NICE National Institute for Health and Care Excellence

NICE guidance

Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Dacomitinib is recommended, within its marketing authorisation, as an option for untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) in adults. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Locally advanced or metastatic EGFR mutation-positive NSCLC is usually first treated with afatinib, erlotinib or gefitinib.

Evidence from a randomised controlled trial shows that people who take dacomitinib live longer than people who take gefitinib. They also live longer before their disease gets worse. An indirect comparison suggests there is no difference between dacomitinib and afatinib in terms of how long people live or how long it is before their disease gets worse.

There is some uncertainty about the assumptions used in the cost-effectiveness modelling. But the most plausible cost-effectiveness estimate is within what NICE normally considers an acceptable use of NHS resources. So dacomitinib is recommended.

2 Information about dacomitinib

Marketing authorisation indication

2.1 Dacomitinib (Vizimpro, Pfizer), as monotherapy, is intended for 'the first-line treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer with epidermal growth factor receptor-activating mutations'.

Dosage in the marketing authorisation

2.2 Based on the company submission, dacomitinib is given orally at a dosage of 45 mg until disease progression or unacceptable toxicity. Dacomitinib is available in 3 dose strengths: 45 mg, 30 mg and 15 mg.

Price

2.3 The list price is £2,703 for 30×15 mg, 30×30 mg or 30×45 mg capsules.

2.4 The company has a commercial arrangement. This makes dacomitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical need

People would welcome a new treatment option

3.1 The patient experts highlighted that epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) tends to present late, so people have more advanced disease at diagnosis compared with the wider NSCLC population. The patient experts also noted that dacomitinib may improve overall survival, which is especially important to patients and their families. The committee agreed that people with EGFR mutation-positive NSCLC would welcome additional treatment options that improve overall survival.

Clinical management

Erlotinib, gefitinib and afatinib are appropriate comparators

3.2 The clinical experts explained that in line with NICE guidance, locally advanced or metastatic EGFR mutation-positive NSCLC is usually first treated with a tyrosine kinase inhibitor such as erlotinib, gefitinib or afatinib (see NICE technology appraisal guidance on erlotinib, gefitinib and afatinib). The committee understood that afatinib is more common in NHS clinical practice in England because as a second-generation tyrosine kinase inhibitor it is better than both erlotinib and gefitinib (first-generation tyrosine kinase inhibitors) in terms of prolonging progression-free survival. The committee also understood that afatinib is associated with more adverse events than erlotinib and gefitinib, so it is generally only offered to people with good Eastern Cooperative Oncology Group (ECOG) performance status. The clinical experts explained that this would also be the

case for dacomitinib. The committee agreed that although afatinib is the most commonly used tyrosine kinase inhibitor and has a similar adverse-event profile to dacomitinib, gefitinib and erlotinib were also used in established NHS practice in England. So gefitinib and erlotinib were also listed as comparators in NICE's final scope.

Clinical evidence

Evidence from an open-label randomised controlled trial is relevant and high quality

3.3 The main clinical evidence came from ARCHER 1050, a multicentre, open-label, phase 3 randomised controlled trial. It compared the efficacy and safety of dacomitinib (n=227) with gefitinib (n=225) in adults with untreated locally advanced or metastatic EGFR mutation-positive NSCLC. Patients had either the exon 19 deletion (del19) or exon 21 (L858R) EGFR mutation. The trial included 71 study sites in 7 countries (China, Hong Kong, Japan, Republic of Korea, Italy, Poland and Spain). The primary outcome was progression-free survival, determined by blinded independent review committee. Secondary outcomes included overall survival, objective response rate, length of response, adverse events, time to treatment failure and health-related quality of life. After disease progression, patients could have subsequent treatment with a different drug (see section 3.6). The committee noted that in the trials used to inform NICE technology appraisal guidance on erlotinib, gefitinib and afatinib, the comparator was chemotherapy. But in ARCHER 1050 the comparator was gefitinib (the trial compared a second-generation tyrosine kinase inhibitor [dacomitinib] with a first-generation tyrosine kinase inhibitor [gefitinib]). The committee concluded that ARCHER 1050 was a well-conducted trial providing high-quality evidence relevant to the appraisal.

The treatment arms in ARCHER 1050 are well balanced

3.4 The ERG noted that in the trial, 64.3% of patients having dacomitinib were women compared with only 55.6% of patients having gefitinib. The committee was aware

that there was some evidence to suggest that tyrosine kinase inhibitors tend to be more effective at treating EGFR mutation-positive NSCLC in women than in men, and so the trial could be biased in favour of dacomitinib. But the clinical experts did not consider sex to be an important factor. The committee concluded that the treatment arms in ARCHER 1050 were generally well balanced.

Dacomitinib improves progression-free and overall survival compared with gefitinib

3.5 The results of ARCHER 1050 showed that dacomitinib statistically significantly improved progression-free survival compared with gefitinib (14.7 months for dacomitinib compared with 9.2 months for gefitinib; hazard ratio [HR] 0.589, 95% confidence interval [CI] 0.47 to 0.74). Exploratory analyses also showed that dacomitinib improved overall survival compared with gefitinib (34.1 months for dacomitinib compared with 26.8 months for gefitinib; HR 0.760, 95% CI 0.58 to 0.99). During consultation, the company manufacturing gefitinib highlighted that the overall survival Kaplan–Meier curves for dacomitinib and gefitinib crossed at around 11 months (and possibly at around 36 months too). The company suggested that this shows that a specific subgroup (or subgroups) derives more benefit from gefitinib than dacomitinib. Although the committee acknowledged that the Kaplan–Meier curves did cross, it concluded that overall dacomitinib is associated with improved progression-free and overall survival compared with gefitinib.

It is unclear how subsequent treatments may affect overall survival in ARCHER 1050

3.6 In ARCHER 1050, patients who stopped taking the study drug (dacomitinib or gefitinib) could then have subsequent treatment with a different drug (the company considered the subsequent treatments to be confidential so they cannot be reported here). But the committee noted that these subsequent treatments did not reflect the type and proportion of those used in clinical practice in the NHS in England. The committee agreed that there was uncertainty about how subsequent treatments may have affected the overall survival estimates in ARCHER 1050, and that it would consider this in its decision making.

The results of ARCHER 1050 are generalisable to NHS clinical practice in England

3.7 The committee considered whether the baseline characteristics of patients in ARCHER 1050 reflected those seen in NHS clinical practice in England. It noted that the patients in the trial had only the exon 19 deletion (del19) or exon 21 (L858R) EGFR mutations. The clinical experts explained that these 2 mutations account for around 90% of all EGFR mutations. Also, most trials only include people with these mutations, including the trials that were carried out with other tyrosine kinase inhibitors. The committee acknowledged that although other mutations may not respond as well to dacomitinib, the Committee for Medicinal Products for Human Use (CHMP) did not restrict its positive opinion for dacomitinib to these 2 mutations (see section 2). The committee therefore agreed that the EGFR mutation status of patients in ARCHER 1050 generally reflected that seen in NHS clinical practice in England. It also noted that the trial included a large proportion of patients of Asian family origin (74.9% in the dacomitinib treatment arm and 78.2% in the gefitinib treatment arm) because many of the trial centres were in East Asia. It recalled that ethnicity was a prespecified subgroup in ARCHER 1050, and that the company had provided analyses in response to clarification, but the results were underpowered (overall survival: Asian family origin subgroup HR 0.81, 95% CI 0.6 to 1.11; non-Asian family origin subgroup HR 0.72, 95% CI 0.43 to 1.20. The results for progression-free survival are considered academic in confidence by the company and so cannot be reported here). During consultation, the company manufacturing gefitinib highlighted evidence suggesting that Asian ethnicity has been identified as a favourable independent prognostic factor for overall survival in NSCLC, irrespective of smoking status. The committee noted that in the company's overall survival analyses for ethnicity, dacomitinib showed a survival benefit compared with gefitinib in both the non-Asian and Asian family origin subgroups. Although ARCHER 1050 was not powered for subgroup analyses, the results were all aligned and were in favour of dacomitinib (except for the subgroup with ECOG performance status 0). The committee noted that there appeared to be much better progression-free survival for the Asian family origin subgroup, which was not reflected in overall survival for the same population. The committee agreed that there was no conclusive evidence that ethnicity has a significant effect on overall survival. Because the trial was not powered for subgroup analyses, the committee considered that the results from the whole trial population would be

generalisable to the population seen in clinical practice in England. The committee noted that ARCHER 1050 excluded people with brain metastases: these are associated with a poor prognosis and often occur in people with EGFR mutation-positive NSCLC. This was an important difference between ARCHER 1050 and the LUX-Lung 7 trial (used in the comparison of afatinib with gefitinib; see section 3.9), in which 16% of patients had brain metastases. The committee concluded that overall, the trial results from ARCHER 1050 were generalisable to NHS clinical practice in England.

Dacomitinib is associated with more adverse events and may need more dose reductions than gefitinib

3.8 The committee noted that dacomitinib had a higher incidence of common adverse events than gefitinib, and that there were more dose reductions in the dacomitinib treatment arm than in the gefitinib treatment arm (66.1% and 8.0% respectively). The committee was also aware that second-generation tyrosine kinase inhibitors such as afatinib are associated with more adverse events, whereas first-generation tyrosine kinase inhibitors are generally better tolerated (see section 3.2). The clinical experts agreed that the differences in the drugs' adverse-event profiles are well known and this is reflected in how they are used in clinical practice. That is, they are used according to whether a person is well enough for treatment, which is typically categorised by ECOG performance status. Although the clinical experts acknowledged that adverse events associated with second-generation tyrosine kinase inhibitors could be effectively managed in clinical practice, they highlighted that the adverse events were detrimental to people's quality of life. The Cancer Drugs Fund clinical lead also highlighted NHS England's concerns about the toxicity of dacomitinib and the high rates of adverse events that are likely to be seen in practice. The committee agreed that dacomitinib had a higher incidence of adverse events and needed more dose reductions than gefitinib. It concluded that how this affected health-related quality of life and resource costs for managing adverse events should be fully captured in the cost-effectiveness analysis.

The results from the company's fractional polynomial network meta-analysis are uncertain

3.9 The company did a network meta-analysis to compare dacomitinib with the other comparators in the scope, afatinib and erlotinib. It did a fractional polynomial network meta-analysis as described by Janssen et al. (2011), because it considered that the proportional hazards assumption may have been violated in ARCHER 1050 (that is, the hazard ratios were not constant over time). The committee understood that fractional polynomial network meta-analysis differs from a traditional network meta-analysis in that it fits hazard ratios that can vary over time rather than being constant. Based on the evidence from clinical experts, other phase 3 randomised controlled trials and previous NICE appraisals, the company assumed equivalence between gefitinib and erlotinib. The committee agreed that this assumption was appropriate. The company obtained the relative effect estimates of progression-free and overall survival for afatinib and dacomitinib compared with gefitinib from the LUX-Lung 7 trial (which compared afatinib with gefitinib). In its submission, the company presented the projected means for progression-free and overall survival along with the medians compared with the observed data from ARCHER 1050, to provide face validity for the model (the company considered the results to be commercial in confidence and so they cannot be reported here). The committee recalled the ERG's concerns about differences in patients' baseline characteristics in ARCHER 1050 and LUX-Lung 7, specifically the proportion of patients of Asian family origin and the presence of brain metastases (see section 3.7). The committee agreed that these differences, in particular the exclusion of people with brain metastases from ARCHER 1050, added uncertainty to any estimates from the analysis. The ERG also expressed concerns about extrapolating progression-free and overall survival outcomes from fractional polynomial models: they tend to over-fit to the tail of the data, often resulting in implausible survival extrapolations. The committee noted that these concerns were supported by the large number of models that the company had to reject because of the clinically implausible extrapolations of survival outcomes. The committee concluded that the results from the company's fractional polynomial network meta-analysis were uncertain.

There is no statistically significant difference between dacomitinib and afatinib in terms of progression-free and overall

survival

3.10 The ERG did its own indirect treatment comparison to address these uncertainties, and because the company's model did not report hazard ratios for progression-free or overall survival between dacomitinib and afatinib. The ERG did a fixed-effects network meta-analysis using data from ARCHER 1050 for dacomitinib and from LUX-Lung 7 for afatinib. The company agreed with the ERG's approach to estimating the hazard ratios. The results suggested that dacomitinib might be better than afatinib in terms of extending progression-free and overall survival, but there was no significant difference between the 2 treatments (progression-free survival HR 0.80, 95% CI 0.57 to 1.12; overall survival HR 0.88, 95% CI 0.61 to 1.29). The committee recalled that there was uncertainty around any estimates from a network meta-analysis that used data from ARCHER 1050 and LUX-Lung 7, because of the differences between the trials in terms of baseline patient characteristics (and because the proportional hazards assumption may have been violated in ARCHER 1050). It concluded that any estimates were uncertain and based on the evidence available there was no statistically significant difference between dacomitinib and afatinib in terms of extending progression-free and overall survival.

The company's economic model

The company's model is appropriate for decision making

3.11 The company used a partitioned-survival economic model that included 3 health states: pre-progression, post-progression and death. The model included either dacomitinib, afatinib, gefitinib or erlotinib as first-line treatment, followed by osimertinib (if T790M mutation-positive) or chemotherapy. The committee was concerned that the model captured only the costs and not the clinical benefits of subsequent treatments. However, the committee concluded that the model was generally appropriate and consistent with the models used in other appraisals for NSCLC.

Survival extrapolation

There are uncertainties in how the company modelled progression-free survival

3.12 In its original base case, the company modelled progression-free survival for gefitinib using a generalised gamma curve fitted to the gefitinib treatment arm of ARCHER 1050. It modelled progression-free survival for erlotinib by assuming equivalent efficacy with gefitinib. It then used the fractional polynomial network meta-analysis (model P1=0.5, P2=1.5) to obtain time-varying hazard ratios for afatinib and dacomitinib relative to gefitinib (see section 3.10), before applying these to the gefitinib extrapolation. The committee had concerns about the company's modelling of progression-free survival:

- The progression-free survival for gefitinib after 2 years potentially underestimated the quality-adjusted life years (QALYs) and costs for the comparators.
- The extrapolation of dacomitinib and afatinib relied on results from the fractional polynomial network meta-analysis, which were themselves uncertain (see section 3.9).
- The progression-free survival curves suggested that dacomitinib had the highest progression-free survival up to 38 months, after which afatinib had the highest progression-free survival. The committee agreed that there was no clinical rationale for dacomitinib to be less effective than the comparators in terms of progression-free survival after 38 months.

  The committee agreed that there was uncertainty around the company's modelling of progression-free survival because of the implausibility of the results. This made the company's incremental cost-effectiveness ratios (ICERs) highly uncertain.

The ERG's modelling of progression-free survival is appropriate

3.13 In its original base case, the ERG used the log-normal parametric curve for

gefitinib and the fractional polynomial network meta-analysis for the other comparators (P1=0.5, P2=1). The afatinib extrapolation remained implausible so the ERG assumed the progression-free survival of afatinib to be equal to the mean progression-free survival of dacomitinib and gefitinib after 36 months. It also did a scenario analysis in which it assumed the progression-free survival of afatinib to be equal to the mean progression-free survival of dacomitinib and gefitinib after 55 months. Although it recognised the uncertainties, the committee preferred this approach because it produced more plausible results than the company's base case. It therefore agreed that the ERG's modelling of progression-free survival was appropriate and its decision making should be based on this.

The company's modelling of overall survival produces some implausible results

3.14 In its original base case, the company modelled overall survival in the same way it modelled progression-free survival (see section 3.12). The committee had concerns about the company's modelling of overall survival:

- The generalised gamma curve may underestimate overall survival with gefitinib.
- The modelling suggested that the efficacy of afatinib relative to gefitinib decreased over time while the efficacy of dacomitinib improved over time; clinical expert advice to the ERG questioned the plausibility of this. The clinical experts acknowledged that effective treatments may provide some benefit for a limited time after stopping treatment, but the committee recalled that there was no evidence to suggest that afatinib and dacomitinib provided different benefits after stopping treatment.
- Dacomitinib appears to provide benefits both before and after disease progression. This is unlikely to be plausible, because it is uncommon for progression-free survival to mirror post-progression survival, and even less common for progression-free survival to be extended into post-progression survival.

The committee therefore agreed that the company's modelling of overall

survival produced some implausible results.

The ERG's modelling of overall survival is the most appropriate for decision making

3.15 In its original 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). It assumed equal efficacy for overall survival between all treatments after 36 months. The ERG acknowledged that assuming equal efficacy from 48 or 60 months could also be considered plausible and explored these in scenario analyses. The ERG also did a scenario analysis in which it assumed equivalent post-progression survival for all treatments after 71 months. The committee agreed that there was uncertainty around the company's modelling of overall survival because of the implausibility of the results (see section 3.14) and that all the ERG's scenario analyses were clinically plausible. The committee concluded that its decision making should be based on the ERG's modelling of overall survival.

The extrapolation of overall survival data after 36 months is highly uncertain

3.16 During consultation the company highlighted that the committee had accepted that all of the ERG's overall survival analyses (see section 3.15) were clinically plausible. It commented that the committee should further consider the ERG's scenario analysis in which equivalent post-progression survival for all treatments after 71 months was assumed. The committee noted the company's rationale for assuming equivalent post-progression survival for all treatments after 71 months. The company asserted that the ERG's base-case assumption of equal efficacy for overall survival modelling after 36 months cannot be considered plausible given the proportion of patients having treatment at 36 months who would be expected to get clinical benefit from ongoing treatment. The company also asserted that a scenario assuming equal post-progression survival after 71 months was the most clinically plausible scenario given the results of its 3 post-hoc analyses of post-progression survival from ARCHER 1050:

- For the intention-to-treat population, the company calculated post-progression survival from the date of progression-free survival (independent review committee) to the date of overall survival event or censored date as applicable. It considered that the results (considered academic in confidence by the company, and therefore cannot be reported here) suggested that there was an improvement in post-progression survival in the dacomitinib arm compared with the gefitinib arm (hazard ratio less than 1). Therefore the company considered that equivalent post-progression survival should be a worst-case scenario.

- The company did a second post-progression survival analysis which only included patients with an observed progression-free survival event. It considered the results (considered academic in confidence by the company, and therefore cannot be reported here) to be conservative because patients whose disease progresses early have a longer follow up post progression and a higher chance of death before censoring. The company further commented that for these patients it was more likely that the true (uncensored) post-progression survival was reached compared with patients who were on therapy for longer.

- The company did a third analysis to determine the extent to which longer progression-free survival is associated with longer post-progression survival. It calculated post-progression survival for 3 equally sized groups in ARCHER 1050 based on progression-free survival duration. The company commented that for the intention-to-treat population (including both dacomitinib and gefitinib patients), there was a significant difference between the post-progression survival curves based on progression-free duration (results considered academic in confidence by the company, and therefore cannot be reported here) for both the dacomitinib and the gefitinib arms.

  The committee acknowledged that clinical expert opinion had suggested that similar post-progression survival between comparator treatments would be expected. However, the committee understood that neither the ERG's original scenario analysis in which equivalent post-progression survival for all treatments after 71 months was assumed (see section 3.15) nor the company's post-hoc analyses accounted for treatment discontinuations or subsequent treatments. The ERG reiterated at the second committee meeting

that the company's fractional polynomial analysis of the observed data from ARCHER 1050 and the ERG's restricted cubic spline analysis of the reconstructed data both showed the loss of the initial overall survival benefit of dacomitinib compared with gefitinib and afatinib before 36 months. The committee was aware that with 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. Similarly, in the ERG's analysis, the hazard ratio crossed 1 at roughly 24 months before also increasing sharply. The committee was also aware that the ERG did a sensitivity analysis in which it censored the survival times of the 10 most recent overall survival events in the dacomitinib arm of ARCHER 1050. The ERG commented that it was clear that dacomitinib's efficacy on overall survival in the trial reduced before 31 months. Therefore implementing the hazard ratio from 36 months may not be conservative, but in line with the observed data. The ERG again explained that it preferred to use the hazard ratio for overall survival equal to 1 at 36 months because the fractional polynomial extrapolations for overall survival all provided implausible results. The committee recognised that extrapolating overall survival after 36 months was highly uncertain because of the lack of trial data. It concluded that it should consider the overall survival data extrapolation after 36 months further when determining the most plausible ICER (see section 3.23).

Health-related quality of life

The model should include age-related disutilities

3.17 In its original base case the company used utility values from ARCHER 1050 for dacomitinib and gefitinib for progression-free disease (the company considers the values to be academic in confidence and therefore cannot be reported here). The company assumed that the utility value for afatinib would be the same as that of dacomitinib, and that the value for erlotinib would be the same as that of gefitinib, based on the similarity of their respective adverse-event profiles. The committee considered that this was appropriate. However, the company did not

include any age-related disutilities. The committee accepted that these should have been included in the model given the starting age of the population modelled and the length of the time horizon.

Using utility values for progressed disease from ARCHER 1050 or Labbé is not appropriate

3.18 In its original base case the company used a utility value of 0.64 from Labbé (2017) for progressed disease. The ERG considered it more appropriate to use utility values from ARCHER 1050 for progressed disease (the values are academic in confidence and cannot be reported here). This was because there were limitations with the data from Labbé (including differences in patient baseline characteristics between ARCHER 1050 and Labbé, in particular the exclusion of people with brain metastases from ARCHER 1050). However, the clinical experts commented that the difference between the ARCHER 1050 and Labbé utility values would be unlikely to translate into a clinically meaningful difference. During consultation, the company reiterated its view that the Labbé utility value was the most appropriate to use. It highlighted that the ARCHER 1050 utility value for progressed disease only represented 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 during additional lines of therapy, disease progression and time before death. The ERG considered the ARCHER 1050 population to be most relevant to this appraisal in terms of disease stage and the interventions people had. The committee agreed that neither the ARCHER 1050 nor the Labbé utility value was ideal, but each had their merits. The committee also recalled that a utility value of 0.678 was used in NICE's technology appraisal guidance for osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (now replaced by NICE's technology appraisal guidance on osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer). It was also considered appropriate in the ongoing appraisal of osimertinib for untreated EGFR-positive non-small-cell lung cancer. The committee acknowledged that the utility value for progressed disease was not a significant factor in the cost-effectiveness analysis but agreed that it was appropriate to use the utility value of 0.678 for progressed disease.

The analyses should include disutilities associated with adverse events

3.19 In its original base case, the company did not include any disutilities for adverse events but incorporated a one-off treatment-specific disutility in a scenario analysis. The company's rationale for not including these disutilities was that the utility values from ARCHER 1050 would already incorporate the effect of adverse events through EQ-5D-3L data collected during the trial. To include treatment-specific utility decrements for adverse events would effectively double count the effect of adverse events. However, the ERG considered that the base-case analysis should include treatment-specific disutilities for adverse events. Many of the most common adverse events are limited in duration, and the EQ-5D-3L only captures how people feel on the day they complete it. The clinical experts also explained how the EQ-5D-3L does not capture the full impact of certain adverse events, such as diarrhoea, on health-related quality of life. The committee concluded that it was more appropriate to include disutilities associated with adverse events in the base-case analyses.

Resource use and costs

The company's assumptions about health benefits and costs of subsequent therapies are implausible

3.20 In its original base case, the company assumed that 71% of people having tyrosine kinase inhibitors would also have disease progression and second-line treatment. Of these, 56% would develop the T790M mutation and have osimertinib and the other 44% would have chemotherapy. The model also assumed that 48% of the original cohort would have third-line treatment; of these, 56% would have chemotherapy (the same people who had second-line osimertinib) and 44% would have docetaxel (the same people who had second-line chemotherapy). The committee was aware of NICE's statement on handling comparators and treatment sequences on the Cancer Drugs Fund. This states that 'products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals'. The committee accepted

that it was appropriate for osimertinib to be included in the treatment sequence in the model for dacomitinib, because this appraisal started before the position statement came into effect. The committee noted that the proportions and subsequent treatments used in the model did not reflect those used in ARCHER 1050 (see section 3.6). The Cancer Drugs Fund clinical lead explained that the proportions of people having second- and third-line treatments were higher than those seen in NHS clinical practice (50% to 60% for second line and 25% to 30% for third line). Also, osimertinib has been used less than would be expected in NHS clinical practice in England (8% to 13%), so the model overestimates its use. The clinical experts agreed that the proportions of people having subsequent treatments in the model were too high. The committee understood that the company had used the same proportions for second- and third-line treatments for all 4 tyrosine kinase inhibitors; so, although the exact proportions were inaccurate, the costs applied to the dacomitinib and comparator treatment arms were the same. But the committee recalled that the model did not capture the clinical benefits of subsequent treatment. It concluded that the company's assumptions about treatment costs and benefits in the model did not reflect the type and proportion of subsequent treatments taken by patients in the trial.

Results of the cost-effectiveness analyses

The company's updated deterministic base-case ICER for dacomitinib was below £30,000 per QALY gained

3.21 The company's 2 updated base-case analyses provided in response to consultation both included:

- an increased discount in dacomitinib's commercial arrangement
- the committee's preferred modelling of progression-free survival (see section 3.13)
- age-related disutilities (see section 3.17)
- disutilities for adverse events (see section 3.19).

Updated base case 1 included:

- equivalent post-progression survival (hazard ratio=1) from 71 months (see section 3.16)
- the Labbé post-progression utility value (0.64; see section 3.18).

Updated base case 2 included:

- no additional survival benefit (hazard ratio=1) after 60 months (see section 3.15)
- the Labbé post-progression utility value (0.64; see section 3.18).

When the updated final commercial arrangement was included, both base cases resulted in ICERs below £30,000 per QALY gained. Because the dacomitinib commercial arrangement is confidential, the exact ICERs cannot be reported here.

The ERG's updated base-case ICER for dacomitinib is over £30,000 per QALY gained

3.22 The ERG provided its updated preferred base case. This included the comparator commercial arrangements and the dacomitinib commercial arrangement that was submitted in response to consultation, assuming:

- no additional survival benefit after 36 months (see section 3.16)
- the post-progression utility value from ARCHER 1050 (see section 3.18).

The committee noted that the ERG's updated base case was above £30,000 per QALY gained. The ERG also provided scenario analyses with ICERs for:

- no additional survival benefit after 48 months
- no additional survival benefit after 60 months and

- equivalent post-progression survival (hazard ratio=1 from 71 months).

The committee noted that the ICERs for no additional survival benefit after 60 months and for equivalent post-progression survival were both below £30,000 per QALY gained. The ICER for no additional survival benefit after 48 months was above £30,000 per QALY gained. Because dacomitinib and the comparators have confidential commercial arrangements, the exact ICERs cannot be reported here. However, these ICERs did not include the company's final commercial arrangement (see section 3.23).

The most plausible ICER for dacomitinib is within the range normally considered to be a cost-effective use of NHS resources

3.23 The committee was aware that the differences among the company's and ERG's base cases and the alternative scenario ICERs were driven by the different assumptions about overall survival for all treatments. It recalled that the ERG's updated base case assumed equal efficacy for all treatments after 36 months (see section 3.22). But the company's updated base cases submitted in response to consultation assumed either equivalent post-progression survival from 71 months (updated base case 1, see section 3.21) or no additional survival benefit after 60 months (updated base case 2, see section 3.21). The committee noted the range of ICERs produced by the ERG's updated base case and scenario analyses and the company's 2 updated base-case analyses. The committee recognised that there were no clinical data from ARCHER 1050 after 36 months and that all the economic modelling predicted a hazard ratio for overall survival equal to 1 from 36 months. The committee accepted the company's position that the ERG's original base-case analysis, which assumed no additional survival after 36 months, resulted in a proportion of patients having treatment with dacomitinib at 36 months who would be expected to have clinical benefit from this ongoing treatment (see section 3.16). The committee also recognised clinical opinion that post-progression survival could be similar between treatments because of ongoing tyrosine kinase inhibitor treatment. After considering the trial data, the economic modelling and clinical opinion, the committee felt that on balance the cost-effectiveness estimates for dacomitinib would lie between the ERG's updated base-case analysis (hazard ratio for overall survival equal to 1 at

36 months) and the company's updated base case 1 (equal post-progression survival from 71 months). The committee decided that the most plausible ICER for dacomitinib would approximate to the ICER associated with the ERG's scenario analysis for assuming equal efficacy from 48 months (because dacomitinib and the comparators have confidential commercial arrangements, the exact ICERs cannot be reported here). When the company submitted analyses incorporating the final commercial arrangement, it included the assumption that there was no survival gain after 48 months and a utility value of 0.678 (see section 3.18). The ICER for this analysis was below £30,000 per QALY gained (dacomitinib has a confidential commercial arrangement so the exact ICER cannot be reported here). The committee therefore concluded that the most plausible ICER for dacomitinib was within the range normally considered to be a cost-effective use of NHS resources (dacomitinib and the comparators have confidential commercial arrangements so the exact ICERs cannot be reported here).

End of life

Dacomitinib does not meet the end-of-life criteria

3.24 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company submission stated that dacomitinib does not meet the end-of-life criteria. The committee considered the clinical evidence and agreed that life expectancy for people with untreated locally advanced or metastatic EGFR mutation-positive NSCLC having standard care is more than 2 years: in ARCHER 1050, the median overall survival with gefitinib was 26.8 months (95% CI 23.7 to 32.1). The committee therefore concluded that dacomitinib did not meet the end-of-life criteria for this indication.

Innovation

The model adequately captures the benefits of dacomitinib

3.25 The company considered dacomitinib to be innovative, highlighting that it improves survival compared with gefitinib, erlotinib and afatinib. The clinical experts agreed that dacomitinib is an effective second-generation tyrosine kinase inhibitor and that people would welcome additional treatment options. However, they also highlighted that there is no evidence to support dacomitinib's use for patients with brain metastases because they were excluded from ARCHER 1050. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.

Conclusion

Dacomitinib is recommended for routine use in the NHS

3.26 Having considered all the available evidence for dacomitinib, the committee concluded that dacomitinib was a cost-effective use of NHS resources for untreated locally advanced or metastatic EGFR mutation-positive NSCLC.

Other factors

3.27 No equality or social value judgement issues were identified.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has EGFR mutation-positive non-small-cell-lung cancer and the healthcare professional responsible for their care thinks that dacomitinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Luke Cowie
Technical lead

Nicola Hay
Technical adviser

Joanne Ekeledo
Project manager

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