Public observer slides

NICE National Institute for Health and Care Excellence

Dacomitinib for untreated epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer [ID1346]

Chair's presentation

2nd appraisal committee meeting

Committee D, 23rd May 2019 (previous meeting 20th March 2019)

Lead team: David Meads, Bernard Khoo & Malcolm Oswald

ERG: Warwick Evidence

NICE technical team: Luke Cowie & Nicola Hay

Company: Pfizer

Dacomitinib (Pfizer)

Marketing authorisation	Dacomitinib as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR-activating mutations
Administration & dose	One oral 45mg dose daily until disease progression or unacceptable toxicity (available in three dose strengths – 45mg, 30mg and 15mg)
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)

[redacted]

Recap: ARCHER 1050 trial

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), 45mg orally, once daily
Comparator, dose	Gefitinib (n=224), 250mg 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

3

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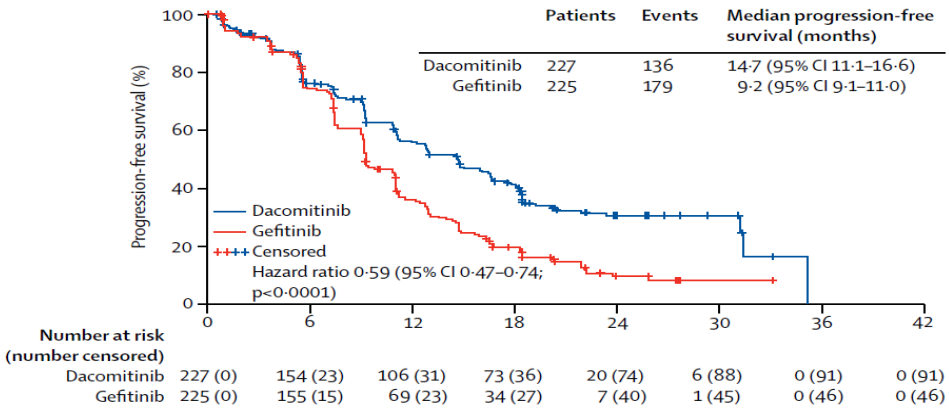
Recap: ARCHER 1050 results for PFS

- 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)

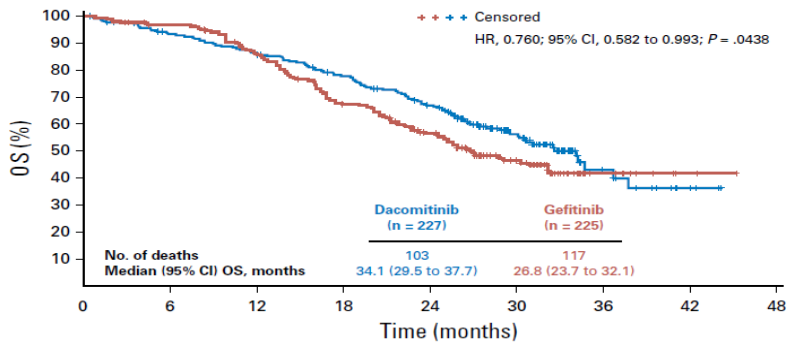
Number at risk (number censored)								
Dacomitinib	227 (0)	154 (23)	106 (31)	73 (36)	20 (74)	6 (88)	0 (91)	0 (91)
Gefitinib	225 (0)	155 (15)	69 (23)	34 (27)	7 (40)	1 (45)	0 (46)	0 (46)

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

[redacted]

Recap: ARCHER 1050 results for OS

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



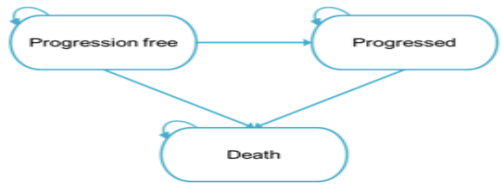
No. at risk:									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Subgroup: Asian HR 0.81 (95% CI: 0.60-1.11), Non-Asian HR 0.72 (95% CI: 0.43-1.20)

[redacted]

5

Recap: Company's economic model



Economic model	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

[redacted]

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Recap: Company's & ERG's preferred base case

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) • 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 ARCHER 1050 = [redacted]
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]

7

ACD preliminary recommendation

‘Dacomitinib is not recommended, within its marketing authorisation, for untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) in adults’

[redacted]

Recap: ACD considerations (1)

Issue	Committee's consideration	ACD
Relevant comparators	Afatinib, gefitinib and erlotinib	3.2
Clinical effectiveness	• Dacomitinib improves PFS and OS compared with gefitinib • Impact of subsequent treatments on OS is uncertain	3.5 3.6
Clinical evidence	ARCHER 1050 trial is generalisable to NHS clinical practice in England	3.7
Network meta-analysis	Results from the fractional polynomial analysis are uncertain	3.9
Indirect treatment comparison	No statistical difference between dacomitinib and afatinib for PFS and OS	3.10

[redacted]

Recap: ACD considerations (2)

Issue	Committee's consideration	ACD
Model structure	Appropriate for decision making	3.11
Extrapolation of PFS	• Company's modelling of PFS is uncertain • ERG's modelling of PFS is appropriate for decision making	3.12 3.13
Extrapolation of OS	• Company's modelling of OS was implausible • ERG's modelling of OS was appropriate for decision making	3.14 3.15
Progression-free utility values	The assumed equivalence of dacomitinib with afatinib, and gefitinib with erlotinib is appropriate	3.16
Progressed disease utility values	Using values from ARCHER 1050 is appropriate	3.17

[redacted]

Recap: ACD considerations (3)

Issue	Committee's consideration	ACD
Disutility for treatment-related AEs	Reasonable to include	3.18
Subsequent treatments	Model does not reflect the type and proportion of subsequent treatments received in ARCHER 1050	3.19
End of life criteria	Not met	3.22
Innovation	No evidence of benefits that had not been captured	3.23
Cancer Drugs Fund	Mature data: little uncertainty that would be resolved through further data collection	3.25
Incremental cost-effectiveness ratio (ICER)	Most plausible ICER above £30,000 per QALY gained	3.21

ACD consultation responses

- Consultee comments from:
  - Pfizer (the company)
  - AstraZeneca (comparator company, gefitinib)
- No commentator or web comments

[redacted]

12

ACD consultation comments: AstraZeneca

- The ACD (3.5) concluded that dacomitinib is associated with improved PFS and OS compared with gefitinib. However, the crossing of the KM curve at around 11 months (and possibly a 2nd time at around 36 months) suggests that a specific subgroup or subgroups derives more benefit from gefitinib than dacomitinib.

- The ACD (3.7) states that the results of the pre-specified subgroup of patients according to ethnicity could not be reported because it was considered academic in confidence. However, the hazard ratio for OS and median OS for both Asians and non-Asians has been in the public domain since June 2018.

- It is worth noting that Asian ethnicity has been identified as a favourable independent prognostic factor for OS in NSCLC, irrespective of smoking status (Ou, et al., J. Thorac Oncol 2009; 4(9): 1083) and that this has been a consideration by previous committees when appraising treatments in similar settings (e.g. TA310).

[redacted]

13

ACD consultation comments: Company

Committee preference	Company response
ERG's modelling of PFS	**Accepted**
ERG's modelling of OS	**Not accepted** (see slide 15)
Progressed disease utility value from ARCHER 1050	**Not accepted** (see slide 16)
Inclusion of age-related disutilities	**Accepted**
Inclusion of disutilities for AEs	**Accepted**
ERG correction of gefitinib PAS in model	**Accepted**

[redacted]

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ACD consultation comments: company

Assuming equal efficacy for overall survival after 36 months (ACD paragraph 3.15):

- The ERG base-case assumes equal efficacy for OS between all treatments beyond **36** months. The ERG and committee acknowledged alternative scenarios with equal efficacy from **48, 60** and **71** months. The committee should consider that the most clinically plausible scenario is that there is **no additional survival gain beyond 71 months**.
  - The ERG base-case predicts that [redacted]% of patients will be on treatment at 36 months in the dacomitinib arm in contrast to only [redacted]% of patients in the gefitinib/erlotinib arm remaining on treatment. It is not plausible to assume no further benefit for these patients.
  - The median PPS in the ITT population was [redacted] months in the dacomitinib arm and [redacted] months in the gefitinib arm. These data suggest that there was a numerical improvement in post-progression survival in the dacomitinib arm compared to the gefitinib arm (hazard ratio [HR] <1).
  - More patients in the dacomitinib arm (n=[redacted]) had unknown PPS because both PFS and OS were censored compared to the gefitinib arm (n=[redacted]). If these patients had the opportunity to continue in the ARCHER 1050 trial, the PPS gain would likely increase.
  - An additional analysis was conducted that showed a positive association between PFS and PPS.

[redacted]

15

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ACD consultation comments: company

Post-progression utility value (ACD paragraph 3.17):

- Progressed disease utility values are not available from ARCHER 1050.
- EQ-5D administered at the post-progression follow-up from ARCHER 1050, only represents a single time point very close to disease progression. Cannot be considered robust enough to capture the gradual decline in quality-of-life during additional lines of therapy and progression and the time prior to death.
- Post-progression follow-up values applied in the committee preferred analysis ([redacted]) only represent a utility decrement of [redacted], which is at odds with previous NICE advanced NSCLC appraisals.
- In the current appraisal of osimertinib for untreated EGFR+ advanced NSCLC, the committee preferred the value of 0.678, representing a progression decrement of 0.116 (0.794-0.678).
- In the appraisal of atezolizumab for NSCLC, where progressed utility values >15/>5/<5 weeks were 0.58, 0.43 and 0.35, respectively. Utility values from the literature Nafees (2008) and Chouaid (2013) with values of 0.47 and 0.46 for progressed disease, have been accepted by committees in numerous previous NICE NSCLC appraisals.
- The value from Labbé (0.64) should be applied in the base-case analysis.

[redacted]

16

ACD comments: Company's updated analysis

The company undertook updated analyses using the list prices for afatinib and erlotinib, the PAS for gefitinib and the up-dated PAS for dacomitinib, and made the following changes:

- No survival gain beyond 60 months
- No additional survival benefit beyond 71 months
- Using the post-progression utility value from Labbé et al.
- Under the ERG's base-case assumptions
- No survival gain beyond 60 months and using the post-progression utility values from Labbé et al.
- No additional survival benefit beyond 71 months and using the post-progression utility values from Labbé et al.

[redacted]

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Company's updated deterministic base case

#	Company adjustment	ICER dacomitinib (updated PAS) versus		
		Gefitinib (with PAS)	Afatinib (list price)	Erlotinib (list price)
1	Slight post-progression decrement (No survival gain beyond 60 months)	[redacted]	[redacted]	[redacted]
2	Equal post-progression survival (No additional survival benefit beyond 71 months)	[redacted]	[redacted]	[redacted]
3	Labbe post-progression utility	[redacted]	[redacted]	[redacted]
ERG analysis		[redacted]	[redacted]	[redacted]
Company revised base-case (1+3)		[redacted]	[redacted]	[redacted]
Company revised base-case (2+3)		[redacted]	[redacted]	[redacted]

[redacted]

18

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ERG's response to company's comments: Equal Efficacy for OS after 36 months (1)

- [redacted]% of dacomitinib patients are alive at 36 months, the majority of which ([redacted]% vs [redacted]%) are in the post-progression health-state and not on first-line treatment. This contradicts the company's preferred alternative scenario, where the treatment effect increases across the time horizon, until the implementation of a hazard ratio of 1 from 71 months.
- The company's post-hoc analysis of the ITT population does not suggest any meaningful difference has been observed despite the lack of a stated significance threshold. The company presents median post-progression survival times for both arms, but the lack of Kaplan-Meier plots, mean survival estimates or confidence intervals makes it difficult to ascertain the robustness of the apparent difference.
- The company's analysis of only patients with an observed progression-free survival (PFS) event time introduces bias. Again, there are little data, and the analysis does not allow for any robust conclusion to be drawn.
- The company's analysis of post-progression survival times produced statistically significant HRs between the three groups based on PFS time, but these groups did not take account of the intervention received and it is potentially misleading to infer differences between the two arms of ARCHER 1050.

[redacted]

ERG's response to company's comments: Equal Efficacy for OS after 36 months (2)

- The ERG reiterated the evidence that supported its initial selection of the hazard ratio=1 from 36 months - the company's fractional polynomial analysis to the trial data, and the ERG's restricted cubic spline analysis:
  - In the company's best fitting second order fractional polynomial model (P1 = 1, P2 = 1.5), the hazard ratio between dacomitinib and gefitinib crossed 1 at roughly **27 months**, and then increased sharply, with similar patterns reported for all other second order models.
  - The ERG's restricted cubic spline model that digitised OS data from ARCHER 1050 and LUX-Lung 7 trials, shows that the HR for dacomitinib vs. gefitinib crosses 1 at roughly **24 months**.
  - The ERG's sensitivity analysis using the restricted cubic spline model with the final 10 OS events in the dacomitinib treatment arm of ARCHER 1050 (all events beyond [redacted] months, equating to 10% of the total events in the dacomitinib arm) shows that dacomitinib efficacy on OS observed in the trial diminishes before **31 months**.

[redacted]

ERG's response to company's comments: Progressed disease utility values

- The ERG are aware that the utility value derived from ARCHER 1050 only captures a small amount of time following disease progression, however the patient population is the most relevant to this appraisal, in terms of disease stage and the interventions that they have received.
- The study by Labbé et al. provides a utility value that covers a range of time following disease progression, it is generated from a heterogeneous population. Most notably, the study includes patients with stage I to IV disease, who had had previously received and currently receiving a wide range of interventions.
- The ERG acknowledged that neither source is ideal, and that both have their merits. The ERG's preference is to remain with the value obtained from the ARCHER 1050 trial, as it is more consistent with the other values included in the model, which also come from the ARCHER 1050 trial.

[redacted]

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ERG's updated preferred base case

- Based on the assumed comparator PAS versus the revised PAS for dacomitinib under the following assumptions:
  - No additional survival benefit beyond 36 months
  - Using the post-progression utility value of [redacted] derived from the ARCHER 1050 trial

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

[redacted]

22

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ERG's scenario analysis: no additional survival benefit after 48 months, 60 months and equivalent post-progression survival

Treatment	Incremental costs (£)	Incremental QALY	ICER (£)
Scenario 1: Hazard ratio = 1 from 48 months			
Gefitinib	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]
Scenario 2: Hazard ratio = 1 from 60 months			
Gefitinib	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]
Scenario 3: Equivalent post-progression survival, hazard ratio = 1 from 71 months			
Gefitinib	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]

QALY, quality adjusted life-years gained

[redacted]

23

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Key issues

- What is the most appropriate assumption for overall survival?
  - equal efficacy for overall survival from 36 months?
  - equal efficacy from 60 months
  - equal efficacy from 71 months (equal post-progression survival)?
- What is the most appropriate progressed disease utility value?
  - [redacted]?
  - 0.64?
- What is the committee's preferred ICER?
- Are there any potential equality issues?

[redacted]