NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment	Response
Boehringer Ingelheim	Boehringer Ingelheim Ltd acknowledges the recommendations of the ACD, and as a result, all but two changes made to the cost effectiveness model by the ERG have been included when generating revised results. The two changes not included are febrile neutropenia cost (as the ACD suggests the ERG estimate is too high) and overall survival (OS) modelling (as the ACD suggests there is uncertainty around the ERG methodology). In order to model overall survival, the model now uses the Kaplan Meier (KM) data directly (preferred by the Appraisal Committee), and then extrapolates this beyond the time of the trial data to account for the lifetime horizon of the cost effectiveness model. National Lung Cancer Audit Data Set (LUCADA) data (real world data that the Appraisal Committee noted was a preferred source of evidence) is used to extrapolate the KM data beyond the cutoff time point; when the proportion of patients remaining at risk (alive) drops to a certain percentage (5% in the base case) the probability of staying alive is calculated in each cycle from the lognormal (best statistical and visual fit to LUCADA data) parametric model of LUCADA data. The probability of death calculated at the corresponding specific time point (i.e. within cycle X) from the LUCADA-based curve is applied as the transition probability in cycle X of the model to estimate the OS for the nintedanib plus docetaxel arm and for the docetaxel only arm. The effect of varying the cutoff point at which the KM data is extrapolated with LUCADA has also been investigated. Additionally, in order to further take account of uncertainty around the revised base case, overall survival modelling using KM data with LUCADA extrapolation has been incorporated into the probabilistic sensitivity analysis. The two points from the ACD which Boehringer Ingelheim Ltd would specifically like to address are set out in the remainder of this document. 1. **The ACD states that "patients with an ECOG performance status of 2 would occasionally have docetaxel for their non-small cell lung cancer" and "the**	Comment noted. The Committee considered the company's revised economic analyses including the Committee's preferred approach to overall survival modelling – using the Kaplan-Meier data from the trial and extrapolating with the LUCADA registry data. The Committee concluded that both the company and the ERG used plausible methods, that other methods exist, and that it is not possible to establish 1 one correct extrapolation method. See FAD section 4.13.

Consultee	Comment	Response
	population in the trial was generally younger than those seen in clinical practice where the average age is over 65"	
	Referring to section 4.3 of the ACD: "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 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". Section 4.3 clearly states that the committee considered the LUME-Lung 1 trial to be generalisable to patients suitable for treatment with docetaxel monotherapy (and therefore nintedanib plus docetaxel).	Comments noted. No action required.
	It is important to note that the marketing authorisation for nintedanib is in combination with docetaxel, and thus patients must be able to receive and tolerate docetaxel treatment. For this reason, the population for nintedanib will be younger and fitter than the average second line non-small cell lung cancer patient, and were in the trial required to have acceptable liver, renal and other specified organ /physiological function that would allow for docetaxel administration without contraindication at baseline. The younger average age of docetaxel patients is supported by IPSOS data (BI Data on File: ONC14-54) which shows that in 2014, the average age of second line non-small cell lung cancer patients with adenocarcinoma histology, receiving docetaxel was 61.5 years. Both elderly patients (≥70years of age) and also very elderly patients (≥75 years of age) were allowed to be recruited in the LUME Lung 1 trial. There were no restrictions regarding the inclusion of elderly or very elderly patients in LUME Lung 1 and there was no active effort to limit the number of ≥70 year old patients in the study. The distribution observed is the	Comments noted. The Committee was aware that the 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 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. See FAD section 4.4.

Consultee	Comment	Response
	result of implementation of the inclusion criteria limited to ECOG PS 0-1 and other organ function tests defined in the eligibility criteria. In patients ≥70 years, the HR for OS at the final survival analysis was 0.83 (95% CI, 0.49, 1.41; p=0.4899), and in patients with adenocarcinoma <70 years, the HR for OS was 0.83 (95% CI, 0.69, 0.99; p=0.0434). The p-value for the interaction between treatment and subgroup variable was 0.9737. This is also above any accepted threshold that would be considered meaningful, and therefore it is a strong indicator that there is no interaction between age and treatment effect as measured by OS (BI Data on File: ONC 14-32). The age of patients in LUME Lung 1 is consistent with other second line non-small cell lung cancer trials (BI Data on File: ONC 14-32). In addition to this, it is important to note that performance status and biological age of patients is more important than chronological age when considering the generalizability of these results. The IPSOS data (BI Data on File: ONC 14-54) also reports that 99% of second line non-small cell lung cancer patients with adenocarcinoma histology, receiving docetaxel were of Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. LUME-Lung 1 patients were all of PS 0-1, demonstrating that the patients' fitness in LUME-Lung 1 representative of patients fit enough to receive and tolerate docetaxel treatment in UK clinical practice. **2. In section 4.18 of the ACD, it is stated that the committee considered the evidence insufficient to show that nintedanib + docetaxel offered an additional 3 months compared with docetaxel monotherapy. The ACD also states that LUME Lung 1 showed a median extension in overall survival of 2.3 months. The ACD also states that estimates to extension of life must be "plausible, objective and robust".** Regarding the mention of a median overall survival (OS) gain of 2.3 months from LUME Lung 1: • As stated by the nominated committee member presenting the cost effectiveness section during the 1st appraisal committee meeting, we should be looking at mean overall survival when considering end of life criteria • 15% of patients remained alive at the end of the trial and as a result the overall survival from the trial is not representative of the entire treated population The restricted mean OS gain of nintedanib + docetaxel vs docetaxel monotherapy in LUME Lung 1 was 2.87 months (see Table 1). At this time point, 15% of patients were	Comments noted. No action required.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>still alive, and as such the restricted mean is not an accurate representation of the OS gain of the entire investigated population. Table 2 provides the results of a number of different OS extrapolations, including sensitivity analyses around the cut-off point for the extrapolation of the Kaplan Meier data with LUCADA data. All methods of extrapolation explored met or exceeded the extension in OS of 3 months, including that of the ERG which reported an incremental OS gain of 3.05 months in favour of nintedanib plus docetaxel.

In addition, when OS is incorporated into the PSA (using Kaplan Meier data extrapolated using LUCADA with a cutoff of 5% patients remaining at risk) 4277 simulations (out of 5000 run) resulted in an OS gain of =>3 months (86%).

It is therefore clear that the extension to life provided by nintedanib + docetaxel vs docetaxel monotherapy meets the 3 month requirement of the end of life criteria. This estimate is plausible as the restricted mean is very close to 3 months with a substantial proportion of patients still alive. The estimate is robust and consistent as all methods of extrapolation lead to an OS gain of >3months and probabilistic sensitivity analysis meets the criteria 86% of the time.

Table 1: Mean overall survival from LUME Lung 1 trial
<table>
<tr><th>Overall Survival</th><th>mean</th><th>S.e.</th><th>lb 95% CI</th><th>ub 95% CI</th></tr>
<tr><td>Docetaxel</td><td>13.67</td><td>0.59</td><td>12.51</td><td>14.83</td></tr>
<tr><td>Nintedanib plus Docetaxel</td><td>16.54</td><td>0.75</td><td>15.07</td><td>18.01</td></tr>
<tr><td>Difference</td><td>2.87</td><td></td><td></td><td></td></tr>
</table>

Table 2: Incremental OS of nintedanib +docetaxel vs docetaxel monotherapy; Modelling Scenarios
<table>
<tr><th>Overall Survival</th><th>Incremental Lys</th><th>Incremental Life Months</th></tr>
<tr><td>Mixed: KM & LUCADA-Lognormal (5% patients at risk cut-off)</td><td>0.27</td><td>3.24</td></tr>
<tr><td>Mixed: KM & LUCADA-Lognormal (2.5% patients at risk cut-off)</td><td>0.27</td><td>3.24</td></tr>
</table>
</td><td>Comments noted. Considering that the estimates modelled in the company's sensitivity analyses for the mean extension to life without using the most optimistic assumptions ranged between 3.00 months and 4.08 months, the Committee agreed that an extension of greater than 3 months was probable. See FAD sections 3.49 and 4.19.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
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<tr><td>Mixed: KM & LUCADA-Lognormal (7.5% patients at risk cut-off)</td><td>0.25</td><td>3.00</td></tr>
<tr><td>Mixed: KM & LUCADA-Lognormal (5% patients at risk cut-off), PSA average</td><td>0.27</td><td>3.24</td></tr>
<tr><td>Separate – Loglogistic (base-case)</td><td>0.34</td><td>4.08</td></tr>
<tr><td>Mixed: KM & SEER-Lognormal</td><td>0.28</td><td>3.36</td></tr>
<tr><td>Mixed curves: KM & Separate Loglogistic</td><td>0.34</td><td>4.08</td></tr>
</table>

Summary
The key conclusions to be drawn from this document are:
• Regarding generalizability of LUME-Lung 1 to patient population:
• Section 4.3 of the ACD clearly states that the committee considered the LUME-Lung 1 trial to be generalisable to patients suitable for treatment with docetaxel monotherapy (and therefore nintedanib plus docetaxel).
• Patients receiving nintedanib must be fit enough to receive docetaxel
• The age of the patients in LUME-Lung 1 is in line with patients being treated with docetaxel
• There is no interaction between age and treatment effect measured by OS in LUME-Lung 1
• The performance status of patients in LUME-Lung 1 is in line with that seen in clinical practice for patients receiving docetaxel

Regarding meeting end of life criteria:
• It was stated by the Appraisal Committee that mean OS should be used when considering EOL
• With 15% of patients still alive, the mean OS increase for nintedanib plus docetaxel was 2.87 months compared to docetaxel monotherapy
• When using OS modelling methodology preferred by the Appraisal Committee, the OS increase consistently exceeds the required 3 month extension in OS.</td><td>Comments noted. See detailed responses above.

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Consultee	Comment	Response
	This is also the case for all other OS methodology explored, including that of the ERG • When the revised base case OS is investigated in the PSA, the mean increase is ≥3 months 86% of the time.	
NHS England	NHS England note the comment in paragraph 4.2 that "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". It is not clear whether this was taken into account within the modelling. NHS England would want the Guidance to be explicit that this practice is not supported, particularly if the Guidance changes to recommending nintedanib. It is unlikely that nintedanib for the indication under consideration will be supported by the CDF based on current clinical outcome data.	Comment noted. The clinical expert explained that, in clinical practice, patients might stay on nintedanib plus docetaxel even after disease progression if symptoms are controlled. However, the Committee was aware that this differed from the protocol of the LUME-Lung 1 trial on which the clinical evidence is based, and agreed that nintedanib should stop at disease progression. See FAD section 4.3.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted. No action required.
Roy Castle Lung Cancer Foundation	1. Specific Point In paragraph 4.18, it indicates that 'patients in LUME-Lung 1 trial were potentially younger and fitter than patients in clinical practice in England' and as such, 'may not achieve the level of survival benefit reported in the trial'. However, we would ask the Appraisal Committee to note that patients both in the Trial and in general clinical practice, would need to be fit enough to receive docetaxel, which is a relatively toxic therapy. Thus, this patient group, by definition, is younger and fitter than the average lung cancer patient, in this setting.	Comment noted. The Committee was aware that the 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 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

Consultee	Comment	Response
		as those with an ECOG status of 0 and 1. 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. See FAD section 4.4.
	Taking this in to account may alter the Committee's discussion and decision on extension of life and so,'End of Life' criteria.	Comment noted. The Committee considered the estimates modelled in the company's sensitivity analyses for the mean extension to life without using the most optimistic assumptions ranged between 3.00 months and 4.08 months. The Committee agreed that an extension of greater than 3 months was probable. The Committee concluded that nintedanib plus docetaxel fulfilled the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment. See FAD sections 3.49, 3.50 and 4.18.
	2. General Point As indicated in 4.1, we would remind the Committee that therapy options available to patients in this second line indication are very limited. Neither of the two current options (Docetaxel alone and Erlotinib) markedly alter survival. Thus, the addition of Nintedanib to Docetaxel, for a very small defined group of patients, does represent a significant improvement.	Comment noted. 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. The recommendations in the FAD have been amended to 'nintedanib in combination with docetaxel is recommended, within its marketing authorisation, as an option for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy, only if the company provides nintedanib with the discount agreed in the patient access scheme'. See FAD sections 1.1 and 4.20.

Consultee	Comment	Response

Comments received from clinical experts and patient experts

None received

Comments received from commentators

None received

Comments received from members of the public

None received

Boehringer Ingelheim Limited's Response to Appraisal Consultation Document (ACD) for Nintedanib for the Second-line Treatment of Non-Small Cell Lung Cancer

Boehringer Ingelheim Ltd acknowledges the recommendations of the ACD, and as a result, all but two changes made to the cost effectiveness model by the ERG have been included when generating revised results. The two changes not included are febrile neutropenia cost (as the ACD suggests the ERG estimate is too high) and overall survival (OS) modelling (as the ACD suggests there is uncertainty around the ERG methodology).

In order to model overall survival, the model now uses the Kaplan Meier (KM) data directly (preferred by the Appraisal Committee), and then extrapolates this beyond the time of the trial data to account for the lifetime horizon of the cost effectiveness model. National Lung Cancer Audit Data Set (LUCADA) data (real world data that the Appraisal Committee noted was a preferred source of evidence) is used to extrapolate the KM data beyond the cutoff time point; when the proportion of patients remaining at risk (alive) drops to a certain percentage (5% in the base case) the probability of staying alive is calculated in each cycle from the lognormal (best statistical and visual fit to LUCADA data) parametric model of LUCADA data. The probability of death calculated at the corresponding specific time point (i.e. within cycle X) from the LUCADA-based curve is applied as the transition probability in cycle X of the model to estimate the OS for the nintedanib plus docetaxel arm and for the docetaxel only arm.

The effect of varying the cutoff point at which the KM data is extrapolated with LUCADA has also been investigated.

Additionally, in order to further take account of uncertainty around the revised base case, overall survival modelling using KM data with LUCADA extrapolation has been incorporated into the probabilistic sensitivity analysis.

The two points from the ACD which Boehringer Ingelheim Ltd would specifically like to address are set out in the remainder of this document.

1. **The ACD states that "patients with an ECOG performance status of 2 would occasionally have docetaxel for their non-small cell lung cancer" and "the population in the trial was generally younger than those seen in clinical practice where the average age is over 65"**

Referring to section 4.3 of the ACD:

"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 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"****.*

Section 4.3 clearly states that the committee considered the LUME-Lung 1 trial to be generalisable to patients suitable for treatment with docetaxel monotherapy (and therefore nintedanib plus docetaxel).

It is important to note that the marketing authorisation for nintedanib is in combination with docetaxel, and thus patients must be able to receive and tolerate docetaxel treatment. For this reason, the population for nintedanib will be younger and fitter than the average second line non-

small cell lung cancer patient, and were in the trial required to have acceptable liver, renal and other specified organ /physiological function that would allow for docetaxel administration without contraindication at baseline. The younger average age of docetaxel patients is supported by IPSOS data (BI Data on File: ONC14-54) which shows that in 2014, the average age of second line non-small cell lung cancer patients with adenocarcinoma histology, receiving docetaxel was 61.5 years. Both elderly patients (≥70years of age) and also very elderly patients (≥75 years of age) were allowed to be recruited in the LUME Lung 1 trial. There were no restrictions regarding the inclusion of elderly or very elderly patients in LUME Lung 1 and there was no active effort to limit the number of ≥70 year old patients in the study. The distribution observed is the result of implementation of the inclusion criteria limited to ECOG PS 0-1 and other organ function tests defined in the eligibility criteria.

In patients ≥70 years, the HR for OS at the final survival analysis was 0.83 (95% CI, 0.49, 1.41; p=0.4899), and in patients with adenocarcinoma <70 years, the HR for OS was 0.83 (95% CI, 0.69, 0.99; p=0.0434). The p-value for the interaction between treatment and subgroup variable was 0.9737. This is also above any accepted threshold that would be considered meaningful, and therefore it is a strong indicator that there is no interaction between age and treatment effect as measured by OS (BI Data on File: ONC 14-32). The age of patients in LUME Lung 1 is consistent with other second line non-small cell lung cancer trials (BI Data on File: ONC 14-32).

In addition to this, it is important to note that performance status and biological age of patients is more important than chronological age when considering the generalizability of these results. The IPSOS data (BI Data on File: ONC 14-54) also reports that 99% of second line non-small cell lung cancer patients with adenocarcinoma histology, receiving docetaxel were of Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. LUME-Lung 1 patients were all of PS 0-1, demonstrating that the patients' fitness in LUME-Lung 1 representative of patients fit enough to receive and tolerate docetaxel treatment in UK clinical practice.

2. **In section 4.18 of the ACD, it is stated that the committee considered the evidence insufficient to show that nintedanib + docetaxel offered an additional 3 months compared with docetaxel monotherapy. The ACD also states that LUME Lung 1 showed a median extension in overall survival of 2.3 months. The ACD also states that estimates to extension of life must be "plausible, objective and robust".**

Regarding the mention of a median overall survival (OS) gain of 2.3 months from LUME Lung 1:

- As stated by the nominated committee member presenting the cost effectiveness section during the 1st appraisal committee meeting, we should be looking at mean overall survival when considering end of life criteria
- 15% of patients remained alive at the end of the trial and as a result the overall survival from the trial is not representative of the entire treated population

The restricted mean OS gain of nintedanib + docetaxel vs docetaxel monotherapy in LUME Lung 1 was 2.87 months (see Table 1). At this time point, 15% of patients were still alive, and as such the restricted mean is not an accurate representation of the OS gain of the entire investigated population. Table 2 provides the results of a number of different OS extrapolations, including sensitivity analyses around the cut-off point for the extrapolation of the Kaplan Meier data with LUCADA data. All methods of extrapolation explored met or exceeded the extension in OS of 3 months, including that of the ERG which reported an incremental OS gain of 3.05 months in favour of nintedanib plus docetaxel.

In addition, when OS is incorporated into the PSA (using Kaplan Meier data extrapolated using LUCADA with a cutoff of 5% patients remaining at risk) 4277 simulations (out of 5000 run) resulted in an OS gain of =>3 months (86%).

It is therefore clear that the extension to life provided by nintedanib + docetaxel vs docetaxel monotherapy meets the 3 month requirement of the end of life criteria. This estimate is plausible as the restricted mean is very close to 3 months with a substantial proportion of patients still alive. The estimate is robust and consistent as all methods of extrapolation lead to an OS gain of >3months and probabilistic sensitivity analysis meets the criteria 86% of the time.

Table 1: Mean overall survival from LUME Lung 1 trial

Overall Survival	mean	S.e.	lb 95% CI	ub 95% CI
Docetaxel	13.67	0.59	12.51	14.83
Nintedanib plus Docetaxel	16.54	0.75	15.07	18.01
Difference	2.87			

Table 2: Incremental OS of nintedanib +docetaxel vs docetaxel monotherapy; Modelling Scenarios

Overall Survival	Incremental LYs	Incremental Life Months
Mixed: KM & LUCADA-Lognormal (5% patients at risk cut-off)	0.27	3.24
Mixed: KM & LUCADA-Lognormal (2.5% patients at risk cut-off)	0.27	3.24
Mixed: KM & LUCADA-Lognormal (7.5% patients at risk cut-off)	0.25	3.00
Mixed: KM & LUCADA-Lognormal (5% patients at risk cut-off), PSA average	0.27	3.24
Separate – Loglogistic (base-case)	0.34	4.08
Mixed: KM & SEER-Lognormal	0.28	3.36
Mixed curves: KM & Separate Loglogistic	0.34	4.08

KM = Kaplan-Meier; LY = life years;

Summary

The key conclusions to be drawn from this document are:

<u>Regarding generalizability of LUME-Lung 1 to patient population:</u>

- Section 4.3 of the ACD clearly states that the committee considered the LUME-Lung 1 trial to be generalisable to patients suitable for treatment with docetaxel monotherapy (and therefore nintedanib plus docetaxel).
- Patients receiving nintedanib must be fit enough to receive docetaxel
- The age of the patients in LUME-Lung 1 is in line with patients being treated with docetaxel
- There is no interaction between age and treatment effect measured by OS in LUME-Lung 1
- The performance status of patients in LUME-Lung 1 is in line with that seen in clinical practice for patients receiving docetaxel

Regarding meeting end of life criteria:

- It was stated by the Appraisal Committee that mean OS should be used when considering EOL
- With 15% of patients still alive, the mean OS increase for nintedanib plus docetaxel was 2.87 months compared to docetaxel monotherapy
- When using OS modelling methodology preferred by the Appraisal Committee, the OS increase consistently exceeds the required 3 month extension in OS. This is also the case for all other OS methodology explored, including that of the ERG
- When the revised base case OS is investigated in the PSA, the mean increase is ≥3 months 86% of the time.

References

BI Data on File: ONC 14-54. Patient Profile - mNSCLC Adenocarcinoma Line 2 Receiving Docetaxel UK MAT Q3 2014

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Vargatef (nintedanib) in combination with docetaxel is for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme has been developed in order to support the cost effectiveness case for Vargatef.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The scheme is a commercial in confidence simple discount patient access scheme (PAS). A confidential discount will be applied to the list price of Vargatef.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS applies to the entire licensed population.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any criteria and the discounted price will be reflected on all original invoices for the product.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100%

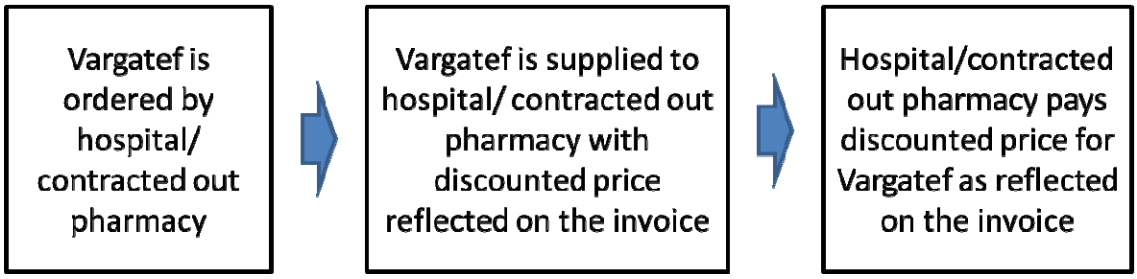
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

A fixed net price (which will not vary with any change to the UK list price) will apply to all packs of Vargatef (nintedanib). The approved discounted price in the scheme will be the price paid by the NHS at the point of sale so there is no requirement for the calculation of rebates.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

NHS organisations will be required to sign a Confidential Disclosure Agreement to take part in the scheme. There are no associated administrative processes required with the scheme as stock for the product will be ordered in the usual way and the approved discounted price will be paid at the point of sale by the NHS and will be reflected on all original invoices.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

The scheme will remain in place until NICE next reviews the guidance on the product.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No issues have been identified by Boehringer Ingelheim Ltd in this regard.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

A Confidential Disclosure Agreement will need to be signed by NHS stakeholders before the discounted price can be shared. A copy is included in the appendices.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

NA

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The model incorporates all changes made by the ERG except febrile neutropenia cost and their overall survival methodology. The base case overall survival methodology now uses Kaplan Meier data extrapolated with National Lung Cancer Audit Data Set (LUCADA) data, with the additional option to change the point at which the Kaplan Meier data is extrapolated. These changes are designed to reflect the preferences of the committee as suggested in the ACD.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the "Settings" tab, cell E39 allows the user to enter the level of discount applied to the list price for nintedanib. All but two alterations made by the ERG were included when generating results. The two alterations not included are febrile neutropenia

cost (as the ACD suggests the ERG estimate is too high) and OS modelling (as the ACD suggests there is uncertainty around the ERG methodology).

Additionally, to model overall survival, the model now uses the Kaplan Meier (KM) data directly (preferred by NICE), and then extrapolates this beyond the time of the trial data to account for the lifetime horizon of the cost effectiveness model. LUCADA data (real world data source preferred by NICE) is used to extrapolate the KM data beyond the cut-off time point; when the proportion of patients at risk drops to a certain percentage (5% in the base case) the probability of staying alive is calculated in each cycle from the lognormal (best statistical and visual fit to the LUCADA data) parametric model of LUCADA data. This probability of death calculated at the corresponding specific time point (i.e. within cycle X) from the LUCADA-based curve is applied as transition probability in cycle X of the model to estimate the OS for nintedanib+docetaxel and for docetaxel arm.
The results below also investigate the influence of changing the cut-off point at which the KM data is extrapolated ("efficacy" tab cell E16); the base case uses 5% of patients remaining at risk (alive) within the KM data, and the sensitivity analyses investigate a cut-off of both 2.5% and 7.5% patients remaining at risk.
Overall survival using KM with LUCADA extrapolation has been incorporated into the probabilistic sensitivity analysis.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS does not change the clinical data; the clinical data is the same as in the main submission document (Boehringer Ingelheim 2014).

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

NA

Table 1 Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		
…		
Total implementation/ operation costs		

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

NA

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 3 Base-case cost-effectiveness results without PAS

	Nintedanib + docetaxel	**Docetaxel**
Intervention cost (£)	[redacted]	662
Other costs (£)	[redacted]	PF Monitoring: 841 PF AE management: 387 PP Drug + admin: 1,087 PP management: 4,911 Progression: 125 Total: 7,351
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	1.61	1.34
LYG difference	N/A	0.27
QALYs	1.05	0.87
QALY difference	N/A	0.18
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; PF: Progression free; PP: Post progression

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 4 Base-case cost-effectiveness results with PAS

	Nintedanib + docetaxel	Docetaxel
Intervention cost (£)	[redacted]	662
Other costs (£)	[redacted]	PF Monitoring: 841 PF AE management: 387 PP Drug + admin: 1,087 PP management: 4,911 Progression: 125 Total: 7,351
Total costs (£)	16,306	8,013
Difference in total costs (£)	N/A	8,293
LYG	1.61	1.34
LYG difference	N/A	0.27
QALYs	1.05	0.87
QALY difference	N/A	0.18
ICER (£)	N/A	46,580

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; PF: Progression free; PP: Post progression

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5 Base-case incremental results without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	[redacted]	1.34	0.87				
Nintedanib+ docetaxel	[redacted]	1.61	1.05	[redacted]	0.27	0.18	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6 Base-case incremental results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	8,013	1.34	0.87				
Nintedanib+ docetaxel	16,306	1.61	1.05	8,293	0.27	0.18	46,580

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The tornado diagrams below are run in the same way as described in the main submission document (Boehringer Ingelheim, 2014).

Figure 1: Tornado Diagram – Nintedanib plus Docetaxel vs Docetaxel (range 20%); Threshold = £50,000. Without PAS

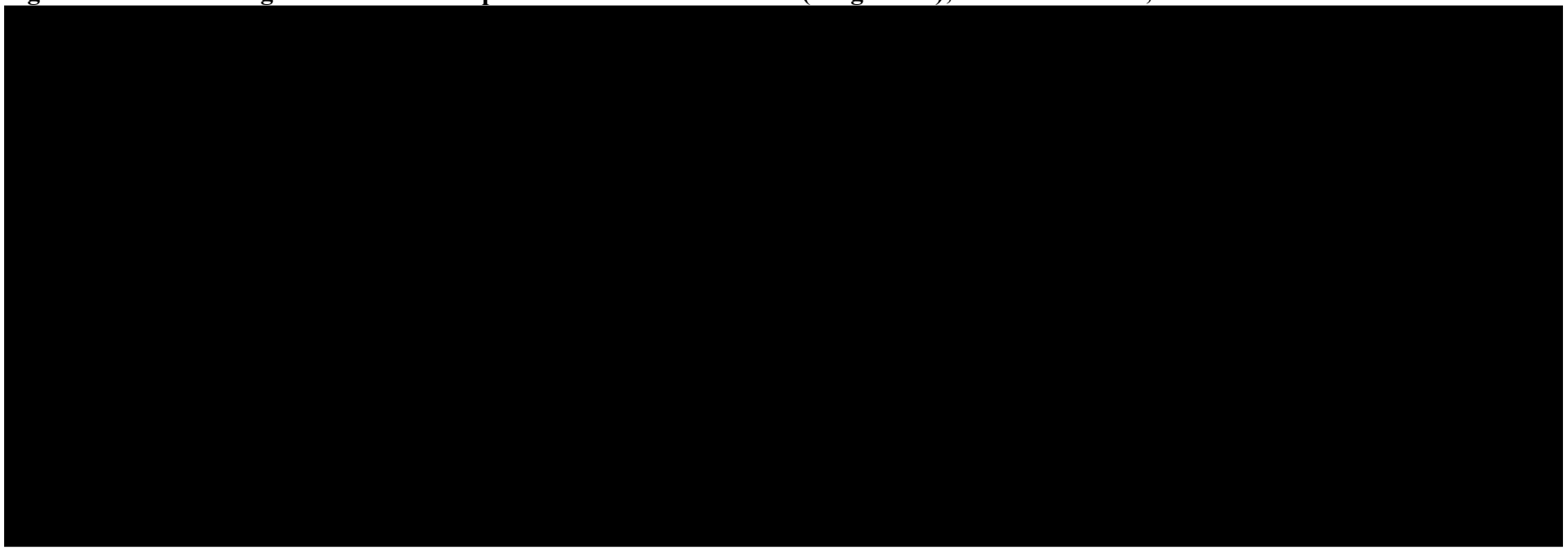
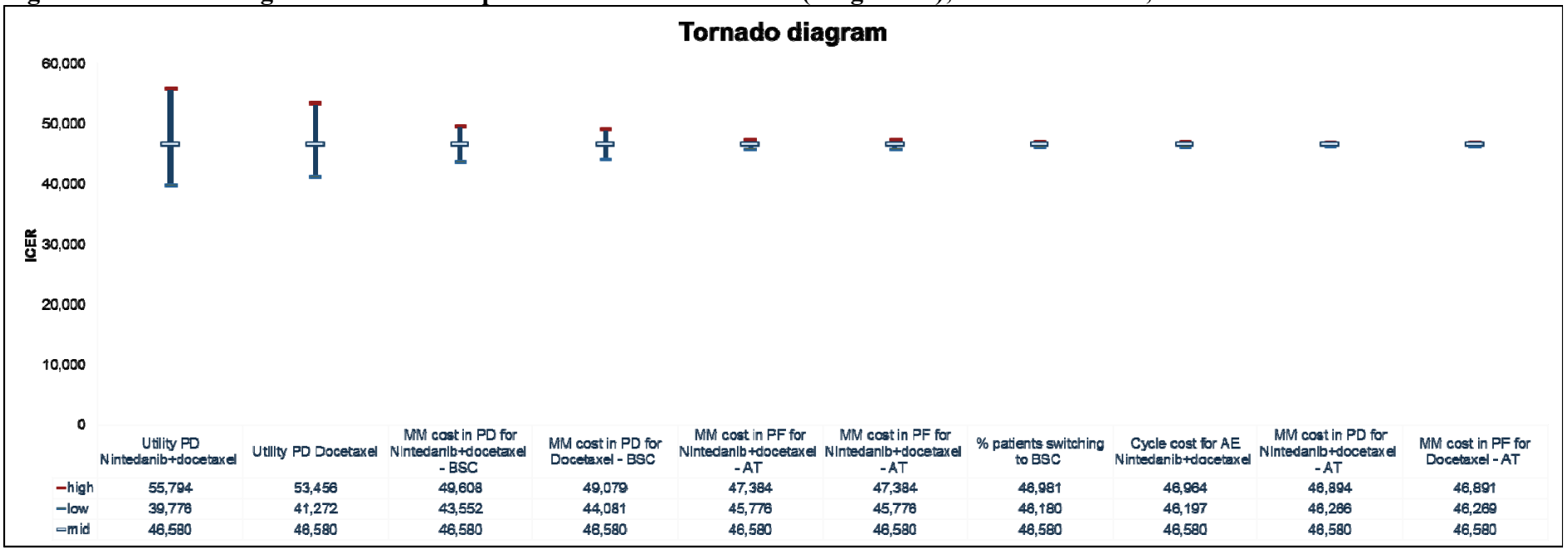


Figure 2: Tornado Diagram – Nintedanib plus Docetaxel vs Docetaxel (range 20%); Threshold = £50,000. With PAS



	Utility PD Nintedanib+docetaxel	Utility PD Docetaxel	MM cost in PD for Nintedanib+docetaxel - BSC	MM cost in PD for Docetaxel - BSC	MM cost in PF for Nintedanib+docetaxel - AT	MM cost in PF for Nintedanib+docetaxel - AT	% patients switching to BSC	Cycle cost for AE Nintedanib+docetaxel	MM cost in PD for Nintedanib+docetaxel - AT	MM cost in PF for Docetaxel - AT
high	55,794	53,456	49,608	49,079	47,384	47,384	46,981	46,964	46,894	46,891
low	39,776	41,272	43,552	44,081	45,776	45,776	46,180	46,197	46,266	46,269
mid	46,580	46,580	46,580	46,580	46,580	46,580	46,580	46,580	46,580	46,580

In addition to the one way sensitivity analysis, scenario analyses were carried out to vary the cut-off point at which the LUCADA data is used to extrapolate the KM data. The cut-off point stated is the number of patients remaining at risk at the point the LUCADA data is used to extrapolate the overall survival. Note that at base case cut-off point and those investigated in the sensitivity analyses, nintedanib + doectaxel extends overall survival by >3 months when comparing to docetaxel monotherapy, thus fulfilling this requirement to meet end of life criteria.

Table 7: 2.5% cut-off point; without PAS discount

Distributions used – OS: Mixed KM&LUCADA Lognormal; PFS: ERG methodology

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nintedanib + Docetaxel	[redacted]	1.59	1.04	-	-	-	-	-
Docetaxel	[redacted]	1.33	0.86	[redacted]	0.27	0.18	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 8: 2.5% cut-off point; with PAS discount

Distributions used – OS: Mixed KM&LUCADA Lognormal; PFS: ERG methodology

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nintedanib + Docetaxel	£16,187	1.59	1.04	-	-	-	-	-
Docetaxel	£7,903	1.33	0.86	£8,284	0.27	0.18	£46,813	£46,813
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 9: 7.5% cut-off point; without PAS discount

Distributions used – OS: Mixed KM&LUCADA Lognormal; PFS: ERG methodology

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nintedanib + Docetaxel	[redacted]	1.60	1.04	-	-	-	-	-
Docetaxel	[redacted]	1.35	0.88	[redacted]	0.25	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 10: 7.5% cut-off point; with PAS discount

Distributions used – OS: Mixed KM&LUCADA Lognormal; PFS: ERG methodology

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nintedanib + Docetaxel	£16,230	1.60	1.04	-	-	-	-	-
Docetaxel	£8,059	1.35	0.88	£8,171	0.25	0.16	£49,894	£49,894
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Additional scenario analyses were carried out in the same way as described in the main submission (Boehringer Ingelheim, 2014) for utility values. Note that when using the values from Chouaid (2013), in the post-progression state a conservative assumption was used; the utility is assumed to be equal to the third/fourth line progressive disease state. In reality, the patients in the model are more likely to also include patients from the second-line progressive disease and third/fourth line PF states, both of which have higher utilities than the third/fourth line progressive disease state.

Table 11: Impact of Utility Scenarios

OS: Mixed KM&LUCADA Lognormal; PFS: KM Curve (used until time horizon)

Scenarios	ICER (£/QALY) Nindetanib + Docetaxel versus: Docetaxel	
	Without PAS discount	With PAS discount
Base-case	[redacted]	£46,580
LOCF for PFS	[redacted]	£47,825
Chouaid (2013) for both PFS and PD	[redacted]	£57,473

ICER = incremental cost-effectiveness ratio; LOCF = last-observation carried forward; PFS = progression-free survival; QALYs = quality-adjusted life years

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis was carried out as described in the maijn submission. In addition, the overall survival modelling now used in the base case (KM with LUCADA extrapolation) has been incorporated into the PSA to take account of uncertainty around these data.

Note that when 5% patients remaining at risk is used as the cut-off, of the 5000 PSA runs, nintedanib + docetaxel extends overall survival compared to docetaxel monotherapy by =>3 months 4277 times (86% of the time). This further supports the robustness of the evidence around meeting the extension in overall survival of 3 months required for the end of life criteria.Please present scenario analysis results as described for the main manufacturer/sponsor submission (Boehringer Ingelheim, 2014) of evidence for the technology appraisal.

Table 12: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib plus docetaxel versus docetaxel without PAS

	Incremental cost	Incremental QALY	Incremental LY	ICER
Deterministic Values	[redacted]	0.18	0.27	[redacted]
Average value for PSA	[redacted]	0.18	0.27	[redacted]

Figure 3: Incremental cost-effectiveness scatterplot for nintedanib + docetaxel versus docetaxel without PAS

Figure 4: Cost effectiveness acceptability curve for nintedanib +docetaxel versus docetaxel without PAS

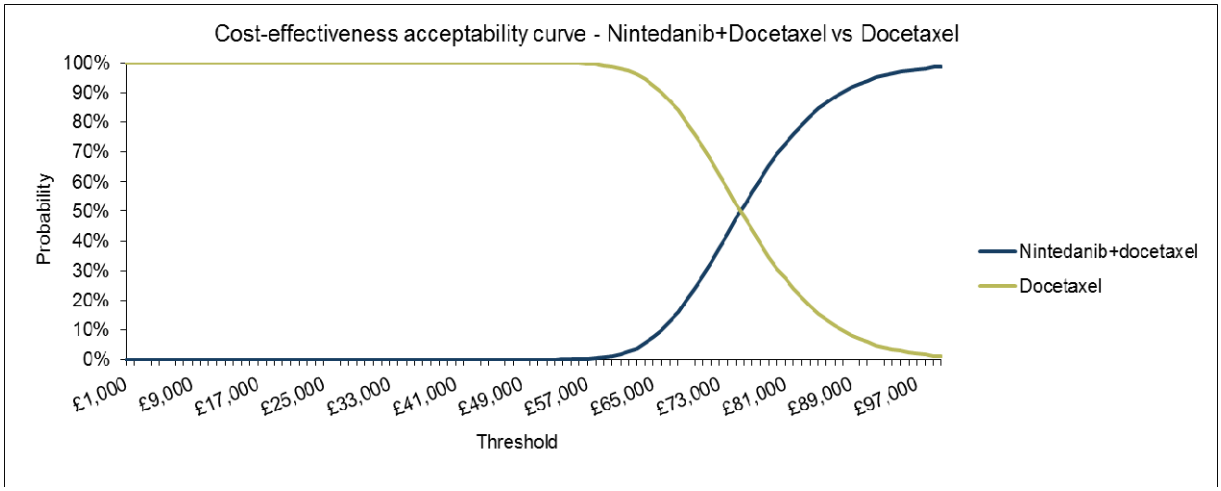


Table 13: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib plus docetaxel versus docetaxel with PAS

	Incremental cost	Incremental QALY	ICER
Deterministic Values	£8,293	0.18	£46,580
Average value for PSA	£8,289	0.18	£46,517

Figure 5; Incremental cost-effectiveness scatterplot for nintedanib + docetaxel versus docetaxel with PAS

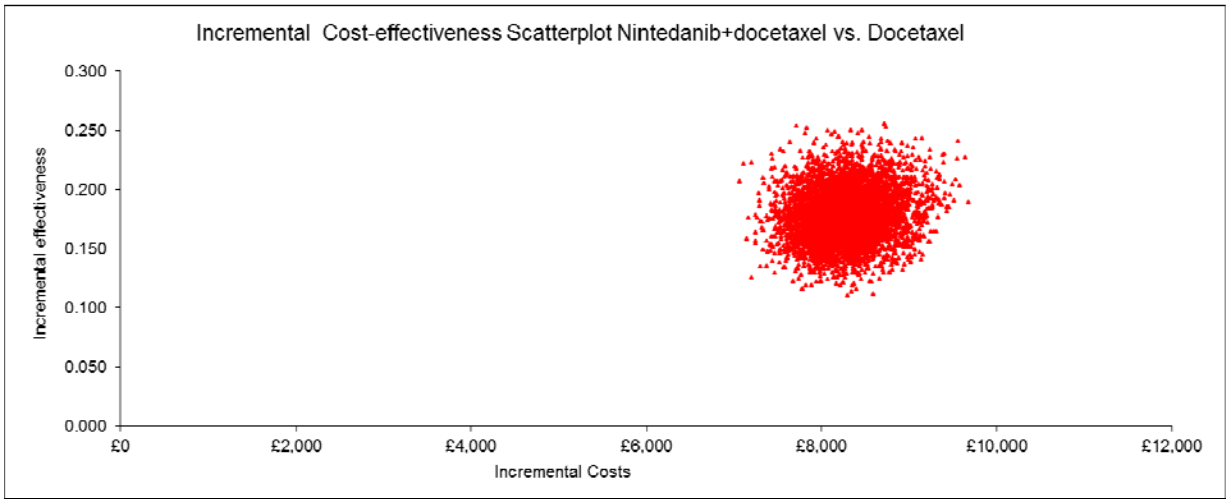
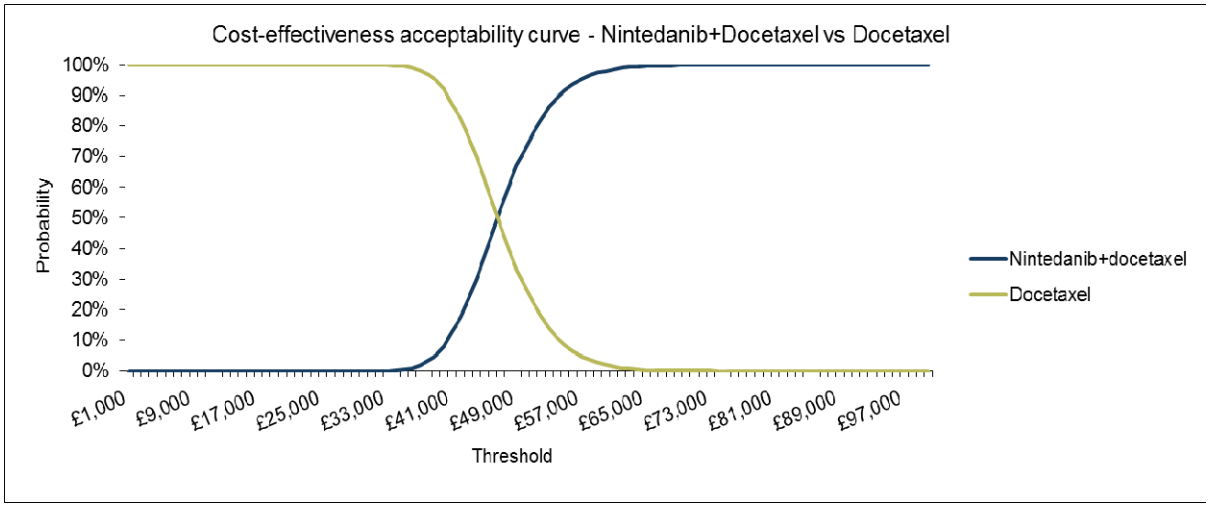


Figure 6: Cost effectiveness acceptability curve for nintedanib +docetaxel versus docetaxel with PAS



4.11 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

NA

Impact of patient access scheme on ICERs

4.12 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 14 Results showing the impact of patient access scheme on ICERs

	ICER (£) for nintedanib + docetaxel versus:	
	docetaxel	
	Without PAS	**With PAS**
Scenario 1 (base-case)	[redacted]	46,508
2.5% OS cut-off	[redacted]	46,813
7.5% OS cut-off	[redacted]	49,694
LOCF for PFS	[redacted]	47,825
Chouaid (2013) for both PFS and PD	[redacted]	57,473

PAS: patient access scheme.

5 References

Boehringer Ingelheim. Single Technology Appraisal. Nintedanib in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. 2014.

Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol. 2013;8(8):997-1003.

6 Appendices

6.1 Appendix A: Additional documents

6.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

6.2 Appendix B: Details of outcome-based schemes

6.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

6.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

6.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

6.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

6.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

6.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

6.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

6.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

6.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Dear [redacted],

As previously indicated, I did not receive notice of this ACD until your email on 21st January. As such, we have not been able to scrutinise the document and respond within the time frame. However, we would wish the Appraisal Committee to take note of the following -

1. Specific Point
In paragraph 4.18, it indicates that 'patients in LUME-Lung 1 trial were potentially younger and fitter than patients in clinical pracitice in England' and as such, 'may not achieve the level of survival benefit reported in the trial'. However, we would ask the Appraisal Committee to note that patients both in the Trial and in general clinical practice, would need to be fit enough to receive Docetaxel, which is a relatively toxic therapy. Thus, this patient group, by definition, is younger and fitter than the average lung cancer patient, in this setting. Taking this in to account may alter the Committee's discussion and decision on extension of life and so,'End of Life' criteria.

2. General Point
As indicated in 4.1, we would remind the Committee that therapy options available to patients in this second line indication are very limited. Neither of the two current options (Docetaxel alone and Erlotinib) markedly alter survival. Thus, the addition of Nintedanib to Docetaxel, for a very small defined group of patients, does represent a significant improvement.

We look forward to hearing the outcome of the Appraisal Committee's further deliberations.

Best wishes,

NHS England Response to NICE ACD – Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (ID438)

Please find NHS England's response to the ACD – Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (ID438) which has been reviewed by the Chemotherapy CRG

NICE has recommended within the ACD that:

> 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.

Has all of the relevant evidence been taken into account?
Yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
NHS England note the comment in paragraph 4.2 that "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". It is not clear whether this was taken into account within the modelling. NHS England would want the Guidance to be explicit that this practice is not supported, particularly if the Guidance changes to recommending nintedanib.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
See above
Any other comments
It is unlikely that nintedanib for the indication under consideration will be supported by the CDF based on current clinical outcome data.

Contact details

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Job title or role	[redacted]
Email address	[redacted]

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ADDENDUM 2

This report was commissioned by the NIHR HTA Programme as project number 13/106/01

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Contains CIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Following a meeting of the NICE Technology Appraisal Committee (AC) meeting on 19th November 2014, NICE issued an Appraisal Consultation Document (ACD) indicating its preliminary decision that "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."

Subsequently, evidence was submitted by the company in support of a proposed Patient Access Scheme (PAS) by which nintedanib would be supplied to NHS users at a discounted price. This includes a revised version of the decision model previously submitted to NICE, taking account of issues of concern detailed in the ACD.

This addendum presents a critique by the independent Evidence Review Group (ERG) of the revisions made by the company to their decision model, together with alternative analytic methods and assumptions relating to the main unresolved questions affecting the estimation of the cost-effectiveness of nintedanib.

2 COMPANY MODEL AMENDMENTS

The ERG report for this appraisal identified 12 separate issues where they considered that the decision model required amendment. (NB these were referred to in the ERG report as 11 changes because separate amendments to the costing of docetaxel and nintedanib were considered under a single heading in the ERG report). In the version of the model submitted in support of the PAS application, the company have accepted 10 of the ERG model changes leaving only two issues in dispute:

- the most appropriate cost to be applied to patients experiencing at least one episode of febrile neutropenia (FN)
- the most reliable approach to estimating the lifelong gain in overall survival (OS) attributable to use of nintedanib

In the version of the model originally submitted by the company, the application of the ERG estimated FN cost per patient had only a minor impact on the calculated incremental cost-effectiveness ratio (ICER), increasing it by £595 per QALY gained. By contrast the ERG approach to modelling OS had the effect of increasing the ICER by £17,811 per QALY gained, and therefore this Addendum is focussed on a comparison of the different methods proposed by the company and the ERG for estimating long-term OS in the patients who participated in the LUME-Lung 1 clinical trial.

The original version of the decision model submitted by the company estimated progression-free survival (PFS) by applying Log Normal survival models separately to each treatment arm of the model, calibrated from the trial Kaplan-Meier (K-M) results. None of the original trial PFS results were used directly in the model. Similarly, OS was represented in the original model by separate Log Logistic survival models, calibrated from the trial OS K-M results without direct use of the trial K-M data in the model. The unmodified decision model yielded an estimated ICER of £50,776 per QALY. (Table 2 Scenario A)

The version of the decision model proposed by the ERG was based on the principle of employing primary trial data as far as possible, and only using projective modelling to represent the estimated long-term survival experience of patients surviving close to the end of trial follow-up, whose future mortality risks are unlikely to be reliably predictable from the those high-risk patients who died much earlier in the trial. The ERG identified stable trends in mortality risk in the latter stages of the clinical trial, and calibrated separate projective models from K-M trial data. This approach was employed for both PFS and OS estimation. The ERG modified decision model including all 12 proposed amendments yielded a revised base case estimated ICER of £85,292 per QALY. (Table 2 Scenario B)

If only the 10 ERG amendments accepted in the company PAS application (i.e. excluding ERG amended FN costs and replacing the ERG OS modelling method with an alternative model) are applied, the estimated ICER reduces to [redacted] per QALY. Finally, when the proposed PAS price discount of [redacted] is applied, the estimated ICER is £46,580 per QALY. (Table 2 Scenario D)

3 PROJECTIVE MODELLING OF OVERALL SURVIVAL

The company has developed a revised approach to modelling long-term survival trends. This involves using the area under the Kaplan-Meier curves from the LUME-Lung 1 trial up to a pre-determined point, and then applying per cycle mortality risks based on the log-normal model fitted to an extract of LUCADA data. This involves several assumptions:

- Since the LUCADA data do not differentiate between different types of treatment, the use of a single set of risk estimates for projecting both LUME-Lung 1 trial arms assumes commonality of long-term risk profiles which precludes any differential outcomes (increasing or decreasing survival advantage) between the trial arms beyond the selected point at which the LUCADA trend is introduced.

- The LUCADA trend is introduced at different time points in the two treatment arms, but the risks applied at any subsequent common time point are the same in the two

trial arms, implying that the effect of treatment on surviving patients' future survival in either arm is identical. It also ensures that any survival advantage apparent at the time of introducing the LUCADA trend is preserved thereafter.

- The times at which estimated survival trends are switched between K-M observed data to the LUCADA log-normal trend are determined in terms of a common proportion of patients (5% in the company base case) in the LUME-Lung 1 trial who are still at risk (i.e who are still alive and have not been censored for any reason). This approach leads to significant risk of bias; the combination of better survival in the nintedanib trial arm and random differences in the number of patients censored ensures that the long-term projection of survival operates over different time frames and starts with different proportions of survivors according to K-M estimation (more than 15% for nintedanib and less than 12% for placebo). This means that any uncertainty in the LUCADA log-normal estimated parameters has a proportionately larger effect on nintedanib OS estimates than on placebo OS estimates, resulting in potentially larger absolute OS errors in the nintedanib arm than in the placebo arm.

The ERG has encountered similar issues in previous appraisals and found that this type of risk can be avoided by applying a long-term trend in both arms of the model at different time points corresponding to the same K-M estimated survival level (chosen to balance the maximum use of direct K-M evidence whilst reducing as far as possible the inevitable uncertainty from small numbers of survivors towards the end of the trial). This is illustrated in Figure 1, where the ERG have applied the LUCADA trend from times at which both trial arms exhibit an estimated OS of about 12.6% (horizontal dashed line A -- B). In addition the mortality risks applied from this point onward are derived from the risks found in the LUCADA trend corresponding to a starting point where the estimated OS of 12.6% occurs. This is equivalent to assuming that the survival advantage evident between the trial arms at the switching point is preserved thereafter, but is not increased or decreased. In simple terms, the survival advantage is equivalent to the long-term trend for the nintedanib arm being the same as that of the placebo arm shifted forwards in time by a fixed amount (i.e from U-V to X-Y).

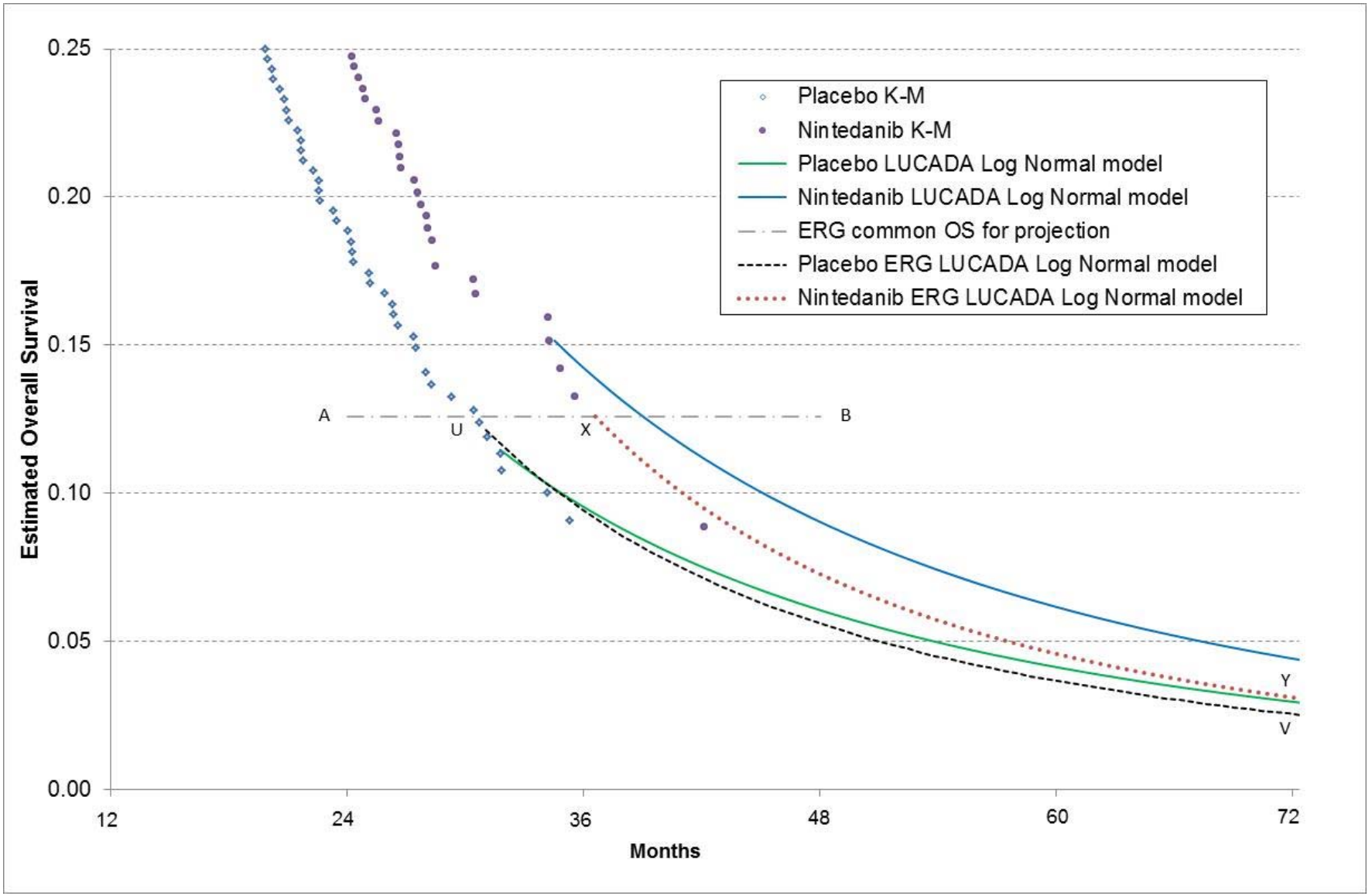

Figure 1 Comparison of two methods for applying a parametric projective model to extend survival data beyond available trial data

4 COST-EFFECTIVENESS SCENARIOS

Table 2 provides details of the cost-effectiveness results for nintedanib plus docetaxel compared with docetaxel including the company's original base case (Scenario A), and the ERG's preferred revised base case (Scenario B). In addition, the table includes the manufacturer's revised base case, in which the ERG revised FN cost is not applied, and a new model for OS combining K-M survival estimates with a log-normal survival model calibrated against a data extract from the LUCADA database (Scenario C). An alternative version of Scenario C is also shown in which the ERG introduces the LUCADA model at the same level of estimated K-M survival in each arm (Scenario E). Scenarios D and F calculate new ICERs for Scenarios C and E applying the PAS proposed discounted price.

Table 1 is provided to indicate the levels of PAS discount which would be required for Scenarios B, D and F to yield an estimated ICER no greater that a range of four specific cost-effectiveness acceptability thresholds.

Table 1: PAS discount required to obtain an estimated ICER no greater than specified cost-effectiveness values

ICER threshold	Scenario B	Scenario C	Scenario E
£20,000 / QALY	[redacted]	[redacted]	[redacted]
£30,000 / QALY	[redacted]	[redacted]	[redacted]
£40,000 / QALY	[redacted]	[redacted]	[redacted]
£50,000 / QALY	[redacted]	[redacted]	[redacted]

5 SUMMARY

In response to the ACD issued in December 2014, the company has presented revised cost-effectiveness analyses which accept all but two of the model amendments suggested by the ERG. Only one of these two issues is important to the assessment of cost-effectiveness: the method of estimating long-term OS gain. The company has presented new analyses involving a new projective modelling approach, combined with a PAS discounted price for nintedanib. The ERG considers that there are problems with the way this change has been implemented, and has demonstrated an alternative more robust approach. This indicates that nintedanib plus docetaxel compared with current treatment generates an ICER greater than £50,000/QALY despite the proposed PAS discounted price. In addition the estimated gain in life years is reduced to 2.69 months.

Table 2: Cost-effectiveness results for nintedanib plus docetaxel vs docetaxel: summary of base case modelling variants

Model scenario & ERG revisions	Nintedanib + docetaxel			Docetaxel			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
A. Company's first base-case [as in Table 40 ERG report]	[redacted]	[redacted]	1.810	[redacted]	[redacted]	1.419	+ £11,051	+ 0.218	+ 0.391	£50,776	-
B. ERG revised base case [as in Table 40 ERG report]	[redacted]	[redacted]	1.493	[redacted]	[redacted]	1.238	+ £13,437	+ 0.158	+ 0.255	£85,292	+ £34,516
C. ERG revised base case (excl. FN change) with new OS model	[redacted]	1.050	1.709	£8,014	0.872	1.411	[redacted]	+ 0.178	+ 0.298	[redacted]	[redacted]
D. C with proposed PAS discount [as in Company PAS submission]	£16,307	1.050	1.709	£8,014	0.872	1.411	+ £8,293	+ 0.178	+ 0.298	£46,580	- £4,196
***E*. ERG revised base case (excl. FN change) using ERG implementation method for new OS model**	[redacted]	0.996	1.604	£7,880	0.856	1.380	[redacted]	+ 0.140	+ 0.224	[redacted]	[redacted]
F. E with proposed PAS discount	£15,850	0.996	1.604	£7,880	0.856	1.380	+ £7,970	+ 0.140	+ 0.224	£56,804	+ £6,028

Costs and QALYs discounted; Life years undiscounted
OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; FN = febrile neutropenia