NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer

1 Recommendations

1.1 Ramucirumab, in combination with docetaxel, is not recommended within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer in adults whose disease has progressed after platinum-based chemotherapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with ramucirumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Ramucirumab (Cyramza, Eli Lilly and Company) is a fully human immunoglobulin G1 monoclonal antibody. It blocks the vascular endothelial growth factor receptor-2, which plays an important role in the formation of new blood vessels in tumours.
Marketing authorisation	Ramucirumab in combination with docetaxel for treating locally advanced or metastatic non-small cell lung cancer in adults with disease progression after platinum-based chemotherapy.
Adverse reactions	The summary of product characteristics includes the following very common adverse reactions: neutropenia, fatigue or asthenia, leukopenia, epistaxis, diarrhoea and stomatitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	It is administered intravenously in a hospital outpatient setting. The recommended dose of ramucirumab is 10 mg/kg on day 1 of a 21-day cycle, before docetaxel infusion.
Price	Ramucirumab costs £500 per 10-ml vial (containing 100 mg ramucirumab) and £2,500 per 50-ml vial (containing 500 mg ramucirumab). The company estimated that the mean cost of ramucirumab was £3,733 per cycle with an average of 6 treatment cycles. The average cost of a course of treatment is estimated to be approximately £22,400. Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Eli Lilly and Company and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company submission considered 2 populations; the full population (including people with squamous and non-squamous non-small-cell lung cancer [NSCLC]) and a subgroup of people with non-squamous NSCLC.

3.2 The company's systematic review identified 1 relevant randomised controlled trial: REVEL. This was a phase III, international, multicentre, randomised, placebo-controlled, double-blind trial investigating ramucirumab plus docetaxel (n=628) compared with placebo plus docetaxel (the docetaxel-alone group; n=625) in adults with stage IV NSCLC whose disease had progressed during or after platinum-based therapy for locally advanced or metastatic disease.

3.3 The primary outcome was overall survival; secondary outcomes included progression-free survival, objective response rate, disease control rate and safety and quality of life as captured by the Lung Cancer Symptom Scale (LCSS) and the EQ-5D health questionnaire.

3.4 In the full population, compared with docetaxel alone, ramucirumab plus docetaxel:

- improved overall survival by 1.4 months (hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.75 to 0.98; p=0.024) and
- improved progression-free survival by 1.5 months (HR 0.76; 95% CI 0.68 to 0.86; p<0.0001).

In the subgroup of patients with non-squamous disease, compared with docetaxel alone, ramucirumab plus docetaxel:

- improved overall survival by 1.4 months (HR 0.83; p=0.02) and
- improved progression-free survival by 0.9 months (HR 0.77; p<0.001).

In the subgroup of patients with squamous disease, compared with docetaxel alone, ramucirumab plus docetaxel:

- improved overall survival by 1.3 months (HR 0.88; p=0.319) and
- improved progression-free survival by 1.5 months (HR 0.76; p=0.019).

3.5 The company reported that the percentage of patients who had at least 1 adverse event of any grade during treatment was similar between treatment arms: 97.8% in the ramucirumab plus docetaxel group compared with 96.1% in the docetaxel-alone group. Fatigue, neutropenia and febrile neutropenia were the grade 3 or higher adverse events that occurred during treatment in more than 10% of patients.

3.6 The company did a network meta-analysis to estimate the relative treatment effect of ramucirumab plus docetaxel compared with nintedanib plus docetaxel for the subgroup of patients with non-squamous disease, using data from REVEL and the LUME-Lung 1 trial. LUME-Lung 1 compared nintedanib plus docetaxel with docetaxel alone. The company's analyses assumed that the histologies of non-squamous NSCLC and adenocarcinoma were the same given that nintedanib plus docetaxel is licensed specifically for adenocarcinoma. Hazard ratios for overall survival and progression-free survival were calculated using a Bayesian network meta-analysis and assuming proportional hazards. The results did not show any difference between ramucirumab plus docetaxel and nintedanib plus docetaxel (overall survival HR 1.01; 95% CI 0.82 to 1.25, progression-free survival HR 0.99; 95% CI 0.78 to 1.26).

Cost effectiveness

3.7 The company presented a de novo, partitioned survival economic model based on 3 health states; pre-progression, post-progression and death. Patients remained in the pre-progression state until disease progression or death. In the post-progression state patients had either best supportive care or post-progression treatments.

3.8 Five parametric models were used to consider goodness of fit to the overall survival and progression-free survival data from REVEL. Curves were fitted to both the adjusted (taking into account a number of covariates) and unadjusted Kaplan–Meier data. However the company

considered that the adjusted models provided the best fit and used them in its base case.

3.9 For overall survival the company considered that the proportional hazards assumption (that is, the relative risk of an event is fixed irrespective of time) held. Therefore a single parametric curve was fitted to the entire data set with treatment included as a covariate. The company chose a log-logistic distribution to extrapolate overall survival in its base case.

3.10 For progression-free survival the company noted that the proportional hazards assumption was violated. Therefore the company generated separate parametric curves for ramucirumab plus docetaxel and docetaxel alone and considered that the generalised gamma model provided the best fit for both treatment groups.

3.11 For comparing ramucirumab plus docetaxel with nintedanib plus docetaxel, the company applied its network meta-analysis hazard ratio to the docetaxel-alone curves from REVEL to estimate overall survival for nintedanib plus docetaxel, and used the adjusted log-logistic model for ramucirumab plus docetaxel.

3.12 The company's deterministic base-case incremental cost-effectiveness ratio (ICER) for ramucirumab plus docetaxel compared with docetaxel alone for the full population was £194,919 per quality-adjusted life year (QALY) gained. The company's deterministic base-case ICER for ramucirumab plus docetaxel compared with nintedanib plus docetaxel for the subgroup of patients with non-squamous NSCLC was £1,106,497 per QALY gained (excluding the nintedanib patient access scheme).

3.13 The company carried out a number of scenario analyses for both populations (see the company submission for more details). For the full population, the ICERs for ramucirumab plus docetaxel compared with docetaxel alone were between £189,068 and £230,272 per QALY gained.

For the subgroup of patients with non-squamous disease, the company's scenario analyses ranged from ramucirumab plus docetaxel being dominated (that is, more expensive and less effective) by nintedanib plus docetaxel to £1,246,442 per QALY gained (excluding the nintedanib patient access scheme).

Evidence review group key issues

3.14 The ERG considered that REVEL was good quality and accurately presented the risks and benefits of ramucirumab plus docetaxel compared with docetaxel alone.

3.15 The ERG was concerned that the company used the population from REVEL with non-squamous disease rather than the population with adenocarcinoma when comparing ramucirumab plus docetaxel with nintedanib plus docetaxel. However, when the ERG compared the overall survival curves for the non-squamous and adenocarcinoma groups from REVEL they appeared to have some similarities. The ERG also found similarities in the progression-free survival data and therefore considered that the inconsistency in the populations compared would have little effect on the cost-effectiveness results.

3.16 The ERG noted that although the company's log-logistic model provided a good fit for the ramucirumab plus docetaxel group, the fit for the docetaxel-alone group was poor. From approximately 10 months onwards the docetaxel-alone log-logistic curve underestimated the observed overall survival in the Kaplan–Meier plot. The ERG considered that if the curve was fitted to any comparator (docetaxel alone or nintedanib plus docetaxel) of ramucirumab plus docetaxel it would underestimate the efficacy of the comparator. Therefore, separate curves should be fitted to the groups.

3.17 The ERG was concerned about using the network meta-analysis hazard ratios to model overall survival and progression-free survival because:

- they imposed proportional hazards between compared treatments
- they forced a log-logistic curve shape onto the comparator, which was unlikely to reflect the observed data
- they attached the generated curve on the time axis (of the survival curve plot) according to the position of the REVEL docetaxel survival curve and
- the log-logistic model could be an inaccurate estimate of the intervention and comparators.

The ERG considered that the resulting survival curves may not represent the situation fully. It therefore explored using a linear trend model to estimate overall survival in scenario analyses (see the ERG report for more details).

3.18 The ERG noted that the company assumed that quality of life was the same in each group while on treatment (that is, the company pooled the EQ-5D values from the trial) but made small allowances for different side effects. The ERG also had some concerns about the way the company had calculated the cost of ramucirumab based on the average number of weeks of treatment rather than the average number of ramucirumab doses. However the ERG did not consider that this significantly affected the ICER.

3.19 The ERG made some adjustments to the company's base-case, resulting in an ICER of £175,000 per QALY gained for ramucirumab plus docetaxel compared with docetaxel alone for the full population. The ERG's adjustments to the company's base-case produced an ICER for ramucirumab plus docetaxel compared with nintedanib plus docetaxel of £1,600,000 per QALY gained for the subgroup of patients with non-squamous NSCLC (excluding the nintedanib patient access scheme).

3.20 The ERG carried out a number of scenario analyses for both populations. For the full population, the ICERs for ramucirumab plus docetaxel

compared with docetaxel alone were between £167,000 and £247,000 per QALY gained, with an ICER of £177,000 when the linear trend model was used to estimate overall survival. For the subgroup of patients with non-squamous disease, the ERG's scenario analyses ranged from ramucirumab plus docetaxel being dominated by nintedanib plus docetaxel to £1,900,000 per QALY gained (excluding the nintedanib patient access scheme). When the ERG included the nintedanib patient access scheme (confidential simple discount), this increased the ICERs further. The ERG also carried out a scenario analysis using a linear trend model for overall survival in the subgroup of patients with squamous disease. This resulted in an ICER of £167,000 per QALY gained for ramucirumab plus docetaxel compared with docetaxel alone.

3.21 The ERG applied the linear trend model to the REVEL results for patients receiving docetaxel alone. Overall survival was:

- 14.4 months (full population)
- 15.32 months (subgroup with non-squamous disease) and
- 11.19 months (subgroup with squamous disease).

Comparing ramucirumab plus docetaxel with docetaxel alone, the linear trend model showed a mean extension in overall survival of:

- 2.2 months (full population)
- 3.9 months (subgroup with non-squamous disease) and
- 1.1 months for the population with squamous disease.

Comparing ramucirumab plus docetaxel with nintedanib plus docetaxel for the subgroup of patients with non-squamous disease, the mean extension in overall survival was 0.16 months, with less gain if only the adenocarcinoma population was considered.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ramucirumab, having considered evidence on the nature of non-small-cell lung cancer (NSCLC) and the value placed on the benefits of ramucirumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

4.1 The committee heard from the clinical and patient experts about the nature of locally advanced and metastatic NSCLC that has progressed after chemotherapy. The committee heard that the symptoms of NSCLC can be debilitating and difficult to manage. It understood that the prognosis for people with NSCLC is poor, and heard that only about a quarter of people with NSCLC that has progressed after platinum-based chemotherapy have good general health, with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (fully active) or 1 (restricted in strenuous activity, but can walk about). The committee also heard that there are limited treatment options available to people whose disease has progressed after platinum-based chemotherapy and whose disease does not express a specific tumour marker. The clinical and patient experts emphasised that any extension to survival and improvement in quality of life are important to people with NSCLC and their families. The committee recognised the importance of having effective and tolerable treatment options for people with NSCLC that has progressed after platinum-based chemotherapy.

4.2 The committee considered the relevant comparators for ramucirumab plus docetaxel. It noted that the company presented only comparisons with docetaxel and nintedanib plus docetaxel, although the NICE scope included erlotinib, crizotinib and nivolumab. It understood that people who

have epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive tumours would have erlotinib (in line with NICE's technology appraisal guidance on erlotinib and gefitinib for NSCLC). People with anaplastic lymphoma kinase (ALK)-positive tumours would be expected to have crizotinib (which is not recommended in NICE's technology appraisal guidance, but is being considered for the new Cancer Drugs Fund). The committee agreed that although the mechanism of action of ramucirumab is independent of mutation status, ramucirumab plus docetaxel is unlikely to be used as an alternative to these targeted treatments. Therefore erlotinib and crizotinib would not be relevant comparators for this appraisal. The committee also noted that the company did not include nivolumab as a comparator because the draft NICE recommendation was negative and nivolumab is not established clinical practice for NSCLC in England. The committee heard from the clinical experts that the treatment options relevant to this appraisal included docetaxel (in line with NICE's guideline on lung cancer) and nintedanib plus docetaxel for people with NSCLC of adenocarcinoma histology only (as in NICE's technology appraisal guidance on nintedanib for NSCLC). The committee was aware that the marketing authorisation for ramucirumab specifies using it with docetaxel. It agreed that most people likely to be offered ramucirumab would have similar characteristics to those offered docetaxel or nintedanib plus docetaxel, such as an ECOG performance status of 0 or 1 and previous platinum-based treatment. The committee also noted that although NICE has recommended nintedanib plus docetaxel for people with NSCLC of adenocarcinoma histology, in clinical practice some patients may still be receiving docetaxel alone. It also heard that there is another subgroup of patients who have non-squamous NSCLC that is not adenocarcinoma, but is not otherwise specified. These patients cannot have nintedanib plus docetaxel and would receive docetaxel alone, although this would be fewer than 10% of the population with non-squamous disease. The committee also

recognised that nintedanib and ramucirumab have different mechanisms of action and different side effect profiles and may therefore be given to different patients although acknowledged this population would be small. The committee concluded that docetaxel alone was the appropriate comparator for ramucirumab plus docetaxel for the full population and for the subgroups of patients with squamous NSCLC and non-squamous NSCLC, and that nintedanib plus docetaxel was the appropriate comparator for the subgroup of patients with non-squamous NSCLC.

Clinical effectiveness

4.3 The committee considered the data from the REVEL trial, which compared ramucirumab plus docetaxel with docetaxel alone and formed the basis of the clinical effectiveness evidence in the company's submission. The committee noted that REVEL was of good quality. Approximately 72% of the population in both groups had non-squamous disease. All patients had an ECOG status of 0 or 1 and were generally younger than those seen in clinical practice. The clinical experts stated that although the trial population was younger than seen in clinical practice, the results would still be relevant to the UK population. The committee noted that of the 1,253 people in REVEL only 38 were from the UK. The committee noted that the company had not provided the number of patients who continued to smoke during the trial and the number who had opioids or steroids for symptomatic treatment of tumours. It heard from the clinical experts that in the UK almost all patients stop smoking at diagnosis. Because the number of UK patients in the trial was small, the committee considered these data important and was concerned that the company was unable to provide them. However, the committee concluded that the results of REVEL would be relevant and generalisable to most patients in routine clinical practice in England.

4.4 The committee considered the results of REVEL. It noted that the REVEL data were mature, meaning that most people had either died or their

disease had progressed. However, for the mean survival values to be calculated with certainty all patients would have to have died or their disease progressed. It noted that the company compared ramucirumab plus docetaxel with docetaxel alone in the full population and also in subgroups of patients with non-squamous and squamous NSCLC, although REVEL was not powered for subgroup histology. The committee acknowledged that the differences in overall survival and progression-free survival between ramucirumab plus docetaxel and docetaxel alone for the full population were statistically significant (1.4 months and 1.5 months respectively). The committee agreed that the difference in median overall survival was likely to underestimate the mean survival benefit of ramucirumab plus docetaxel because, in lung cancer as with other cancers, a small minority of patients may live longer than others. The committee noted statistically significant improvements in overall survival and progression-free survival (1.4 months and 0.9 months respectively) with ramucirumab plus docetaxel compared with docetaxel alone for the subgroup of patients with non-squamous disease. For the subgroup of patients with squamous disease, the committee noted that the difference of 1.5 months in progression-free survival was statistically significant between the 2 treatment groups. The overall survival difference was not statistically significant, although the committee acknowledged that the trial was not powered for subgroup histology. The committee concluded that ramucirumab plus docetaxel was more effective than docetaxel alone in people with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy.

4.5 The committee discussed the indirect comparison of ramucirumab plus docetaxel and nintedanib plus docetaxel in the company's network-meta analysis. It heard that the evidence review group (ERG) had some concerns about the methodology, reporting and outcome of the analysis, including the exclusion of some studies and the minimal reporting of variables from some of the studies. However, the committee did not

consider these to be serious issues and concluded that the network meta-analysis was acceptable. The committee noted that the hazard ratios from the analysis showed no difference between ramucirumab plus docetaxel and nintedanib plus docetaxel (see section 3.6). The committee also noted that the company had assumed that the populations with non-squamous disease and adenocarcinoma were the same when comparing ramucirumab plus docetaxel with nintedanib plus docetaxel. It considered that this was appropriate because the Kaplan–Meier curves from REVEL were very similar. The committee concluded that the network meta-analysis showed ramucirumab plus docetaxel to be similar in efficacy to nintedanib plus docetaxel.

4.6 The committee discussed concerns about the safety and adverse effects associated with ramucirumab plus docetaxel. It heard from the clinical and patient experts that most of the adverse events associated with ramucirumab plus docetaxel were related to docetaxel rather than ramucirumab. The committee noted that there was an increase in febrile neutropenia associated with ramucirumab plus docetaxel. It heard from the clinical experts that approximately 50% of patients taking docetaxel are hospitalised because of adverse events and that adding ramucirumab to docetaxel is not expected to greatly affect hospital admission rates. It also heard from the patient experts that patients would accept the additional adverse events for the potential benefits of the treatment. The committee was also aware that in REVEL there was no increase in hospital visits for people taking ramucirumab plus docetaxel compared with those taking docetaxel alone. The committee concluded that the evidence suggests that ramucirumab plus docetaxel has an acceptable safety profile compared with docetaxel alone.

Cost effectiveness

4.7 The committee considered the model submitted by the company and whether it captured the natural history of NSCLC. It agreed that the

company had structured the model well, the model was similar to other economic models submitted to NICE for the same disease and the 15-year time horizon was appropriate for this disease. The committee concluded that the outlined structure of the model was acceptable for assessing the cost effectiveness of ramucirumab plus docetaxel.

4.8 The committee noted that the company provided separate analyses comparing ramucirumab plus docetaxel with docetaxel alone for the full population and with nintedanib plus docetaxel and docetaxel alone for the population with non-squamous disease. It also noted that the ERG presented additional analyses comparing ramucirumab plus docetaxel with docetaxel alone for the population with squamous disease. The committee was satisfied that these analyses were consistent with its previous conclusion on the appropriate comparators for the different populations (see section 4.2).

4.9 The committee discussed how the company modelled overall survival and the ERG's critique of this. The committee noted that for the comparison of ramucirumab plus docetaxel with docetaxel alone, the company had assumed that proportional hazards applied. Therefore it fitted a single log-logistic curve to the data from the ramucirumab plus docetaxel and the docetaxel-alone groups to extrapolate overall survival. The committee heard from the ERG that the log-logistic curve was a good fit for the ramucirumab plus docetaxel data but not for the docetaxel-alone data so separate models should have been fitted to the different groups. The committee noted the ERG's comment that the company's modelling approach underestimated survival for the docetaxel-alone group compared with the observed data in the Kaplan–Meier curve. The committee also heard from the ERG that the underestimation would continue in the extrapolation, providing ramucirumab plus docetaxel with a survival gain of approximately 44%, which was not reflected in the trial data. The committee also noted that because the docetaxel curve was

used to model the nintedanib plus docetaxel group for the subgroup of patients with non-squamous disease, survival for the nintedanib plus docetaxel group would also be underestimated relative to ramucirumab plus docetaxel. The committee was also concerned that the company's approach assumed that the probability of death reduced over time. The committee and the clinical experts did not consider this assumption to be valid and consistent with similar lung cancer appraisals, in which the probability of death becomes constant over time. It was aware that the ERG presented exploratory analyses using a linear trend model to extrapolate survival from month 13 onwards because the trial data showed a constant hazard for death after 11 months. However, the committee acknowledged that the selection of this time point was arbitrary. It also acknowledged that there were different approaches to the modelling and that there was uncertainty around the point of extrapolation. On balance the committee preferred the ERG's approach because the linear trend model provided a better fit to the trial data than the company's log-logistic model. The committee concluded that the ERG's approach to modelling survival was more reasonable than the company's approach and better reflected the data from the trial.

4.10 The committee discussed how health-related quality of life was incorporated into the economic model. It noted that the company's model assumed that quality of life was the same in each group while on treatment (that is, the company pooled the EQ-5D values from the trial) but made small allowances for different side effects. The committee did not consider this assumption appropriate given that the trial data showed statistically significant differences between the arms at baseline. The committee noted that the incremental cost-effectiveness ratio (ICER) increased when the ERG applied the mean changes from baseline, for both arms, to the company's pooled mean baseline values for progression-free survival. It also noted that the company assumed a constant quality of life for those whose disease had progressed, based on

the end-of-treatment EQ-5D values from REVEL. However, the company's systematic review supported an assumption that quality of life decreased during subsequent lines of treatment but this was not taken into account in their modelling. The committee noted the ERG's comment that this assumption had little effect on the results. The committee concluded that when mature trial data are available, it would be more appropriate to use the actual quality-of-life values from the trial rather than making assumptions about quality of life in the base case.

4.11 The committee discussed the costs included in the company's base case. It heard from the ERG that the company had calculated the cost of ramucirumab based on the average number of weeks of treatment rather than the average number of doses. The committee noted that the ERG did not agree with the company's method because it could under- or overestimate the cost of ramucirumab and whether it was an under-or overestimate was unknown. The committee concluded that the cost of ramucirumab should be calculated by dose per administration and not dose per week.

4.12 The committee discussed the most plausible ICER for ramucirumab plus docetaxel compared with docetaxel alone, for the full population and for the population with non-squamous disease. It noted that the company's deterministic base-case ICER for ramucirumab plus docetaxel compared with docetaxel alone, for the full population, was £195,000 per quality-adjusted life year (QALY) gained. However when using the ERG's amended base case, the ICER was reduced to £175,000 per QALY gained. When using the committee's preferred survival modelling incorporating the linear trend model, the ICER was £177,000 per QALY gained. The committee noted that the company had not included an analysis for the patients with non-squamous disease that is not adenocarcinoma but is not otherwise specified. However, the company's ICER for the whole subgroup of patients with non-squamous disease was

£182,000 per QALY gained, with the ERG's amended base case producing an ICER of £163,000 per QALY gained. Therefore the committee concluded that the most plausible ICERs for ramucirumab plus docetaxel compared with docetaxel alone for the full population and for the population with non-squamous disease were well over the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

4.13 The committee discussed the most plausible ICER for ramucirumab plus docetaxel compared with nintedanib plus docetaxel (with and without the nintedanib patient access scheme) for the population with non-squamous disease. The committee noted that the company's deterministic base-case analyses showed a very small QALY difference of 0.02, and an additional cost of £11,724 (without the nintedanib patient access scheme), leading to an ICER (without the nintedanib patient access scheme) of £1.1 million per QALY gained. The company also carried out a range of scenario analyses; ICERs (without the nintedanib patient access scheme) ranged from ramucirumab plus docetaxel being dominated (that is, more expensive and less effective) by nintedanib plus docetaxel when the treatment effect of ramucirumab plus docetaxel was applied indefinitely, to £1.2 million per QALY gained when published utility values were applied. The committee also noted that the incremental QALYs for these scenarios were all small (−0.005 to 0.032) but that ramucirumab plus docetaxel was always more expensive than nintedanib plus docetaxel (incremental costs were £11,439 to £12,128 without the nintedanib patient access scheme). When the ERG's preferred assumptions were applied to the model, the ICER (without the nintedanib patient access scheme) was £1.6 million per QALY gained. The ICERs including the nintedanib patient access scheme were greater than those without it; however these ICERs are confidential because the nintedanib patient access scheme is commercially confidential and cannot be reported here. Therefore the committee concluded that the most plausible ICER for ramucirumab plus docetaxel

compared with nintedanib plus docetaxel was well over the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

End-of-life considerations

4.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. It heard from the clinical and patient experts that the life expectancy of patients needing treatment after having platinum-based chemotherapy for NSCLC was less than 2 years. The committee also noted that the ERG's linear trend model suggested that for the full population having docetaxel alone, life expectancy would be 14.4 months; for the population with non-squamous disease having docetaxel alone, life expectancy would be 15.3 months and for the population with squamous disease having docetaxel alone, life expectancy would be 11.2 months. The committee concluded that the criterion for short life expectancy was met.

4.15 The committee considered the criterion for extension to life. It noted that the median extension in overall survival in REVEL for ramucirumab plus docetaxel compared with docetaxel alone was 1.4 months for both the full population and the population with non-squamous disease and 1.3 months for the population with squamous disease (see section 3.3). It also considered the results of the linear trend model, when comparing ramucirumab plus docetaxel with docetaxel alone (mean extension in overall survival of 2.2 months for the full population, 3.9 months for the population with non-squamous disease and 1.1 months for the population with squamous disease) and with nintedanib plus docetaxel (a mean extension in overall survival of 0.16 months, with less gain if only the adenocarcinoma population was considered). The committee considered that the extension-to-life criterion was met only for the population with non-squamous disease when comparing with docetaxel alone. It was not

met for the full population or the population with squamous disease when comparing with docetaxel alone, or for the population with non-squamous disease who would otherwise receive nintedanib plus docetaxel. The committee concluded that ramucirumab plus docetaxel met the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment only for the population with non-squamous disease, when ramucirumab plus docetaxel is compared with docetaxel alone. It also concluded that, given the very high ICERs, the magnitude of additional weight needed to be assigned to the QALY benefits would be too great for ramucirumab plus docetaxel to be considered a cost-effective use of NHS resources. Therefore, the committee could not recommend ramucirumab plus docetaxel as a cost-effective use of NHS resources.

4.16 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee understood that the company wanted ramucirumab to be considered for funding through the Cancer Drugs Fund, but because of the timing of this appraisal the company had not had an opportunity to present their case. The committee considered that the most plausible ICER for ramucirumab (see sections 4.12 and 4.13) and all of the ICERs presented for the full population and the subgroups, were substantially higher than the range normally considered a cost-effective use of NHS resources. Therefore ramucirumab did not have plausible potential for satisfying the criteria for routine use. The committee also considered that although there were uncertainties in the evidence for this appraisal, the clinical effectiveness evidence from REVEL was mature (see section **Error! Reference source not found.**) and there were no clinical uncertainties that could be addressed by collecting outcome data from people in the NHS, which could be used to inform a subsequent update of the guidance. The committee concluded that ramucirumab did not meet the criteria to be considered for funding through the Cancer Drugs Fund.

4.17 The committee discussed whether ramucirumab was innovative in its potential to make a significant and substantial impact on health-related benefits. It heard from the clinical and patient experts that there were few options for treating NSCLC with no positive tumour marker and that ramucirumab would provide another option. However, the committee concluded that having an extra treatment option for NSCLC did not mean that ramucirumab was innovative. It also concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.18 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer**	**Section**
Key conclusion		
Ramucirumab, in combination with docetaxel, is not recommended within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults whose		1.1

disease has progressed after platinum-based chemotherapy. The committee concluded that ramucirumab plus docetaxel was more effective than docetaxel alone based on the results of the REVEL trial and similar in efficacy to nintedanib plus docetaxel based on a network meta-analysis. The committee concluded that the most plausible ICERs were well over the range that would normally be considered a cost-effective use of NHS resources. The committee concluded that ramucirumab plus docetaxel met the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment only for the population with non-squamous disease, when ramucirumab plus docetaxel is compared with docetaxel alone.		4.4, 4.5 4.12, 4.13 4.15
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee understood that the prognosis for people with NSCLC is poor, and heard that only about a quarter of people with NSCLC that has progressed after platinum-based chemotherapy have good general health. It also heard that treatment options for people whose disease has progressed after platinum-based chemotherapy and does not express a specific tumour marker, are limited.	4.1
The technology		
Proposed benefits of the technology	The committee concluded that ramucirumab plus docetaxel was more effective than docetaxel alone in people with locally	4.4

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy. The committee heard from the clinical and patient experts that there were few options for treating NSCLC with no positive tumour marker and that ramucirumab would provide another option. However, the committee concluded that having an extra treatment option for NSCLC did not mean that ramucirumab was innovative.	4.17
What is the position of the treatment in the pathway of care for the condition?	The committee was aware that the marketing authorisation for ramucirumab specifies using it with docetaxel, and agreed that most people likely to be offered ramucirumab would have similar characteristics to those offered docetaxel or nintedanib plus docetaxel, such as an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and previous platinum-based treatment.	4.2
Adverse reactions	The committee concluded that the evidence suggests that ramucirumab plus docetaxel has an acceptable safety profile compared with docetaxel alone.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of	The committee noted that the REVEL trial, which compared ramucirumab plus docetaxel	4.3

evidence	with docetaxel alone, was of good quality.	
Relevance to general clinical practice in the NHS	The committee concluded that the results of REVEL would be relevant and generalisable to most patients in routine clinical practice in England.	4.3
Uncertainties generated by the evidence	The committee noted that in REVEL approximately 72% of the population in both groups had non-squamous disease, all patients had an ECOG status of 0 or 1 and were generally younger than those seen in clinical practice. It also noted that of the 1,253 people in REVEL only 38 were from the UK. The committee noted that the company had not provided the number of patients who continued to smoke during the trial and the number who had opioids or steroids for symptomatic treatment of tumours.	4.3
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	REVEL included subgroups of people with squamous and non-squamous disease although the trial had not been powered for these.	4.4
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee was aware that the median extension in overall survival in REVEL for ramucirumab plus docetaxel compared with docetaxel alone was 1.4 months for both the full population and the population with non-squamous disease and 1.3 months for the	4.4, 4.15

	population with squamous disease. It also considered the results of the linear trend model, when comparing ramucirumab plus docetaxel with nintedanib plus docetaxel giving a mean extension in overall survival of 0.16 months, with less gain if only the adenocarcinoma population was considered. The committee concluded that ramucirumab plus docetaxel was more effective than docetaxel alone in people with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy.	
Evidence for cost effectiveness		
Availability and nature of evidence	The committee agreed that the company had structured the model well, the model was similar to other economic models submitted to NICE for the same disease and the 15-year time horizon was appropriate for this disease.	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that for the comparison of ramucirumab plus docetaxel with docetaxel alone, the company had assumed that proportional hazards applied. The committee heard from the ERG that separate models should have been fitted to the different groups. The committee noted that the company's modelling approach underestimated survival for the docetaxel-alone group compared with the observed data	4.9

	and this would continue in the extrapolation. The committee was also concerned that the company's approach assumed that the probability of death reduced over time. The committee noted that the company's model assumed that quality of life was the same in each group while on treatment (that is, the company pooled the EQ-5D values from the trial) but made small allowances for different side effects.	4.10
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee concluded that when mature trial data are available, it would be more appropriate to use the actual quality-of-life values from the trial rather than making assumptions about quality of life in the base case. The committee also concluded that there were no additional gains in health-related quality of life over those already included in the quality-adjusted life year (QALY) calculations.	4.10 4.17
Are there specific groups of people for whom the technology is particularly cost	No	-

effective?		
What are the key drivers of cost effectiveness?	The key drivers of cost effectiveness were the parametric models applied to the overall survival data and the extrapolation of these data.	4.9
Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that the company's ICER for ramucirumab plus docetaxel compared with docetaxel alone, for the full population, was £195,000 per QALY gained and reduced to £175,000 per QALY gained when using the ERG's amended base case. When incorporating the linear trend model the ICER was £177,000 per QALY gained. The company's ICER for the subgroup of patients with non-squamous disease was £182,000 per QALY gained and reduced to £163,000 per QALY gained using the ERG's amended base case. The committee considered the most plausible ICER for ramucirumab plus docetaxel compared with nintedanib plus docetaxel, for the population with non-squamous disease, was £1.1 million per QALY gained (without the nintedanib patient access scheme). When the ERG's preferred assumptions were applied to the model, the ICER (without the nintedanib patient access scheme) was £1.6 million per QALY gained. The ICERs including the nintedanib patient access scheme were	4.12, 4.13

	greater than those without it; however these ICERs are commercial in confidential and cannot be reported here. The committee concluded that the most plausible ICERs for ramucirumab plus docetaxel compared with docetaxel alone and for ramucirumab plus docetaxel compared with nintedanib plus docetaxel were well over the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).	
Additional factors taken into account		
Patient access schemes (PPRS)	The committee considered analyses incorporating the confidential patient access scheme for nintedanib.	4.13
End-of-life considerations	The committee concluded that the criterion for short life expectancy was met; however estimates from the trial and model showed that the criterion for extension to life was met only for the population with non-squamous disease and only when docetaxel alone was the comparator. The committee concluded that ramucirumab plus docetaxel met the criteria to be considered as a life-extending, end-of-life treatment only for the population with non-squamous disease, when ramucirumab plus docetaxel is compared with docetaxel alone.	4.14, 4.15

Equalities considerations and social value judgements	No equality issues were raised during this appraisal.	–

5 Review of guidance

NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Vice chair, appraisal committee
June 2016

6 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.

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Technical Lead

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