NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Pfizer**
   a. Letter from Pfizer in response to ACD
   b. Consultation comments form
   c. Letter from Pfizer following second committee meeting

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. AstraZeneca

There were no comments on the ACD from the experts or through the website consultation.

4. **Evidence Review Group critique of company comments on the ACD**

5. **Evidence Review Group response to Chair queries**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Pfizer UK	**Assumption 1: Assuming equal efficacy for overall survival after 36 months** **Pfizer does not believe that the Committee should assume equal efficacy beyond 36 months as it is not clinically plausible to assume dacomitinib has a decrement post-progression.** The ERG base-case assuming equal efficacy for overall survival between all treatments after 36 months results in the ERG base-case predicting mean post-progression survival of [redacted] month for dacomitinib, [redacted] months for gefitinib/erlotinib and [redacted] months and afatinib. The ERG and Committee acknowledged alternative scenarios with equal efficacy from 48 months, 60 months and 71 months (equal post-progression survival). The 36-month scenario cannot be considered clinically plausible given the proportion of patient on treatment at 36 months and the lack of events informing the arbitrary 36-month cut-off. The latter scenario of equal post-progression survival is the most clinically plausible given the post hoc analysis of post-progression survival from ARCHER 1050, clinical opinion and prognosis beyond progression. **High proportion on treatment with dacomitinib at 36 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. Therefore, is it not plausible to assume there is no further benefit for these patients that are still on treatment. **Post-progression survival in ARCHER** Post-hoc analyses of post-progression survival from ARCHER 1050 was calculated from the date of progression-free survival (PFS) per IRC review to the date of overall survival (OS) event or censored date as applicable). The PFS data are based on the primary completion data cut-off date (29 July 2016) and the OS data are based on the OS Final Analysis data cut-off date (17 February 2017). In the ITT population, the estimated hazard ratio of PPS for dacomitinib versus gefitinib was [redacted] based on the stratified analysis,	Thank you for your comment. The committee considered the different scenarios for assuming equal efficacy for overall survival between all treatments. The committee noted each of the justifications presented here in favour of the assumption for equal post-progression survival but was not convinced of its clinical plausibility. But the committee also accepted that the ERG's preferred assumption of equal efficacy after 36 months might be too conservative. The

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			indicating a [redacted] reduction in the risk of post-progression death in favour of dacomitinib. The median PPS was [redacted] months in the dacomitinib arm and [redacted] months in the gefitinib arm. These data, albeit from post-randomization subgroups, suggest that there was a numerical improvement in post-progression survival in the dacomitinib arm compared to the gefitinib arm (hazard ratio [HR] <1). Thus, equivalent post-progression survival should be considered as a worst-case scenario. **Post-progression survival and censoring in ARCHER** The above analysis used the ITT population and therefore, included patients with censored PFS events. Therefore, to explore the impact of this censoring, a further PPS analysis was undertaken only including patients with an observed PFS event. The estimated hazard ratio of PPS for dacomitinib versus gefitinib was [redacted] (95% CI: [redacted]) with a 1-sided p-value of [redacted] based on the stratified analysis, indicating a [redacted] reduction in the risk of post-progression death in favour of dacomitinib. The median PPS was [redacted] months in the dacomitinib arm and [redacted] months in the gefitinib arm. The results above are also likely to be conservative because patients who progress early have a longer follow up post progression and higher chance of death before censoring. For these patients it is more likely that the true (uncensored) PPS is reached compared with patients who are on therapy for longer. The table below shows that there were more observations in the gefitinib arm ([redacted]) compared to the dacomitinib arm ([redacted]) where PPS was known because of recorded events for both PFS and OS. The table also shows that there were many more patients in the dacomitinib arm ([redacted]) compared to the gefitinib arm ([redacted]) where PPS was unknown because both PFS and OS were censored. If these patients had the opportunity to continue in the ARCHER 1050 trial, the PPS gain would likely increase and be reflected in the data. As dacomitinib is a more effective therapy, with more censoring in both PFS and OS, the likelihood that the true PPS has been reached is lower with dacomitinib and this would likely underestimate the PPS gain with dacomitinib.	committee agreed that the most plausible ICER approximates most closely to the ERG's scenario analysis for assuming equal efficacy from 48 months (see section 3.23 of the FAD).

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Table 1. Censoring and PPS estimation

PFS event	OS event	dacomitinib 227 n (%)	gefitinib 225 n (%)	
yes	yes	[redacted]	[redacted]	true PPS is known
yes	no	[redacted]	[redacted]	true PPS is censored
no	yes	[redacted]	[redacted]	PPS is overestimated
no	no	[redacted]	[redacted]	true PPS is not known

Post-progression survival and correlation with PFS

An additional analysis was conducted to evaluate the extent to which longer PFS is associated with longer PPS. The methodology used in Negrier et al. 2014 was adopted whereby PPS was calculated for 3 equally sized groups based on PFS duration. This analysis suggests that for the ITT population of ARCHER 1050 (including both dacomitinib and gefitinib patients), there was a significant difference between the PPS curves based on PFS duration. Compared with the lowest PFS duration group ([redacted]), PPS was significantly longer in the group with [redacted] ([redacted]). Similarly, compared with the lowest PFS duration group, PPS survival was significantly longer in the group with PFS≥14.6 ([redacted]). As expected, there was a large amount of censoring in the group of patients with the longest PFS, indicating that PPS gain in this population relative to the population in the lowest PFS strata, would be even higher if the analysis were done with more mature data. The positive association between PFS and PPS was also shown for the gefitinib arm.

In summary, these results indicate that longer PFS is associated with longer PPS and that the assumption of equal PPS between dacomitinib and gefitinib is highly conservative and can be considered a worst-case scenario. Indeed, the evidence suggests that PPS is at least as long for dacomitinib compared with gefitinib, and possibly even longer because of censoring and the positive

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			relationship between PFS and PPS. **Clinical opinion** The ERG clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis. **Tumour response and subsequent treatments** Given similar response rates there is no meaningful difference expected in the tumour size upon progression and upon progression there is no difference in available subsequent treatments (osimertinib, platinum doublet chemotherapy). Therefore, there is no clinical rational for patients on dacomitinib to have an inferior prognosis upon prognosis compared to comparator TKIs and thus no difference in post-progression survival.	
2	Consultee (company)	Pfizer UK	**<u>Assumption 2: Progressed disease utility values from alternative sources</u>** **Pfizer do not believe that the Committee should consider the single post-progression follow-up utility from ARCHER 1050 as representative to the entire time in the progressed disease state (primary progression until death).** The company does not disagree with the ERG and the Committee that from a methodical perspective, it may be more appropriate to use utility values from trials when they are available. However, 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. Therefore, it cannot be considered robust enough to capture the gradual decline in quality-of-life for these patients during potential additional lines of therapy and progression and the time prior to death. Thus, as expected the post-progression follow-up values applied the committee preferred analysis ([redacted]) only represent a utility decrement of [redacted], which is at odds with previous NICE advanced NSCLC appraisals. Of note, the current appraisal of osimertinib in patient with untreated EGFR+ advanced NSCLC, the committee preferred value is 0.678, representing a progression decrement of 0.116 (0.794-0.678). This can also be considered a relatively high progressed disease value given that it only accounts for patient progression-free on second line treatment, thus not accounting for further progression and declining quality-of-life prior to death.	Thank you for your comment. The committee considered the different values for progressed disease and agreed that neither value from ARCHER 1050 or Labbé was ideal, and that both had their merits. The committee also recalled the utility value used in the appraisal of osimertinib for treating locally advanced or metastatic EGFR T790M mutation-

<table>
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<tr><td></td><td></td><td></td><td>The decline in utility prior to death has been demonstrated in a previous NSCLC appraisal of atezolizumab in NSCLC, where progressed utility values >15/>5/<5 weeks were 0.58, 0.43 and 0.35, respectively. Although they are not the most robust evidence from the literature Nafees (2008) and Chouaid (2013) with values of 0.47 and 0.46 for progressed disease, these have been accepted by committee's as the preferred values in numerous previous NICE NSCLC appraisals.

Therefore, the value from Labbe (0.64) that is considered the most appropriate from the literature by the ERG, should be applied in the base-case analysis.</td><td>positive non-small-cell lung cancer (TA416) and also in the ongoing appraisal of osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302]. The committee agreed that it was appropriate to use the utility value of 0.678 for progressed disease see section 3.18 of the FAD).</td></tr>
<tr><td>3</td><td>Consultee (company)</td><td>Pfizer UK</td><td><u>Cost-effectiveness summary of Pfizer's adjustments to the ERG analysis</u>

Table 2 summarises the single change and all change ICERs for each of these adjustments.

Table 2. Cost-effectiveness estimates with PAS
<table>
<tr><th rowspan="2">#</th><th rowspan="2">Company adjustment</th><th colspan="3">ICER
dacomitinib ([redacted]% PAS) versus</th></tr>
<tr><th>Gefitinib (with PAS)</th><th>Afatinib (list price)</th><th>Erlotinib (list price)</th></tr>
<tr><td>1</td><td>Slight post-progression decrement (No survival gain beyond 60 months)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2</td><td>Equal post-progression survival (No additional survival benefit beyond 71 months)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3</td><td>Labbe post-progression utility</td><td rowspan="4">[redacted]</td><td rowspan="4">[redacted]</td><td rowspan="4">[redacted]</td></tr>
<tr><td colspan="2">ERG analysis</td></tr>
<tr><td colspan="2">Company revised base-case (1+3)</td></tr>
<tr><td colspan="2">Company revised base-case (2+3)</td></tr>
</table></td><td>Thank you for your comment. The committee noted the ICERs for these two updated base cases, and also the sensitivity analysis for the PAS discount (see section 3.21 of the FAD).</td></tr>
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<tr><td></td><td></td><td></td><td>
The adjustments made to the ERG structural changes impact the cost-effectiveness estimates and are likely to alter the committee's preliminary decision of not recommending dacomitinib to patients with EGFR+ NSCLC. The ICER falls below £30,000 per QALY gained (£[redacted]/QALY). The threshold analysis is presented in Table 3 indicated that the PAS for erlotinib and afatinib would have to exceed [redacted]% and [redacted]%, respectively for the ICER to be above the £30,000 per QALY threshold.

Table 3. Cost-effectiveness estimates with Company revised base-case (2+3) and erlotinib/afatinib at varying discounts (dacomitinib with PAS)
<table>
<tr><th rowspan="2">Comparator discount</th><th colspan="2">ICER dacomitinib versus</th></tr>
<tr><th>Erlotinib</th><th>Afatinib</th></tr>
<tr><td>5%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>10%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>15%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>20%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>25%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>30%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>35%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>40%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>45%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>50%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>55%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>60%</td><td>[redacted]</td><td>[redacted]</td></tr>
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</td><td></td></tr>
</table>

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			65% [redacted] [redacted] 70% [redacted] [redacted] 75% [redacted] [redacted] 80% [redacted] [redacted] 85% [redacted] [redacted] 90% [redacted] [redacted] 95% [redacted] [redacted] Abbreviations: ICER: incremental cost-effectiveness ratio	
4	Consultee (company)	Pfizer UK	Correction required in 3.8. The company disagree that dacomitinib had more dose reductions than gefitinib as dose reduction is not possible with gefitinib as it is only available in one strength (250mg tablet). In addition, an abstract presented in the IASLC World Lung Conference in September 2018 assessed the efficacy benefit of dacomitinib in patients that received dose reductions from 45mg, to 30mg or 15mg, in the ARCHER-1050 trial[1]. The IASLC abstract demonstrated that patients who had reduced their dose to manage AEs (66.1%, n=150; 87 patients reduced to 30 mg, and 63 patients reduced to 15 mg) experienced improved AE incidence and similar efficacy benefit compared to all dacomitinib-treated patients[1].	Thank you for your comment. We agree that gefitinib is only available in one dose strength, but note that a footnote in the original company submission states that dose reductions with gefitinib were achieved through 'every other day' dosing.

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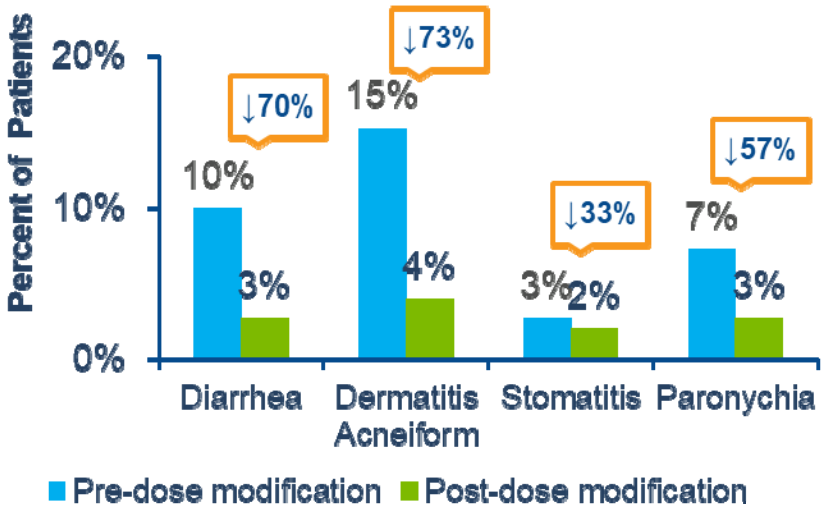
Efficacy in Dacomitinib dose-reduced vs. all Dacomitinib-treated patients[2]

	Dose-reduced patients (n=150)	All VIZIMPRO-treated (n=227)
mPFS	16.6 mo [95% CI: 14.6, 18.6]	14.7 mo [95% CI: 11.1,16.6]
ORR	79.3% [95% CI: 72.0, 85.5]	74.9% [95% CI: 68.7, 80.4]
mOS	36.7 mo [95% CI: 32.6, NR]	34.1 mo [95% CI: 29.5, 37.7]



1. World Conference – Lung Cancer 2018, Abstract Book. WCLC2018-Abstract-Book_vF-LR-REV-SEPT-25-2018.pdf. T. Mok, K. Nakagawa, R. Rosell, K. Lee, J. Corral, M.R. Migliorino, A. Pluzanski, R. Linke, G.

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			Devgan, E. Sbar, S. Quinn, T. Wang, Y. Wu. EFFECTS OF DOSE MODIFICATIONS ON THE SAFETY AND EFFICACY OF DACOMITINIB FOR EGFR MUTATION-POSITIVE NSCLC. MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1 WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00. 2. US (FDA) VIZIMPRO prescribing information (Pfizer, 2018).	
5	Consultee (company)	Pfizer UK	Correction required in 3.15: In its base case, the ERG used the log-logistic curve for gefitinib and the fractional polynomial network meta-analysis for the other comparators **(P1=0.5, P2=1)**. Should be updated with the following: In its base case, the ERG used the log-logistic curve for gefitinib and the fractional polynomial network meta-analysis for the other comparators **(P1=-0.5)**.	Thank you for your comment. This correction has been made (see section 3.15 of the FAD).
6	Consultee (company)	Pfizer UK	Correction required in 3.20: 'using the log-logistic parametric curve for gefitinib and the results from the fractional polynomial network meta-analysis **(P1=0.5, P2=1)** for the other comparators' Should be updated with the following: 'using the log-logistic parametric curve for gefitinib and the results from the fractional polynomial network meta-analysis **(P1=-0.5)** for the other comparators'	Thank you for your comment. This reference has been removed and so there is no correction to be made in this section of the FAD.
7	Consultee (comparator company)	AstraZeneca UK	**Inaccurate description of overall survival benefit** In the summary of why the committee made the recommendations in the ACD (page 3) and paragraph 3.5, it is stated that the committee concluded that dacomitinib is associated with improved progression-free and overall survival compared with gefitinib. The ARCHER-1050 study demonstrated a significant improvement in OS in the dacomitinib group compared with the gefitinib group (HR of 0.760 [95% CI 0.582, 0.993] p=0.0438). Median OS with dacomitinib was 34.1 months [95% CI 29.5, 37.7] and 26.8 months [95% CI 23.7, 32.1] for gefitinib, which was clinically relevant. However, it is clear that for the ITT population, the Kaplan-Meier survival curves cross-over at least once at around 11 months (and potentially a second time at approximately 36 months) (see Figure from Mok et al., J. Clin Oncol 2018,: 36: 2244) suggesting that a specific subgroup, or subgroups, of patients derive more benefit from gefitinib than dacomitinib.	Thank you for your comment. The committee noted that the overall survival Kaplan Meier curves for dacomitinib and gefitinib crossed at least once. It concluded that overall dacomitinib is associated with improved progression-free and overall survival compared with gefitinib (see

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			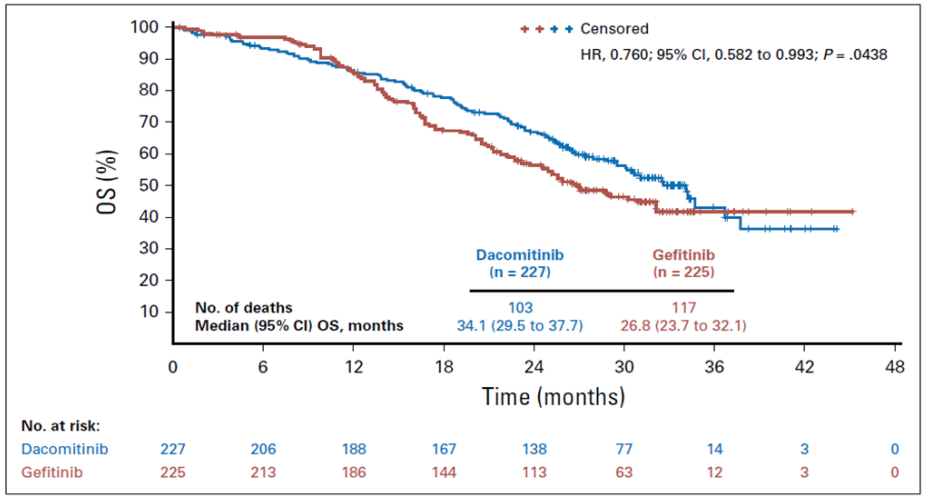 It is perhaps more accurate therefore to conclude that although there is some evidence that dacomitinib is associated with improved overall survival compared with gefitinib, there is evidence that a specific subgroup, or subgroups, of patients derive more benefit from gefitinib than dacomitinib.	section 3.5 of the FAD).
8	Consultee (comparator company)	AstraZeneca UK	**Public data marked as confidential** In paragraph 3.7 of the ACD (p7 and 8) it is stated that the results of the pre-specified subgroup of patients according to ethnicity was considered academic in confidence by the company and could not be reported. It is worth noting that the HR for OS and median OS for both Asians and non-Asians within ARCHER-1050 have been available in the public domain since June 2018 (Mok et al., J. Clin Oncol 2018, 36: 2244).	Thank you for your comment. During the committee meeting, the company agreed with your correction and the committee were made aware that the overall survival hazard ratio for the Asian subgroup compared with the non-Asian subgroup is in the

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			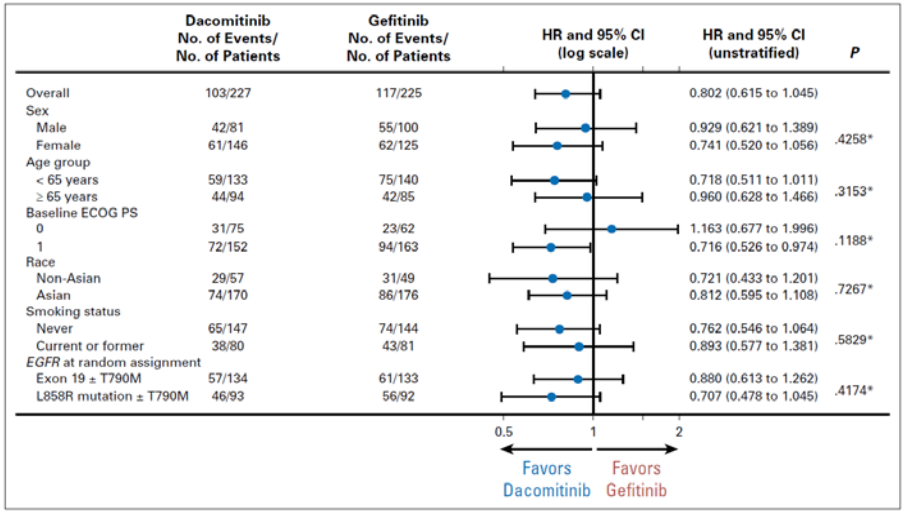 Subgroup analysis of PFS suggested that efficacy was driven by the Asian group (HR 0.51 [95% CI 0.39, 0.66]). The PFS HR in the non-Asian group was not statistically significant (HR 0.89 [95% CI 0.57, 1.39]) In Asian patients (53.8% censored), median OS was 34.2 months (95% CI 30.1, not reached [NR]) with dacomitinib versus 29.1 months (95% CI 25.2, NR) with gefitinib (preliminary HR 0.812 [95% CI 0.595, 1.108] p=0.1879). In non-Asian patients (43.4% censored), median OS was 29.5 months (95% CI 20.7, NR) with dacomitinib versus 20.6 months (95% CI 16.1, 25.5) with gefitinib (preliminary HR 0.721 [95% CI 0.433, 1.201] p=0.2073). 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).	public domain. The FAD has also been updated accordingly (see section 3.7 of the FAD).

9th May 2019

Dear Professor Gary McVeigh,

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

Pfizer is disappointed with the Committee's draft recommendation. Dacomitinib is a step forward in the management of untreated EGFR-positive non-small-cell lung cancer patients and we believe that several assumptions that drove this recommendation are flawed and lack clinical validity.

Pfizer welcomes the Committee's views of recognising the additional clinical benefit of dacomitinib as well as the generalisability and high quality of the pivotal trial that informed the submission (ARCHER 1050).

We hope that the information contained within this response will provide sufficient evidence for the Committee to reconsider current assumptions, in particular those with regards to post-progression survival benefit. Pfizer has also submitted a revised PAS.

In this response, Pfizer presents further adjustments to the Committee's set of preferred economic estimates which included: equal post-progression survival and lower post-progression utility. We note that some of the ERG adjustments were not clinically plausible as they were not aligned with the observed data, clinicians' opinion and previous appraisals.

The cumulative impact of the above changes improves the cost-effectiveness (versus gefitinib with PAS) to £[redacted] per QALY gained. Given the confidential nature of the erlotinib and afatinib PAS, a threshold analysis is presented that varies the PASs from 5% to 95% at 5% intervals to aid the Committee in its decision making. This analysis indicated that the PAS for erlotinib and afatinib would have to exceed [redacted]% and [redacted]%, so that the ICER is above the £30,000 per QALY threshold.

Pfizer is very keen to find a timely solution to avoid lengthy delays in the access of this important treatment option to patients.

Yours sincerely,

[redacted]

[redacted]Assumption 1: Assuming equal efficacy for overall survival after 36 months

Pfizer does not believe that the Committee should assume equal efficacy beyond 36 months as it is not clinically plausible to assume dacomitinib has a decrement post-progression.

The ERG base-case assuming equal efficacy for overall survival between all treatments after 36 months results in the ERG base-case predicting mean post-progression survival of [redacted]month for dacomitinib, [redacted] months for gefitinib/erlotinib and [redacted] months and afatinib. The ERG and Committee acknowledged alternative scenarios with equal efficacy from 48 months, 60 months and 71 months (equal post-progression survival).

The 36-month scenario cannot be considered clinically plausible given the proportion of patient on treatment at 36 months and the lack of events informing the arbitrary 36-month cut-off. The latter scenario of equal post-progression survival is the most clinically plausible given the post hoc analysis of post-progression survival from ARCHER 1050, clinical opinion and prognosis beyond progression.

High proportion on treatment with dacomitinib at 36 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. Therefore, is it not plausible to assume there is no further benefit for these patients that are still on treatment.

Post-progression survival in ARCHER

Post-hoc analyses of post-progression survival from ARCHER 1050 was calculated from the date of progression-free survival (PFS) per IRC review to the date of overall survival (OS) event or censored date as applicable). The PFS data are based on the primary completion data cut-off date (29 July 2016) and the OS data are based on the OS Final Analysis data cut-off date (17 February 2017).

In the ITT population, the estimated hazard ratio of PPS for dacomitinib versus gefitinib was [redacted]based on the stratified analysis, indicating a [redacted]reduction in the risk of post-progression death in favour of dacomitinib. The median PPS was [redacted]months in the dacomitinib arm and [redacted]months in the gefitinib arm. These data, albeit from post-randomization subgroups, suggest that there was a numerical improvement in post-progression survival in the dacomitinib arm compared to the gefitinib arm (hazard ratio [HR] <1). Thus equivalent post-progression survival should be considered as a worst case scenario.

Post-progression survival and censoring in ARCHER

The above analysis used the ITT population and therefore, included patients with censored PFS events. Therefore, to explore the impact of this censoring, a further PPS analysis was

undertaken only including patients with an observed PFS event. The estimated hazard ratio of PPS for dacomitinib versus gefitinib was [redacted](95% CI: [redacted]) with a 1-sided p-value of [redacted] based on the stratified analysis, indicating a [redacted] reduction in the risk of post-progression death in favour of dacomitinib. The median PPS was [redacted] months in the dacomitinib arm and [redacted] months in the gefitinib arm.

The results above are also likely to be conservative because patients who progress early have a longer follow up post progression and higher chance of death before censoring. For these patients it is more likely that the true (uncensored) PPS is reached compared with patients who are on therapy for longer. The table below shows that there were more observations in the gefitinib arm ([redacted]) compared to the dacomitinib arm ([redacted]) where PPS was known because of recorded events for both PFS and OS. The table also shows that there were many more patients in the dacomitinib arm ([redacted]) compared to the gefitinib arm ([redacted]) where PPS was unknown because both PFS and OS were censored. If these patients had the opportunity to continue in the ARCHER 1050 trial, the PPS gain would likely increase and be reflected in the data. As dacomitinib is a more effective therapy, with more censoring in both PFS and OS, the likelihood that the true PPS has been reached is lower with dacomitinib and this would likely underestimate the PPS gain with dacomitinib.

Table 1. Censoring and PPS estimation

PFS event	OS event	dacomitinib 227 n(%)	gefitinib 225 n (%)	
yes	yes	[redacted]	[redacted]	true PPS is known
yes	no	[redacted]	[redacted]	true PPS is censored
no	yes	[redacted]	[redacted]	PPS is overestimated
no	no	[redacted]	[redacted]	true PPS is not known

Post-progression survival and correlation with PFS

An additional analysis was conducted to evaluate the extent to which longer PFS is associated with longer PPS. The methodology used in Negrier et al. 2014 was adopted whereby PPS was calculated for 3 equally sized groups based on PFS duration. This analysis suggests that for the ITT population of ARCHER 1050 (including both dacomitinib

and gefitinib patients), there was a significant difference between the PPS curves based on PFS duration. Compared with the lowest PFS duration group ([redacted]), PPS was significantly longer in the group with [redacted] ([redacted]). Similarly, compared with the lowest PFS duration group, PPS survival was significantly longer in the group with PFS≥14.6 ([redacted]). As expected, there was a large amount of censoring in the group of patients with the longest PFS, indicating that PPS gain in this population relative to the population in the lowest PFS strata, would be even higher if the analysis were done with more mature data. The positive association between PFS and PPS was also shown for the gefitinib arm.

In summary, these results indicate that longer PFS is associated with longer PPS and that the assumption of equal PPS between dacomitinib and gefitinib is highly conservative and can be considered a worst-case scenario. Indeed, the evidence suggests that PPS is at least as long for dacomitinib compared with gefitinib, and possibly even longer because of censoring and the positive relationship between PFS and PPS.

Clinical opinion

The ERG clinical adviser stated that it was reasonable to assume equivalent post-progression survival for the comparators in this analysis.

Tumour response and subsequent treatments

Given similar response rates there is no meaningful difference expected in the tumour size upon progression and upon progression there is no difference in available subsequent treatments (osimertinib, platinum doublet chemotherapy). Therefore, there is no clinical rational for patients on dacomitinib to have an inferior prognosis upon prognosis compared to comparator TKIs and thus no difference in post-progression survival.

Assumption 2: Progressed disease utility values from alternative sources

Pfizer do not believe that the Committee should consider the single post-progression follow-up utility from ARCHER 1050 as representative to the entire time in the progressed disease state (primary progression until death).

The company does not disagree with the ERG and the Committee that from a methodical perspective, it may be more appropriate to use utility values from trials when they are available. However, 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. Therefore, it cannot be considered robust enough to capture the gradual decline in quality-of-life for these patients during potential additional lines of therapy and progression and the time prior to death. Thus, as expected the post-progression follow-up values applied the committee preferred analysis ([redacted]) only represent a utility decrement of [redacted], which is at odds with previous NICE advanced NSCLC appraisals.

Of note, the current appraisal of osimertinib in patient with untreated EGFR+ advanced NSCLC, the committee preferred value is 0.678, representing a progression decrement of 0.116 (0.794-0.678). This can also be considered a relatively high progressed disease value given that it only accounts for patient progression-free on second line treatment, thus not accounting for further progression and declining quality-of-life prior to death.

The decline in utility prior to death has been demonstrated in a previous NSCLC appraisal of atezolizumab in NSCLC, where progressed utility values >15/>5/<5 weeks were 0.58, 0.43 and 0.35, respectively. Although they are not the most robust evidence from the literature Nafees (2008) and Chouaid (2013) with values of 0.47 and 0.46 for progressed disease, these have been accepted by committee's as the preferred values in numerous previous NICE NSCLC appraisals.

Therefore, the value from Labbe (0.64) that is considered the most appropriate from the literature by the ERG, should be applied in the base-case analysis.

Cost-effectiveness summary of Pfizer's adjustments to the ERG analysis

Error! Reference source not found. summarises the single change and all change ICERs for each of these adjustments.

Table 2. Cost-effectiveness estimates with PAS

#	Company adjustment	ICER dacomitinib ([redacted]% 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]

The adjustments made to the ERG structural changes impact the cost-effectiveness estimates and are likely to alter the committee's preliminary decision of not recommending dacomitinib to patients with EGFR+ NSCLC. The ICER falls below £30,000 per QALY gained (£[redacted]/QALY). The threshold analysis is presented in Table 3 indicated that the PAS for erlotinib and afatinib would have to exceed [redacted]% and [redacted]%, respectively for the ICER to be above the £30,000 per QALY threshold.

Table 3. Cost-effectiveness estimates with Company revised base-case (2+3) and erlotinib/afatinib at varying discounts (dacomitinib with PAS)

Comparator discount	ICER dacomitinib versus	
	Erlotinib	Afatinib
5%	[redacted]	[redacted]
10%	[redacted]	[redacted]
15%	[redacted]	[redacted]
20%	[redacted]	[redacted]
25%	[redacted]	[redacted]
30%	[redacted]	[redacted]
35%	[redacted]	[redacted]
40%	[redacted]	[redacted]
45%	[redacted]	[redacted]
50%	[redacted]	[redacted]
55%	[redacted]	[redacted]
60%	[redacted]	[redacted]
65%	[redacted]	[redacted]
70%	[redacted]	[redacted]
75%	[redacted]	[redacted]
80%	[redacted]	[redacted]
85%	[redacted]	[redacted]
90%	[redacted]	[redacted]
95%	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio

References

S. Négrier, A.G. Bushmakin, J.C. Cappelleri, B. Korytowsky, R. Sandin, C. Charbonneau, M.D. Michaelson, R.A. Figlin, R.J. Motzer, Assessment of progression-free survival as a surrogate end-point for overall survival in patients with metastatic renal cell carcinoma, European Journal of Cancer, Volume 50, Issue 10, 2014, Pages 1766-1771.

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Pfizer Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	

Comment number	**Comments** Insert each comment in a new row.

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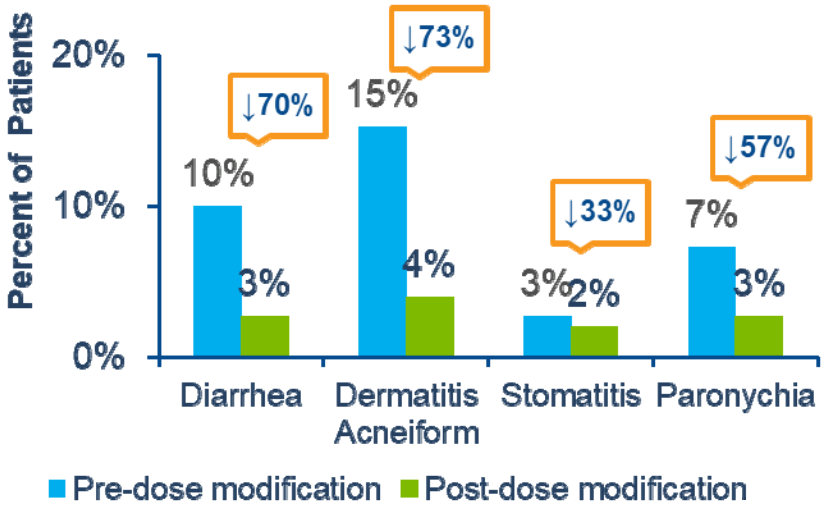
	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Correction required in 3.8. The company disagree that dacomitinib had more dose reductions than gefitinib as dose reduction is not possible with gefitinib as it is only available in one strength (250mg tablet). In addition, an abstract presented in the IASLC World Lung Conference in September 2018 assessed the efficacy benefit of dacomitinib in patients that received dose reductions from 45mg, to 30mg or 15mg, in the ARCHER-1050 trial[1]. The IASLC abstract demonstrated that patients who had reduced their dose to manage AEs (66.1%, n=150; 87 patients reduced to 30 mg, and 63 patients reduced to 15 mg) experienced improved AE incidence and similar efficacy benefit compared to all dacomitinib-treated patients[1].

Efficacy in Dacomitinib dose-reduced vs. all Dacomitinib-treated patients[2]

	Dose-reduced patients (n=150)	**All VIZIMPRO-treated (n=227)**
mPFS	16.6 mo [95% CI: 14.6, 18.6]	14.7 mo [95% CI: 11.1,16.6]
ORR	79.3% [95% CI: 72.0, 85.5]	74.9% [95% CI: 68.7, 80.4]
mOS	36.7 mo [95% CI: 32.6, NR]	34.1 mo [95% CI: 29.5, 37.7]



1. World Conference – Lung Cancer 2018, Abstract Book. WCLC2018-Abstract-Book_vF-LR-REV-SEPT-25-2018.pdf. T. Mok, K. Nakagawa, R. Rosell, K. Lee, J. Corral, M.R. Migliorino, A. Pluzanski, R. Linke, G. Devgan, E. Sbar, S. Quinn, T. Wang, Y. Wu. EFFECTS OF DOSE MODIFICATIONS ON THE SAFETY AND EFFICACY OF DACOMITINIB FOR EGFR MUTATION-POSITIVE NSCLC. MA26 NEW

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	THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1 WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00. 2. US (FDA) VIZIMPRO prescribing information (Pfizer, 2018).
2	Correction required in 3.15: In its base case, the ERG used the log-logistic curve for gefitinib and the fractional polynomial network meta-analysis for the other comparators **(P1=0.5, P2=1)**. In its base case, the ERG used the log-logistic curve for gefitinib and the fractional polynomial network meta-analysis for the other comparators **(P1=-0.5)**.
3	Correction required in 3.20: 'using the log-logistic parametric curve for gefitinib and the results from the fractional polynomial network meta-analysis **(P1=0.5, P2=1)** for the other comparators' Should be updated with the following: 'using the log-logistic parametric curve for gefitinib and the results from the fractional polynomial network meta-analysis **(P1=-0.5)** for the other comparators'

Insert extra rows as needed

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Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

Professor Gary McVeigh
NICE, Level 1, City Tower,
Piccadilly Plaza,
Manchester,
M1 4BT

11th June 2019

CONFIDENTIAL

Dear Professor McVeigh,

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

Following the second Appraisal Committee meeting held on 23rd May 2019, Pfizer has increased the confidential discount for dacomitinib from [redacted] to [redacted] on the current list price of £2,703.00 per 30-tablet pack (confidential net price from [redacted] to [redacted]).

When populating the economic model with the assumptions concluded by the Committee (assumed equal efficacy [HR=1] for overall survival between all treatments after 48 months and a post-progression utility value of 0.678) the ICER reduces from [redacted], with the new discount. Thereby, demonstrating cost-effectiveness in the Committee's preferred base-case.

We thank you for your assistance with this submission and are happy to discuss this further with you as required.

Your sincerely,
[redacted]

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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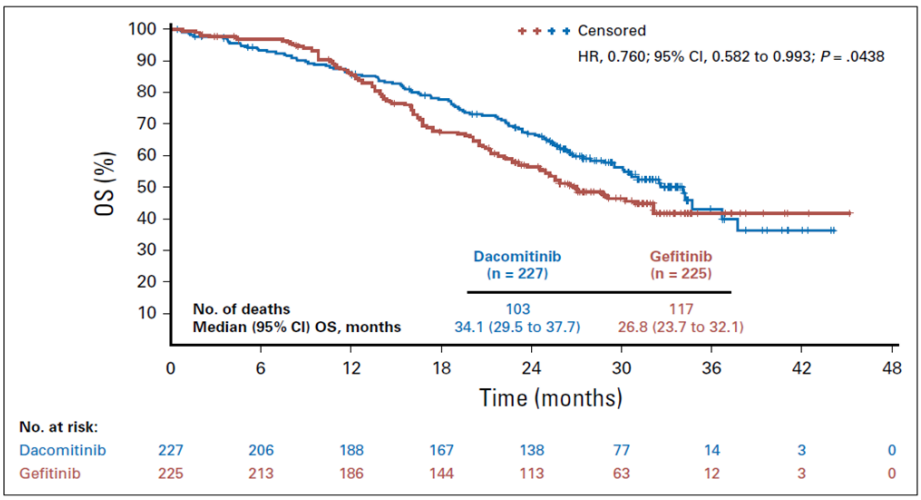
	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Inaccurate description of overall survival benefit** In the summary of why the committee made the recommendations in the ACD (page 3) and paragraph 3.5, it is stated that the committee concluded that dacomitinib is associated with improved progression-free and overall survival compared with gefitinib. The ARCHER-1050 study demonstrated a significant improvement in OS in the dacomitinib group compared with the gefitinib group (HR of 0.760 [95% CI 0.582, 0.993] p=0.0438). Median OS with dacomitinib was 34.1 months [95% CI 29.5, 37.7] and 26.8 months [95% CI 23.7, 32.1] for gefitinib, which was clinically relevant. However, it is clear that for the ITT population, the Kaplan-Meier survival curves cross-over at least once at around 11 months (and potentially a second time at approximately 36 months) (see Figure from Mok et al., J. Clin Oncol 2018,: 36: 2244) suggesting that a specific subgroup, or subgroups, of patients derive more benefit from gefitinib than dacomitinib.  It is perhaps more accurate therefore to conclude that although there is some evidence that dacomtinib is associated with improved overall survival compared with gefitinib, there is evidence that a specific subgroup, or subgroups, of patients derive more benefit from gefitinib than dacomitinib.
2	**Public data marked as confidential** In paragraph 3.7 of the ACD (p7 and 8) it is stated that the results of the pre-specified subgroup of patients according to ethnicity was considered academic in confidence by the company and could not be reported. It is worth noting that the HR for OS and median OS for both Asians and non-Asians within ARCHER-1050 have been available in the public domain since June 2018 (Mok et al., J. Clin Oncol 2018,: 36: 2244).

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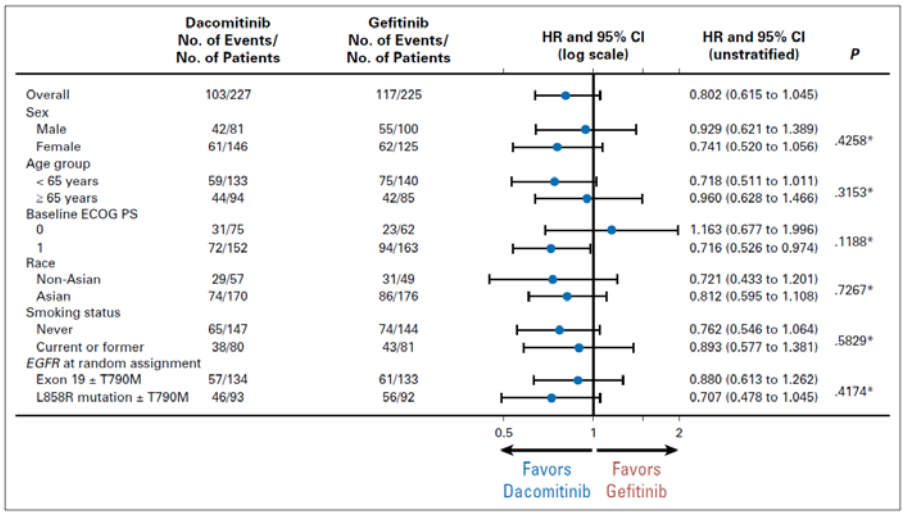

Subgroup analysis of PFS suggested that efficacy was driven by the Asian group (HR 0.51 [95% CI 0.39, 0.66]). The PFS HR in the non-Asian group was not statistically significant (HR 0.89 [95% CI 0.57, 1.39])
In Asian patients (53.8% censored), median OS was 34.2 months (95% CI 30.1, not reached [NR]) with dacomitinib versus 29.1 months (95% CI 25.2, NR) with gefitinib (preliminary HR 0.812 [95% CI 0.595, 1.108] p=0.1879).
In non-Asian patients (43.4% censored), median OS was 29.5 months (95% CI 20.7, NR) with dacomitinib versus 20.6 months (95% CI 16.1, 25.5) with gefitinib (preliminary HR 0.721 [95% CI 0.433, 1.201] p=0.2073).

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).

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Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346): ERG Addendum 2 of the non-confidential appendix reporting analysis undertaken on the basis of the updated Patient Access Scheme discount

Produced by: **Warwick Evidence**, University of Warwick, Coventry, CV4 7AL

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Date completed: 14 May 2019

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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]).

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Rider on responsibility for report:

This report should be referenced as follows:

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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 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 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.

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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1 ERG Response to company's comments on ACD1

Summary of company submission: The company has provided comments on two key points included in the committee's preferred assumptions, that also featured in the evidence review group's (ERG) base case analysis. The company also provided incremental cost effectiveness ratios (ICERs) exploring a range of scenarios that incorporate their new patient access scheme (PAS) discount.

1.1 Assumption 1: Assuming Equal Efficacy for overall survival after 36 months.

The company provide several arguments against the ERG's preference for assuming an equal hazard rate on the comparators beyond 36 months. The company's preference is to use a utility value provided by.

Firstly, the company draw attention to the number of patients remaining in the progression-free health-state on the dacomitinib arm, and thus receiving first line treatment. The company believes that the fact that [redacted] of dacomitinib patients are still receiving dacomitinib treatment at 36 months means that it is unreasonable to assume there is no overall survival (OS) benefit beyond this point. By comparison, there are [redacted] remaining on treatment in the gefitinib arm, and [redacted] in the afatinib arm at 36 months. It is worth noting that [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. Given that there is a minority remaining on treatment, it further questions the company's preferred alternative scenario, where the treatment effect is not sustained, but increases across the time horizon, until the implementation of a hazard ratio of 1 from 71 months. Note also that the economic model did not account for the higher discontinuation rate which was observed in the dacomitinib arm of ARCHER 1050, nor does it consider the potential impact of later lines of treatment, both of which may confound long hazard rates.

Secondly, the company presents the results of an analysis performed on the post-progression survival data from ARCHER 1050, using the intention-to-treat (ITT) population. The company's results are potentially misleading as they have presented a 1-sided p-value which assumes the post-progression survival is greater for those on dacomitinib when hypothesis testing. Also, this is a post-hoc analysis, meaning the data were not collected with the aim of answering a question on post-progression survival. Whilst a 2-sided p-value would likely be much higher, even using the 1-sided p-value does not suggest any meaningful difference has been observed despite the lack of a

stated significance threshold. It is unclear to the ERG how the company can classify a scenario of equal post-progression survival times as worst case from this information. The company presents median post-progression survival times for both arms, but does not present any further supporting evidence such as Kaplan-Meier plots, mean survival estimates or confidence intervals. Thus it is difficult to ascertain the robustness of the apparent difference in median post-progression survival times.

Thirdly, the company repeated the analysis of post-progression survival data, considering only patients with an observed progression-free survival (PFS) event time, i.e. ignoring censored patients. Immediately this introduces an additional source of bias, and again the company presents a 1-sided p-value. Again, there are little data, and the analysis does not allow for any conclusion to be drawn. The company presents comparison of the median survival times for this new population but again, without additional supporting information, it is unclear whether these can be treated as reliable statistics for the true behaviour of post-progression survival.

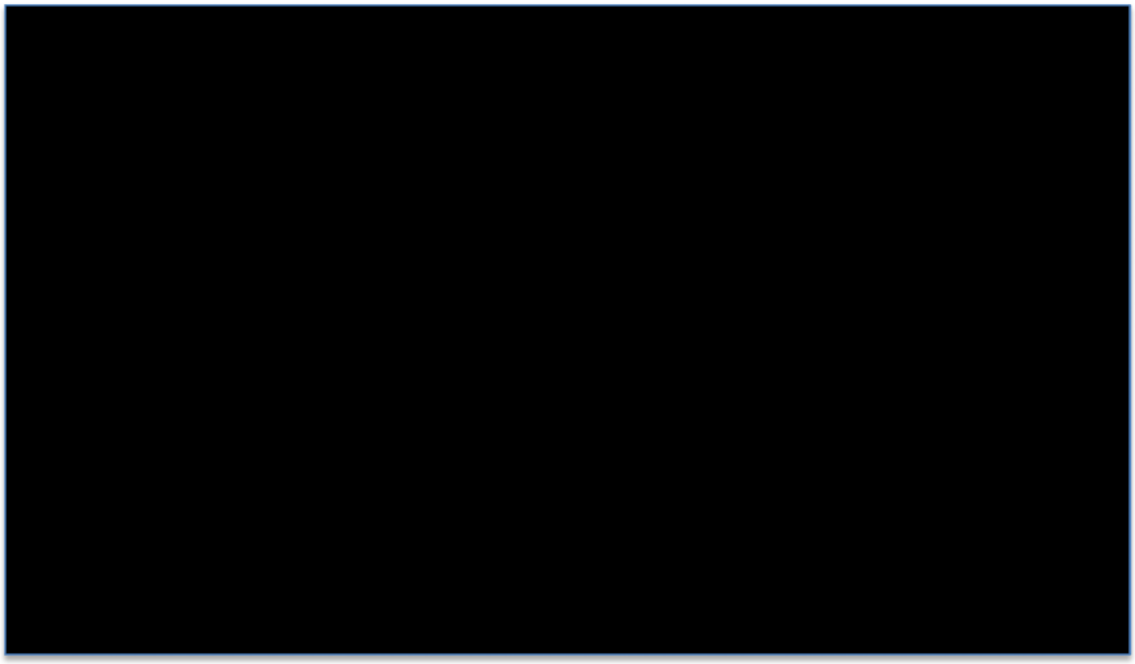
Fourthly, the company conducted an analysis comparing the post-progression survival times of three different groups of patients from the ARCHER 1050 trial, using methodology presented by Négrier et al. [1] The groups were formed based on PFS event time, namely PFS<7.3 months, PFS between 7.3 and 14.6 months, and PFS >14.6 months. The analysis produced statistically significant hazard ratios between the three groups. However this is an analysis comparing three drastically different groups in terms of PFS survival without consideration of intervention received, and it is potentially misleading to extend to inferences between the two arms of the ARCHER 1050 trial, where the PFS differences are of a lesser degree.

The ERG acknowledge that the assumption of equal post-progression could be considered plausible, but maintain that the most relevant evidence from ARCHER 1050 does not support this view.

In response to the company's comments, the ERG would like to draw attention to the evidence that supported the initial selection of the hazard ratio=1 from 36 months. Both the company's fractional polynomial analysis to the trial data, and the ERG's restricted cubic spline analysis to the reconstructed data demonstrated a clear loss of the benefit of dacomitinib on the hazard scale within the observed period of the trial. 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 proceeding to increase sharply, with similar patterns reported for all other second

order models (Figure 1). Similarly, in the ERGs analysis, the hazard ratio crossed 1 at roughly 24 months before also increasing sharply (Figure 2).

As a sensitivity analysis, the ERG censored the survival times of the 10 most recent OS events in the dacomitinib arm of ARCHER 1050, which is all events beyond [redacted] months and equates to 10% of the total events that occurred in the dacomitinib arm (Figure 3). It is clear that the diminishment of dacomitinib efficacy on OS observed in the trial occurs before 31 months, thus implementing the hazard ratio from 36 months may not be conservative, but in line with the observed data.



[redacted]

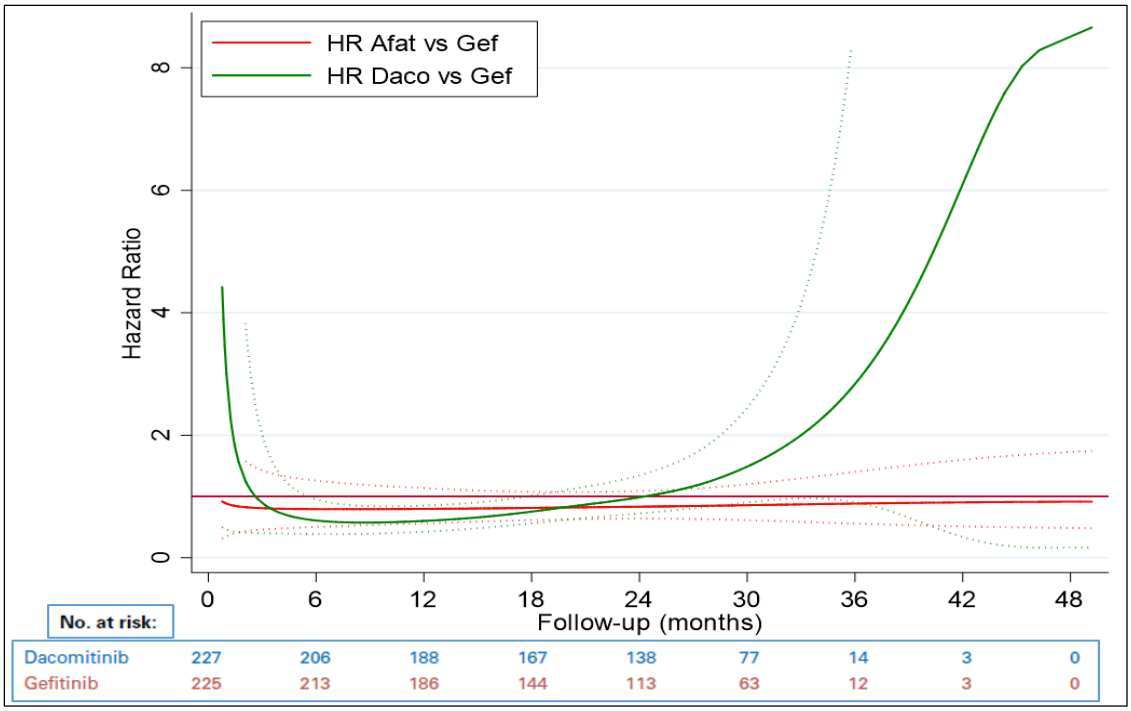


Figure 2: OS hazard ratio from spline model fitted to digitised data from ARCHER 1050[2] and LUX-Lung 7[3]

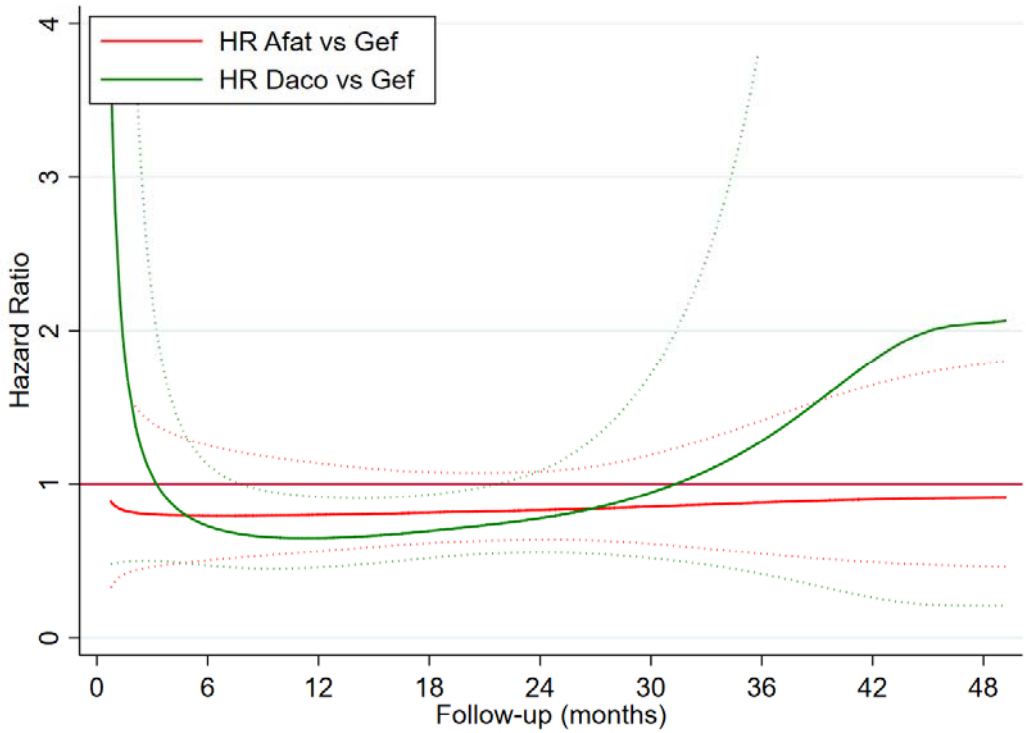


Figure 3: OS hazard ratio from spline model fitted to digitised data from ARCHER 1050[2] and LUX-Lung 7[3] with the final 10 OS events on the dacomitinib arm instead censored at time of event.

1.2 Assumption 2: Progressed disease utility values from alternative sources.

In the second section, the company argues against the use of the committee's and ERG's preference to use the post-progression utility value of [redacted] based on data collected in the ARCHER 1050 trial. The company's preferred source of a post-progression utility value is from Labbé et al. [4]

The ERG are aware that the utility value derived from ARCHER 1050 [2] 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 company's preferred utility value comes from Labbé et al. Whilst this study provides a utility value that covers a range of time following disease progression for EGFR positive patients using UK weighting, 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 acknowledges that neither source is ideal, and that both have their merits. But it is the ERG's preference 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.

2 Verification of the company's new analyses

2.1 Introduction

In this document, we verified the revised confidential discount for dacomitinib in the form of a simple patient access scheme (PAS) submitted on the 9th May 2019. Second, we verified the cost-effectiveness estimates submitted by the company. Third, we undertook further analyses as requested by NICE under the revised PAS for dacomitinib and assumed PAS for all comparators based on the company's new base-case assumptions, the committee's preferred assumptions and the ERG's preferred assumptions.

2.2 Verification of the revised PAS

The company revised the confidential discount for dacomitinib from [redacted] to [redacted], which reduces the list price of £2,703 per 30-table pack to [redacted]. The discounted price accurately reflects the increase in the PAS.

2.2.1 Verification of the cost-effectiveness estimates submitted by the company

The company undertook further analyses using the list prices for afatinib and erlotinib, applying the PAS for gefitinib and dacomitinib, and making 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. [4]

- Under the ERG's base-case assumptions
- No survival gain beyond 60 months and using the post-progression utility values from Labbé et al. [4]
- No additional survival benefit beyond 71 months and using the post-progression utility values from Labbé et al. [4]

Table 1: Deterministic results, no survival gain beyond 60 months

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 2: Deterministic results, no additional survival benefit beyond 71 months

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 3: Deterministic results, using the post-progression utility value from Labbé et al.

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 4: Deterministic results, under the ERG's base-case assumptions

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Table 5: Deterministic results, no survival gain beyond 60 months and using the post-progression utility values from Labbé et al.

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

Table 6: Deterministic results, no additional survival benefit beyond 71 months and using the post-progression utility values from Labbé et al.

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

In summary, the ERG's results presented in Table 1 to Table 6 were in good agreement with the company's results.

2.2.2 Verifying company revised base-case (2+3) and varying the discounts for erlotinib/afatinib

The company undertook analyses using the dacomitinib with PAS and varying discounts for erlotinib/afatinib under the following assumptions:

- No additional survival benefit beyond 71 months and
- Using Labbe et al.[4] post-progression utility of 0.64

Under these assumptions, the ERG's verified analyses were in good agreement with the company's analyses. However, it should be noted that the ICER remained unchanged for the comparison between dacomitinib (under the revised PAS) versus gefitinib (with PAS).

3 ERG's analyses under the revised PAS for dacomitinib and assumed PAS for all comparators

In section 3.1 through to section 3.3, we report the results based on the assumed comparator PAS versus the revised PAS for dacomitinib under the following assumptions:

- Company new base-case
  - No additional survival benefit beyond 71 months
  - Using the post-progression utility of 0.64 obtained from Labbé et al. [4]
- Committee preferred assumptions
  - Equal post-progression (no survival benefit beyond 71 months)
  - Using the post-progression utility value of [redacted] derived from the ARCHER 1050 trial[2]
- ERG's base-case
  - No additional survival benefit beyond 36 months
  - Using the post-progression utility value of [redacted] derived from the ARCHER 1050 trial

3.1 Deterministic results, under the company's new base-case

The results in Table 7 show that under these assumptions, gefitinib is the least costly and is the least effective, while dacomitinib is the most costly and most effective treatment. Treatment with gefitinib dominates erlotinib, being cheaper but is equally as effective. The comparison between gefitinib and afatinib is extendedly dominated by the comparison between gefitinib and dacomitinib, with an ICER of approximately [redacted] per QALY.

Table 7: Deterministic results, under the company's new base-case

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					

3.2 Deterministic results, under the committee's preferred assumptions

These results in Table 8 show the impact of changing the post-progression utility value from 0.64 to [redacted]. As expected, the mean expected costs across all strategies remained the same, while the expected mean QALYs yielded increased across all strategies. Erlotinib and afatinib continued to be dominated and extendedly dominated respectively, with the comparison between gefitinib and dacomitinib resulted in an ICER of approximately [redacted] per QALY gained.

Table 8: Deterministic results, under the committee's preferred assumptions

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

3.3 Deterministic results, under the ERG's preferred assumptions

Under these assumptions, it can be seen in Table 9 that reducing the survival benefit from 71 months to 36 months resulted in a decrease to the expected mean QALYs yielded for afatinib and dacomitinib. The incremental benefit between gefitinib and dacomitinib has reduced, which resulted in an increase to the ICER to approximately [redacted] per QALY gained.

Table 9: Deterministic results, under the ERG's preferred assumptions

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

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained

Under the revised PAS for dacomitinib and assumed PAS for all comparators the overall these results showed that the ICER for the comparison between gefitinib and dacomitinib ranged from approximately [redacted] to [redacted] per QALY.

Table 10: Scenario analysis, no additional survival benefit after 48 months, 60 months and equivalent post-progression between comparators (reported in terms of cost per QALY)

Treatment	Expected mean costs (£)	Incremental costs (£)	Pre-progression QALY	Post-progression QALY	Expected mean QALY	Incremental QALY	ICER (£)
ERG's preferred base-case assumptions							
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Hazard ratio = 1 from 48 months							
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Hazard ratio = 1 from 60 months							
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[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)							
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY, quality adjusted life-years gained							

In Table 10, we present the results for the scenario analyses by changing the assumption about no survival benefit after 48 months, 60 months and 71 months for afatinib and dacomitinib compared to the ERG's base-case assumption of no survival benefit between afatinib and dacomitinib beyond 36 months. These results show that there is a greater increase in the expected mean QALYs yielded for afatinib and dacomitinib the later the equivalent survival benefit is implemented. The expected mean QALYs for dacomitinib assuming no survival benefit beyond 36 months was [redacted], which increased to [redacted] by assuming no survival benefit beyond 71 months. Increasing the time point from where there is no survival benefit reduced the ICER from approximately [redacted] to [redacted] per QALY for the comparison between dacomitinib and gefitinib. All other treatment strategies remained dominated or extendedly dominated.

References

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Please find our reply to Professor McVeigh's queries below. We hope that you will find these helpful. Please do not hesitate to get in touch should there be any further questions.

Query 1. I understand at 3 years with [redacted]% alive and [redacted]% post progression and off initial Rx that the company assertion that the treatment effect of dacomitinib increases could be challenged. However, we are comparing with gefitinib with [redacted]% on Rx and afatinib with [redacted]% on Rx but as a proportion of the % alive (which I do not know). If an even higher % are post progression in the comparator arms and off 1st line Rx then, on a relative basis, is it not plausible the HR=1 at a later time point?

We agree with Professor McVeigh's point, and can present output from the economic model which show a greater proportion of alive patients are on first line treatment in the dacomitinib population, than the comparators. We accept that on this single discussion point, it would potentially support an implementation of the HR=1 from later than 36 months, however, the differences are of a similar magnitude at 48 months. (~[redacted]% between treatments at 36 months compared with ~[redacted]% at 48 months)

We maintain that the observed data from ARCHER 1050 shows a clear loss of efficacy in terms of the OS hazard ratio, which was visible even when replacing the final ten events in the dacomitinib arm to instead be censored.

At 36 months we can confirm the following percentages of patients are in the following health states:

	% PFS at 36 months (% of alive)	% PPS at 36 months (% of alive)	% OS at 36 months
Dacomitinib	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]

Repeating this at 48 months (without implementing the HR=1 at 36 months), you would obtain the following values:

	% PFS at 48 months (% of alive)	% PPS at 48 months (% of alive)	% OS at 48 months
Dacomitinib	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]

Query 2. Just from a clinical perspective I cannot understand why the HR (fig 1) relationship for OS is so different for dacomitinib vs afatinib given they are both 2nd generation TKI inhibitors.

We also agree with the contrasting differences in behaviour of OS hazard ratios between afatinib and dacomitinib. This was something we commented on in our initial report, and led to us performing an

analysis using the OS curve from afatinib for dacomitinib. Also note that a significant difference

between afatinib and dacomitinib was not found from the company's network meta-analysis.

When performing the analysis as per the ERG base case but with afatinib OS used for dacomitinib,

with the new PAS, the ICER is in the region of £[redacted]/QALY.

With Regards

The ERG team