NICE National Institute for Health and Care Excellence

Dacomitinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer

Lead team presentation

Lead Team: Bernard Khoo, David Meads and Malcolm Oswald

ERG: Warwick Evidence

Technical team: Luke Cowie & Nicola Hay

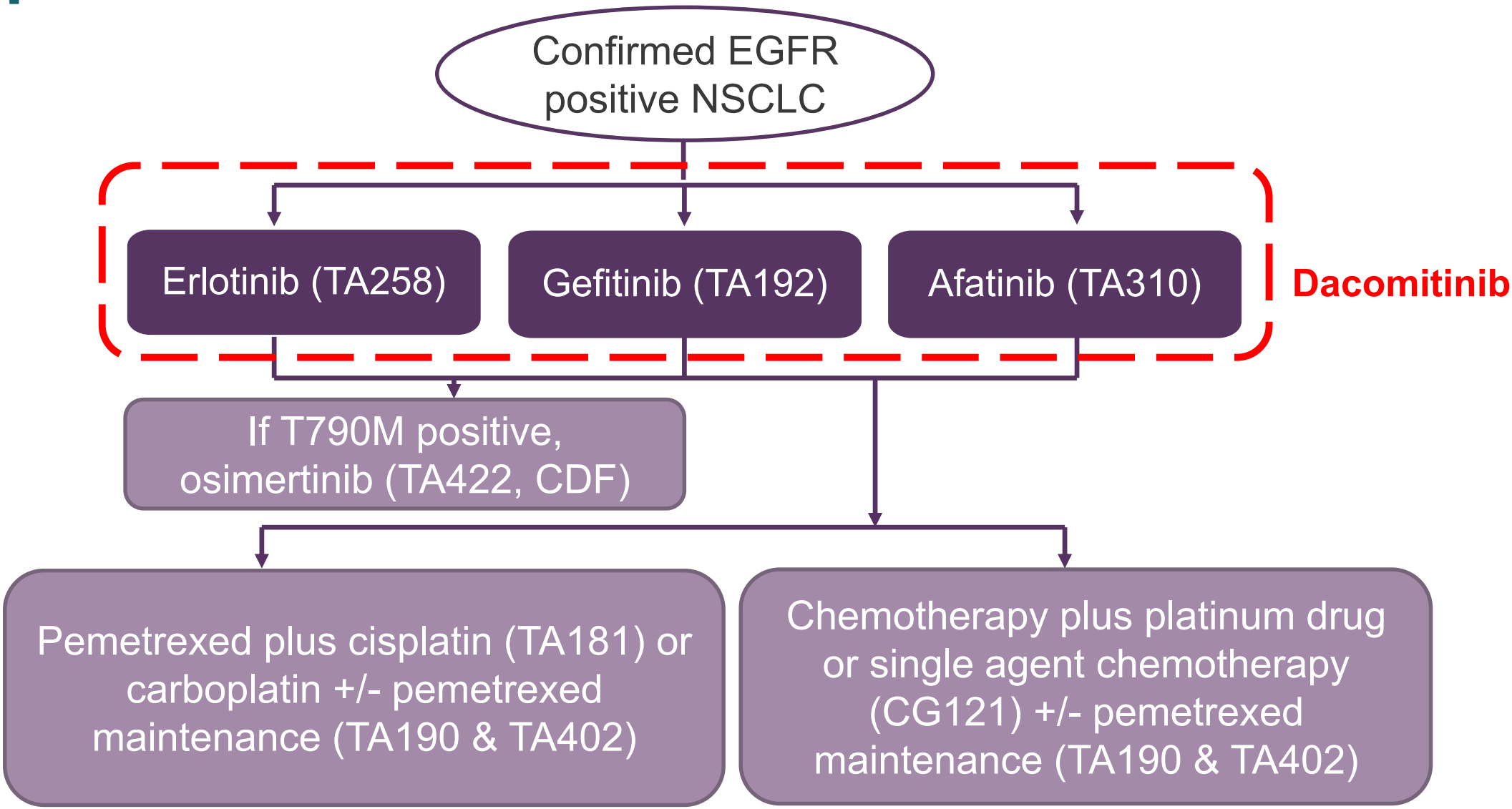
Company: Pfizer

20th March 2019

Preview: 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 L858Arg 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 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?

Treatment pathway in the UK: EGFR positive NSCLC



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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: XXXXX 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 XXXXX list price and XXXXX (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

[redacted]

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.

[redacted]

Clinical expert perspective

Submissions from British Thoracic Oncology Group, clinical specialist

- There is an unmet need → comparators can control the disease but progression occurs on average within 12 months
- Patients whose biopsy does not show T790M mutation are not offered Osimertinib and are "often reluctant to switch of EGFR inhibitor to chemotherapy"
- Archer 1050 trial:
  - Improved overall and progression-free survival over 1st/2nd generation EGFR inhibitors
  - Real world data matches relatively well to trial data except people with poorer ECOG performance status and active brain metastases do worse than trial population
  - 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"
- Implementation of Dacomitinib:
  - In specialist oncology clinics, where doctors already well trained in management of EGFR side-effects, and EGFR testing well embedded in NHS
  - few differences except longer time on therapy, and dose adjustments with some patients

[redacted]

Patient expert perspective

Submission received from Roy Castle Lung Foundation

- Like other NSCLC patients, “EGFR positive patients have a poor outlook on disease progression...symptoms such as breathlessness, cough and weight loss...distressing for loved ones”
- EGFR positive patients “tend to be younger, more are female and more are never smokers…present late, having more advanced disease at diagnosis”
- Dacomitinib:
  - Trial suggests improved overall survival over comparator – “of paramount importance to this patient population and their families”
  - Rashes and diarrhoea most common grade 3 to 4 side-effects but anecdotal experience reports that dacomitinib relatively well tolerated
  - Oral therapy – easy to administer

[redacted]

NHS England comments

- Of comparators, afatinib used most in NHS England and superior to gefitinib in prolonging PFS but no extension of OS
- Afatinib has most side-effects (compared with erlotinib & gefitinib) and in NHS practice offered to patients at the fitter end of the spectrum. Dacomitinib also likely to be given to fitter patients, due to its considerable side effect profile
- NHS England notes that 76% of ARCHER 1050 study were Asian. Despite known limitations of subgroup analysis, NHS England has uncertainties as to whether ITT benefit of dacomitinib would fully translate into outcomes for patients in England
- 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 about the toxicities (in particular much higher rates of diarrhoea and cutaneous toxicity) likely to be seen in practice in England
- Company has modelled a 2nd line treatment rate with osimertinib of 56% which is too high. Company indicates 2nd line systemic treatment rate in EGFR-mutated NSCLC is 71% and 3rd line treatment rate is 48%. Likely figures in NHS practice would be 50-60% and 25-30% respectively

[redacted]

Clinical effectiveness

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

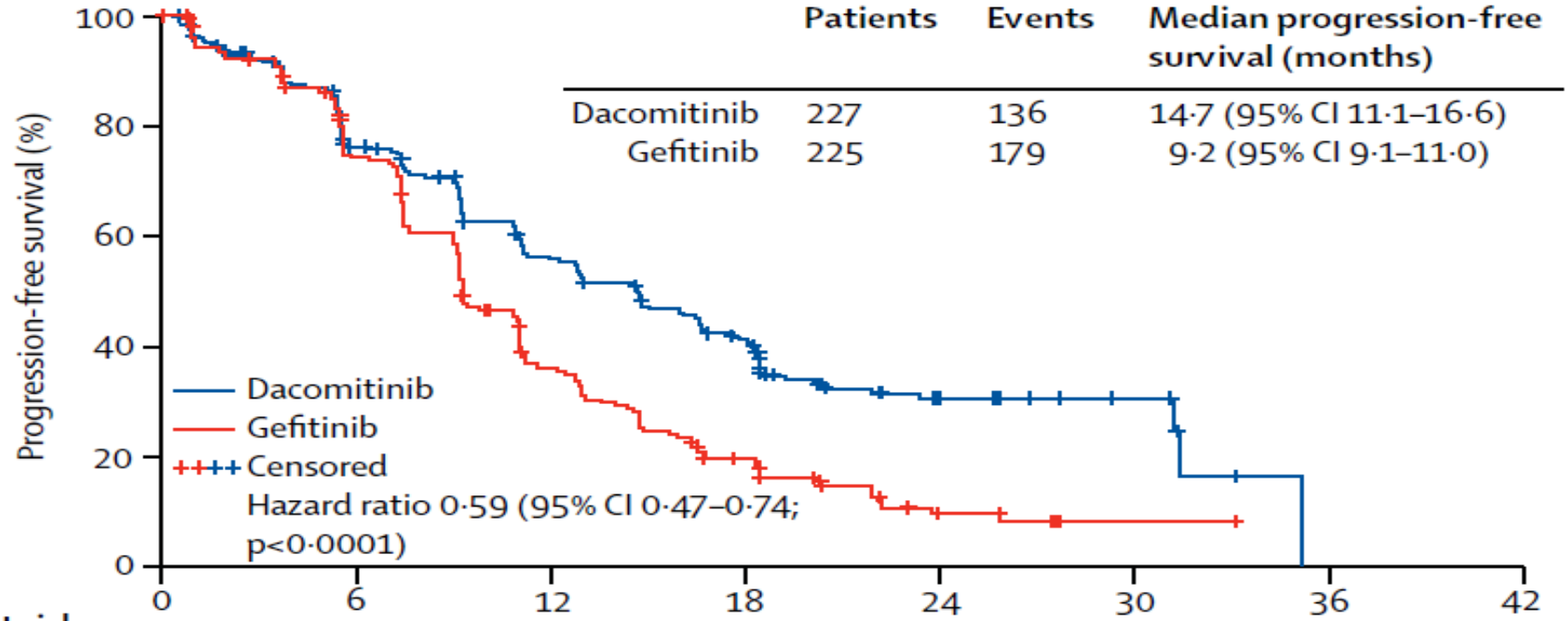
Archer 1050: Baseline characteristics

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)

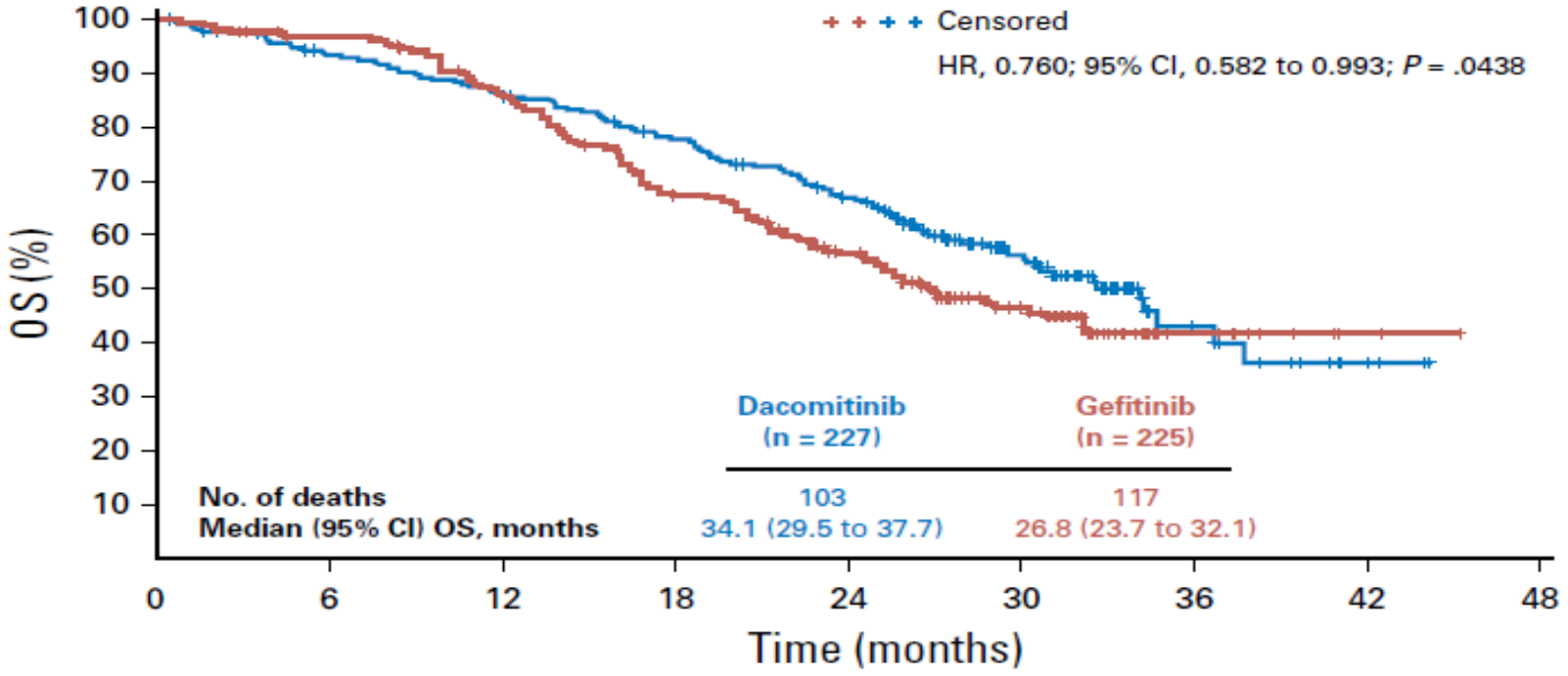
Number at risk (number censored)								
Dacomitinib	227 (0)	154 (23)	106 (31)	73 (36)	20 (74)	6 (88)	0 (91)	0 (91)
Gefitinib	225 (0)	155 (15)	69 (23)	34 (27)	7 (40)	1 (45)	0 (46)	0 (46)

Subgroup: Asian HR [redacted] (95% CI: [redacted]), Non-Asian HR [redacted] (95 % CI: [redacted])

[redacted]

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



Subgroup: Asian HR [redacted] (95% CI: [redacted]), Non-Asian HR [redacted] (95% CI: [redacted])

[redacted]

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

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

[redacted]

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]: XXXX	Baseline: 74.7 (SD 17.6) End of study[a]: XXXX	Baseline: -1.6 End of study[a]: XXXXXX
Utility index	Baseline: XXXXXX End of study[a]: XXXX	Baseline: XXXXXX End of study[a]: XXXX	Baseline: XXXX End of study[a]: XXXXXX

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

[redacted]

ARCHER 1050: Treatment-related adverse events occurring in ≥20% of patients

Adverse event, %	Dacomitinib N=227		Gefitinib N=224	
	Grade(s)		Grade(s)	
	1–2	3	1–2	3
Diarrhoea	XXX	XXX	XXX	XXX
Paronychia	XXX	XXX	XXX	XXX
Dermatitis acneiform	XXX	XXX	XXX	XXX
Stomatitis	XXX	XXX	XXX	XXX
Decreased appetite	XXX	XXX	XXX	XXX
Dry skin	XXX	XXX	XXX	XXX
Alopecia	XXX	XXX	XXX	XXX
ALT increased	XXX	XXX	XXX	XXX
AST increased	XXX	XXX	XXX	XXX

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

- No grade 4 or 5 AEs other than XXX grade 5 diarrhoea in dacomitinib treatment arm

[redacted]

Dacomitinib and afatinib have a higher incidence of common AEs than other TKIs

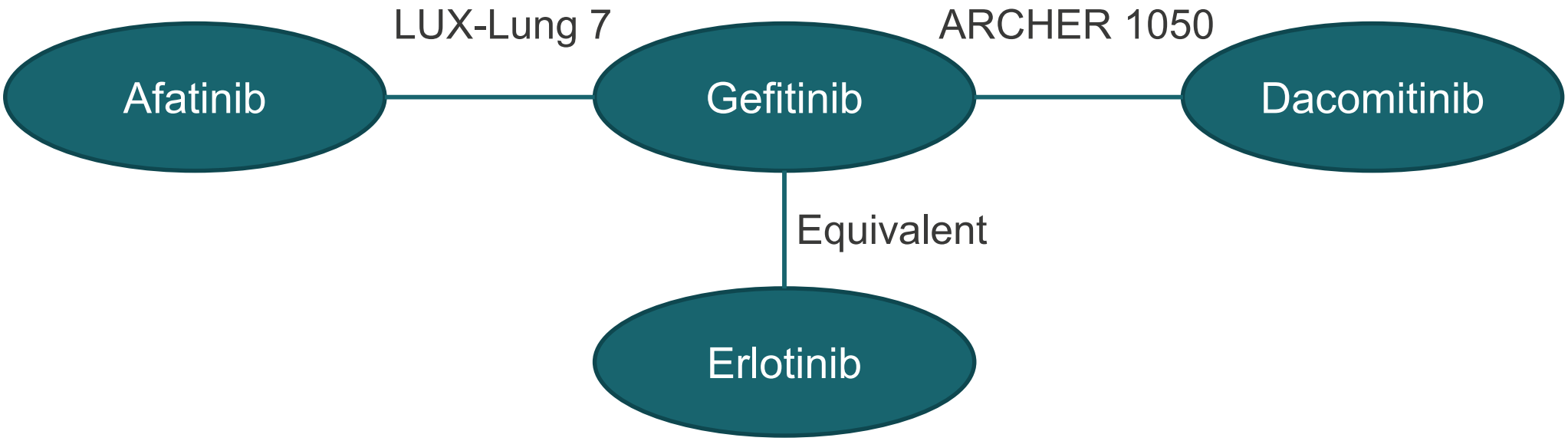
Drug	Diarrhoea	Stomatitis / Mucositis	Paronychia	Dermatitis acneiform
Dacomitinib	85%	41%	62%	49%
Gefitinib (TA192)	34 to 54%	15 to 40%	14 to 32%	15 to 66%
Erlotinib (TA258)	25 to 57%	13%	4%	NR
Afatinib (TA310)	88 to 95%	52 to 72%	33 to 57%	81 to 89%

ARCHER 1050: dacomitinib had significantly more dose reductions than gefitinib*

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)

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

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



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 at time of study entry.

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	-	-	-

[redacted] *Generated with 'base' gefitinib generalised gamma curve

ERG's exploratory analysis: fixed effect NMA

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 (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			

- ERG undertook an indirect treatment comparison for PFS and OS
- For both 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.

[redacted]

Key issues – clinical effectiveness

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- Is it reasonable to assume equal efficacy between erlotinib and gefitinib?

[redacted]

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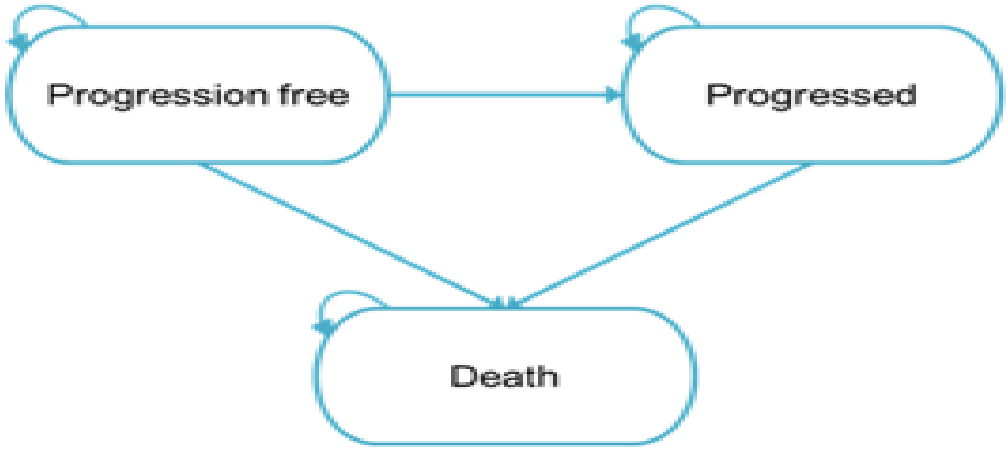
Company: Pfizer

20th March 2019

Preview: 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 treatment specific utilities AND 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?
- Are the end of life criteria met?
- Is dacomitinib innovative? Are there any equalities issues?

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

[redacted]

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

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

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

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)

[redacted]

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

Distribution	Proportion alive at		
	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[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 OS curves for dacomitinib, afatinib & erlotinib by applying time-varying hazard ratios to gefitinib curve

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.

[redacted]

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)

[redacted]

Company inputs: utility values

	Mean utility (95% CI)	Source
Progression-free		
Dacomitinib	XXX (XXX to XXX)	EQ-5D from ARCHER 1050
Gefitinib	XXX (XXX to XXX)	EQ-5D from ARCHER 1050
Afatinib	XXX (XXX to XXX)	Assumed equal to dacomitinib based on similarity of safety profile
Erlotinib	XXX (XXX to XXX)	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

- ERG supports use of PF utility data from the trial, but feels that PD utility values should also be from the trial rather than the literature
- ERG used all values from the trial and included disutility for aging and AEs

[redacted]

Adverse events included in the model

Grade 3 or higher occurring in >5% of patients

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%)

- Grades 1 and 2 excluded from model
- Company's base case did not include disutilities for AEs
- Company included one-off utility decrement in scenario analysis
- ERG did not accept inclusion of disutility decrements in the base-case would constitute 'double counting', and specifically included a disutility decrement in their base-case analysis.

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]	-	-
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Company's probabilistic ICER for dacomitinib is [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

[redacted]

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

[redacted]

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]	-
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

[redacted]

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	[redacted]	-	[redacted]	-	[redacted]	-
Gefitinib survival projection (PFS) using log-normal	[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]
Gefitinib survival projection (OS) using log-logistic	[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]

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression utility from ARCHER 1050	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correction of the PAS applied to gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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	[redacted]	-	[redacted]	-	-
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- ERG's probabilistic ICER for dacomitinib is [redacted]

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

[redacted]

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	[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

[redacted]

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

[redacted]

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]	-	-
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

[redacted]

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]	-	-
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

[redacted]

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	XXXXX	-	XXX	-	-
Dacomitinib	XXXXX	XXXXX	XXX	XXX	XXXXX
Gefitinib	XXXXX	XXXXX	XXX	XXX	XXXXX
Afatinib	XXXXX	XXXXX	XXX	XXX	XXXXX

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

[redacted]

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	[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

[redacted]

Additional ERG scenario analysis results: dacomitinib (with PAS) versus comparators (list price)

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Scenario 1: No additional survival benefit (OS HR=1) after 48 months					
Erlotinib	[redacted]	-	[redacted]	-	-
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No additional survival benefit (OS HR=1) after 60 months					
Erlotinib	[redacted]	-	[redacted]	-	-
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Equivalent post-progression survival from ERG base case (HR=1 from 71 months)					
Erlotinib	[redacted]	-	[redacted]	-	-
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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).

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

[redacted]

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

[redacted]

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 treatment specific utilities AND 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?
- Are the end of life criteria met?
- Is dacomitinib innovative? Are there any equalities issues?