false positives, i.e. the null hypothesis is really true, and the significant result due to chance). This issue was raised by the FDA reviews and they concluded that all PRO analyses were considered exploratory since they did not have a prespecified multiplicity adjustment.

4.2.3 Summary results from ARCHER 1050

The ERG report summarises the blinded IRC results where reported (the ERG considers these to be the most valid); investigator-assessed results can be viewed in the CS and are generally consistent with the blinded IRC analyses except where noted. The key results are summarised in Table 5.

Table 5: Summary of ARCHER 1050 results.

Outcome	Dacomitinib N=227	Gefitinib N=225
PFS (blinded IRC)		
Patients with PFS event, n (%)	136 (59.9)	179 (79.6)
Median PFS, months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI), P-value (1-sided)	0.59 (0.47, 0.74), p<0.0001	
OS		
Deaths, n (%)	103 (45.4)	117 (52.0)
Median months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI), P-value (2-sided)	0.76 (0.58, 0.99), p=0.044	
BOR (blinded IRC)		
Complete response, n (%)	12 (5.3)	4 (1.8)
Partial response, n (%)	158 (69.6)	157 (69.8)

Stable, n (%)	30 (13.2)	27 (12.0)
Progressive disease, n (%)	12 (5.3)	15 (6.7)
Intermediate, n (%)	15 (6.6)	22 (9.8)
Objective response rate (CR plus PR), n (%)	170 (74.9)	161 (71.6)
95% exact CI	(68.7, 80.4)	(65.2, 77.4)
DoR (blinded IRC)		
Number with a response (CR or PR), n (%)	170 (74.9)	161 (71.6)
Median, months (95% CI)a	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)
Stratified HR (95% CI)	0.40 (0.31, 0.53) p<0.0001	
Descriptive summary of response duration (months), n	170	161
Mean (standard deviation)	12.78 (7.68)	9.17 (5.55)
Median (range)	12.02 (0.0-34.3)	8.11 (0.0-32.2)
Time to treatment failure (blinded IRC)		
Median, months (95%CI)	11.1 (9.2, 14.6)	9.2 (7.6, 9.4)
Stratified HR (95% CI), 1-sided p-value	0.67 (0.54, 0.83), p<0.0001	

[a]Kaplan-Meier estimates of response duration (months) quartiles (95% CI), based on the Brookmeyer-Crowley method.
BOR = best overall response; CI = confidence interval; CR = complete response; DoR = duration of response; HR = hazard ratio; INV = investigator assessment; IRC = independent review committee; ITT = intent-to-treat; PFS = progression-free survival; PR = partial response.

Survival

Median follow-up for PFS based on blinded IRC review was 22.1 months (dacomitinib) and 23.0 months (gefitinib) (CS Table 71, CSR). A statistically significant improvement was found in the primary outcome, PFS assessed by blinded IRC, with dacomitinib compared with gefitinib [median 14.7 months vs 9.2 months, HR 0.59 (95% CI 0.47, 0.74) p<0.0001] (Table 5). PFS at 12 months for dacomitinib vs gefitinib was 55.7% (95% CI 48.5, 62.3) vs 35.9% (95% CI 29.3, 42.4) and at 24 months was 30.6% (95% CI 23.8, 37.5) vs 9.6% (95% CI 5.6, 15.0). The Kaplan-Meier plot is presented in CS Figure 4. Investigator-assessed PFS results were similar (CS Table 16, CS Figure 5).

Median follow-up for OS was 31.1 months (dacomitinib) and 31.4 months (gefitinib). Median survival improved with dacomitinib compared with gefitinib [median 34.1 months vs 26.8 months, HR 0.76 (95% CI 0.58, 0.99), p=0.044]. The Kaplan-Meier plot is presented in CS Figure 6. OS at 30 months for dacomitinib vs gefitinib was 56.2% (95% CI 49.0, 62.8) vs 46.3% (95% CI 39.3, 53.1).

The ERG notes discrepancies in the HRs reported for the ITT population between of the primary and subgroup analyses in the CS, this is discussed in the subgroup analyses results below.

Response rate and duration

There was no statistically significant difference in the objective response rate (complete response + partial response) for dacomitinib compared with gefitinib [74.9% (95% CI 68.7, 80.4) vs 71.6% (95% CI 65.2, 77.4), p=0.194] assessed by blinded IRC (Table xx). The investigator-assessed ORR was similar (CS Table 16), although the proportion in the dacomitinib arm assessed by investigators as having a complete response was slightly lower than by blinded IRC review ([redacted] vs [redacted]), and the proportion with a partial response higher ([redacted] vs [redacted]).

The median duration of response by blinded IRC review was significantly longer in the dacomitinib arm compared with gefitinib [Kaplan-Meier estimates of response duration quartiles 14.8 months vs 8.3 months, HR 0.40 (95% CI 0.31, 0.53), p<0.0001]. The Kaplan-Meier plot is presented in CS Figure 7, and in CS Figure 8 for investigator assessment.

Time to treatment failure

The median time to treatment failure according to blinded IRC review was statistically significantly longer with dacomitinib compared with gefitinib [11.1 months (95% CI 9.2, 14.6) vs 9.2 months (7.6, 9.4); HR 0.67 (95% CI 0.54, 0.83), 1-sided p-value <0.0001)]. Kaplan-Meier plots for blinded IRC review and investigator assessment are presented in CS Figures 9 and 10, respectively.

Health-related quality of life

Response rates for the patient reported outcomes (PRO) were described as high, with over 90% completion for most cycles. Results are reported for the PRO analysis set (Section 4.2.2). Disease-related symptoms assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13 (cough, dyspnoea, pain in chest, pain in arm or shoulder, pain in other parts, fatigue) reduced in both groups (CS Figure 11); only the reduction in chest pain was significantly greater with dacomitinib than gefitinib (-10.24 vs -7.44, p=0.024). There was no adjustment to the significance level for multiple testing (Section 4.2.2).

The treatment-related symptoms assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13, diarrhoea and sore mouth, both worsened significantly more with dacomitinib compared with

gefitinib, and these changes were considered clinically meaningful (diarrhoea: 19.88 vs 7.32, p<0.0001; sore mouth 15.09 vs 3.51, p<0.0001; CS Figure 11).

There was a small improvement in global quality of life that was not clinically meaningful in either group, although it was statistically significantly better with gefitinib than with dacomitinib (4.94 vs. 0.2, p=0.0002).

There were no differences between treatments in time to deterioration (time from randomisation to the first time a patient's score showed a ≥10 point increase from baseline) for individual disease-related symptoms or the composite of symptoms [HR 1.17 (95% CI 0.93, 1.48), p=0.5327].

The CS presents absolute values for the EQ-5D-3L VAS and utility index and the difference between treatments (CS Table 18). The ERG assumes that these are end of study values, however this is not clearly stated. EQ-5D results are not reported in the trial publication [1] (and only the baseline VAS scores are reported in its Appendix). The CS refers to changes from baseline*: "Changes from baseline in the EQ-5D visual analogue scale (VAS) were small and not clinically meaningful in either treatment group, although gefitinib was associated with a significantly greater change from baseline than dacomitinib in VAS and utility index scores"*, however change scores are not presented in CS Table 18. Statistically significant differences in the absolute VAS score and utility index were observed in favour of gefitinib (Table 6).

Table 6: EQ-5D-3L absolute scores (PRO Population)

	Dacomitinib (n=224)	**Gefitinib (n=221)**	**Difference**
VAS	Baseline: 73.1 (SD 19.6) [redacted]	Baseline: 74.7 (SD 17.6) [redacted]	Baseline: -1.6 [redacted]
Utility index	[redacted]	[redacted]	[redacted]

EQ-5D = European Quality of Life-5 Dimensions; PRO = patient-reported outcome; VAS = visual analogue scale.
[a]Assumed by ERG.

ERG summary

Dacomitinib led to improvements in survival outcomes (PFS and OS) compared with gefitinib at the latest data cuts, although this favourable effectiveness was not always mirrored in other

secondary outcomes (for example ORR, HRQoL) when ERG-preferred blinded IRC assessments were used.

Subgroups

The NICE scope did not specify any relevant subgroups. The CS presents subgroup analyses based on pre-specified baseline characteristics for PFS (blinded IRC: CS Figure 12, investigator assessment: CS Figure 13) and overall survival (CS Figure 14).

A consistent effect was seen in most subgroups, with two exceptions where the hazard ratio favoured gefitinib (but was not statistically significant): i) blinded IRC review and investigator assessed PFS in the age category ≥75 years, although the very small sample size is noted. Overall survival was not presented for this age category (< 65 years; ≥65 years only presented). ii) overall survival for baseline ECOG PS 0. Tests of interaction for PFS were provided in clarification response A9 and were non-significant with the exception of the Asian versus non-Asian subgroup. The tests of interaction for overall survival were not statistically significant in all cases, although the authors of the 2018 publication note that the study was not designed to have sufficient power to test interaction.[29] As discussed in Section 3 the Asian and non-Asian subgroups showed a consistent effect for OS, and a statistically significant effect in the Asian subgroup, but not the non-Asian subgroup, for PFS. These subgroups should therefore be viewed with caution.

The CS also presented blinded IRC review PFS and OS for the subgroup who received dacomitinib dose reductions compared with the overall dacomitinib arm (CS Figures 26 and 27, respectively), but not the dacomitinib subgroup without dose reductions. Both PFS and OS were slightly higher, but not statistically significantly different, in the subgroup with dose reductions compared with the overall dacomitinib arm [PFS: 16.6 months (95% CI 14.6, 18.6) vs 14.7 months (95% CI 11.1, 16.6); OS: 36.7 months (95% CI 32.6, NR) vs 34.1 months (95% CI 29.5, 37.7)]

The ERG notes discrepancies in the HRs for the whole population OS between CS Figure 6 (discussed above) and CS Figure 14, and between the HRs for the whole population IRC PFS in CS Figure 4 (discussed above) and CS Figure 12. For investigator PFS, CS figures 5 and 13 match. These differences may be due to stratification. For example, the footnotes to CS figures 4 and 5 refer to a stratified Cox Regression (although the stratification factor for race seems to differ) and the text relating to CS figure 6 states stratified analysis (there is no footnote to CS figure 6). However, the text relating to CS figure 4 and 5 states 'unstratified log-rank test', even though CS

figure 4 states 'stratified p-value based on the stratified long-rank test'. CS figures 12 and 13 state 'unstratified log-rank test' but this was not stated for CS figure 14.

ERG summary: no subgroups were specified in the NICE scope. However, it would appear that overall, the company's subgroups showed similar results to the whole population analyses, although caution is required given the small sample sizes of many of the subgroups.

Adverse events

The median duration of treatment was longer in the dacomitinib arm ([redacted] weeks, range [redacted]) compared with the gefitinib arm ([redacted] weeks, range [redacted]); no adjustment was made to adverse event frequency data.

The CS presents a summary of adverse events in CS Table 23 for all-cause adverse events and treatment-related adverse events, although it omits treatment-related adverse events leading to dose reductions and leading to temporary discontinuation. The ERG has sourced these from the CSR (Table 7).

Table 7: Summary of adverse events

Adverse event	Dacomitinib N=227	Gefitinib N=224	Dacomitinib N=227	Gefitinib N=224
	All-causality AEs, %		Treatment-related AEs, %	
AE	99.6	98.2	[redacted]	[redacted]
SAE	27.3	22.3	[redacted]	[redacted]
AE Grade 3/4	[redacted]	[redacted]	[redacted]	[redacted]
AE Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
AE Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
AE Grade 5	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to dose reduction[b]	66.1	8.0	[redacted]	[redacted]
AE leading to temporary discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to permanent discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

[a] CSR Table 38. [b] Dose reduction to manage toxicity due to AE(s) is described in the protocol as every other day dosing for gefitinib. AE = adverse event; SAE = serious adverse event.

All-cause adverse events leading to permanent discontinuation were presented in CS Table 28. A similar proportion of people in both groups experienced any all-cause (99.6% vs 98.2%) and treatment-related adverse events [redacted]. Serious adverse events were slightly higher

in the dacomitinib group (all-cause: 27.3% vs 22%[redacted]), and a higher proportion of the dacomitinib group experienced grade 3 adverse events [redacted]. However, grade 4 adverse events were low and similar between groups [redacted]. There were [redacted] deaths due to treatment-related adverse events in each arm.

More people in the dacomitinib group experienced adverse events leading to a dose reduction (all-cause: 66.1% vs 8.0%[redacted], temporary discontinuation [redacted], or to a lesser extent, permanent discontinuation [redacted]. The protocol for dose reduction differed between treatments: dacomitinib participants had dose reductions of the daily dose whereas gefitinib participants had the dose maintained and the frequency reduced to every other day. Treatment-related adverse events are summarised in Table 8.

Table 8: Treatment-related adverse events occurring in [redacted] of patients

Adverse event, %	**Dacomitinib N=227**				**Gefitinib N=224**			
	Grade(s)				**Grade(s)**			
	1–2	**3**	**4**	**5**	**1–2**	**3**	**4**	**5**
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.								

The most common grade 1-2 adverse events related to dacomitinib were diarrhoea ([redacted]), paronychia (nail infection, [redacted]), stomatitis (mouth inflammation, [redacted]) and dermatitis acneiform (skin reaction, [redacted]). For gefitinib these were diarrhoea ([redacted]), increase in aspartate transaminase (AST; [redacted]) and alanine transaminase (ALT; [redacted]) (associated with liver toxicity), and dermatitis acneiform ([redacted]). The most common grade 3 adverse events related to dacomitinib were acneiform ([redacted]), diarrhoea ([redacted]) and paronychia ([redacted]), while those related to gefitinib were and increase in ALT ([redacted]) and AST ([redacted]). All-causality adverse events are presented in CS Table 24 and follow a similar pattern.

Specific adverse events resulting in dose reductions, temporary discontinuation and permanent discontinuation are presented in CS Tables 26, 27 and 28, respectively. The most common all-cause adverse events leading to dose reduction were dermatitis acneiform (20.3%), paronchyia (16.7%) and diarrhoea (8.4%) for dacomitinib and increased ALT (2.7%) and AST (2.2%) for gefitinib. The median time to dose reduction was 2.8 months (Inter-quartile range, IQR, 1.3–4.2 months) for dacomintib, with a median duration of 11.3 months (IQR 4.8–18.9 months). The median time to dose reduction for gefitinib was 3.3 months (IQR 2.4–4.2 months); median duration 5.2 months (IQR 2.5–7.9 months). Temporary discontinuation of dacomitinib resulted most commonly from dermatitis acneiform ([redacted]), paronchyia ([redacted]) and diarrhoea ([redacted]), and of gefitinib due to increased ALT ([redacted]) and AST ([redacted]). Treatment-related adverse events leading to permanent discontinuation of dacomitinib included dermatitis acneiform ([redacted]) and diarrhoea ([redacted]), and those leading to permanent discontinuation of gefitinib included increased ALT ([redacted]).

ERG summary: overall there were similar rates of all-cause and treatment-related adverse events between dacomitinib and gefitinib. However, there were higher rates of any all-cause and any treatment related Grade 3 adverse event and serious adverse event with dacomitinib (based on observation of the proportions only), and dose reductions or temporary discontinuations were more frequently observed with dacomitinib.

4.2.4 Other dacomitinib trials

The ERG identified five additional trials of dacomitinib 45 mg once daily in NSCLC to inform the evidence base on adverse events (dose escalation studies were not considered). One of these[36] was undertaken in treatment naive patients, the rest were undertaken in previously treated patients therefore a different patient population to the NICE scope (Table 9).

- Phase 2 single-arm study (NCT00818441) of dacomitinib in advanced NSCSC (adenocarcinoma subtype) as first-line treatment.[36]

- ARCHER 1009 (NCT01360554): Phase 3 RCT of dacomitinib vs erlotinib in locally advanced or metastatic NSCLC, previously treated with one or two previous regimens of chemotherapy.[37]

- NCIC CTG BR.26 (NCT01000025): Phase 3 RCT of dacomitinib vs placebo in advanced or metastatic NSLCC previously treated with up to three previous lines of chemotherapy and either gefitinib or erlotinib.[38]

- Phase 2 RCT (NCT00769067) of dacomitinib dacomitinib vs erlotinib in advanced NSLC and one or two prior chemotherapy regimens for advanced disease.[39]

- Phase 2 single-arm study (NCT00548093) of dacomitinib in advanced stage NSCLC after failure of prior chemotherapy and erlotinib.[40]

Consistent with ARCHER 1050, dermatitis acneiform and diarrhoea were the most common grade 3 or higher adverse events across the trials, with rates varying slightly. Rates of grade 3 paronychia were lower in these trials, ranging from 1-4%, compared with 7.5% in ARCHER 1050. Serious adverse events, where reported, appeared more often in the phase 3 placebo-controlled trial of dacomitinib, however these also occurred in 36% of the placebo group.[38]

In summary, adverse events in the wider evidence base of dacomitinib in NSCLC are consistent with those in ARCHER 1050. This summary reflects that of the FDA risk review of dacomitinib which concluded that dacomitinib's adverse event profile is similar to other EGFR TKI agents used to treat NSCLC.

Table 9: Adverse events in other dacomitinib trials in NSCLC

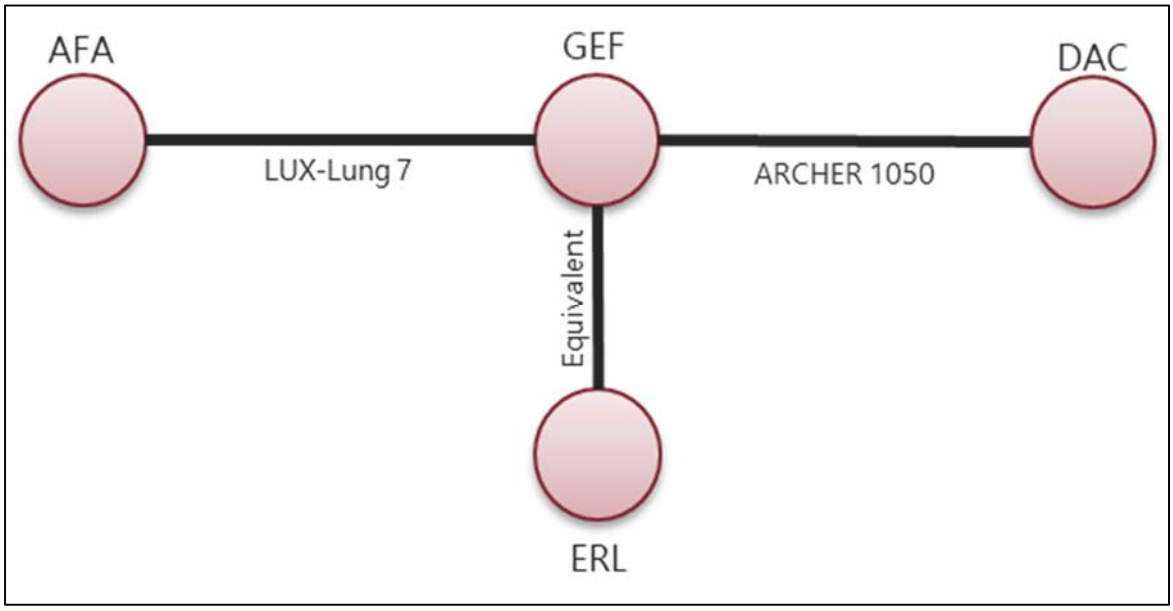
	Phase 2 single-arm[a] [36]	ARCHER 1009[37]		NCIC CTG BR.26[38]	Phase 2 RCT[39]		Phase 2 single arm [40]
	n=89	Dacomitinib n=432	Erlotinib n=436	Dacomitinib n=477	Dacomitinib n=93	Erlotinib n=94	Dacomitinib n=66
Adverse events, grade ≥3, %	NR	Grade 3: 29 Grade 4: 2 Grade 5: <1	Grade 3: 21 Grade 4: <1 Grade 5: <1	NR	NR	NR	Grade 3/4: 27
Most frequent AEs grade ≥3, %	Dermatitis acneiform: 18 Diarrhoea: 15	Diarrhoea: 11 Rash: 7 Stomatits: 3	Rash: 3 Decreased appetite: 3 Diarrhoea: 2	Diarrhoea: 12 Acneiform rash: 10	Diarrhoea: 12 Dermatitis acneiform: 11 Paronychia: 3	Dermatitis acneiform: 6 Diarrhoea: 4	Diarrhoea: 12 Dermatitis acneiform: 6
Serious AEs, %	NR	12	9	39	NR	NR	18[b]

[a] 54 patients started on 30mg/day. [b]States none was treatment related. NR: not reported.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As stated in Section 4.1.2 the ERG agrees that none of the other trials identified in the SLR and the broader network are relevant to the current assessment. The NMA compared dacomitinib to afatinib. The common comparator was gefitinib which had been the comparator treatment in the ARCHER 1050 and LUX-Lung 7 trials. The LUX-Lung 7[27, 28] trial compared of afatinib with gefitinib in previously untreated EGFR mutation positive adults with stage IIIB or IV NSCLC.

No formal comparison with erlotinib was made as there was no trial that linked in the network and the CS therefore made the assumption that erlotinib and gefitinib were clinically equivalent based on previous NICE committee discussions. The ERG has identified five systematic reviews that despite some differences in their included studies (related to differences in eligibility criteria) generally show no significant differences between gefitinib and erlotinib (see Appendix Table 16). The ERG therefore consider that the treatments are likely to be equivalent and that the assumption in the CS is therefore reasonable. The resulting evidence network is presented in Figure 2 which is a reproduction of CS Figure 16.



Abbreviations: AFA = afatinib; DAC = dacomitinib; ERL = erlotinib; GEF = gefitinib.

Figure 2: Evidence network for the indirect comparison.

4.3.1 The LUX-Lung 7 trial

The CS presents a risk of bias assessment of the LUX-Lung 7 trial in CS Appendix Table 75. The ERG agrees with most of the company's assessments (Table 10), but notes the absence of reporting of one of the pre-specified outcomes (time to objective response) indicating potential reporting bias. The ERG also notes the higher proportion of women in the gefitinib arm compared with afatinib (67% vs 57%). This difference may be due to chance, but as discussed previously gender may be a prognostic factor, therefore the risk of selection bias is uncertain. The company gives the trial an overall judgement of high risk of bias due to the open-label design. The ERG agrees with this as the trial has a high risk of performance bias (differences between groups in care provided or in exposure to other factors), but notes that the risk of detection bias and attrition bias is low.

Table 10: Risk of bias assessment of LUX-Lung 7.

	Company judgement	ERG judgement
Sequence generation	Low risk	Low risk
Allocation concealment	Low risk	Low risk
Important baseline imbalance	Low risk No significant differences in baseline characteristics between arms	Imbalance in gender. No statistical testing
Blinding of participants and researchers	High risk	High risk
Blinding of outcome assessment	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk
Selective reporting	Low risk All outcomes measured were reported	High risk Time to objective response not reported
Other bias	Unclear risk Trial sponsored by pharmaceutical company	Low risk No other bias apparent
OVERALL JUDGEMENT	High risk This trial was open-label	High risk

Table 11 shows the key baseline characteristics of patients included in LUX-Lung 7. Overall, in terms of age, race, smoking status, ECOG performance status, disease stage and EGFR mutation, the characteristics of patients in each arm of the LUX-Lung 7 trial are balanced. There was a difference of 10 percentage points in the proportion of males and females, with fewer women in the afatinib group. However, despite potential for better survival and response to EGFR tyrosine kinase inhibitors in women as discussed above, the afatinib group still had improved outcomes compared with gefitinib.

Table 11: Baseline characteristics in LUX-Lung 7.

Baseline characteristic	**Afatinib N=160**	**Gefitinib N=159**
Male, n (%)	69 (43)	53 (33)
Female, n (%)	91 (57)	106 (67)
Age, years, median (range)	63 (30-86)	63 (32-89)
White, n (%)	48 (30)	54 (34)
Black/African American, n (%)	1(1)	0
Asian, n (%)	94 (59)	88 (55)
Missing[a], n (%)	17 (11)	17 (11)
Never smoked, n (%)	106 (66)	106 (67)
Light ex-smoker[b], n (%)	21 (13)	19 (12)
Other current or ex-smokers, n (%)	33 (21)	34 (21)
ECOG performance status 0, n (%)	51 (32)	47 (30)
ECOG performance status 1, n (%)	109 (68)	112 (70)
Stage IIIB at screening, n (%)	8 (5)	3 (2)
Stage IV at screening, n (%)	152 (95)	156 (98)
Exon 19 deletionc, n (%)	93 (58)	93 (58)
Leu858Arg, n (%)	67 (42)	65 (41)
Leu858Arg + Exon 19 deletion, n (%)	0	1 (1)

[a]Patient recruited in French sites did not have their ethnic origin recorded. [b] Less than 15 pack years and stopped more than one year before diagnosis. [c]One patient in the afatinib group with wild-type EGFR was erroneously included in the trial and was reported as exon 19 deletion at the time of randomisation by the investigator.

The ERG has summarised the key results from the LUX-Lung 7 trial in Table 12 alongside those of ARCHER 1050 to allow an overview of the gefitinib results (as the common comparator in the indirect comparison) from both trials. Median PFS and TTF in the gefitinib arm of ARCHER 1050 were less than in LUX-Lung-7 giving a bigger difference between gefitinib and dacomitinib. However median OS and ORR were higher in the gefitinib arm of ARCHER 1050 than in LUX-Lung 7.

The LUX-Lung 7 authors note that ORR in the gefitinib arm (56%) was somewhat lower than in previous phase 3 trials (62% to 74%, investigator review) but do not provide an explanation. The proportion of adverse events grade ≥ 3 were comparable in the gefitinib arms between trials, with both trials finding increased ALT/AST the most common event. It is possible that these differences are in part a reflection of differences in the participant characteristics, see discussion below on transitivity in the NMA.

Table 12: Comparison of key results in ARCHER 1050 and LUX-Lung 7.

	ARCHER 1050		LUX-Lung 7	
Outcome	**Dacomitinib n=227**	**Gefitinib n=225**	**Gefitinib n=160**	**Afatinib n=159**
Median PFS, months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)	10.9 (9.1, 11.5)	11.0 (10.6, 12.9)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)	24.5	27.9
Objective response rate (CR plus PR), %	74.9	71.6	56	70
Median DOR, months (95% CI)	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)	8.4 (IQR 6.2, 13.1)	10.1 (IQR 5.6, 16.8)
Median TTF, months (95%CI)	11.1 (9.2, 14.6)	9.2 (7.6, 9.4)	11.5 (10.1, 13.1)	13.7 (11.9, 15.0)
Adverse events, grade ≥3, %	Grade 3/4: [redacted] Grade 5: [redacted]	Grade 3/4: [redacted] Grade 5: [redacted]	52	57
Most frequent AEs grade ≥3, %	Dermatitis acneiform: 14 Diarrhoea: 8 Paronychia: 7	ALT increase: 8 AST increase: 4	ALT/AST increase: 9 Rash/acne: 3	Diarrhoea: 13 Rash/acne: 9 Fatigue: 6
[a] CSR Table 38.				

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Methodology of the NMA

Although the NMA undertaken by the company has only included two RCTs, it represents a key component of the present appraisal as it allows the indirect comparison of dacomitinib to one of the comparators in the decision problem (afatinib). Hence, the ERG has critically appraised the methodology of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency.

The periods of enrolment for the two trials were December 2011-August 2013 and May 2013-March 2015 in Lux-Lung 7 and ARCHER respectively. The ERG considers these relatively similar. CS Appendix Table 70 compares the key patient characteristics in the trials across all four treatment groups. The CS states that characteristics were equally distributed both between trial arms within each trial and across trials, and that there was no statistically significant difference in baseline characteristics within any given trial.

The ERG agrees that the populations in ARCHER 1050 and LUX-Lung-7 trials are fairly comparable, although there are differences in race [LUX-Lung-7 has a higher proportion of white participants (23% vs 32%) and a lower proportion of Asian participants (77% vs 57%), with race unknown in 11%] and LUX-Lung 7 did not exclude brain metastases (16% of participants had brain metastases at baseline).

There is a very slight imbalance in the proportions with stage IV disease (including at study entry, see Table 13) between trials (approximately 92.5% in Archer 1050 and 96.6% in Lux-Lung 7). The proportion of 'never' smokers was similar between trials, however current or ex-smokers were categorised differently between the trials so cannot be compared.

Table 13: Comparison of key baseline characteristics in the two trials in the NMA

Trial Name	ARCHER 1050		LUX-Lung 7	
Arm	**Dacomitinb**	**Gefitinib**	**Afatinib**	**Gefitinib**
N	227	225	160	159
Median Age, years	62	61	63	63
Males, %	36	44	43	33
Asian, %	75	78	59	55
ECOG 0, %	33	28	32	30
ECOG 1, %	67	72	68	70
Brain Metastases, %	0	0	16	15
Stage IV, %	81[a]	81[a]	95	98
Never smoker, %	65	64	66	67
Del 19, %	59	59	58	58
L858R, %	41	41	42	42

[a] Proportion at screening; in addition, 11% of dacomitinib and 12% of gefitinib were classified as 'unknown' but were newly diagnosed with stage IV a time of study entry.

Transitivity assumption

The CS did not explicitly assess the transitivity assumption and whether it was violated. If this assumption is compromised or does not hold, the consistency assumption can also be violated, which can lead to biased estimates from the NMA.

There is no formal test to determine whether the transitivity assumption does hold. However, this can be examined looking at the distribution of population characteristics that are effect modifiers across the treatment comparisons of a network.

As previously indicated, the included RCTs had populations with notable differences in terms of proportion with the presence of brain metastases and the proportion of Asians and a very slight imbalance in terms of severity. In the example of the proportion of Asians across the two trials, in the ARCHER 1050 trial, subgroup analyses by ethnicity (Asians vs non-Asians) suggest potential differences of effect in the dacomitinib versus gefinitib comparison for PFS. Given these differences in baseline characteristics the ERG considers that there is the potential that transitivity assumption is violated.

Consistency assumption

In the absence of any closed loops formed in the network, the consistency between direct and indirect comparisons cannot be assessed.

Proportional hazards

The CS assessed the proportional hazards assumption through log cumulative hazard plots and Schoenfeld residual analysis for PFS and OS in the ARCHER 1050 and LUX-Lung 7 trials. The CS concluded that the proportional hazards assumption was violated for OS in ARCHER 1050 and was potentially violated for PFS in LUX-Lung 7. As there was potential for violation in at least one of the trials, the company undertook a fractional polynomial (FP) analysis which they considered that it reduced the risk of bias in the NMA. This was described in CS B.2.9.2 and Appendix D.6. A traditional indirect comparison was also undertaken as a scenario analysis. This was described in CS Appendix D.7.

Fractional polynomial NMA

The FP NMA differs from a traditional NMA in that that it fits hazard ratios that can vary over time rather than being constant. This approach was used to obtain relative effect estimates of PFS and OS for afatinib and dacomitinib compared to gefitinib, which was modelled using a generalised gamma curve to the data observed in ARCHER 1050.

FPs are able to model behaviour that traditional parametric approaches may not be able to capture. However, there is danger that FPs will over-fit and as a result, any extrapolations made may be implausible.

The company explored fitting first and second order FP models to the PFS and OS outcome data for the relevant trials, in line with the methodology suggested by Jansen 2011[41]. The company digitised graphs to recreate IPD from the LUX-Lung 7 trial, and analysed this alongside the data from ARCHER 1050. They fitted models in a Bayesian framework, with suitably vague priors and compared model goodness-of-fit using the deviance information criterion (DIC), where a difference of more than 5 units from the lowest scoring model as initially used to reduce the number of models taken into further consideration.

For PFS, the company presented the survival curves from the seven FP models that had DIC scores within 5 units of the lowest DIC, all of which were applied to a generalised gamma fitted to the gefitinib arm of ARCHER 1050. The best fitting FP model to the PFS data resulted in a pessimistic extrapolation for dacomitinib, resulting from a sharply increasing hazard ratio from around 2 years. The company then chose the second best fitting model and concluded that these results were plausible.

For OS, the company applied a similar approach, but found that none of the models within 5 DIC of the best fitting model provided a plausible extrapolation for dacomitinib and afatinib. This was reportedly the case for all second-order FP models used and so the company focused on the single order FP models. The company chose the best fitting single order model as they felt it provided plausible estimates.

The company does not provide detailed results from their FP-NMA nor any interpretation, only presenting goodness-of-fit statistics, estimates of mean and median survival, and graphs of survival and hazard ratios. It is unclear whether the company has concluded that there is a statistically significant difference between any of the comparators or not based on this analysis.

The ERG has concerns over the use of FP by the company. Whilst they appear to be implemented correctly, FPs may not be suitable for extrapolating due to their tendency to over-fit, as well as to be influenced by tail data. This is supported by the large number of models that the company was forced to exclude due to the implausible hazard ratios estimated.

While the FP analysis may be suitable for drawing inference on the observed period of the trials, caution should be taken due to the possibility of overfitting to tail data. It is, thus, unclear whether the FP analysis is suitable for extrapolation of PFS and OS in this appraisal.

Traditional NMA

As noted above, the CS undertook a traditional NMA using the Bucher method[42] using gefitinib as the common comparator. This preserves the randomisation within the included trials. The CS states that the baselines characteristics between the two included trials were generally well balanced. As noted above the ERG considers there is a potential for the transitivity assumption to be violated. The CS hazard ratios from the NMA for PFS (independent review) and OS are presented in CS Tables 80 and 81 respectively. While the CS states that an indirect treatment comparison was undertaken, the ERG has noted that the findings from this indirect comparison were neither presented in the main report, nor in the CS Appendix. In addition, no HR (for OS or PFS) of afatinib relative to dacomitinib were visible in the cost-effectiveness model. In order to bring more clarity, the ERG has therefore undertaken an indirect treatment comparison for PFS and OS. The data used for the indirect comparison can be seen in Table 14.

Table 14: Data included in the ERG NMA.

Trial name	Treatment	Comparator	PFS			OS		
			HR	95%CI		HR	95%CI	
ARCHER 1050	Dacomitinib	Gefitinib	0.59	0.47	0.74	0.76	0.58	0.99
Lux-Lung 7	Afatanib	Gefitinib	0.74[1]	0.57	0.95	0.86	0.66	1.12

[1]In the original submission the CS used HR of 0.73 from an earlier data cut of the Lux-Lung trial; 0.74 is available in the supplementary files of the most recent publication.[28].

The ERG undertook a fixed-effect NMA using the network package on STATA (frequentist framework). We generated the surface under the cumulative ranking curve (SUCRA) to rank each intervention. The SUCRA denotes the probability of an intervention being superior in effectiveness, here expressed in terms of diminishing the risk of progression or death (PFS), and the risk of death (OS).

Results for the indirect comparison between dacomitinib and afatinib are shown in the league table (Table 15) with regards to PFS and OS. In the absence of closed loops within the network (no mixed direct and indirect evidence), the results from the comparisons for afatinib versus gefitinib and dacomitinib versus gefitinib are unchanged compared to those reported in the previous table (pairwise comparisons).

Table 15: ERG NMA league table

PFS HR (95%CI)				
Drug	**SUCRA**	**Dacomitinib**	**Afatinib**	**Gefitinib**
Dacomitinib	0.95		0.80 (0.57-1.12)	0.59 (0.47-0.74)
Afatinib	0.55			0.74 (0.57-0.95)
Gefitinib	0.00			
OS HR with 95%CI				
Drug	**SUCRA**	**Dacomitinib**	**Afatinib**	**Gefitinib**
Dacomitinib	0.86		0.88 (0.61-1.29)	0.76 (0.58-0.99)
Afatinib	0.58			0.86 (0.66-1.12)
Gefitinib	0.06			

For PFS, analyses based on SUCRA values suggest higher probability that dacomitinib is superior to afatinib but there is no significant difference between the two drugs (PFS HR 0.80; 95% CI 0.57-1.12).

As for PFS, OS analyses based on SUCRA values suggest higher probability that dacomitinib is superior to afatinib but there is no significant difference between the two drugs (OS HR 0.88; 95% CI 0.61-1.29).

In summary, there were greater SUCRA values for dacomitinib with respect to both survival outcomes, however there was no statistically significant difference between dacomitinib and afatinib.

Given the potential violation of transitivity assumption which was previously emphasized, these analyses must be viewed as exploratory.

ERG summary

The CS adequately describes the methods of their NMA approaches and provides a justification for using the FP analysis which the ERG considers to be reasonable. However, the ERG has concerns over the use of the FP analysis, in particular with respect to the extrapolations (see Section 5.2.6 below) but also because there are no detailed results or interpretation of the findings. In addition, the CS does not adequately assess the included study populations for transitivity and the ERG considers that the transitivity assumption may be violated. Finally, the CS does not present results of the indirect comparison between dacomitinib and afatinib. Although caution is recommended in the interpretation of the ERG analyses these show no significant differences between the two respective treatments.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work carried out by the ERG has been described under the relevant subheadings above (see Section 4.2.3 for ERG summary of adverse events from other dacomitinib trials; Table 12 for comparison of key results between ARCHER 1050 and LUX-Lung 7 trials; and Section 4.4 for ERG's indirect comparison of dacomitinib and afatinib via the traditional NMA).

4.6 Conclusions of the clinical effectiveness section

A reasonable quality systematic review identified a single relevant trial which compared dacomitinib with gefitinib in EGFR-positive NSCLC. The ERG did not identify any other trials of relevance to the decision problem for effectiveness but did identify other trials of dacomitinib for safety outcomes. The included trial, ARCHER 1050, had a high risk of performance bias owing to the open label design and there are imbalances in potential prognostic factors between arms. A statistically significant improvement in the primary outcome of PFS was found in favour of dacomitinib and some, but not all, secondary outcomes also favoured dacomitinib. There were higher rates of some adverse events with dacomitinib. The ERG has raised some issues with the trial statistics that should be considered when interpreting the results of the trial.

As there was no trial evidence comparing dacomitinib to either erlotinib or afatinib, an NMA was undertaken to compare dacomitinib to afatinib. The CS made a reasonable assumption that erlotinib is equivalent to gefitinib. There are a number of areas of uncertainty in the NMA including whether the

populations in the two trials were homogeneous enough to be compared and the suitability of the results to the extrapolations required for the cost-effectiveness analysis.

The CS stated that patient characteristics of the ARCHER 1050 trial were representative of the intended population, however, the ERG believes the trial population may not be generalisable to the population in England and Wales. The ERG requested further details to allow a comparison of the demographic characteristics from ARCHER 1050 and the intended population to be made (clarification A7). The company responded that no UK specific information was identified, and noted that patient characteristics were similar to those in other clinical trial populations and these had been acknowledged at recent [NICE technology appraisal] committees as being broadly generalisable. The ERG notes that the population of ARCHER 1050 was limited to the two most common EGFR mutations and excluded people with brain metastases, who would make up a reasonable proportion of EGFR-positive NSCLC cases in first-line clinical practice. There was also a high proportion of Asian participants. There is no consistent evidence for the influence of ethnicity on outcomes in EGFR mutation positive NSCLC, including from the company's own subgroup analyses, but the ERG notes uncertainty as to whether the observed effectiveness of dacomitinib compared to gefitinib could be expected to be repeated in the UK population.

5 COST-EFFECTIVENESS

This section describes and critiques the following comparisons, which were presented in the CS:

- Dacomitinib with confidential PAS discount put forward by the company versus comparators (afatinib, erlotinib and gefitinib) with PAS discounts calculated and assumed to be true by the company (presented in the main body of the Company Submission (CS) and appraised below, in Section 5.3.1.)
- Dacomitinib at list price versus comparators at list price (presented in the CS Appendix M and appraised in Section 5.3.2. below)

During communication with the NICE Technical Team for this appraisal, it was requested and agreed that a further comparison should be carried out and presented in the ERG report:

- Dacomitinib with the company's PAS discount versus the gefitinib, erlotinib and afatinib at list prices (not presented in the CS, reported in Section 5.4 below).

In addition, the ERG has prepared a Confidential Appendix, which is provided as a separate document and focuses on the comparison between:

- Dacomitinib with confidential PAS discount applied by Pfizer versus comparators with confirmed confidential PAS discounts provided by NICE.

In the ERG's opinion, the latter comparison—reported in the Confidential Appendix accompanying this report—is likely to be the most relevant and informative for decision making.

5.1 ERG comment on company's review of cost-effectiveness evidence

The company undertook a systematic review of the cost-effectiveness literature to identify studies post 2012 that reported the results of economic analyses for people receiving treatment for EGFR mutation-positive advanced/metastatic NSCLC.

The company provided an appropriate description of the cost-effectiveness systematic review, which included the search strategy, inclusion/exclusion criteria, and a synopsis of the studies included in the review. On clarification the company also provided with reason those studies excluded from the review.

5.1.1 Search strategy

Searches were conducted on 1 August 2018 in a range of relevant databases (MEDLINE (PubMed), Embase (Ovid), The HTA Database and NHSEED via the Cochrane Library (Wiley), EconLIT

(EBSCO)). The methods used were similar to those used in a previous submission for the same condition.[43] Searches were limited to records identified as published after 1 January 2012, in English. Certain publication types (editorials, letters and commentaries) and records with terms for animals (unless they also included terms for humans) were excluded.

In addition, five relevant conferences, NICE and the Scottish Medicines Consortium websites and reference lists of relevant systematic reviews were searched. No record of a search of Clinicaltrials.gov is included, although searches in this source are mentioned in CS appendix G (section G.1.3). Database search terms were optimised for sensitivity, combining a suitable range of terms for NSCLC and cost-effectiveness.

5.1.2 Inclusion criteria

A summary of the inclusion criteria used to identify potentially relevant studies is presented in Table 16 below.

Table 16: Eligibility criteria for cost-effectiveness searches.

Category	Definition
Patient population	Adults (≥18) with locally advanced (stage IIIb) or metastatic (stage IV) EGFR+ NSCLC previously untreated with systemic cancer therapies (i.e. receiving first-line therapy)
Interventions	Dacomitinib
Comparator	• Erlotinib • Gefitinib • Afatinib
Outcomes	• QALYs/DALYs/LYG (total and incremental) • Costs: total, drug costs, other costs (per arm) • ICERs: cost per QALY/DALY/LYG, cost per event avoided
Study type	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses • Cost-consequence analyses • Systematic reviews of any of the above (included at the abstract review stage, then excluded following hand-searching of their reference lists at the full-text review stage)
Language of publication	English language
Limitations	Studies published before 6 March 2012
DALY, disability life-years; EGFR, epidermal growth factor receptor; ICERs, incremental cost-effectiveness ratio; LYG, life years gained; NSCLC, non-small cell lung cancer; QALY, quality adjusted life-years.	

5.1.3 Included studies

Of the 6714 titles/abstracts screened, 31 publications representing 28 unique studies were included in the review, with three studies being health technology assessment (HTA) monographs and three being Scottish Medical Consortium (SMC) submissions, published after 2012. The majority of the publications identified were abstracts, while one study[44] was a full publication. All of the studies identified assessed the cost-effectiveness of treatments for a population of patients with EGFR mutation-positive NSCLC; however, none of the studies identified included dacomitinib as a comparator. Table 17 reports the economic characteristics and results of the studies included in the systematic review.

The company's systematic review of the published cost-effectiveness studies describing dacomitinib as a first-line treatment for EGFR M+ with advanced/metastatic NSCLC did not identify any relevant references. The ERG are satisfied with the company's systematic review and are confident that the company has not missed any relevant cost-effectiveness studies that included dacomitinib.

Table 17: Summary of the key characteristics of the cost-effectiveness studies identified

Author	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Outcomes	Results
Chouaid et al., 2017[44]	EGFR positive with advanced/metastatic NSCLC	Afatinib compared to gefitinib	French National Health Authority; 10 years	Partitioned survival model with monthly cycle lengths	Progression-free, progressed and dead	Lux-Lung 7 trial	Chouaid et al. 2013	LYG and QALYs	ITT population: approximately €45,200 per QALY. PSA showed that afatinib compared to gefitinib had a probability of 1 of being cost-effective at WTP thresholds > €70,000 per QALY
TA258[45]	EGFR positive with advanced/metastatic NSCLC	Erlotinib compared to gefitinib	NHS and PSS; 10 years	Semi-Markov with monthly cycle lengths	Progression-free, progressed disease and dead	EURTAC trial	Nafees et al. 2008	LYG and QALY	The ICER for erlotinib compared to gefitinib is approximately £21,900 per QALY. PSA showed that erlotinib compared to gefitinib had a probability of 0.63 of being cost-effective at a WTP threshold of £30,000 per QALY
TA310[43]	EGFR positive with advanced/metastatic NSCLC	Afatinib compared to gefitinib and erlotinib	NHS and PSS; 10 years	Partitioned survival model with monthly cycle lengths	Progression-free, progressed and dead	LUX-Lung 3 trial, and mixed treatment comparison	LUX-Lung trial, Chouaid et al. 2012, Nafees et al. 2008	LYG and QALYs	The ICER for afatinib compared to erlotinib was approximately £10,100 per QALY gained, whilst it was approximately £17,800 per QALY for the comparison between afatinib and gefitinib. PSAs were redacted.
TA192[46]	EGFR positive with advanced/metastatic NSCLC	Gefitinib compared to chemotherapy	NHS and PSS; 5 years	Markov state transition model with 21-day cycles	Progression-free (stable disease), progression-free (treatment response), disease progression (2nd line docetaxel or erlotinib or BSC) and dead	Mixed treatment comparison	Nafees et al. 2008	QALYs	The ICER for gefitinib compared to gemcitabine/cisplatin was approximately £28,600 per QALY. At a WTP threshold of £30,000 per QALY, there was a 0.18 probability of gefitinib likely to be cost-effective when compared to gemcitabine/carboplatin

EGFR, epidermal growth factor receptor; NHS, National Health Service; LYG, life years gained; NSCLC, non-small cell lung cancer; PSA, probabilistic sensitivity analysis; PSS, personal social services; QALY, quality adjusted life-years; WTP, willingness-to-pay

5.1.4 Systematic review of studies reporting resource use and costs.

The company's systematic review of relevant studies reporting information on resource use and costs is in the form of an update of a previous review. Briefly, the company identified a recent systematic review conducted in March 2017,[47] and updated/extended the search contained in it to cover the remaining period until August 2018. The search was restricted to studies published in English that reported resource use and costs from a UK perspective. A wide range of cost and resource use terms were included in the database searches. However, database searches may have missed some studies because they included terms for the stage of the disease (advanced/metastatic) and a basic set of UK search terms (a more sensitive, validated UK geographic search filter for Medline is available[48]). From the 82 titles/abstracts screened, one study[49] was identified. The main objective of this study was to describe the rate of neutropenic sepsis in people with NSCLC treated with docetaxel monotherapy following relapse after first-line therapy in a 'real world' UK clinical setting. Additionally, other objectives were to document the resource use and costs associated with the management of NSCLC patients with confirmed or suspected neutropenic sepsis.

5.1.5 Systematic review of HRQoL studies

The company performed a systematic review to identify relevant HRQoL evidence for use in the submitted cost-effectiveness analysis. This was an update of a previous systematic review which was conducted in March 2017 to inform the submission for TA529.[47]

Searches were carried out on 1 August 2018 in a range of relevant databases (MEDLINE (Ovid), Embase (Ovid), CDSR, DARE, CENTRAL, The HTA Database and NHSEED via the Cochrane Library (Wiley), EconLIT (EBSCO)). Searches were limited to records identified as published after 1 January 2017. A list of the eligibility criteria used by the company can be seen in Table 18. In addition, five relevant conferences, NICE and the Scottish Medicines Consortium websites and reference lists of relevant systematic reviews were searched. Database searches combined a suitable range of terms for NSCLC, but were less sensitive than the searches undertaken for the clinical and published cost-effectiveness studies reviews because they included terms for the stage of the disease (advanced/metastatic) and a number of specific HRQoL terms (e.g. "utility values" OR "utility scores" rather than utilit*).

Table 18: Eligibility criteria for inclusion in the utility review.

PICOS Domain	Inclusion criteria	Exclusion criteria
Patient population	Adults (≥18) with locally advanced (stage IIIb) or metastatic (stage IV) NSCLC. Advanced or metastatic lung cancer patients could be the focus of the study or could alternatively be a subgroup of a broader lung cancer patient population, as long as results were presented separately for the advanced or metastatic lung cancer patients specifically.	• Patients without advanced or metastatic lung cancer • Patients only identified as having lung cancer • A mixed patient population by disease stage, with results not presented separately for advanced or metastatic lung cancer patients • Populations with other cancers • Adolescents and children
Intervention(s)	None specified	
Comparator(s)	None specified	
Outcome measures	Health state utility as measured by one of: • Any generic QOL scale with established utility scoring or • A direct measure of health state utility such as TTO or SG	• No health state utility data • Health state utilities not presented by stage of disease • Health utilities not presented by line of treatment • Health state utility data not "novel" (e.g. the study was a cost-utility study, with utilities obtained from the literature)
Study design	• Studies reporting directly-elicited utility values and utility decrements • Observational studies that measured HRQoL and utilities (or utility decrements) • RCTs of treatments for NSCLC, where the investigators collected HRQoL data as the primary or secondary outcome measure, and from which utility estimates were collected using validated elicitation measures (e.g. EQ-5D, SF-6D) • SLRs of any of the above (included at the abstract review stage, then excluded following hand-searching of their	• Non-specific systematic literature reviews or meta-analyses • Editorials or notes or letters to the editor • Studies containing no primary data • Studies which do not report utility or disutility scores from a validated instrument • Conference abstracts which do not report utility values

	reference lists at the full-text review stage)	
Restrictions	• English language	• Non-English language articles • Date of publication prior to 17 March 2017
EQ-5D, EuroQol five dimensions; HRQoL, Health-related quality of life; NSCLC, Non-small-cell lung cancer; QOL, quality of life; RCTs, randomised controlled trials; SF-6D, Short-Form Six-Dimension; SG, standard gamble; SLR, systematic literature review; TTO, time trade-off.		

5.1.6 Results

The company performed a systematic review to identify relevant health quality of life evidence for use in the cost-effectiveness analysis. This was a search updating a previous systematic that was conducted in March 2017 to inform the submission for TA529.[47] The search for TA529 identified 33 publications resulting in 22 separate studies eligible for inclusion.

In the updated search, three publications covering three unique studies and three HTA submissions were identified for inclusion.

- Nafees et al. (2008)[50] used a questionnaire which had been adapted and validated by clinical experts from an existing metastatic breast cancer health state questionnaire, to describe metastatic NSCLC patients receiving second-line treatment. Standard gamble interviews were performed with 100 members of the UK general public to elicit societal utility values for various stages of NSCLC and grade III-IV toxicities associated with treatment. Utility values of 0.653 for stable disease and no side effects, and 0.473 with progressive disease were derived.

- Labbé et al.[2] sought to derive health state utility scores using the EQ-5D-3L questionnaire in a longitudinal cohort of 475 Canadian outpatients diagnosed with metastatic lung cancer across various disease states (EGFR, anaplastic lymphoma kinase [ALK], SCLC, wild-type NSCLC). Varying follow up time occurred between patients with a median of 12 months (range: 0-201 months) post-diagnosis. Utility values obtained for the EGFR population (n = 112/475) using UK preference weights elicited through time-trade off (TTO)[51] stable on most appropriate treatment (TKI) 0.77±0.02 and 0.64±0.03 for progressive disease.

- Huang et al., (2017)[52] evaluated the cost-effectiveness of pembrolizumab compared with standard-of-care (SoC) platinum-based chemotherapy as first-line treatment in patients with metastatic non-small-cell lung cancer (NSCLC). They used EQ-5D values obtained from patients in the KEYNOTE-024 randomised controlled trial which consisted of patients aged ≥18 years (mean age 64 years) with a diagnosis of stage IV NSCLC but specifically without EGFR-activating mutations or ALK translocations. Time-to-death utilities from pooled treatment groups were reported but despite use of EQ-5D-3L it was unclear which population-based preference weights were applied to generate utilities.

The systematic review also identified three NICE Technology Appraisal documents: TA483[53], TA484[54] and TA520,[55] which were fully reported on in Appendix H of the company submission.

5.1.7 Conclusions

The company's systematic review of the published cost-effectiveness evidence assessing dacomitinib as a first-line treatment for EGFR M+ with advanced/metastatic NSCLC did not identify any relevant cost-effectiveness studies. The ERG are satisfied with the company's systematic review and are reasonably confident that there are no relevant cost-effectiveness studies that include dacomitinib as a comparator in the specific patient population. Additionally, we are satisfied that the company undertook a systematic review to identify studies reporting resource use, costs and HRQoL information, and we consider these reviews to have used appropriate methods.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

As part of their submission to NICE, the company made available a detailed description of their economic analysis and a partitioned survival model developed in Microsoft Excel®. A combined summary and critique of the inputs and methods employed in the submitted economic analysis is presented in the following sections.

5.2.1 NICE reference case checklist

The ERG have undertaken an evaluation of the CS in relation to the NICE reference case. Findings are summarised in Table 19 below.

Table 19: NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Defining the decision problem	The scope developed by NICE	Decision problem clearly stated and is in line with the scope developed by NICE
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for this population	Dacomitinib is being compared to gefitinib, erlotinib or afatinib
Patient group	As per NICE final scope, the population refers to: People living with advanced NSCLC	As per NICE final scope
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes between the technologies being compared	15-year time horizon
Synthesis of evidence on outcomes	Systematic review	Systematic review was undertaken by the company
Outcome measure	Quality adjusted life-years	Results reported in terms of quality adjusted life-years
Health states for QALY	Described using a standardised and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
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	The company undertook PSA and reported these results
Sensitivity analysis		The company undertook a range of sensitivity analyses.

HRQoL; health-related quality of life; NHS; National Health Service; NICE; National Institute for Health and Care Excellence; NSCLC; non-small cell lung cancer; PSA; probabilistic sensitivity analysis; QALY, quality-adjusted life years;

5.2.2 Model structure

The company constructed a partitioned survival model to show the experience of a cohort treatment naïve participants with locally advanced or metastatic non-small cell lung cancer with activating mutations in epidermal growth factor receptor (EGFR) who may undergo treatment with dacomitinib compared to gefitinib, erlotinib or afatinib. Partitioned survival modelling considers the progression-free survival curve and the overall survival curve directly, with the time in progression calculated using the difference in area between the two curves (see Figure 3). The company's model is characterised by three health states: progression-free, post-progression (progressed disease) and dead. Figure 4 shows the illustrative model structure.

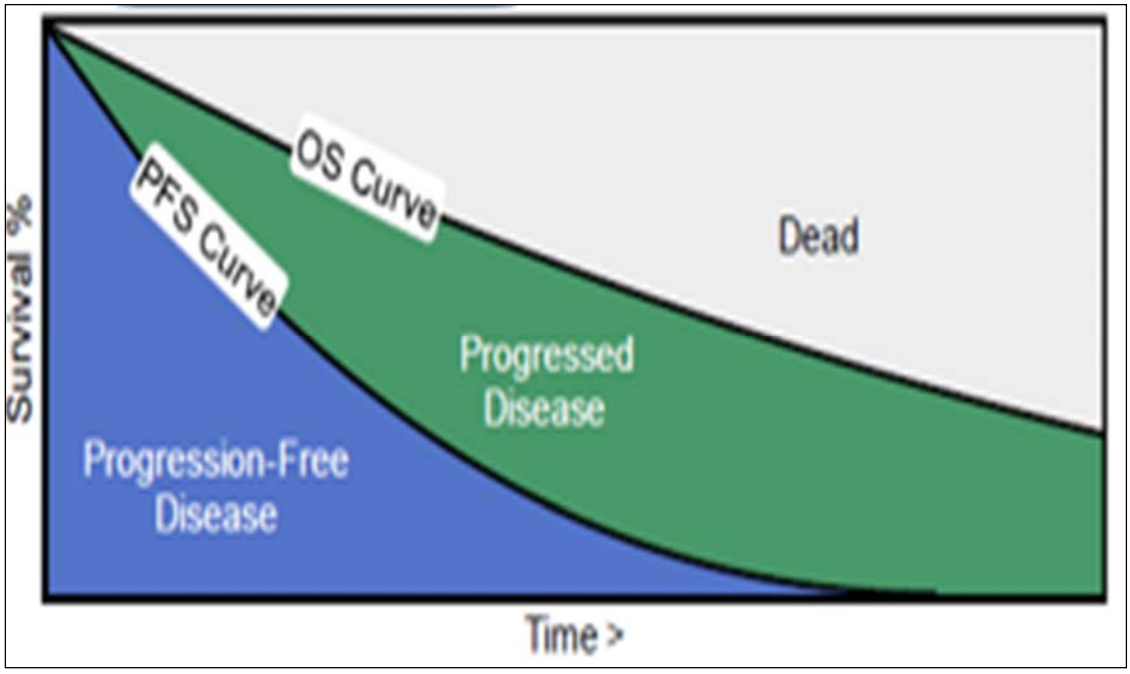


Figure 3: Illustrative survival model (obtained from the CS)

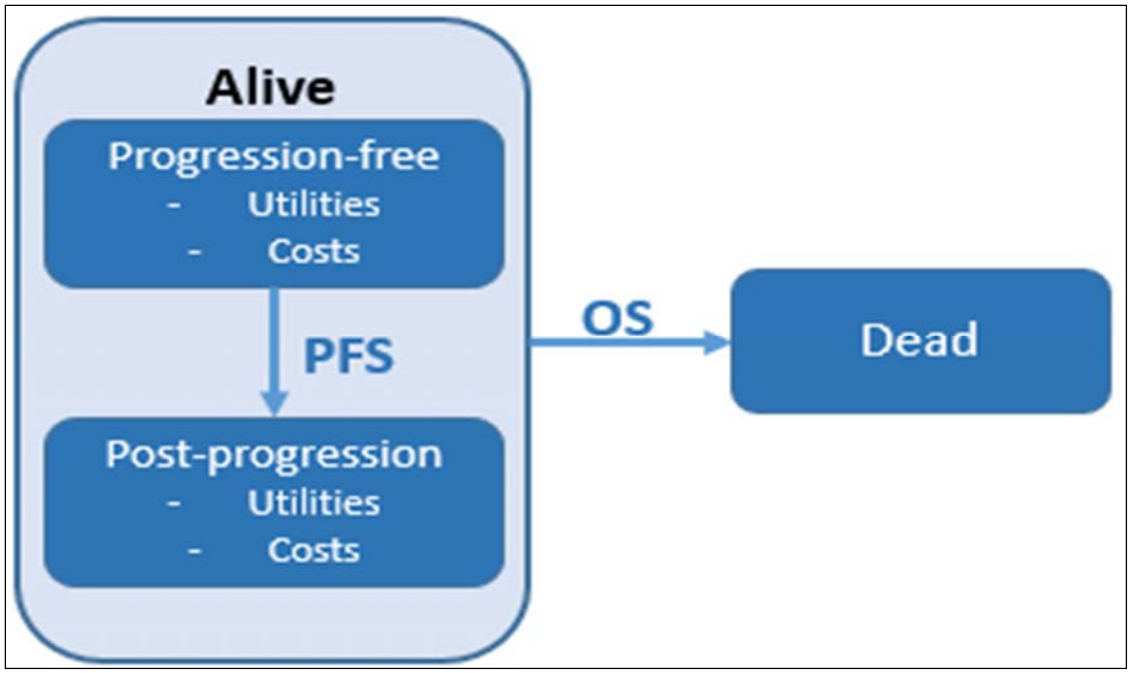


Figure 4: Illustrative model structure (obtained from the submission)

The model started from a hypothetical cohort of people, all of whom began in the progression-free health state. Over time, people were at risk of progression or death. Transitions between health states was unidirectional and occurred at the end of each 28-day cycle, where people remained in the same health state or progressed. Each cycle, people incurred costs and accrued benefits (QALYs) depending on the health state they occupied. A half-cycle correction was applied in the base-case and the model concluded at a 15-year time horizon.

ERG summary

The partitioned survival model appears to capture the key important features (overall survival and progression-free survival) of people living with locally advanced or metastatic NSCLC with EGFR. However, it should be noted that model does not capture survival following second and third-line treatment directly or separately. Instead, time in post-progression survival was derived using the area under the curve approach; the difference in the survival between overall and progression-free survival. The 28-day cycle length is adequate to capture the changes to the disease over short periods of time.

5.2.3 Population

The expected EMA marketing authorisation is for treatment-naïve people with locally advanced or metastatic NSCLC with activating mutations in EGFR. The population modelled was based on the participants in the ARCHER-1050 phase III clinical trial. In the ARCHER 1050 trial participants were randomised to dacomitinib or gefitinib. Details of the patient characteristics in the ARCHER 1050 trial are presented in Section 4.2.1. Patients in the modelled cohort had an average starting age of 62 years with 60% being female, which reflected some of the characteristics of people included in ARCHER 1050. An average body surface area of 1.75m^2 was used to estimate the dosing for second and third-line treatment. This was calculated based on the weighted average by gender of males 1.89m^2 and females 1.65m^2. In general, the ERG was satisfied that the population modelled resembled the patient participants included in the ARCHER 1050 trial.

Upon request at the clarification stage, the company further provided an updated model that allowed for subgroup analyses to be undertaken separately for the Asian and non-Asian sub-populations.

5.2.4 Intervention and comparators

First line treatment

The company's base-case analysis evaluated the cost-effectiveness of dacomitinib compared to gefitinib, erlotinib and afatinib. In the model, the dosing schedule for people receiving dacomitinib was 45mg/day, and the comparators: gefitinib was 250mg/day, erlotinib 150mg/day and afatinib 40mg/day. All drugs taken orally and in keeping with their marketing authorisation.

Subsequent treatments

Following disease progression, it was assumed that 71% and 48% of people would receive second- and third-line treatment, respectively. This assumption is based on participants who would be unable or unwilling to receive subsequent treatment. It was assumed that 60% of people who were treated with first- or second-generation tyrosine-kinase inhibitors (TKIs) would develop the T790M mutation and would receive second-line treatment, with majority receiving osimertinib. The company further stated that a proportion of people would have false negative tests or there would be difficulties with obtaining a sample for a biopsy. All other participants received platinum doublet chemotherapy. For third-line treatment, participants who received osimertinib treatment, then received platinum doublet chemotherapy and for those who received second-line platinum doublet chemotherapy, then received docetaxel.

Table 20: Second- and third-line treatments.

Subsequent treatment	Proportion of people receiving second- and third-line treatment	
	Second-line (%)[a]	Third-line (%)[b]
Osimertinib	56%	-
Platinum doublet chemotherapy	44%	56%
Docetaxel	-	44%
[a] model assumed that 71% of people who progressed received second-line treatment [b] model assumed that 48% of original cohort received third-line treatment		

ERG summary

The comparators included in the base-case analysis were considered to be appropriate to be compared against dacomitinib, and in line with the NICE scope for treatment of first-line EGFR+ patients. All comparators were in keeping with their marketing authorisation and licensed dosing schedule. Also, the ERG considers that the subsequent treatments following first-line treatment to be appropriate. However, it was not clear what strategy/methods that were used to identify the EGFR-T790M mutation to guide subsequent treatment decisions.

5.2.5 Perspective, time horizon and discounting

The perspective/viewpoint of the analysis is that of the NHS and personal social services (PSS) perspective, which is in line with the NICE Guide to the Methods of Technology Appraisal.[56] The model assumes a 15-year time horizon, which is long enough to capture the long-term costs and benefits of treatment. This time horizon reflects the maximum life expectancy of the cohort predicted by the base-case parametric survival analysis, where <1% of the cohort were alive at 15 years under the company's base-case assumptions. In the base-case, costs and benefits are discounted at a rate of 3.5% per annum. A number of sensitivity and scenario analyses were undertaken by the company. The company presented sensitivity results based on changes made to the time horizon of the economic analysis, annual discount rates for costs and benefits.

ERG Summary

The perspective, time horizon and discount rates chosen by the company are in line with the NICE recommendations,[56] and are appropriate to the decision problem.

5.2.6 Treatment effectiveness and extrapolation

Four clinical outcomes from ARCHER 1050 were used to inform the transitions between health states in the model:

- Progression-free survival
- Overall survival
- Adverse events of treatment
- Health-related quality of life

5.2.6.1 Time-to-event extrapolation

The company chose to extrapolate both PFS and OS using a combination of parametric and fractional polynomial (FP) models. A generalised gamma model was fitted separately to both the observed PFS and OS data of the gefitinib arm of ARCHER 1050 and extrapolated across the model time horizon. The data used for PFS extrapolation was obtained from Wu et al. (data cut July 2016),[1] whereas the OS data came from Mok et al. (data cut February 2017).[29]

Equivalent efficacy was assumed between gefitinib and erlotinib, whereas for afatinib and dacomitinib, time-varying hazard ratios of their relative effects to gefitinib were estimated using a FP network meta-analysis (NMA). The hazard ratios were then applied to the generalised gamma extrapolation of gefitinib to predict PFS and OS for dacomitinib and afatinib. The ERG have concerns over this approach, as the resulting extrapolations from FP models can be unstable and extremely implausible. The company encountered this during their model selection process, and excluded many FP models based on their implausibility. FP models offer benefits to traditional parametric curves when fitting to survival data with unusual hazard profiles, but it is unclear whether they offer a benefit when extrapolating.

5.2.6.2 Progression-free survival

The company selected a parametric curve for gefitinib through consideration of visual fit, goodness-of-fit statistics and clinical plausibility. They also compared predicted quantiles to those observed in ARCHER 1050. The parametric models had a similar visual fit, and the goodness-of-fit statistics suggested that the Weibull, log-logistic and generalised gamma were the best fitting to the data. The company's clinical experts stated that whilst the 3-year estimates for the log-logistic and log-normal were too optimistic, the 5-year estimates were realistic. The log-logistic and log-normal

curves were similar, with log-normal having higher PFS estimates for the first four years, but lower predictions beyond this. Across the time horizon, the log-normal had a slightly lower estimate for mean PFS.

The company opted for the generalised gamma, despite stating that its 3 and 5 year PFS estimates were too low when examined by their clinical experts. They also explored using a log-normal curve as an alternative scenario.

The extrapolations were compared to external sources of data: LUX-Lung 7[28], WJTOG 3405[57] and Lin 2016[58]. Note that the PFS population from ARCHER 1050 and LUX-Lung 7 had high levels of censoring and so their long-term follow-up is not complete. In general, the LUX-Lung 7 population were broadly similar to ARCHER 1050, perhaps slightly unhealthier, as mentioned in the ERG critique of the company's NMA. The WJTOG 3405[57] population appear healthier as they generally had a lower ECOG score and less had stage IV disease. Lin 2016[58] had the unhealthiest population due to the proportion of patients with brain metastases and the fact that a large number of patients entered the study on 2nd or later line of therapy. A comparison of the best three fitting models and log-normal, alongside the external sources of PFS data are shown in Table 21.

Table 21: Predictions for gefitinib PFS

Distribution	**Mean**	**Median**	**Proportion progression-free at**			
			2 years	**3 years**	**4 years**	**5 years**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050[1] (n=225)	-	9.23	9.6%	-	-	-
LUX-Lung 7[28] (n=159)	-	10.9	7.75%	4.92%	-	-
WJTOG 3405[57] (n=86)	-	9.6	12-14%	6-7%	6-7%	6-7%
Lin 2016[58] (n=137*)	-	12.1	16%	8.9%	3.6%	0%

*Patients received either gefitinib or erlotinib. Values in this table were extracted before the half cycle correction was applied. All entries in this table are based on the company's initial submission which used PFS data from Park 2016, and not Paz-Ares 2017.

It is apparent that the pessimistic extrapolations for PFS correspond with the increasing hazard function, which results from the generalised gamma model, as shown in Figure 5. The ERG suggest a decreasing hazard better represents the observed data in ARCHER 1050, and will result in a more plausible long-term extrapolation.

Figure 5: Hazard plot of PFS for gefitinib ARCHER 1050

Considering this, the ERG believe the company's generalised gamma extrapolation may be too pessimistic beyond two years, and considered the log-normal and log-logistic models, and alternatively using a two-phase piecewise model (e.g. KM data followed by a parametric extrapolation), in later analyses.

The company modelled the PFS for erlotinib by assuming equivalent efficacy with gefitinib. The PFS for both dacomitinib and afatinib were extrapolated using the FP model with P1 = 0.5 and P2 = 1.5, chosen by the company as the model with best fitting model that yielded plausible estimates, applied to the generalised gamma model fitted to the ARCHER 1050 gefitinib population. The company rejected the best fitting model as it predicted a sharp increase in the dacomitinib HR from 24 months, and opted for the P1 = 0.5 and P2 = 1.5 which was among the best fitting and yielded relatively more plausible results, but still predicted a sharp increase in the dacomitinib hazard from 36 months (Figure 6).

In the initial company submission, the FP NMA used PFS data generated from the Park et al. 2016 paper[27] of LUX-Lung 7. However, the company submitted an updated economic model during the appraisal process using PFS data from the Paz-Ares 2017 paper[28] of LUX-Lung 7.[28] The KM graphs of the two papers look very similar (Figure 7), and it was expected that this update would have minimal impact on the economic model, however it significantly changed the resulting HRs from the company's FP NMA (Figure 6). This demonstrates how sensitive the FP NMA models can be, and suggests that considerable uncertainty remains in the extrapolations. The company's corresponding survival curves are shown in Figure 8.

Figure 6: Comparison of PFS Hazard Ratios vs gefitinib from company FP NMA (P1=0.5, P2=1.5)

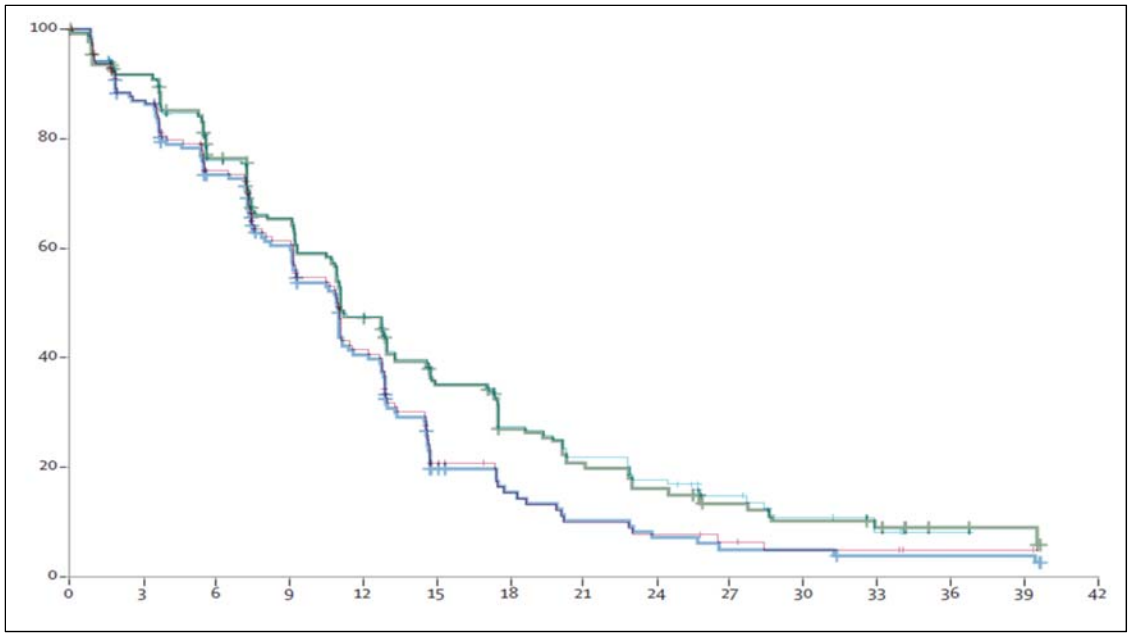


Figure 7: Comparison of PFS KM Curves from Park 2016 and Paz-Ares 2017 for LUX-Lung 7

Figure 8: PFS curves under company base-case: generalised gamma and P1=0.5, P2=1.5

The company's base-case analysis, shown in Figure 8, applying the P1=0.5, P2=1.5 to the gen-gamma curve resulted in PFS curves which suggest that dacomitinib has the highest PFS until 38 months, beyond which afatinib has the highest PFS. There were less than 5% of patients remaining in the PF health state across all treatments at 38 months suggesting the impact of this implausibility may be small. However when gefitinib is modelled using a log-normal curve, dacomitinib crosses both the gefitinib and afatinib curves, due to the higher tail of the log-normal graph combined with the sharply increasing dacomitinib hazard ratio. The ERG believe that this model is pessimistic of the PFS for dacomitinib, and optimistic for afatinib.

The ERG were not aware of any clinical rationale for dacomitinib to have less progression-free patients than the comparators, and this led us to consider the other FP models provided by the company, applied to the log-normal extrapolation. The only model to improve the PFS for dacomitinib was the P1=0.5, P2=1 FP model, however this resulted in implausibly optimistic predictions for the afatinib (Figure 9). Hence, the ERG considered alternative approaches to the company's FP NMA to produce plausible extrapolations for afatinib.

Figure 9: PFS Curve of P1=0.5, P2=1

To improve the plausibility of the extrapolation for afatinib, the ERG first considered assuming that the number of patients remaining progression-free on afatinib would match the number progression-free on dacomitinib, from where the afatinib and dacomitinib curves cross at 55 months.

This assumption prevented the over-optimistic extrapolation for afatinib, but implied that the initial benefit of dacomitinib relative to afatinib, in terms of proportion of progression-free patients, is lost from 55 months. This was considered unlikely by the ERG, due to the fact that patients would still be receiving treatment. This assumption was explored by the ERG in a scenario analysis.

To further improve the afatinib extrapolation the ERG chose a novel approach to model the PFS of afatinib from 36 months, which is roughly when the observed period for PFS ends in both ARCHER 1050 and LUX-Lung 7, as the mean average of the proportions progression-free in both the gefitinib and dacomitinib arms. This maintains the difference in PFS curves, and provides plausible extrapolations for all comparators in the economic model. A comparison of the survival curves against the company's preferred PFS curves are shown in Figure 10. The ERG believe that this approach may underestimate the number of PFS patients in the dacomitinib arm beyond 48 months as it uses the hazard ratios shown in Figure 11, where the HR for dacomitinib appears to grow exponentially. This would result in an underestimation of both the costs and QALYs of dacomitinib, as patients beyond this point are likely to remain progression-free and on first-line treatment for

less time in the model than expected, potentially underestimating the ICER. The consequence of the ERG's assumption of linking the efficacy of dacomitinib and afatinib is that the afatinib extrapolation beyond 48 months may also be affected. The ERG were not able to robustly improve this assumption within the model provided by the company in the timeframe of this appraisal. A comparison of the models is shown in Table 22.

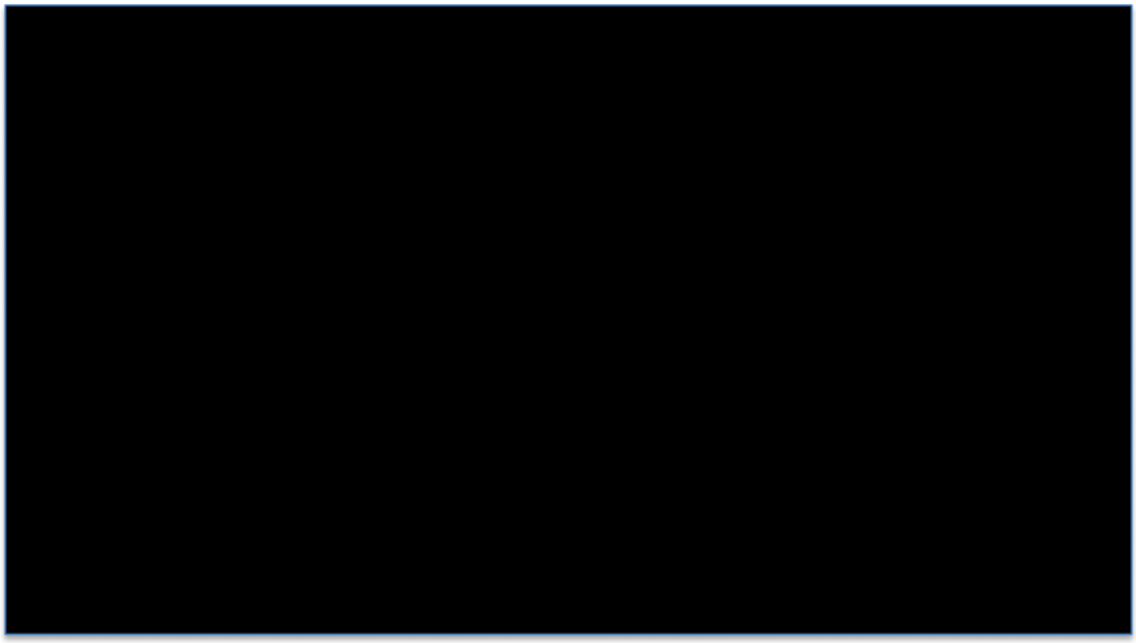


Figure 10: Comparison of Company (dashed) and ERG (solid) preferred PFS extrapolations.

Figure 11: Hazard Ratios of Company (solid) and ERG (dashed) preferred PFS FP model.

Table 22: PFS Predictions for Dacomitinib and Afatinib

Distribution	Drug	Mean (months)	Median (months)	Proportion PF at			
				2 years	3 years	4 years	5 years
Gefitinib Log Normal	Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5, P2=1.5 on Gen Gamma (Company Base-case)	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5, P2=1.5 on Log-Normal	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5, P2=1 on Log-Normal	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5, P2=1 on Log-Normal with Afatinib PFS = Dacomitinib PFS from 55 months	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5, P2=1 on Log-Normal with Afatinib PFS = mean of Dacomitinib and Gefitinib PFS from 36 months.	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050 [1] (n=225)	Dacomitinib	-	14.65	30%	-	-	-
LUX-Lung 7 [28] (n=160)	Afatinib	-	11.0	16%	9%	-	-
Values in this table were extracted before the half cycle correction was applied. All entries in this table are based on the company's latest, using PFS data from Paz-Ares 2017.							

ERG Summary

The company approach to PFS was pessimistic for all considered first-line treatments. The ERG chose a different parametric curve (log-normal) for gefitinib that predicts more patients to be progression-free at 5 years than under the company's assumptions. When applying the HR from the company's FP NMA, the extrapolations appeared implausible. The ERG chose a different FP model (P1=0.5, P2= 1) which improved the dacomitinib PFS extrapolation, but may still be pessimistic in the tail. The afatinib extrapolation remained implausible, and so the ERG resorted to modelling the proportion of progression-free afatinib patients as the mean of the proportions from the dacomitinib and gefitinib progression-free populations.

5.2.6.3 Overall survival

The company took a similar approach in their modelling of OS. They fitted a range of parametric models to the OS data from the gefitinib arm of ARCHER 1050 and selected a model based on the statistical goodness-of-fit, clinical plausibility and visual fit. Predictions are shown in Table 23 below, alongside comparisons to external data.

The company selected the generalised gamma as they felt the predictions were most in line with the external studies, and explored the log-logistic in a scenario analysis. The ERG believe that the generalised gamma may underestimate OS for gefitinib patients in ARCHER 1050 as the estimates are consistently below what was observed in Lin 2016, which has an unhealthier population than ARCHER 1050. The ERG's clinical adviser also stated that they expected up to 5% of patients to still be alive at 15 years. Hence the ERG will consider the log-logistic distribution as it is consistent with the 5 and 7 year data from both Lin 2016 and WJTOG 3405, in addition to exploring using KM data followed by a parametric curve, in later analyses. The log-logistic distribution also had the lowest AIC and BIC scores.

Table 23: OS goodness of fit and predictions for gefitinib.

Distribution	AIC	BIC	Mean (months)	Median (months)	Proportion (%) alive at				
					3 years	5 years	7 years	10 years	15 years
Exponential	488.64	492.06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	461.29	468.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	474.30	481.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	455.76	462.59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	463.23	470.06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	460.69	470.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM + Expo	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	-	-	-	26.84	41.8%	-	-	-	-
LUX-Lung 7	-	-	-	24.5	32.3%	-	-	-	-
WJTOG 3405	-	-	-	34.8	48%	20%	-	-	-
Lin 2016	-	-	-	30.9	40%	15%	6.5%	-	-

Values in this table were extracted before the half cycle correction was applied.

The company modelled the OS of erlotinib by assuming equivalent efficacy with gefitinib. For afatinib and dacomitinib, the company applied the time varying hazard ratios obtained from their FP NMA of the OS data from the ARCHER 1050 and LUX-Lung 7 trials. The company initially considered second-order FPs as these were the best fitting to the data, however none provided a plausible extrapolation, a consensus shared by the ERG. The company selected the best fitting first order FP (P1=-0.5) as they felt it provided plausible predictions for both afatinib and dacomitinib. The hazard ratios are shown in Figure 12, and the corresponding survival curves in Figure 13.

Figure 12: Hazard ratios applied to gefitinib extrapolation comparators in company base-case (P1=-0.5)

Figure 13: OS Curves from company base-case

It is apparent that the effect of afatinib relative to gefitinib decreases and appears to tend towards 1 across the time horizon of the model, which could be interpreted as a gradual waning effect. However, the efficacy of dacomitinib appears to increase across the time horizon, with the hazard ratio reducing. This results in a clear difference between the long term OS predictions for dacomitinib and gefitinib (Figure 13), of which the ERG's clinical advisor was unconvinced. When applied to the log-logistic extrapolation, the company's FP predicts [redacted]% alive on dacomitinib compared to [redacted] % on gefitinib.

The ERG are not aware of any evidence or clinical rationale to support this optimistic prediction for dacomitinib, nor the contrast between the behaviours of the dacomitinib PFS and OS ratios. Recall that for PFS, under the company's FP NMA the HR for dacomitinib grew seemingly exponentially, yet for OS the HR for dacomitinib improves constantly over time. Whilst for afatinib, the PFS improved over time whilst the OS worsened. This contrast between afatinib and dacomitinib is not supported by any clinical rationale, and sheds further doubt over the reliability of the FP analysis extrapolations. The ERG did not consider the other single order FP HR model to be an improvement in terms of plausibility, with the survival curves for dacomitinib appearing to be almost identical.

Recall also that the company failed to provide evidence of a significant difference between dacomitinib and afatinib for OS in their clinical section. The ERG considered alternative approaches to the extrapolation of dacomitinib OS, including the assumption of equivalency of dacomitinib and afatinib by assuming the FP OS HR from afatinib for both interventions. A summary of the predictions made by the models explored by the ERG is presented in Table 24.

Table 24: OS predictions for dacomitinib and afatinib

Distribution	Drug	Mean	Median	Proportion alive at				
				3 years	5 years	7 years	10 years	15 years
Gefitinib Gen Gamma	Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5 on Gen Gamma (Company base-case)	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5 on Log-Logistic	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant HR on Log-Logistic	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM + Exponential	Dacomitinib Afatinib*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5 on Gen Gamma with HR=1 after 3 years	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P1=0.5 on Log-Logistic with HR=1 after 3 years	Dacomitinib Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050[1] (n=225)	Dacomitinib	-	34.1	43.1%	-	-	-	-
LUX-Lung 7[28] (n=160)	Afatinib	-	27.9	38.2%	-	-	-	-
Values in this table were extracted before the half cycle correction was applied. *Model functionality did not allow comparison with afatinib to be made when using KM+Parametric Fit								

When considering alternative approaches to OS modelling, the ERG noted that the observed OS data from ARCHER 1050 were heavily censored from 30 months onwards, and so we could not be certain of the behaviour of the OS curves beyond this point. Given the unreliability of the FP models in this appraisal, the ERG requested that the company would implement an assumption of a HR=1 for the OS of all comparators from 36 months. This approach avoids the extrapolating with the FP output, and instead uses the hazard modelled by the parametric model fitted to the gefitinib arm of ARCHER 1050, accounting for the perceived benefit that occurred during the observed trial follow-up. This request was also based on the lack of relevant data beyond 36 months. For example, ARCHER 1050 had 14 and 12 patients at risk at 36 months in the dacomitinib and gefitinib arms respectively, which fell to 3 and 3 at 42 months respectively. The ERG also digitised the cumulative hazard plots of OS from ARCHER 1050 provided by the company. These were seen to be parallel from 27 months, suggesting there was no difference in OS efficacy beyond this point.

The ERG acknowledge that implementing the HR=1 assumption from 48 months and 60 months could also be considered plausible, and investigated these in scenario analyses.

The ERG also fitted a restricted cubic spline model to digitised OS data from ARCHER 1050 and LUX-Lung 7 trials, Figure 14, which shows that the HR for dacomitinib vs gefitinib crosses 1 at roughly 24 months. This is consistent with the second order FP models fitted by the company which also demonstrated a similar diminishing of the OS benefit on the hazard scale. It is worth noting that at 24 months there remains 138 and 113 people at risk of death in dacomitinib and gefitinib arms respectively, meaning this reduction in effect should not be dismissed as a result of censoring.

Whilst the company did provide this functionality to the model, they objected to its use on the following grounds:

- It is based on censored data that is driven small patient numbers
- It disregards the trend seen in the observed data prior to this point
- It abandons the parametric curve fits that have been modelled in line with DSU guidelines[59]

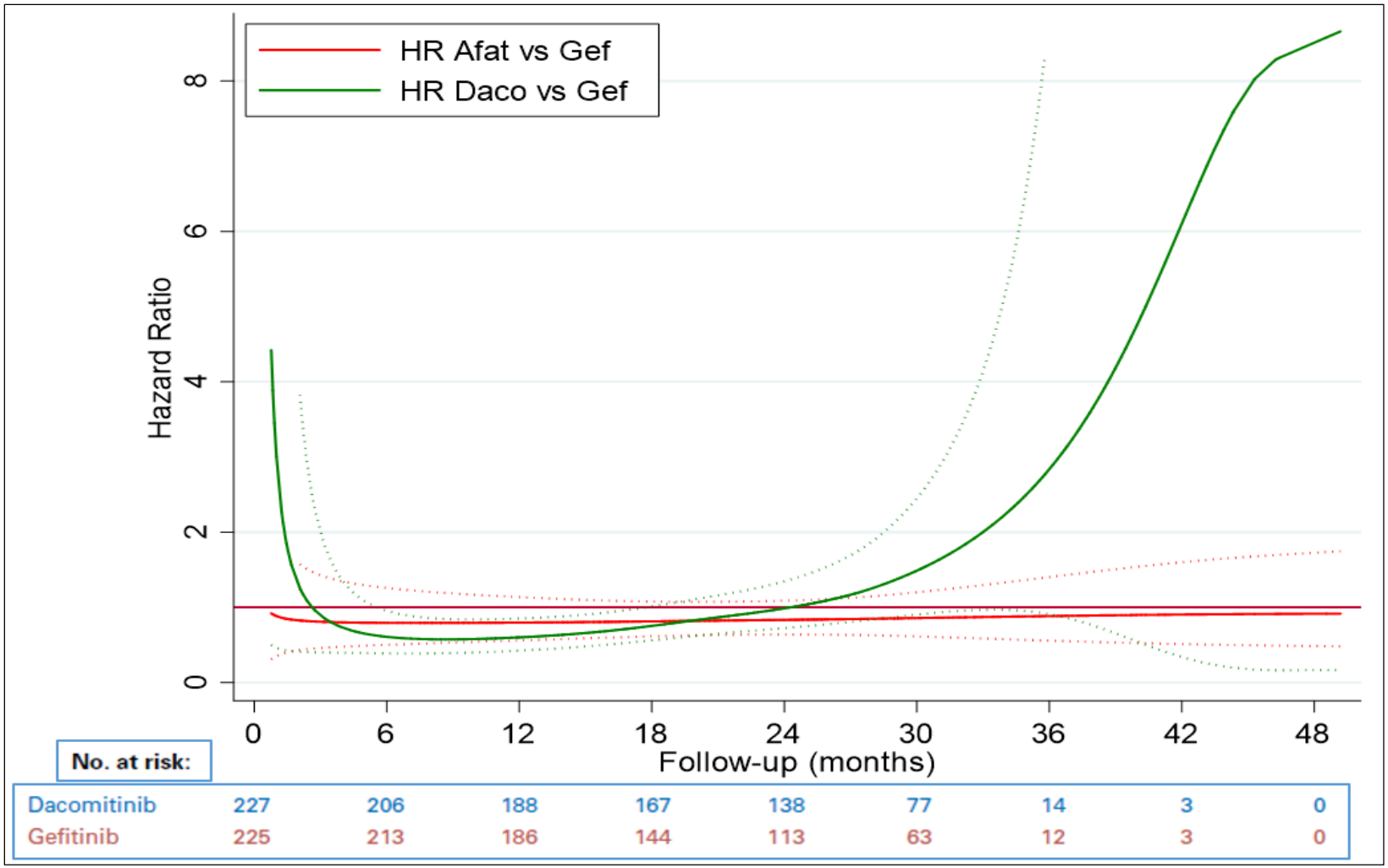


Figure 14: OS hazard ratio from spline model fitted to digitised data from ARCHER 1050 and LUX-Lung 7

The ERG agree with the first point, that it is unclear what happens beyond the trial follow-up, but this argument could be placed against the company's own base-case analysis . The second point is unclear to the ERG. The trends are most accurately captured by the second order FP models (see company appendix D.6.3), which almost all demonstrated a sharply increasing OS hazard from around 20 months. The ERG also performed their own analysis on digitised data from ARCHER 1050, and fitted flexible parametric models using restricted cubic splines[60], which confirmed a trend of a sharply increasing hazard from around 2 years. Finally, without the company being more specific in their third point, the ERG believe their criticism to incorrect as the generalised gamma parametric curve fitted to the gefitinib arm is unaffected by this assumption.

The company also argued that implementing the OS HR=1 from 3 years results in a lower post-progression survival for dacomitinib patients than the comparators, which led them to question the clinical validity. However, assuming that dacomitinib offers the most pre-progression survival gain, it is plausible that post-progression survival could be equal or less than the post-progression survival of the comparators, whilst still providing some overall survival benefit. This is common for interventions when benefits in surrogate markers (e.g. PFS) are not repeated to the same degree in the primary outcome (e.g. OS).

The company state that implementing this assumption underestimates the OS benefit by comparing the observed median gain in OS (7.3 months) to the predicted mean gain in OS when applying the assumption to their base-case (2.9 months). Firstly, the ERG do not believe that this is a meaningful comparison due to the difference in the definition of the two measures. Secondly, under the company's base-case assumptions the median difference is 4.57 months, which is also unaffected by the 36 month equal efficacy assumption. Thirdly, the widest interval in the OS KM plot from ARCHER 1050 is at roughly 22 months with a difference of approximately 12% between arms. Yet under the company's base-case analysis at 22 months the difference is 4.5%, which is unaffected by the application of OS HR=1 from 36 months.

The ERG's clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis, however the nature of the partitioned survival model meant that this could not be implemented as the post-progression survival is estimated as the difference between the PFS and OS.

In summary, the ERG were not aware of the clinical rationale of the efficacy of dacomitinib improving throughout the economic model as modelled by the company, particularly once the

majority of patients had moved to later lines of treatment. The survival curves for the ERG preferred OS assumptions are shown in Figure 15.

The ERG also requested to be able to model OS for dacomitinib parametrically, without using the FP NMA results.

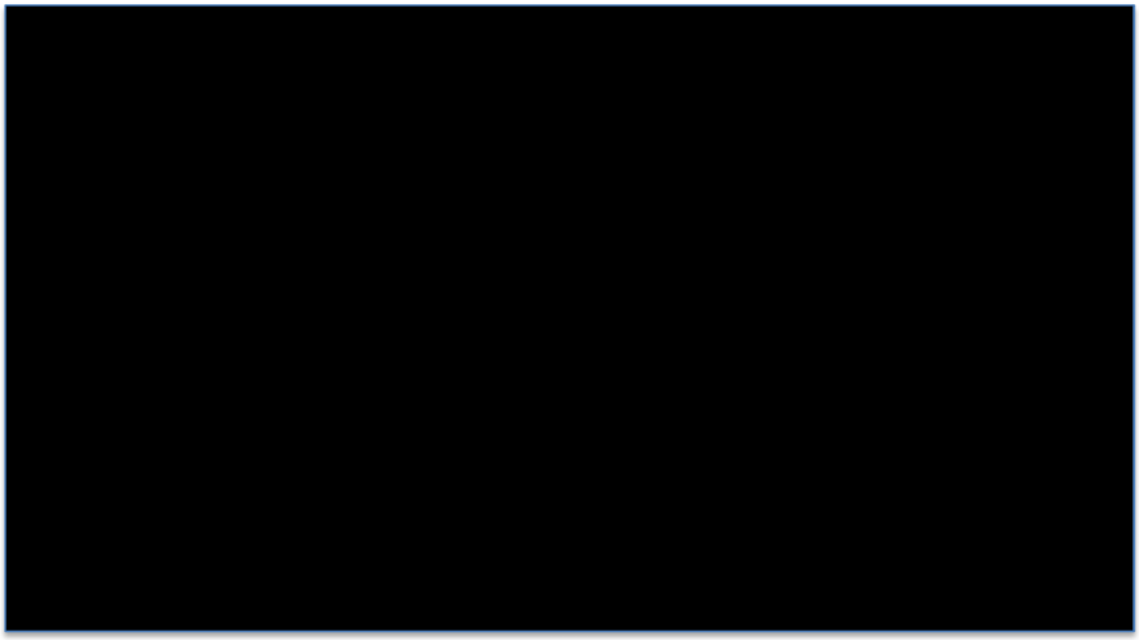


Figure 15: ERG preferred OS extrapolation (log-logistic and HR=1 from 36 months)

ERG Summary

The company's OS modelling was thought to be too pessimistic for all interventions. The ERG chose a different parametric curve to model the OS of gefitinib (log-logistic). The results of the company's OS FP NMA were inconsistent with the results obtained from the same analysis performed on the PFS data, and resulted in implausible extrapolations, with the benefit of dacomitinib improving across the time horizon of the economic model. The ERG preferred to not rely on the FP NMA extrapolation, and instead assume a HR=1 from 36 months for OS across all comparators. This maintained the benefits occurred in the period supported by observed data from clinical trials, and resulted in plausible extrapolations across the full time horizon of the economic model.

Under the company's base-case assumptions, it can be seen that dacomitinib appears to provide both pre-progression and post-progression benefit (Table 25). The ERG consider this unlikely to be plausible as it is uncommon for PFS benefits to be mirrored to the same degree in post-

progression survival, and less common for the PFS benefits to be extended in post-progression survival. Under the models fitted with ERG's preferred PFS and OS assumptions, dacomitinib provides an OS and PFS benefit over the comparators, but has a shorter post-progression survival time, consistent with the scenario of the degree of the pre-progression benefit not being repeated in the OS benefit as has been observed in ARCHER 1050 (PFS HR: 0.59, OS HR: 0.76).

Table 25: Comparison of pre-progression and post-progression survival gains

Scenario		Pre Progression Incremental Life Years (Dacomitinib difference)	Post Progression Incremental Life Years (Dacomitinib difference)	Total Incremental Life Years (Dacomitinib difference)
Company Base-case	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS log-logistic	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS matched to Afatinib	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 3 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 4 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 5 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]

5.2.7 ERG's exploratory survival analysis

5.2.7.1 Progression-free survival

The ERG investigated modelling separately the PFS of dacomitinib from ARCHER 1050 using parametric models, and KM data followed by parametric models fitted to data beyond 8 month, chosen because it was at this point that the KM curves separated. However, none of the parametric curves produced using these models produced a better model than those discussed above. Since the

PH assumption was violated in ARCHER 1050 for PFS, the ERG did not consider using the HR from the traditional NMA within the economic analysis

5.2.7.2 Overall survival

The ERG also investigated modelling OS in the same way, though the switch from KM to parametric model was at 12 months. The parametric fits did not provide plausible extrapolations to the dacomitinib data, however the KM and exponential did provide a very good visual fit for both arms of ARCHER 1050, and plausible extrapolation for the dacomitinib arm. However, this approach assumed a constant treatment effect of dacomitinib across the model time horizon, which resulted in larger differences between the predicted OS of dacomitinib and gefitinib across the time horizon of the model than were observed in ARCHER 1050, which there is no evidence to support. This analysis did not allow the comparison to afatinib or erlotinib in the company's economic model. The ERG did consider using the HR from the traditional NMA for OS within the economic analysis, however this analysis also maintained a treatment effects across the model time horizon, and resulted in optimistic extrapolations for dacomitinib compared to the comparators.

The ERG performed a sensitivity analysis of their spline model, to investigate the possibility of overfitting to the tail. We fitted the model to the digitised ARCHER 1050 trial as before, but replaced the event status for the final death events occurring in the dacomitinib arm. The ERG found that even when the final 10 death events were instead marked as being censored at their time of event, the spline model still predicted a rising hazard ratio which crosses one at roughly 32 months.

5.2.8 Adverse events

The company claims to have considered the impact on costs and HRQoL associated with treatment-related AEs within the model which represent AEs of Grade 3 or higher that occur in >5% of patients in at least one treatment of interest. They assumed that Grade 1/2 AEs had negligible impact on costs and HRQoL so were therefore excluded. This approach was reasoned by reference to how AEs had been addressed in previous TA submissions.[61-63] Probabilities of incurring an AE for dacomitinib, gefitinib, and by established precedent of equivalence erlotinib, were taken from the ARCHER 1050 trial. The incidences of AEs for afatinib were taken from the LUX-Lung 7 study. Table 26 includes the final list of AEs that met the criteria specified by the company and are applied in the model.

Table 26: List of adverse events included in the model

Adverse event	Dacomitinib (n=227)	Gefitinib (n=224)	Afatinib (n=160)	Erlotinib*
ALT increased	2 (0.9%)	18 (8.0%)	0 (0.0%)	18 (8.0%)
Diarrhoea	18 (7.9%)	1 (0.4%)	21 (13.1%)	1 (0.4%)
Fatigue	0 (0.0%)	0 (0.0%)	9 (5.6%)	0 (0.0%)
Paronychia	17 (7.5%)	3 (1.3%)	3 (1.9%)	3 (1.3%)
Rash (grouped term)	55 (24.2%)	1 (0.4%)	15 (9.4%)	1 (0.4%)
*Erlotinib assumed equivalent to Gefitinib (see Section B.2.9.1)				

The ERG finds error in the company's use of 7.9% as the proportion of patients experiencing diarrhoea at Grade 3 or above. This is the cumulative value for Grades 3-4 but 0.4% patients experienced grade 5 diarrhoea in the dacomitinib group which has not been counted. Therefore the model input should have been 8.3% rather than the 7.9% used.

Additional data supplied by the company during the clarification process provided AE data per cycle by frequency reported for grades 3 and above at a >2% threshold. Table 27 summarises this new data showing a discernible difference between AE frequencies in patients from the >5% to >2% level. (N.B. rash was not calculated due to lack of clarity as to how the company had defined rash as a grouped term.)

Table 27: Treatment related adverse events occurring in >2% of patients

Type of AE	Dacomitinib n=227 Frequency (percentage)			Gefitinib n=224 Frequency (percentage)		
Stomatitis		[redacted]			[redacted]	
ALT increase						
Diarrhoea						
Paronychia						

In addition to frequency, this data also suggests that the mix of AEs considered may also be different with the notable inclusion of stomatitis that could potentially be relevant at >5% threshold. The further data provided could not definitively show a low rate of recurrence as suggested by the company and to which they attribute as the ability of clinicians to manage these events through dose reduction and discontinuation. It is noted that dose reduction due to AEs was required in 64.8% of dacomitinib patients versus 8.0% of gefitinib patients (see Table 7 and further discussion in clinical effectiveness section).

5.2.9 Mortality

General population background mortality was estimated using the UK life tables for 2015-2017 obtained from the Office of National Statistics (ONS).[64] A weighted average to reflect the proportion of male (40%) and female (60%) and starting age (62 years) of participants in the ARCHER 1050 trial was used to derive the probability of people dying in each model cycle. These probabilities were then used to adjust overall survival, which estimated as the maximum of the general population's survival and the trial participants' overall survival.

5.2.10 Health-related quality of life

For HRQoL values the company used the PF utilities obtained from the ARCHER 1050 trial[1] (see Table 28) which are derived from EQ-5D-3L values as per the NICE reference case. The company report a high patient completion rate (>90%) of nearly all questions at each time point although exact numbers are not provided. A mixed-effects regression model was used to obtain utility scores in an effort to mediate auto-correlation between individual patient repeated measures. The company provided sufficient methodological detail in their reporting for analysis and reproduction of data given baseline data.

Table 28: EQ-5D-3L PFS utility values by treatment from ARCHER 1050

Treatment	Mean	95% CI
Dacomitinib	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]
CI = confidence interval		

Treatment specific utilities were used in the base-case in contrast to non-treatment specific values in previous NSCLC appraisals which the ERG considers good practice given the availability of this data. Utility values for afatinib and erlotinib were assumed to be equal to dacomitinib and erlotinib respectively with justification by the company on grounds of similar safety profiles and the equivalence precedent set by the NICE committee on TA310.[43]

The company stated in their submission that:

"Given that EQ-5D was not collected beyond progression in ARCHER 1050, the PD utility was sourced from the literature…"

However, in the protocol and reporting of the ARCHER 1050 trial, it indicated that;

"Patient reported outcomes were assessed at days 1 (baseline), 8, and 15 of cycle one, on day 1 of subsequent cycles, at the end-of treatment visit, and at the post-treatment follow up visit." [1] (p. 1456).

The company were able to provide these values during the clarification process which are presented in Table 29.

Table 29: Summary of mean EQ-5D health index score.

Time point	Dacomitinib				Gefitinib			
	Median	Mean	95% CI	n	Median	Mean	95% CI	n
End of treatment	[redacted]	[redacted]	[redacted]	121	[redacted]	[redacted]	[redacted]	145
Post-treatment	[redacted]	[redacted]	[redacted]	75	[redacted]	[redacted]	[redacted]	107
CI : confidence interval								

In light of the company's original assertion that this trial data was not collected, they used a post disease (PD) progression utility value of 0.64 from the literature.[2] (see Table 30) The use of health utility scores resulting from the Labbé et al, 2017 study was well justified as an alternative source of utility data as it represents real world data obtained from a longitudinal study of EGFR-NSCLC patients directly from EQ-5D-3L. An alternative value from Nafees et al. (2008) sourced in the systematic review was rejected by the company as this study did not meet the NICE reference case.[56] EQ-5D was not used and values were not derived from patients, therefore it was not considered a robust source. In addition, a recent repeat of this study by Nafees et al. in 2017 that was identified in the systematic review, reported a PF value of 0.883 and PD of 0.166,[65] which further demonstrates the unreliability of the original Nafees et al. (2008) study.[50]

The health state utility values obtained from the Labbé, 2017 study[2] would be the ERGs preferred source of utility values from the literature. The ERG finds the company's reasoning for using these values over the Nafees, 2008[50] compelling and appropriate. Similarly, the ERG finds the health state utility values used by Huang (2017)[52] equally less convincing for use in the model as the KEYNOTE-024 trial was directed at patients specifically without EGFR-activating mutations or ALK translocations.

However, whilst the ERG considers the Labbé et al, 2017[2] values appropriate for use in scenario analysis (when both the PF value of 0.77 and PD value 0.64 are used simultaneously) it prefers the use of PD scores obtained from the ARCHER 1050 trial to be used in the base-case. This continues

the differential approach in treatment arms utilised for the PF utility values with EQ-5D scores obtained from 182 patients from the ARCHER 1050 trial (75 dacomitinib arm, 107 gefitinib arm) rather than the 81 patients on a wider variety of TKI treatments in the Labbé et al, 2017 study. Although Labbé et al. presents longitudinal data, mean number of encounters per patient were only 3.2 over the full disease spectrum[2] and use of ARCHER 1050 values is further strengthened as it meets DSU recommendations to maintain the same data source for HUS values wherever possible [3], (pg 11) whilst also adhering to the NICE reference case.[56]

Table 30: Summary of utility values used in company's cost-effectiveness analysis.

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Progression-free – Dacomitinib	[redacted]	[redacted]	B.3.4.1	Pre-progression utilities sourced from ARCHER-1050 trial in line with the NICE reference case Comparator values assumed equal based on the similarity of safety profiles
Progression-free – Gefitinib	[redacted]	[redacted]		
Progression-free – Afatinib	[redacted]	[redacted]		
Progression free – Erlotinib	[redacted]	[redacted]		
Progressed disease	0.64 (0.03)	NR	B.3.4.3.1	Based on the results of the systematic review (see section B.3.4.3 in CS) the study by Labbé et al. provided most appropriate values from the literature

NR, not reported

The company have used a model time horizon of 15 years with starting age of 62 years. The health utility scores (HUS) are not adjusted over the time horizon to reflect age-related disutility. The ERG believes it would be appropriate to do so given both the starting age and length of time horizon used and follows guidance by the NICE DSU to account for potential changes in HUS due to age and comorbidities [3] (pg 21).

The company did not include AE decrements within the base-case which was justified in order to avoid double counting due to the treatment specific PF values from ARCHER 1050 that were used. They assumed the effect of any AEs were already captured due to the nature of them as trial data.

Instead, scenario analysis was used to apply a one-off utility decrement. Utility decrements assigned to each AE were stated by the company to have been derived from LUX-Lung 3 and LUX-Lung 1 trials which were referenced in the CS to those used in TA310[43] for the evaluation of afatinib. It appears that a covariant was estimated using regression analysis for the disutility value attributed to each AE. A summary of inputs is provided (see Table 31). An updated literature search of HRQoL and disutility tolls did not identify any other feasible sources of data from which disutility tolls could have been sourced. A SLR conducted by Brown et al. 2017 [66] found only four studies reported disutility tolls, across which considerable variability was found, and inconsistencies in measuring and reporting did not allow robust comparison. The ERG is therefore satisfied with the disutility tolls used by the company.

Table 31: Adverse event utility decrements and durations

Adverse event	Utility Decrement (SE)	Source/assumption	Duration (days [range])	Source/ assumption
ALT increased	0	Assumed zero; laboratory findings only with no hospitalization or symptoms indicated	-	-
Diarrhoea	-0.147 (0.045)	Derived from EQ-5D with UK values set from LUX-Lung 3	6.6 (5.95-7.25)	Derived from LUX-Lung 3
Fatigue	-0.179 (0.053)	Derived from EQ-5D with UK values set from LUX-Lung 1	32.0 (27.76 -36.24)	Derived from LUX-Lung 1
Paronychia	-0.202 (0.028)	Assumed equal to rash	12.3 (11,51 -13.09)	Assumed equal to rash
Rash (grouped term)	-0.202 (0.028)	Derived from EQ-5D with UK values set from LUX-Lung 3	12.3 (11,51 -13.09)	Derived from LUX-Lung 3
EQ-5D; European Quality of Life-5 Dimensions; SE, standard error				

The company calculated the one-off utility decrements applied during scenario analysis by multiplying the disutility toll 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 in the first cycle of the model. The ERG is satisfied with the overall method used by the company in their calculation.

The company's suggestion that including disutility decrements in their base-case would constitute 'double-counting' as the patient collected EQ-5D from the trial would already capture a HRQoL detriment, is viewed as unfounded by the ERG. EQ-5D data was collected on day one of each 28-day cycle[1] whereas average duration of the 2 most common frequently reported treatment related AE in dacomitinib patients, diarrhoea (7.9%) and paronychia (7.5%), were assumed to occur for a duration of 6.6 and 12.3 days respectively. As the EQ-5D asks patients about their health state on the day of the month they complete the form (EuroQol, 1990),[67] it is likely that a large proportion of adverse events were not captured in the trial data.

Therefore, the ERG strongly believes that disutility is not fully represented in the company's base-case and that the inclusion of the treatment specific disutility decrements is founded.

Scenario analyses were conducted by the company (see Table 32). In one scenario, non-treatment specific PF utility values from the ARCHER-1050 trial were used, with the Labbé (2017)[2] PD value and in a subsequent scenario analysis values from the Labbé (2017)[2] study were used for both PF and PD values. Rather than this being the only change made within each scenario, the company also chose to include AE disutilities, reporting the model output for both changes simultaneous. Whilst the ERG has previously discussed the company's use of AE disutilities, their inclusion of two parameter changes within each scenario analysis is also not considered appropriate. The ERG would prefer single parameter changes to be applied in each scenario to clarify the effect of each.

Table 32: Summary of HRQoL scenario analyses

Scenario	Base-case	Scenario description	Reference in submission
Utility (PF) with AEs	Treatment specific utility based on ARCHER 1050 and assumption [redacted]	Non-treatment specific PF utility based on ARCHER 1050 [redacted], PD from Labbé 2017 (0.64) with AE disutility's	B.3.4.5
Utility (PF) with AEs	Treatment specific utility based on ARCHER 1050 and assumption [redacted]	Non-treatment specific PF utility based on Labbé (0.77), PD from Labbé (0.64) with AE disutility's	B.3.4.5

ERG Summary

The ERG supports the company's use of treatment specific PF health utility values obtained from the ARCHER-1050 trial for use in the model. However, it feels that PD progression values should

also have been taken from the same source (as they were available) rather than using an alternative value from the literature. This will be presented in the ERG's base-case analysis.

The HRQoL values that were obtained by the literature were well justified and appropriate for use within scenario analysis. The ERG believes it would be appropriate to adjust HUS over the 15-year time horizon of the model to reflect health related disutility and will be applied in the ERG's base-case analysis.

The ERG finds the rationale for omitting AE disutilities from the base-case on the grounds of double counting to be unfounded and will specifically include a disutility decrement in their base-case analysis. Last, the ERG believes disutilities associated with AEs have been under-represented within the model and is concerned that other AEs such as stomatitis should have been considered as clinically these are relevant.

5.2.11 Resource use and costs

Total costs estimated in the model comprised of cost of dacomitinib (drug acquisition and drug administration), subsequent treatment and administration costs, resource use and costs associated with each health state, treatment related to adverse events and terminal care costs, all from the perspective of the NHS and PSS.

Intervention and comparators

The drug regimen for dacomitinib and gefitinib was based on the dosing schedule used within the ARCHER 1050 protocol. People randomised to the intervention and comparator received 45mg and 250mg, respectively, both taken once daily and orally. Table 33 reports the list price per packet for the intervention and the comparators. Given that treatments were oral therapies, only costs for a dispensing fee of £9.40 was applied for each treatment. In the model, the company presented drug acquisition costs based on a discounted price for dacomitininb under the patient access scheme (PAS) approved by the Department of Health. Additionally, the company provided discounted costs based on the assumed PAS for each comparator (see Table 34). It must be noted that the ERG is unable to comment on the accuracy of the assumed PAS discounts.

A PAS discount, the details of which are available in the public domain, is in effect for gefitinib. An error was identified in the application of the PAS discount for gefitinib in the economic model. In the model, a charge for gefitinib is applied on receipt of the 3rd packet of treatment, while, upon

seeking confirmation about the exact arrangement, it transpired that a charge incurred on receipt of the 4th packet of treatment. A relevant correction was made in the economic model.

Table 33: Units costs of intervention and comparators.

Treatment	Dosing schedule	Pack size	Package price (£)	Cost per model cycle (£)
Dacomitinib	45 mg once daily, orally	30	[redacted]	[redacted]
Gefitinib	250 mg once daily, orally	30	£2,167.71	£2,023.20
Afatinib	40 mg once daily, orally	28	£2,023.28	£2,023.28
Erlotinib	150 mg once daily, orally	30	£1,631.53	£1,522.76

Table 34: Units costs of intervention and comparators based on PAS and assumed PAS.

Treatment	Dosing schedule	Pack size	Package price (£)	Cost per model cycle (£)
Dacomitinib	45mg once daily, orally	30	[redacted]	[redacted]
Gefitinib	250mg once daily, orally	30	£2,167.71	£2,023.20
Afatinib	40mg once daily, orally	28	[redacted]	[redacted]
Erlotinib	150mg once daily, orally	30	[redacted]	[redacted]

Subsequent treatment costs

Drug acquisition costs for subsequent treatment were based on the dosing schedule as per Summary of product Characteristics (SmPC). The cost for osimertinib consisted of drug costs and dispensing fee for a dose of 80mg once daily taken orally. The CS stated that an average body surface area of 1.75m^2 was used to calculate the dosing for all other subsequent treatments (pemetrexed, carboplatin, cisplatin and docetaxel). Drug acquisition costs and administration costs for intravenous therapies are presented in Table 35 and Table 36 respectively, and these are in line with their respective SmPCs.

Table 35: Drug acquisition cost of subsequent treatment

Treatment	Dosing schedule	Pack size	Package price (£)	Cost per model cycle (£)
Osimertinib	80 mg once daily	30	£5,770.00	£5,385.33
Pemetrexed	500 mg/m^2 every 21 days	1 vial	£800.00	£1,866.67
Carboplatin	400 mg/m^2 every 21 days	1 vial	£18.73	£38.85
Cisplatin	75 mg/m^2 every 21 days	1 vial	£4.48	£15.68
Docetaxel	75 mg/m^2 every 21 days	1 vial	£14.74	£32.34

Table 36: Drug administration costs for subsequent treatment (obtained from CS)

Treatment		Administration	IV infusion time	Cost per administration	Source
Osimertinib		Oral	-	£9.40	PSSRU 2017[68]
PDC	Pemetrexed with carboplatin	Intravenous	15-60 minutes	£241.07	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance[69]
	Pemetrexed with cisplatin	Intravenous	160 minutes	£355.54	SB14Z; Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[69]
Docetaxel		Intravenous	60 minutes	£241.07	SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance[69]

IV, intravenous; PDC, platinum doublet chemotherapy

Health state costs

Resource use associated with the routine monitoring and disease management of people in the progression-free and progressed health states were combined with the frequency and the unit costs for each item of resource to derive the total cost for each health state. Resource use consisted of visits to various health care professionals (general practitioner and cancer nurse), blood tests

(complete blood count and biochemistry) and imaging (computerised tomography and chest x-ray), all assumed to be undertaken during outpatient visits.

Resource use was based on information obtained from previous technology appraisals.[43, 45, 46] The model assumed that the frequency and the proportion of people requiring disease management is the same across all treatments. Table 37 shows the total costs per cycle for disease management by health state. The total costs associated with people in the progression-free and progressed disease health state were £186.53 and £190.43, respectively.

Table 37: Total costs for routine monitoring and disease management by health state (obtained from the CS)

Items	Use in model	Unit cost (£)	Progression-free survival		Progressed disease	
			Frequency	Frequency per model cycle	Frequency per cycle	% of patients
Outpatient visit	Medical Oncology - Non-Admitted Face-to-Face Attendance, Follow-up	£172.67	0.75 visits per month	0.69	1 visit per month	0.92
GP visit	GP per surgery consultation lasting 9.22 minutes	£38.00	10% patients; 1 per month	0.09	28% patients 1 per month	0.26
Cancer nurse	N10AF: Specialist Nursing, Cancer Related, Adult, Face to face	£82.09	20% of patients; receive 1 per month	0.18	10% patients 1 per month	0.09
Complete Blood Count	DAPS05: Haematology	£3.06	0.75 per month	0.69	1 per month	0.92
Biochemistry	DAPS04: Clinical Biochemistry	£1.13	0.75 per month	0.69	1 per month	0.92
CT scan (other)	RD26Z: Computerised Tomography Scan of Three Areas, with Contrast (outpatient)	£122.51	30% patients; 0.75 per month	0.21	5% patients 0.75 per month	0.03
Chest X-ray	DAPF: Direct Access Plain Film	£29.78	0.75 per month	0.69	30% patients 0.75 per month	0.21
Total cost per 28-day cycle			**£186.53**		**£190.43**	

Cost of treating adverse events

The model included costs of treating adverse events (≥Grade 3 that occurred in >5% of participants in at least one treatment of interest) by comparator. Table 38 shows the proportion of people who experienced adverse events as well as the costs associated with treating each event. However, limiting adverse events without providing the count data on the number of adverse events, means that multiple adverse events experienced by the same participant would be under-represented in the model. For example, a participant may experience an adverse event on multiple occasions, but this would have only been captured as a single occurrence in the model (a one-off cost for the treatment of the adverse event).

Table 38: Costs of treating adverse events

Adverse events	Cost per adverse event (£)	Proportion of people who experienced adverse events (%)			
		Dacomitinib	Gefitinib	Afatinib	Erlotinib
Diarrhoea	£462.08	7.9%	0.4%	13.1%	0.4%
Fatigue	£592.48	0.0%	0.0%	5.6%	0.0%
ALT increased	£0	0.9%	8.0%	0.0%	8.0%
Paronychia	£436.17	7.5%	1.3%	1.9%	1.3%
Rash	£436.17	24.2%	0.4%	9.4%	0.4%

From these proportions and unit costs per adverse event the company derived a weighted costs for treating adverse events by comparator (see Table 39). These costs were applied as one-off costs but only to the first cycle of the model.

Table 39: Total costs of treating adverse events, by treatment

Treatment	Management costs
Dacomitinib	£175
Gefitinib	£10
Afatinib	£143
Erlotinib	£10

Terminal care costs

The model includes a one-off terminal care costs of £4,593 incurred at death to account for the resource use and costs associated with patient monitoring and supportive care in the months prior the death for people in the progression-free and post-progression health states. This cost is based on resource use obtained from Brown et al.,[70] and calculated as a weighted-average based on the

percentage of people receiving care at home (27.3%), hospital (55.80%) or within a hospice (16.90%).

ERG summary

The costs included in the model is in keeping with the viewpoint of the analysis that is from the NHS and PSS perspective, and reported in current prices. All costs incurred are appropriately discounted, using the recommended discount rate of 3.5% per annum. Though there were no discrepancies (for example, between the costs for drug acquisition (using the list prices) and administration costs, and costs associated with the treatment of adverse events), there were concerns relating to costs that might have been excluded from the analysis.

Notably, resource use and costs associated with unscheduled hospital admissions, MRI scans for suspected brain metastases or cord compression and costs associated with the diagnosis of T790M (personal communication with clinical expert). With this in mind, we consider that these costs included in the model are likely to be an underestimate of the true costs associated with managing/treating people with NSCLC.

5.2.12 Overview of model assumptions and ERG critique

In Table 40 , we present the company's modelling assumptions with comments from the ERG.

Table 40: Model assumptions with ERG's comments.

Assumption	Justification	ERG's comments
Model		
15-year time horizon	*"Aligned with the maximum life expectancy of the cohort predicted by the base-case parametric survival analysis (<1% alive at 15 years) (see section B.3.3.1.3)"*	We consider this time horizon appropriate to reflect all important differences in costs and outcomes between the technologies being compared.
EGFR + NSCLC	*"Population identical to the ARCHER 1050 phase III clinical study, in line with the scope of the current appraisal and with the expected EMA marketing authorization".*	The population modelled is in line with the expected EMA marketing authorization. The population reflects the ARCHER 1050 trial and is in line with the scope.

Comparators: afatanib, erlotinib and gefitinib	*"In line with the NICE scope"*	As listed in the scope developed by NICE.
Partitioned survival model	*"Captures the chronic nature of the condition and two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life. Commonly used in previous oncology NICE appraisals, including NSCLC"*	The ERG considers it appropriate to use a partitioned survival model to capture the nature of the condition. However, the company could have included other health states to better capture survival following 2nd and 3rd line treatments.
Four week (28-day) cycle length	*"Aligns with the schedule of the ARCHER 1050 trial, captures differences in dosing on a monthly basis."*	Appropriate cycle length.
Drug acquisition and administration costs for oral treatments are not half-cycle corrected	*"Oral treatments were assumed to be dispensed at the beginning of the cycle"*	This is a reasonable assumption.
Survival		
Erlotinib was assumed to have equal efficacy (PFS and OS) and safety to geftinib	*"In line with previous NICE and SMC committee conclusions and the supporting data from the recent RCT subgroup analysis."*	This is a reasonable assumption.
Proportional hazards was assumed to be potentially violated for PFS and OS	*"Given potential violation in at least one trial in the network (tested using log cumulative hazard plots and Schoenfeld residuals) a FP NMA was utilised to allow hazards to vary over time in the base-case analysis. A traditional ITC was also explored in a sensitivity analysis."*	The ERG considers that the proportional hazard assumption was potentially violated in the ARCHER 1050, so it would have been appropriate to consider other methods. Despite FP models being a plausible fit to the observed data, there is considerable uncertainty in the extrapolations.
Utility		
Progression free utility values were assumed to be treatment specific	*"ARCHER 1050 collected EQ-5D aligned with the NICE reference case. There was a statistically significant difference observed between dacomitinib and gefitinib in EQ-5D, however it did not exceed a minimally important difference. Therefore, a conservative assumption was made to apply*	This is a reasonable assumption.

	treatment specific utilities in the base-case and a single non-treatment value was explored in scenario analysis."	
Disutility due to adverse events was not included in the base-case model	*"Given that treatment specific values were applied in the base-case that are elicited from the EQ-5D on treatment (thus capturing disutilities on treatment), it was considered that including separate disutilities for adverse events would be double counting. A one-off disutility was explored in scenario analysis."*	The ERG did not consider that the inclusion of AE disutilities would constitute as double-counting because it is unlikely that the EQ-5D had been administered at the time-point when the events occurred. Hence, disutility would have been under represented.
Costs		
Relative dose intensity was not included in the model	*"Given that all primary treatments were administered orally, RDI was not considered relevant."*	This is a reasonable assumption.
Complete vial sharing was assumed	*"Only subsequent treatments were administered intravenously. Therefore, for simplicity these therapies were estimated using the lowest cost per mg of any vial."*	This is a reasonable assumption.
The cost of adverse events are applied as a one-off cost at the start of treatment	*"The majority of adverse events will occur within the first year of treatment and any adverse events occurred beyond the first year will only have a minimal difference due to discounting."*	The ERG considers this a strong assumption, as people are likely to experience multiple/or re-occurring adverse events and the costs for treating these events would be underestimated.
The proportion of patients receiving cisplatin or carboplatin in PDC was assumed from PROFILE 1014	*"These values have been applied in a previous NSCLC appraisal and are therefore considering representative of UK clinical practice."*	This is a reasonable assumption.
EGFR, epidermal growth factor receptor; EMA, European marketing authorsation; NSCLC, non-small cell lung cancer; OS, overall survival; PDC, platinum doublet chemotherapy; PFS, progression free survival; SMC, Scottish Medicines Consortium.		

5.3 Cost-effectiveness results

The following section presents the cost-effectiveness results reported in the CS (main submission document and supplementary appendix). In the CS, results have been reported on the basis of:

- Dacomitinib with confidential PAS discount versus comparators (erlotinib, afatinib and gefitinib) with PAS discounts assumed by the company (presented in the main submission document).

- Dacomitinib and comparators (erlotinib, afatinib and gefitinib) at list prices (presented in the accompanying CS Appendix).

The results of each these analyses are appraised and critiqued in Section 5.3.1 and Section 5.3.2, respectively.

5.3.1 Cost-effectiveness results: dacomitinib (with PAS) versus comparators (with company's assumed PAS).

The company reports deterministic and probabilistic results, as well as sensitivity analysis for the comparison between dacomitinib (with PAS) versus gefitinib, erlotinib and afatinib (with assumed PAS). Outcomes are reported in terms of life years gained and quality adjusted life years gained results reported in the form of an incremental cost-effectiveness ratio (ICER) expressed as cost per LYG or cost per QALY. Additionally, we report the deterministic and probabilistic results that are based on the list prices for dacomitinib and the list price of the comparators, along with the sensitivity analyses.

Company's main analysis results (dacomitinib PAS vs. comparators with assumed PAS)

The results in Table 41 show that dacomitinib is more expensive than all comparators and is expected to yield [redacted] QALYs, and is associated with an ICER of approximately [redacted] per QALY gained when compared to gefitinib.

Table 41: Deterministic results, company base-case using the assumed PAS for comparators (discounted)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Results in the form of LYG show that dacomitinib is more expensive than all comparators and is expected to yield [redacted] LYG and has an ICER of approximately [redacted] per LYG (see Table 42).

Table 42: Deterministic results, company base-case using the assumed PAS for comparators (discounted).

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean LYGs	Incremental LYGs	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained

Company's probabilistic sensitivity analysis results (dacomitinib PAS vs. comparators assumed PAS)

Probabilistic sensitivity analysis was undertaken for the outcome cost per QALY only. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to majority of the key model input parameters, and these were considered appropriate. However, were there was missing information about the standard error, the company assumed it to be 5% of the mean. Applying a standard error equal to 5% of the mean may not represent the true uncertainty about the input value. As presented in Table 43, the results for the PSA are in line with the results from the deterministic results.

Table 43: Probabilistic results, company base-case using the assumed PAS for comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Each simulation for the incremental costs and incremental QALYs for dacomitinib versus gefitinib, erlotinib and afatinib was graphed/plotted on a cost-effectiveness plane (see Figure 16), along with the respective cost-effectiveness acceptability curves (CEACs). For 10,000 simulations, the scatterplot shows considerable uncertainty around the incremental QALYs, and less so for the incremental costs. This may be a result of the company assuming some of the resource use and/or costs estimates used to derive costs to be constant/fixed. Note, the scatterplot presents dacomitinib against each of the three comparator drugs (showing incremental costs and QALYs) and where the legend indicates the comparator drug being visualised.

Figure 17 shows the results of the PSA in the form of a CEAC for the comparison between dacomitinib and all comparators included in the analysis. The curves show the proportion of simulations in which treatments are cost-effective at different willingness-to-pay thresholds for a QALY. Results show that at a WTP threshold of £30,000 per QALY dacomitinib compared to all other comparators has a probability of [redacted] of being cost-effective.

Figure 16: Scatterplot of strategies on the cost-effectiveness plane, company base-case using assumed PAS for comparators

Figure 17: Cost-effectiveness acceptability curve, company base-case using assumed PAS for comparators

In general, the ERG considers the distributions used around key input parameters to be appropriate. However, by applying a 5% standard error to means, when unknown, may have underestimated the uncertainty around these parameters.

Company's deterministic sensitivity analysis results (dacomitinib PAS vs. comparators assumed PAS)

A number of deterministic sensitivity analyses were undertaken to explore the impact on the ICER to making changes to key model input parameters. Parameters were varied according to the lower and upper bound of their respective 95% confidence interval (CI) or by assuming uncertainty of ±25% of the point estimate where the confidence intervals were missing. The results are presented in the form of tornado diagrams and are shown in Figure 18 through to Figure 20.

Similar results are seen for the comparison between dacomitinib versus gefitinib/erlotinib, which showed that the monthly discount rate applied to costs and benefits are the key drivers of cost-effectiveness. Applying a lower value of 0% and upper value of 6% based on an annual discount rate resulted in a decrease to in the ICER to approximately [redacted] and an increase to approximately [redacted] per QALY.

Figure 18: Tornado diagram for the comparison of dacomitinib versus gefitinib, using the assumed PAS for comparators

Figure 19: Tornado diagram for the comparison of dacomitinib versus erlotinib, using the assumed PAS for comparators

Likewise for the comparison between dacomitinib versus afatinib showed that the monthly discount rate applied to benefits and the time horizon were the key drivers to the cost-effectiveness. Applying a lower value of 0% and upper value of 6% based on an annual discount rate resulted in a decrease to in the ICER to approximately [redacted] and an increase to approximately [redacted] per QALY.

Figure 20: Tornado diagram for the comparison of dacomitinib versus afatinib, using the assumed PAS for comparators

The company undertook one-way sensitivity analyses across a range of model input parameters, mainly time horizon, discount rates applied to both costs and benefits, utility values for PFS and PPS, probabilities of receiving 2nd and 3rd line treatment, costs associated with medical resource use, cost for treating adverse events, and terminal care costs. All of which are appropriate; however, the ERG consider other inputs could have been included: starting age of the population, different plausible survival models applied to the observed data for PFS (and OS), frequency of adverse events, and the proportion of participants in each care setting.

Company's scenario analysis results (dacomitinib PAS vs. comparators assumed PAS)

A range of scenario analyses were undertaken to determine the impact to the base-case ICER, by making changes to some assumptions:-

- Fitting a log-normal parametric model to PFS and log-logistic to OS for gefitinib instead of the generalised gamma
- Selection of different FP models for PFS and OS
- Treatment effect based on the conventional NMA instead of using the FP NMA
- Non-treatment specific PFS utility value ([redacted]) based on ARCHER 1050 with disutilities associated with adverse events
- Non-treatment specific PFS utility value (0.77) based on Labbé with disutilities associated with adverse events
- Including treatment beyond disease progression for dacomitinib and the comparators oppose to discontinuing treatment upon progression

The results for each change made and the impact to the base-case results are presented in Table 44 through Table 46 for the comparison between dacomitinib and the comparators. As seen in Table 44, under the scenario of using log-normal and log-logistic parametric curves for PFS and OS, respectively had the greatest impact to the base-case ICER for the comparison between dacomitinib and gefitinib.

Table 44: Results of base-case scenario analysis for the comparison between dacomitinib and gefitinib.

Scenario	Dacomitinib			Gefitinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]							
Gefitinib survival projection (PFS)	[redacted]							
Gefitinib survival projection (OS)	[redacted]							
FP model (PFS)	[redacted]							
FP model (OS)	[redacted]							
NMA methodology (PFS and OS)	[redacted]							
Utility (PF - ARCHER) with AEs	[redacted]							
Utility (PF - Labbé) with AEs	[redacted]							
Treatment beyond progression	[redacted]							

The results for each change made and the impact to the base-case results for the comparison between dacomitinib and erlotinib is presented in Table 45. The scenarios of using the log-normal parametric curve for gefitinib survival projection of PFS and treatment beyond progression had the greatest impact to the base-case ICER, with both changes leading to a decrease to the ICER.

Table 45: Results of base-case scenario analysis for the comparison between dacomitinib and erlotinib.

Scenario	Dacomitinib			Erlotinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analysis results for the comparison between dacomitinib and afatinib is presented in Table 46. The scenarios of using the log-logistic parametric curve for gefitinib survival projection of OS and treatment beyond progression had the greatest impact to the base-case ICER, with both changes leading to a decrease to the ICER. Using the results from the NMA for PFS and OS resulted in an increase to the ICER.

Table 46: Results of base-case scenario analysis for the comparison between dacomitinib and afatinib.

Scenario	Dacomitinib			Afatanib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]							
Gefitinib survival projection (PFS)								
Gefitinib survival projection (OS)								
FP model (PFS)								
FP model (OS)								
NMA methodology (PFS and OS)								
Utility (PF - ARCHER) with AEs								
Utility (PF - Labbé) with AEs								
Treatment beyond progression								

The company presented results for the PSA undertaken around the outcome cost per QALY gained. In general, the company used appropriate distributions around the model input parameters varied. However, the ERG noted that distributions could have been placed around other inputs to reflect the uncertainty, instead of keeping these inputs fixed. A range of sensitivity and scenario analyses were undertaken. These results showed that the discount rate applied to benefits and using the log-logistic parametric curve to model OS for gefitinib were the key drivers to the ICERs.

5.3.2 Cost-effectiveness results: dacomitinib (list price) versus comparators (list prices).

Results for the comparison between dacomitinib, erlotinib, afatinib and gefitinib at list prices were presented in the CS Appendix M.

Company's main results (all treatments at list prices)

Using the list prices for dacomitinib and its comparators lead to an increase to the expected mean costs, whilst the expected mean QALYs remained constant. In Table 47 the results show that gefitinib was dominated by erlotinib, and afatinib was extendedly dominated by the comparison between dacomitinib and erlotinib. Hence, the ICER for the comparison between dacomitinib versus erlotinib was approximately [redacted] per QALY gained.

Table 47: Deterministic results, company base-case using the list prices.

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

Results in the form of LYG show that dacomitinib is more expensive than all comparators and is expected to yield [redacted] LYG and has an ICER of approximately [redacted] per LYG (see Table 48).

Table 48: Deterministic results, company base-case using the list prices.

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean LYGs	Incremental LYGs	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained					

Company's probabilistic sensitivity analysis results (all treatments at list prices)

Using the list prices, the ICER results of the PSA are similar/in-line with the results based on the deterministic analysis (Table 49). The results of the PSA slightly underestimates to expected mean costs for each comparator and slightly overestimates the expected mean QALYs yielded.

Table 49: Probabilistic results, company base-case using the list prices.

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean LYGs	Incremental LYGs	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained

The output of the PSA is given graphically in the scatterplot depicted in Figure 21 and is plotted in the form of CEACs in Figure 22. According to this output, the probability of dacomitinib being cost-effective at a WTP threshold of £30,000 per additional QALY is [redacted]

Figure 21: Scatterplot of strategies on the cost-effectiveness plane, company base-case using list prices

Figure 22: Cost-effectiveness acceptability curve, company base-case using the list prices

Deterministic sensitivity analysis results (all treatments at list prices)

Similar results are seen for the comparison between dacomitinib versus gefitinib/erlotinib in deterministic sensitivity analyses (see Figure 23 and Figure 24), which showed that the monthly discount rate applied to benefits is the key driver of cost-effectiveness.

Likewise for the comparison between dacomitinib versus afatinib the discount rate applied to benefits and time horizon appears to be the key drivers of the ICER (see Figure 25).

Figure 23: Tornado diagram for the comparison of dacomitinib versus gefitinib, using the list prices

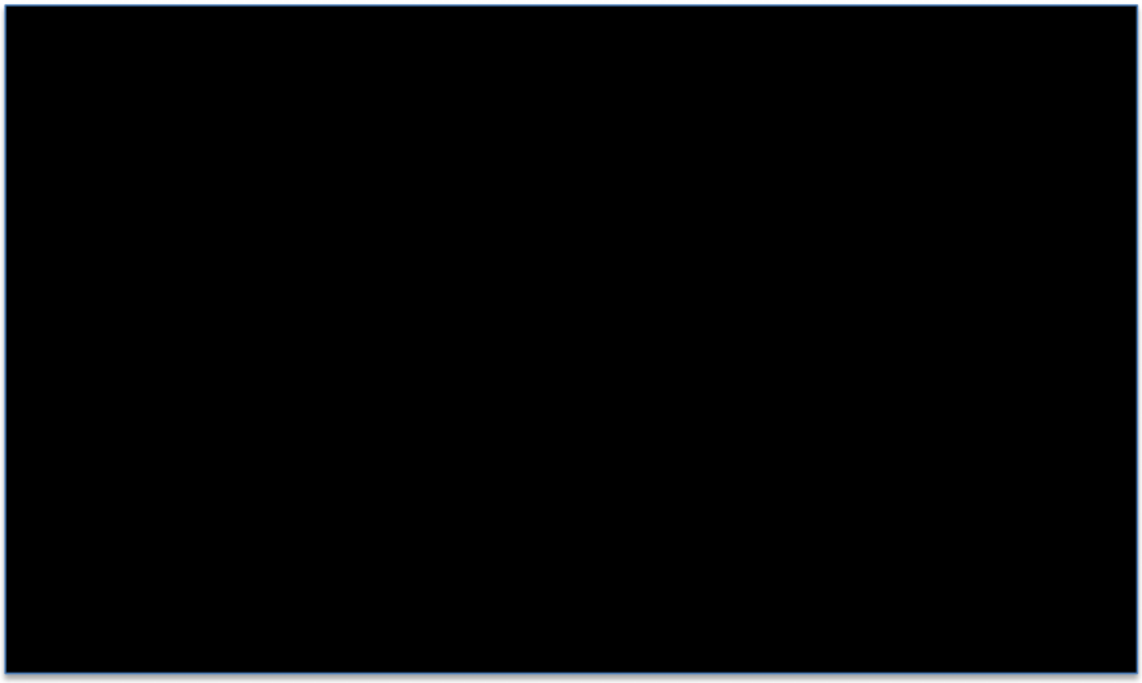


Figure 24: Tornado diagram for the comparison of dacomitinib versus erlotinib, using the list prices

Figure 25: Tornado diagram for the comparison of dacomitinib versus afatinib, using the list prices

Company's scenario analysis results (all treatments at list prices)

The results for each change made and the impact to the base-case results are presented in Table 50 through to Table 52 for the comparison between dacomitinib and the comparators, using the list prices. As seen in these Tables , under the scenario of using log-logistic parametric curves for OS had the greatest impact to the base-case ICER for dacomitinib against all comparators.

Table 50: Results of base-case scenario analysis for the comparison between dacomitinib and gefitinib (using the list prices)

Scenario	Dacomitinib			Gefitinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51: Results of base-case scenario analysis for the comparison between dacomitinib and erlotinib (using list prices)

Scenario	Dacomitinib			Erlotinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52: Results of base-case scenario analysis for the comparison between dacomitinib and afatinib (using list prices)

Scenario	Dacomitinib			Afatinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3.3 Model validation and face validity check

The company provided validity checks by comparing their clinical and cost-effectiveness results against those in previous studies. Briefly, from the model the company reported median PFS and OS for gefitinib, then compared these results to previous studies that included gefitinib as a comparison. Table 53 and Table 54 show the comparisons between the company's model and those reported in published studies for PFS and OS for gefitinib, respectively.

Table 53: PFS outcome for gefitinib versus previous published studies.

	Median	Proportion progression-free at			
		1 year	2 years	3 years	5 years
Base-case (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUX-Lung 7	10.9	39.5%	5.6%	1.5%	-
Lin 2016	12.1	54%	16.2%	8.4%	0.0%
WJTOG 3405	9.6	41.6%	12.4%	6.2%	-

Table 54: OS outcome for gefitinib versus previous published studies.

	Median	Proportion alive at						
		1 year	2 years	3 years	5 years	6 years	7 years	8 years
Base-case (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUX-Lung 7	24.5	84.6%	50.9%	32.7%	-			
Lin 2016	30.9	89.9%	66.3%	39.3%	14.6%	10.5%	6.6%	0.0%
WJTOG 3405	34.8	85.1%	64.3%	47.5%	21.0%	10.9%	6.8%	-

In addition to model validity checks, the company consulted with two clinical experts who provided information on key inputs used in the cost-effectiveness model.

ERG summary

Based on the parametric curves used, the ERG notes that the model predicts similar PFS and OS results for gefitinib as those observed in previous studies. However, we consider that the long-term extrapolations based on these parametric models to be pessimistic.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

5.4.1 The ERG's suggested amendments

On the basis of the critique of the submitted economic model, the ERG suggests an amended base-case. The rationale for these amendments has been given alongside the critique provided in Section 5.2 and is briefly summarised below.

- Changes in PFS: As explained in Section 5.2.6.2, the ERG consider that the extrapolations based on the generalised parametric curve for PFS along with the selected results from the FP NMA to be pessimistic beyond two years. Hence, we used the log-normal parametric curve for gefitinib with the results from the FP NMA to derive the survival for the other comparators (P1= 0.5, P2=1). Also, we assumed that afatinib PFS to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards.

- Changes in OS: As noted in Section 5.2.6.3, the ERG considers that OS estimates based on the generalised gamma parametric curve for patients randomised to gefitinib in ARCHER 1050 are consistently below what was observed in Lin et al. (2016)[58], which was an unhealthier than the population in ARCHER 1050. Additionally, expert advise sought by the ERG indicated that up to 5% of patients would be expected to be alive at 15 years. Hence, we used the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assumed equal efficacy, on the hazard scale, from 36 months onwards. Extrapolations based on the log-logistic parametric curve was consistent at 5- and 7-year data from both Lin et al. (2016)[58] and WJTOG 3405[57].

- Disutilities associated with adverse events: As explained in Section 5.2.10, the ERG deems that application of disutility values associated with AEs is necessary, as it is unlikely that the EQ-5D had been administered at the time-point where these AEs occurred. Hence, we included disutilities associated with AEs.

- Post-progression utility values: The ERG used a weighted-mean utility value for post-progression from the ARCHER 1050 trial. We considered these values to be more appropriate, in line with the NICE DSU reccommendations to maintain the same data source for health state values.[3] (see a Section 5.2.10).

- Age-related disutilities: The health utility values used in the model were not age-adjusted. Including age-related disutilites takes into consideration the effect of ageing on a person's HRQoL. We derived age-related disutilities from the widely used algorithm published by Ara and colleagues.[4]

- Correction to how the PAS for gefitinib had been applied in the model: On inspection, the ERG identified that the publicly available PAS discount for gefitinib had been applied incorrectly in the economic model (see Section 5.2.11). An amendment was made in the model to correct for this error.

During communication with the NICE Technical Team overlooking this appraisal, it was agreed that ERG will undertake and present an additional analysis based on the the comparison between dacomitinib (applying the company's PAS discount) versus the comparators (at list prices). This analysis forms the basis on which any ERG amendments and preferred assumptions are applied.

For each of these amendments, the values used in the company's base-case analysis and the values preferred by the ERG (given in bold) can be found in 55 below. Results of the ERG base-case analysis are presented in Section 6.1.

Table 55. Values and assumptions used in the ERG's base-case analysis.

Parameter	Values in company's base-case	ERG's preferred value	Section where justification is given
PFS for gefinitib	Generalised gamma; FP NMA (P1=0.5; P2=1.5)	Log-normal; FP (P1=0.5;P2=1); assumed PFS equal to mean PFS for dacomitinib and gefitinib from 36 months	Section 5.2.6.2
OS for gefinitib	Generalised gamma; FP NMA (P1=0.5; P2=1.5)	Log-logistic; FP(P1=0.5;P2=1); assumed equal efficacy, on the hazard scale, from 36 months onwards	Section 5.2.6.3
Incorporation of disutility due to AEs	Not included in the model	Diarrhoea: -0.15 Fatigue: -0.18 ALT increased: 0.00 Paronychia: -0.20 Rash: -0.20	Section 5.2.10

Post-progression utility value	0.64	[redacted]	
Age-related disutilities	Not applied in the model	Applied in the model	
Patient access scheme for gefitinib	Applied in cycle 2	Applied in cycle 3	Section 5.4.1
PFS: progression free survival; OS: overall survival; AEs: adverse events			

5.4.2 Probabilistic sensitivity analysis

The ERG re-run the PSA in order to obtain results that reflect the values and assumptions forming the ERG suggested base-case. The revised PSA results (joint distribution of cost and QALY estimates) were generated through 10,000 iterations and are depicted in the cost-effectiveness plane and cost-effectiveness acceptability curves presented in Section 6.2.

5.4.3 Additional deterministic analyses

The ERG undertook additional scenario analyses, where amendments made as part of the ERG's base-case were assigned alternative values. The following scenario analyses were undertaken:-

- For PFS, use the log-normal parametric curve for gefitinib with the results from the FP NMA to derive the survival for the other comparators (P1= 0.5, P2=1). Assume afatinib PFS assumed to be equal to the mean PFS of dacomitinib and gefitinib from 55 months onwards
- For OS, use the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assume equal efficacy
- Post-progression utility values obtained from Labbé et al.[2]
- Clinical effectiveness results from the company's NMA for OS

The main findings of this additional work are presented in Section 6.3 below.

5.5 Conclusions of the cost-effectiveness section

The company submission is based on a partitioned survival model used to show the experience of a cohort treatment naïve participants with locally advanced or metastatic non-small cell lung cancer with activating mutations in epidermal growth factor receptor (EGFR). The model is used to evaluate the cost-effectiveness of dacomitinib compared to gefitinib, erlotinib and afatinib. The

model captures the clinical and economic outcomes for this patient population, by incorporating clinical effectiveness information from the ARCHER 1050 trial, as well as using a novel FP NMA to model the survival for PFS and OS for the comparators. The costs included in the model relate to the direct costs incurred, including drug acquisition and administration costs, subsequent treatment costs, management costs, and costs associated with treatment of adverse events and terminal care treatment. While the model captures the key features of people living with NSCLC and includes some relevant costs and benefits; under the company's assumptions the base-case results are likely to be higher than that presented.

The company's base-case results are based on applying a discount of [redacted] to the cost of dacomitinib in the form of a PAS compared to the assumed PAS for the comparators. Under these assumptions, the company reported a deterministic ICER of approximately [redacted] when compared to gefitinib. Results from the PSA showed that there was a [redacted] probability that dacomitinib was cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

On inspection, no major errors in the company's model were identified. The results reported in the company submission reflected those in the model submitted. However, there were some concerns. First, the modelling of PFS and OS of gefitinib was pessimistic, potentially underestimating the number of QALYs and costs for all comparators. Secondly, the extrapolation of dacomitinib and afatinib was reliant on results from the FP NMA, the majority of which were not considered plausible by the ERG. Third, we noted that there were some resource use and costs that have been excluded from the analysis: unscheduled hospital admissions, MRI scans for suspected brain metastases or cord compression and costs associated with the diagnosis of T790M. Fourth, the company's base-case results excluded age-related disutilities, and disutilities associated with adverse events. Additionally, post-progression utility values were obtained from the literature, and not those collected from the ARCHER 1050 trial. The ERG believes that it is more appropriate to include these disutilities, as well as using the utility values obtained from the trial, which is more in line with the NICE DSU recommendations.[3] Last, the economic model has applied the (publicly available) PAS discount for gefinitinib incorrectly.

The majority of the ERG's concerns have been addressed, which is reflected in the ERG's preferred assumptions and thus base-case. However, it should be noted that the ERG's base-case reports the results based on the comparison between dacomitinib (PAS) versus the list prices for all comparators, which is not directly comparable to the company's base-case ICER.

6 IMPACT OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Impact of ERG changes on the company's base-case results.

In this section, we present the results following the changes in methods, parameters and inputs detailed above, executed one at a time. Results are presented for:

- the comparison between dacomitinib (with PAS discount) versus comparators (with company's assumed PAS discount) (i.e. the company's base-case analysis, presented in the main CS document)
- the comparison between dacomitinib (with PAS discount) versus comparators (at list prices, given in the CS Appendix).

6.1.1 Impact of ERG's suggested changes on comparison between dacomitinib (PAS) versus comparators (company's assumed PAS).

In Table 56, Table 57 and Table 58, we present the results for each change made and its impact on the company's results relating to PAS applied to dacomitininb versus the company's assumed PAS for each comparator. Across all comparisons and scenarios, the greatest impact to the pairwise ICERs was observed after using the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assuming equal efficacy, on the hazard scale, from 36 months onwards.

It must be noted that the tables below report the results for pairwise comparison (e.g. dacomitinib versus gefitinib; dacomitinib versus erlotinib and dacomitinib versus afatinib) so that the impact of each assumption on the resulting ICER can be seen more clearly (last two columns in the tables). An alternative presentation, focusing on the impact of each assumption on the results for all treatments (incremental comparison) is presented in Appendix (Section 10.1.1).

Table 56: Results of scenario analysis for the comparison between dacomitinib and gefitinib (dacomitinib PAS vs gefitinib assumed PAS).

Scenario	Dacomitinib			Gefitinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction of the PAS applied to gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 57: Results of scenario analysis for the comparison between dacomitinib and erlotinib (dacomitinib PAS vs erlotinib assumed PAS)

Scenario	Dacomitinib			Erlotinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction of the PAS applied to gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 58: Results of scenario analysis for the comparison between dacomitinib and afatinib. (dacomitinib PAS vs afatinib assumed PAS)

Scenario	Dacomitinib			Afatinib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction of the PAS applied to gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.1.2 Impact of ERG's suggested changes on the comparison between dacomitinib (PAS) versus erlotinib, gefitinib and afatinib (list prices).

In Table 59, Table 60 and Table 61 we present the exploratory analysis results based on the comparison between dacomitinib (with the company's PAS discount applied) versus comparator (at list prices). As it can be seen in Table 59 and Table 61 across all scenarios dacomitinib continued dominating gefitinib and afatinib, respectively.

Table 60 reports the results based on the comparison between dacomitinib and erlotinib. Applying the PAS discount to dacomitinib and using the list price for erlotinib, resulted in an ICER of approximately [redacted] per QALY. The scenario of fitting the log-normal parametric curve to gefitinib with the results of the FP NMA (selecting P1= 0.5, P2=1) and assuming the PFS for afatinib to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards had the greatest impact to the ICER, with an increase to approximately [redacted] per QALY.

ERG summary

Here we undertook exploratory analyses based on the company's base-case, which applied a discount in the form of a PAS to dacomitinib and assumed PAS for the comparators. Based on our changes made, across all comparisons and scenarios, using the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assumed equal efficacy, from 36 months onwards had the greatest impact to the pairwise ICERs. Additionally, we undertook scenario analyses using the PAS discount for dacomitinib and list prices for all comparators. As expected, dacomitinib dominated gefitinib and afatinib, across all scenarios. The pairwise comparison between dacomitinib and erlotinib showed that the total expected mean costs for dacomitinib was more than the costs for erlotinib. Under the scenario of using the log-normal parametric curve for gefitinib with results from the FP NMA to derive survival for erlotinib (and afatinib) and assuming afatinib PFS to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards had the greatest impact to the model.

Table 59: Results of scenario analysis for the comparison between dacomitinib and gefitinib (both at list prices)

Scenario	Dacomitinib			Gefitinib			ICER
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 60: Results of base-case scenario analysis for the comparison between dacomitinib and erlotinib (both at list prices)

Scenario	Dacomitinib			Erlotinib			ICER	% change in ICER
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61: Results of base-case scenario analysis for the comparison between dacomitinib and afatinib (both at list prices)

Scenario	Dacomitinib			Afatinib			ICER
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS) using log-normal and P1=0.5; P2=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS) using log-logistic and HR=1 from 36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2 Results of ERG base-case analysis.

As explained in Section 5.4.1, following communication with the NICE Technical Team, it was agreed that the ERG base case analysis should relate to

- dacomitinib (with PAS discount proposed by manufacturer) versus comparators (at list prices).

Carrying out all of the changes detailed in Section 5.4.1 simultaneously, that is, implementing the ERG's preferred assumptions, gave the following results.

A table detailing changes in the submitted economic model spreadsheet in order to implement each of ERG ammendments is given in Appendix 10.1.3. (Appendix Table 17).

6.2.1 ERG base-case results (dacomitinib with PAS vs comparators at list prices)

In Table 62, we present the results for the comparison between dacomitinib (PAS) versus comparators (list prices), whilst keeping all other assumptions fixed, before the ERG suggested amendments were implemented. These results show that dacomitinib dominated gefitinib and afatinib, thus being less costly and more effective. In comparison to erlotinib, dacomitinib was approximately [redacted] more expensive and expected to yield [redacted] more QALYs, with an ICER of approximately [redacted] per QALY gained.

Table 62. Deterministic results using the PAS for dacomitinib and the list prices for the comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

In Table 63, we present the results of analysis based on the ERG preferred assumptions. Based on our preferred assumptions the results show that treatment with erlotinib had the lowest total mean

costs and was expected to yield the lowest number of QALYs. Treating people with dacomitinib yielded the highest number of QALYs and had a corresponding total mean cost of approximately [redacted] per QALY gained. Dacomitinib was cheaper and yielded more QALYs than gefitinib and afatinib, hence dominated these strategies. Therefore, applying the [redacted] discount to dacomitinib compared to erlotinib (using list price), and under the ERGs preferred assumptions resulted in an ICER of approximately [redacted] per QALY.

Table 63: ERG base-case results (point estimates, dacomitinib with PAS vs comparators at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

6.2.2 ERG's sensitivity analyses (dacomitinib with PAS vs comparators at list prices)

In Table 64, we report the PSA results based on the outcome cost per QALY only. These results show that the PSA slightly underestimated the expected mean costs across all comparators, while the expected mean QALYs are in line with the deterministic results. Gefitinib and afatinib continued to be dominated by dacomitinib. In comparison to erlotinib, dacomitinib had an ICER of approximately [redacted] per QALY.

Table 64: ERG probabilistic sensitivity analysis results, using the assumed the PAS for dacomitinib and list prices for comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

In Figure 26 and Figure 27, we present the results of the PSA in the form of a scatterplot on the cost-effectiveness plane and a CEAC, respectively. Results from 10,000 simulations show that there is considerable uncertainty in the incremental QALYs and less so for the incremental costs. Note, the scatterplot presents dacomitinib against each of the three comparator drugs (showing incremental costs and QALYs) and the legend indicates the comparator drug being visualised. For the comparison between dacomitinib and afatininb a small number of iterations/simualtions are in the south-west quadrant, which signifies that dacomitinib may be less costly and less effective than afatinib.

At a WTP threshold of £30,000 per QALY, [redacted] of the simulations for the comparison between dacomitinib and erlotinib were below and up to the threshold.

Figure 26: Scatterplot of strategies on the cost-effectiveness plane, ERG base-case

Figure 27: Cost-effectiveness acceptability curve, ERG base-case

6.2.3 ERG scenario analysis (dacomitinib with PAS vs comparators at list prices)

As explained in Section 5.4.3, in order to test the impact of using values alternative to those employed in the ERG base-case analysis, the ERG performed additional scenario analyses. Briefly, the alternative specifications were:

- For PFS, use the log-normal parametric curve for gefitinib with the results from the FP NMA to derive the survival for the other comparators (P1= 0.5, P2=1). Assume afatinib PFS assumed to be equal to the mean PFS of dacomitinib and gefitinib from 55 months onwards
- For OS, use the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assume equal efficacy
- Post-progression utility values obtained from Labbé et al.[2]
- Clinical effectiveness results from the company's NMA for OS

The results for these analyses are presented in Table 65 through to Table 68. The results show that dacomitinib dominated gefitinib and afatinib for all scenarios. When compared to erlotinib, across all scenarios dacomitib remained cost-effective.

Table 65: ERG scenario analysis, using the log-normal parametric curve for gefitinib

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 66: ERG scenario analysis, using the log-logistic parametric curve for gefitinib

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 67: ERG scenario analysis, using utility values reported in Labbé et al.

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 68: ERG scenario analysis, using results from the NMA for overall survival

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

ERG summary

We undertook scenario analyses based on the ERG's preferred assumptions, and using PAS discount for dacomitinib and list prices for other comparators. Across all scenarios, dacomitinib dominated gefitinib and afatinib; however, remained cost-effective when compared to erlotinib.

7 END OF LIFE

The company has not presented a case in support of dacomitinib as an 'end of life' treatment. NICE prescribes that, for an 'end of life' case to be made, the appraised treatment needs to satisfy all of the following criteria: i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and; iii) the treatment is licensed or otherwise indicated, for small patient populations. The ERG considers that these criteria are not met.

8 OVERALL CONCLUSION

The evidence of clinical effectiveness for dacomitinib in EGFR-positive NSCLC comes from an RCT comparing dacomitinib to gefitinib and a NMA comparing dacomitinib to afatinib. The ARCHER 1050 trial found a favourable effect for dacomitinib on many key outcomes, including PFS, although the risk of performance bias, baseline imbalance in potential prognostic factors and some ERG identified issues with the trial statistics should be considered. The NMA used a fractional polynomial approach and the methods were reasonably described and the approach justified. Areas of uncertainty include whether the populations in the two trials were homogeneous enough to be compared and the suitability of the results to the extrapolations required for the cost-effectiveness analysis. Finally, the ERG believes the submitted evidence may not be generalisable to the population in England and Wales.

The company's economic analysis was based on a partitioned survival model programmed in Microsoft Excel. The ERG considered the choice of model and its structure to be appropriate to capture the long-term costs and benefits for treating people with EGFR+ advance/metastatic NSCLC with dacomitinib compared to the comparators. The comparators included in the base-case analysis were appropriate, and in line with the NICE scope for treatment of first-line EGFR+

patients. All comparators were in keeping with their marketing authorisation and licensed dosing schedule.

Reasonable methods were used to identify information to populate the economic model, with the clinical information obtained from the ARCHER 1050 trial and a fractional polynomial network meta-analysis. The resource use and costs were in keeping with the viewpoint of the economic analysis, with information obtained from the key trial as well as from the published sources. Under the company's assumptions, the base-case deterministic ICER was approximately [redacted] per QALY gained. Probabilistic sensitivity analysis results showed that dacomoitinib had a [redacted] probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Alterations were made to the company's economic model that formed the basis for the ERG's model, which resulted in differences between the company's base-case results and those reported by the ERG. It should be noted that the company's results were presented on the basis of the comparison between dacomitinib with PAS discount and comparators with assumed/speculated PAS discounts (company's base case), while the ERG's preferred assumptions were applied to the comparison between dacomitinib with PAS versus comparators at list prices. The latter comparison could be viewed as favouring the intervention.

We highlighted several areas or concern/uncertainty, which shows that the company's ICER could potentially be overestimated. First, the extrapolations for PFS and OS of gefitinib was pessimistic, potentially underestimating the number of QALYs and costs for all comparators. Second, the extrapolation of dacomitinib and afatinib was reliant on results from the FP NMA, the majority of which were not considered plausible by the ERG. Third, the exclusion of some resource use and costs from the analysis: unscheduled hospital admissions, MRI scans for suspected brain metastases or cord compression and costs associated with the diagnosis of T790M. Fourth, the exclusion of age-related disutilities, and disutilities associated with adverse events. Additionally, post-progression utility values were obtained from the literature, and not those collected from the ARCHER 1050 trial. Last, the economic model has applied the (publicly available) PAS discount for gefinitinib incorrectly.

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10 APPENDICES

10.1.1 ERG's individual parameter changes.

To determine the impact of the ERG's preferred assumptions on the company's results, the ERG modified the latest version of the company's economic model (submitted as part of the company's response to ERG's request for clarifications, in February 2019) by implementing the following amendments:

- For PFS, use the log-normal parametric curve for gefitinib;
- For PFS, use the log-normal parametric curve for gefitinib with the results from the FP NMA to derive the survival for the other comparators (p1= 0.5, p2=1). Assume afatinib PFS assumed to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards;
- For OS, use the log-logistic parametric curve for gefitinib;
- For OS, use the log-logistic parametric curve for gefitinib with the results from the FP NMA, and assume equal efficacy, on the hazard scale, from 36 months onwards;
- Include disutilities associated with adverse events;
- Use the post-progression utility value from the ARCHER 1050 trial;
- Including age-related disutilites from the study published by Ara and colleagues[4];
- Correction to how the PAS for gefitinib had been applied in the model;

The remainder of this section presents the obtained results for: (i) the comparison between the PAS for dacomitinib versus the company assumed PAS for the comparators (hereafter comparison (i)), and (ii) the comparison between dacomitinib versus comparators, all at list prices (hereafter comparison (ii)).

PFS, log-normal parametric curve for PFS data for gefitinib

In this exploratory analysis, we fitted the log-normal parametric curve to the observed progression-free survival data for gefitinib, then exptrapolated beyond the trial time horizon. Other PFS curves

for dacomitinib, afatinib and erlotinib were generated by applying the time-varying hazard ratios from the FP NMA to the log-normal gefitinib extrapolation. Appendix Table 1 and Appendix Table 2 present the results for this change. For comparison (i), the ICER for dacomitinib versus gefitinib (the non-dominated treatment) is approximately [redacted] per QALY. For comparison (ii), the ICER for dacomitinib versus erlotinib is approximately [redacted] per QALY.

Appendix Table 1. Exploratory results, fitting the log-normal parametric curve to PFS data for gefitinib (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 2. Exploratory results, fitting the log-normal parametric curve to PFS data for gefitinib (all treatments at least prices).

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

PFS, log-normal parametric curve for gefitinib and assumed afatinib PFS to be equal to the mean PFS of dacomitinib and gefitinib from 36 months onwards

The results for these analyses are presented in Appendix Table 3 and Appendix Table 4. Assuming that the PFS for afatinib is equal to the mean PFS for dacomitinib and gefitinib from 36 months onwards resulted in an ICER for dacomitinib versus gefitinib of about [redacted] per QALY for

comparison (i), and an ICER for dacomitinib versus erlotinib of approximately [redacted] per QALY for comparison (ii).

Appendix Table 3. Exploratory results, PFS for afatinib is assumed to be the mean survival for gefitinib and dacomitinib from 36 months onwards (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 4. Exploratory results, PFS for afatinib is assumed to be the mean survival for gefitinib and dacomitinib from 36 months onwards (all treatments at least prices).

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Overall survival, log-logistic curve to OS data for gefitinib

We fitted the log-logistic parametric curve to the observed OS data for gefitinib, then extrapolated beyond the trial time horizon. This change resulted in a slight increase to the expected mean costs and mean QALYs across all comparators for comparison (i). The ICERs for comparison (i) and comparison (ii) can be seen in Appendix Table 5 and Appendix Table 6, respectively.

Appendix Table 5. Exploratory results, fitting the log-logistic parametric curve to OS data for gefitinib (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 6. Exploratory results, fitting the log-logistic parametric curve to OS data for gefitinib (all treatments at list prices)

Treatment	Expected mean costs (£	Incremental [illegible] (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

OS, log-logistic curve to OS data for gefitinib and assumed equal efficacy, on the hazard scale, from 36 months onwards

Here, we fitted the log-logistic parametric curve to the OS data for gefitinib and assumed a hazard ratio of 1 is applied from 36 months onwards. Applying a HR=1 results in reduction to the post-progression survival and thus post-progression QALYs (results not shown). For comparison (i) afatininb is associated with an approximate ICER of [redacted] per QALY as compared to gefitinib. The ICER for dacomintinib compared to afatinib is approximately [redacted] per QALY. Under these assumptions resulted in an increase to the ICERs. (see Appendix Table 7). For comparison (ii), the ICER for afatinib (versus gefinitib) and dacomitinib (versus afatinib) are over [redacted] and [redacted] per QALY, respectively (Appendix Table 8).

Appendix Table 7. Exploratory results, log-logistic curve for OS gefitinib and HR of 1 after 36 months (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 8. Exploratory results, log-logistic curve for OS gefitinib and HR of 1 after 36 months (all treatments at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Disutilities associated with adverse events

This analysis is based on including disutilities associated with adverse events. The ERG considers that these experiences by the participants are not adequately captured in the company's base case analysis. The results are presented in Appendix Table 9 and Appendix Table 10 for comparisons (i) and (ii) respectively.

Appendix Table 9. Exploratory results, including disutilities associated with adverse events (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 10. Exploratory results, including disutilities associated with adverse events (all treatments at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Post-progression utility value from the ARCHER 1050 trial

In the original submission, the company assigned a utility value of 0.64 (SE:0.03) obtained from the Labbé and colleagues[2] for people in the post-progression health state. In response to our clarification question, the company provided utility values based on EQ-5D data collected at the end-of-treatment/post-treatment follow-up visits, by trial treatment arm. From the mean utility values submitted we derived a weighted-mean value of [redacted] and, in this analysis we assigned this to people in the post-progression health-state. The results are presented below (Appendix Table 11 and Appendix Table 12). The impact of this change resulted in an increase to the expected mean QALYs across all comparators, while the expected mean costs remained fixed. For comparison (i), the ICER for dacomitinib (versus gefitinib) is approximately [redacted] per QALY. For comparison (ii), the ICER for dacomitinib (versus erlotinib) is over [redacted] per additional QALY.

Appendix Table 11. Exploratory results, using the post-progression utility value from ARCHER 1050 trial (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 12. Exploratory results, using the post-progression utility value from ARCHER 1050 trial (all treatments at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Age-related disutilities

In this analysis, we have included age-related disutilities which takes into consideration the effect of ageing on a person's health-related quality of life. These age-related disutilities have been derived by an algorithm, which estimates the general population utility scores as a function of age and gender.[4] Results for comparisons (i) and (ii) appear in Appendix Table 13 and Appendix Table 14 .

Appendix Table 13. Exploratory results, including age-related disutilities in the model (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 14. Exploratory results, including age-related disutilities in the model (all treatments at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Correction to how the PAS for gefitinib had been applied in the model

This analysis corrects the application of the PAS arrangement for gefitinib, by applying the charge incurred on receipt of the fourth packet of treatment. The ERG received confirmation from the manufacturer via NICE. As expected this change resulted in a derease to the expected mean costs for gefitinib, and expected to yield [redacted] QALYs. For comparison (i), the resulting ICER for dacomitinib combared to gefitinib is approximately [redacted] per QALY. The particular change in PAS is not relevant to the comparision (ii) (i.e. all treatments at least prices), so no results for this comparison are reported below.

Appendix Table 15. Exploratory results, correcting the PAS arrangement applied to gefitinib (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

10.1.2 Evidence on the equivalence of erlotinib and gefitinib

Appendix Table 16. SR/MAs on the equivalence of erlotinib and gefitinib

	Haspinger 2015	***Lee 2014***	***Liang 2014***	***Haaland 2014***	***Yang 2017***
SR design	**Indirect comparison using RCTs**	**Indirect comparison using RCTs**	**Indirect comparison using RCTs**	**Indirect comparison using RCTs**	**Direct comparison including non-randomised data**
Search	PubMed, Cancer-Lit, Embase-databases and Cochrane-Library; The proceedings of the 2008–2014 conferences of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and International Association for the Study of Lung Cancer (IASLC), World Conference of Lung Cancer; unpublished RCTs were considered for inclusion.	PubMed, ASCO and ESMO congress databases	PubMed, EMBASE and the Central Registry of Controlled Trials of the Cochrane Library; abstract books and presentations of major recent meetings of American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and World Conference on Lung Cancer in 2008–2012; reference lists	Medline (PubMed); American Society of Clinical Oncology Meeting Library, European Cancer Congress 2013, Chinese Clinical Trial Registry, clinicaltrials.gov, EU Clinical Trials Register, and UMIN Clinical Trials Registry; limited to clinical trials published within the last 5 years	PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure from inception through 17 December 2016, limited to "human studies" where possible, with no restrictions placed on the time, language and format (abstract or full text) of publication; abstracts of 40 American Society of Clinical Oncology and European Society of Medical Oncology meetings, including their annual meetings and the meetings related to lung cancer, two major trial registration websites

					(www.clinicaltrials.gov/ and www.who.int/ictrp/); reference lists
Inclusion	Nine RCTs of gefitinib, erlotinib, afatinib	Four Asian randomised controlled phase-III trials of erlotinib and gefitinib	Twelve phase III RCTs that investigated EGFR-TKIs (erlotinib, gefitinib, afatinib and icotinib)	Eight RCTs of gefitinib, erlotinib, afatinib	Eight randomized trials and 82 cohort studies with a total of 17,621 patients assessing gefitinib, erlotinib and afatinib
Treatment line	First line	First line	First or second line	First line	14 studies were conducted in first-line settings, 21 in ≥second-line settings, and the others in both or did not specify the line of treatment
Outcome	Overall response, safety	Progression-free survival	Objective response rate (ORR), progression free survival (PFS), overall survival (OS)	Progression-free survival, overall response rate and disease control rate	Progression-free survival, overall survival, overall response rate, disease control rate
Conclusion	All treatments had similar efficacy but they differ for toxicities; the main toxicity of erlotinib was diarrhoea, gefitinib gave hypertransaminasemia and afatinib skin toxicity,	Difference in favour of erlotinib	No statistically significant differences in efficacy	Differences among gefitinib, erlotinib, and afatinib were not statistically significant	All three drugs had similar effectiveness. Less dose reduction (RR, 0.34; 95% CI, 0.21 to 0.54, p<0.0001) and grade 3/4 adverse events (RR, 0.78; 95% CI 0.65 to 0.94,

	mucositis and diarrhoea. Treatment discontinuation was more frequent in the afatinib group, but comparable for erlotinib and gefitinib.				p=0.01) with gefitinib than with erlotinib. Gefitinib was associated with more grade 3/4 liver dysfunction (RR, 2.88; 95% CI, 1.56 to 5.28, p=0.0007), but fewer grade 3/4 rash (RR, 0.43; 95% CI, 0.27 to 0.70, p=0.0005), any-grade diarrhoea (RR, 0.83; 95% CI, 0.75 to 0.93, p=0.0007), any-grade nausea/vomiting (RR, 0.60; 95% CI, 0.43 to 0.85, p=0.003), and grade 3/4 paronychia (RR, 0.19; 95% CI, 0.04 to 0.84, p=0.03) compared with erlotinib. Although the majority of included studies were observational and potential imbalance in patient characteristics between gefitinib and erlotinib groups could be of concern, sensitivity analyses that included the studies with low risk of bias only showed that the summary estimates were robust and very close to those

					from the overall meta-analyses.
Sponsor/ conflict of interest	All authors of this manuscript declare no potential conflicts of interest.	Funded by Roche. Prof Author has received educational grant, research contracts, and donations from pharmaceutical companies including AstraZeneca, Boehringer Ingelheim, Eisai, Janssen, Pfizer, Novartis, and Roche.	The authors have no support or funding to report. The authors have declared that no competing interests exist.	Funding not stated. Dr. de Castro has received honoraria from Astra Zeneca, Boehringer Ingelheim, and Roche. Dr. Lopes has received honoraria and research funds from Astra Zeneca, Eli Lilly, Roche, and Sanofi. The remaining authors declare no conflict of interest.	Grant sponsors: Faculty Postdoctoral Fellowship Scheme from Faculty of Medicine of the Chinese University of Hong Kong. The authors declare no conflict of interest.
Included studies	IPASS Mok, 2009 Gefitinib WJTOG3405 Mitsudomi, 2010 Gefitinib NEJ002 Maemondo, 2010 Gefitinib First-SIGNAL Han, 2012 Gefitinib TORCH Gridelli, 2012 Erlotinib OPTIMAL Zhou, 2011 Erlotinib	IPASS Gefitinib WJTOG Gefitinib OPTIMAL Erlotinib NEJGSG Gefitinib	IPASS Gefitinib First-SIGNAL Gefitinib NEJ0027 Gefitinib WJTOG 3405 Gefitinib INTEREST* Gefitinib V 15–32* Gefitinib	IPASS Gefitinib West Japan Gefitinib North-East Japan Gefitinib First-SIGNAL Gefitinib OPTIMAL Erlotinib EURTAC Erlotinib LUX-Lung 3 Afatinib LUX-Lung 6 Afatinib	8 RCTs (n/group); % ≥2nd line: Jin Y 2016 China G vs. E (50/50); NR Kim ST 2012 Korea G vs. E (48/48); 100% ≥2nd line Lin QX 2016 China G vs. E (25/25); NR Park K 2016 Korea G vs. A (159/160); 0% ≥2nd line

	EURTAC Rosell, 2011 Erlotinib LUX-Lung 3 Sequist, 2012 Afatinib LUX-Lung 6 Wu, 2013 Afatinib		OPTIMAL Erlotinib EUTRAC Erlotinib TITAN1* Erlotinib LUX-lung 3 Afatinib LUX-lung 6 Afatinib ICOGEN* Icotinib *=Previously treated		Soria JC 2015 Global E vs. A (397/398); 100% ≥2nd line Urata Y 2016 Japan G vs. E (279/280); 100% ≥2nd line Xie YL 2015 China G vs. E (27/23); 0% ≥2nd line Yang JJ 2015 China G vs. E (128/128); 36% ≥2nd line plus 80 retrospective cohort studies and 2 prospective cohort studies

10.1.3 ERG's changes in the economic model.

Appendix Table 17. Description of changes made in the economic model for the purposes of ERG's analyses.

Description of changes to the economic model for ERG's base-case and scenario analyses	Implementation of the change in the model
ERG's individual parameter changes to the company's base-case	
Change PFS distribution for gefitinib to log-normal	"Clinical Inputs" tab, change cell F48 to 'Log-normal'
Change afatinib PFS extrapolation to be the mean of dacomitinib and gefitinib from 36 months	1. Ensure log-normal PFS distribution is chosen, alongside PFS FP model of P1=0.5 and P2=1. 2. "Survival Curves" tab. Copy cells J18:J214. Paste as values back into J18:J214. 3. Replace cell J58 with '=AVERAGE(H58, I58)'. 4. Drag this formula down for the rest of column J, until cell J214
Change OS distribution for gefitinib to log-logistic	"Clinical Inputs" tab, change cell F19 to 'Log-logistic'
Change OS distribution for gefitinib to log-logistic and OS HR =1 from 36 months	"Clinical Inputs" tab, change cell F19 to 'Log-logistic' and "Clinical Inputs" tab, change cell J18 to 'Yes'
Add adverse event disutility	"Utility" tab, change cell E20 to 'Yes'
Change post-progression utility to reflect value from ARCHER 1050	"Utility" tab, change cell E12 to '0.72'
Add age-related disutility	"Utility" tab, please see ERG's model to see changes. The implementation is completed with the adjustment to formulae in "Model Engine" tab: AA20 change to '=(INDEX(i.UtilityPFS.Inputs,macro.IncludeComp)+ Utility!H40)*T20' and drag down for the rest of the column AA. AB20 change to =((i.UtilityPPS.Inputs)+Utility!H40)*U20 And drag down for the rest of column AB.
Correct the implementation of Gefitinib PAS	"Model Engine" tab. In cell AL20, change formula to: '=IF(AND(macro.IncludeComp=2,'Medical Costs_Drugs'!$J$13="Yes"),IF(C20=3,12200,0),ME.TxCost_UnitCost)*J20' Drag this formula down for the rest of column AL
ERG's preferred assumptions (all changes made simultaneously)	
Change afatinib PFS extrapolation to be the mean of dacomitinib and gefitinib from 36 months	1. Ensure log-normal PFS distribution is chosen, alongside PFS FP model of P1=0.5 and P2=1. 2. "Survival Curves" tab. Copy cells J18:J214. Paste as values back into J18:J214.

	3. Replace cell J58 with '=AVERAGE(H58, I58)'. 4. Drag this formula down for the rest of column J, until cell J214
Change OS distribution for gefitinib to log-logistic and OS HR =1 from 36 months	"Clinical Inputs" tab, change cell F19 to 'Log-logistic' and "Clinical Inputs" tab, change cell J18 to 'Yes'
Add adverse event disutility	"Utility" tab, change cell E20 to 'Yes'
Change post-progression utility to reflect value from ARCHER 1050	"Utility" tab, change cell E12 to '0.72'
Add age-related disutility	"Utility" tab, please see ERG's model to see changes. The implementation is completed with the adjustment to formulae in "Model Engine" tab: AA20 change to '=(INDEX(i.UtilityPFS.Inputs,macro.IncludeComp)+ Utility!H40)*T20' and drag down for the rest of the column AA. AB20 change to =((i.UtilityPPS.Inputs)+Utility!H40)*U20 And drag down for the rest of column AB.
Correct the implementation of Gefitinib PAS	"Model Engine" tab. In cell AL20, change formula to: '=IF(AND(macro.IncludeComp=2,'Medical Costs_Drugs'!$J$13="Yes"),IF(C20=3,12200,0),ME.TxCost_UnitCost)*J20' Drag this formula down for the rest of column AL
Scenario analyses based on ERG's preferred assumptions	
Afatinib equivalent to dacomitinib from crossing point	1. Ensure log-normal PFS distribution is chosen, alongside PFS FP model of P1=0.5 and P2=1. 2. Go to tab "Survival Curves" 3. Copy Cells J18:J214 4. Create new tab and paste as values 5. Copy those values, and paste back into J18 on "Survival Curves" tab 6. In cell J78 of "Survival Curves", replace the value with the formula "=H78" and drag this formula down for all below cells in column J , until J214. 7. Re-run model
Assuming equal efficacy between afatinib and dacomitinib	Ensure that log-logistic OS distribution is selected. "FP NMA HR" tab, copy values from cells E17 to M17, then paste values into E17 to M16. Re-run the model
Change post-progression utility value to that obtained from Labbé et al.	"Utility" tab, change E12 to '0.64'
Clinical effectiveness results from the company's NMA for OS	"Clinical Inputs" tab, for overall survival select 'constant HR (NMA BC)' from the drop down box

Additional changes	
Remove comparator PASs assumed by company	"Medical Costs_Drugs" tab, change cell J13 to 'No', and cells J14 and J15 to '0%'

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer [ID1346]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 4 March** using the below proforma 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 proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

ERG scenarios not reported in results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92 The equally plausible scenarios considering no additional survival benefit beyond 48 and 60 months (OS HR=1) are reported in Table 25; however, these scenarios appear to not have been considered when computing the cost-effectiveness estimates. By doing so, the report seems to bias the results and to direction the reader of the report to the most conservative analyses.	Please consider the equally plausible scenarios in which no additional survival benefit beyond 48 and 60 months is observed (OS HR=1)in the cost-effective analyses. These results should be reported in the ERG report.	It is stated in the ERG report (page 88) that '*The ERG acknowledge that implementing the HR=1 assumption from 48 months and 60 months could also be considered plausible, and investigated these in scenario analyses*.' In order to provide the committee with all the available data for decision making these scenarios should be included in the report.	The ERG accept that assuming a HR =1 from 48 or 60 months may also be plausible, but maintain that implementing this adjustment from 36 months is the most plausible option that is also supported by the available evidence. The loss of the initial OS benefit of dacomitinib over gefitinib was observed in ARCHER 1050, as captured by the company's 2nd order fractional polynomial models and the ERG's resctricted cubic spline model, was maintained even when the ten latest events in the dacomitinib arm were instead censored in the ERGs analysis of the digitised data. There is no factual error, and the ERG are happy to present additional analyses if requested by NICE.
Page 90 It is stated that: '*The ERG's*	Please consider a scenario in which the equivalent post-progression between all comparators is assumed. The scenario	In addition to the clinical adviser comments it reads in the ERG report that '*assuming that dacomitinib offers the most pre-*	The ERG accepts that post-progression survival could be manipulated by varying the

clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis, however the nature of the partitioned survival model meant that this could not be implemented as the post-progression survival is estimated as the difference between the PFS and OS.'	can be easily added to the model by simply changing the treatment waning scenario to equal 70 months. The approach will have some minor limitations associated with discounting; however it predicts almost equivalent PPS across all treatments. The proposed change to the wording is as follows: '*The ERG's clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis, however the nature of the partitioned survival model meant that this could not be implemented* ***explicitly. Nonetheless, a simple naïve adjustment was made to the model to assess the impact of the potential impact assumption and this was included in scenario analysis***.'	*progression survival gain, it is plausible that post-progression survival could be equal or less than the post-progression survival of the comparators*' (page 90). As such, the ERG base-case that predicts an afatinib PPS benefit over gefitinib/erlotinib is inconsistent.	time at which the HR = 1 assumption is implemented. However, the optimal timing for the implementation of this assumption is influenced by many factors in the economic model and could not be readily investigated by the ERG in the timeframe of this appraisal. There is no factual error, and the ERG are happy to undertake and present additional analyses if requested by NICE.

Issue 1 Incorrect interpretation of hazard ratios

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89: Figure 14 '*Under the models fitted with ERG's preferred PFS and OS assumptions, dacomitinib provides an OS and PFS benefit over the comparators, but has a shorter post-progression survival time, consistent with the scenario*	The ERG interpretation of hazard ratios is incorrect. The company suggests the following wording to be removed from the ERG report *'Under the models fitted with ERG's preferred PFS and OS assumptions, dacomitinib provides an OS and PFS benefit over the comparators, but has a shorter post-progression survival time, consistent with the scenario of the degree of the pre-progression benefit not being*	This is an incorrect interpretation of hazard ratios given that hazard ratios demonstrate a relative effect and not an absolute effect. To have an equivalent absolute gain in PFS and OS (i.e. equivalent post-progression survival) does not require an equivalent hazard ratio given that PFS and OS are different	The ERG agrees that HR demonstrate a relative effect, rather than an absolute effect, and have removed the HR values from the end of the sentence. The rest of the sentence is still valid.

of the degree of the pre-progression benefit not being repeated in the OS benefit as has been observed in ARCHER 1050 (PFS HR: 0.59, OS HR: 0.76).'	*repeated in the OS benefit as has been observed in ARCHER 1050 (PFS HR: 0.59, OS HR: 0.76).'*	baselines. For example a 5 month gain in both PFS and OS (i.e. equal post-progression survival) over a control with 10 month PFS and 20 month OS would not provide the same hazard ratios for PFS and OS.	

Issue 2 Inaccuracies between ERG proposed base-case and ERG reported statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 88-89 It is stated that: '*The ERG agree with the first point' that the assumption of a HR=1 for the OS of all comparators from 36 months is 'based on censored data that is driven small patient numbers'.*	The scenario assuming no survival benefit beyond 36 months should be removed from consideration for decision making.	Given that the ERG acknowledges that the 36 months cut-off is '*based on censored data that is driven small patient numbers'* other scenarios should be considered. In addition, with this arbitrary cut-off applied the resulting survival curves for dacomitinib and afatinib do not have external validity. The predicted mean OS under this ERG scenario results in a 1.0 month mean gain for dacomitinib ([redacted]) versus afatinib ([redacted]), which is misaligned with the median gains over gefitinib of 7.3 and 3.4 months observed respectively in ARCHER 1050 and LUX-Lung 7. Although these are medians, it is implausible that a doubled median gain would result in only 1 month mean survival gain.	The company have misquoted the ERG report. The sentence in question reads: *"The ERG agree with the first point, that it is unclear what happens beyond the trial follow-up, but this argument could be placed against the company's own base-case analysis"* The company has not provided evidence to suggest that there is a significant difference in OS between afatinib and dacomitinib, and so it is plausible that any difference between the interventions may be slight. The ERG also maintain that it is incorrect to compare mean and median gains in survival.

Page 92 ERG PFS and OS HR=1 at 3 years provides clinically implausible post-progression life years		The ERG reports on page 90 that '*the ERG's clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis*.' The company is in agreement with the statement of the clinical adviser given that upon progression there is no clinical rationale for patients to have differing prognosis given they are eligible for the same subsequent treatments and will present with similar prognosis.	There is no factual error here. It is clinically plausible for there to be variation in post-progression survival times, as seen in trials where the difference in mean PFS exceeds the difference in mean OS.
Page 92: Table 25 ERG PFS and OS HR=1 at 3 years provides clinical implausible predictions compared to the ERG base-case PFS		The ERG base-case predicts that on the dacomitinib arm [redacted]% of patients will be on treatment at 36 months. This is inconsistent with the assumption that there is no additional benefit of dacomitinib after 3 years compared to gefitinib. Only [redacted]% of patients in the gefitinib arm are on treatment at 36 months.	The HR=1 assumption was generated by the need to obtain a plausible extrapolation using the model provided by the company, whilst also being consistent with what was observed in ARCHER 1050.
Page 88: Incorrect interpretation '*The ERG also digitised the cumulative hazard plots of OS from ARCHER 1050 provided by the company. These were seen to be parallel from 27 months, suggesting there was no difference in OS efficacy beyond*	The ERG's interpretation of the cumulative hazards is incorrect. As such, the company suggests the following wording to be removed from the ERG report: *'The ERG also digitised the cumulative hazard plots of OS from ARCHER 1050 provided by the company. These were seen to be parallel from 27 months, suggesting there was no difference in OS*	Parallel cumulative hazard plots suggest that proportional hazards holds and not that the hazard is the same between the treatment. They do not suggest that there is no further benefit. The convergence observed just beyond this time points is due to the	The company's interpretation would be correct if it was referring to log-cumulative hazard plots, which are parallel when proportionality is present. In the present case, the company's interpretation is incorrect, as cumulative hazard

this point.'	*efficacy beyond this point.'*	immaturity of the data (censoring) that was acknowledge by the ERG in clarification question B6.	plots are not parallel under a proportional hazards assumption.

Issue 3 PFS KOL feedback

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 74: Incorrect interpretation '*The company opted for the generalised gamma, despite stating that its 3 and 5 year PFS estimates were too low when examined by their clinical experts. They also explored using a log-normal curve as an alternative scenario*.'	The company suggest the following amendment: *'The company opted for the generalised gamma, despite stating that* ***PFS was considered to be underestimated when examined by their clinical experts. They also explored using a log-normal curve as an alternative scenario; however this was considered to overestimate PFS by their clinical expert.****'*	CS page 101: 'Clinicians suggested they would expect the true survival to fall somewhere between the upper and lower models'	There is no factual error. The ERG would like to point out that the company's original submission states that the log-normal curve "was considered to **slightly** overestimate long-term PFS".

Issue 4 Neglect of plausible scenario that are pivotal for decision making

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 120 *'These results showed that the discount rate applied to benefits and using the log-logistic parametric curve to model OS for gefitinib were the key drivers to the ICERs.'* Page 125	Given the omission of treatment beyond progression, the company suggest the following amendments: • on page 120: 'These results showed that the discount rate applied to benefits**, using the log-logistic parametric curve to model OS for gefitinib and including treatment beyond progression** were the key drivers to	Despite the ERG acknowledging that treatment beyond progression is a key driver in scenario analysis; it appears to have been neglected from all ERG analysis with no justification. This is a concern for the company given the large impact on the cost-effectiveness this assumption has and the availability of TTD data was queried during	We have amended the text to: 'These results showed that the discount rate applied to benefits**, using the log-logistic parametric curve to model OS for gefitinib and including treatment beyond progression** were the key drivers to the ICERs and

'As seen in these Tables, under the scenario of using log-logistic parametric curves for OS had the greatest impact to the base-case ICER for dacomitinib against all comparators.'	the ICERs and including treatment beyond progression.' • on page 125: 'As seen in these tables, under the scenario of using log-logistic parametric curves for OS **and including treatment beyond progression** had the greatest impact to the base-case ICER for dacomitinib against all comparators.' Due to these omissions, the treatment beyond progression scenario included in the MS (where a fixed cost is applied upon progression) should be included within the ERG scenario analyses.	ERG clarification B11.	including treatment beyond progression.' 'on page 125: 'As seen in these tables, under the scenario of using log-logistic parametric curves for OS **and including treatment beyond progression** had the greatest impact to the base-case ICER for dacomitinib against all comparators.' Treatment beyond progression is included in the company's scenario analysis. However, the ERG did not present a scenario analysis as the company's model (latest version: ID1346 dacomitinib company model v0.3 060219 JE [ACIC]) omitted the time-to-treatment discontinuation data.

Issue 5 Incorrect interpretation of follow-up visit utility value

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16: Incorrect interpretation *'On clarification, the company provided utility values collected from participants in ARCHER 1050 trial who were in the post-*	The utility values provided in response to clarification question B10 have been misinterpreted. Therefore, the company suggest the following amendment: *'On clarification, the company provided utility values collected from participants in ARCHER 1050 trial **at a single***	The values provided in the response to clarification question B10 only represent data collected at a single post-treatment follow-up (at least 28 days, and no more than 35 days after end of treatment visit	The ERG maintain that sentence in question is valid. However, to improve the clarity of this sentence, we will amend to: *'On clarification, the company provided utility values*

progression health state.'	***post-treatment follow-up (at least 28 days, and no more than 35 days after end of treatment visit).***'	assessments). Patients are in the post-progression state from the points of progressing until death, therefore the utility values must capture the gradual decline over the patients remaining life, especially prior to death. Therefore, this single post-treatment follow-up value does not capture the quality-of-life fully across the post-progression state.	*collected from participants in ARCHER 1050 trial in the* **post-progression state at follow-up visit (28-35 days following end of treatment visit).'** *CS section B.3.3.4. states:* *"Patients were assumed to be treated until progression, with PFS being used as a proxy for treatment duration."* Therefore, the post-treatment follow up which occurred after the end of treatment is within the company's defined 'post-progression' health state as stated by the ERG. The post-progression state in the company model contains progressing patients and patients on 2nd and 3rd line therapy. The company used utility figures reported in the Labbe et al. 2017 study of 0.64 but Labbe et al. also report utility values of 0.72 for patients not on other systemic treatments typically chemotherapy. Longitudinal results in Labbe et al. are collected over a mean of 12 months from date of diagnosis with mean of 3.2 encounters per patient with no

			data on time-length how long into the progressing stage or proximity to death these patients were when EQ-5D was captured. Based on a sample of n=81 progressing patients. ARCHER figures based on n=182. The Labbe et al. results in the CS sensitivity analysis were 0.77 for PFS and 0.64 for PD representing a 0.13 decrease in utility. The ERG use a value for gefitinib and erlotinib of [redacted] for PFS and 0.72 for PD representing a similar decrease of [redacted]. A sensitivity analysis using the Labbe et al. result for PD was also conducted by the ERG.
Page 18: Incorrect interpretation '*However, as ARCHER 1050 trial utility data were available for PD'*	The utility values provided in response to clarification question B10 have been misinterpreted. Therefore, the company suggests the following wording to be removed from the ERG report: *'However, as ARCHER 1050 trial utility data were available for PD'*.	Same as above.	Same as above
Page 96: Incorrect interpretation '*In light of the company's original assertion that this trial data was*	The utility values provided in response to clarification question B10 have been misinterpreted. Therefore, the company	Same as above.	*"Given that EQ-5D was not collected beyond progression in ARCHER 1050, the PD utility*

not collected'	suggests the following wording to be removed from the ERG report: '*In light of the company's original assertion that this trial data was not collected*'		*was sourced from the literature." (CS, p.112).* As discussed above, the post-treatment follow up collection was in the post-progression period defined by the company, therefore it was collected. However, for clarity, we will amend to ***"The company did not recognize the post-treatment utility values from ARCHER 1050 as a post disease (PD) progression value, therefore it used a PD utility of 0.64 from the literature"***.

Issue 6 Adverse event disutility double counting

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 99 '*The company's suggestion that including disutility decrements in their base-case would constitute 'double-counting' as the patient collected EQ-5D from the trial would already capture a HRQoL detriment, is viewed as unfounded by the ERG. EQ-5D data was collected on day one of each 28-*	The company disagrees with the ERGs conclusion. Therefore, the company suggest the text is substituted with the following: ***'Within the company base-case, AE disutility's were not included to avoid 'double counting' as the treatment specific PF values were assumed to already capture the effect of any AEs as these were informed by the trial data.'***	The ERG is suggesting that the utilities measured in ARCHER 1050 do not represent the adverse events observed in ARCHER 1050. However, there is no other clear explanation for the difference in EQ-5D observed in both ARCHER 1050 and LUX-Lung (MS Section 3.4) other than the differences in safety profiles of the treatments (MS	This is not a factual error. The ERG has explained the limitations of using EQ-5D to capture AE data clinical trial. The ERG believes adverse events have not been **fully** captured by the company's use of treatment specific PF values and as such state "*it is likely that a large proportion of*

day cycle whereas average duration of the 2 most common frequently reported treatment related AE in dacomitinib patients, diarrhoea (7.9%) and paronychia (7.5%), were assumed to occur for a duration of 6.6 and 12.3 days respectively. As the EQ-5D asks patients about their health state on the day of the month they complete the form (EuroQol, 1990), it is likely that a large proportion of adverse events were not captured in the trial data. *Therefore, the ERG strongly believes that disutility is not fully represented in the company's base-case and that the inclusion of the treatment specific disutility decrements is founded*.'		Section B.2.10.4).	*adverse events were not captured in the trial data".*
Page 100 '*The ERG finds the rationale for omitting AE disutilities from the base-case on the grounds of double counting to be unfounded and will specifically include a disutility decrement in their base-case analysis*.'	The company disagrees with the ERGs conclusion. Therefore, the company suggests the following wording to be removed from the ERG report: 'The ERG finds the rationale for omitting AE disutilities from the base-case on the grounds of double counting to be unfounded and will specifically include a disutility decrement in their base-case analysis.'	Same as above.	Same as above
Page 108 *'The ERG did not consider that the inclusion of AE disutilities would constitute as double-*	The company disagrees with the ERGs conclusion. Therefore, the company suggest the text is substituted with the following: ***'This is a reasonable assumption.'***	Same as above.	Same as above

counting because it is unlikely that the EQ-5D had been administered at the time-point when the events occurred. Hence, disutility would have been under represented.'			

Issue 7 Proportion of European sites

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: Incorrect percentage reported on '*There were no UK sites participating in the trial and only [redacted] of sites were from European countries.*'	The company suggest the following amendment: 'There were no UK sites participating in the trial and [redacted] of sites were **in** European countries.'	Of the 71 sites the following were in Europe: Italy (13 sites), Poland (3 sites), and Spain (17 sites)).	This is an error by the ERG, as the sentence should have reflected the proportion of participants rather than the proportion of sites (as per p33 in the ERG report). In response, we have amended the text to: ***There were no UK sites participating in the trial. The proportion of participants from European countries was approximately [redacted].***

Issue 8 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15: 'elevant'	'**r**elevant'		Thank you, we have made the necessary correction.
Page 25: 'dacomininib'	'dacomi**t**inib'		Thank you, we have made the necessary correction, and also

			further corrected pages 47 and 159.
Page 36 'ECFR'	'E**G**FR'		Thank you, we have made the necessary correction.
Page 93 'acrossthe'	'across the'		We were unable to locate this mistake in our report, and could not perform a correction.

Issue 9 Gender balance in ARCHER 1050

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32: Misrepresentation of CS '*The CS states that the difference in gender was not unexpected given the higher frequency of EGFR mutations among females than males. However, this does not explain the imbalance since EGFR mutations were required for inclusion and randomisation should have ensured an even distribution between arms.*'	Given that this is an incorrect interpretation of the company's comment in the CS, the company suggests the following wording to be removed from the ERG report '*The CS states that the difference in gender was not unexpected given the higher frequency of EGFR mutations among females than males. However, this does not explain the imbalance since EGFR mutations were required for inclusion and randomisation should have ensured an even distribution between arms.*'	The CS is discussing the difference between the portion of males and females as stated by the ERG and not the balances of females between treatment arms which the ERG is alluding to.	When discussing the baseline characteristics of the ARCHER 1050 trial, the CS states (page 38) "*Although there was some differences in gender (females comprised 64.3% and 55.6% of the dacomitinib and gefitinib arms, respectively), this was not unexpected as EGFR mutations in NSCLC are more common among females*". It was not clear to the ERG that this was referring to the ratio of females to males as clarified here and was interpreted by the ERG as referring to the different proportions of females in the dacomitinib and gefitinib arms given the data presented. Although this is not a factual

			error, the ERG have changed the text to: ***The CS refers to the difference in proportions of females and males in the trial (which is expected given higher frequency of EGFR mutations in females) but makes no reference to the difference in the rates of females across the arms of the trials.***

Issue 10 Gender and ECOG prognostic factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32: Not presented data from ARCHER 1050 '*Gender is a potential prognostic factor (see Section 4.2.1). The CS states that generally there is no difference in outcomes between ECOG PS 0 and 1, citing ARCHER 1050 as evidence.*'	This statement from the ERG is not fully represented of the data from ARCHER 1050. Therefore, the company suggest the following amendment: '**Gender and ECOG are potential prognostic factors, however no significant difference were observed in either PFS or OS in ARCHER 1050 for these subgroups (insignificant interaction p-values).**'	Non-significant interaction terms for PFS (A9 response) and OS (Figure 14 MS) were observed in ARCHER 1050 for both gender and ECOG status.	The CS make no reference to the difference in gender as a prognostic factor and this statement is the ERG's summary of the evidence subsequently reviewed in the ERG report. With regard to performance status the ERG state that the evidence from ARCHER 1050 is used to show there is no difference in outcomes in the PS subgroups. No further action required.

Issue 11 Inaccurate summary of ARCHER 1050 secondary outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 58: Incorrect reporting of the data *'A statistically significant improvement in the primary outcome of PFS was found in favour of dacomitinib and some, but not all, secondary outcomes also favoured dacomitinib.'*	This statement from the ERG is not fully representative of the data from ARCHER 1050. Therefore, the company suggest the following amendment: '*A statistically significant improvement in the primary outcome of PFS was found in favour of dacomitinib**. Statistically significant improvements were also observed in secondary outcomes of PFS by investigator assessment, OS, DoR and TTF.**'*	All secondary outcomes (PFS investigator assessment, OS, ORR, DoR, TTF) numerically favoured dacomitinib in ARCHER 1050 (CS Section B.2.6.3) with PFS investigator assessment, OS, DoR and TTF all reaching statistical significance.	This is an overall summary and reflects the data, which for some secondary outcomes showed a statistically significant effect and for others did not. The data themselves are reported in more detail elsewhere in the ERG report. No action required.

Issue 12 Traditional proportional hazard NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 56: *'As noted above, the CS undertook a traditional NMA using the Bucher method42 using gefitinib as the common comparator. This preserves the randomisation within the included trials. The CS states that the baselines characteristics between the two included trials were generally well balanced. As noted above the ERG considers there is a potential for the transitivity assumption to be violated. The CS hazard ratios from the NMA for PFS (independent review) and*	This statement is an incorrect interpretation of the company's comment in the CS. Therefore, the company suggest the following amendment: '*As noted above, the CS undertook a traditional NMA akin to the Bucher method[42] using gefitinib as the common comparator. This preserves the randomisation within the included trials. The CS states that the baselines characteristics between the two included trials were generally well balanced. As noted above the ERG considers there is a potential for the transitivity assumption to be violated. The CS hazard ratios from the NMA for PFS (independent review) and OS are presented in CS Tables 80 and 81 respectively.*'	As discussed in the CS (page 67), the traditional NMA undertaken by the company was akin to the Bucher method in that it used gefitinib as the common comparator however this was applied in the model naïvely to the baseline gefitinib curve. Therefore, there are no formal outputs from the traditional NMA to report in the main text or appendix.	There is no factual error. The ERG maintain that the company failed to present the results for the pairwise comparison of afatinib and dacomitinib.

OS are presented in CS Tables 80 and 81 respectively. While the CS states that an indirect treatment comparison was undertaken, the ERG has noted that the findings from this indirect comparison were neither presented in the main report, nor in the CS Appendix.'			

Issue 13 Incorrect description of model transition inputs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 73 'Four clinical outcomes from ARCHER 1050 were used to inform the transitions between health states in the model: • Progression-free survival • Overall survival • Adverse events of treatment • Health-related quality of life'	The statement from the ERG is incorrect, therefore, the company suggest the following amendment: '**Two** clinical outcomes from ARCHER 1050 were used to inform the transitions between health states in the model: • Progression-free survival • Overall survival'	Adverse events and HRQoL did not inform the model transitions.	We accept this error and we have amended the text to : ***Two clinical outcomes from ARCHER 1050 were used to inform the transitions between health states in the model:*** • ***Progression-free survival*** • ***Overall survival***

Issue 14 Unclear statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 85: Unclear and CIC	The statement from the ERG is unclear, therefor the company cannot suggest an	Not clear what the percentages are referring to and percentages should	CIC marking and a clarification about the time point these

marking 'When applied to the log-logistic extrapolation, the company's FP predicts 6.9% alive on dacomitinib compared to 2.4% on gefitinib.'	amendment.	be CIC marked if related to survival outputs.	percentages refer to have now been added: 'When applied to the log-logistic extrapolation, the company's FP predicts [redacted] alive on dacomitinib compared to [redacted] on gefitinib ***at 5 years.***

Issue 15 CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89: Figure 14	Please mark as CIC	Not marked as CIC in line with all other survival analyses.	This figure was produced using publicly available data. Confidential marking is not necessary.

Issue 16 Misrepresentation of stomatitis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 94: '*In addition to frequency, this data also suggests that the mix of AEs considered may also be different with the notable inclusion of stomatitis that could potentially be relevant at >5% thres*hold.'	Given that this is an incorrect interpretation of the company's comment in the CS, the company suggests the following wording to be removed from the ERG report: '*In addition to frequency, this data also suggests that the mix of AEs considered may also be different with the notable inclusion of stomatitis that could potentially be relevant at >5% threshold*'	Please see response to Response B9ii. It was explain that stomatitis was an outlier given that of the 26 events that are reported across 8 patients that experienced grade 3 stomatitis, 17 of these 26 events were from a single patient.' Therefore, due to this single outlier it is incorrect to suggest it should be included under the 5% threshold.	The wording has been amended to: ***"The mix of AEs represented in table 27 shows the inclusion of stomatitis. Clarification data from the company reported [redacted] events across [redacted] patients experiencing grade 3 stomatitis, [redacted]. However, stomatitis is a dermatological AE commonly***

			associated with irreversible EGFR TKI inhibitors (Melosky et al., 2015) and showed clinically meaningful worsening in HRQOL in dacomitinib patients assessed using the EORTC QOL questionnaire in ARCHER 1050. Therefore, inclusion of stomatitis in AE data may be relevant and warranted." *Ref:* Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki-induced dermatologic adverse events. *Curr Oncol*. 2015;22(2):123-32.
Page 100 *'Last, the ERG believes disutilities associated with AEs have been under-represented within the model and is concerned that other AEs such as stomatitis should have been considered as clinically these are relevant.'*	Given that this is an incorrect interpretation of the company's comment in the CS, the company suggests the following wording to be removed from the ERG report: *'Last, the ERG believes disutilities associated with AEs have been under-represented within the model and is concerned that other AEs such as stomatitis should have been considered as clinically these are relevant.'* to be removed from the ERG report.	Same as above.	The ERG states 2 concerns which are based on trial data and on wider evidence: 1. disutilities associated with AEs have been under-represented within the model 2. other AEs such as stomatitis should have been considered as clinically these are relevant The impact of stomatitis (sore mouth) within ARCHER 1050 patients was clinically significant in dacomitib patients

			and therefore its inclusion as an AE could be justified. (Wu et al., 2017, p.1463) No amendment required.

Issue 17 Missing inference of impact of missing cost on cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 106 *'With this in mind, we consider that these costs included in the model are likely to be an underestimate of the true costs associated with managing/treating people with NSCLC.'*	The company believe the ERG statement is missing an interpretation of the impact. Therefore, the company suggest the following amendment: *'With this in mind, we consider that these costs included in the model are likely to be an underestimate of the true costs associated with managing/treating people with NSCLC.* ***However, they would have been applied equally to all treatment so would therefore have had no incremental impact on costs.'***	This is a minor limitation and it should be emphasised that this has no impact on the cost-effectiveness.	We do not consider that there is a factual error in this sentence, hence no change to the text is necessary. The ERG maintain that there is no certainty that the use of the excluded resources (MRI scans for suspected brain metastases or cord compression and costs associated with the diagnosis of T790M), will be equal or comparable between the treatment groups. No justification for such an assumption, or evidence to support it, is offered in the CS. Given this, the ERG consider that it would be inappropriate to state that the costs would have been equal across treatments (and therefore would have no impact on the

			cost-effectiveness analysis), as the company suggests in their proposed amendment.

Issue 18 ERG has not commented on validation compared to previous CE analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 129 'Based on the parametric curves used, the ERG notes that the model predicts similar PFS and OS results for gefitinib as those observed in previous studies. However, we consider that the long-term extrapolations based on these parametric models to be pessimistic.'	The company believes the ERG has omitted validation presented in the CS. Therefore, the company suggest that the ERG includes validation to previous CE analysis and acknowledge that these provide external validity for the company base-case.	ERG has failed to mention previous CE analysis validation which compared LYs CS pg. 136 	The ERG has presented validation compared to observed studies in section 5.3 of the ERG report. This comparison of different extrapolations, which were obtained using different approaches without any consideration of the heterogeneity of the studies, should be treated with caution.

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346). ERG Addendum 1.

Produced by: **Warwick Evidence**

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Date completed: 15th March 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/156/04

Declared competing interests:

PA, EL, DG, MJ, RC, JP, JK, XA, JC, JG, JM and LA declare no competing interests.

LA declares an honorarium received from Pfizer for participation in a panel set up to provide expert opinion on aspects of an unrelated submission to NICE (Tofacitinib for moderately to severely active ulcerative colitis [TA574]).

Acknowledgements:

The ERG team are grateful to Dr John Green (BSc MBChB DM FRCPE FRCP) who acted as an expert clinical advisor throughout the course of this appraisal.

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This report should be referenced as follows:

Auguste P., Loveman E., Gallacher, D., Jordan M., Court R, Patterson J., Kaur J., Green J., Colquit J., Armoiry X., Mason J and Andronis L. *Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346): A Single Technology Appraisal.* Warwick Evidence, University of Warwick, February 2019.

Contributions of authors

Lazaros Andronis (Senior Research Fellow) led and co-ordinated the project; **Peter Auguste** (Research Fellow) co-ordinated and conducted the appraisal of the economic evidence; **Emma Loveman** (Senior Researcher) co-ordinated and conducted the appraisal of clinical effectiveness evidence; **Daniel Gallacher** (Research Fellow) conducted the appraisal of statistical elements in the submission; **Mary Jordan** (Research Associate) contributed to the appraisal of the economic evidence; **Rachel Court** (Information Specialist) conducted ERG searches and the critique of the company searches; **Jacoby Paterson** (Clinical Fellow) contributed to the appraisal of the clinical effectiveness evidence; **Jatinder Kaour** (Academic F2 Doctor) contributed to the appraisal of the clinical effectiveness evidence; **John Green** (Consultant in Oncology) contributed to the appraisal of the clinical effectiveness evidence; **Jill Colquit** (Senior Researcher) contributed to the appraisal of the clinical effectiveness evidence; **Xavier Armoiry** (Professor of Pharmacology) contributed to the appraisal of statistical elements (Network Meta Analysis), **James Mason** (Professor of Health Economics) contributed to the appraisal of the economic evidence. All listed authors contributed to writing sections of the report, and reviewed and commented on the final version of the report.

Additional Scenario Analyses

In response to a request by NICE, we have undertaken additional analyses in relation to the following scenarios:

- No additional survival benefit (OS HR=1) are assumed after 48 months and 60 months.
- Equivalent post-progression survival is assumed between all comparators.

Analyses reported here relate to the comparison between dacomitinib with the company's PAS discount applied versus all comparators at their list prices. Results are presented in terms of additional cost per life-year gained (LYG) and additional cost per quality-adjusted life year (QALY) gained in

Table 1 and Table 2, respectively.

Table 1: Scenario analyses (no additional survival benefit after 48 months and 60 months, and equivalent post-progression between comparators) reported in terms of cost per LYG.

Treatment	Expected mean costs (£)	Incremental costs (£)	Progression-free LYG	Post-progression LYG	Expected mean LYG	Incremental LYG	ICER (£)
ERG's preferred base-case assumptions							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Hazard ratio = 1 from 48 months							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Hazard ratio = 1 from 60 months							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 (Equivalent post-progression survival from ERG base case, by implementing hazard ratio = 1 from 71 months)							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG: life-years gained							

Table 2: Scenario analyses (no additional survival benefit after 48 months and 60 months, and equivalent post-progression between comparators) reported in terms of cost per QALY gained.

Treatment	Expected mean costs (£)	Incremental costs (£)	Progression-free LYG	Post-progression QALY	Expected mean QALY	Incremental QALY	ICER (£)
ERG's preferred base-case assumptions							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Hazard ratio = 1 from 48 months							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Hazard ratio = 1 from 60 months							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 (Equivalent post-progression survival from ERG base case, by implementing hazard ratio = 1 from 71 months)							
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY, quality adjusted life-years gained							

We present in Table 3 the scenario analyses conducted along with the details of each change made.

Table 3: Summary of the additional changes made to undertake scenario analyses

Description of ERG change to economic model	Implementation of the change in the model
Scenario 1: Hazard ratio = 1 from 48 months	Change following formulae in sheet "FP NMA HR" K243 change, and drag down: =IF(AND(user_HR1_36months=2,B243>48),1,EXP(K$237+K$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,K$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0))) L243 change and drag down: =IF(AND(user_HR1_36months=2,B243>48),1,EXP(L$237+L$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,L$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0)))
Scenario 2: Hazard ratio = 1 from 60 months	K243 change, and drag down: =IF(AND(user_HR1_36months=2,B243>60),1,EXP(K$237+K$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,K$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0))) L243 change and drag down: =IF(AND(user_HR1_36months=2,B243>60),1,EXP(L$237+L$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,L$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0)))
Scenario 3 (Equivalent post-progression survival from ERG base case, by implementing hazard ratio = 1 from 71 months)	K243 change, and drag down: =IF(AND(user_HR1_36months=2,B243>71),1,EXP(K$237+K$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,K$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0))) L243 change and drag down: =IF(AND(user_HR1_36months=2,B243>71),1,EXP(L$237+L$238*IF($L$231,LN($C243),$C243^$L$229)+IF($L$233,L$239*IF($L$232,LN($C243),$C243^$L$230)*IF($L$234,LN($C243),1),0)))

Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346). – ERG Erratum

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Date completed: 13th March 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/156/04

Declared competing interests of the authors
None

gefitinib, and these changes were considered clinically meaningful (mean scores diarrhoea: 19.88 vs 7.32, p<0.0001; sore mouth: 15.09 vs 3.51, p<0.0001).

Statistically significant differences in the EQ-5D absolute VAS score and utility index were observed in favour of gefitinib.

Rates of any all-cause and treatment-related adverse events were similar between dacomitinib and gefitinib. There were slightly higher rates of any all-cause and any treatment-related grade 3 adverse event and serious adverse events with dacomitinib (based on observation of the proportions only), and dose reductions or temporary discontinuations were more frequently observed with dacomitinib.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS systematic review of clinical effectiveness was generally well executed. Two studies that the CS excluded from their broader review may have been eligible, however, these omissions would not have affected the results seen. Overall the ERG considered there to be a low chance of systematic error in the findings of the review.

The main clinical evidence for dacomitinib was drawn from the ARCHER 1050 trial which was a multi-centre study comparison with gefitinib. The trial had a high risk of performance bias (owing to the open-label design) but low risks of detection and attrition bias.

The ARCHER 1050 trial presents a number of potential issues in terms of representativeness to the population of England and Wales. There were no UK sites participating in the trial. The proportion of participants from European countries was approximately [redacted]. There was a high proportion of Asian participants, the population was limited to two epidermal growth factor receptor (EGFR) mutations only (albeit the most common ones), and the trial excluded people with brain metastases. In addition, there are imbalances in potential prognostic factors between arms.

The ERG have no concerns about the analysis sets used in the ARCHER 1050 trial or with the censorship and management of missing data used. The outcome measures appear appropriate. With regard to the trial statistics, the CS did not justify why a one-sided p-value was used for PFS and a two-sided p-value for OS and it is unclear to the ERG why there were different data time cut-off points for these two key analyses. The company did not provide significance thresholds alongside p-values presented throughout their submission, and it was unclear to the ERG whether formal

hypotheses were being tested or whether conclusions should be drawn, particularly for the sub-group analyses. The ERG considers that caution is required in the interpretation of the analysis of OS, as the proportional hazards assumption was violated. For patient reported outcomes, there was no adjustment for multiple comparisons.

The CS undertook a network meta-analysis (NMA) comparing dacomitinib with afatinib. The ERG agrees that other than the LUX-Lung 7 trial of afatinib versus gefitinib, there were no other relevant trials for the comparison. The CS adequately described the methods of their NMA approaches and provides a reasonable justification for using the fractional polynomial (FP) analysis. Despite this, the ERG has concerns over the use of the FP analysis with respect to the extrapolations for the survival outcomes but also because there are no detailed results or interpretation of the findings of the FP analysis.

In addition, the CS does not adequately assess the included study populations for transitivity and the ERG considers that the transitivity assumption may be violated. Finally, the CS does not present results of the indirect comparison between dacomitinib and afatinib. Although caution is recommended in the interpretation of the ERG analyses, these show no significant differences between the two respective treatments for PFS or OS.

1.4 Summary of cost-effectiveness evidence submitted by the company

The CS included a systematic review of economic evidence, a review of evidence on resource use and costs, a separate review to identify studies that measure health-related quality of life (HRQoL) in people with non-small-cell lung cancer (NSCLC) patients, and an electronic partitioned survival model built in a widely available spreadsheet application (Microsoft Excel ®).

The search for cost-effectiveness studies comparing the use of dacomitinib against other treatments did not identify any relevant references. The majority of the studies identified evaluated the cost-effectiveness of other treatments. Few relevant studies reporting resource use and costs were identified.

The company constructed a partitioned survival model to trace a cohort of treatment naïve patients with locally advanced or metastatic EGFR-positive NSCLC who may undergo treatment with dacomitinib compared to gefitinib, erlotinib or afatinib. Partitioned survival modelling considers the PFS and the OS curve directly, with the time in post-progression calculated using the difference

in area between the two curves. The company's model comprised three health states: progression-free, post-progression (progressed disease) (PD) and dead.

The model started from a hypothetical cohort of people reflective of the participants in the ARCHER 1050 trial,[1] all of whom began in the progression-free (PF) health state. Over time, people were at risk of progression or death. Transitions between health states was unidirectional and occurred at the end of each 28-day cycle, where people remained in the same health state or progressed. In each cycle, people incurred costs and accrued benefits depending on the health state they occupied. A half-cycle correction was applied in the base-case and the model concluded at a 15-year time horizon.

The company modelled PFS for gefitinib and erlotinib using a generalised gamma curve fitted to the gefitinib arm of ARCHER 1050. They then performed a FP NMA to obtain time-varying hazard ratios for afatinib and dacomitinib and apply these to the gefitinib extrapolation. The ERG found the company's predictions to be pessimistic and preferred a log-normal extrapolation and alternative adjustments for the comparators.

Similarly, for OS the company used a generalised gamma curve for gefitinib and applied HR obtained from FP NMA for the dacomitinib and afatinib. The ERG argues for a log-logistic extrapolation for gefitinib and suggests assuming a HR of 1 from 3 years onwards for the comparators.

Health-related quality of life values for the pre-progression health states were derived from the EQ-5D collected from the ARCHER 1050 study,[1] while utility values for the post-progression health state were obtained from the literature.[2] On clarification, the company provided utility values collected from participants in ARCHER 1050 trial[1] who were post-progression state at follow-up visit (28-35 days following end of treatment visit).. The ERG preferred the use of these utility values; hence they were included in the ERG's base-case. The impact of treatment related adverse events was not accounted for directly in the company's base-case analysis, as it was assumed that these would have been captured by EQ-5D data collected in the trial. However, the ERG argues that it is unlikely that quality of life decrements associated with treatment related AEs are captured by the EQ-5D, unless it is arranged for the instrument to be administered at the same time of these events. Utility decrements (disutilities) were included in the ERG's base-case for treatment related adverse events.

3 Critique of company's definition of decision problem

3.1 Decision problem

The company's decision problem is as follows:

- **Population**: People with untreated locally advanced or metastatic NSCLC with EGFR activating mutation(s).
- **Intervention**: dacomitinib
- **Comparators**: afatinib, erlotinib, gefitinib
- **Outcomes**: overall survival (OS); progression-free survival (PFS); overall response rate (ORR); duration of response (DoR); adverse events (AE); health-related quality-of-life (HRQoL).

There are no subgroups in the NICE scope or in the company decision problem, and there are no special considerations. The company's decision problem is consistent with the NICE scope. The evidence presented from the ARCHER 1050 trial has some deviations from the decision problem as summarised in Table 1.

Table 1: Differences between the decision problem and the evidence provided in the CS.

Issue	ERG comments
Population	
The ARCHER 1050 trial population have either exon 19 deletion (del19) or exon 21 L858R (L858R) substitutions.	This is a narrower population than all EGFR mutations as covered in the scope. Clarification A10 confirms that these were the established activating mutations at the time of design of the ARCHER 1050 trial. The ERG clinical advisor states this has been a common eligibility criteria in clinical trials. These two mutations make up approximately 90% of EGFR mutations (clarification response A4) but it is possible that the other mutations have less favourable responses to treatment. The European Medicines Agency (EMA) have published a positive opinion in January 2018 for dacomitinib monotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR activating mutations.[9] The ERG notes that the FDA approval for dacomitinib is in EGFR del19 or L858R substitutions specifically.[10]

However, of these potential comparator studies only one study was actually used in the comparison because there were no links between the other studies in the network (discussed in Section 4.3). This study, the LUX-Lung 7 trial[27, 28] included participants who would match the decision problem of the current appraisal (previously untreated adults with stage IIIB or IV NSCLC and EGFR mutation positive). Appendix D.1.7 lists reference details for included studies and excluded studies with reasons.

A PRISMA style flow-diagram with numbers is presented. Not all excluded studies were available in the original CS, but these were subsequently provided in response to clarification request A2. A two-stage study selection process was undertaken (titles and abstract screening, full paper screening) by two independent reviewers with arbitration from a third reviewer if necessary, for the main SLR. The CS does not state how studies were screened out of the network but the exclusions appear appropriate.

4.1.3 Critique of data extraction

The approach to the data extraction is appropriate (data extraction was by two independent, blinded reviewers and after reconciling differences a third reviewer could be included to reach consensus for any remaining discrepancies, data were extracted in to a pre-specified extraction form).

4.1.4 Quality assessment

The company assessed the quality of the ARCHER 1050 RCT using NICE recommended criteria (CS Table 15) and the Cochrane risk of bias tool (CS Appendix Table 75). There were some differences in the company's responses between these tools, which are summarised in Table 2. The ERG generally agrees with the company's judgements, and notes the potential performance bias (systematic differences in care or in exposure to other factors) that may arise from the open-label design. The risk of detection bias was considered to be low due to blinded IRC review of PFS and ORR (details of how blinding was achieved was provided in clarification response A12).

There was a higher proportion of women (64.3% vs 55.6%) and people with ECOG PS 0 (33% vs 28%) in the dacomitinib arm compared with the gefitinib arm (Section 4.2). The reason for these imbalances is unclear and could be due to selection bias (despite appropriate procedures in place) or could be due to chance. The CS refers to the difference in proportions of females and males in the trial (which is expected given higher frequency of EGFR mutations in females) but makes no

reference to the difference in the rates of females across the arms of the trials. Gender is a potential prognostic factor (see Section 4.2.1). The CS states that generally there is no difference in outcomes between ECOG PS 0 and 1, citing ARCHER 1050 as evidence. The ERG's clinical advisor noted that PS 0 and 1 are usually grouped together in trials, however there is evidence overall that ECOG PS may be an independent prognostic factor (see Section 4.2). The risk of selection bias is therefore uncertain.

The company gives the trial an overall judgement of high risk of bias due to the open-label design. The ERG agrees with this as the trial has a high risk of performance bias (differences between groups in care provided or in exposure to other factors), but notes that the risk of detection bias and attrition bias is low.

Table 2: Risk of bias assessment of ARCHER 1050.

Assessment criteria	**Company response**		**ERG response** (Cochrane tool)
	NICE criteria (CS Table 15)	**Cochrane tool (CS Appendix Table 75)**	
Method used to generate random allocations adequate?	Yes	Low risk	Low risk
Allocation adequately concealed?	Not applicable[a] Open label study	Low risk	Low risk
Groups similar at the outset of the study in terms of prognostic factors?	Yes	Low risk	Imbalance in gender and PS[b]
Care providers and participants blind to treatment allocation?	Not applicable Open label study	High risk	High risk
Outcome assessors blind to treatment allocation?		Low risk	Low risk
Unexpected imbalances in drop-outs between groups?	No	Low risk [d]	Low risk [d] Differences explained
Were the statistical analyses undertaken appropriate? [c]	Yes		
Evidence to suggest authors measured more outcomes than they reported?	No	Low risk	Low risk
Other bias	NR	Unclear Sponsored by pharmaceutical company	Low risk No other bias apparent
Overall judgement	NR	High risk Open-label	High risk

NR, not reported. [a]The company's response is referring to masking of treatment, rather than concealment of the allocation sequence, which the ERG considered appropriate as a central interactive web response system was used. [b] Potential prognostic factors (although not an item on the Cochrane tool). [c]Question as worded in CS Table 15; the full question should be 'Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?' [d]Cochrane risk of bias criterion: Attrition bias due to amount, nature or handling of incomplete outcome data.

Table 4: Baseline characteristics in ARCHER 1050

Baseline characteristic	Dacomitinib N=227	Gefitinib N=225
Male, n (%)	81 (35.7)	100 (44.4)
Female, n (%)	146 (64.3)	125 (55.6)
Age, years, median (range)	62 (28-87)	61 (33-86)
Age, years, mean (SD)	61.2 (11.26)	60.9 (10.17)
White, n (%)	56 (24.7)	49 (21.8)
Black, n (%)	1 (0.4)	0
Asian, n (%)	170 (74.9)	176 (78.2)
Japanese, n (%)	40 (17.6)	41 (18.2)
Mainland Chinese, n (%)	114 (50.2)	117 (52.0)
Other East Asian, n (%)	16 (7.0)	18 (8.0)
Never smoked, n (%)	147 (64.8)	144 (64.0)
Ex-smoker, n (%)	65 (28.6)	62 (27.6)
Smoker, n (%)	15 (6.6)	19 (8.4)
ECOG performance status 0, n (%)	75 (33)	62 (28)
ECOG performance status 1, n (%)	152 (67)	163 (72)
Stage IIIB at screening, n (%)	18 (8)	16 (7)
Stage IV at screening, n (%)	184 (81)	183 (81)
Unknown at screening [a], n (%)	25 (11)	26 (12)
del19, n (%)	134 (59)	133 (59)
L858R, n (%)	93 (41)	92 (41)
[a] Newly diagnosed with stage IV at time of study entry.		

There are more female compared with male participants in both treatment groups. The company has referred to this in their summary and have stated that this was to be expected, given the higher proportion of EGFR mutations in NSCLC occurring in females. Nonetheless, 64.3% are female in the dacomitinib group compared with 55.6% in the gefitinib group. The CS states in section B.2.13.2.2 that gender is not a prognostic factor for PFS in EGFR+ NSCLC, citing the ARCHER 1050 trial as evidence. The ERG has identified evidence which suggests that female gender may be an independent prognostic factor for NSCLC, including in those with EGFR-mutation positive NSCLC, summarised below.[30-33] In addition, evidence suggests that females respond better to

dacomitinib were acneiform ([redacted]), diarrhoea ([redacted]) and paronychia ([redacted]), while those related to gefitinib were and increase in ALT ([redacted]) and AST ([redacted]). All-causality adverse events are presented in CS Table 24 and follow a similar pattern.

Specific adverse events resulting in dose reductions, temporary discontinuation and permanent discontinuation are presented in CS Tables 26, 27 and 28, respectively. The most common all-cause adverse events leading to dose reduction were dermatitis acneiform (20.3%), paronchyia (16.7%) and diarrhoea (8.4%) for dacomitinib and increased ALT (2.7%) and AST (2.2%) for gefitinib. The median time to dose reduction was 2.8 months (Inter-quartile range, IQR, 1.3–4.2 months) for dacomitinib, with a median duration of 11.3 months (IQR 4.8–18.9 months). The median time to dose reduction for gefitinib was 3.3 months (IQR 2.4–4.2 months); median duration 5.2 months (IQR 2.5–7.9 months). Temporary discontinuation of dacomitinib resulted most commonly from dermatitis acneiform ([redacted]), paronchyia ([redacted]) and diarrhoea ([redacted]), and of gefitinib due to increased ALT ([redacted]) and AST ([redacted]). Treatment-related adverse events leading to permanent discontinuation of dacomitinib included dermatitis acneiform ([redacted]) and diarrhoea ([redacted]), and those leading to permanent discontinuation of gefitinib included increased ALT ([redacted]).

ERG summary: overall there were similar rates of all-cause and treatment-related adverse events between dacomitinib and gefitinib. However, there were higher rates of any all-cause and any treatment related Grade 3 adverse event and serious adverse events with dacomitinib (based on observation of the proportions only), and dose reductions or temporary discontinuations were more frequently observed with dacomitinib.

4.2.4 Other dacomitinib trials

The ERG identified five additional trials of dacomitinib 45 mg once daily in NSCLC to inform the evidence base on adverse events (dose escalation studies were not considered). One of these[36] was undertaken in treatment naive patients, the rest were undertaken in previously treated patients therefore a different patient population to the NICE scope (Table 9).

- Phase 2 single-arm study (NCT00818441) of dacomitinib in advanced NSCSC (adenocarcinoma subtype) as first-line treatment.[36]

5.2.6 Treatment effectiveness and extrapolation

Two clinical outcomes from ARCHER 1050 were used to inform the transitions between health states in the model:

- Progression-free survival
- Overall survival

5.2.6.1 Time-to-event extrapolation

The company chose to extrapolate both PFS and OS using a combination of parametric and fractional polynomial (FP) models. A generalised gamma model was fitted separately to both the observed PFS and OS data of the gefitinib arm of ARCHER 1050 and extrapolated across the model time horizon. The data used for PFS extrapolation was obtained from Wu et al. (data cut July 2016),[1] whereas the OS data came from Mok et al. (data cut February 2017).[29]

Equivalent efficacy was assumed between gefitinib and erlotinib, whereas for afatinib and dacomitinib, time-varying hazard ratios of their relative effects to gefitinib were estimated using a FP network meta-analysis (NMA). The hazard ratios were then applied to the generalised gamma extrapolation of gefitinib to predict PFS and OS for dacomitinib and afatinib. The ERG have concerns over this approach, as the resulting extrapolations from FP models can be unstable and extremely implausible. The company encountered this during their model selection process, and excluded many FP models based on their implausibility. FP models offer benefits to traditional parametric curves when fitting to survival data with unusual hazard profiles, but it is unclear whether they offer a benefit when extrapolating.

5.2.6.2 Progression-free survival

The company selected a parametric curve for gefitinib through consideration of visual fit, goodness-of-fit statistics and clinical plausibility. They also compared predicted quantiles to those observed in ARCHER 1050. The parametric models had a similar visual fit, and the goodness-of-fit statistics suggested that the Weibull, log-logistic and generalised gamma were the best fitting to the data. The company's clinical experts stated that whilst the 3-year estimates for the log-logistic and log-normal were too optimistic, the 5-year estimates were realistic. The log-logistic and log-normal

It is apparent that the effect of afatinib relative to gefitinib decreases and appears to tend towards 1 across the time horizon of the model, which could be interpreted as a gradual waning effect. However, the efficacy of dacomitinib appears to increase across the time horizon, with the hazard ratio reducing. This results in a clear difference between the long term OS predictions for dacomitinib and gefitinib (Figure 13), of which the ERG's clinical advisor was unconvinced. When applied to the log-logistic extrapolation, the company's FP predicts [redacted]% alive on dacomitinib compared to [redacted]% on gefitinib at 5 years.

The ERG are not aware of any evidence or clinical rationale to support this optimistic prediction for dacomitinib, nor the contrast between the behaviours of the dacomitinib PFS and OS ratios. Recall that for PFS, under the company's FP NMA the HR for dacomitinib grew seemingly exponentially, yet for OS the HR for dacomitinib improves constantly over time. Whilst for afatinib, the PFS improved over time whilst the OS worsened. This contrast between afatinib and dacomitinib is not supported by any clinical rationale, and sheds further doubt over the reliability of the FP analysis extrapolations. The ERG did not consider the other single order FP model to be an improvement in terms of plausibility, with the survival curves for dacomitinib appearing to be almost identical.

Recall also that the company failed to provide evidence of a significant difference between dacomitinib and afatinib for OS in their clinical section. The ERG considered alternative approaches to the extrapolation of dacomitinib OS, including the assumption of equivalency of dacomitinib and afatinib by assuming the FP OS HR from afatinib for both interventions. A summary of the predictions made by the models explored by the ERG is presented in Table 24.

progression survival, and less common for the PFS benefits to be extended in post-progression survival. Under the models fitted with ERG's preferred PFS and OS assumptions, dacomitinib provides an OS and PFS benefit over the comparators, but has a shorter post-progression survival time, consistent with the scenario of the degree of the pre-progression benefit not being repeated in the OS benefit as has been observed in ARCHER 1050.

Table 25: Comparison of pre-progression and post-progression survival gains

Scenario		**Pre Progression Incremental Life Years (Dacomitinib difference)**	**Post Progression Incremental Life Years (Dacomitinib difference)**	**Total Incremental Life Years (Dacomitinib difference)**
Company Base-case	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS log-logistic	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS matched to Afatinib	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 3 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 4 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]
ERG PFS and OS HR=1 at 5 years	Dacomitinib Gefitinib/Erlotinib Afatinib	[redacted]	[redacted]	[redacted]

5.2.7 ERG's exploratory survival analysis

5.2.7.1 Progression-free survival

The ERG investigated modelling separately the PFS of dacomitinib from ARCHER 1050 using parametric models, and KM data followed by parametric models fitted to data beyond 8 month, chosen because it was at this point that the KM curves separated. However, none of the parametric curves produced using these models produced a better model than those discussed above. Since the

Table 26: List of adverse events included in the model

Adverse event	Dacomitinib (n=227)	Gefitinib (n=224)	Afatinib (n=160)	Erlotinib*
ALT increased	2 (0.9%)	18 (8.0%)	0 (0.0%)	18 (8.0%)
Diarrhoea	18 (7.9%)	1 (0.4%)	21 (13.1%)	1 (0.4%)
Fatigue	0 (0.0%)	0 (0.0%)	9 (5.6%)	0 (0.0%)
Paronychia	17 (7.5%)	3 (1.3%)	3 (1.9%)	3 (1.3%)
Rash (grouped term)	55 (24.2%)	1 (0.4%)	15 (9.4%)	1 (0.4%)
*Erlotinib assumed equivalent to Gefitinib (see Section B.2.9.1)				

The ERG finds error in the company's use of 7.9% as the proportion of patients experiencing diarrhoea at Grade 3 or above. This is the cumulative value for Grades 3-4 but 0.4% patients experienced grade 5 diarrhoea in the dacomitinib group which has not been counted. Therefore the model input should have been 8.3% rather than the 7.9% used.

Additional data supplied by the company during the clarification process provided AE data per cycle by frequency reported for grades 3 and above at a >2% threshold. Table 27 summarises this new data showing a discernible difference between AE frequencies in patients from the >5% to >2% level. (N.B. rash was not calculated due to lack of clarity as to how the company had defined rash as a grouped term.)

Table 27: Treatment-related adverse events occurring in >2% of patients

Type of AE	**Dacomitinib n=227** Frequency (percentage)	**Gefitinib n=224** Frequency (percentage)
Stomatitis	[redacted]	[redacted]
ALT increase	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]

The mix of AEs represented in table 27 shows the inclusion of stomatitis. Clarification data from the company reported [redacted]. However, stomatitis is a dermatological AE commonly associated with irreversible EGFR TKI inhibitors[71] and showed clinically meaningful worsening in HRQOL in dacomitinib patients assessed using the EORTC QOL questionnaire in ARCHER 1050. Therefore, inclusion of stomatitis in AE data may be relevant and warranted. The further data provided could not definitively show a low rate of recurrence as suggested by the company and to which they attribute as the ability of clinicians to manage these events through dose reduction and discontinuation. It is noted that dose reduction due to AEs was required in 64.8% of dacomitinib patients versus 8.0% of gefitinib patients (see Table 7 and further discussion in clinical effectiveness section).

"Patient reported outcomes were assessed at days 1 (baseline), 8, and 15 of cycle one, on day 1 of subsequent cycles, at the end-of treatment visit, and at the post-treatment follow up visit." [1] (p. 1456).

The company were able to provide these values during the clarification process which are presented in Table 29.

Table 29: Summary of mean EQ-5D health index score.

Time point	Dacomitinib				Gefitinib			
	Median	Mean	95% CI	n	Median	Mean	95% CI	n
End of treatment	[redacted]	[redacted]	[redacted]	121	[redacted]	[redacted]	[redacted]	145
Post-treatment	[redacted]	[redacted]	[redacted]	75	[redacted]	[redacted]	[redacted]	107
CI : confidence interval								

The company did not recognize the post-treatment utility values from ARCHER 1050 as a PD progression value, therefore it used a PD utility of 0.64 from the literature.[2] (see Table 30). The use of health utility scores resulting from the Labbé et al, 2017 study[2] was well justified as an alternative source of utility data as it represents real world data obtained from a longitudinal study of EGFR-NSCLC patients directly from EQ-5D-3L. An alternative value from Nafees et al. (2008) sourced in the systematic review was rejected by the company as this study did not meet the NICE reference case.[56] EQ-5D was not used and values were not derived from patients, therefore it was not considered a robust source. In addition, a recent repeat of this study by Nafees et al. in 2017 that was identified in the systematic review, reported a PF value of 0.883 and PD of 0.166,[65] which further demonstrates the unreliability of the original Nafees et al. (2008) study.[50]

The health state utility values obtained from the Labbé, 2017 study[2] would be the ERGs preferred source of utility values from the literature. The ERG finds the company's reasoning for using these values over the Nafees, 2008[50] compelling and appropriate. Similarly, the ERG finds the health state utility values used by Huang (2017)[52] equally less convincing for use in the model as the KEYNOTE-024 trial was directed at patients specifically without *EGFR*-activating mutations or *ALK* translocations.

However, whilst the ERG considers the Labbé et al, 2017[2] values appropriate for use in scenario analysis (when both the PF value of 0.77 and PD value 0.64 are used simultaneously) it prefers the use of PD scores obtained from the ARCHER 1050 trial to be used in the base-case. This continues

Table 46: Results of base-case scenario analysis for the comparison between dacomitinib and afatinib.

Scenario	Dacomitinib			Afatanib			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib survival projection (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP model (OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA methodology (PFS and OS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - ARCHER) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility (PF - Labbé) with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company presented results for the PSA undertaken around the outcome cost per QALY gained. In general, the company used appropriate distributions around the model input parameters varied. However, the ERG noted that distributions could have been placed around other inputs to reflect the uncertainty, instead of keeping these inputs fixed. A range of sensitivity and scenario analyses were undertaken. These results showed that the discount rate applied to benefits, using the log-logistic parametric curve to model OS for gefitinib and including treatment beyond progression were the key drivers to the ICERs and including treatment beyond progression.

Figure 25: Tornado diagram for the comparison of dacomitinib versus afatinib, using the list prices

Company's scenario analysis results (all treatments at list prices)

The results for each change made and the impact to the base-case results are presented in Table 50 through to Table 52 for the comparison between dacomitinib and the comparators, using the list prices. As seen in these tables, under the scenario of using log-logistic parametric curves for OS and including treatment beyond progression had the greatest impact to the base-case ICER for dacomitinib against all comparators.

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Appendix Table 5. Exploratory results, fitting the log-logistic parametric curve to OS data for gefitinib (dacomitinib PAS vs. comparators assumed PAS)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Appendix Table 6. Exploratory results, fitting the log-logistic parametric curve to OS data for gefitinib (all treatments at list prices)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

OS, log-logistic curve to OS data for gefitinib and assumed equal efficacy, on the hazard scale, from 36 months onwards

Here, we fitted the log-logistic parametric curve to the OS data for gefitinib and assumed a hazard ratio of 1 is applied from 36 months onwards. Applying a HR=1 results in reduction to the post-progression survival and thus post-progression QALYs (results not shown). For comparison (i) afatinib is associated with an approximate ICER of [redacted] per QALY as compared to gefitinib. The ICER for dacomitinib compared to afatinib is approximately [redacted] per QALY. Under these assumptions resulted in an increase to the ICERs. (see Appendix Table 7). For comparison (ii), the ICER for afatinib (versus gefitinib) and dacomitinib (versus afatinib) are over [redacted] and [redacted] per QALY, respectively (Appendix Table 8).