

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Nintedanib for previously treated locally  
advanced, metastatic, or locally recurrent  
non-small-cell lung cancer**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nintedanib in combination with docetaxel in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the [committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using nintedanib in combination with docetaxel in the NHS in England.

For further details, see the [Guides to the technology appraisal process](#).

**The key dates for this appraisal are:**

Closing date for comments: 26<sup>th</sup> January 2015

Second Appraisal Committee meeting: 10<sup>th</sup> February 2015

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

## **1 Appraisal Committee's preliminary recommendations**

- 1.1 Nintedanib in combination with docetaxel is not recommended within its marketing authorisation for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy.
- 1.2 People currently having treatment initiated within the NHS with nintedanib in combination with docetaxel that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

## **2 The technology**

- 2.1 Nintedanib (Vargatef, Boehringer Ingelheim) is a small molecule tyrosine-kinase inhibitor. It blocks 3 receptor classes that promote angiogenesis and tumour growth: vascular endothelial growth factor receptors; fibroblast growth factor receptors; and platelet-derived growth factor receptors  $\alpha$  and  $\beta$ . Nintedanib has a UK marketing authorisation 'in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy'.
- 2.2 In the LUME-Lung 1 trial (comparing nintedanib plus docetaxel with docetaxel alone; see section 3.2), diarrhoea, nausea and vomiting

occurred more often with nintedanib plus docetaxel than with docetaxel alone.

- 2.3 According to the company, nintedanib costs £2151.10 for a 30-day pack of 150 mg and 100 mg capsules for oral use. The recommended dose is 200 mg twice daily. This can be reduced to 150 mg or 100 mg twice daily in patients who experience adverse events. Costs may vary in different settings because of negotiated procurement discounts.

### **3 The company's submission**

The Appraisal Committee (section 8) considered evidence submitted by Boehringer Ingelheim and a review of this submission by the Evidence Review Group (ERG; section 9).

#### ***Clinical effectiveness***

- 3.1 The company did a systematic literature review of studies evaluating the efficacy and safety of all second-line treatments for non-small-cell lung cancer. For nintedanib, it identified 1 relevant randomised controlled trial, the LUME-Lung 1 trial, from which it took the key clinical evidence for the comparison of nintedanib plus docetaxel with placebo plus docetaxel (hereafter referred to as docetaxel alone).
- 3.2 The LUME-Lung 1 trial (n=1314) was a phase III, multicentre, placebo-controlled, double-blind, randomised (1:1) controlled trial comparing nintedanib plus docetaxel with docetaxel alone. The trial was carried out in 211 centres in 27 countries (including the UK). Eligible patients were adults who had locally advanced, metastatic or locally recurrent non-small-cell lung cancer and whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. Randomisation was stratified by

4 variables: Eastern Cooperative Oncology Group (ECOG) score (0 or 1); previous bevacizumab treatment (yes or no); presence of brain metastases (yes or no); and histology (squamous or non-squamous). Patients in the nintedanib group had nintedanib (200 mg) twice daily, on day 2 to 21 of a 21-day cycle, plus docetaxel (75 mg/m<sup>2</sup>) on day 1 of the 21-day cycle. If patients experienced adverse events, the trial design specified reducing the dose of nintedanib from 200 mg twice daily to 150 mg twice daily and then to 100 mg twice daily, and reducing the dose of docetaxel from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>. Patients in the nintedanib group who had at least 4 cycles of nintedanib plus docetaxel could then have nintedanib alone. Patients in the placebo group had placebo twice daily on day 2 to 21 of a 21-day cycle, and docetaxel dosing as in the nintedanib group. In the placebo group, reducing the dose of docetaxel (from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>) was permitted if adverse events occurred. Treatment in both groups stopped when patients' disease progressed or if they experienced unacceptable adverse events. The trial investigators followed-up patients every 6 weeks before disease progression and every 6 to 8 weeks after disease progression until the patient died or was lost to follow-up.

- 3.3 Progression-free survival, measured radiologically, was the primary outcome in the LUME-Lung 1 trial and was defined as time from randomisation to death or disease progression when progression preceded death. Progression-free survival was determined by a central independent review by radiologists using the modified Response Evaluation Criteria in Solid Tumours (RECIST). The key secondary outcome in LUME-Lung 1 was overall survival. Overall survival was defined as the time from randomisation to death (irrespective of cause of death). Other secondary outcomes included progression-free survival by local investigator review, tumour response by both central independent review and

investigator review, clinical improvement (defined as lengthening the time to deterioration in body weight), health-related quality of life, safety, and tolerability.

3.4 The primary progression-free survival analysis was to be done when 713 patients had experienced (centrally assessed) disease progression or death (cut-off November 2010) to detect a hazard ratio of 0.78 with 90% statistical power. The primary analysis was based on the intention-to-treat population. According to the company, the study remained unblinded between final analysis for progression-free survival and for overall survival. The final analysis of overall survival was done when 1151 patients had died, and was designed to permit investigators to detect an 18% increase in median overall survival or a hazard ratio of 0.85. At final analysis of overall survival, the company did a follow-up analysis of all events including disease progression or death (February 2013). To be considered statistically significant, the p value had to be less than 0.00043 for primary progression-free survival, less than 0.05 for final progression-free survival and less than 0.04984 for the final overall survival analysis.

3.5 The analyses in LUME-Lung 1 were extended beyond the original specification of the statistical analysis plan, to validate findings from a hypothesis-generating analysis of the LUME-Lung 2 trial which compared nintedanib or matching placebo plus pemetrexed. This change to the statistical analysis plan was introduced after the initial analysis for primary progression-free survival analysis, but before database lock for the final overall survival analysis (February 2013). From the analysis of LUME-Lung 2, the company identified that patients whose disease had progressed within 9 months after the start of their first-line therapy, and patients who had adenocarcinoma, would benefit most from treatment with

nintedanib. A hierarchical overall survival statistical analysis was therefore introduced prospectively into the LUME-Lung 1 trial, by amending the trial statistical analysis plan. In LUME-Lung 1 the company tested overall survival in an intention-to-treat sequential fashion: first patients with adenocarcinoma whose disease had progressed within 9 months of starting first-line therapy, followed by all patients with adenocarcinoma, and finally the overall trial population.

3.6 The focus of the company's submission to NICE was on patients with adenocarcinoma because this was the population will likely be specified in the marketing authorisation for nintedanib. In LUME-Lung 1, of the 1314 patients randomised, 759 patients had non-squamous cell carcinoma (of whom 658 had adenocarcinoma) and 555 had squamous cell carcinoma. The company considered the baseline characteristics of patients in LUME-Lung 1 with adenocarcinoma, such as sex, age, race, smoking status and ECOG score, to be similar between the treatment groups, and similar to patients seen in clinical practice who have been diagnosed with adenocarcinoma. Of the patients in the trial with adenocarcinoma, 62.5% were men, the mean age was 58.5 (standard deviation 10.1) years, 76.9% were white, 70.4% had an ECOG performance status of 1, and 7.4% of patients had brain metastases. In the LUME-Lung 1 trial, 18.0% of the patients with adenocarcinoma in the nintedanib group and 18.2% in the docetaxel alone group had pemetrexed-platinum therapy as first-line therapy; 0.9% of patients in the nintedanib plus docetaxel group and 0.6% of patients in the docetaxel alone group had pemetrexed-non-platinum therapy. Approximately 56% of patients in each treatment arm had post-study therapy. Data on epidermal growth factor receptor (EGFR) mutations were not routinely collected in the LUME-Lung 1 trial. During the clarification stage of

the appraisal, the company stated that this had been retrospectively collected from a sample of patients in the LUME-Lung 1 trial. The results from the sample are considered to be academic in confidence and therefore cannot be reported.

- 3.7 The results for progression-free and overall survival for the adenocarcinoma population in LUME-Lung 1 are given in table 1. The company presented the results of the primary progression-free survival analysis for the overall trial population and for people with adenocarcinoma whose disease had progressed within 9 months of starting first-line therapy (see table 1 for the adenocarcinoma group).



**Table 1 Progression-free and overall survival results for the adenocarcinoma population in LUME-Lung 1 (cut-off November 2010 and February 2013)**

Outcome		Nintedanib plus docetaxel	Docetaxel alone	HR (95% CI)
Progression-free survival (central independent review)	Primary analysis at November 2010, 7.1 month follow-up (median, months)	4.0	2.8	0.77 (0.62–0.96)
	Final analysis at February 2013, 31.7 month follow-up (median, months)	4.2	2.8	0.84 (0.71–1.00)
Overall survival (final analysis at February 2013) (median, months)		12.6	10.3	0.83 (0.70–0.99)
Abbreviations: HR, hazard ratio; CI, confidence interval				

3.8 The company provided Kaplan–Meier curves in patients with adenocarcinoma for progression-free survival (primary analysis [November 2010]) and follow-up analysis [February 2013]) and overall survival (final analysis, February 2013). The Kaplan–Meier curves for progression-free survival (primary analysis) separated after 6 weeks and remained separated until approximately 7 months. The Kaplan–Meier curves for overall survival (final analysis) in patients with adenocarcinoma separated after 6 months and remained apart over the entire observation period of about 36 months.

3.9 The company did subgroup analyses at the time of the final overall survival analysis (February 2013). Most pre-specified and post-hoc progression-free survival subgroup analyses showed the effect of

nintedanib plus docetaxel to be consistent with the treatment benefit seen in the primary analysis.

- 3.10 The company collected health-related quality of life in the LUME-Lung 1 trial. This was measured at the screening visit, at 21-day intervals during treatment, at the end of treatment and at the first follow-up visit. The investigators used 3 questionnaires: EQ-5D, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC lung cancer-specific supplementary module (EORTC QLQ-LC13). Investigators found no differences in global health status, quality of life or self-reported health-related quality of life reported for the time to deterioration for coughing, breathlessness or pain between the nintedanib plus docetaxel group compared with the docetaxel alone group. Health-related quality-of-life scores at time of randomisation were available for the whole trial population but not for the adenocarcinoma subgroup. Statistically significant improvements were seen in 3 individual pain items ('have pain' [p=0.0332], 'pain in chest' [p=0.0196] and 'pain in arm and shoulder' [p=0.0004]) in favour of nintedanib plus docetaxel, while time to deterioration for diarrhoea was significantly shorter with nintedanib plus docetaxel.
- 3.11 The company did a mixed treatment comparison to compare nintedanib plus docetaxel with erlotinib because erlotinib was specified as a comparator in the final scope issued by NICE. However, the company commented that it did not consider erlotinib to be the main comparator to nintedanib plus docetaxel because patients considered fit enough to have treatment with nintedanib plus docetaxel would also be considered fit enough to have docetaxel alone rather than erlotinib. The company did a systematic review and identified 9 trials to include in its mixed treatment comparison. The trials included erlotinib, pemetrexed and

gefitinib. The company assumed that the effectiveness of docetaxel and pemetrexed did not differ, to allow as many treatments to be compared with nintedanib plus docetaxel as possible.

3.12 The results of the analysis from the mixed treatment comparison for nintedanib plus docetaxel compared with docetaxel alone (4 trials) showed that nintedanib plus docetaxel significantly improved overall survival (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.70 to 0.99) and progression-free survival (HR 0.77, 95% CI 0.62 to 0.96) compared with docetaxel alone. Nintedanib plus docetaxel also significantly improved overall survival (HR 0.64, 95% CI 0.46 to 0.90) and progression-free survival (HR 0.70, 95% CI 0.50 to 1.00). The Bucher indirect comparisons supported these findings (overall survival HR 0.56, 95% CI 0.38 to 0.82; progression-free survival HR 0.58, 95% CI 0.39 to 0.87) for nintedanib plus docetaxel compared with erlotinib.

3.13 The company provided data on drug-related adverse events that occurred with an incidence of 5% or more in both treatment groups in the adenocarcinoma subgroup for the duration of the trial. Diarrhoea (43.4% compared with 24.6%), nausea (28.4% compared with 17.7%) and vomiting (19.4% compared with 12.3%) occurred more often with nintedanib plus docetaxel than with docetaxel alone. Deaths from adverse events, not attributed to disease progression, were more common in the nintedanib plus docetaxel (6.3%) than the docetaxel alone (2.4%) groups. However, in the nintedanib plus docetaxel group the median duration of nintedanib plus docetaxel treatments was 4.2 months (with 5 cycles of docetaxel) and the docetaxel alone group received treatment for a median duration of 3.0 months (with 4 cycles of docetaxel). There were more grade 3 or greater adverse events and grade 3 or greater serious adverse events in the nintedanib

plus docetaxel group (75.9% and 31.3%) than in the docetaxel alone group (68.5% and 27.6%).

- 3.14 To compare the adverse events of nintedanib with chemotherapeutic regimens other than docetaxel, the company compiled data on fatigue, nausea and diarrhoea. These were the only safety outcomes reported in a consistent format in more than 1 trial. The company also stated that, because few trials reported these outcomes and because of the low incidence of adverse events, it compared nintedanib plus docetaxel with other treatments using the sensitivity analysis in which the company assumed docetaxel and pemetrexed were equally effective. In the mixed-treatment comparison of adverse events, the LUME-Lung 1 did not connect with the other studies. The results suggested that nintedanib plus docetaxel was significantly more likely to lead to diarrhoea than docetaxel alone or pemetrexed, but not than erlotinib. The risk of fatigue was similar for all treatments.

### ***Cost effectiveness***

- 3.15 The company provided a partitioned survival Markov model containing 3 health states: progression free (on or off treatment); progressed disease; and death. All patients enter the model in the progression-free state. At the beginning of each time period patients could either remain in the same health state or progress to a worse health state, that is, from progression free to progressed or death, or from progressed disease to death. The model used the partitioned survival method to determine the proportion of patients in each of the 3 health states during each model cycle. The company modelled 3-weekly cycle lengths, a half-cycle correction and a time horizon of 15 years. All costs and outcomes were discounted by 3.5% and the company stated that all costs were from the NHS and Personal Social Services perspective, although

the company included only NHS costs in the model. In the company's base-case analysis, it compared nintedanib plus docetaxel with docetaxel alone. In the company's secondary analysis, it compared nintedanib plus docetaxel with erlotinib. The model included people with locally advanced, metastatic or locally recurrent adenocarcinoma whose disease progressed following first-line chemotherapy. The company assumed that patients have best supportive care on stopping second-line treatment, although some people in the progressed disease state can have subsequent treatments (5% erlotinib, 25% platinum doublet therapy and 70% best supportive care). The company included the cost of subsequent treatments in the model but made no assumptions about their efficacy.

3.16 Kaplan–Meier survival curves for overall survival and progression-free survival for nintedanib plus docetaxel and for docetaxel alone were available from the LUME-Lung 1 trial and showed the proportion of patients in the model's 3 health states at each time point. Progression-free survival data from LUME-Lung 1 were mature and the proportions of censored patients in both treatment groups were similar. However, to extrapolate trial data beyond the time horizon of the trial, the company analysed overall survival and progression-free survival data using parametric survival curves fitted using 2 approaches:

- Joint models including data from both treatment groups using a term for treatment and the same distributions for each group.
- Separately modelled curves to each randomised treatment group.

The company tested the 'fit' of the curves using Akaike information criteria (AIC). The company interpreted the intercept and scale parameters of the separately fitted curves to indicate that the

curves should not be forced into the same model, and therefore selected separate curves by treatment group for progression-free survival and overall survival. The log-normal model had the lowest AIC among the separate progression-free survival fits and the Weibull model had the lowest AIC among the separate proportional hazard models for progression-free survival; therefore, these were selected to model progression-free survival. The log-logistic model had the lowest AIC among the separately fitted overall survival models and the Weibull model had the lowest AIC among the separate proportional hazard models for overall survival; therefore, these were selected to model the overall survival data. The company stated that it tested the validity of the data by showing the results to a group of 'key opinion leaders' (clinicians) and by comparing the it with data from the National Lung Cancer Audit (LUCADA, UK) and Surveillance, Epidemiology and End Result (SEER, USA).

- 3.17 Progression-free and overall survival curves were not available for erlotinib. The company obtained these by taking the progression-free survival and overall survival curves for nintedanib plus docetaxel and applying the hazard ratio from the mixed treatment comparison to reflect the relative effectiveness of erlotinib to nintedanib plus docetaxel. The company considered that proportional hazards could only be used if the survival distribution was a proportional hazards model using the exponential, Weibull or Gompertz extrapolations. Based on the goodness of fit, a Weibull distribution was chosen for erlotinib and, therefore, erlotinib could only be evaluated in the model if this distribution was selected for both progression-free survival and overall survival. The cost-effectiveness analysis that compared erlotinib plus docetaxel compared with docetaxel alone used hazard ratios from the mixed-treatment comparison base case, with the hazard ratio being 0.7

(95% CI 0.5 to 1.0) for progression-free survival and 0.64 (95% CI 0.46 to 0.90) for overall survival.

3.18 The company collected health-related quality-of-life data in the LUME-Lung 1 trial using EQ-5D questionnaires, which it used in a longitudinal model to adjust for certain baseline characteristics including ECOG score, prior treatment with bevacizumab, presence of brain metastases, health status and key adverse events. In the progression-free survival health state, the company estimated utility values from week 0 to 30 in 3-week intervals without a treatment term. The company extrapolated the trend it observed up to week 30 to provide data beyond this time point, which it incorporated into its base case. To estimate utility values for the progressed disease state, the company used utility values from the LUME-Lung 1 trial. Utility values for progression-free survival and progressed disease from the literature (Chouaid et al. 2013), which included patients with non-small-cell lung cancer in the UK, Europe, Canada, Australia and Turkey, were used in the sensitivity analyses. The model also incorporated the impact of adverse events on health-related quality of life using utility decrements associated with each adverse event. The company acknowledged that the model may have double counted disutility as people may have more than 1 adverse event.

3.19 In the model, the company assumed that patients would take two 100 mg capsules of nintedanib. The company modelled an option of patients taking one 150 mg capsule. The price of both formulations is the same. In the model, nintedanib plus docetaxel was given for a minimum of 4 cycles before nintedanib could be administered alone. The model included no administration cost associated with nintedanib, but a cost of £155 for docetaxel. Intravenous docetaxel was modelled at a concentration of

75 mg/m<sup>2</sup> on day 1 of a 21-day cycle. For the comparison of nintedanib plus docetaxel with erlotinib, a 30-tablet pack of erlotinib was £1631.53 (MIMS list price [2013]). The company noted that erlotinib has a patient access scheme, which it took into account by doing several sensitivity analyses in which a range of discounts were applied to the list price of erlotinib. The company assumed that the cost of best supportive care was £406.63 per 3-week cycle.

- 3.20 The company used resource questionnaires and an interview with an oncologist who specialises in lung cancer to determine health state costs. Three main areas of resource use were considered: routine follow-up (type and frequency of physician visit, laboratory tests and radiological scans); treatment at time of progression (hospitalisations, physician visits, laboratory tests, radiological scans and procedures used); and resource use during best supportive care or palliative care (initial tests, procedures, hospitalisations, physician visits, laboratory tests, radiological scans and procedures). The unit costs of visit procedures and laboratory tests were mainly derived from the National Schedule of reference costs (2012/13) and some visit costs were taken from the Personal Social Services Research Unit.
- 3.21 The company's base case incremental cost-effectiveness ratio (ICER) for nintedanib plus docetaxel compared with docetaxel alone was £50,776 per quality-adjusted life year (QALY) gained (incremental costs £11,051, incremental life years gained 0.33, and incremental QALYs 0.22).
- 3.22 The company did a range of deterministic sensitivity analyses. These included alternative hazard ratios for progression-free survival, hazard ratios for overall survival, utility values for progressed disease, model costs for progressed disease, risk of stopping nintedanib and docetaxel per cycle, and percentage of



patients switching to best supportive care. Of these, the greatest effect on cost effectiveness was from a change in the utility value of progressed disease (replacing the LUME-Lung 1 trial data with published values; Chouaid et al. 2013), which resulted in ICERs between approximately £44,000 and £60,000 per QALY gained.

- 3.23 The company did 5000 model iterations to derive mean probabilistic ICERs for nintedanib plus docetaxel compared with docetaxel alone and erlotinib. The results showed that nintedanib plus docetaxel had a 2% probability of being cost effective at the level of £30,000 per QALY gained and a 50% chance of being cost effective at the level of £50,000 per QALY gained, compared with docetaxel alone.
- 3.24 The company also did various scenarios to change the survival modelling. When incorporating Weibull parametric curves to extrapolate both progression-free survival and overall survival, the resulting ICER was £69,884 per QALY gained. When the Kaplan–Meier curves from the LUME-Lung 1 trial were used for the period of the trial only and not for the 15-year time horizon, and assuming that all patients died immediately after final data lock, the ICER increased to £119,209 per QALY gained. For the remaining scenarios, the company used the progression-free survival Kaplan–Meier curve from the LUME-Lung 1 trial, for the duration of the time horizon, and the overall survival Kaplan–Meier curve extrapolated using either registry data (LUCADA or SEER) or parametric curves (log-logistic or Weibull curves) to estimate ICERs of £56,769, £58,660, £48,264 and £65,274 per QALY gained respectively.
- 3.25 The company did several other scenario analyses altering resource use, utility values and time horizon. When the resource use costs were replaced with those from NICE technology appraisal guidance on [Afatinib for treating epidermal growth factor receptor mutation-](#)

[positive locally advanced or metastatic non-small-cell lung cancer appraisal](#), the ICER increased to £52,692 per QALY gained. When the company used the 'last observation carried forward' to calculate the ICER, it increased only slightly to £51,496 per QALY gained. When published utility values (Chouaid et al. 2013) were used, the ICER rose to £65,408 per QALY gained. Using time horizons of 3, 5 and 10 years resulted in ICERs of £98,119 £70,951 and £55,132 per QALY gained respectively.

- 3.26 The company's ICER for the comparison of nintedanib plus docetaxel compared with erlotinib was £27,008 per QALY gained (incremental costs £7,571, incremental QALYs 0.28).
- 3.27 The probabilistic sensitivity analysis for nintedanib plus docetaxel compared with erlotinib showed that nintedanib plus docetaxel had a 65% probability of being cost effective at the level of £30,000 per QALY gained and a 94% chance at the level of £50,000 per QALY gained.

### ***ERG's critique and exploratory analyses***

- 3.28 The ERG considered that the LUME-Lung 1 trial was well designed, with a low risk of bias and good randomisation, and noted that the trial was only unblinded at the end and provided mature data. The characteristics of patients with adenocarcinoma at baseline were well balanced between the nintedanib plus docetaxel and docetaxel alone groups in the ERG's opinion.
- 3.29 The ERG was concerned about the generalisability of the results from LUME-Lung 1 to patients seen in clinical practice in England. It considered that patients in the trial were potentially fitter and younger than those seen in clinical practice in England. The ERG highlighted the following dissimilarities in patient characteristics:

- The trial excluded patients with clinically significant pleural effusion, or evidence of cavitory or necrotic tumours, with significant coronary disease, or on anticoagulation (except low-dose heparin) or antiplatelet therapy (except aspirin). The ERG considered the trial population to have a better prognosis than patients seen in clinical practice in England.
- There were differences in the proportion of patients having third-line treatments. The ERG commented that patients in England are less likely to have third-line treatment than those in the trial (55.8%).
- The proportion of patients in the trial aged 65 years or older was smaller than the proportion seen in clinical practice.

3.30 The ERG noted that, in LUME-Lung 1, only 18.8% of patients with adenocarcinoma had pemetrexed as first-line therapy, and that most had platinum-based therapies. Conversely, the ERG considered that most patients in England would have pemetrexed as first-line treatment. The company did not include subgroups by first-line treatment (other than bevacizumab) in its submission.

3.31 The ERG was concerned that the company limited its submission to patients with adenocarcinoma even though only around 50% of the patients in the LUME-lung 1 trial had adenocarcinoma, which itself was neither a stratification factor at randomisation nor a pre-defined subgroup. However, the ERG noted that, in the trial, patients with adenocarcinoma constituted most of the patients with non-squamous cell carcinoma, which was a stratification factor. Also, because baseline characteristics among patients with adenocarcinoma were well-balanced across the 2 treatment groups, the ERG suggested that the analyses were acceptable.

3.32 The ERG questioned the validity of the hazard ratios calculated by the company using Cox proportional hazards modelling from the LUME-Lung 1 trial data for progression-free survival and overall survival. This model requires that the hazard (that is, the risk of an event occurring at a particular time conditional on having survived to that time) is a constant ratio between the patterns of events in the 2 treatment arms at any time since randomisation. The ERG noted that the progression-free survival curve for the LUME-Lung 1 trial groups diverge after 6 weeks and then converge after approximately 1 year so the proportional hazards assumption was not likely to be met. The ERG did a similar analysis of the overall survival data to test whether the proportional hazards assumption applied and concluded that it did not. The ERG stated that, because the proportional hazards assumption was not supported by the LUME-Lung 1 trial data for estimating the relative effectiveness of nintedanib plus docetaxel compared with docetaxel alone, using methods based on proportional hazard assumptions is inappropriate.

- 3.33 The ERG considered it inappropriate to do a mixed-treatment comparison because:
- The proportional hazards assumption was not supported by the LUME-Lung 1 trial data for progression-free or overall survival. Because the LUME-Lung 1 trial is the only trial providing evidence for nintedanib plus docetaxel, any comparison with this trial means that any estimation of the relative effectiveness of nintedanib plus docetaxel compared with erlotinib (that is, a calculated hazard ratio) lacks credibility and invalidates the comparison.
  - The trials included in the mixed treatment comparisons varied with respect to patient baseline characteristics and so were

heterogeneous between trials. Trials varied by age, EGFR mutation status, ECOG score, sex, whether patients had smoked and response to prior therapy. This heterogeneity may mean that the trials are too dissimilar to allow a valid comparison of outcomes in a mixed treatment comparison.

- The company assumed that docetaxel and pemetrexed were equally effective in the mixed treatment comparison. The ERG was not aware of any evidence that supported this assumption in an adenocarcinoma population.

3.34 The ERG commented on the way with which the company had fitted a variety of parametric functions to the available trial data and used these in the model to predict the results beyond those available from the trial. The ERG considered the company's approach to be flawed because the main reason for curve fitting is to anticipate what will happen to patients who remain 'at risk' at the time of the data cut-off point. In LUME-Lung 1, however, most patients had died, their disease had progressed or they had stopped treatment at the time of the data cut-off point. Therefore, extrapolating in this situation could have biased projections because it was based on the few survivors still at risk and could have led to fitting inappropriate functions.

3.35 The company fitted parametric functions based on descriptive data from SEER and LUCADA, but it was not possible for the ERG to assess whether this approach was valid. The ERG inferred from the company's submission that the SEER results were related to all-cause mortality from the date of stage 4 diagnosis. For the LUCADA data, the ERG understood that the data were related to second-line chemotherapy, but had no information on first-line treatments. The ERG commented that it was difficult to assess

whether the company's chosen parametric survival functions were valid and reflected the patient population in this appraisal.

- 3.36 The ERG identified 11 aspects of the company's base-case model that involved errors in data analysis, parameter values or methodology. The ERG corrected these to estimate the ICER, but still considered that the model generated uncertainty in overall survival, progression-free survival and time to treatment. The ERG applied 11 different amendments to the company's base case. These are outlined in sections 3.37–3.48.
- 3.37 The company's base-case assessment of nintedanib plus docetaxel compared with docetaxel alone indicated an undiscounted overall survival gain of 4.7 months. The ERG noted that only 15% of this gain occurred in the pre-progression phase. The ERG stated that this is unusual because, in locally advanced and metastatic cancers, the benefit from treatment normally occurs before disease progression while patients have active treatment. The ERG did its own analysis using the data for overall survival and progression-free survival from the trial, and noted that overall survival was linear for both groups after 300 days and continued indefinitely. This showed that the extrapolation used in the exponential model is appropriate, and the ERG calculated a long-term hazard ratio of 0.83 for overall survival in favour of nintedanib plus docetaxel. The ERG produced a cumulative hazard plot that suggested that patients in LUME-Lung 1 who survived beyond disease progression continued to gain survival benefit associated with treatment. The ERG estimated overall survival using the area under the curve (AUC) by applying the Kaplan–Meier results directly, and then projected long-term overall survival using the exponential trends. The ERG estimated mean overall survival in the docetaxel treatment arm as 453.0 days (14.9 months) and

545.7 days (17.9 months) for the nintedanib plus docetaxel treatment group, resulting in an estimated mean overall survival difference of 92.7 days (3.05 months). The ERG commented that this difference was considerably lower than the company's estimate of a mean overall survival gain of 4.7 months. Replacing the company's difference in mean overall survival with the ERG's increased the ICER to £68,587 per QALY gained (incremental costs £10,497, incremental QALYs 0.153).

3.38 The ERG noted that the company's model base-case assessment of nintedanib plus docetaxel compared with docetaxel alone indicated a mean gain in (undiscounted) progression-free survival of 28.6 days. This was based on calibrating a log-normal hazard distribution to each group in the trial and replacing the trial data with the log-normal curve for the duration of the model time horizon until all patients' disease had progressed or they died. Here, the extent of advantage in mean progression-free survival can be readily estimated directly from the Kaplan–Meier analysis results because the progression-free survival data were mature, by comparing the AUC estimates up to the point when the curves converge. The ERG identified that the curves converged at day 375. The difference in the AUCs at this time was 36.4 days, which suggested that the company's model had underestimated progression-free survival (28.6 days). The ERG incorporated its own result into the company's model and used a common long-term exponential model from day 375 onwards. This increased the ICER to £52,445 per QALY gained (incremental costs £11,527, incremental QALYs 0.220).

3.39 The ERG used a similar approach to estimate duration of treatment in the 2 groups of patients in the LUME-Lung 1 trial. This increased the discounted cost per patient and the incremental cost per patient

increased by 2.2% in both groups, and the ICER increased to £51,930 per QALY gained (incremental costs £11,298, incremental QALYs 0.218).

- 3.40 The ERG commented that the company costed both nintedanib plus docetaxel and docetaxel alone using the average number of patients having treatment across each cycle. The ERG commented that adjusting mid cycle is not accurate for docetaxel treatment in either group because patients have treatment on the first day of a 3-week cycle. The error underestimated the quantity and cost of drugs used in the trial. The ERG's correction of this error increased the ICER to £53,839 per QALY gained (incremental costs £11,717, incremental QALYs 0.218).
- 3.41 The ERG commented that the company calculated the average cost per dose of docetaxel using body surface area relevant to the UK population, but did not take into account the sex of the patients. The company also only costed the full 75 mg/m<sup>2</sup> dose rather than the reduced dose of 60 mg/m<sup>2</sup>. The ERG considered it more accurate to cost the reduced dose, and then create a weighted average based on the proportions of the 2 doses recorded in the trial. The ERG considered that the nintedanib capsules would likely be dispensed with docetaxel, so any missed dosing was unlikely to have an effect on the dispensing pattern. Therefore, the ERG considered a reduction in cost through a randomised dose intensity index from trial data to be inappropriate. The ERG re-estimated the overall average cost per dose of docetaxel using separate subgroups for men and women, and also re-estimated the randomised dose index multiplier to match the balance of full and reduced doses. The ERG estimated an overall mean cost for nintedanib treatment per cycle using the LUME-Lung 1 trial data.



This caused the ICER to increase to £52,587 per QALY gained (incremental costs £11,445, incremental QALYs 0.218).

- 3.42 The cost of treating the adverse event of febrile neutropenia was included in the company's model at £2012.10 per patient affected. The ERG noted that this is substantially lower than the figure estimated by the NICE Decision Support Unit in 2007 and the updated figure used in the ongoing multiple technology appraisal for erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy, which used £5240.40 per episode and a mean cost per patient of £7352.54 (assuming 1.4 episodes per patient). Using these revised costs, the ICER increased to £51,372 per QALY gained (incremental costs £11,180, incremental QALYs 0.218).
- 3.43 The ERG also noted that there were discrepancies in monitoring costs in the progression free health state when patients were still on active treatment. The company assigned monitoring costs of £188 per cycle to patients in the nintedanib plus docetaxel group and £205 per cycle to those having docetaxel alone s. The ERG noted that this was because the company had incorrectly applied additional physician monitoring every 2 to 3 months for patients who had completed active treatment, to patients still on active treatment with docetaxel. When the ERG reallocated costs, the ICER increased to £51,140 per QALY gained (incremental costs £11,130, incremental QALYs 0.218).
- 3.44 In the opinion of the ERG, the company modelled discounting incorrectly, basing the discounting on the 3-weekly cycle rather than annually. The ERG's amendment decreased the ICER to £50,532 per QALY gained (incremental costs £11,189, incremental QALYs 0.221).

- 3.45 The main adverse events in LUME-Lung 1 trial were stage 3 or 4 diarrhoea and fatigue. The company indicated that the disutility for diarrhoea was low ( $-0.04$ ), whereas for fatigue it was much higher ( $-0.21$ ). The ERG also noted that the company indicated a statistically significant difference between effect sizes in the 2 treatment groups, with a disutility of  $-0.326$  for the nintedanib plus docetaxel group and of  $-0.101$  for the docetaxel alone group. The ERG suggested that fatigue was a more serious side effect for those having nintedanib plus docetaxel. The company used an average disutility for the 2 treatment groups, whereas the ERG applied a disutility to the 2 groups separately. The ERG's amendment resulted in an ICER of £50,830 per QALY gained (incremental costs £11,051, incremental QALYs 0.217).
- 3.46 In the model, the company assumed that patients who had finished active treatment accrued the costs of having palliative nursing care every week and a bone scan every 3 weeks, in addition to a chest X-ray every 2 to 3 months and a physician visit once a year. The company's clinical experts suggested that only a chest X-ray would be needed and not the palliative care or bone scan. In the ERG's opinion, this reflected an error that significantly reduced the care costs of patients in a stable condition after second-line treatment. The ERG's amendment resulted in an ICER of £53,470 per QALY gained (incremental costs £11,637, incremental QALYs 0.218).
- 3.47 The ERG noted that the company's model followed the protocol used in the LUME-Lung 1 trial, which allowed patients to have unlimited docetaxel treatment (exceeding 40 cycles). The ERG explained that, in the UK, patients have up to 4 cycles of docetaxel because of unacceptable adverse events. Although the company's model allowed the number of cycles to be restricted, the ERG found an error that limited the number of cycles to 5 rather than to

4. When the ERG applied its own model adjustment and restricted the cycles to 4, this affected only the drug acquisition and administration costs, but not whether limiting docetaxel treatment would have an effect on the adverse events profile or patient prognosis. Both of these could affect the costs associated with treatment and the quality-of-life effects. This reduced the base-case incremental cost per patient by 5.4% and reduced the ICER to £48,060 per QALY gained (incremental costs £10,452, incremental QALYs 0.217).

- 3.48 The ERG provided an ICER that incorporated all its amendments simultaneously to produce an ICER for nintedanib plus docetaxel of £85,292 per QALY gained compared with docetaxel alone (incremental costs £13,437, incremental QALYs 0.158). The ERG also provided an ICER that included all amendments excluding analyses of the number of cycles of docetaxel. This produced an ICER of £82,995 per QALY gained (incremental costs £13,087, incremental QALYs 0.158).
- 3.49 The ERG applied 7 of the 11 amendments it had identified when analysing nintedanib plus docetaxel compared with docetaxel alone to the modelling of nintedanib plus docetaxel compared with erlotinib. The ICERs ranged from £24,975 per QALY gained (incremental costs £7,069, incremental QALYs 0.283) to £28,307 per QALY gained (incremental costs £8,147, incremental QALYs 0.288).
- 3.50 The ERG also took into account the impact of the patient access scheme for erlotinib by assuming different discounts; the resulting ICERs ranged from £28,307 per QALY gained when the discount was 0% to £38,375 per QALY gained when the discount was 50%. However, the ERG still concluded that it did not consider erlotinib to be a suitable comparator.

## 4 Consideration of the evidence

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

4.1 The Committee heard from the clinical and patient experts about the nature of locally advanced, metastatic and locally recurrent non-small-cell lung cancer that has progressed after chemotherapy. The Committee heard that the symptoms from non-small-cell lung cancer can be debilitating, and many symptoms such as breathlessness are difficult to manage. It understood that the prognosis for patients with non-small-cell lung cancer is poor, and heard from the clinical and patient experts that only about half of people with non-small-cell lung cancer that has progressed after chemotherapy have good general health, and very few of these people have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (fully active) or 1 (restricted in strenuous activity, but ambulatory). The Committee also heard that treatment options currently available to people whose disease has progressed after chemotherapy are limited to docetaxel and erlotinib, neither of which has a substantial impact on survival. The clinical and patient experts emphasised that any extension to survival and improvement in quality of life are important to people with non-small-cell-lung cancer and their families. The Committee recognised the importance of having effective and tolerable treatment options for people with non-small-cell lung cancer that has progressed after chemotherapy.

4.2 The Committee considered the clinical pathway for people with non-small-cell lung cancer. The Committee was aware that the presence of epidermal growth factor receptor (EGFR)-tyrosine kinase (TK) mutation in the tumour influences prognosis and determines treatment choice in the first- and second-line setting. It understood that most EGFR-TK mutation positive non-small-cell lung cancer is treated with an EGFR-TK inhibitor as first-line treatment (in line with the NICE technology appraisal guidance on [gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer](#) and [erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer](#)), followed by either erlotinib (in line with NICE technology appraisal guidance on [erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer](#)) or docetaxel (in line with NICE's guideline on [lung cancer](#)) if the disease has progressed after chemotherapy. It also understood that EGFR-TK negative mutation non-small-cell lung cancer is treated with either pemetrexed (in line with NICE technology appraisal guidance on [pemetrexed for the first-line treatment of non-small-cell lung cancer](#)) or docetaxel (in line with NICE's guideline on [lung cancer](#)) followed by either docetaxel or erlotinib (in line with the NICE technology appraisal guidance on [erlotinib for the treatment of non-small-cell lung cancer](#)) if disease has progressed after chemotherapy. The Committee was aware that the mechanism of action of nintedanib is independent of EGFR-TK mutation status, and therefore noted that either erlotinib or docetaxel might, in principle, be considered as comparators to nintedanib. The Committee heard from the clinical expert that, until recently, erlotinib and docetaxel were considered to be equally effective but that erlotinib has a more favourable side-effect profile. However,

the clinical expert explained that clinical practice has changed since the publication of NICE technology appraisal guidance on [erlotinib for the treatment of non-small-cell lung cancer](#): now, people considered to be fit in terms of ECOG performance status (that is, with an ECOG performance score of 0 or 1) are offered docetaxel as a second-line treatment, while those with poor fitness (an ECOG status of 2) are offered erlotinib. The Committee was aware that the expected marketing authorisation for nintedanib specifies giving it with docetaxel, and agreed that most people likely to be offered nintedanib have similar patient characteristics to those offered docetaxel, such as ECOG performance status of 0 or 1 and having had first-line treatment. The clinical expert explained that, in clinical practice, patients might stay on nintedanib plus docetaxel even after disease progression if symptoms are controlled, but that this would happen only in a small proportion of patients. The Committee also agreed that most people treated with erlotinib second-line would differ from people treated with nintedanib plus docetaxel in terms of ECOG performance status and first-line treatments. The Committee concluded that docetaxel alone was the only appropriate comparator to nintedanib plus docetaxel, and that it would not consider any further comparison of nintedanib plus docetaxel with erlotinib.

### ***Clinical effectiveness***

- 4.3 The Committee considered the clinical effectiveness data from the LUME-Lung 1 trial comparing nintedanib plus docetaxel with docetaxel alone, which formed the basis of the clinical-effectiveness evidence in the company's submission. The Committee noted that LUME-Lung 1 was a good quality trial, that patients remained on treatment until disease progression, that the study remained unblinded between analysing the primary outcome

of progression-free survival and the secondary outcome of overall survival, and that treatment crossover was not permitted. The Committee discussed the Evidence Review Group (ERG)'s concerns about the generalisability of the results to clinical practice in England, in that the trial excluded patients with clinically significant pleural effusion, cavitary or necrotic tumours, patients with significant cardiovascular disease, patients receiving anticoagulation therapy (except low-dose heparin) or antiplatelet therapy (except daily aspirin less than or equal to 325 mg/day), and patients with an ECOG performance status of 2. The Committee was aware that patients with cavitary or necrotic tumours were more likely to have squamous cell lung cancer rather than adenocarcinoma, and are not included in this appraisal. The Committee also heard from the clinical expert that patients with adenocarcinoma are generally not treated with anticoagulants other than low molecular weight heparin, and would only receive 75 mg aspirin per day, meaning that these exclusion criteria were unlikely to affect the generalisability of the trial. The Committee noted the ERG's concerns that the trial excluded patients with an ECOG performance score of 2 and that the patients enrolled in the trial were generally younger and fitter than those seen in clinical practice. The clinical expert commented that patients with an ECOG performance status of 2 would only occasionally have docetaxel for their non-small-cell lung cancer. The clinical expert stated that the population in the trial was generally younger than those seen in clinical practice, where the average age is over 65 years. The Committee agreed that the trial was not generalisable to all patients with adenocarcinoma whose disease had progressed after chemotherapy or for patients with an ECOG score of 2, but it was generalisable to patients offered docetaxel monotherapy as second-line treatment, such as those with an

ECOG status of 0 and 1. The Committee also discussed the ERG's concerns about the LUME-Lung 1 trial protocol allowing unlimited docetaxel treatment, with the maximum number of docetaxel cycles being 41. The clinical expert explained that, in clinical practice in England, patients would generally have 4 cycles of docetaxel, because a higher number of cycles would produce unacceptable adverse effects, although rarely some may have up to 6 cycles. The Committee concluded that the results from the LUME-Lung 1 trial were relevant and generalisable to most, but not all, patients in routine clinical practice in England.

4.4 The Committee considered the results of the LUME-Lung 1 trial. It noted that the company presented results for the overall trial population (n=1314) and also for a subgroup (658 of the total trial population) with adenocarcinoma, which had not been a pre-specified subgroup. However, nintedanib plus docetaxel was granted a marketing authorisation only for treating adenocarcinoma and not other histological subtypes. The Committee, however, accepted that adenocarcinoma constituted most cases of non-squamous carcinoma, a pre-specified subgroup in the LUME-Lung 1 trial (658 of 759 patients). The Committee would have preferred adenocarcinoma to have been a stratification factor. However, it concluded that the efficacy data from the subgroup with adenocarcinoma were the most relevant for decision-making because this is the population that is expected to be specified in the marketing authorisation for nintedanib.

4.5 The Committee considered the clinical effectiveness of nintedanib plus docetaxel compared with docetaxel alone for treating people with adenocarcinoma. The Committee was aware, based on the final analysis after a median follow-up of approximately 32 months, that the gain in median progression-free survival was 1.4 months



and the gain in median overall survival was 2.3 months. The Committee noted that the difference in median overall survival of 2.3 months reflected a statistically significant effect but agreed that this was a clinically small, benefit. The Committee noted that the data in the trial were mature, meaning that most people had either died or their disease had progressed but that, for the mean values to be calculated with certainty, all patients would have to have died or their disease progressed. It was disappointed that the company had not provided the results of the estimated mean difference in progression-free survival for patients with adenocarcinoma and that, when asked, the company was unable to provide a value for the restricted mean difference in overall survival. The Committee agreed that the difference in median overall survival was likely to underestimate the mean survival benefit of nintedanib plus docetaxel because, in lung cancer as with other cancers, a small minority of patients may live relatively longer than others. The Committee was aware that the restricted mean difference (based on the unlikely and conservative assumption that all remaining patients die immediately at the end of the trial) would help in an understanding of the anticipated mean overall survival benefit. The Committee concluded that nintedanib plus docetaxel was more effective than docetaxel alone in people with adenocarcinoma whose disease has progressed after chemotherapy, but that the magnitude of the benefit was uncertain.

- 4.6 The Committee discussed concerns about safety and adverse effects associated with nintedanib plus docetaxel. It heard from the clinical and patient experts that most of the adverse events associated with nintedanib plus docetaxel were related to docetaxel rather than nintedanib. The clinical and patient experts highlighted that patients are willing to tolerate adverse events associated with nintedanib, such as diarrhoea, because of the added benefit from

nintedanib. The Committee noted that there was an increase in the number of deaths associated with nintedanib plus docetaxel compared with docetaxel alone. The Committee accepted the company's explanation that the deaths in the nintedanib plus docetaxel treatment arm of the trial, although attributed to nintedanib, resulted instead from patients' underlying comorbidities. The Committee was aware that, overall, fewer patients treated with nintedanib plus docetaxel died than treated with docetaxel alone. The Committee concluded that current evidence suggests that nintedanib plus docetaxel has an acceptable safety profile compared with docetaxel alone and that patients are willing to tolerate the adverse effects.

### ***Cost effectiveness***

- 4.7 The Committee considered the structure of the model submitted by the company and whether it captured the natural history of adenocarcinoma of the lung. The Committee agreed that the company had structured the model well, and that it was similar to other economic models submitted to NICE for the same disease area and that the 15-year time horizon was appropriate for this disease. The Committee noted that the company had used utility values in its model that had been obtained from EQ-5D data collected during the LUME-Lung 1 trial in line with the NICE reference case. The Committee concluded that the outlined structure of the model was acceptable for assessing the cost effectiveness of nintedanib plus docetaxel.
- 4.8 The Committee discussed how the company extrapolated overall survival in the model by fitting parametric curves to the data and the ERG's critique of this. The Committee observed that the Kaplan–Meier curves for progression-free survival from the final analyses for nintedanib plus docetaxel and docetaxel alone

converged after approximately 1 year into the trial (see sections 3.16 and 3.17). The Committee understood that this means that the proportional hazards assumption (the relative risk of an event is fixed irrespective of time) cannot be applied. The ERG explained that the proportional hazards assumption is fundamental for applying a Weibull parametric curve, but is not needed for log-normal or log-logistic curves. The Committee concluded that, because the proportional hazard function cannot be applied to the progression-free survival data, the use of a Weibull curve was not appropriate for the extrapolation.

4.9 The Committee then considered whether each treatment should be modelled separately or jointly using a hazard ratio for progression-free and overall survival (see section 3.16). The Committee accepted that separate modelling was more appropriate than joint modelling because joint modelling could not accommodate the possibility that nintedanib might fundamentally alter the natural history of the disease.

4.10 The Committee then considered whether it was more appropriate for the company to replace the trial data with a parametric model (as the company did in its base case), or to use the trial data and a parametric model only for the period beyond the end of the trial. The Committee was aware of 2 divergent views: that modelled data might be more generalisable than data from a single trial, but that it can also be considered preferable to 'maximise' use of trial data, particularly when the data are mature. The Committee concluded from the model's residual values that the company's base case log-logistic curve did not provide a good fit to the actual trial data. On balance, the Committee would have preferred the company to use the Kaplan–Meier curves from the trial within its base-case analysis, followed by extrapolation beyond the trial data, using a

similar method to the ERG. However, the Committee was aware that such an approach depends on the point at which the extrapolation starts. The Committee queried how sensitive the results were to the point of extrapolation, but the ERG explained that it had not done such exploratory analyses. The Committee considered that the ERG's approach to modelling therefore also resulted in uncertainty. When looking at the extrapolated data beyond the trial period, the Committee noted that the company's overall survival curves for nintedanib plus docetaxel and docetaxel alone continued to diverge for the 15-year time horizon, suggesting ongoing and indefinite benefit beyond the end of treatment. The Committee considered this implausible, and noted that the respective curves from the ERG remained parallel after 9–10 years. The Committee was not persuaded that any of the overall survival projections presented were plausible for a population with a poor prognosis. The Committee was aware that alternative methods of modelling the data, such as piecewise modelling, may have better reflected the data. The Committee concluded that both the company's and ERG's modelling approaches led to uncertainty in the survival results.

- 4.11 The Committee discussed the company's scenario analyses which used registry data to validate the parametric curves, namely the National Lung Cancer Audit Data (LUCADA) from the UK and data from the Surveillance, Epidemiology and End Result (SEER) from the United States. The Committee understood that the company took the last point of the trial data and extrapolated it with the registry data over the remaining time horizon. It heard from the company that it was unable to provide any further details of the registries other than: the LUCADA was matched by age, sex and second-line treatment and contained information from patients in UK, and the SEER data was matched for age, sex and race but not

for line of treatment and contained information from patients from the United States. Although the data provided by the company on the external validity of the LUCADA registry data was limited because it did not provide information on the population of interest, that is, second-line adenocarcinoma patients, the Committee agreed that of the 2 registry data, LUCADA was the most appropriate to use in this appraisal. .

4.12 The Committee discussed how health-related quality of life was incorporated into the economic model, noting that the company had used EQ-5D values from the LUME-Lung 1 trial in its base case for progression-free survival and progressed disease. The Committee was aware that the utility values were independent of the treatment, were measured early in the course of the health state, and that mean utility values were used for the progressed disease state, which the company considered to be conservative. The Committee noted that the progressed disease utility values were not much lower than those for progression-free disease. It noted that the company had also used alternative utility values published by Chouaid et al. (2013), which had a higher utility value for progression-free survival and much lower utility value for progressed disease than those taken from the LUME-Lung 1 trial. The Committee noted that the incremental cost-effectiveness ratio (ICER) was sensitive to the source of the utility values. The Committee concluded that the utility value from the LUME-Lung 1 trial overestimated the average value throughout the course of progressed disease because it was measured early in progressed disease.

4.13 The Committee discussed the costs of the adverse events in the company's economic model, and particularly the figure of £2012.10 to treat febrile neutropenia. The ERG explained that this was

substantially lower than the costs used in previous appraisals (review of TA162 and TA175) of more than £5000 when adjusted for inflation to current costs. The Committee heard from the clinical expert that this figure seemed high and that a range of £2000 to £3000 was reasonable. The Committee concluded that the cost of a patient being treated for febrile neutropenia would lie somewhere between the cost used by the company and that calculated by the ERG, and would be around £3000.

4.14 The Committee discussed the use and cost of docetaxel in clinical practice in England. It heard from the clinical expert that patients normally have up to 4 cycles of docetaxel and occasionally up to 6 cycles, but very rarely more because of the associated adverse events. In the LUME-Lung 1 trial, and therefore in the company's model, patients were able to have up to 41 cycles of docetaxel. The Committee noted that the ERG did exploratory analyses in which it restricted the number of docetaxel cycles to 4. The Committee was aware this would reduce the costs of docetaxel in both treatment groups. However, the Committee noted that the ERG could not determine what effect reducing the number of docetaxel cycles would have on the adverse events profile, patient prognosis and the resulting effects on costs and quality-of-life. The Committee concluded that uncertainty exists as to the effect of a reduction in docetaxel cycles.

4.15 The Committee discussed the 11 amendments that the ERG made to the company's model and how these affected the ICER. The Committee considered the ICER was most sensitive to the following amendments:

- using the ERG's estimates of overall survival, based on the Kaplan–Meir data and extrapolating for the remaining time horizon (see section 3.37)

- using a mid-cycle adjustment (see section 3.40)
- changing stable disease costs (see section 3.46)
- reducing docetaxel to 4 cycles (see section 3.47)

The Committee was aware of the uncertainties surrounding the overall survival estimate provided by the ERG because these depended on the point from which onwards the trial data were extrapolated. The ERG also performed an analysis removing its own overall survival estimate and using the company's overall survival estimate, but maintaining the amendments related to costs. The Committee agreed that the ERGs amendments related to costs were reasonable.

- 4.16 The Committee discussed whether it could define which ICER was the most plausible for nintedanib plus docetaxel compared with docetaxel alone: the company's £50,800 per quality-adjusted life year (QALY) gained or the ERG's £85,300, which incorporated all 11 amendments (see sections 3.36). Bearing in mind the uncertainty with the extrapolation methods used by both the company and the ERG (see section 4.10), the Committee considered the company's estimated ICER of £59,000 per QALY gained for a model that used trial data followed by modelling with the LUCADA data. The Committee concluded that, when adding to this the amendments by the ERG not related to the extrapolation, the ICER was likely to be near £70,000 per QALY gained. It also concluded that the ICER would further increase when taking into account the issues around the generalisability of the patient population, utility values and the costs associated with treating patients with nintedanib after disease. The Committee concluded that these ICERs were all higher than what is normally considered to be an appropriate use of NHS resources.

4.17 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months compared with current NHS treatments.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.18 The Committee heard from the clinical and patient experts that the life expectancy of patients needing second-line treatment for non-small-cell lung cancer was shorter than 2 years and accepted that the criterion of short life expectancy was met. The Committee accepted the company's estimate that the total population was less than 800 patients. However, the Committee considered the evidence was insufficient to show that nintedanib plus docetaxel offered an additional 3 months compared with current NHS treatment (that is, docetaxel). The Committee noted the median extension in overall survival in the LUME-Lung 1 trial for nintedanib plus docetaxel compared with docetaxel alone was 2.3 months, and that normally nintedanib would not provide a 3-month benefit



for most patients. The Committee was concerned that, when asked at the meeting, the company was unable to provide a restricted mean for extension of life, and that neither the company nor the ERG could provide confidence intervals for their estimates of the mean extension data provided by the model. The Committee remembered that the clinical expert had stated that patients in the LUME-Lung 1 trial were potentially younger and fitter than patients in clinical practice in England (see section 4.3) and therefore patients in clinical practice may not achieve the level of survival benefit reported in the trial. The Committee noted that company's base case model suggested that the mean extension compared with docetaxel was 3.96 months, and that the ERG's exploratory analyses suggested a mean survival of 3.05 months, based on the ERG's preferred base-case ICER which incorporates all 11 amendments. The Committee was aware that the estimate depended on assumptions around extrapolation. Mindful that it must be persuaded that the estimates of the extension to life are robust (see section 4.10) and that the assumptions used in the base case are plausible, objective and robust, the Committee concluded that nintedanib plus docetaxel did not fulfil the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment. The Committee also concluded that, even if the end-of-life criteria had been met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for nintedanib plus docetaxel into the range representative of a cost-effective treatment. The Committee therefore could not recommend nintedanib plus docetaxel as a cost-effective use of NHS resources.

- 4.19 The Committee discussed whether nintedanib was innovative in its potential to make a significant and substantial impact on health-related benefits. It heard from the patient expert that patients

consider nintedanib to be innovative. The Committee also heard from the clinical and patient experts that there were few options for treating patients with non-small-cell adenocarcinoma who need second-line treatment and that nintedanib would provide another option. However, the Committee agreed that just having an extra treatment option for non-small-cell lung cancer did not mean that nintedanib was innovative. The Committee also concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4.20 The Committee noted a potential equality issue that was raised during the scoping workshop. A workshop attendee suggested that the LUME-Lung 1 trial excluded patients whose disease progressed after maintenance therapy but that some patients now have maintenance therapy after first-line induction therapy. The marketing authorisation wording implies that this group is included ‘in combination with docetaxel for adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy’. The Committee was aware that people having maintenance therapy are not a ‘protected group’ according to the equality legislation, and that there was no trial evidence for the effectiveness of nintedanib in this group. Therefore, it concluded that it is unclear whether this group would get a benefit from nintedanib plus docetaxel and agreed that this did not present an equality issue.

***Summary of Appraisal Committee’s key conclusions***

TAXXX	<b>Appraisal title: Nintedanib for previously treated locally advanced, metastatic or locally recurrent non-small-cell lung cancer</b>	<b>Section</b>
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<b>Key conclusion</b>		
<p>Nintedanib in combination with docetaxel is not recommended within its marketing authorisation for treating locally advanced, metastatic or recurrent adenocarcinoma of the lung that has progressed after first-line chemotherapy.</p>		1.1
<p>From the data on median overall survival from the trial the Committee concluded that nintedanib plus docetaxel provided a statistically significant but clinically small benefit. However, the ICER based on the Committee's preferred assumptions was likely to be near £70,000 per QALY gained, and would increase when taking into account issues around the generalisability of the patient population, utility values and the costs associated with treating patients with nintedanib after disease progression.</p>		4.5, 4.16
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard that treatment options currently available to people whose disease has progressed after chemotherapy are limited to docetaxel and erlotinib, neither of which has a substantial impact on survival.</p>	4.1
<b>The technology</b>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee concluded that nintedanib plus docetaxel was more effective than docetaxel alone in people with adenocarcinoma whose disease has progressed after chemotherapy.</p> <p>It heard from the patient expert that patients consider nintedanib to be innovative. The Committee also heard from the clinical and patient experts that there were few options for treating patients with non-small-cell adenocarcinoma who need second-line treatment and that nintedanib would provide another option. However the Committee considered that having just an extra treatment option for non-small-cell lung cancer did not mean that nintedanib was innovative.</p>	<p>4.5</p> <p>4.19</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee agreed that most people treated with erlotinib second-line would differ from people treated with nintedanib plus docetaxel in terms of ECOG performance status and first-line treatments. The Committee concluded that docetaxel alone was the only appropriate comparator to nintedanib plus docetaxel, and that it would not consider any further comparison of nintedanib plus docetaxel with erlotinib.</p>	<p>4.2</p>

Adverse reactions	The Committee concluded that current evidence suggests that nintedanib plus docetaxel has an acceptable safety profile compared with docetaxel alone and that patients are willing to tolerate the adverse effects.	4.6
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee noted that LUME-Lung 1 was a good quality trial, that patients remained on treatment until disease progression that the study remained unblinded between analysing the primary outcome of progression-free survival and the secondary outcome of overall survival, and that treatment crossover was not permitted.	4.3
Relevance to general clinical practice in the NHS	The Committee was aware that NICE's guideline on <a href="#">lung cancer</a> indicated that docetaxel can be offered to people with non-small-cell lung cancer that has progressed after chemotherapy.	4.2
Uncertainties generated by the evidence	The Committee noted the ERG's concerns about the generalisability of the trial because it excluded patients with clinically significant pleural effusion, cavitory or necrotic tumours, patients with significant cardiovascular disease, patients receiving anticoagulation therapy (except low-dose heparin) or antiplatelet therapy (except daily aspirin $\leq 325$ mg/day), or patients an ECOG	4.3

	<p>performance score of 2 and the patients enrolled in the trial were generally younger and fitter than those seen in clinical practice. It heard from the clinical expert that, in clinical practice, the average age of this patient group is over 65 years.</p> <p>The Committee also discussed the LUME-Lung 1 trial protocol allowing unlimited docetaxel treatment with the maximum number of docetaxel cycles received being 41. The clinical expert explained that, in clinical practice in England, people would generally have 4 cycles of docetaxel, because a higher number of cycles would produce unacceptable adverse effects, although rarely patients may have up to 6 cycles.</p>	<p align="center">4.3</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No specific Committee consideration</p>	<p align="center">-</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee was aware, based on the final analysis after a median follow-up of approximately 32 months, that the gain in median progression-free survival was 1.4 months and the gain in median overall survival was 2.3 months. The Committee agreed that the difference in median overall survival of 2.3 months reflects a statistically significant but clinically small benefit.</p>	<p>4.5</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The Committee agreed that the company had structured the model well, and that it was similar to other economic models submitted to NICE for the same disease area and that the 15-year time horizon was appropriate for this disease. The Committee noted that the company had used utility values in its model that had been obtained from EQ-5D data collected during the LUME-Lung 1 trial, in line with the NICE reference case.</p>	<p>4.7</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee observed that because the Kaplan–Meier curves for progression-free survival for nintedanib plus docetaxel and docetaxel alone converged after approximately 7 months into the trial, one cannot apply the proportional hazards assumption. The ERG explained that the proportional hazards assumption is fundamental for applying a Weibull parametric</p>	<p>4.8</p>

	<p>curve, but is not needed for lognormal or log-logistic curves. The Committee concluded that because the proportional hazard function cannot be applied to the progression free survival data, the use of a Weibull curve was not appropriate for the extrapolation.</p> <p>The Committee would have preferred the company to use the Kaplan–Meier curves from the trial within its base-case analysis, followed by extrapolation beyond the trial data, using a similar method to the ERG but was aware such an approach depends on the point at which the extrapolation starts and can result in uncertainty. The Committee was aware that alternative methods of modelling the data, for example piecewise modelling, may have better reflected the data.</p> <p>The Committee discussed the company’s scenario analyses which used registry data to validate the parametric curves, namely the National Lung Cancer Audit Data (LUCADA) from the UK and data from the Surveillance, Epidemiology and End Result (SEER) from the United States. Although the data provided by the company on the external validity of the LUCADA registry data was limited because it did not provide data on the population of interest, that is, second-line adenocarcinoma patients, the Committee agreed that of the 2 registry data, LUCADA was the most</p>	<p>4.10</p> <p>4.11</p>
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	appropriate to use in this appraisal.	
Incorporation of health-related quality-of-life benefits and utility values	The Committee concluded that the utility value from the LUME-Lung 1 trial overestimated the average value throughout the course of progressed disease because it was measured early in progressed disease.	4.12
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 observed that there were no additional gains in health-related quality of life over those already included in the QALY calculations.	4.19
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable to this appraisal.	-
What are the key drivers of cost effectiveness?	The key driver of cost effectiveness was the extrapolation methods of overall survival.	4.8 to 4.11, 4.16

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered the company's estimated ICER of £59,000 per QALY gained for a model that used trial data followed by modelling with the LUCADA registry data. The Committee concluded that when adding to this the amendments by the ERG, not related to the extrapolation, the ICER was likely to be near £70,000 per QALY gained. It also concluded that it would further increase when taking into account the issues around generalisability of the patient population, utility values and the costs associated with treating patients with nintedanib after disease.</p>	<p>4.16</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable to this appraisal.</p>	<p>-</p>
<p>End-of-life considerations</p>	<p>The Committee concluded the criteria of short life expectancy and small population size were met.</p> <p>Regarding the life extension, the Committee noted the median extension in overall survival benefit in the LUME-Lung 1 trial for nintedanib plus docetaxel was 2.3 months, and that normally nintedanib would not provide a 3-month benefit for most patients. Mindful that it must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the base case are plausible, objective and robust, the Committee</p>	<p>4.18</p>

	concluded that nintedanib plus docetaxel did not fulfil the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment.	
Equalities considerations and social value judgements	A potential equality issue was raised during the scoping workshop related to the exclusion of patients whose disease progressed after maintenance therapy. The Committee was aware that people having maintenance therapy are not a 'protected group' according to the equality legislation, and that there was no trial evidence for the effectiveness of nintedanib in this group. Therefore, it concluded that it is not clear if this group would get a benefit from nintedanib plus docetaxel, and agreed that this therefore did not present an equality issue.	4.20

## 5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

### Published

- [Lung cancer: The diagnosis and treatment of lung cancer](#). NICE clinical guideline 121 (2011).
- [Erlotinib for the treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 162 (2008). Currently being reviewed with TA175.

- [Pemetrexed for the treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 124 (2007).
- [NICE Pathway: Lung cancer](#) (2012).

### **Under development**

- Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175). NICE technology appraisal guidance, publication expected TBC.

## **6 Proposed date for review of guidance**

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

Amanda Adler

Chair, Appraisal Committee

November 2014

## **7 Appraisal Committee members, guideline representatives and NICE project team**

### ***Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no

meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

**Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital

**Professor Ken Stein**

Professor of Public Health, Peninsula College of Medicine and Dentistry, University of Exeter

**Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

**Dr Jeff Aronson**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

**Professor John Cairns**

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

**Mr Matthew Campbell-Hill**

Lay member

**Mr Mark Chapman**

Health Economics and Market Access Manager, Medtronic UK

**Dr Lisa Cooper**

Echocardiographer, Stockport NHS Foundation Trust

**Dr Neil Iosson**

Locum General Practitioner

**Mrs Anne Joshua**

NHS 111 Pharmacy Lead, Patients and Information, NHS England

**Professor Daniel Hochhauser**

Consultant in Medical Oncology, UCL Cancer Institute

**Dr Miriam McCarthy**

Consultant, Public Health, Public Health Agency, Northern Ireland

**Professor Ruairidh Milne**

Professorial Fellow in Public Health, Wessex Institute, University of Southampton

**Dr Peter Norrie PhD, MSc, RN**

Principal Lecturer, De Montfort University, Leicester

**Mr Chris O'Regan**

Head of Health Technology & Outcomes Research, Merck Sharp & Dohme

**Mr Alun Roebuck**

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Dr Sanjeev Patel**

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Danielle Preedy**

Lay member

**Mr Cliff Snelling**

Lay member

**Mr David Thomson**

Lay member

**Dr Nicky Welton**

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

**Dr Nerys Woolacott**

Senior Research Fellow, Centre for Health Economics, University of York

***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.

**Caroline Hall**

Technical Lead

**Nicola Hay**

Technical Adviser

**Jeremy Powell**

Project Manager

## **8 Sources of evidence considered by the Committee**

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

National Institute for Health and Care Excellence

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Appraisal consultation document – Nintedanib for previously treated locally advanced, metastatic or locally recurrent non-small-cell lung cancer

Issue date: December 2014

- Fleeman N, Bagust A, Boland A et al, Nintedanib for previously treated locally advanced or metastatic non-small cell lung cancer, October 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Boehringer Ingelheim

II. Professional/expert and patient/carer groups:

- Roy Castle Lung Cancer Foundation
- British Thoracic Oncology Group
- British Thoracic Society
- Cancer Research UK
- Royal College of Pathologists
- Royal College of Physicians

III. Commentator organisations (did not provide written evidence and without the right of appeal):

- Roche Products
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on nintedanib by attending the initial Committee



discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Thomas Newsom-Davis, Consultant Medical Oncologist, Chelsea & Westminster Hospital, nominated by NCRI/RCP/RCR/ACP – clinical expert
- Dr Jesme Fox, Medical Director, Roy Castle Lung Cancer Foundation, nominated by Roy Castle Lung Cancer Foundation – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Boehringer Ingelheim