NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted. The Evidence Review Group appendices discussing the confidential comparator Patient Access Schemes in this appraisal are completely confidential and have therefore not been included in these papers.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Decision problem

- Docetaxel is the main comparator for the full population and nintedanib plus docetaxel for the non-squamous population but the NICE scope also included nivolumab, crizotinib and erlotinib. The company stated that nivolumab, erlotinib and crizotinib are not relevant comparators for this appraisal (see Table 1). The ERG agreed that erlotinib and crizotinib are not relevant comparators; however it argued that nivolumab is an appropriate comparator and should have been included. Which treatments are the relevant comparators for ramucirumab plus docetaxel for this appraisal?

Clinical-effectiveness

- Does the committee consider the company's network meta-analysis to be valid given the ERG's concerns about some of the assumptions used, particularly the assumption of proportional hazards.

- Nintedanib plus docetaxel is licensed for adenocarcinoma histology only. For the comparison with nintedanib plus docetaxel, the company used data for the non-squamous subgroup based on the assumption that non-squamous and adenocarcinoma histologies are synonymous. Are the results of the mixed treatment comparison comparing ramucirumab plus docetaxel with nintedanib plus docetaxel valid?

Cost effectiveness

- The company had collected health-related quality of life data in the REVEL trial. Utility values for progression-free survival and progressed disease from the literature (Chouaid et al.) were also tested during the sensitivity analyses in the model. These utility values were taken from non-small cell lung cancer patients who were being treated in the UK, Europe, Canada, Australia and Turkey. What are the most appropriate utility values to use for the progression-free survival or progressed disease, those from the REVEL trial or those from the Chouaid et al published study? If the former, does the REVEL EQ-5D data support an assumption of no differences between the groups during progression-free survival?

- What are the committee's views on the company's approach to modelling survival, given the ERG's concerns that proportional hazards assumptions are not valid for overall survival and that separate models should be fitted to the treatment groups?

- What are the committee's views on the assumptions used to model costs and resource use in the model?

    - The ERG considered the use of 'treatment utilisation' percentages in calculating maximum patient weights, estimating patient body surface

areas and the inclusion of the number of ramucirumab vials associated with this to be an unusual method

- What duration of ramucirumab treatment should be applied in the model? Data from the REVEL trial were applied to the company's model. Would it be more appropriate to assume that the number of ramucirumab administrations is taken from the progression-free survival model, with there being no maximum number of administrations, as the company did for nintedanib?

- The ERG considered the exclusion of the cost of subsequent cycles of chemotherapy (SB15Z at £314) in the company's model to be appropriate. Should these costs be included?

- Does the committee agree with the ERG's model revisions and sensitivity analyses?

- What are the committee's preferred assumptions?

Other considerations

- Are the end-of-life criteria met for this appraisal?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ramucirumab within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after platinum-based chemotherapy.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with locally advanced or metastatic non-small-cell lung cancer that has progressed after platinum-based chemotherapy		-	This matches the final NICE scope.
Int.	Ramucirumab in combination with docetaxel		-	This matches the final NICE scope.
Com.	• Docetaxel • Erlotinib (subject to ongoing NICE review) • Nivolumab (for people with squamous tumour histology) • Nintedanib in combination with docetaxel (For people with adenocarcinoma) • Crizotinib (For people with anaplastic-lymphoma-kinase-positive NSCLC)	• Docetaxel • For people with adenocarcinoma tumour histology only: • Nintedanib in combination with docetaxel	• Erlotinib, nivolumab and crizotinib were excluded as comparators. Erlotinib would be provided to patients whose tumour confirmation is delayed but were suspected EGFR positive. • Nivolumab is currently undergoing NICE appraisal and not yet in routine use in UK clinical practice • Crizotinib only given to patients who are confirmed ALK. Additionally, ALK mutation status was not collected routinely in REVEL trial	The company's submission differs from the final NICE scope because the comparators, nivolumab and crizotinib have been excluded from the company's decision problem. The ERG considers nivolumab should be a comparator.

Out.	•overall survival •progression-free survival •response rates •adverse effects of treatment •health-related quality of life.		This matches the final NICE scope.

2 The technology and the treatment pathway

2.1 Ramucirumab is a fully human immunoglobulin G1 monoclonal antibody. It specifically blocks the vascular endothelial growth factor receptor-2, which plays an important role in angiogenesis (formation of new blood vessels) in tumours. Ramucirumab received a marketing authorisation for gastric cancer and gastro-oesophageal junction adenocarcinoma in December 2014 and received an extension to the licence, in January 2016, to include non-small cell lung cancer (NSCLC) and colorectal cancer. The marketing authorisation for NSCLC is 'ramucirumab in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy'.

2.2 NSCLCs account for 85–90% of all lung cancers and the prognosis is generally poor. The treatment pathway for NSCLC is summarised in Figure 1. NICE clinical guideline 121 (CG121) recommends platinum-based chemotherapy (cisplatin or carboplatin, in combination with gemcitabine, vinorelbine, docetaxel or paclitaxel) as a first-line option for people with untreated stage III or IV NSCLC and good performance status. Alternatively, people may receive pemetrexed in combination with cisplatin if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (NICE technology appraisal 181). If subsequent treatment is appropriate, docetaxel monotherapy should be considered (NICE clinical guideline 121). NICE technology appraisals 310 and 374 also recommend afatinib and erlotinib respectively for some people with NSCLC: TA310 recommends afatinib for epidermal growth factor receptor (EGFR) positive tumours if the person has not previously had an EGFR tyrosine kinase (EGFR-TK) inhibitor, and TA374 recommends erlotinib for some people with either EGFR positive tumours (only if the person received chemotherapy first-line because of delayed

diagnosis of EGFR status) or whose EGFR status is unknown (only if the result of an EGFR mutation diagnostic test is unobtainable and the tumour is very likely to be EGFR mutation-positive). Nintedanib in combination with docetaxel is recommended for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology (NICE technology appraisal 347). People with anaplastic-lymphoma-kinase-positive NSCLC may receive second-line treatment with crizotinib (not recommended by NICE in technology appraisal 296 but currently funded via the Cancer Drugs Fund). The company proposes that ramucirumab could be considered in the second-line setting.

Figure 1. Current treatment pathway for people with non-small-cell lung cancer receiving non-targeted platinum-based chemotherapy first-line.

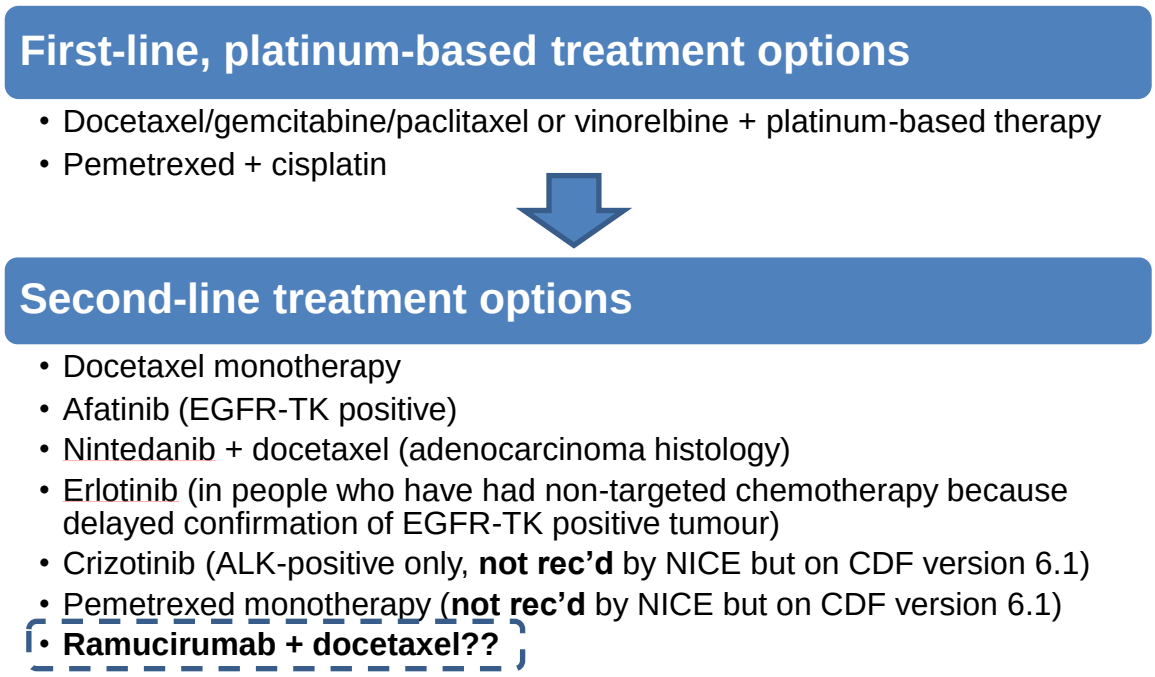


Table 2 Technology

	Ramucirumab	Docetaxel	Nintedanib plus docetaxel
Marketing authorisation	Received January 2016 – Ramucirumab in combination with docetaxel is indicated for the treatment of adult	Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy	Nintedanib is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-

	patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy.		small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy
Dosage and administration	10mg/kg on day 1 of a 21 day cycle, prior to docetaxel infusion.	75 mg/m^2, intravenously over 60 minutes, every 3 weeks	200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle
List price	500mg = £2,500 (list price) 100mg = £500 (list price)	140-mg vial = £900	100mg capsules, 120 capsule 12 x 10 capsules = £2151.10 (list price) 150mg capsules, 60 capsule 6 x 10 capsules = £2151.10 (list price)

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 All consultees noted that the most common treatment for NSCLC patients who have received platinum therapy is docetaxel. However, docetaxel can only be used to treat NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 because of the toxicity of the treatment. Patients with adenocarcinoma can receive nintedanib plus docetaxel and patients with anaplastic-lymphoma-kinase (ALK) positive NSCLC can be treated with crizotinib via the Cancer Drugs Fund. A patient expert noted that not all approved treatment are available to all patients. A clinical expert indicated that there are some differences in the use of docetaxel to treat NSCLC with some clinicians choosing not to use it because the overall survival rate in patients is not much greater than best supportive care.

3.2 Patient experts considered finding a cure and overall survival to be the most important outcomes but also that quality of life is a major factor for people with NSCLC.

3.3 A professional organisation commented that the majority of patients receiving ramucirumab plus docetaxel would have the same frequency of visits as patients receiving docetaxel alone, although chair time would increase by approximately 1 hour every three weeks. However, both a professional organisation and a clinical expert considered that some patients may go on to receive a longer duration of therapy with additional visits.

3.4 A patient expert commented that ramucirumab plus docetaxel might cause a slight increase in some side effects but did not indicate which treatment this comparison was with. The expert did consider that these increased side effects would be tolerable and acceptable to patients but that people with a greater number of co-morbidities might not be able to receive ramucirumab treatment. However, it was acknowledged that this issue applies to all treatments and not specifically to ramucirumab. A professional organisation commented that ramucirumab was generally well tolerated in the REVEL trial but that hypertension of all grades was more common in the ramucirumab group, although generally manageable. The organisation commented that there was an increase in febrile neutropenia with ramucirumab plus docetaxel compared to docetaxel alone. The organisation also noted that as ramucirumab is a monoclonal antibody, which inhibits angiogenesis, there are a number of toxicities of special interest associated with anti-angiogenic therapy that may require scrutiny but did not indicate which toxicities. A patient organisation commented that patients reported severe bleeding, blood clots, elevation of blood pressure and may impair wound healing when receiving ramucirumab.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 1 relevant randomised controlled trial: REVEL. This was a phase 3, international, multicentre, randomised, placebo-controlled, double-blind trial investigating ramucirumab plus docetaxel (n=628) compared with placebo plus docetaxel (known from here on as docetaxel alone group; n=625) in the second-line setting for adults with stage IV NSCLC who had progressed during or after platinum-based therapy for advanced or metastatic disease. The company considered the demographic and baseline disease characteristics to be generally balanced between the treatment groups. The trial took place in 216 sites across 26 countries, including the United Kingdom (see table 14, page 44 company submission). The primary outcome was overall survival; secondary outcomes included progression free survival, objective response rate, disease control rate and safety and quality of life (QoL) as captured using the Lung Cancer Symptom Scale (LCSS) and EQ-5D.

4.2 Patients received study treatment every 3 weeks until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient or investigator. The median number of cycles of docetaxel in the REVEL trial was 4 for both the ramucirumab plus docetaxel group and docetaxel alone group but some patients received considerably more (mean = 5.5 cycles in ramucirumab plus docetaxel group and 4.9 cycles in docetaxel alone group). The mean number of infusions of ramucirumab and docetaxel, for the full population, also differed in the REVEL trial (6.1 and 5.5 respectively). A summary of the patient characteristics in the REVEL trial is presented in Table 3. Full details of the REVEL trial can be found in section 4.3 of the company submission.

Table 3. Patient characteristics in REVEL trial, intention-to-treat population (summarised from company submission table 18, page 54).

	Ramucirumab + docetaxel (N=)	Placebo + docetaxel (N=)
Age: median (range), years	62 (21-85)	61 (25-86)
<65	62.3%	65.1%
≥65	37.7%	34.9%
<70	79.8%	80.0%
≥70	20.2%	20.0%
Sex: % male	66.7%	66.4%
Race: % white	83.8%	80.5%
Pathological diagnosis at study entry:		
Non-squamous	72.4%	71.6%
Adenocarcinoma	60.0%	55.7%
Large cell	2.2%	3.4%
Non-squamous, other	11.8%	12.5%
Squamous	25%	27.4%
ECOG status: % ECOG 0	33.0%	31.8%
Disease stage: % stage IV at initial diagnosis	76.8%	81.8%
Previous platinum-based therapy	99.2%	99.5%
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand		

ERG comments

4.3 The ERG considered that the REVEL trial was of good quality, with a low risk of selection bias. The demographic and baseline characteristics were balanced between the treatment groups and the trial included patients whose disease had progressed following previous chemotherapy so were the correct patient group. The ERG also considered the REVEL trial accurately presented the risks and benefits of ramucirumab plus docetaxel compared with docetaxel alone.

Clinical trial results

4.4 The company presented results of the final analysis from the REVEL trial. Ramucirumab plus docetaxel was associated with statistically significant improvements in overall survival and significantly reduced risk of disease progression or death (see Table 4 and Figure 2). The company noted that the robustness of the primary overall survival analysis was demonstrated by four sensitivity analyses, where hazard ratios ranged from 0.81 to 0.86 (p ≤0.027).

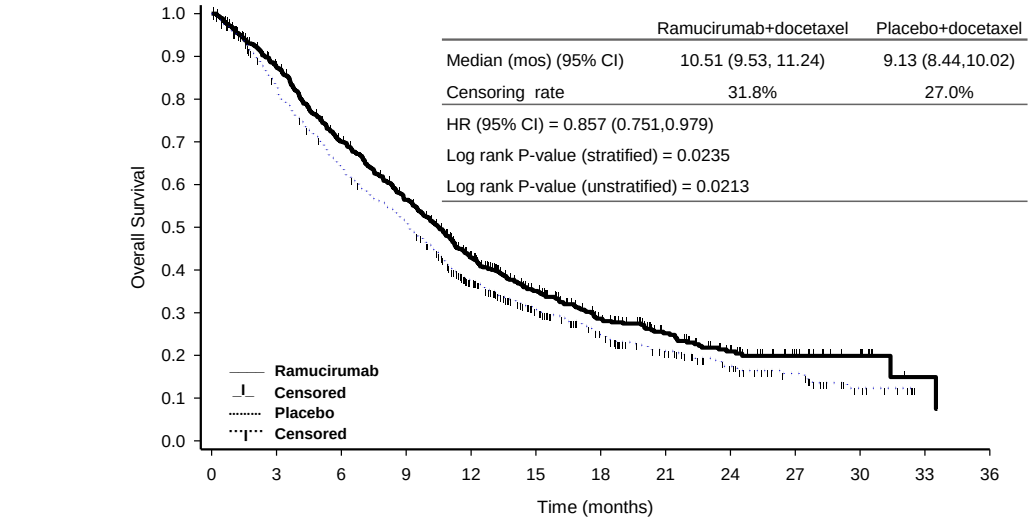
Table 4. Clinical effectiveness overall survival and progression-free survival results in REVEL (intention-to-treat population; taken from company submission pages 59 and 61)

	RAM+DOC N = 628	**PBO+DOC N = 625**
Overall survival		
Median (95% CI), months	**10.5 (9.5, 11.2)**	**9.1 (8.4, 10.0)**
Hazard ratio (95% CI)	0.857 (0.751, 0.979)	
Overall survival at 12 months: % (95% CI)	42.9 (38.9, 46.9)	37.7 (33.8, 41.5)
Overall survival at 24 months: % (95% CI)	20.9 (17.0, 25.1)	17.5 (13.8, 21.5)
Progression-free survival		
Median (95% CI), months	**4.5 (4.2, 5.3)**	**3.0 (2.8, 3.9)**
Hazard ratio (95% CI)	0.762 (0.677, 0.859)	
Progression-free survival at 3 months: % (95% CI)	64.7 (60.7, 68.3)	50.1 (46.1, 54.0)
Progression-free survival at 6 months: % (95% CI)	35.9 (32.0, 39.8)	29.1 (25.5, 32.7)
Progression-free survival at 9 months: % (95% CI)	21.8 (18.5, 25.3)	16.6 (13.8, 19.7)
Progression-free survival at 12 months: % (95% CI)	12.2 (9.6, 15.1)	7.1 (5.2, 9.5)
Objective response (CR+PR) rate	**22.9%**	**13.6%**
Response rate (95% CI)	(19.7%, 26.4%)	(11.0%, 16.5%)
	P<0.001	

Disease control (CR+PR+SD) rate	64.0%	52.6%
Disease control rate (95% CI)	(60.1%, 67.8%)	(48.6%, 56.6%)
	P<0.001	
95% CI, 95% confidence interval Source: company submission page 59 and 61 (Tables 21 and 22)		

Figure 2. Overall survival and progression-free survival results in REVEL (company submission page 60 and 61)

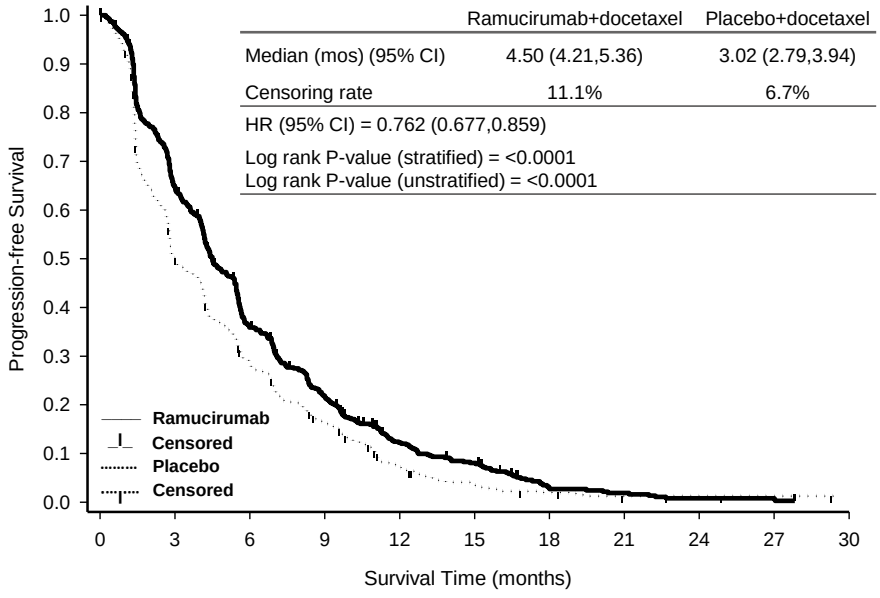
A. Overall survival



Patients at Risk

Ramucirumab+docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

B. Progression-free survival



Patients at Risk

Ramucirumab +docetaxel	628	383	204	120	59	38	11	7	3	3	0
Placebo + docetaxel	625	301	172	95	37	17	9	4	3	2	0

4.5 The effect of ramucirumab plus docetaxel on quality of life was measured, in the REVEL trial (where there was a validated translation), using the Lung Cancer Symptom Scale (LCSS) and the EQ-5D. During the clarification stage the company was unable to provide information stating which regions had a valid EQ-5D translation but confirmed that 'translation not available' data were collected but that this was not a common response. Time to deterioration in ECOG performance status and for the LCSS items was similar between the two treatment groups. Also, there were minimal changes from baseline in EQ-5D index or Visual Analogue Scale (VAS) in either group. Scores in both arms decreased at the end-of-treatment assessment. For further information on EQ-5D see section 5.8.

Subgroup analyses

4.6 The company stated that the REVEL trial was not powered for subgroup analyses. However, there were 13 pre-specified subgroups; 4 stratification factors (ECOG, sex, prior maintenance therapy and geographic region) and 9 other pre-specified factors (smoking history, histology, best response to platinum chemotherapy, prior taxane therapy, prior bevacizumab therapy, EGFR mutation status, age, race, time since prior therapy). There were also 3 additional subgroups not pre-specified in the statistical analysis plan (best response to platinum-based therapy, liver metastases and central nervous system metastases; see Figures 10 and 11 in the company submission). An improvement in overall survival and progression-free survival was consistently observed across most pre-specified subgroups. A consistent treatment effect was observed in patients regardless of histology (squamous or non-squamous).

ERG comments

4.7 The ERG considered the company's systematic review to be reasonable and that the searches were appropriate. However, the process of study selection was not described by the company and therefore the ERG could not comment on this. The ERG noted one secondary publication of health-related quality of life data from the REVEL trial but this was published after the company submission searches were performed. The ERG did not identify any ongoing studies.

4.8 The ERG considered that the REVEL trial was adequately powered to detect treatment differences between the two treatment groups. It also noted that final data were provided and that these included all randomised patients for the efficacy outcomes. The ERG also considered that the trial statistics were appropriate although noted that statistical comparisons of the EQ-5D data were not provided.

Network-meta analysis

The full population

4.9 The company conducted a network meta-analysis to provide relative treatment effect estimates for ramucirumab plus docetaxel compared with nintedanib plus docetaxel and erlotinib using data from 22 trials. The company noted that the network was restricted to studies that provided patient characteristics for the relevant treatment-covariate interaction and therefore contained fewer studies in some parts compared with previously published network meta-analyses. Although the NICE scope included nivolumab and crizotinib as comparators, the company considered they were not relevant comparators (see Table 1).The company had originally presented analyses comparing ramucirumab plus docetaxel with erlotinib for the EGFR-TK negative sub-population. However, given the recommendations in the recently published technology appraisal guidance for erlotinib (TA374) the company stated that these analyses were no longer valid. The company did not present any comparison with erlotinib for the EGFR-TK positive sub-population because it is expected that these people would receive a targeted therapy prior to being considered for ramucirumab and those who have progressed on erlotinib would not be retreated with erlotinib. Therefore only the comparison with nintedanib plus docetaxel (LUME-Lung1 trial, see Table 5) is discussed in more detail from here on.

Table 5. Details of the LUME-Lung1 trial for nintedanib plus docetaxel compared with docetaxel.

Trial design	Patient population	Treatment	Doses	Trial outcomes
Randomised controlled trial including: China, South Korea, India,	• Histologically or cytologically confirmed stage IIIB/IV recurrent NSCLC.	Nintedanib plus docetaxel (n = 655). Placebo plus	Docetaxel 75 mg/m^2 by IV infusion on day 1 plus nintedanib 200 mg twice	Primary: progression-free survival • Secondary: overall

South Africa, and 23 European countries N = 1,314	• Age ≥ 18 years, having received 1 previous chemotherapy. • ECOG PS 0-1. • ≥ 1 target lesion measurable according to RECIST.	docetaxel (n = 659)	daily orally on day 2-21, every 3 weeks. Docetaxel 75 mg/m^2 by IV infusion on day 1 plus placebo on days 2-21, every 3 weeks.	survival • Toxicity • Health-relate quality of life

4.10 The network meta-analysis looked specifically at overall survival, progression-free survival and objective response rate. Hazard ratios for overall survival and progression-free survival were calculated using a Bayesian network-meta analysis and assuming proportional hazards. Both fixed and random effects models were applied. When developing hazard ratios for the comparison with nintedanib plus docetaxel (for both the non-squamous and squamous populations) the company noted that in the comparison for the squamous population, the proportional hazards assumptions were violated. However, the company considered this was not an issue because nintedanib plus docetaxel is only recommended by NICE for the non-squamous population (adenocarcinoma).

4.11 The company carried out a set of heterogeneity and inconsistency analyses for each endpoint; overall survival, progression-free survival and objective response rate, providing evidence of treatment-by-covariate interactions. The company considered that this made subgrouping the data in the network inappropriate and it was not possible to fit the standard meta-regression models recommended by NICE. The company instead conducted analyses that allowed different interactions between treatment and population type using a hierarchical exchangeable structure, which allowed nintedanib to vary by histology (non-squamous and adenocarcinoma histologies were presumed to be equal). In the REVEL trial 79.5% of non-squamous patients had confirmed adenocarcinoma histology.

4.12 When calculating overall survival and progression-free survival for ramucirumab plus docetaxel compared with nintedanib plus docetaxel using the hierarchical exchangeable model, the fixed-effect model gave a similar fit compared with the random-effects model, showing no significant difference between these analyses. The fixed-effect model was chosen by the company. The results are shown in Table 6.

Table 6. Overall survival and progression-free survival network-meta analyses hazard ratios; unadjusted, fixed effects model (taken from company submission pages 88 and 91)

Intervention	Comparator			
	Overall survival		Progression-free survival	
	Docetaxel (total population)	Nintedanib plus docetaxel (non-squamous)	Docetaxel (total population)	Nintedanib plus docetaxel (non-squamous)
Nintedanib plus docetaxel (non-squamous)	0.85 (0.71, 1.00)		0.77 (0.62, 0.95)	
Ramucirumab plus docetaxel (all populations)	0.86 (0.75, 0.98)	1.01 (0.82, 1.25)	0.76 (0.68, 0.86)	0.99 (0.78, 1.26)

4.13 When calculating the objective response rate using the hierarchical exchangeable model, the fixed-effect model again gave a similar fit compared with the random-effects model. The fixed-effects model was chosen by the company. The objective response rate pairwise network meta-analysis is shown in Table 7.

Table 7. Objective response rate network-meta analyses differences in probit scores; unadjusted, fixed effects model (taken from company submission page 93)

Intervention	Comparator	
	Docetaxel (total population)	Nintedanib plus docetaxel (non-squamous)
Nintedanib plus docetaxel (non-squamous)	0.35 (0.17, 0.53)	
Ramucirumab plus docetaxel	0.41 (0.27, 0.54)	0.05 (-0.18, 0.28)

The subgroup – adenocarcinoma

4.14 Given that nintedanib plus docetaxel is only recommended by NICE for people with adenocarcinoma, the company presented an additional indirect comparison for this population using the subgroup results from the REVEL trial. The results of this subgroup analysis were used to validate the results of the network meta-analysis presented in Table 6. These results were not used in the company's model for the non-squamous subgroup, although the company stated that the results supported the conclusions regarding the relative efficacy of ramucirumab plus docetaxel compared with nintedanib plus docetaxel.

ERG comments

4.15 The ERG had a number of concerns regarding the network-meta analysis methodology, reporting and outcomes including the exclusion of some studies from the company's network-meta analysis and the minimal reporting of some variables from some of the studies.

4.16 The ERG considered that the use of a Bayesian network-meta analysis and frequentist models appeared appropriate but the company provided limited details for some of the analyses. The ERG did however consider the method used to determine the presence of statistical heterogeneity as adequate.

4.17 The ERG noted that the company only reported fixed-effect analyses in its main report because the company considered that the hierarchical model had taken into account any heterogeneity and that random-effects models were therefore not required. However the company did provide the fixed- and random-effects model during clarification and the ERG considered that this data did not highlight any significant differences.

4.18 The ERG was concerned that the assumption of similarity of treatment effects between the studies was not stated or justified by the company.

However, the ERG considered that the company provided appropriate justification for using hierarchical models including treatment-by-covariate interactions and sparse evidence in the network-meta analysis. However, the ERG was concerned that issues of sparse evidence may also result in non-convergence of models, particularly random-effects models. The ERG noted that this was not considered in the company submission because the company suggested that comparable models were estimated using both fixed- and random-effects models.

Adverse effects of treatment

4.19 The company presented detailed adverse event data from the REVEL trial in section 4.12 of its submission. The company reported that the percentage of patients who experienced at least one treatment emergent adverse event of any grade was similar between treatment arms: 97.8% in the ramucirumab plus docetaxel group compared with 96.1% in the docetaxel alone group. A higher percentage of patients in the ramucirumab plus docetaxel group than the docetaxel alone group experienced Grade 3 or greater treatment emergent adverse events (78.9% vs 71.8% respectively). Fatigue, neutropenia and febrile neutropenia were the grade 3 or greater treatment emergent adverse event experienced by more than 10% of the patients. The number of deaths that occurred while on treatment and up to 30 days after the last dose occurred at a similar frequency in both treatment arms (8.5% in the ramucirumab plus docetaxel group compared with 9.4% in the docetaxel alone group).

4.20 Due to the anti-angiogenic mechanism of action of ramucirumab, a number of adverse events were considered to be of special interest including hypertension, bleeding/haemorrhagic events, venous thromboembolic events and gastrointestinal perforation (see pages 103 and 104 of company submission for further information).

ERG comments

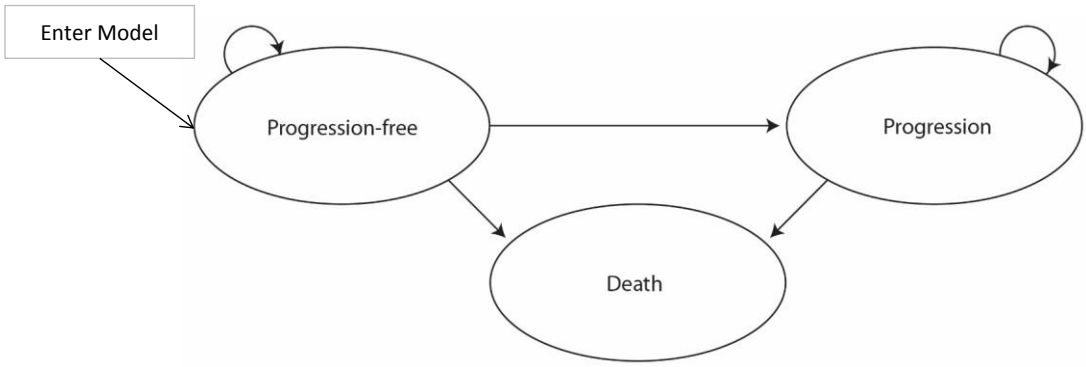
4.21 The ERG noted an inconsistency in the numbers of deaths from the REVEL trial reported, with the number for the ramucirumab plus docetaxel group being 31 (4.9%) but the treatment-emergent adverse events reported being 34 (5.4%; page 101 of company submission). The company did not explain the reason for this difference.

5 Cost-effectiveness evidence

Model structure

5.1 The company presented a de novo, partitioned survival economic model based on 3 health states; pre-progression, post-progression and death. The cycle length was set to 21 days and a 15 year time horizon was used. A half-cycle correction was also applied. The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

Figure 3. Model structure (taken from company model structure tab)



ERG comments

5.2 The ERG considered that the model was well constructed and transparent. It noted that the model should have incorporated a discount rate of 3.5% but due to modelling error the rate was 10.9%. It also noted that half cycle correction was not applied to the direct drug costs or administration for ramucirumab and docetaxel but was applied to the direct drug costs of nintedanib.

Model details

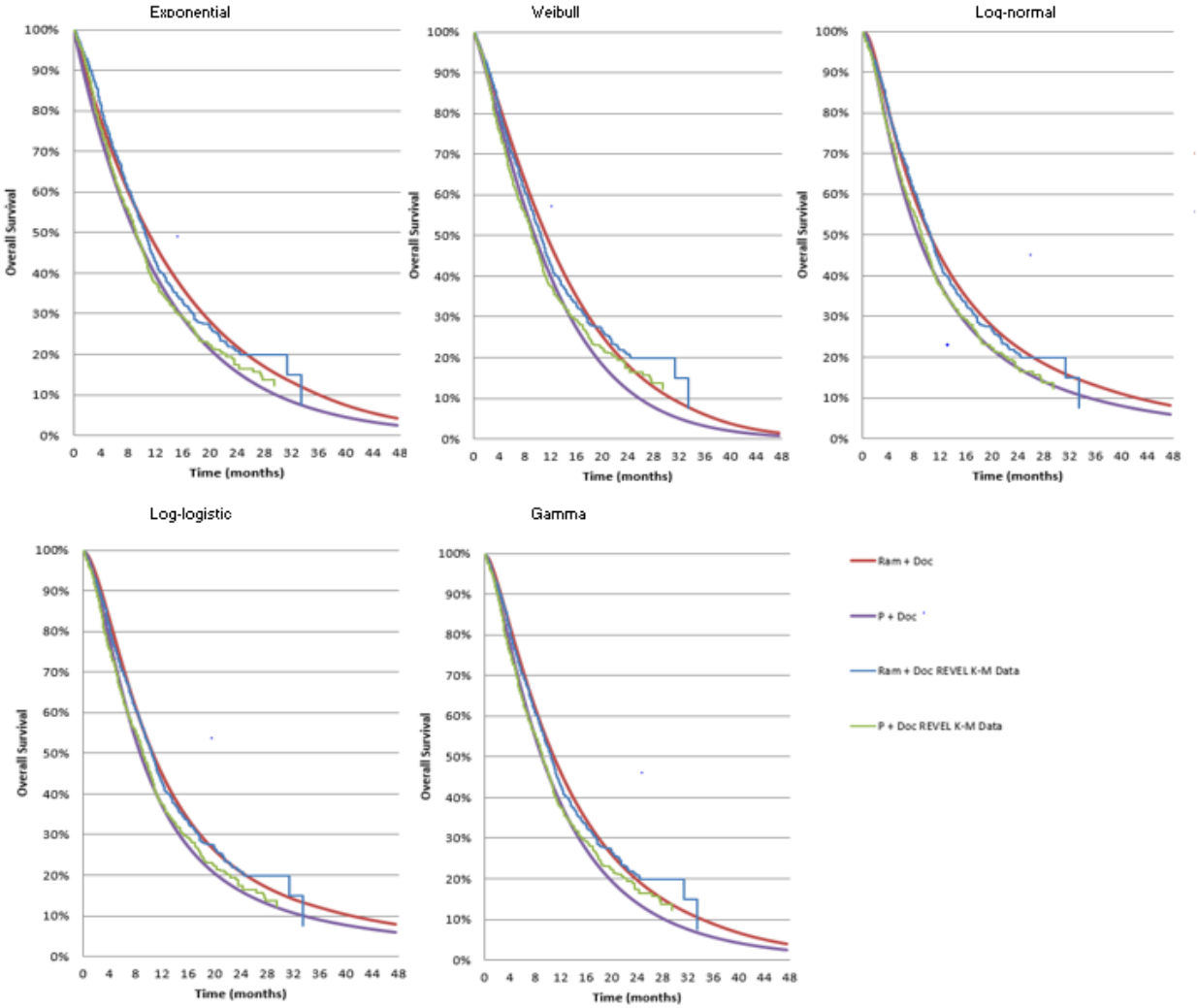
5.3 All patients entered the model in the pre-progression state and were allocated to treatment with ramucirumab plus docetaxel or one of the relevant comparators (docetaxel alone or nintedanib plus docetaxel). Patients remained in this state until disease progression or death. The number of ramucirumab and docetaxel administrations was based upon the REVEL mean values, while the number of nintedanib administrations was based upon the inferred progression-free survival curve. In the post-progression state, post-platinum treatment was stopped and patients received either best supportive care (70% of people) or post-progression treatments (25% receive vinorelbine and carboplatin; 5% erlotinib). This state captured the decreased health-related quality of life associated with progressed disease. The number of people in the death state was based on all-cause mortality from the REVEL trial, coupled with a hazard ratio for nintedanib plus docetaxel.

5.4 Five parametric models were used to consider goodness of fit to the overall survival and progression-free survival data from the REVEL trial: exponential, weibull, lognormal, log-logistic and gamma. The curves were fitted to both the adjusted (taking into account the covariates; see section 4.12) and unadjusted Kaplan-Meier data. For both overall survival and progression-free survival, the company considered that the multivariate (adjusted) models provided a better fit and a slightly more conservative assumption of survival compared with the unadjusted models. Therefore the multivariate models were used in the base case. In the company's model, time in the 'pre-progression' state was estimated directly from the progression-free survival curve and time in the post-progression state was the difference between the overall survival and progression-free survival curves.

5.5 The overall survival Kaplan-Meier curve required extrapolation because not all the patients had died at the end of the REVEL trial. On inspecting the overall survival curve from the REVEL trial, the company considered

that the proportional hazards assumption held and therefore a single parametric curve was fitted to the entire dataset with treatment included as a covariate. The company selected a log-logistic distribution to extrapolate overall survival in its base case (see Figure 4).

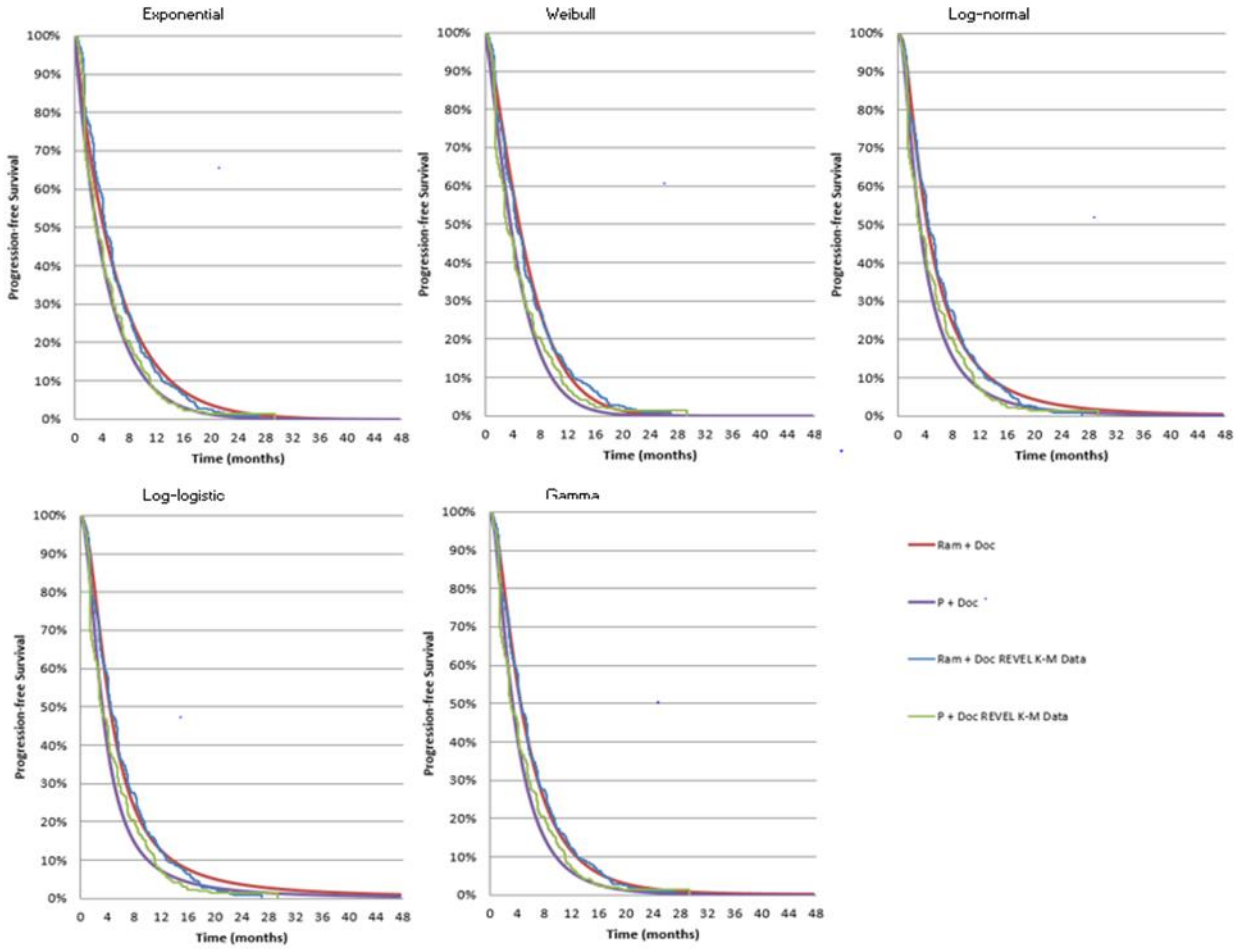
Figure 4. Overall survival Kaplan–Meier and multivariate (adjusted) parametric survival curves (taken from company submission page 129)



5.6 When considering the extrapolation of the progression-free survival Kaplan-Meier curve from the REVEL trial, the company noted that the proportional hazards assumption was violated. The company therefore generated separate parametric curves for ramucirumab plus docetaxel

and docetaxel alone. The company considered that the generalised gamma provided the best fit across both treatment groups.

Figure 5. Progression-free survival Kaplan–Meier and multivariate (adjusted) parametric survival curves (taken from company submission page 135)



5.7 For comparing ramucirumab plus docetaxel with nintedanib plus docetaxel, the company applied its network-meta analysis hazard ratio (see Table 6) to the docetaxel alone curves from REVEL to get overall survival for nintedanib plus docetaxel, and used their multivariate loglogistic model of overall survival for ramucirumab plus docetaxel overall survival. Doing this ensures proportional hazards between docetaxel alone and nintedanib plus docetaxel, but violates proportional hazards between docetaxel alone and ramucirumab plus docetaxel and between nintedanib plus docetaxel and ramucirumab plus docetaxel.

5.8 Adverse events that were grade 3 or higher and occurred in at least 5% of patients in either group in the REVEL trial and were included in the model (see section 4.19). The model also included 2 adverse events (nausea/vomiting and rash [assumed to be reported as "infusion-related reaction" in the REVEL trial]) taken from an additional study collecting utilities associated with metastatic non-small-cell lung cancer and key adverse events resulting from systemic anticancer treatment (Nafees et al., 2008). The model considered that any adverse events occurred once and the company explained that this assumption was based on clinical expert input. The rate of adverse events were varied in the company's sensitivity analyses by varying the total cost to treat adverse events rather than changing individual adverse event rates (see section 5.14). To be able to compare the adverse events of ramucirumab plus docetaxel with nintedanib plus docetaxel the company identified all trials that were considered for the NMA for neutropenia for each indirect comparator, noted the incidence of adverse events that were grade 3 or higher, pooled the incidence rate and from these identified all grade 3 or higher adverse events that occurred in at least 5% of patients.

5.9 Health-related quality of life was incorporated into the model by applying utility scores to each health state. The utility scores were derived from EQ-5D utility index data collected in the REVEL trial (see section 4.5). The company applied mean post-baseline EQ-5D scores for progression-free (0.706) and progressed disease (0.599). The modelled disutilities associated with treatment-specific adverse events were sourced from the literature (Nafees et al, 2008). The company also performed a scenario analysis incorporating alternative utility values from the Chouaid study 2013, as were incorporated in the nintedanib appraisal (TA347). The results of the Chouaid study provided a utility value of 0.74 for progression-free survival and 0.46 for progressed disease. The company also performed another scenario which included a QALY decrease applied to the last cycle before death to reflect the predicted sudden decline in health-related quality of life just before death (see Table 12).

5.10 The model incorporated costs associated with each health state. For consistency the company took these costs from the nintedanib appraisal (TA347). Resources were costed using the most recent cost year available and taken from NHS reference costs (2013/14), PSSRU unit costs of health and social care, or inflated from TA347 where required.

5.11 In the model the cost of ramucirumab and the comparators were comprised of the premedication cost, drug acquisition cost and drug administration cost. In the model all patients being treated were assumed to have received premedication; £35.54 for ramucirumab plus docetaxel and £32.11 for nintedanib plus docetaxel or docetaxel alone. The costs of the comparator drugs themselves were estimated separately from time spent in the pre-progression health state (for further information see section 5.5 of company submission). For ramucirumab the average total dose required was based on the recommended dose of 10 mg/kg and weighted 33.4% for females (average weight 67.17 kg) to 66.6% for male (average weight 76.79 kg). For docetaxel the average total dose required was based on the recommended dose of 75 mg/m^2 and weighted 33.4% for females (average body surface area of 1.72 m^2) to 66.6% for male (average body surface area 1.91 m^2). For oral nintedanib the percentage of medication (95.7%) taken during the progression-free survival period was used instead of treatment duration or dose intensity. All comparators were presumed to be administered on an outpatient basis. The average number of infusions and treatment duration are shown in Table 8 and Table 9. The model also includes adverse events costs and other costs associated with the management of NSCLC, including the cost of post-progression treatments.

Table 8. Number of Infusions Received

Regimen	Mean	SE
Ram + Doc (REVEL - overall)		
Ramucirumab	6.1	0.211
Docetaxel	5.5	0.178
P + Doc (REVEL - overall)	4.9	0.168

Ram + Doc (REVEL - non-squamous)		
Ramucirumab	6.3	0.249
Docetaxel	5.6	0.210
P + Doc (REVEL - non-squamous)	5.1	0.204
Nin + Doc		
Nintedanib	n/a	n/a
Docetaxel	4.785	0.180

Table 9. Treatment Duration

Regimen	Mean	SE
Ram + Doc (REVEL - overall)	19.7	0.675
P + Doc (REVEL - overall)	16.9	0.642
Ram + Doc (REVEL - non-squamous)	20.0	0.785
P + Doc (REVEL- non-squamous)	17.6	0.757
Nin + Doc	17.088	0.783

Company's base-case results and sensitivity analysis

In the base case, for the full population ramucirumab plus docetaxel was associated with associated with additional costs of £24,288 and 0.125 additional quality-adjusted life years adjusted life years (QALYs), compared with docetaxel, giving an incremental cost incremental cost effectiveness ratio (ICER) of £194,919 per QALY gained when compared when compared with docetaxel alone (see

5.12 Table 10). For the non-squamous population, when comparing ramucirumab plus docetaxel with nintedanib plus docetaxel the incremental cost effectiveness ratio (ICER) was £1,106,497 per QALY gained (including an additional cost of £11,724 and additional QALYs of 0.011; see Table 11).

Table 10. Base-case results ramucirumab plus docetaxel compared docetaxel in the ITT REVEL population (full population; taken from company submission Table 79, page 163)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Docetaxel	£10,995	0.692	-	-	-
Ramucirumab + docetaxel	£35,283	0.816	£24,288	0.125	£194,919
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio					

Table 11. Base-case results ramucirumab plus docetaxel compared with nintedanib plus docetaxel in the non-squamous subgroup (taken from company submission Table 81, page 163)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs baseline (£/QALY)	ICER RAM+ DOC vs NIN+ DOC
Docetaxel	£11,534	0.724	-	-	-	
Nintedanib + docetaxel	£25,064	0.852	£13531	0.128	£105,621	
Ramucirumab + docetaxel	£36,789	0.863	£11,724	0.011	£182,082	£1,106,497
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio						

5.13 The company presented both deterministic and probabilistic sensitivity analyses. The deterministic sensitivity analyses showed that when comparing ramucirumab plus docetaxel with docetaxel alone the model results were most sensitive to the cost of ramucirumab, the discount rates for health outcomes, the number of ramucirumab infusions and the discount rates for costs. For the comparison with nintedanib plus docetaxel in the non-squamous subgroup the most influential parameters were the hazard ratios for progression-free survival and overall survival, followed by the price of ramucirumab and nintedanib.

Company scenarios

5.14 The company presented a series of scenario analyses to explore the effect of assumptions about survival modelling. When changing key

parameters such as the time horizon, choice of distribution used to fit the survival curves and the assumptions used to extrapolate the treatment effect beyond the trial data, the greatest effect on the ICER for the comparison of ramucirumab plus docetaxel with docetaxel alone, for the full population, was when the unadjusted survival data were used (see Table 12). For the comparison of ramucirumab plus docetaxel with nintedanib plus docetaxel, in the non-squamous subgroup, changing the survival curve to a generalised gamma curve had a greater effect on the ICER than for the full population or the other parameters changed in the scenarios (see Table 13).

Table 12 Scenario analyses for the full population (taken from company submission Table 90, page 178)

Scenario	Incremental Costs (Discounted)	Incremental QALYs (Discounted)	ICER (Discounted)
Base case	£24,288	0.125	£194,919
1. Unadjusted parametric survival functions for OS and PFS	£24,140	0.105	£230,272
2: Generalized gamma for OS	£24,066	0.113	£213,803
3. Time horizon 10 years	£24,236	0.122	£198,997
4. Time horizon lifetime (20 years)	£24,306	0.126	£193,580
5. Treatment effect for OS applied indefinitely	£24,367	0.129	£189,068
6. No treatment effect upon end of trial follow-up	£24,275	0.124	£195,909
7. Published health state utilities (Chouaid et al., 2013)	£24,288	0.118	£206,175
8. QALY penalty applied to last cycle before death	£24,288	0.125	£194,617
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio			

Table 13. Scenario analyses for the non-squamous subgroup. Comparison of ramucirumab plus docetaxel with nintedanib plus docetaxel (taken from company submission Table 92, page 180)

Scenario	Incremental Life-Years (Undiscounted)	Incremental Costs (Discounted)	Incremental QALYs (Discounted)	ICER (Cost/QALY Gained, Discounted)
Base case	0.020	£11,724	0.011	£1,106,497
1. Unadjusted parametric survival functions for OS and PFS	NA	NA	NA	NA
2: Generalized gamma for OS	0.067	£12,128	0.032	£373,633
3. Time horizon 10 years	0.016	£11,735	0.011	£1,049,964
4. Time horizon lifetime (20 years)	0.011	£11,721	0.010	£1,127,055
5. Treatment effect for OS applied indefinitely	-0.049	£11,439	-0.005	Dominated
6. No treatment effect upon end of trial follow-up	0.019	£11,765	0.013	£918,030
7. Published health state utilities (Chouaid et al., 2013)	0.013	£11,724	0.009	£1,246,442
8. QALY penalty applied to last cycle before death	NA	NA	NA	NA
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio				

5.15 The company validated the extrapolation of the overall survival data against a recent UK model and compared the non-squamous subgroup with the company and ERG base cases in the nintedanib appraisal (TA347). The company also validated the model's overall survival results against real world data for NSCLC patients in the UK. The company concluded that the results for ramucirumab were valid. It was unable to validate the data using that collected by the Royal College of Physicians (RCP) as part of the National Lung Cancer Audit (LUCADA) because the data were not available by stage of disease or line of therapy. The

company compared the summary data from LUCADA (2010) but concluded that because of limitations in the LUCADA data a firm conclusion from the comparison could not be made. However the company concluded that the model showed good cross validity with the nintedanib appraisal (TA347).

ERG comments

5.16 The ERG noted that the company had carried out a comparison of ramucirumab plus docetaxel with nintedanib plus docetaxel using the non-squamous population in the REVEL trial rather than a population of people with adenocarcinoma, as approved by NICE (TA347). However when the ERG compared the overall survival curves for the non-squamous and adenocarcinoma groups from the REVEL trial they appeared fairly similar (see Figure 28 in ERG report). The ERG observed a similar outcome for the progression-free survival data and therefore considered that this inconsistency in the population for the comparison would little have impact on the cost-effectiveness results.

5.17 The ERG rebuilt the company's deterministic model using the company's assumptions and the results generated were in agreement with the company. The ERG noted that although the loglogistic model provided a good fit for the ramucirumab plus docetaxel group (see Figure 4) the fit for the docetaxel alone group was poorer. From approximately 10 months onwards the docetaxel alone loglogistic curve underestimated the observed survival shown in the Kaplan-Meier plot. This underestimation would have continued in the extrapolation (and been included in the company's model) with the ERG considering that approximately 44% of the gain from ramucirumab over docetaxel being gained after the observed data. The ERG considered that in using this method, any comparator of ramucirumab plus docetaxel would have reduced efficacy and for this reason models should be independently fitted to the data for the 2 groups, ramucirumab plus docetaxel and docetaxel alone.

5.18 The ERG was concerned about the use of the NMA hazard ratios to model overall survival and progression-free survival, for the following reasons:

- this imposes proportional hazards between compared treatments and in the opinion of the ERG there is no theoretical reason to expect proportional hazards to hold for two treatments that differ in their mode of action
- it forces a loglogistic curve shape onto the comparator which is unlikely to reflect that observed in studies for that treatment
- it attaches the generated curve on the time axis according to the position of the REVEL docetaxel survival curve
- if the loglogistic model for the REVEL docetaxel arm is an overestimate or underestimate of survival then the comparators will be the same

The ERG considered that the resulting survival curves may therefore not represent the situation fully.

5.19 The ERG noted that the company considered its loglogistic extrapolation as valid by comparing the estimates of life years gained for the non-squamous population with those modelled in the nintedanib appraisal. However, the ERG was unsure how this supported the company's approach because in the nintedanib appraisal the company used direct Kaplan-Meier estimates from the trials and then applied mortality risks at a certain point rather than applying proportional hazards loglogistic modelling. Given that single trials were used to derive survival data for ramucirumab and nintedanib, the ERG considered it important to report the observed evidence from the clinical trials used in the network-meta analysis rather than replacing results with the uncertainty of the NMA-fitted curves. The ERG considered it difficult to judge the extent to which this was an issue in the company submission due to lack of information and therefore attempted to provide more detailed survival information by

estimating life years gained and progression-free life months gained (see sections 5.25 onwards)

5.20 The ERG noted that the company had taken EQ-5D values from the Chouaid et al., (2013) study in a scenario analysis but that the company had misreported the value of the second-line progressive disease (0.59) and instead reported and used the third/fourth-line value of 0.46. The ERG considered that perhaps the progressed disease value of 0.46 was too low and that a value between this and 0.59 would have been more appropriate.

5.21 The ERG also noted that the company's model assumed that quality of life was the same in each group while on treatment except for small allowances in different side effects. It also noted that the company assumed a constant quality of life for those who had progressed, based on the REVEL trial end of treatment EQ-5D values. However, the company's systematic review supported an assumption that quality of life decreased during subsequent lines of treatment and the ERG considered that applying Chouaid et al., (see section 5.20) quality of life decrements for both initial and subsequent lines of therapy may have been sensible in a sensitivity analysis if not in the base case.

5.22 The ERG considered the use of 'treatment utilisation' percentages in calculating maximum patient weights, estimating patient body surface areas and the inclusion of the number of ramucirumab vials associated with this to be an unusual method. Data supplied at clarification caused the ERG to conclude that it was not appropriate to apply the company estimated drug utilisation percentage for ramucirumab.

5.23 The ERG considered the exclusion of the cost of subsequent cycles of chemotherapy (SB15Z at £314), in the company's model, to be acceptable because applying the same cost regardless of the complexity may not also reflect the situation. However for completeness, the ERG included this in a scenario analysis.

ERG model revisions and exploratory analyses

5.24 The ERG revised the company model to:

- Correct the errors in discounting
- Apply the same patient characteristics for the PFS curves as for the OS curves
- Remove half cycle correction from nintedanib drug costs
- Apply a 100% drug utilisation percentage for ramucirumab
- Exclude the nintedanib drug administration costs

Results of the ERG's revisions to the company's base case are presented in Table 14. For the non-squamous subgroup, the ERG also presented results taking into account the confidential patient access scheme (PAS) discount for nintedanib. The ERG calculated that due to the nintedanib PAS the direct drug costs of ramucirumab are around [redacted] higher than those of nintedanib.

Table 14 ERG revisions to the company's base case (taken from Tables 5 and 6, ERG's confidential appendix)

	RAM+DOC vs DOC		RAM+DOC vs NIN+DOC	
	Δ Cost	**ICER**	**Δ Cost**	**ICER**
ERG's Base case (all patients without PAS)	£26,161	£175k	-	-
ERG's Base case (non-squamous without nintedanib PAS)	£27,268	£163k	£12,899	£1.6mn
ERG's Base case (non-squamous with nintedanib PAS)	£[redacted]	£[redacted]	£[redacted]	£[redacted]

5.25 Given the ERG's concerns about the company's approach to modelling overall survival, the ERG estimated life year gained and progression-free survival months gained using data from the relevant trials. For the trials not containing ramucirumab the ERG digitised the published Kaplan-Meier curves and reconstructed individual patient level data. To be consistent with the company's use of loglogistic models, the ERG then fitted separate loglogistic models for each group individually for overall survival and estimated mean life years gained over 15 years. The life years gained data were estimated from the area under the Kaplan-Meier curve (see Table 15) and over a 15 year time horizon using separate unadjusted loglogistic models (Table 16). Based on these results, the ERG considered that the loglogistic extrapolations provided a gain between 31% and 36% for the REVEL trial populations, more than 50% for the squamous population (Brahmer et al 2015) and 33% and 23% respectively for the adenocarcinoma nintedanib and docetaxel populations.

Table 15. ERG's estimated life years gained (overall survival) based on area under the curve of the reconstructed Kaplan-Meier plots (taken from table 22, page 66 of ERG report).

STUDY	Population	Intervention LYG	Control LYG	Intervention Gain LYG (months)	Observation Period Φ
REVEL	Non squamous	RAM 1.22	DOC 1.07	0.154 (1.85)	32.5
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab 0.94	DOC 0.66	0.281 (3.37)	22
REVEL	Squamous	RAM 0.96	DOC 0.86	0.100 (1.20)	32.4
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib 1.28	DOC 1.11	0.166 (1.99)	36
REVEL	Adenocarcinoma	RAM 1.25	DOC 1.09	0.158 (1.90)	32.5
REVEL	All	RAM 1.15	DOC1.03	0.121 (1.45)	32.5
Φ months, the KM observation period used was kept the same for both arms. DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab					

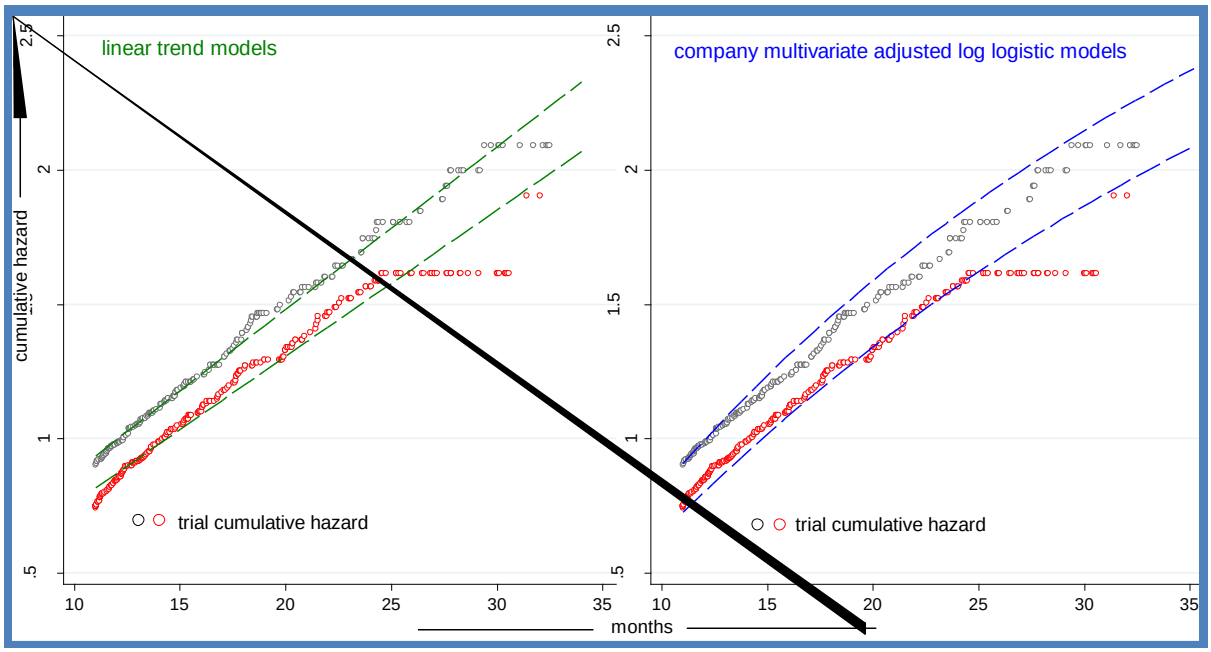
Table 16. ERG's estimated life years gained (overall survival) over a 15 year time horizon estimated using separate unadjusted loglogistic models for each group (taken table 23, page 67 of ERG report).

STUDY	Population	Intervention LYG	Control LYG	Intervention Gain LYG (months)
REVEL	Non squamous	RAM 1.805	DOC 1.589	0.216 (2.59)
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab 2.14	DOC 1.36	0.780 (9.36)
REVEL§	Squamous	RAM 1.371	DOC 1.205	0.166 (1.99)
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib 1.891	DOC 1.436	0.455 (5.46)
REVEL	Adenocarcinoma	RAM 1.947	DOC 1.649	0.298 (3.58)
REVEL*	All	RAM 1.67	DOC 1.48	0.186 (2.23)

§ Data from CS Table 93 for the REVEL non-squamous population indicates 1.666 and 1.390 LYG for nintedanib and docetaxel groups respectively providing an intervention gain of 0.276 LY. * Equivalent data from CS Table 45 using multivariate adjusted model intervention provides LYG estimates of 1.574 and 1.319 for Ramu and Doce arms respectively with an intervention gain of 0.255 LY.
DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab

5.26 The ERG noted that when observing cumulative hazard plots for the full trial population, there was a linear trend from 11 months onwards for each group, suggesting that from this time onwards a constant hazard fitted the data (see Figure 6). The ERG therefore considered that the linear trend model was superior to the loglogistic model if proportional hazards were to be used. It noted that when survival was calculated using area under the curve, from 0 to 13 months and the remainder taken from the linear trend model area under the curve, from 13 months until 15 years, the ramucirumab plus docetaxel group showed 16.5 months survival and the docetaxel alone group showed 14.3 months survival. This indicated that ramucirumab plus docetaxel provided an extra 2.2 months survival. The ERG considered that this reduction in survival compared to the company's 3.06 months gain using the multivariate loglogistic model was due to less accrual of survival benefit beyond the observed trial data for ramucirumab.

Figure 6. ERG's linear trend model and company's adjusted loglogistic model (taken from Figure 6, page 72 of ERG report).



5.27 When considering the non-squamous population in the REVEL trial the ERG noted that the linear trend model, preferred by the ERG, delivered an estimated 3.9 months mean survival gain compared with 3.6 months from the adjusted loglogistic model. Both of these models suggested benefit beyond that observed in the trial data (see Figure 9, page 74 of ERG report).

5.28 The ERG noted that for the squamous population in the REVEL trial the adjusted loglogistic model underestimated the observed cumulative hazard from approximately 10 months for ramucirumab plus docetaxel and from approximately 15 months for docetaxel alone. The ERG's linear trends calculating cumulative hazards were less clear. The ERG fitted a linear trend from 14 to 24 months and used this to model survival beyond the observed data. This delivered an estimated 1.5 months survival for the ramucirumab plus docetaxel group compared with 2.15 months from the company's model. The company did not provide an adjusted loglogistic model of overall survival for the adenocarcinoma population. When the ERG fitted loglogistic models separately to each treatment group, for the

adenocarcinoma population, an estimated mean survival of 3.6 months was calculated compared with 2.6 months using the linear trend model (based on the observed cumulative hazards between 13 and 25 months; see Figure 11 in ERG report). A summary of estimates in mean overall survival gain produced by the company and the ERG are shown in Table 17.

Table 17. Estimates of mean months gain in overall survival in the REVEL trial according to the patient group and the extrapolation model (taken from Table 27, page 76 of the ERG report).

Patient group	Treatment	MV ADJUSTED LL	Linear trend ¥	Separate LL to each arm ¥
All patients	RAM + DOC PBO + DOC	18.89 15.83 Net gain 3.06 Φ	16.6 14.4 Net gain 2.2	20.05 17.83 Net gain 2.23
Non-squamous	RAM + DOC PBO + DOC	20.148 16.68 Net gain 3.47 §	19.23 15.32 Net gain 3.91	21.66 19.07 Net gain 2.59
Squamous	RAM + DOC PBO + DOC	16.13 13.99 Net gain 2.15 §	12.28 11.19 Net gain 1.08	16.45 14.46 Net gain 1.99
Adenocarcinoma	RAM + DOC PBO + DOC	NM	18.95 16.40 Net gain 2.55	23.36 19.78 Net gain 3.58

¶ Results apply for a 15 year time horizon. DOC: docetaxel; LL: log logistic models; MV: multivariate; NM: no multivariate model was supplied in the CS; PBO: placebo; RAM: ramucirumab.
Φ From CS table 45. § not reported in the CS, estimates based on ERG analysis of Kaplan Meier data supplied by the company. ¥ estimates based on ERG analysis of Kaplan Meier data supplied by the company.

5.29 For progression-free survival, the ERG considered that on visual inspection the gamma models did not fit the REVEL trial observed data well. It noted that the model fit for the ramucirumab plus docetaxel group was better than the fit for the docetaxel alone group with the docetaxel alone group having lower accumulative progression-free survival than in the trial (see Figure 5). The ERG calculated progression-free life months gained for the different populations, using observed trial data, by

estimating area under the curve over a 15 year time horizon using separate unadjusted gamma models for each arm (see table 24 and 25, page 69 in ERG report). For all groups where data from the REVEL trial were available (all patients, non-squamous, squamous and adenocarcinoma) the company's multivariate adjusted gamma model delivered greater gain (18 to 22%) than estimates from the Kaplan-Meier data.

5.30 The ERG noted that because greater utility is attached to the progression-free state than other states in the company's economic model, the company's choice to use a gamma model rather than Kaplan-Meier data could influence the cost effectiveness of ramucirumab plus docetaxel compared with docetaxel alone. The ERG considered that on visual inspection the gamma models did not fit the REVEL trial observed data well, with the model fit for the ramucirumab plus docetaxel group being better than for the docetaxel group alone. Fitting a model to the docetaxel alone group produced a lower accumulative progression-free survival than resulted in the trial.

5.31 The ERG conducted a sensitivity analysis which applied the mean changes from baseline for progression-free survival to the pooled mean baseline value of 0.701 to yield progression-free survival quality of life estimates of 0.643 for ramucirumab plus docetaxel and 0.681 for docetaxel (see section 5.32).

5.32 The ERG performed 15 sensitivity analyses (see Table 18, Table 19 and Table 20):

- Applying the unadjusted rather than the multivariate (adjusted) overall survival and progression-free survival curves for the all patient modelling (see section 5.25).
- Applying the Weibull curves for overall survival.
- Not tapering the hazard ratio for overall survival.

- For the non-squamous modelling for the comparison with docetaxel alone applying the company ramucirumab + docetaxel all patient overall survival hazard ratio of 0.86 and all patients progression-free survival hazard ratio of 0.76 to the docetaxel overall survival and progression-free survival curves for consistency of approach with nintedanib plus docetaxel.
- Applying the ERG's linear trends overall survival curves, without tapering (section 5.28).
- Applying the ERG's linear trends overall survival curves, without tapering, and the Kaplan-Meier progression-free survival curves (section 5.29).
- Reinstating the ramucirumab drug utilisation percentage (section 5.10).
- Assuming that the number of ramucirumab administrations is conditioned by the progression-free survival curve with there being no maximum number of administrations while in progression-free survival.
- Reducing the drug utilisation of nintedanib by 2.7% to reflect the mean number of treatment durations reported in the company submission for the nintedanib STA.
- Assuming no Japanese or far eastern patients within the company adjusted curves.
- Assuming a progression-free survival quality of life of 0.643 for ramucirumab plus docetaxel and of 0.701 for docetaxel, while also removing the adverse event quality of life decrements (section 5.31).
- Assuming a progression-free survival quality of life of 0.74 and a post-progression survival quality of life of 0.46 taken from Chouaid et al (2013; section 5.20).
- Applying the SB15Z £314 cost for subsequent infusions regardless of regime (section 5.23).
- Including the administration costs for nintedanib
- Applying a £7,352 cost for febrile neutropenia
- Revising the costs of post-progression survival active treatment to apply three IV administrations per 3 week cycle.

Table 18. ERG univariate sensitivity analyses: Total population (taken from ERG report Table 78, page 142)

	RAM+DOC vs DOC		
	Δ Cost	**ΔQALY**	**ICER**
ERG's Base case revision (total population)	£26,161	0.150	£175k
Unadjusted curves	£26,024	0.127	£204k
Weibull OS	£25,573	0.118	£217k
No OS taper	£26,224	0.153	£171k
HRs for RAM+DOC	..	..	..
ERG LT OS	£26,124	0.148	£177k
ERG LT OS and KM PFS	£26,310	0.144	£182k
RAM drug util %	£24,961	0.150	£167k
No max RAM admins	£36,936	0.150	£247k
NIN drug util -2.7%	..	..	..
No Jap/Far East	£26,103	0.146	£178k
REVEL PFS QoL by arm	£26,161	0.120	£218k
Chouaid QoL	£26,161	0.139	£189k
Subs IV admin £314	£26,111	0.150	£175k
NIN admin cost	..	..	..
Feb neutr £7,352	£26,474	0.150	£177k
PPS weekly IV cost	£26,365	0.150	£176k

Table 19. ERG univariate sensitivity analyses <u>without</u> nintedanib PAS: (taken from ERG report Table 80, page 145)

	RAM+DOC vs DOC			RAM+DOC vs NIN+DOC		
	Δ Cost	**ΔQALY**	**ICER**	**Δ Cost**	**ΔQALY**	**ICER**
Base case	£27,268	0.167	£163k	£12,899	0.008	£1.6mn
Weibull OS	£26,808	0.142	£188k	£13,563	0.044	£307k
No OS taper	£27,350	0.172	£159k	£12,300	-0.024	Dom'td
HRs for RAM+DOC	..	..	..	£12,380	-0.020	Dom'td
ERG LT OS	£28,808	0.251	£114k	..	..	..
ERG LT OS and KM PFS	£29,012	0.248	£117k	..	..	..
RAM drug util %	£26,029	0.167	£156k	£11,660	0.008	£1.4mn
No max RAM admins	£38,743	0.167	£232k	£24,374	0.008	£3.0mn
NIN drug util -2.7%	..	..	..	£13,252	0.008	£1.6mn
No Jap/Far East	£27,210	0.164	£166k	£12,873	0.007	£1.9mn
REVEL PFS QoL by arm	£27,268	0.137	£199k	..	..	..
Chouaid QoL	£27,268	0.152	£179k	£12,899	0.007	£1.8mn
Subs IV admin £314	£27,219	0.167	£163k	£12,843	0.008	£1.6mn
NIN admin cost	..	..	..	£12,062	0.008	£1.4mn
Feb neutr £7,352	£27,580	0.167	£165k	£13,372	0.008	£1.6mn
PPS weekly IV cost	£27,527	0.167	£165k	£12,914	0.008	£1.6mn
Dom'td; dominated (less effective and more expensive than comparator)						

Table 20. ERG univariate sensitivity analyses with nintedanib PAS: Non-squamous (taken from Table 7, ERG's confidential appendix)

	RAM+DOC vs DOC			RAM+DOC vs NIN+DOC		
	Δ Cost	**ΔQALY**	**ICER**	**Δ Cost**	**ΔQALY**	**ICER**
Base case	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
Weibull OS	[redacted]	0.142	[redacted]	[redacted]	0.044	[redacted]
No OS taper	[redacted]	0.172	[redacted]	[redacted]	-0.024	[redacted]
HRs for RAM+DOC				[redacted]	-0.020	[redacted]
ERG LT OS	[redacted]	0.251	[redacted]	-	-	-
ERG LT OS and KM PFS	[redacted]	0.248	[redacted]	-	-	-
RAM drug util %	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
No max RAM admins	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
NIN drug util -2.7%				[redacted]	0.008	[redacted]
No Jap/Far East	[redacted]	0.164	[redacted]	[redacted]	0.007	[redacted]
REVEL PFS QoL by arm	[redacted]	0.137	[redacted]			
Chouaid QoL	[redacted]	0.152	[redacted]	[redacted]	0.007	[redacted]
Subs IV admin £314	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
NIN admin cost	-	-	-	[redacted]	0.008	[redacted]
Feb neutr £7,352	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
PPS weekly IV cost	[redacted]	0.167	[redacted]	[redacted]	0.008	[redacted]
Dom'td; dominated (less effective and more expensive than the comparator)						

Additional ERG scenario analyses (subgroups)

5.33 **Scenario 1 (squamous subgroup)**: The ERG used linear trends to model overall survival in the squamous subgroup and this resulted in an incremental cost of £24,528, incremental QALYs of 0.144 and an ICER of £167k per QALY gained for ramucirumab plus docetaxel compared to docetaxel alone, as compared with £177k per QALY gained for the total population. The slight improvement in the cost effectiveness estimate arises from the reduction in the net drug costs due to the reduced number of ramucirumab administrations being slightly greater than the fall in net

QALYs. Further applying the Kaplan-Meier progression-free survival curves resulted in an ICER of £172k per QALY gained as compared to £182k per QALY gained for the total population.

5.34 **Scenario 2 (adenocarcinoma subgroup):** The ERG also used linear trends to model overall survival in the adenocarcinoma subgroup and this resulted in an ICER for ramucirumab plus docetaxel compared to docetaxel of £128k per QALY gained, as compared with £114k per QALY gained for the non-squamous modelling. Further applying the Kaplan-Meier progression-free survival curves resulted in an ICER of £131k per QALY gained as compared to £117k per QALY gained for the non-squamous modelling.

Innovation

5.35 The company considered that ramucirumab is an innovative treatment for locally advanced or metastatic squamous NSCLC:

- There are limited second-line treatment options for patients with locally advanced or metastatic NSCLC that has progressed after platinum based chemotherapy. Recent new treatments have shown efficacy only in specific subgroups. Therefore there is a high unmet need to improve treatment options for NSCLC cancer patients that have progressed after platinum chemotherapy.

- The REVEL trial demonstrated a statistically significant and clinically meaningful improvement in overall survival, progression-free survival and objective response rate across all NSCLC histologies with manageable toxicities and no detrimental effect on quality of life. A clinical expert and a patient and carer organisation also noted ramucirumab to be innovative noting that it would appear to be a beneficial treatment for all NSCLC patients after platinum treatment regardless of histology.

6 End-of-life considerations

Table 21 End-of-life considerations (taken from page 110 of company submission)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Nationally, the median survival for lung cancer is 192 days, i.e. just under 7 months (Interquartile range is 58 – 315 days) and the three-month, one-year and five-year survival rates are 67%, 35% and 9% respectively
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 treatment	Full population (comparison of ramucirumab plus docetaxel with docetaxel): • Company's economic model shows mean overall survival of 3.06 months • ERG's model shows 2.20 months • REVEL trial shows 1.40 months Non-squamous subgroup: • Company's economic model shows mean overall survival ramucirumab+docetaxel compared with docetaxel of 3.47 months • ERG's model shows 2.59 months • REVEL trial shows 1.40 months
The treatment is licensed or otherwise indicated for small patient populations	Patient population with previously treated, advanced gastric cancer / gastro-oesophageal junction cancer who are eligible for treatment is estimated to be 657. Patient population with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy who are eligible for treatment is estimated to be 1,052 Total estimated eligible population across all indications = 1,709

7 Equality issues

7.1 No potential equalities issues have been identified.

8 Authors

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Company evidence submission

December 2015

File name	Version	Contains confidential information	Date
		No	

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List of Abbreviations

Abbreviation	Definition
ACD	Appraisal Consultation Document
AESI	Adverse Events of Special Interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic-Lymphoma-Kinase
ASBI	Average Symptom Burden Index
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BSA	Body Surface Area
BSC	Best Supportive Care
CADTH	Canadian Agency for Drugs and Technologies in Health
CCG	Clinical Commissioning Group
CDF	Cancer Drug Fund
CEA	Cost Effectiveness Analysis Registry from the Center for the Evaluation of Value and Risk in Health
CEAC	Cost Effectiveness Acceptability Curve
CNS	Central Nervous System
CRC	Colorectal Cancer
CRD	University of York Centre for Reviews and Dissemination
CrI	Credible Interval
CRUK	Cancer Research UK
DCR	Disease Control Rate
DOC	Docetaxel
ECOG	Eastern Cooperative Oncology Group
EED	National Health Service Economic Evaluations Database
EGFR	Epidermal Growth Factor Receptor
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ5D	EuroQol-5 Dimensions
ERG	Evidence Review Group
ERL	Erlotinib
ESMO	European Society for Medical Oncology
FDA	Federal Drug Administration
FOLFIRI	Irinotecan, Folinic Acid, and 5-Fluorouracil
GOJ	Gastro-Oesophageal Junction
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental Cost-Effectiveness Ratio

IDMC	Independent Data Monitoring Committee
IRR	Infusion-Related Reaction
LCSS	Lung Cancer Symptom Scale
LUCADA	National Lung Cancer Audit
LYG	Life-Years Gained
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index Medical Specialities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCLA	National Lung Cancer Audit
NICEDSU	National Institute for Health and Care Excellence Decision Support Unit
NIN	Nintedanib
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OSA	One-way Sensitivity Analysis
PDT	Post-Discontinuation Therapy
PPS	Post-Progression Survival
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCP	Royal College of Physicians
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	Rest Of The World
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SACT	Systemic Anti-Cancer Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDF	Survival Distribution Function
SMDM	Society for Medical Decision-Making
SoC	Standard of Care
SPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TSD	Technical Support Document
TTD	Time To Deterioration
VEGFR	Vascular Endothelial Growth Factor Receptors
WHO	World Health Organisation

1. Executive Summary

There are currently few agents routinely used in England for the second-line treatment of advanced non-small cell lung cancer post-platinum. Consequently there is a high unmet need to improve treatment options for non-small cell lung cancer (NSCLC) patients that have progressed after first-line chemotherapy. These patients currently have a very poor prognosis with median survival under seven months (1). Ramucirumab is a new treatment option that offers a clinically meaningful overall survival and progression-free survival advantage over existing therapy with manageable toxicity and maintained quality of life. Ramucirumab qualifies as an end of life treatment and can provide health-related benefits to a very sick population who have limited options.

Lung cancer is the second most common cancer diagnosed in the UK after breast cancer and it is the leading cause of cancer-related death in the UK, accounting for more than 20% of cancer deaths (2). The predominant form of lung cancer is NSCLC. Like most cancers, the prognosis of NSCLC depends considerably on the stage in which the cancer is diagnosed. Because symptoms of the disease are non-specific or absent at early stages of NSCLC, at least 65% of patients present with advanced-stage disease (i.e. stage IIIB or IV) (3, 4). Unfortunately, late presentation translates into poor prognosis and lower survival rates. Nationally, the median survival for lung cancer is 192 days, i.e. just under 7 months (1). Unfortunately lung cancer survival has not shown much improvement in the last 40 years in the UK (5) and lags behind those in some comparative European countries (6).

The burden of lung cancer, its treatments and their related toxicities pervade all aspects of quality of life for patients and their carers; finances, emotional well-being, relationships with friends and family and employment are all adversely affected (7).Thus therapies should be evaluated not only on their effect on overall survival but also progression free survival, objective response rate and impact on quality of life.

1.1 Statement of decision problem

This submission presents the clinical and economic data for ramucirumab plus docetaxel in people with locally advanced or metastatic NSCLC that has progressed after platinum based chemotherapy. Ramucirumab plus docetaxel is compared to docetaxel alone, to erlotinib in EGFR-negative patients, and to nintedanib plus docetaxel in adenocarcinoma patients (Table 1).

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed after platinum based chemotherapy.	Same as scope	N/A
Intervention	Ramucirumab in combination with docetaxel	Same as scope	N/A
Comparator (s)	• Docetaxel • Erlotinib (subject to ongoing NICE review) • Nintedanib in combination with docetaxel for people with adenocarcinoma tumour histology only • Nivolumab for people with squamous tumour histology only. (subject to ongoing NICE appraisal) • Crizotinib for people with anaplastic-lymphoma-kinase (ALK)-positive non-small-cell lung cancer only ((not recommended by NICE but funded via the CDF)	• Docetaxel • Erlotinib (subject to ongoing NICE review) in EGFR-negative patients only • Nintedanib in combination with docetaxel for people with adenocarcinoma tumour histology only	• The comparison to erlotinib is only presented for the EGFR-negative population, in line with the ongoing NICE review [ID620] where clinical specialists stated that most EGFR-positive patients receive an EGFR-TK inhibitor as first-line treatment. They also concluded that the use of EGFR-TK inhibitors for re-treating NSCLC after the failure of first-line EGFR-TK inhibitor treatment is not common in clinical practice. Results for erlotinib for the EGFR-positive patients were therefore not considered relevant to this submission. • Nivolumab is currently undergoing NICE single technology appraisal and therefore is not yet available to the NHS. Thus it is not in routine use in UK clinical practice • Crizotinib is funded by the Cancer Drugs Fund only for patients who have ALK-positive NSCLC. Patients who are confirmed ALK positive would almost certainly receive crizotinib. Additionally, ALK mutation status was not collected routinely in REVEL making a meaningful comparison between ramucirumab and

			crizotinib infeasible.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	Same as scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes (PAS) for the intervention or comparator technologies should be taken into account.	The outcomes of the economic evaluation are expressed in terms of incremental cost per QALY. A 15-year time horizon is used, which for NSCLC patients is equivalent to a lifetime horizon. Costs are considered from an NHS and Personal Social Services perspective.	Nintedanib and erlotinib are available to the NHS with a PAS, but as the nature of the schemes is confidential, it has not been possible to include this within the submission.
Subgroups to be considered	N/A	N/A	N/A
Special considerations including issues related to equity or equality	N/A	N/A	N/A

1.2 Description of the technology being appraised

Table 2 gives an overview of the technology.

Table 2 Technology being appraised

UK approved name and brand name	Approved name: Ramucirumab Brand name: Cyramza ®
Marketing authorisation/CE mark status	EU marketing authorisation expected February 2016
Indications and any restriction(s) as described in the summary of product characteristics	Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy.
Method of administration and dosage	The recommended dose of ramucirumab is 10 mg/kg administered by intravenous infusion over approximately 60 minutes on day 1 of a 21 day cycle, prior to docetaxel infusion. The recommended dose of docetaxel is 75 mg/m2 administered by intravenous infusion over approximately 60 minutes on day 1 of a 21 day cycle. See docetaxel prescribing information for specific dosing advice.

1.3 Summary of the clinical effectiveness analysis

REVEL Study

Ramucirumab (RAM) plus docetaxel (DOC) has been studied in the Phase III, randomised, placebo-controlled REVEL trial, in comparison to placebo (PBO) plus DOC. The trial randomised 1,253 stage IV NSCLC patients who had progressed on or after one prior platinum-based regimen. Baseline patient demographics, disease and other characteristics were balanced between treatment arms (8).

Efficacy outcomes (see Section 4.7)

REVEL met its primary endpoint; RAM+DOC significantly improved overall survival (OS) compared with PBO+DOC (hazard ratio (HR) = 0.857; 95% confidence interval (CI): 0.751, 0.979; p=0.024). Median OS was 10.5 months (95% CI: 9.5, 11.2) in patients receiving RAM+DOC and 9.1 months (95% CI: 8.4, 10.0) in patients receiving PBO+DOC, an increase in OS of 15%.(8) The size of the OS benefit observed in REVEL should be viewed in the context of the very limited current median OS of the overall lung cancer patient population in England, which is currently less than 7 months (1).

OS is the gold standard for establishing clinical benefit in oncology but other endpoints such as progression-free survival (PFS), response rate, patient-reported outcomes and toxicity

help to inform an overall assessment of the benefit-risk profile. RAM+DOC demonstrated consistent benefit across other efficacy endpoints including PFS, overall response rate (ORR) and disease control rate (DCR): (8)

- Median PFS was 4.5 months (95% CI: 4.2, 5.3) in the RAM+DOC arm versus 3.0 months (95% CI 2.8, 3.9) in the PBO+DOC arm, reducing the risk of disease progression or death by 23.8% (HR = 0.762; 95% CI: 0.677, 0.859; p<0.001) and increasing median PFS by 50%. These results suggest that the additional OS benefit observed included additional time in the pre-progression period, where health related QoL is better and patients know that their tumour is not getting bigger.

- More patients responded to treatment with RAM+DOC with a significantly greater ORR and DCR in patients treated with RAM+DOC (ORR: 22.9%; DCR: 64%) compared to PBO+DOC (ORR: 13.6%; DCR 52.6%). This shows that the percentage of patients whose cancer shrinks or completely disappears is significantly higher when treated with RAM+DOC (22.9% versus 13.6%). This can also have important health related QoL benefits for patients, including reduced tumour burden and improvements in symptomatic disease.

Favourable clinical outcomes were observed for OS, PFS, ORR, and DCR with RAM+DOC compared with PBO+DOC for pre-specified non-squamous, adenocarcinoma, and squamous histologic subgroups, consistent with the intent-to-treat population (see Section 4.8) (8). By demonstrating a significant OS, PFS and ORR advantage compared to PBO+DOC in the overall study population, the clinical benefit of RAM+DOC to all NSCLC patients is clear. RAM+DOC provides a clinically meaningful option for NHS patients, irrespective of histology, who currently only have access to a limited number of treatment options.

The quality-of-life (QoL) analysis showed that there were minimal changes from baseline in EQ-5D index or VAS scores while on study therapy, regardless of treatment arm. This suggests that QoL was maintained by treatment with RAM+DOC relative to PBO+DOC. This is very important given the limited survival of patients with metastatic NSCLC. Extending PFS and OS compared to the standard of care (SoC) docetaxel, without impacting QoL, underlines the importance and benefit to patients of ramucirumab as a treatment option.

Safety outcomes (see Section 4.12)

The REVEL safety population consisted of 627 patients in the RAM+DOC arm and 618 patients in the PBO+DOC arm. Rates of TEAEs were similar between treatment arms, with 97.8% of patients treated with RAM+DOC experiencing a TEAE versus 96.1% of patients treated with PBO+DOC.(8)

TEAEs of any grade with incidence ≥ 5% in the RAM+DOC arm than the PBO+DOC arm were neutropenia, stomatitis, epistaxis, oedema peripheral, mucosal inflammation, febrile neutropenia, lacrimation increased and hypertension.(8) A greater incidence of Grade ≥3 hypertension was observed in patients receiving RAM+DOC (5.4%) than in patients receiving PBO+DOC (2.1%) although it was managed adequately with standard anti-hypertensive medication.(8)

The incidence of deaths due to AEs was low and similar in the RAM+DOC arm and the PBO+DOC arm (4.9% vs. 5.7%, respectively).(8)

Network Meta-analysis (see Section 4.10)

A systematic review and network meta-analysis were performed to compare RAM+DOC to the other relevant comparators. A fixed-effects hierarchical exchangeable model fitted the data best in all cases. This NMA methodology allowed for erlotinib (ERL) efficacy to vary by EGFR status and for nintedanib (NIN) +DOC efficacy to vary according to squamous and non-squamous histology.

RAM+DOC has a significantly greater OS, PFS and ORR than both DOC (in all populations) and ERL (in EGFR-negative patients) (Table 3). RAM+DOC was shown to have similar efficacy to NIN+DOC (in the non-squamous subpopulation) for all outcomes (Table 3).

Table 3 Results from NMA

Outcome	**RAM+DOC vs:**		
	DOC (all populations)	ERL (EGFR-negative)	NIN+DOC (non-squamous)
OS	0.86 (0.75, 0.98)	0.70 (0.52, 0.91)	1.01 (0.82, 1.25)
PFS	0.76 (0.68, 0.86)	0.57 (0.43, 0.75)	0.99 (0.78, 1.26)
ORR	0.41 (0.27, 0.54)	0.96 (0.62, 1.34)	0.05 (-0.18, 0.28)

Overall the benefit-risk assessment of RAM+DOC in locally advanced or metastatic NSCLC patients with progression after platinum-based chemotherapy was shown to be favourable,

based on the proven benefit, manageable safety profile, and lack of apparent detriment to QoL. Ramucirumab thus represents a significant new therapeutic option for patients with metastatic NSCLC with progression after platinum-based chemotherapy. This technology can provide meaningful health-related benefits, irrespective of histology to a very sick population who currently have limited treatment options.

1.4 Summary of the cost-effectiveness analysis

Methods

A partitioned survival (area under the curve) model was used for the economic evaluation of RAM+DOC vs relevant comparators (see Section 5.2). This model type has been commonly used in previous appraisals in NSCLC (9, 10), and other cancer types. The model estimates the proportion of patients in progression-free, post-progression and death states at each 21-day cycle. A 15 year time horizon was used, in keeping with the recent TA347 and the appraisal committee's conclusions that this was appropriate for this disease (10). Costs and outcomes were discounted at an annual rate of 3.5%. Treatment is modelled to stop on disease progression, after which 70% of patients receive best supportive care and 30% receive further anticancer therapy.

For OS, a log-logistic multivariate model was fitted to the PBO+DOC and RAM+DOC OS curve from the REVEL trial. For PFS, the assumption of proportional hazards was not deemed to hold, and therefore separate parametric models (generalised gamma, multivariate) were fitted to the RAM+DOC vs PBO+DOC arms from REVEL. For the indirect comparisons the following was done: for ERL, the HR for the EGFR-negative subgroup from the NMA was applied to the PBO+DOC curve. The HR for NIN+DOC from the non-squamous population was applied to the PBO+DOC curve estimated from the non-squamous subgroup of the REVEL trial (see Section 5.3).

Utilities for the pre- and post-progression states were derived from EQ-5D values from the REVEL study (see Section 5.4). Costs are considered from an NHS and Personal Social Services perspective (see Section 5.5).

Results

The results of the model show that ramucirumab in combination with docetaxel extends mean time in PFS (by 1.45 months) and progressed disease (by 1.61 months) compared to docetaxel alone, thus providing an undiscounted life-year gain of 3.06 months compared with

docetaxel alone. The QALY gain associated with ramucirumab plus docetaxel versus docetaxel alone is 0.124, 64% of which is accrued in the pre-progression phase. The additional benefit comes at an incremental cost of £24,294 (Table 4; also see Section 5.7).

Compared to ERL in the EGFR-ve subpopulation, RAM+DOC extends PFS (2.52 months) and survival in progressed disease (3.86 months) to give an undiscounted life-year gain of 6.38 months compared to ERL, with a resulting discounted QALY gain of 0.250 vs. ERL, 55% of which was accrued before progression (Table 5; also see Section 5.7). In the non-squamous subpopulation, RAM+DOC delivers similar QALY benefits to NIN+DOC, although it was more costly (Table 6; also see Section 5.7).

The overall conclusion of the sensitivity and scenario analyses is that the model is robust to changes in key parameters and assumptions (see Section 5.8). The one-way sensitivity analyses showed that the price of ramucirumab is a main driver of the model, along with the discount rate. For the comparison of RAM+DOC to NIN+DOC in the non-squamous subgroup the model became sensitive to the clinical efficacy inputs and assumptions. This reflects the highly similar clinical efficacy of the two drugs which causes small absolute incremental changes to costs and QALYs to have a substantial impact on the ICER and does not reflect the robustness of the model.

Table 4 Base-case results in the ITT REVEL population (overall NSCLC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
DOC	£10,995	1.093	0.692	-	-	-	-
RAM+DOC	£35,283	1.282	0.816	£24,288	0.188	0.125	£194,919

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years. **Note**: Numbers may not compute due to rounding

Table 5 Base case results vs ERL in the EGFR-ve population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER RAM+DOC vs ERL
DOC	£10,995	1.093	0.692	-	-	-	-	
ERL	£13,562	0.895	0.567	£2567	-0.199	-0.125	Dominated	
RAM+DOC	£35,283	1.282	0.816	£21,721	0.387	0.250	£194,919	£86,985

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years. **Note**: Numbers may not compute due to rounding

Table 6 Base-case results vs NIN+DOC in the non-squamous subpopulation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER RAM+DOC vs NIN+DOC
DOC	£11,534	1.146	0.724	-	-	-	-	
NIN+DOC	£25,064	1.338	0.852	£13531	0.192	0.128	£105,621	
RAM+DOC	£36,789	1.357	0.863	£11,724	0.020	0.011	£182,082	£1,106,497

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years. **Note**: Numbers may not compute due to rounding

Interpretation of Results (see Section 5.11)

The cost-effectiveness model has been designed and populated based on rigorous systematic reviews and has undergone extensive internal and external validation. This, along with the robust results as demonstrated by the sensitivity analysis, shows that the model produces highly reliable results.

There is clear evidence that society has a preference for allocating resources to patients with severe diseases and a high unmet need (11). NSCLC is one such condition, given that patient prognosis is so poor and even a small QALY gain is extremely valuable to patients and their families.. Ramucirumab should also be considered under the end-of-life criteria due to the following reasons:

- Patients with advanced or metastatic NSCLC whose disease has progressed on platinum-based therapies have an expected median survival of only 9 months under current treatment with docetaxel (8)
- Due to the high fatality rate of NSCLC, the number of patients that will be alive to receive second-line treatment is small. It is expected that there would be approximately 1000 patients newly eligible for ramucirumab each year (See Section 6).
- Ramucirumab in combination with docetaxel is shown to give an undiscounted life-year gain of 3.06 months compared to docetaxel alone, meeting the criterion for OS benefit.
- The recent NICE appraisal of nintedanib, TA347 (10), concluded that the end-of-life criteria were met in that appraisal. Ramucirumab and nintedanib, both in combination with docetaxel, are shown to have very similar efficacy in the network-meta analysis.

In the model they give an undiscounted life-year gain of 3.47 months (RAM+DOC) and 3.32 months (NIN+DOC) compared to docetaxel alone in the non-squamous subpopulation analysis, respectively. It would therefore be appropriate and consistent to consider the end of life criteria met in the present appraisal.

2. The technology

2.1 Description of the technology

Brand Name	Cyramza ®
Approved Name	Ramucirumab
Therapeutic Class	Angiogenesis inhibitor, human IgG1 monoclonal antibody

Overview of the mechanism of action

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2, thereby preventing activating ligands (VEGF-A, VEGF-C, and VEGF-D) from binding to VEGF Receptor 2 (12, 13). These result in the inhibition of ligand-induced proliferation, downstream signalling components and migration of human endothelial cells: all of which are important for angiogenesis (the formation of new blood vessels) (14, 15). Extensive scientific literature suggests that angiogenesis contributes substantially to cancer growth and metastasis. Furthermore key regulators of angiogenesis and the expression of VEGFs have been correlated with poor prognosis in several solid tumour types, including non-small cell lung cancer (NSCLC) (16).

2.2 Marketing authorisation/CE marking and health technology assessment

Approved indications

Ramucirumab (Cyramza) was approved by the European Commission on 19th December 2014 for the following indications (17):

Gastric Cancer

- Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
- Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.

The company has submitted a type II variation to the European Medicines Agency (EMA) for the following indications:

Non-small cell lung cancer (NSCLC)

- Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy (18).

Colorectal Cancer (CRC)

- Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

Ramucirumab was made commercially available in the UK on 16th January 2015.

European public assessment report (EPAR)

The initial European Union Marketing Authorisation Application (EU MAA) submission for ramucirumab was based on a review of data from the pivotal studies RAINBOW (ramucirumab administered in combination with paclitaxel), and REGARD (19). The opinion of the Committee for Medicinal Products for Human Use (the CHMP) regarding ramucirumab for NSCLC has not yet been issued and therefore a summary of the discussion cannot be incorporated at this point.

Regulatory approval outside the UK

Ramucirumab was approved by the U.S. Food and Drug Administration (FDA) on 21st April 2014 as a single-agent treatment for patients with advanced or metastatic gastric cancer or gastro-oesophageal junction (GC/GOJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy.

Ramucirumab was approved by the U.S. FDA on 5th November 2014 in combination with paclitaxel as a treatment for people with advanced or metastatic GC/GOJ whose cancer has progressed on or after prior fluoropyrimidine or platinum-containing chemotherapy.

Ramucirumab was approved by the U.S. FDA on 12th December 2014 in combination with docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed on or after prior platinum based chemotherapy.

Ramucirumab was approved by the U.S. FDA on 24th April 2015 in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

The Japan Ministry of Health, Labour and Welfare approved Cyramza as a treatment for patients with unresectable, advanced or recurrent GC on 26th March 2015.

The Korean Ministry of Health and Welfare approved Cyramza as a treatment for advanced GC on 15th April 2015.

Other health technology assessment in the UK

Ramucirumab will be appraised by the Scottish Medicines Consortium (SMC). The estimated timeline for submission is in 2016.

2.3 Administration and costs of the technology

Ramucirumab in combination with docetaxel

Ramucirumab can be administered in a hospital outpatient care setting. The recommended dose of ramucirumab is 10 mg/kg on day 1 of a 21 day cycle, prior to docetaxel infusion. The recommended dose of docetaxel is 75 mg/m^2 administered by intravenous infusion over approximately 60 minutes on day 1 of a 21 day cycle. It is recommended that treatment be continued until disease progression or until unacceptable toxicity has occurred.

Table 7 Costs of the technology being appraised

Pharmaceutical formulation	**Concentrate for solution for infusion (sterile concentrate)**
Acquisition cost (excluding VAT) *	500mg = £2,500 (list price) 100mg = £500 (list price)
Method of administration	IV infusion
Doses	The recommended dose of ramucirumab is 10 mg/kg
Dosing frequency	Ramucirumab: Day 1 of a 21 day cycle, prior to docetaxel infusion. Docetaxel: Day 1 of a 21 day cycle
Average length of a course of treatment	21 days
Average cost of a course of treatment (a course of treatment is assumed to be a cycle of treatment for ramucirumab)	Ramucirumab cost per cycle is estimated to be £3733 (assuming wastage and based on REVEL patient weight) Docetaxel cost per cycle is estimated to be £36 (assuming wastage and based on REVEL patient body surface area).
Anticipated average interval between courses of treatments	N/A – treatment as per dosing frequency until disease progression or unacceptable toxicity
Anticipated number of repeat courses of treatments	In the Phase 3 trial, REVEL, the median duration of therapy was 15.0 weeks for the ramucirumab plus docetaxel arm (with a median of 5.0 infusions received).
Dose adjustments	The mean relative dose intensity of ramucirumab in the REVEL trial was 94.6%

Anticipated care setting	Hospital
* indicate whether this acquisition cost is list price or includes an approved patient access scheme	

2.4 Changes in service provision and management

Additional tests and investigations required

The following tests and investigations are required during the course of treatment with ramucirumab:

Table 8 Tests and investigations required during treatment with ramucirumab

	Ramucirumab	Docetaxel
Full blood count	√	√
Renal function test	√	√
Hepatic function test	√	√
Blood pressure	√	
Urinalysis	√	

Full blood counts, renal function tests, and hepatic function tests would be required for treatment with docetaxel and are not specific to ramucirumab only

Premedication

Premedication is recommended with a histamine H1 antagonist (for example diphenhydramine) prior to infusion of ramucirumab. If a patient experiences a Grade 1 or 2 infusion-related reaction (as per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), premedication must be given for all subsequent infusions. If a patient experiences a second Grade 1 or 2 infusion-related reaction (IRR) administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medicinal products: an intravenous histamine H1 antagonist (for example diphenhydramine hydrochloride), paracetamol and dexamethasone.

Impact on healthcare resource use and costs

The dosing schedule of RAM+DOC is similar to that for docetaxel monotherapy: administration is required on day 1 of a 21 day cycle. Therefore apart from drug costs, RAM+DOC is unlikely to increase resource use.

2.5 Innovation

There are currently limited second-line treatment options available for NHS patients in England with locally advanced or metastatic NSCLC that has progressed after platinum

based chemotherapy. Recent new treatments have shown efficacy only in specific subgroups. Therefore there is a high unmet need to improve treatment options for NSCLC cancer patients that have progressed after platinum chemotherapy. New treatment options that have a high response rate and improve overall and progression free survival, without adding significant toxicity while maintaining quality of life, are essential to advancing care for these patients. Ramucirumab offers this innovation.

REVEL demonstrated a statistically significant and clinically meaningful improvement in overall survival, progression-free survival and objective response rate across all NSCLC histologies. A consistent treatment effect was observed in patients regardless of squamous or non-squamous histology with manageable toxicities and no detrimental effect on QoL. Furthermore treatment effect was consistent across all efficacy end points (OS, PFS and overall response rate), which translates to a meaningful clinical benefit to patients. Thus this technology can provide meaningful health-related benefits to a very sick population who have limited options.

3. Health condition and position of the technology in the treatment pathway

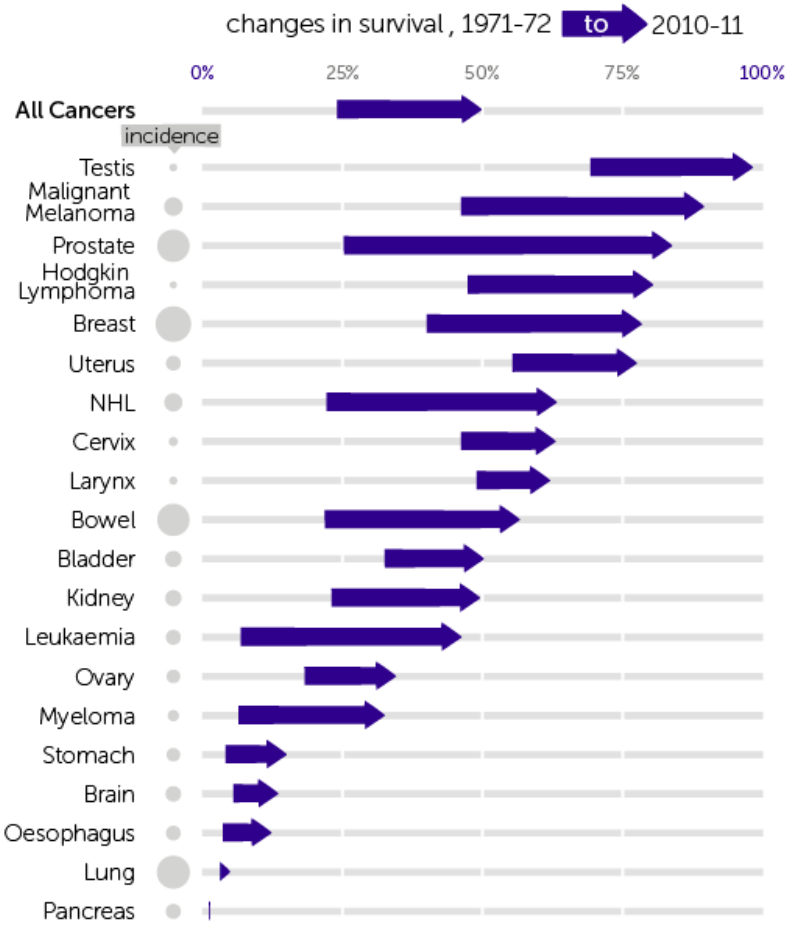
Overview of lung cancer

Lung cancer is the second most common cancer diagnosed in the UK after breast cancer and it is the leading cause of cancer-related death in the UK, accounting for more than 20% of cancer deaths (2). Smoking is the main cause of lung cancer and is linked to about 86% of lung cancer cases in the UK (2). Other known risk factors for lung cancer include exposure to asbestos, arsenic, radon and non-tobacco related polycyclic aromatic hydrocarbons (20). The predominant form of lung cancer is Non-Small Cell Lung Cancer (NSCLC) which accounts for 85% to 90% of all lung cancers (20).The three subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell carcinoma accounting for 30%, 30-40% and 10-15% of all lung cancers respectively with the latter two collectively termed non-squamous lung cancer (21). The symptoms of NSCLC include coughing up blood, malaise, weight loss, shortness of breath and voice loss. Lung cancer incidence is higher, and survival is poorer in people of lower socioeconomic status (7).

Prognosis and Burden of Disease

Like most cancers, the prognosis of NSCLC depends considerably on the stage in which the cancer is diagnosed. Because symptoms of the disease are non-specific or absent at early stages of NSCLC, at least 65% of patients present with advanced-stage disease (i.e. stage IIIB or IV) (3, 4). National Lung Cancer Audit data (LUCADA) shows that 55% of patients with histologically confirmed NSCLC have advanced or metastatic (stage IIIB or stage IV tumours) cancer at the time of presentation (1). Unfortunately, late presentation translates into poor prognosis and lower survival rates. Nationally, the median survival for lung cancer is 192 days, i.e. just under 7 months (Interquartile range is 58 – 315 days) and the three-month, one-year and five-year survival rates are 67%, 35% and 9% respectively (1). Figure 1 below shows that survival for most cancer types is improving due to faster diagnosis and advances in treatment. For example prostate cancer has shown improvement in age-standardised ten-year net survival since the early 1970s, from 25% in 1971-1972 to 84% in 2010-2011. However lung cancer survival has not shown much improvement in the last 40 years in the UK (5) and lags behind those in some comparative European countries (6).

Figure 1 **Age-Standardised Ten-Year Net Survival Trends, Adults (Aged 15-99), Selected Cancers, England and Wales, 1971-2011. Taken from Cancer Research UK (5)**



Breast is for female only. Laryngeal is for male only. Ten-year survival for 2005-2006 and 2010-2011 is predicted using an excess hazard statistical model. Survival for bowel cancer is a weighted average derived from data for colon (C18) and rectum cancer (C19-C20, C21.8). Source: Cancer Research UK (5)

Histology is also an important prognostic factor, as it may determine the choice of treatment. For example the treatment pathway for squamous NSCLC differs from that of non-squamous NSCLC. In addition oncogenes such as the epidermal growth factor receptor (EGFR) mutated oncogene and anaplastic lymphoma kinase (ALK) fusion gene have been validated as reliable targets for selective pathway directed systemic therapies (22). Therefore one of the NICE Quality standards for lung cancer is that “people with lung cancer have adequate tissue samples taken in a suitable form to provide a complete pathological diagnosis including tumour typing and sub-typing, and analysis of predictive markers” (23). The histological diagnosis rate for patients with lung cancer in England and Wales in 2013 was 75% (1). NICE also has the following quality statement “People with stage IIIB or IV non-

small-cell lung cancer and eligible performance status are offered systemic therapy (first- and second-line) in accordance with NICE guidance, that is tailored to the pathological sub-type of the tumour and individual predictive factors".

Lung cancer has a significant impact on society, costing the UK economy an estimated £2.4 billion per year (24). Premature deaths plus time off work, health care costs and unpaid care provided by friends and family account for 50%, 35% and 16% of the cost of lung cancer respectively (24). According to Cancer Research UK (CRUK), each lung cancer patient is thought to cost the UK healthcare system £9,071 annually (25). There were 35,903 cases of lung cancer in England in 2012 representing European age-standardised incidence rates of 76.3 per 100,000 population (2) and according to the National Lung Cancer Audit report (2014){{}} the total annual incidence of lung cancer in England, excluding small cell and mesothelioma was 29,349 (1). Incidence rates between men and women have narrowed in the UK since the 1970s: for every 10 lung cancer cases in women there are around 12 in men (2). Lung cancer incidence rates in men peaked in the late 1970s and since then have decreased by 45%, reflecting the decline in smoking rates in men since around the end of the 1940s (2). Unfortunately lung cancer incidence rates in women have increased by 64% since the late 1970s. This reflects the increase in smoking rates in women between World War II and the 1970s (2).

There were 84,876 admissions for lung cancer in England in 2012, resulting in 295,114 bed-days and 104,273 finished consultant episodes (26). 28,300 deaths from lung cancer were registered in England in the same year. Improving population health outcomes, including the prevention of premature death from cancer, is a key priority for NHS England as reflected by the NHS Outcomes Framework (2014/15) Domain 1: preventing people from dying prematurely and the indicator 1:11: one-year survival from breast, lung and colorectal cancers (27). Indicator 1.11 forms part of the Clinical Commissioning Group (CCG) Outcomes Indicator Set which aims to support Health and Wellbeing Boards and CCGs in their planning of services (27).

Patients with lung cancer suffer more distressing symptoms than other types of cancer patient (28) and frequently have comorbidities and multiple symptoms such as pain, fatigue, anxiety and depression and breathlessness and cough (7). Increased symptom distress not only has a deleterious effect on quality of life but significantly restricts patients' abilities to perform activities of daily living. The burden of lung cancer, its treatments and their related toxicities pervade all aspects of quality of life for patients and their carers; finances,

emotional well-being, relationships with friends and family and employment are all adversely affected (7).Thus therapies are evaluated not only on their effect on overall survival but also progression free survival, objective response rate and impact on quality of life.

UK Lung Cancer Clinical guidelines/guidance

The National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) have published clinical guidelines (CG121 (29) and SIGN137 (7)) that provide recommendations for good practice in the diagnosis and treatment of lung cancer in England and Wales and in Scotland. NICE has also published a number of guidance documents that are relevant to NSCLC. These are summarised in Table 9 below

Table 9 Relevant NICE documents

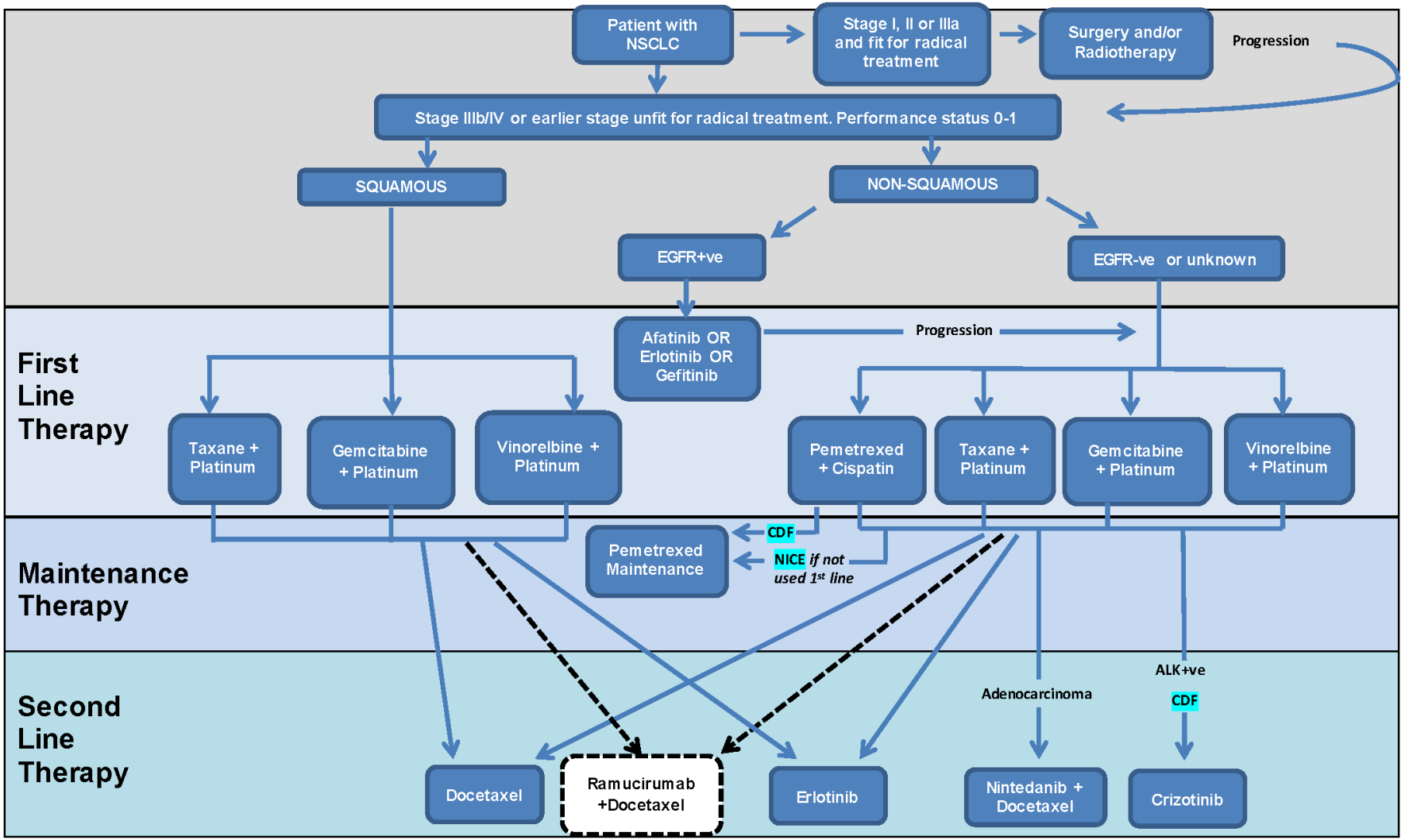
NICE Clinical Guideline/Guidance	Patient group	Recommended treatment
First-line		
CG121 (29) The diagnosis and treatment of lung cancer	All patients with NSCLC of good performance status (WHO 0 or 1 or Karnofsky score of 80 to 100)	Platinum doublet docetaxel, gemcitabine, vinorelbine or paclitaxel. Or single agent if unable to tolerate platinum therapy
TA192 (30) Gefitinib for the first-line treatment of locally advanced or metastatic NSCLC	EGFR M+ only	Gefitinib if provided at agreed PAS price
TA258 (31) Erlotinib for the first-line treatment of locally advanced or metastatic EGFR M+ NSCLC	EGFR M+ only	Erlotinib if provided at the agreed PAS price
TA181 (32) Pemetrexed for the first-line treatment of NSCLC	Confirmed adenocarcinoma or large cell (non-squamous) only	Pemetrexed+cisplatin
Maintenance following first-line		
TA190 (33) Pemetrexed for the maintenance treatment of NSCLC	Non-squamous (adenocarcinoma or large cell) without disease progression after 1st line platinum chemotherapy with gemcitabine, paclitaxel or docetaxel	Pemetrexed
Second-line		
CG121 (29) The diagnosis and treatment of lung cancer	All NSCLC	Docetaxel monotherapy

TA162 (34) Erlotinib for the treatment of NSCLC	All NSCLC	Erlotinib if provided at an overall treatment cost equal to that of docetaxel. It is not recommended in patients for whom docetaxel is unsuitable or contraindicated
TA347 (10) Nintedanib for the treatment of NSCLC	Adenocarcinoma only	Nintedanib + Docetaxel. Nintedanib if provided at the agreed PAS price
TA175 (35) Gefitinib for the treatment of locally advanced or metastatic NSCLC	EGFR M+ only	Gefitinib. NICE was unable to recommend the use in the NHS of gefitinib for the second-line treatment of locally advanced or metastatic NSCLC because no evidence submission was received from the manufacturer or sponsor of the technology
TA124 (36) Pemetrexed for the treatment of NSCLC	All NSCLC	Not recommended

Current treatment pathway

The aims of treatment for NSCLC are to extend survival, improve quality of life and control disease symptoms (37). Patients with NSCLC are offered multimodality therapy (surgery, radiotherapy and chemotherapy in any combinations) according to resectability, stage and performance status. In addition to tumour histology and molecular pathology, treatment strategies should reflect the patient's age, performance status, comorbidities and patient preferences (22). Patients who smoke should be encouraged to stop smoking since smoking cessation improves treatment outcomes (22). Patients with stage I and II NSCLC should be considered for curative surgery whenever possible (7). For many people with stage IIIB or IV disease, the cancer has spread too far for surgery or radiotherapy to be effective, so chemotherapy is recommended. Chemotherapy is offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) (29).

Figure 2 Current UK clinical practice for patients with NSCLC



First-line chemotherapy for advanced or metastatic NSCLC

The initial choice of treatment and subsequent treatment pathway is largely dependent on the tumour histological subtype. For squamous NSCLC a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel, or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) is offered as induction chemotherapy for advanced NSCLC (29). Patients unable to tolerate a platinum combination are offered single-agent chemotherapy with a third-generation drug. Squamous NSCLC is most commonly EGFR-TK mutation-negative.

Since the publication of the NICE TA162 (erlotinib) guide from 2008 (34), there has been greater recognition of the influence of epidermal growth factor receptor (EGFR)-tyrosine kinase (TK) mutation on prognosis and treatment choice. EGFR-TK mutation testing is now routinely carried out in England and Wales often before a first-line treatment is selected. Thus patients with non-squamous NSCLC may be further differentiated as having either EGFR-TK activating mutation positive (M+) or negative (M-) status and approximately 10% of NSCLC tumours in the UK are EGFR-TK M+ (38). Patients with negative or unknown EGFR status are offered a combination of a single third-generation drug plus a platinum drug as induction chemotherapy. Patients may also be offered pemetrexed in combination with cisplatin (if the tumour is adenocarcinoma or large-cell carcinoma) as recommended by NICE in TA181 (32). For EGFR positive tumours, patients are offered afatinib, erlotinib or gefitinib as recommended by NICE TA310 (39), TA258 (31) and TA192 (30) respectively. Those who progress may be offered a combination of a single third-generation drug plus a platinum drug or pemetrexed in combination with cisplatin.

Maintenance chemotherapy for advanced or metastatic NSCLC (non-squamous histology)

Pemetrexed is well established as standard maintenance treatment for patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology. NICE TA190 (33) recommends pemetrexed for this indication if the disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel. NICE TA190 (33) does not recommend pemetrexed maintenance therapy if patients have received pemetrexed in combination with cisplatin as first line treatment. However pemetrexed maintenance therapy has become the standard of care for maintenance eligible patients following first-line pemetrexed/cisplatin treatment in England and is funded by the Cancer Drugs Fund (40).

Second-line chemotherapy for advanced or metastatic NSCLC

There are limited second-line treatment options for patients with locally advanced or metastatic NSCLC that has progressed after previous chemotherapy. Docetaxel has been the standard of care for over a decade and is used second-line in squamous and non-squamous NSCLC. Docetaxel is therefore the primary comparator for this appraisal. NICE CG121 recommends docetaxel or erlotinib monotherapy as second line treatment options for patients progressing after first-line chemotherapy. However erlotinib is generally offered to those with poor fitness (an ECOG status of 2) whereas docetaxel is used for patients with ECOG performance score 0 or 1 (10). Furthermore erlotinib is not recommended in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy (NICE TA162 (34)). In clinical practice, re-treatment with an EGFR-TK inhibitor such as erlotinib is unlikely to be considered for patients whose tumour is EGFR-TK M+ and has progressed after first-line treatment. NICE is currently revising TA162 (34) (erlotinib) and TA175 (35) (gefitinib) in a multiple technology appraisal and the appraisal committee has made some recommendations regarding erlotinib and gefitinib. The appraisal committee recommend erlotinib for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK M+ or in people with unknown EGFR-TK status who meet a number of criteria detailed in the appraisal consultation document (ACD) (41). Erlotinib is not recommended second-line in people with tumours that are EGFR-TK M- and Gefitinib is not recommended second-line in people with tumours that are EGFR-TK M+ (41). However, during the ongoing review clinical experts stated that most patients receive an EGFR-TK inhibitor as first-line treatment in line with NICE guidance. They also concluded that the use of EGFR-TK inhibitors for re-treating NSCLC after the failure of first-line EGFR-TK inhibitor treatment is not common in clinical practice in England because of reduced sensitivity of the tumour to these treatments. Therefore the inclusion of erlotinib in this appraisal has been focused on its use in the EGFR –ve patient population, in line with English clinical practice. Consequently the relevance of erlotinib to this decision problem will be dependent on the wording of the final guidance issued under the multiple technology appraisal. Additionally, following consultation with UK clinical experts, it was confirmed that erlotinib is not widely used second line in clinical practice.Crizotinib and nintedanib in combination with docetaxel are newer treatment options but unlike docetaxel they are only used in specific subtypes of non-squamous NSCLC. NICE (TA347 (10)) recommends nintedanib in combination with docetaxel as an option for treating locally advanced, metastatic or locally recurrent NSCLC

of adenocarcinoma histology that has progressed after first-line chemotherapy. It is therefore included as a comparator for a limited subpopulationof the ramucirumab eligible patients.

Crizotinib was appraised and not recommended by NICE but can be used in England (via the CDF) for the second line treatment of locally advanced or metastatic anaplastic lymphoma kinase (ALK) positive NSCLC where there has been progressive disease following a 1st line platinum-based combination. Patients who are confirmed ALK positive would almost certainly receive crizotinib as their second-line treatment, meaning it is not a relevant comparator for ramucirumab. Additionally, ALK mutation status was not collected routinely in the ramucirumab phase III trial REVEL, thus making a meaningful comparison between ramucirumab and crizotinib infeasible. Nivolumab is licensed for the squamous population and has been included as a comparator in the scope for this appraisal. It is currently undergoing NICE single technology appraisal however and therefore is not yet available to the NHS. Thus it is not in routine use in UK clinical practice and not an appropriate comparator. Finally best supportive care is considered an option for people who are unlikely to tolerate systemic anti-cancer therapy or do not wish to receive it.

Anticipated place of ramucirumab in clinical practice

There are limited therapeutic options for NSCLC patients with progressive disease after platinum-based chemotherapy. Clinical outcomes in this second-line population are poor with ORR of less than 10%, median PFS of less than 4 months and median OS of 7-9 months (42). Recent new treatments have shown efficacy but often only in specific histologies or molecular subgroups. For example there has been a notable lack of significant development in efficacious treatments for squamous NSCLC aside from immuno-oncology products. This may partly be explained by a lack of driver mutations associated with response to approved agents (43). Therefore there is a high unmet need to improve treatment options for all NSCLC patients that have progressed after platinum chemotherapy as no regimen is currently universally accepted as the post-platinum progression standard of care.

Based on the licensed indication, ramucirumab is expected to represent an additional treatment option for locally advanced or metastatic NSCLC that has progressed on or after platinum based chemotherapy. Figure 2 shows that RAM+DOC is a treatment option for both squamous and non-squamous NSCLC. RAM+DOC has been shown to significantly improve OS and PFS in patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy, across all histologies. RAM+DOC also demonstrated

high overall response rates and disease control rates compared to current standard of care and newer treatments.

Analysis of quality-of-life is important to assess the risk-benefit ratio with any new treatment, especially in the second-line setting in which the intent of treatment is palliative. In addition to the improvement of clinical outcomes, the analysis of quality-of-life suggests that no detriment was caused in patient-reported global quality of-life through addition of RAM+DOC in the second-line setting. The manageable safety profile and lack of detrimental effect on quality-of-life supports the consistent benefits seen in the efficacy endpoints.

In conclusion, ramucirumab represents a much needed alternative option that can provide meaningful health-related benefits to a very sick population who have limited options.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

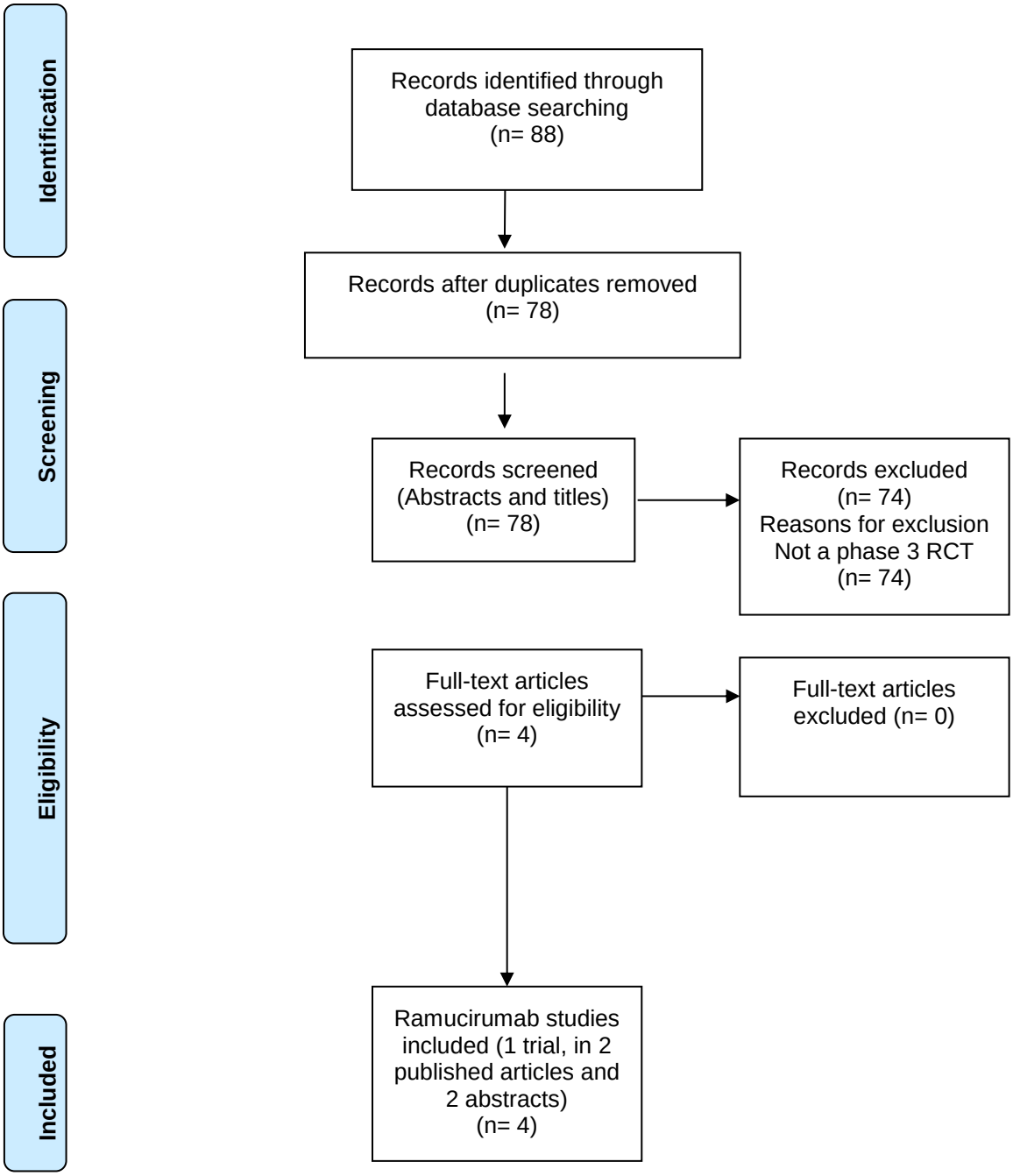
A comprehensive review of the published literature was performed on 12th August 2015 to identify RCTs of ramucirumab for the second-line treatment of adults with advanced or metastatic NSCLC. The literature search was conducted in Medline, Embase, Medline In-Process and the Cochrane Library with no date restrictions applied. Full references were checked for any additional studies that may have provided useful and relevant clinical data. In addition, the website of the American Society of Clinical Oncology (ASCO) was searched electronically for relevant abstracts. Details of the search strategy can be found in Appendix 1. The full eligibility criteria used in the search strategy are presented in Table 10.

Table 10 Eligibility criteria used in search strategy

	Inclusion	Exclusion
Population	Adult patients with advanced or metastatic NSCLC being treated with second-line treatment	Paediatric patients; undergoing first-line treatment; early stage NSCLC
Intervention	Ramucirumab (Cyramza) given as second-line treatment	Ramucirumab (Cyramza) given as first-line treatment or maintenance treatment
Comparator	No restrictions	
Outcomes	Trials with primary outcome measures of either PFS and OS	Trials with primary outcome measures other than OS or PFS
Setting/Study type	Randomised Controlled Trial (phase 3)	Non-randomised trials; phase 1/2 trials; review articles; notes or correspondence; editorials; conference proceedings

The search of the literature yielded 88 records. De-duplication resulted in the removal of 10 records. Following screening of the remaining 78 records, 74 records were excluded. Full texts of the remaining 4 records were obtained. Following the application of exclusion criteria, one trial remained (REVEL). The PRISMA flow diagram in Figure 3 details the number of papers included and excluded at each stage of the review.

Figure 3 PRISMA flow diagram for systematic literature review of ramucirumab clinical studies



The literature search identified 4 publications (2 published articles and 2 conference abstracts) pertaining to REVEL, the phase 3 clinical trial of ramucirumab plus docetaxel in the second-line clinical setting. The published articles are detailed below.

Table 11 REVEL publications

Primary study reference	Additional publications
Garon E, Ciuleanu T, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. The Lancet. 384 (9944) (pp 665-673), 2014.	Garon EB, Cao D, Alexandris E, John WJ, Yurasov S, Perol M; A randomized, double-blind, phase III study of Docetaxel and Ramucirumab versus Docetaxel and placebo in the treatment of stage IV non-small-cell lung cancer after disease progression after 1 previous platinum-based therapy (REVEL): treatment rationale and study design. Clinical lung cancer. 13(6):505-9, 2012 Nov.

4.2 List of relevant randomised controlled trials

This submission is based on clinical data from one phase 3 RCT; REVEL (see Table 12). REVEL (8) was a phase 3, international, multicentre, randomised, placebo-controlled, double-blind trial investigating ramucirumab plus docetaxel versus placebo plus docetaxel in the second-line clinical setting.

Table 12 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
REVEL	RAM+DOC	PBO+ DOC	Patients aged 18 years and older; having an ECOG PS of 0 or 1 and pathologically confirmed squamous or non-squamous stage IV NSCLC that has progressed during or after a single platinum-based chemotherapy regimen.	Garon et al (2014)

Scientific background and study rationale for REVEL

Clinical activity was seen early in the development of ramucirumab (44). At the time of study design and initiation (2010), therapeutic options for NSCLC patients with progressive disease after platinum-based chemotherapy remained very limited. Treatment options that extend survival and maintain QoL without adding significant toxicity were required. Given this and promising early phase clinical data for ramucirumab, a phase 3 study (REVEL) was initiated to evaluate ramucirumab as a potential second-line treatment for patients with advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy. Docetaxel was considered to be an appropriate agent for combination therapy with

ramucirumab because it is approved by regulatory agencies for second-line therapy of NSCLC. Although pemetrexed and erlotinib are also approved and effective drugs in second-line treatment, docetaxel was chosen based on its efficacy in patients with NSCLC, independent of their baseline histology (unlike pemetrexed) or epidermal growth factor receptor (EGFR) mutation status (unlike erlotinib). REVEL was thus set up to compare the efficacy and safety of RAM+DOC with PBO+DOC

4.3 Summary of methodology of the relevant randomised controlled trials

Trial Design

REVEL was a global, randomised, placebo-controlled, double-blind, multicentre phase 3 study that compared RAM+DOC with PBO+DOC in patients with Stage IV NSCLC who had progressed during or after prior platinum-based therapy for advanced/metastatic disease. See Figure 4 for an illustration of the study design and Table 15 for a summary of the trial design.

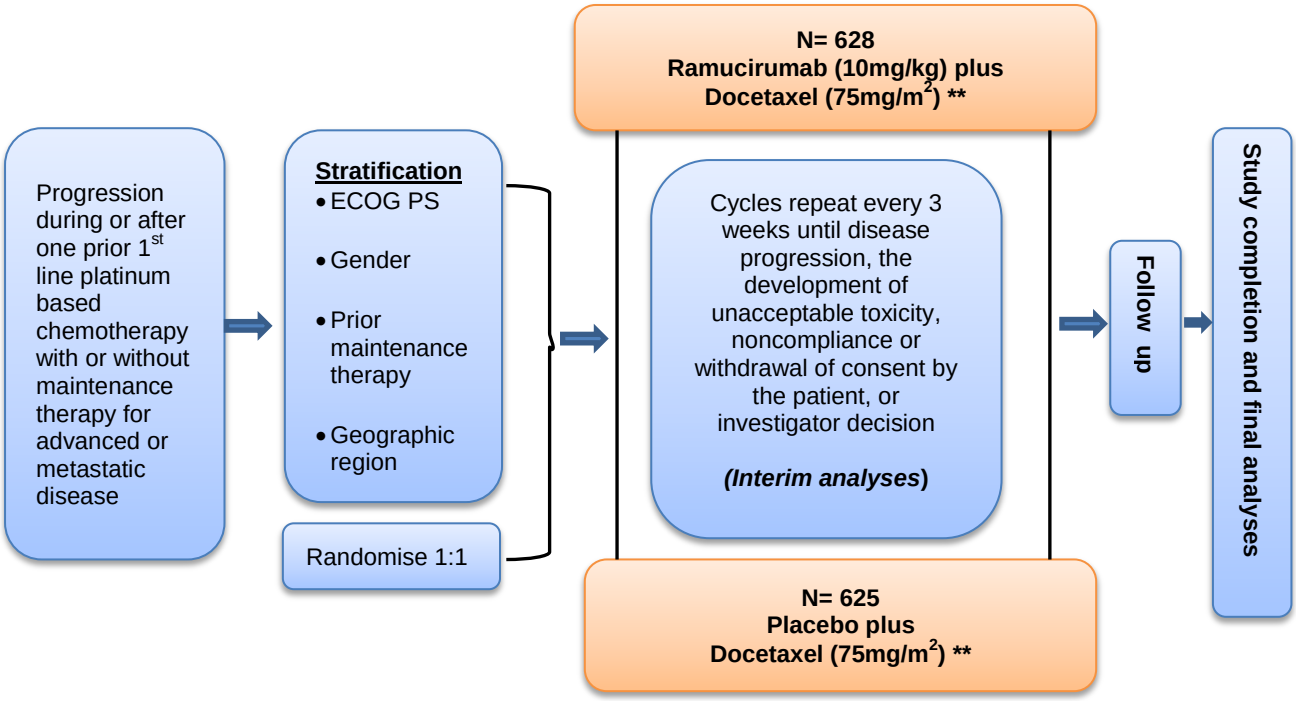
Patients were randomly assigned on a 1:1 basis to receive either:

- Ramucirumab (10 mg/kg, 60-minute intravenous [IV] infusion) in combination with docetaxel (75 mg/m^2, 60-minute IV) administered on Day 1 of a 21-day (3-week) cycle, or
- Placebo (60-minute IV) in combination with docetaxel (75 mg/m^2, 60-minute IV infusion) administered on Day 1 of a 21-day (3-week) cycle.

Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1), sex (female vs. male), prior maintenance therapy (yes vs. no), and geographic region (East Asia vs. rest of the world [ROW]). Randomisation was performed separately within each of the 16 strata (or cells) defined by all combinations of these 4 variables.

Figure 4 REVEL: Trial Design

Abbreviations. ECOG PS = Eastern Cooperative Oncology Group Performance Status; N = number of patients;



**= beginning with protocol amendment, for sites in Korea and Taiwan, new patients received docetaxel at a dose of 60 mg/m^2 Prior to protocol amendment , patients received docetaxel 75mg/ m^2

Changes to Trial Design

The original protocol was issued on 02 July 2010. The protocol was amended 5 times (17 August 2010, 16 December 2010, 18 November 2011, 22 May 2012, and 24 September 2012). Patients were enrolled under protocol versions (a) through (e). Important changes for protocol amendments (a) through (e) are summarised below:

- As requested by the Food and Drug Administration (FDA), the hazard ratio (HR) estimate used for sample size calculation was changed from 0.81 to 0.816, accounting for prior bevacizumab usage. Accordingly, the total number of patients, the number of events needed for final analysis, the estimated number of months for enrolment, and the timing of the third interim analysis was updated.
- As requested by the FDA, prior bevacizumab treatment (no vs. yes) was added to the list of subgroup analysis variables.
- An interim analysis for safety (approximately 6 weeks after the enrolment of the 150th patient) was added to ensure sufficient number of patients with squamous cell histology and patients with prior bevacizumab therapy in both treatment arms for an adequate assessment of safety in these patient groups.

- In May 2012, the independent data monitoring committee (IDMC) recommended to amend the protocol to reduce the dose of docetaxel for patients in East Asia (Korea and Taiwan) from 75 mg/m^2 to 60 mg/m^2. This recommendation was based on the higher rate of neutropenia and febrile neutropenia in patients in East Asia compared to patients from other countries in this study. The IDMC noted that the reduced dose of docetaxel at 60 mg/m^2 would also be consistent with other trials of this nature conducted in East Asia and consistent with the local clinical practice. Therefore, for new patients randomised in Korea and Taiwan beginning with protocol amendment (d), docetaxel was administered at a dose of 60 mg/m^2.

Participants

Key study eligibility criteria are summarised in Table 13 below. The complete list of inclusion/exclusion criteria are provided in Appendix 2.

Table 13 Key eligibility criteria for REVEL

Inclusion Criteria	Exclusion Criteria

• Patients who had disease progression during or after one and only one prior first-line platinum-based chemotherapy regimen with or without maintenance therapy for advanced/metastatic disease
• Patients with recurrent disease after adjuvant or neoadjuvant therapy or patients who had received combined chemotherapy and radiation for locally advanced disease were eligible, if:
  ○ patient had progressive disease within 6 months after completion of adjuvant or neoadjuvant platinum-based therapy (adjuvant therapy was considered the patient's one and only prior first-line, platinum-based chemotherapy); or
  ○ patient had progressive disease more than 6 months after completion of therapy AND had developed progressive disease on or after one subsequent chemotherapy regimen for advanced/metastatic disease.
• Prior bevacizumab as first-line and/or maintenance therapy was allowed.
• Males or females at least 18 years of age.
• The patient had an ECOG PS of 0 or 1 at the time of randomization.
• The patient had histologically or cytologically confirmed NSCLC.
• The patient had Stage IV NSCLC disease at the time of randomization (based on the AJCC, 7th Edition).
• The patient had adequate organ function as defined per study protocol.
	• The patient had disease progression on more than 1 prior chemotherapy regimens (with or without maintenance therapy) for advanced and/or metastatic disease.
	• Patients whose only prior treatment for advanced disease was a tyrosine kinase inhibitor.
	• The patient had radiologically documented evidence of major blood vessel invasion or encasement by cancer or intratumor cavitation, regardless of histology.
	• The patient had a history of uncontrolled hereditary or acquired thrombotic disorder.
	• Patients with a history of gross haemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to randomization.
	• The patient had significant bleeding disorders, vasculitis, or experienced Grade 3/4 GI bleeding within 3 months prior to randomization.
	• History of GI perforation and/or fistulae within 6 months prior to randomization.
	• Prior therapy with docetaxel.
	• Patients with untreated or clinically unstable CNS metastases.

Abbreviations: AJCC = American Joint Committee on Cancer; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; NSCLC = non-small cell lung cancer; PS = performance status.

Study Settings

REVEL took place in 216 sites across 26 countries: Argentina, Austria, Brazil, Canada, France, Germany, Greece, Hungary, India, Israel, Italy, Korea, Mexico, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States.

Table 14 below summarises REVEL patient numbers screened and randomised by site and location

Table 14 Participant Settings and Locations

Country	Number of Sites		Number of Participants Screened	Number of Participants Randomised		
	Screened	Randomised		RAM + DOC N=628 n (%)	PBO + DOC N=625 n (%)	Total N=1253 n (%)
Argentina	7	6	39	16 (2.5)	17 (2.7)	33 (2.6)
Austria	4	4	21	11 (1.8)	9 (1.4)	20 (1.6)
Brazil	5	2	14	4 (0.6)	3 (0.5)	7 (0.6)
Canada	3	3	28	12 (1.9)	7 (1.1)	19 (1.5)
France	7	7	63	21 (3.3)	24 (3.8)	45 (3.6)
Germany	12	12	96	40 (6.4)	42 (6.7)	82 (6.5)
Greece	5	5	59	25 (4.0)	19 (3.0)	44 (3.5)
Hungary	5	4	18	9 (1.4)	4 (0.6)	13 (1.0)
India	9	9	90	22 (3.5)	33 (5.3)	55 (4.4)
Israel	6	6	43	14 (2.2)	8 (1.3)	22 (1.8)
Italy	8	8	63	26 (4.1)	28 (4.5)	54 (4.3)
Korea	6	6	79	34 (5.4)	28 (4.5)	62 (4.9)
Mexico	2	2	40	11 (1.8)	20 (3.2)	31 (2.5)
Netherlands	5	4	40	15 (2.4)	16 (2.6)	31 (2.5)
New Zealand	1	1	11	3 (0.5)	4 (0.6)	7 (0.6)
Norway	2	2	19	10 (1.6)	3 (0.5)	13 (1.0)
Poland	8	8	104	30 (4.8)	33 (5.3)	63 (5.0)
Romania	4	4	95	41 (6.5)	36 (5.8)	77 (6.1)
Russia	5	5	97	28 (4.5)	33 (5.3)	61 (4.9)
Spain	10	9	82	27 (4.3)	23 (3.7)	50 (4.0)
Sweden	4	4	26	10 (1.6)	7 (1.1)	17 (1.4)
Switzerland	5	5	29	12 (1.9)	14 (2.2)	26 (2.1)
Taiwan	7	7	32	9 (1.4)	18 (2.9)	27 (2.2)
Turkey	5	5	59	22 (3.5)	23 (3.7)	45 (3.6)
United Kingdom	8	8	52	19 (3.0)	19 (3.0)	38 (3.0)
United States	94	80	525	157 (25.0)	154 (24.6)	311 (24.8)

Abbreviations: N = total population size; n = number of patients.

Interventions

Patients received ramucirumab or placebo, followed by docetaxel (both treatment arms) on Day 1 of each cycle (21 days [3 weeks]). Ramucirumab (10 mg/kg) or placebo was administered as an approximate 1-hour IV infusion followed by a 1-hour observation period for Cycles 1 and 2. If there was no evidence of an infusion-related reaction (IRR) during the initial 2 cycles of ramucirumab/placebo, then no observation period was required for

subsequent treatment cycles. In the event that an IRR occurred thereafter, then the 1-hour observation was reinstituted. Docetaxel (75 mg/m^2) was administered afterwards as an approximate 60-minute IV infusion. Beginning with protocol amendment (d), for sites in Korea and Taiwan, new patients received docetaxel at a dose of 60 mg/m^2 as an approximate 60-minute IV infusion. For patients from Korea or Taiwan who initiated docetaxel at a starting dose of 75 mg/m^2 prior to Protocol Amendment (d), no dose reduction was necessary unless the patient experienced toxicity. No dose escalations or re-escalations were permitted.

Patients underwent radiographic investigator-assessment of disease status (computed tomography or magnetic resonance imaging) according to the Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST) version 1.1, every 6 weeks (± 3 business days), as calculated from the first dose of study therapy until there was radiographic documentation of progressive disease. The same method of assessment and the same technique was to be used to characterise each identified and reported lesion at baseline and during the study. Patients were treated until there was radiographic or symptomatic progressive disease, toxicity requiring cessation, or withdrawal of consent, or until other withdrawal criteria were met.

Dose modifications and discontinuations

Dose modifications were permitted for ramucirumab if non-life threatening and reversible Grade 3 clinical AE (e.g. fever) considered to be at least possibly related to ramucirumab resolved to Grade ≤1 or pre-treatment baseline within 1 treatment cycle (approximately 3 weeks). If a Grade 4 AE occurred and was deemed at least possibly related to ramucirumab, then ramucirumab was to be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolved to Grade ≤1 or pre-treatment baseline within 1 treatment cycle (approximately 3 weeks), treatment with ramucirumab could be continued at the discretion of the investigator. In these settings, ramucirumab could be re-administered. If a second instance of such an event occurred, ramucirumab was to be subsequently re-administered at a dose of 8 mg/kg every 3 weeks. A second dose reduction to 6 mg/kg every 3 weeks was permitted for a Grade 3 or 4 event. If the dose of ramucirumab was reduced because of potentially related AEs, subsequent dose increases were not permitted. Specific guidelines for ramucirumab dose modifications related to IRRs, hypertension, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding (haemorrhagic) events, proteinuria, gastrointestinal (GI) perforation, congestive heart failure, surgery, impaired wound healing, liver injury/liver

failure, and reversible posterior leukoencephalopathy syndrome (RPLS), and docetaxel dose modifications related to hypersensitivity reactions, hematologic toxicity, fluid retention, and cutaneous toxicity, were detailed in the protocol.

Dose reduction guidelines for docetaxel were as follows: patients who were dosed initially at 75 mg/m^2 and who experienced either febrile neutropenia (disorder characterised by a decrease in absolute neutrophil count <1.0 x 10^9/L with temperature ≥38.5°C), neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3 or 4 non haematological toxicities during docetaxel treatment had treatment withheld until resolution of the toxicity and then resumed at 65 mg/m^2 for the remainder of the study. If the patient again experienced one of the described toxicities, a second dose reduction of docetaxel to 50 mg/m^2 was possible. For East Asian patients beginning with a dose of 60 mg/m^2, a single dose reduction to 50 mg/m^2 was allowed. Patients who developed ≥Grade 3 peripheral neuropathy had docetaxel treatment discontinued entirely. Patients who required a delay of more than 14 days in starting a new cycle of chemotherapy (>35-day interval between consecutive cycles) were removed from treatment. Patients who were discontinued from docetaxel continued to be in the study, with ramucirumab/placebo treatment allowed to continue. Any Grade 3 or 4 nausea and vomiting led to an adaptation in the antiemetic therapy, with docetaxel dosing continuing unchanged. If this approach was not successful, docetaxel was reduced. All implemented dose modifications were permanent. The doses were modified according to the lowest haematology values and the highest degree of non-haematological toxicities observed at any time during the previous cycle.

Supportive care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients in this trial. Supportive care included, but was not limited to, antidiarrheal agents, antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, bone-modifying agents, and granulocyte and erythroid growth factors.

Prohibited therapies

Additional concurrent chemotherapy, radiation therapy (with curative intent), biologic response modifiers, or other investigational anticancer agents were not to be administered to patients during this study.

Outcomes

The primary efficacy variable in this study was overall survival (OS) (8). Secondary efficacy endpoints included progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Secondary outcomes also included safety and quality of life (QoL) as captured using the Lung Cancer Symptom Scale (LCSS) and EQ-5D.

Table 15 Summary of REVEL trial design

Trial Characteristic	I4T-MC-JVBA (REVEL)
Location	• 26 countries: Argentina, Austria, Brazil, Canada, Switzerland, Germany, Spain, France, United Kingdom, Greece, Hungary, Israel, India, Italy, Republic of Korea (Korea), Mexico, Netherlands, Norway, New Zealand, Poland, Romania, Russia, Sweden, Turkey, Taiwan, and United States • 216 sites
Trial Design	Randomised, placebo-controlled, double-blind, multicentre Phase 3 study
Eligibility criteria for participants	Patients aged 18 years and older; having an ECOG PS of 0 or 1 and pathologically confirmed squamous or non-squamous stage IV NSCLC that has progressed during or after a single platinum-based chemotherapy regimen.
Duration of study and Time study was conducted	• First patient was enrolled on 03 December 2010. • Data cut-off date for the CSR was 20 December 2013. (The final study database was validated and locked to include at least a minimum total of 869 events among randomised patients.). • 21 patients still on study at data cut-off date.
Trial drugs	• Intervention (N=628): ramucirumab, 10 mg/kg, 60-minute IV plus docetaxel, 75 mg/m^2, 60-minute IV administered on Day 1 of a 21-day cycle. • Comparator (N=625): equivalent volume of placebo, 60-minute IV, plus docetaxel, 75 mg/m^2, 60-minute IV administered on Day 1 of a 21-day cycle.
Method of randomisation	• The site registered eligible patients by phoning the IVRS. • Patients were assigned a unique study ID number and were randomised to 1 of the 2 treatment arms on a 1:1 basis. Stratified by all combinations of the following 4 prognostic factors: • ECOG PS at baseline (0 vs. 1) • sex(female vs. male) • prior maintenance therapy for advanced NSCLC (yes vs. no) • geographic region (East Asia vs. ROW)
Method of blinding	• This was a double-blind, placebo-controlled study. • Ramucirumab and placebo for injection were identical in appearance in order to preserve blinding.
Primary outcome (including scoring methods and timings of assessments)	• Overall survival**:** Time from date of randomisation to date of death from any cause. • Tumour assessments were performed every 6 weeks (± 3 business days) following first dose of study therapy until radiographically documented progressive disease. Patients that did not have a radiographic progression were assessed every 8 weeks (± 7 days) to obtain information about survival status and disease progression for as long as the patient was alive, or until study completion.

Trial Characteristic	I4T-MC-JVBA (REVEL)
Secondary outcomes (including scoring methods and timings of assessments)	• PFS (time from randomisation until disease progression or death), ORR, and DCR were assessed by investigators according to RECIST v 1.1 at baseline, and every 6 weeks thereafter. • Patient-reported symptoms and quality of life were assessed at baseline, the end of each cycle, and at the end of therapy, using LCSS and EQ-5D questionnaires. • Safety was evaluated based on reported AEs, clinical laboratory assessments, vital signs, and physical examinations. Adverse events were coded using MedDRA version 16.1 and graded using NCI-CTCAE V 4.0. Adverse events were collected at every visit, and collected until at least 30 days after discontinuing study treatment. After this point, only new and ongoing SAEs deemed related to study treatment were collected.
Duration of follow-up	• Post-discontinuation follow-up began the day after the patient and the investigator agreed that the patient will no longer continue study treatment. • The short-term follow-up period began on the day after treatment discontinuation and lasted approximately 30 days. • The long-term follow-up period began 1 day after the short-term follow-up period was completed and continued until death or study completion to collect additional data (e.g., survival data).
Pre-planned subgroups	• ECOG PS (0 vs. 1) • sex (female vs. male) • prior maintenance therapy (yes vs. no) • geographic region (Japan/East Asia vs. ROW) • smoking history (never vs. ever) • histology (nonsquamous vs. squamous) • best response to platinum-based chemotherapy (CR/PR/SD vs. progressive disease) • prior taxane treatment (no vs. yes) • prior bevacizumab treatment (no vs. yes) • EGFR status (wild-type vs. mutation vs. unknown) • age (<65 years vs. ≥65 years and <70 years vs. ≥70 years) • race (White vs. Black vs. Other) • time since prior therapy (<9 months vs. ≥9 months

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Sample size

To detect a Hazard ratio of 0.816 with a two-sided 5% significance level and a power of 85%, a sample size of 621 patients per treatment arm was necessary, given an anticipated 869 observed deaths and 30% censoring rate. Thus the plan was to enrol 1242 patients and randomly allocate them to the two study treatment arms. The actual number of patients enrolled was 1253. The total number of overall survival events among randomised patients was monitored during enrolment and follow-up, to include at least 869 events.

Statistical Methods

The primary efficacy variable in REVEL was overall survival (OS), defined as the time from the date of randomisation until the date of death from any cause. If the patient was alive at the end of the follow-up period (or was lost to follow-up), OS data was censored for analysis on the last date the patient was known to be alive. Tumour assessments were performed every 6 weeks (± 3 business days) following first dose of study therapy until radiographically documented progressive disease. Patients that did not have a radiographic progression were assessed every 8 weeks (± 7 days) to obtain information about survival status and disease progression for as long as the patient was alive, or until study completion.

OS was assessed in the intent-to-treat (ITT) population. Unless otherwise specified, observed data was used and missing data were not imputed or carried forward. OS between treatment arms was compared using a stratified (ECOG status, sex, prior maintenance therapy and geographic region) log-rank test at a two-sided 5% level of significance. The HR was determined using a Cox regression model stratified identically to the primary log-rank test with assigned treatment as the only covariate, reported with 2-tailed 95% confidence intervals (CIs) and Wald's test p-value. Survival curves for the two treatment arms were estimated by the Kaplan-Meier method (median 95% CI).

An interim efficacy analysis for futility was done by an Independent data monitoring committee after 150 OS events. Sensitivity analysis included a stratified log-rank test using preselected stratification factors (ECOG status, sex, prior maintenance therapy and geographic region); estimation of HR using an un-stratified Cox regression model and estimation of HR using a multivariate Cox regression model that was constructed using

preselected stratification factors. A summary of the statistical analysis for REVEL can be found in Table 16.

Secondary efficacy endpoints included progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR). PFS is defined as the time from the date of randomisation until the date of objectively determined progressive disease or death due to any cause. Patients without objectively determined progressive disease who were alive at the end of the follow-up period (or who were lost to follow-up) were censored on the date of the patient's last complete radiographic tumour assessment; if no baseline or post baseline radiologic assessment was available, the patient was censored at the date of randomisation. For PFS, the same analyses used for the analyses of the primary endpoint, OS was performed. The log-rank test of PFS (sensitivity analysis) was also repeated to evaluate whether and to what extent the conclusion of the PFS analysis under the primary definition would be affected under the different censoring rules. The objective response rate (ORR) is the proportion of randomised patients achieving a best overall response of partial response (PR) or complete response (CR) and the disease control rate (DCR) is defined as the proportion of randomised patients achieving a best overall response of PR, CR, or stable disease (SD). Tumour response rate (CR+PR) and DCR (CR+PR+SD) was reported along with exact CIs (95%) and compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

A gatekeeping strategy was utilised to control the overall type I error at 0.05 (2-sided) for the analysis of the primary endpoint (OS) and the secondary endpoints PFS and objective response rate (ORR). Only if the primary OS test was significant would the analysis of PFS be considered inferential. Only if the analysis of PFS was significant would the analysis of ORR be considered inferential.

Table 16 Summary of Statistical Analyses in REVEL

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
REVEL	The sample size calculation was based on a superiority test for comparing OS between the two treatment arms.	OS was compared using a log-rank test (stratified) at a two-sided 5% level of significance. The HR and 95% CIs were determined using a Cox regression model stratified identically to the primary log-rank test with assigned treatment as the only covariate. Kaplan-Meier estimates including 95% CIs were presented for median OS. Sensitivity analysis included estimation of HR using an un-stratified Cox regression model and estimation of HR using a multivariate Cox regression model that was constructed using preselected stratification factors.	The sample size was based on the following assumptions:869 deaths observed among 1242 patients (30% censoring rate); 2-sided 0.05; 85% statistical power assuming OS HR = 0.816 (median OS of 7.5 months in the placebo plus docetaxel arm and 9.2 months in the ramucirumab plus docetaxel arm); randomization ratio of 1:1	Unless otherwise specified, observed data was used and missing data were not imputed or carried forward. Data were imputed for partial dates concerning pivotal efficacy or safety parameter according to rules specified in the statistical analysis plan.

Subgroup Analyses

REVEL was not powered for subgroup analysis. Therefore the goal of the subgroup analyses was to assess internal consistency of study results, and whether there was significant treatment heterogeneity across any of the subgroups. Pre-specified subgroups included stratification and potential prognostic factors. These are listed in Table 17 below. OS and PFS HR and 95% CIs for pre-specified subgroups were estimated using the primary cox regression model. A forest plot of the estimated HRs and their 95% CIs was also generated

Table 17 REVEL pre-specified subgroups

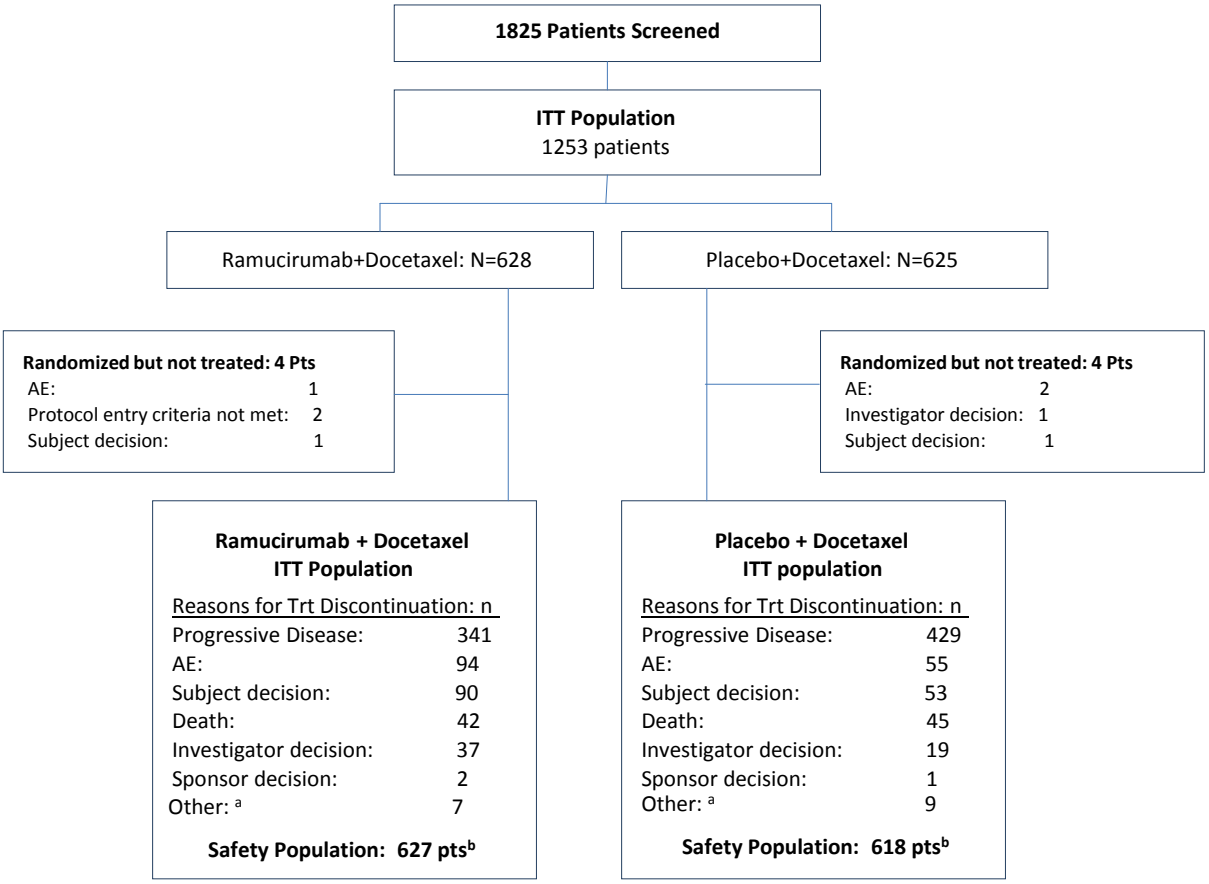
Stratification factors	Other factors
• ECOG PS (0 vs. 1*) • sex (female vs. male*) • prior maintenance therapy (yes vs. no*) • geographic region (Japan/East Asia vs. Rest of the World*)	• smoking history (never* vs. ever) • histology (nonsquamous vs. squamous*) **Note**. Histology was defined based on pathological diagnosis at study entry or initial pathological diagnosis if pathological diagnosis at study entry was missing. • best response to platinum-based chemotherapy (CR/PR/SD vs. progressive disease*) • prior taxane treatment (no* vs. yes) • prior bevacizumab treatment (no* vs. yes) • EGFR status (wild-type vs. mutation* vs. unknown) • age (<65 years vs. ≥65 years* and <70 years vs. ≥70 years*) • race (White* vs. Black vs. Other) • time since prior therapy (<9 months vs. ≥9 months*), with time since prior therapy defined as the time from the start of the prior therapy to randomisation.

* indicates the reference level

4.5 Participant flow in the relevant randomised controlled trials

As summarised in Figure 5 below, 1825 patients were screened and 572 excluded. Reasons for exclusion included presence of untreated CNS metastases, radiological evidence of major blood vessel involvement and inadequate organ function. 1253 patients were randomised (628 patients to the ramucirumab plus docetaxel arm and 625 patients to the placebo plus docetaxel arm), which constituted the ITT population. The first patient in the study was enrolled on 03 December 2010 and the data cut-off date was 20 December 2013. At data cut-off, 21 patients were receiving study treatment. Four patients randomised to the RAM+DOC arm and four patients randomised to the PBO+DOC arm did not receive any treatment. Three patients randomised to the PBO+DOC arm received 1 cycle (1 dose) of ramucirumab instead of placebo, in error. These patients were included in the PBO+DOC arm in the ITT population ("as randomised") and were included in the RAM+DOC arm in the Safety population ("as treated"). Consequently, the Safety population consisted of 627 patients in the RAM+DOC arm and 618 patients in the PBO+DOC arm.

Figure 5 REVEL: Patient disposition



Abbreviations: AE = adverse event; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; Pts = patients; Trt = treatment.

[a] 'Other' includes protocol entry criterion not met and protocol deviation.

[b] Three patients randomised to the placebo plus docetaxel arm received ramucirumab instead of placebo for 1 cycle only, in error.

Baseline patient demographic and clinical characteristics

The demographic and baseline disease characteristics were generally balanced between treatment arms and reflective of the overall population of patients with advanced NSCLC enrolled in clinical trials. Selected demographic characteristics and baseline disease characteristics for the ITT population are summarised in Table 18. Almost all patients (99.4%) had received prior standard platinum-based chemotherapy (8 patients who did not receive prior standard platinum-based chemotherapy were noted as protocol deviators), 22.2% had received prior maintenance therapy (45), 24.3% had received prior taxane (paclitaxel only), and 14.4% had received prior bevacizumab as first-line treatment.

Table 18 Baseline characteristics of patients (intent-to-treat population)

Parameters	I4T-MC-JVBA (REVEL)	
	Ramucirumab + Docetaxel N = 628	Placebo + Docetaxel N = 625
Sex, n (%)		
Female	209 (33.3)	210 (33.6)
Male	419 (66.7)	415 (66.4)
Age (years)		
Median age (range)	62 (21-85)	61 (25-86)
Age group (years), n (%)		
<65	391 (62.3)	407 (65.1)
≥65	237 (37.7)	218 (34.9)
<70	501 (79.8)	500 (80.0)
≥70	127 (20.2)	125 (20.0)
Race, n (%)		
White	526 (83.8)	503 (80.5)
Black or African American	17 (2.7)	16 (2.6)
Asian	74 (11.8)	86 (13.8)
Other	11 (1.8)	20 (3.2)
ECOG performance status[a], n (%)		
0	207 (33.0)	199 (31.8)
1	420 (66.9)	425 (68.0)
Prior maintenance therapy, n (%)		
No	493 (78.5)	482 (77.1)
Yes	135 (21.5)	143 (22.9)
Geographic region, n (%)		
East Asia[b]	43 (6.8)	46 (7.4)
ROW	585 (93.2)	579 (92.6)
Pathological diagnosis at study entry, n (%)	**627**	**624**
Nonsquamous	465 (74.2)	447 (71.6)
Adenocarcinoma	377 (60.0)	348 (55.7)
Large cell	14 (2.2)	21 (3.4)
Nonsquamous, other	74 (11.8)	78 (12.5)
Squamous	157 (25.0)	171 (27.4)
Other diagnoses, not lung cancer	5 (0.8)	6 (1.0)
Disease stage at initial diagnosis, n (%)		
Stage I	22 (3.5)	15 (2.4)
Stage IIA	18 (2.9)	10 (1.6)
Stage IIB	12 (1.9)	10 (1.6)

Parameters	I4T-MC-JVBA (REVEL)	
	Ramucirumab + Docetaxel N = 628	**Placebo + Docetaxel N = 625**
Stage IIIA	50 (8.0)	32 (5.1)
Stage IIIB	43 (6.8)	45 (7.2)
Stage IV	482 (76.8)	511 (81.8)
Missing	1 (0.2)	2 (0.3)
Prior Systemic Therapy, n (%)		
Patients with at least one prior therapy	626 (99.7)	625 (100.0)
Chemotherapy, n (%)	**625 (99.5)**	**625 (100.0)**
Platinums	623 (99.2)	622 (99.5)
Antimetabolites	386 (61.5)	395 (63.2)
Pemetrexed	231 (36.8)	247 (39.5)
Gemcitabine	156 (24.8)	151 (24.2)
Other	2 (0.3)	2 (0.3)
Taxanes	153 (24.4)	152 (24.3)
Vinca Alkaloids	74 (11.8)	68 (10.9)
Topoisomerase Inhibitors[c]	42 (6.7)	34 (5.4)
Alkylating Agent[c]	2 (0.3)	2 (0.3)
VEGF Inhibitors, n (%)	**89 (14.2)**	**93 (14.9)**
Bevacizumab	89 (14.2)	92 (14.7)
Aflibercept	0	1 (0.2)
EGFR Inhibitors, n (%)	**38 (6.1)**	**36 (5.8)**
Tyrosine Kinase Inhibitors	23 (3.7)	25 (4.0)
EGFR Antibodies[c]	15 (2.4)	11 (1.8)
Investigational Drug, n (%)	**34 (5.4)**	**33 (5.3)**
Other, n (%)	**13 (2.1)**	**15 (2.4)**

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ITT intent-to-treat; N = total population size; n = number of patients; ROW = rest of the world; SD = standard deviation. EGFR= epidermal growth factor receptor; VEGF = vascular endothelial growth factor. Note: Percentages are based on the total number of patients per treatment group and patients can be counted in more than 1 category

[a] ECOG performance status data are not available for 1 patient in each treatment arm.

[b] East Asia includes Republic of Korea and Taiwan.

[c] Alkylating agents include cyclophosphamide; topoisomerase inhibitors include, for example, anthracyclines and etoposide; and EGFR antibodies include cetuximab (46).

4.6 Quality assessment of the relevant randomised controlled trials

Randomisation and Allocation

Patients were enrolled using interactive voice response systems (IVRSs) that generated a computerised allocation sequence and implemented the allocation sequence in a concealed way. With IVRS, treatment codes for individual patients were not available at the sites, and thus not easily broken (investigators needed to call the IVRS vendor to break the code). Therefore, the risk of bias associated with the randomisation and allocation methodology was assessed to be low. Assignment to treatment arm was determined by a computer-generated random sequence: patients were randomised in a 1:1 ratio to treatment with either RAM+DOC or PBO+DOC. Each patient was assigned a unique study identification number, which was recorded in all electronic case report forms (eCRFs) and used for all correspondence.

Assessment of risk of bias

The risk of bias due to inadequate blinding was assessed to be low, since (1) only a minimum number of Lilly personnel (e.g. study representative within the IVRS group) had access to the randomisation table and treatment assignments before the study was completed; (2) the investigational drug and placebo had an identical appearance; and (3) standardised procedures were in place to restrict un-blinding. Table 19 provides a summary of measures taken to minimise bias in REVEL.

Table 19 Summary of the Measures Taken to Minimise Bias in REVEL

Concealment of Randomisation	Blinding		
	Participants	Investigators	Outcomes assessors
Computer generated, centralized system (IVRS)	Treatments were identical in appearance Drug and placebo were assigned to patients using IVRS	Treatments were identical in appearance Drug and placebo were assigned to patients using IVRS Treatment assignment was scrambled so that healthcare professionals remained blinded	Drug and placebo were identical in appearance, and assigned to patients using IVRS Treatment group codes and other variables were blinded in the database until primary data lock Treatment assignment was scrambled in the reporting database until the primary data lock

Abbreviation: IVRS = interactive voice response system.

Table 20 presents a quality assessment of REVEL. The trial was completed to the highest standard with adequate randomisation and blinding procedures.

Table 20 Quality assessment results for REVEL

Trial number (acronym)	**I4T-MC-JVBA (REVEL)**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and where appropriate methods used to account for missing data?	Yes, yes
Adapted from Systematic review: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

- In total 1253 patients were randomised; 628 patients to RAM+DOC and 625 patients to PBO+DOC
- Baseline patient demographics, disease and other characteristics were balanced between treatment arms
- RAM+DOC significantly improved OS compared with PBO+DOC (HR = 0.857; 95% CI: 0.751, 0.979; p=0.024).
- Median OS was 10.5 months (95% CI: 9.5, 11.2) in patients receiving RAM+DOC and 9.1 months (95% CI: 8.4, 10.0) in patients receiving PBO+DOC
- Survival rates at 12 and 24 months were higher in the RAM+DOC group than in the PBO+DOC group at 42.9% and 20.9% versus 37.7% and 17.5% respectively
- Median PFS was 4.5 months (95% CI: 4.2, 5.3) in the RAM+DOC arm versus 3.0 months (95% CI 2.8, 3.9) in the PBO+DOC arm, reducing the risk of disease progression or death by 23.8% (HR = 0.762; 95% CI: 0.677, 0.859; p<0.001)
- More patients responded to treatment with RAM+DOC with a significantly greater ORR and DCR in patients treated with RAM+DOC (ORR: 22.9%; DCR: 64%) compared to PBO+DOC (ORR: 13.6%; DCR 52.6%)
- There were minimal changes from baseline in EQ-5D index or VAS scores while on study therapy, regardless of treatment arm
- The time to deterioration (TTD) of ECOG PS to ≥2 was similar between treatment arms (HR = 1.03; 95% CI: 0.85, 1.26).
- The TTD for all LCSS items were similar between the two treatment arms utilising the pre-specified ≥ 15 mm increase from baseline to define deterioration

Primary Outcome – Overall Survival (OS)

The primary outcome of REVEL was OS. Primary and secondary endpoints were analysed using the ITT population. REVEL met its primary endpoint demonstrating a statistically significant and clinically meaningful improvement in OS for RAM+DOC compared to PBO+DOC. This is summarised in Table 21 below.

Table 21 REVEL: OS Results (ITT population)

Outcome	RAM+DOC N = 628	PBO+DOC N = 625	Treatment Difference
Number of Deaths, n (%)	428 (68.2)	456 (73.0)	
Number censored, n (%)	200 (31.8)	169 (27.0)	
Median Survival, months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)	1.4
Log-rank p-value			
Stratified, 2-sided	0.024		
Hazard ratio			
Stratified HR (95% CI)	0.857 (0.751, 0.979)		
Survival rate, %			
12 months (95% CI)	42.9 (38.9, 46.9)	37.7 (33.8, 41.5)	5.3 (-0.3, 10.9)
24 months (95% CI)	20.9 (17.0, 25.1)	17.5 (13.8, 21.5)	3.5 (-2.1, 9.0)

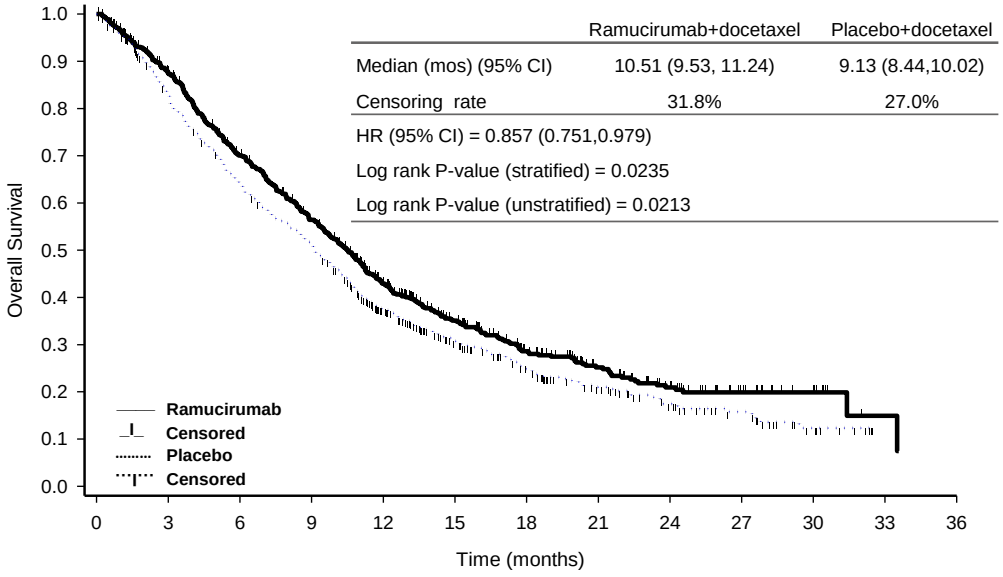
Abbreviations: CI = confidence interval; HR = hazard ratio; N = total population size; n = number of patients.
Note: Overall survival is the duration from randomization to death. For patients who are alive, overall survival is censored at the last contact.

Median OS was 10.5 months for RAM+DOC and 9.1 months for PBO+DOC. RAM+DOC prolonged median survival by 15.4% (1.4 months) and reduced the risk of death by 14.3% (HR = 0.857; 95% CI: 0.751, 0.979; p=0.024). Survival rates at 12 and 24 months were higher in the RAM+DOC group than in the PBO+DOC group at 42.9% and 20.9% versus 37.7% and 17.5% respectively.

The robustness of the primary OS analysis was demonstrated by four sensitivity analyses, where HRs ranged from 0.81 to 0.86 and was similar to those of the primary analysis, all with p ≤0.027. The percentage of patients who received post-discontinuation systemic anticancer therapy (PDT) and the types of PDT used were similar between treatment arms, suggesting that the observed prolongation of OS is due to a treatment effect of the combination of ramucirumab with docetaxel.

Figure 6 shows the Kaplan-Meier plot of OS for the ITT population. The Kaplan-Meier survival curves separated at 1.5 months and remained separate throughout the observation period.

Figure 6 REVEL: Kaplan-Meier plot of OS (ITT population)



Patients at Risk

Ramucirumab+docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months.

Secondary outcomes

Progression-free survival (PFS)

Treatment with ramucirumab significantly reduced the risk of disease progression or death by 23.8% (HR = 0.762; 95% CI: 0.677, 0.859; p<0.001), with a 1.5-month longer median PFS in the RAM+DOC arm than the PBO+DOC arm (4.5 months vs. 3.0 months, respectively). This represents a 50% increase in median PFS over standard of care. At 12 months, the rate of PFS was 12.2% in the RAM+DOC arm versus 7.1% in the PBO+DOC arm. The result is summarised in Table 22 below.

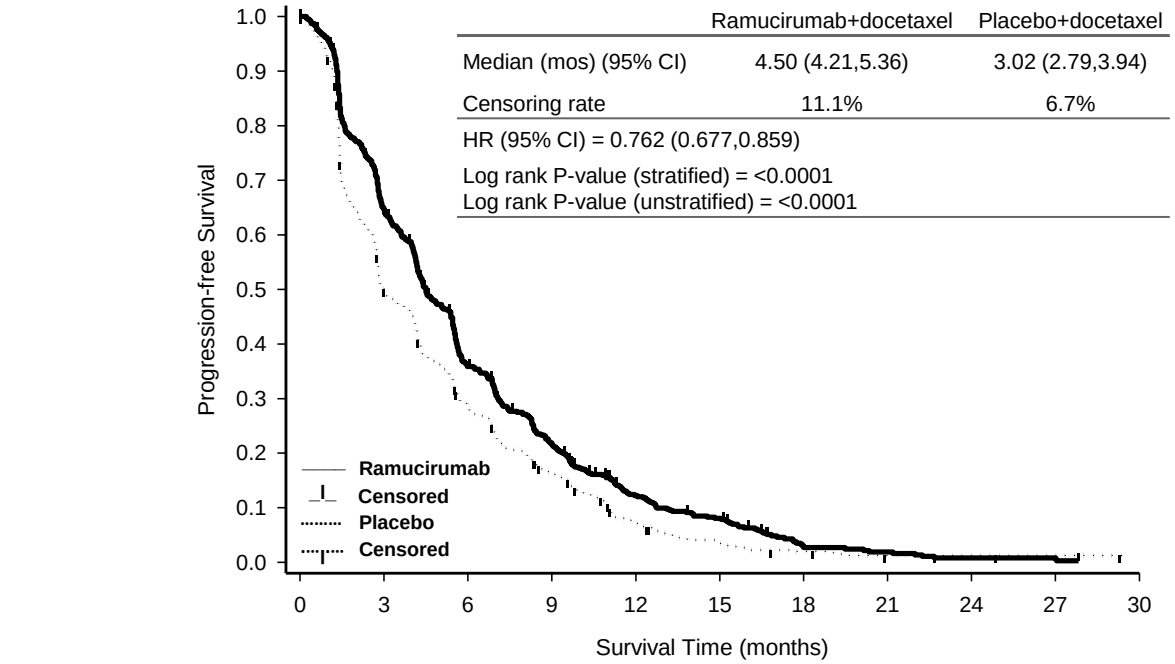
The robustness of the main PFS analysis results was supported by pre-specified sensitivity analyses, as demonstrated by consistent HRs between 0.75 and 0.80, all with p<0.001 Collectively, the sensitivity analyses support the finding of an improvement in PFS associated with RAM+DOC versus PBO+DOC. The type I error for evaluation of PFS as a secondary endpoint was controlled using gatekeeping methodology. Therefore, the statistical significance of the improvement in PFS can be considered inferential.

Table 22 REVEL: PFS Results (ITT population)

Outcome	RAM+DOC N=628	PBO+DOC N=625	Treatment difference
Number of events, n (%)	558 (88.9)	583 (93.3)	
Number censored, n (%)	70 (11.1)	42 (6.7)	
Median PFS, months (95% CI)	4.5 (4.2, 5.3)	3.0 (2.8, 3.9)	1.5
Log-rank p-value			
Stratified	<0.0001		
Hazard ratio			
Stratified HR (95% CI)	0.762 (0.677, 0.859)		
PFS rate (%)			
3 months (95% CI)	64.7 (60.7, 68.3)	50.1 (46.1, 54.0)	14.6 (9.0, 20.1)
6 months (95% CI)	35.9 (32.0, 39.8)	29.1 (25.5, 32.7)	6.8 (1.5, 12.2)
9 months (95% CI)	21.8 (18.5, 25.3)	16.6 (13.8, 19.7)	5.2 (0.7, 9.8)
12 months (95% CI)	12.2 (9.6, 15.1)	7.1 (5.2, 9.5)	5.1 (1.6, 8.6)

Figure 7 shows the Kaplan-Meier plot of PFS for the ITT population.

Figure 7 REVEL: Kaplan-Meier plot of PFS (ITT population)



Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months

Objective Response Rate (ORR) and Disease Control Rate (DCR)

Of the 628 patients randomised to the RAM+DOC arm, 3 patients had a complete response (CR) and 141 patients had a partial response (PR). Of the 625 patients randomised to PBO+DOC, 2 patients had a CR and 83 patients had a PR. Thus the ORR (CR + PR) was significantly improved for the RAM+DOC arm as compared to the PBO+DOC arm (22.9% vs. 13.6%, respectively; p<0.001). This is summarised in Table 23 below. A total of 258 patients in the RAM+DOC arm and 244 patients in the PBO+DOC arm had a best overall response of stable disease (SD). The DCR (CR+PR+SD) for the RAM+DOC arm and the PBO+DOC arm were 64.0% (95% CI: 60.1%, 67.8%) and 52.6% (95% CI: 48.6%, 56.6%), respectively, showing an improvement in DCR in the RAM+DOC arm (p<0.001). Since the type I error for evaluation of ORR as a secondary endpoint was controlled using gatekeeping methodology, the statistical significance of the improvement in ORR can be considered inferential.

Table 23 REVEL: ORR and DCR results (ITT population)

	RAM+DOC N = 628	**PBO+DOC N = 625**	**P-value***
Best overall response [a] n (%)			
Complete response (CR)	3 (0.5)	2 (0.3)	
Partial response (PR)	141 (22.5)	83 (13.3)	
Stable disease (SD)	258 (41.1)	244 (39.0)	
Progressive disease (PD)	128 (20.4)	206 (33.0)	
Unknown/Not done	98 (15.6)	90 (14.4)	
Objective response (CR+PR) rate	**22.9%**	**13.6%**	
95% CI[b] for response rate	(19.7%, 26.4%)	(11.0%, 16.5%)	<0.001
Disease control (CR+PR+SD) rate	**64.0%**	**52.6%**	
95% CI[b] disease control rate	(60.1%, 67.8%)	(48.6%, 56.6%)	<0.001

Abbreviations: CI = confidence interval; CR = complete response; N = total population size; n = number of patients; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Response criteria used was Response Evaluation Criteria In Solid Tumors Version 1.1.

[b] Confidence intervals are based on the exact method.

* The p-value is based on the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

Quality of Life (QoL)

All patients for whom there was a validated translation in which the patient was fluent underwent assessment for symptoms and QoL using the LCSS and the EQ-5D. The patient-reported instruments were administered together and in sequence order, with the LCSS presented first, followed by presentation of the EQ-5D. Patients completed the instruments at baseline (within 14 days prior to randomisation), at approximately Day 21 of each cycle, at

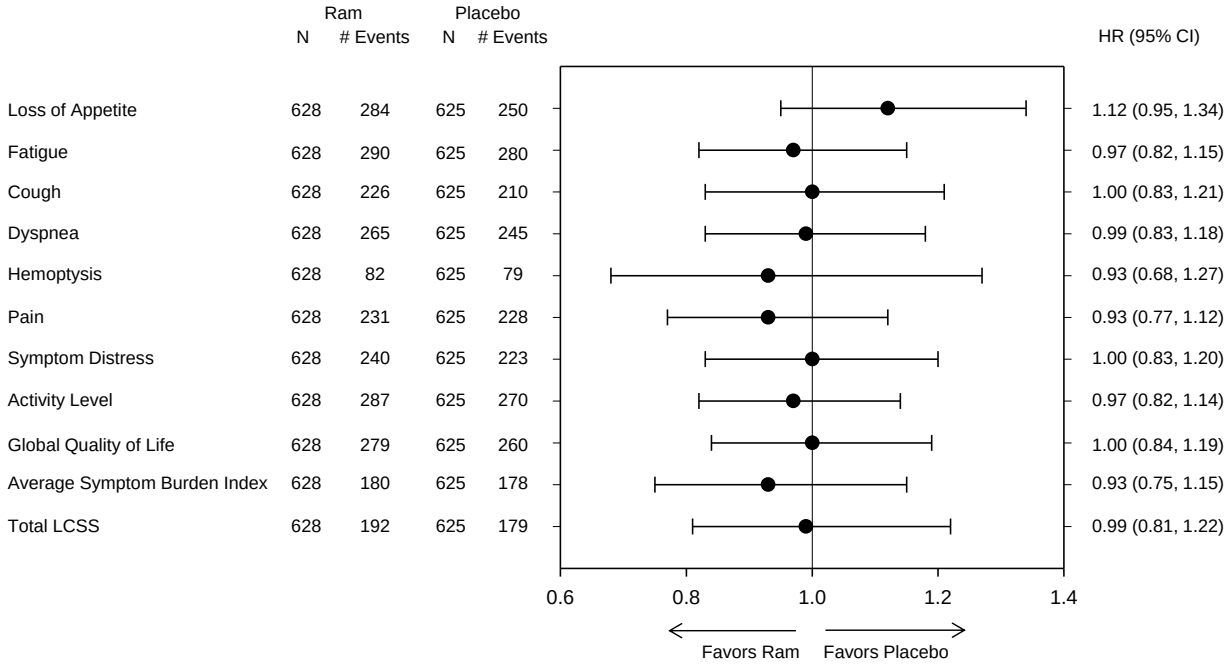
the summary visit, and at the 30-day safety follow-up visit. On days that the patient received study treatment, assessments were completed prior to treatment administration.

Lung cancer symptom scale (LCSS)

Overall (across all time points) for the LCSS, patient compliance for completion was approximately 75% and was generally balanced between treatment arms. At baseline, compliance for LCSS completion was approximately 78% in both treatment arms, while at the 30-day safety follow-up visit, compliance was 61.0% in the RAM+DOC arm and 62.2% in the PBO+DOC arm. The number of expected questionnaires to be completed at each scheduled assessment decreased over time as the number of patients discontinuing from therapy increased, more markedly in the PBO+DOC arm following baseline.

LCSS assessments were used to measure the quality of life (QoL) of study participants and included a total of 11 items; 6 questions focused on lung cancer symptoms (appetite loss, fatigue, cough, shortness of breath, blood in sputum and pain); 3 global items (symptom distress, difficulties with daily activities and quality of life); the average symptom burden index (ASBI - the mean over 6 symptom specific items); and the LCSS total score (the mean over all 9 items). The Time to deterioration (TTD), defined as the time from randomisation to the first 15 mm increase, was calculated for each of the 11 LCSS items. The TTD for all scores were similar between the two treatment arms utilising the pre-specified ≥ 15 mm increase from baseline to define deterioration (see Figure 8). Overall results were consistent with the pre-specified analysis when deterioration was defined in a post hoc sensitivity analysis as a 10-mm increase from baseline. Most of the additional pre-specified analyses suggested that QoL was maintained by treatment with RAM+DOC relative to PBO+DOC. The few differences that were statistically significant were neither consistent nor clinically meaningful. This suggests that overall the observed improvement in OS and PFS was not associated with a reduction in quality of life.

Figure 8 Forest plot for time to deterioration for LCSS (ITT population)



Abbreviations: CI = confidence interval; HR = hazard ratio; LCSS = Lung Cancer Symptom Score; N = total number of patients; Ram = ramucirumab.

EQ5D

Overall (across all time points) for the EQ-5D, patient compliance for completion was approximately 80% and was generally balanced between treatment arms. At baseline, compliance for completion was 80% or greater in both treatment arms, while at the 30-day safety follow-up visit, compliance was 63.9% in the RAM+DOC arm and 65.7% in the PBO+DOC arm. Overall, there were minimal changes from baseline in index or VAS scores while on study therapy, regardless of treatment arm. Scores in both arms decreased at the end-of-treatment assessment.

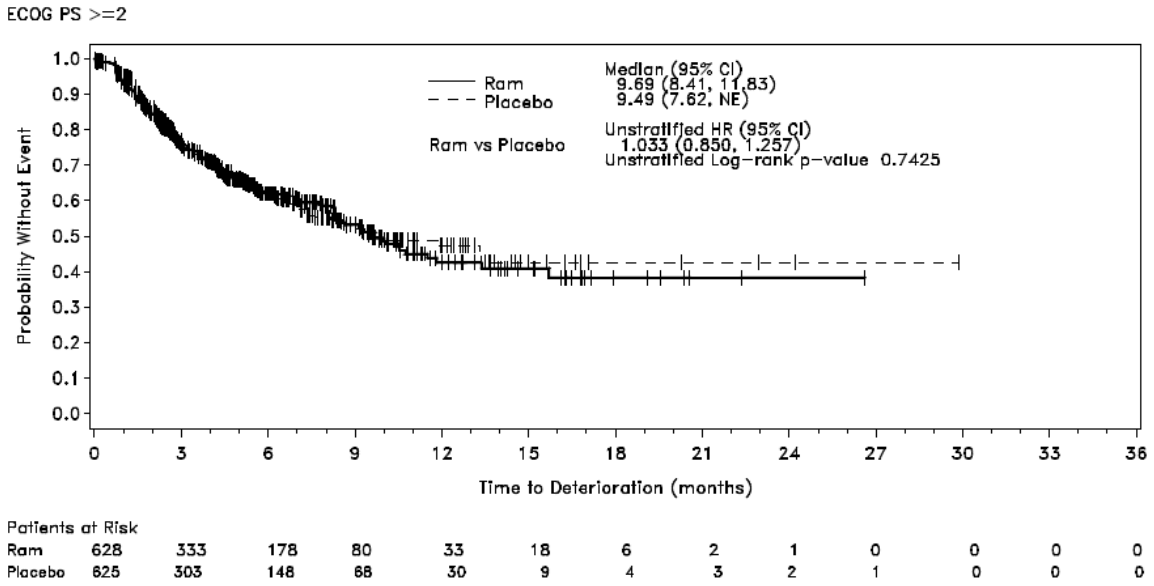
Table 24 REVEL: EQ-5D Results

	RAM+DOC N=628	PBO+DOC N=625
Compliance, n (%)		
Overall	4553 (80.6) / 5651	4041 (79.2) / 5104
Patients completing baseline EQ-5D	521 (83.0)	532 (85.1)
Patients completing end of treatment (30-day follow-up visit) EQ-5D	310 (63.9)	322 (65.7)
EQ-5D Index Score, mean (SD)		
Baseline	0.714 (0.232)	0.687 (0.259)
Cycle 2	0.707 (0.248)	0.692 (0.273)
Cycle 3	0.704 (0.251)	0.707 (0.258)
Cycle 4	0.700 (0.250)	0.721 (0.255)
Cycle 5	0.678 (0.250)	0.752 (0.221)
Cycle 6	0.697 (0.246)	0.740 (0.238)
Cycle 7	0.712 (0.244)	0.741 (0.213)
Cycle 8	0.699 (0.235)	0.727 (0.213)
Cycle 9	0.738 (0.228)	0.698 (0.264)
Cycle 10	0.741 (0.200)	0.700 (0.265)
Cycle 11	0.706 (0.221)	0.743 (0.232)
Cycle 12	0.717 (0.240)	0.725 (0.260)
Cycle 13	0.690 (0.241)	0.719 (0.249)
Cycle 14	0.698 (0.212)	0.746 (0.236)
Cycle 15	0.714 (0.201)	0.802 (0.155)
Cycle 16	0.745 (0.209)	0.763 (0.196)
Summary Visit	0.611 (0.285)	0.579 (0.360)
30-day follow up	0.612 (0.201)	0.595 (0.340)

Time to Deterioration in ECOG Performance Status

Time to deterioration in ECOG performance status is defined as the time from the date of randomisation to the first date observing a change (i.e., deterioration) in ECOG PS to ≥2. Time to deterioration in ECOG PS was analysed using the Kaplan-Meier method and compared using an unstratified log-rank test. The results are presented in Figure 9, below. The time to deterioration of ECOG PS to ≥2 was similar between treatment arms (HR = 1.03; 95% CI: 0.85, 1.26). Approximately two-thirds of patients were censored in this analysis. Time to deterioration using variations on the definition of deterioration of ECOG PS were also similar between treatment arms (95% CIs for the HRs contained 1). Table 25 below is a summary of the results.

Figure 9 Kaplan-Meier graph of time to deterioration (months) for ECOG performance status, intent-to-treat populations, ECOG PS ≥2.



Abbreviations: CI = confidence interval; NE = not estimable; HR = hazard ratio.

In case of no event, the subject is censored at time of the last ECOG PS.

Table 25 Summary of Time to Deterioration (Months) for ECOG Performance Status Intent-to-Treat Population

Criteria for Deterioration	Ramucirumab (N = 628)		Placebo (N = 625)		Hazard Ratio*b (95% CI)	Log-Rank p-value*c
	Events	Median*a (95%CI)	Events	Median*a (95%CI)		
Time to ECOG PS ≥2	212	9.69 (8.41, 11.83)	190	9.49 (7.62, NE)	1.03 (0.85, 1.26)	0.742
Time to ECOG PS ≥3	62	NE (17.54, NE)	67	NE (NE, NE)	0.80 (0.57, 1.13)	0.212
Time to ECOG PS Deterioration by ≥ 1 point	330	4.17 (3.58, 4.86)	291	4.90 (4.17, 5.65)	1.12 (0.96, 1.31)	0.164
Time to ECOG PS Deterioration by ≥ 2 point	95	NE (17.54, NE)	85	NE (NE, NE)	0.99 (0.74, 1.32)	0.925

Abbreviations: CI = confidence interval; N = total population size; NE = Not estimable.

In case of no event, the subject is censored at time of the last ECOG PS.

*a Estimated by the Kaplan-Meier method. Patients who do not provide any post-baseline assessments were censored at the randomisation date.

*b Hazard ratio and 95% CI (Wald) were estimated using an unstratified Cox model.

*c Unstratified log rank p-value.

4.8 Subgroup analysis

There were 13 pre-specified variables in the subgroup analysis. An improvement in OS and PFS was consistently observed across most pre-specified subgroups. The forest plots for OS and PFS subgroup analyses (see Figure 10 and Figure 11 below) included all 13 pre-specified subgroups and three additional variables not pre-specified in the statistical analysis plan (SAP): initial staging, liver metastases, and central nervous system (CNS) metastases. The Forest plots for OS and PFS show that, in most of the pre-specified subgroups, the estimate of treatment effect (as assessed by the un-stratified HR) numerically favours the RAM+DOC arm over the PBO+DOC arm. A statistically significant and clinically meaningful improvement in OS and PFS was consistently observed across squamous and non-squamous histology, in male and female patients, in patients from different geographies, in patients with different smoking status, in patients with different EGFR status and in patients with or without prior taxane, prior maintenance, or prior bevacizumab treatment.

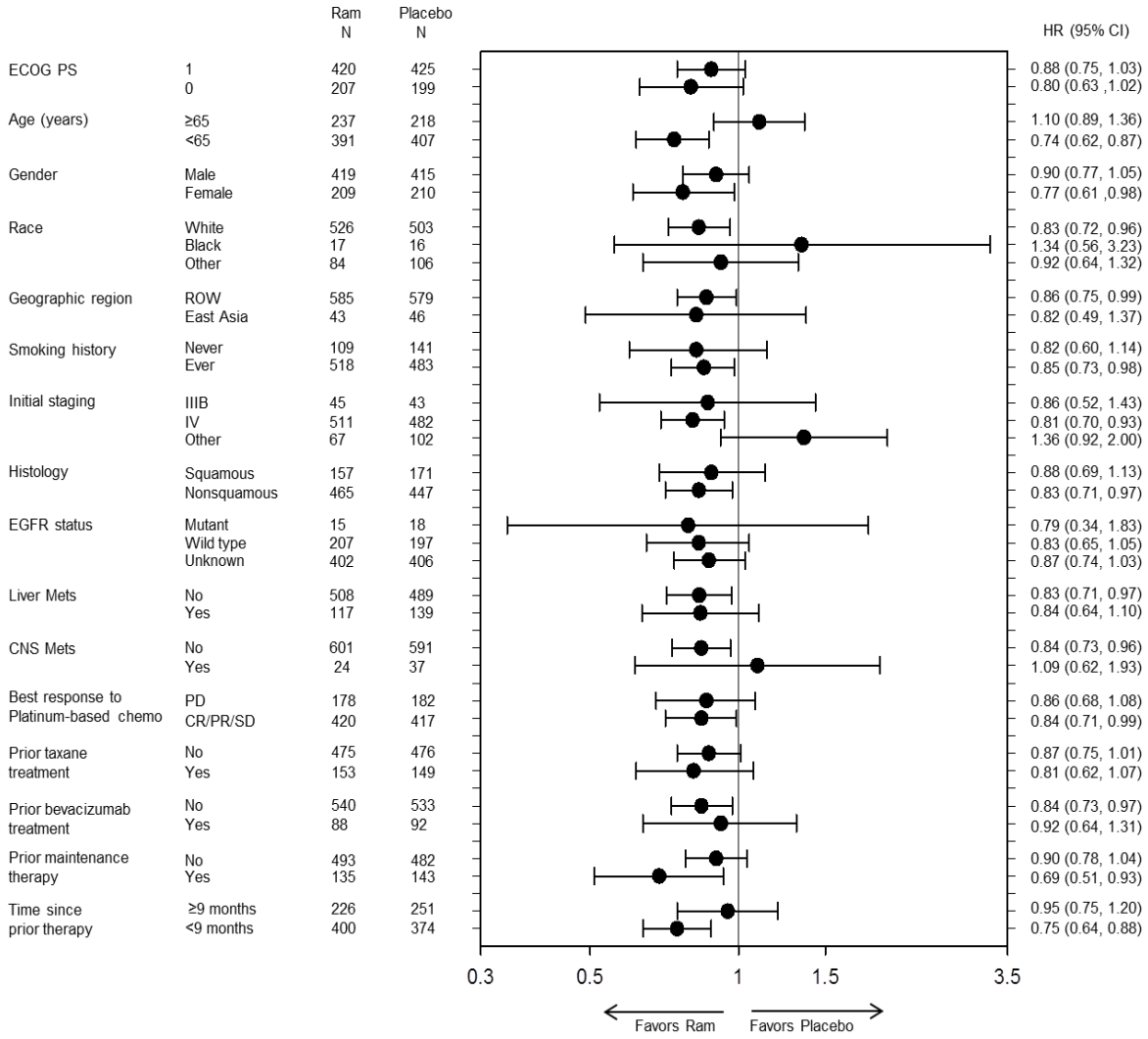
EGFR mutation status was reported by the investigator for 437 patients (35.1%). Although EGFR status was systematically captured in the case report form, EGFR mutation testing was not routine practice in some countries participating in the REVEL trial. The large study population makes it less likely that there is an imbalance in molecular factors such as EGFR mutations. In addition, analysis of patient demographic characteristics according to knowledge of EGFR mutational status showed a similar distribution of main clinical characteristics related to EGFR mutational status, including gender, ethnicity, and smoking status. Furthermore, there was no survival “tail” within the OS curve that is often observed among patients with EGFR mutation treated with an EGFR TKI. Therefore it is unlikely that a survival benefit would be driven by an imbalance in patients with EGFR mutations or by subsequent EGFR TKI treatment for patients with EGFR mutation. Among those with EGFR status known, 23.9% of RAM+DOC patients and 29.4% of PBO+DOC patients received an EGFR TKI post discontinuation. Among patients with EGFR status unknown, it was 27.4% and 21.1%, respectively. A consistent treatment effect was observed in the RAM+DOC arm compared to the PBO+DOC arm, across patients with tumours reported as having either EGFR-mutated, wild type, or unknown mutation status. At the time of initial patient enrolment, neither the EML4-ALK rearrangement testing nor the ALK testing guidelines were available. Therefore, data regarding ALK status were not collected on this study.

For OS, the pre-specified subgroups with unstratified HR >1.0 were patients aged ≥65 years and patients of black race. The Forest plot for OS also showed unstratified HR >1.0 for

patients with an initial disease stage of “other,” and patients with CNS metastases but these were not pre-specified subgroups. Although the OS HR observed for patients of black race was 1.34, this was based on small sample sizes of 17 and 16 in the treatment and control groups respectively, leading to a very wide CI. Moreover, the PFS HR for this subgroup was <1.0. Similarly, patients whose initial disease stage was “other” (e.g. initial stage other than Stage 3b or 4) had an OS HR >1.0 but represent a modestly sized subgroup; PFS treatment effect estimates were consistent across levels of the initial disease stage variable. Finally, patients with CNS metastases represent one additional small subgroup for which the wide CI for OS HR precludes a meaningful assessment of treatment effect in that specific subgroup.

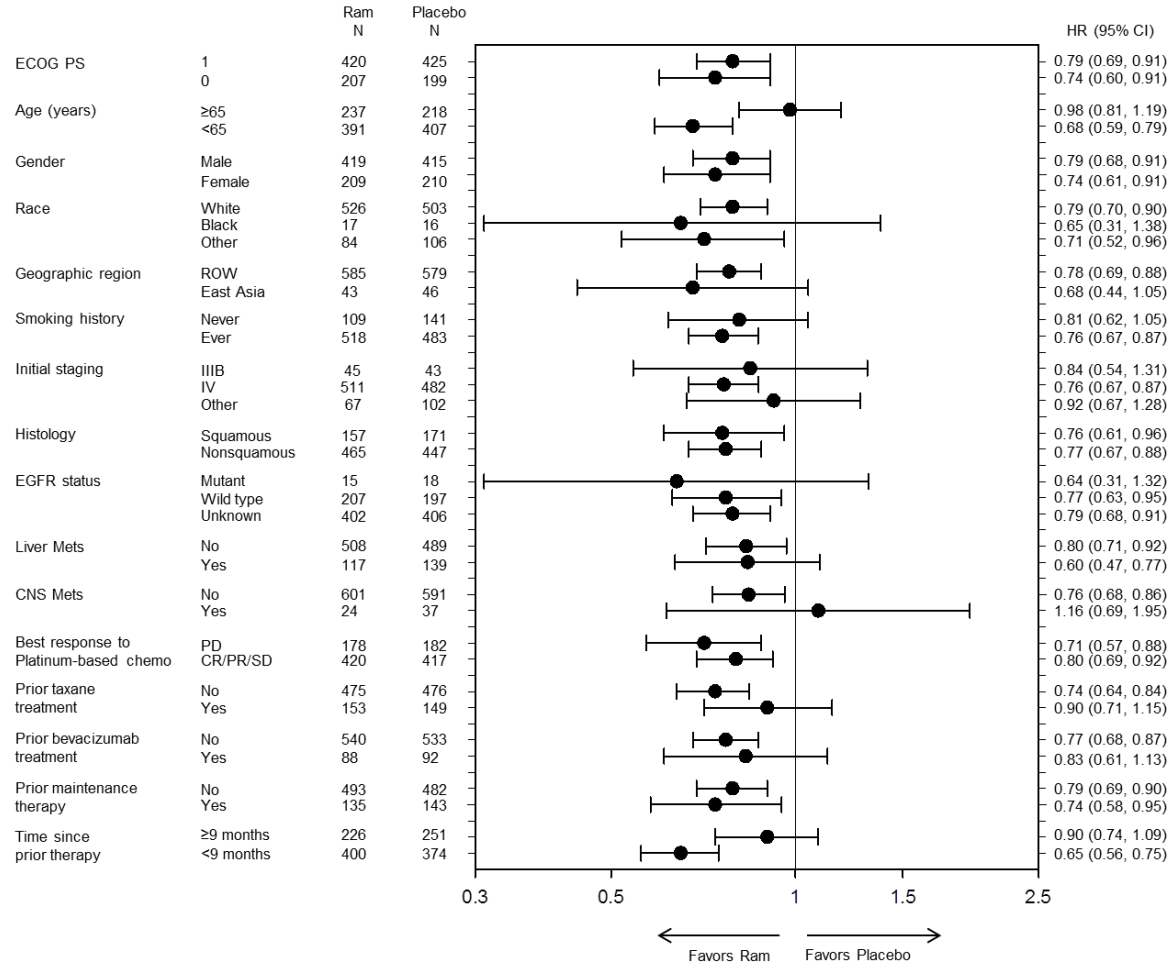
The OS HR (95% CI) observed for the <65 years of age and ≥65 years of age populations were 0.74 (0.62, 0.87) and 1.10 (0.89, 1.36), respectively. A review of the baseline characteristics, pharmacokinetics, exposure, and safety revealed no differences between treatment arms by age subgroups to provide a clear explanation for the OS results in the age subgroups. Furthermore, additional analysis of OS/PFS by age quintiles, adjusted for important prognostic factors, showed that the relationship between treatment effect and age is much less pronounced: OS HRs in the five age quintiles, ranging from youngest to oldest, were 0.67, 0.74, 0.78, 0.92 and 0.87 respectively. This analysis affords a more flexible modelling of the age/treatment effect relationship than simply dividing the population into two groups based on a single, arbitrary value. The safety profile of ramucirumab in patients ≥65 years is consistent with that observed in the younger patients. Therefore, the safety profile of RAM+DOC is considered tolerable and manageable in the older age group. In concert, these observations continue to support the clinically relevant efficacy benefits observed in the ITT patient population in REVEL. In addition, no treatment-by-age interaction was observed in any of the other completed Phase 3 trials with ramucirumab in gastric, colorectal and breast cancer (I4T-IE-JVBD [JVBD; REGARD (47)], I4T-IE-JVBE [JVBE; RAINBOW (48)], I4&-MC-JVBB [JVBB: RAISE (49) and I4T-IE-JVBC [JVBC; ROSE (50)]. The extent of variability in subgroup findings (including age) in REVEL was to have been expected given the large number of subgroups examined in REVEL and under the assumption of a consistent treatment effect throughout the study (51). It is therefore reasonable to interpret the observed interaction in REVEL as an isolated finding. There is no biological rationale to suggest an older patient cannot benefit from ramucirumab treatment.

Figure 10 Forest plot for subgroup analysis of OS (unstratified analysis), ITT population



Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; Mets = metastases; N = number of patients in given category, per arm; PD = progressive disease; PR = partial response; Ram = ramucirumab; SD= stable disease.

Figure 11 Forest plot for subgroup analysis of PFS (unstratified analysis), ITT population



Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; Mets = metastases; N = number of patients in given category, per arm; PD = progressive disease; PR = partial response; Ram = ramucirumab; SD= stable disease.

Histology

A consistent treatment effect was observed in patients regardless of squamous or nonsquamous histology. The subgroup analyses for OS showed that the HR (95% CI) for the squamous and nonsquamous histology subgroups were 0.88 (0.69, 1.13) and 0.83 (0.71, 0.97), respectively. Table 26 and Table 27 below provide the median OS and PFS, respectively, for patients in this subgroup.

Table 26 Summary of Overall Survival by Histology Intent-to-Treat Population

Histology Subgroup	Median OS in months (95% CI)				Unstratified HR	Unstratified Log rank p-value
	RAM+DOC		PBO+DOC			
Nonsquamous (N = 912)	11.1 (9.9, 12.3)	n = 465	9.7 (8.5, 10.6)	n = 447	0.83	0.02
Adenocarcinoma (N = 725)	11.2 (9.9, 12.4)	n = 377	9.8 (8.6, 10.8)	n = 348	0.83	0.039
Large Cell (N = 35)	8.6 (4.2, NA)	n = 14	10.7 (5.7, 13.2)	n = 21	0.73	0.423
Other (N = 152)	10.8 (8.3, 12.3)	n = 74	9.3 (5.0, 11.3)	n = 78	0.86	0.444
Squamous Cell (N = 328)	9.5 (8.0, 10.8)	n = 157	8.2 (6.3, 9.4)	n = 171	0.88	0.319

Abbreviations: CI = confidence interval; HR = hazard ratio; N = total population size; n = number of patients; NA = not applicable;

Note: other nonsquamous includes: 'carcinoma, bronchial', 'carcinoma, lung', 'carcinoma, mixed cell, lung', 'carcinoma, non-small cell, lung nos', 'carcinoma, non-small cell, poorly differentiated, lung', 'carcinoma, small cell, lung', 'carcinoma, undifferentiated, nos' 'carcinosarcoma, lung'

Table 27 Summary of PFS by Histology Intent-to-Treat Population

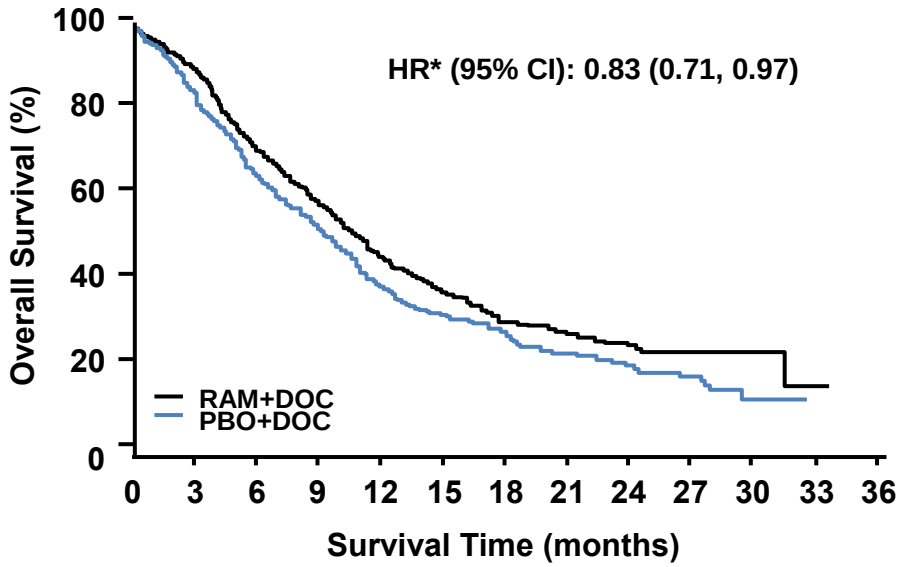
Histology Subgroup	Median OS in months (95% CI)				Unstratified HR	Unstratified Log rank p-value
	RAM+DOC		PBO+DOC			
Nonsquamous (N = 912)	4.6 (4.3, 5.5)	n = 465	3.7 (2.8, 4.1)	n = 447	0.77	<0.001
Adenocarcinoma (N = 725)	4.5 (4.2, 5.5)	n = 377	3.9 (2.8, 4.2)	n = 348	0.78	0.001
Large Cell (N = 35)	2.7 (1.4, 6.0)	n = 14	3.0 (1.3, 5.3)	n = 21	0.7	0.35
Other (N = 152)	5.4 (4.1, 6.2)	n = 74	2.9 (1.7, 4.3)	n = 78	0.72	0.048
Squamous Cell (N = 328)	4.2 (3.6, 5.4)	n = 157	2.7 (2.5, 2.9)	n = 171	0.76	0.019

Abbreviations: CI = confidence interval; HR = hazard ratio; N = total population size; n = number of patients; NA = not applicable;

Note: other nonsquamous includes: 'carcinoma, bronchial', 'carcinoma, lung', 'carcinoma, mixed cell, lung', 'carcinoma, non-small cell, lung nos', 'carcinoma, non-small cell, poorly differentiated, lung', 'carcinoma, small cell, lung', 'carcinoma, undifferentiated, nos' 'carcinosarcoma, lung'

The Kaplan-Meier curves for OS based on nonsquamous and squamous histologies are presented in Figure 12 and Figure 13, respectively. The Kaplan-Meier curves for PFS based on nonsquamous and squamous histologies are presented in Figure 14 and Figure 15 respectively.

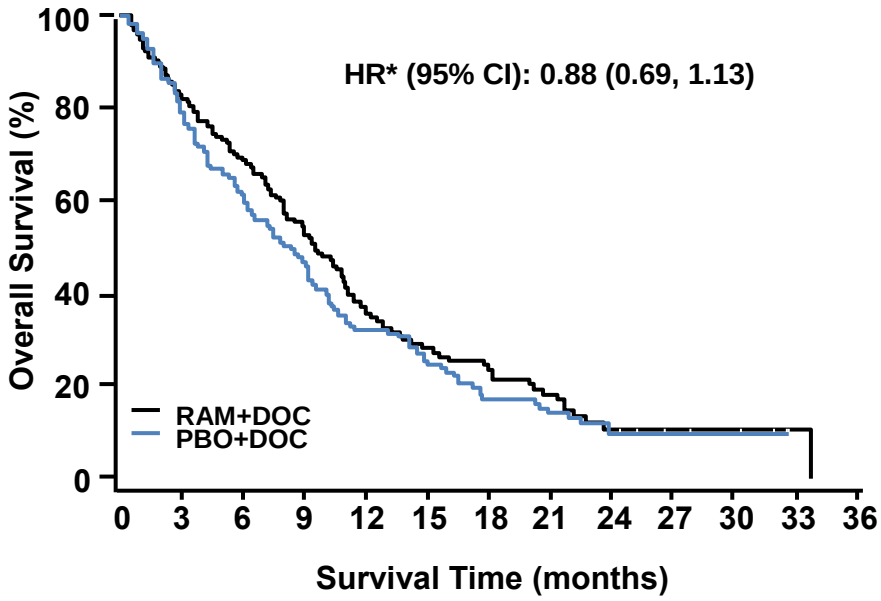
Figure 12 **Kaplan-Meier graph of OS from subgroup analysis of nonsquamous population (unstratified analysis), intent-to-treat population**



RAM+DOC	465	401	311	251	182	125	80	54	39	21	10	1	0
PBO+DOC	447	362	282	226	144	94	64	40	27	18	5	0	0

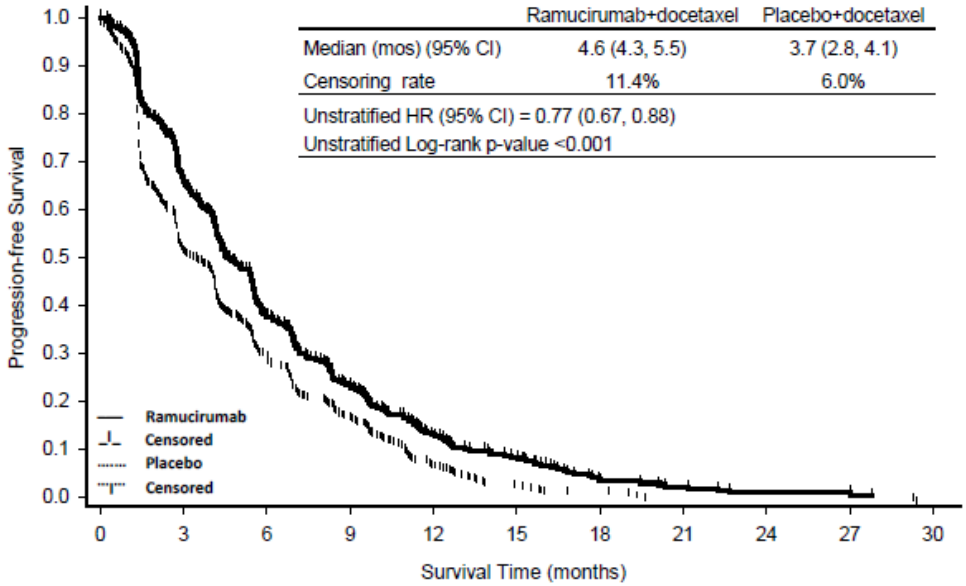
Abbreviations: CI = confidence interval; HR = hazard ratio;

Figure 13 **Kaplan-Meier graph of OS from subgroup analysis of squamous population (unstratified analysis), intent-to-treat population**



RAM+DOC	157	124	103	78	49	31	23	16	6	2	1	1	0
PBO+DOC	171	132	99	75	48	31	20	14	8	5	4	0	0

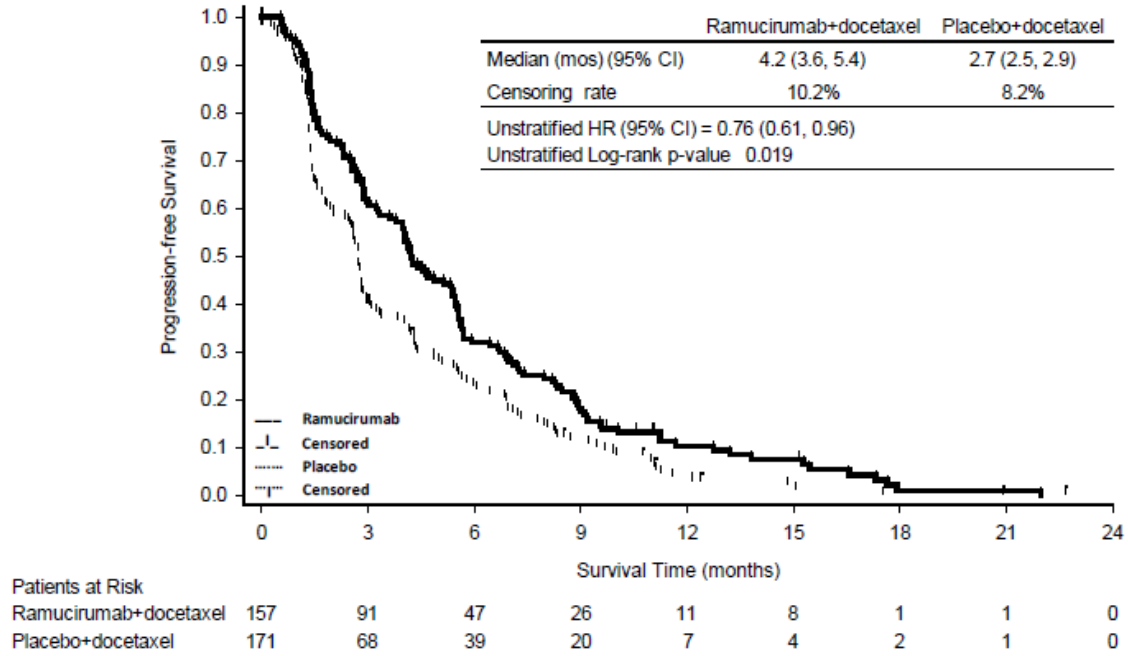
Figure 14 **Kaplan-Meier graph of PFS from subgroup analysis of nonsquamous population (unstratified analysis), intent-to-treat population**



Patients at Risk											
Ramucirumab+docetaxel	465	291	157	94	48	30	10	6	3	3	0
Placebo+docetaxel	447	229	131	73	29	12	6	2	2	2	0

Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months

Figure 15 Kaplan-Meier graph of PFS from subgroup analysis of squamous population (unstratified analysis), intent-to-treat population



Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months

Overall, the degree of variability observed in the magnitude of treatment effect across subgroups was within the range expected for a study of this size with a relatively large number of subgroup analyses being examined (51).

4.9 Meta-analysis

No head-to-head randomised clinical trials were found that provided evidence of the efficacy and safety of RAM+DOC versus nintedanib or erlotinib in the second-line treatment of advanced or metastatic NSCLC. Therefore, no direct meta-analysis was performed and instead the evidence networks were analysed via a network meta-analysis. Details of this analysis are provided in Section 4.10.

4.10 Indirect and mixed treatment comparisons

A network meta-analysis (NMA) was performed to provide relative treatment effect estimates for ramucirumab versus relevant comparators, looking specifically at OS, PFS and ORR. The estimates of comparative efficacy of ramucirumab generated by the NMA were also used to inform the economic model. In order to perform the NMA, a systematic literature review (SLR) was conducted to identify RCT evidence for the efficacy and safety of

RAM+DOC and other agents and regimens used in the second-line treatment of adult patients with advanced or metastatic NSCLC.

Search strategy

In order to identify relevant studies, searches were conducted in the following electronic databases on 26th June 2014, and then again on 2nd September 2015:

- MEDLINE (using the PubMed platform)
- MEDLINE In-Process (using the PubMed platform)
- Embase (using the Elsevier platform)
- Biosciences Information Service (using the Dialog Platform)
- The Cochrane Library (using the Wiley platform), including the following:
    - The Cochrane Database of Systematic Reviews
    - The Cochrane Central Register of Controlled Trials
    - Database of Abstracts of Reviews of Effectiveness

There were no date, language, or geographical restrictions on the database searches; non-English articles deemed relevant for inclusion in the meta-analysis were translated. In addition, searches were performed for abstracts or posters in the following conference proceedings, from 1st January 2012, to 24th June 2014, and then again from 24th June 2014 to 2nd September 2015:[a]

- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Association for the Study of Lung Cancer (IASLC) (https://www.iaslc.org/)

Detail search terms used are provided in Appendix 3. The inclusion criteria used in the SLR are detailed in Table 28.

[a] It is expected that high-quality studies reported in abstracts before 2012 would have been published in a peer-reviewed journal

Table 28 Inclusion criteria for the systematic review of RCTs

Criteria	Included
Study design	• Randomized, controlled, prospective phase 2 and 3 clinical trials • Long-term follow-up studies (e.g., open-label follow-up of randomized, clinical trials) [a] • Systematic reviews and meta-analyses [b]
Population	Patients aged ≥ 18 years with NSCLC who met the following criteria: • Have advanced or metastatic NSCLC • Are undergoing second-line treatment with or without prior maintenance therapy • Have either squamous or non-squamous types of NSCLC
Interventions [c]	Trials that include any of the following interventions in at least one study arm: • Afatinib • Albumin-bound paclitaxel • Bevacizumab • Ceritinib • Cetuximab • Crizotinib • Docetaxel • Erlotinib • Etoposide • Gefitinib • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Nab-paclitaxel • Nintedanib (in combination with docetaxel) • Nivolumab • Paclitaxel • Pembrolizumab [d] • Pemetrexed • Ramucirumab (in combination with docetaxel) • Topotecan • Vindesine • Vinorelbine • Vinblastine
Outcomes [e]	• Overall survival • Progression-free survival • Tumour response • Toxicity • Quality of life (measured by a validated tool)

Abbreviation: NSCLC = non-small cell lung cancer.
Note: Any issues with trial design were reported via the quality-assessment process.
[a] Data for overall survival and progression-free survival from long-term follow-up studies were used to inform the economic model.
[b] Systematic reviews and meta-analyses were used for identification of primary studies.
[c] Included studies investigated these treatments as either monotherapy or combination therapy and had at least one of the interventions of interest in at least one study arm. The list of comparators was based on the NCCN and ESMO guidelines and potential market entrants for NSCLC.

[d] Only included for the updated search conducted on 2nd September 2015, to reflect the developing clinical landscape.
[e] At least one, but not all, of the listed outcomes was required for inclusion in this review.

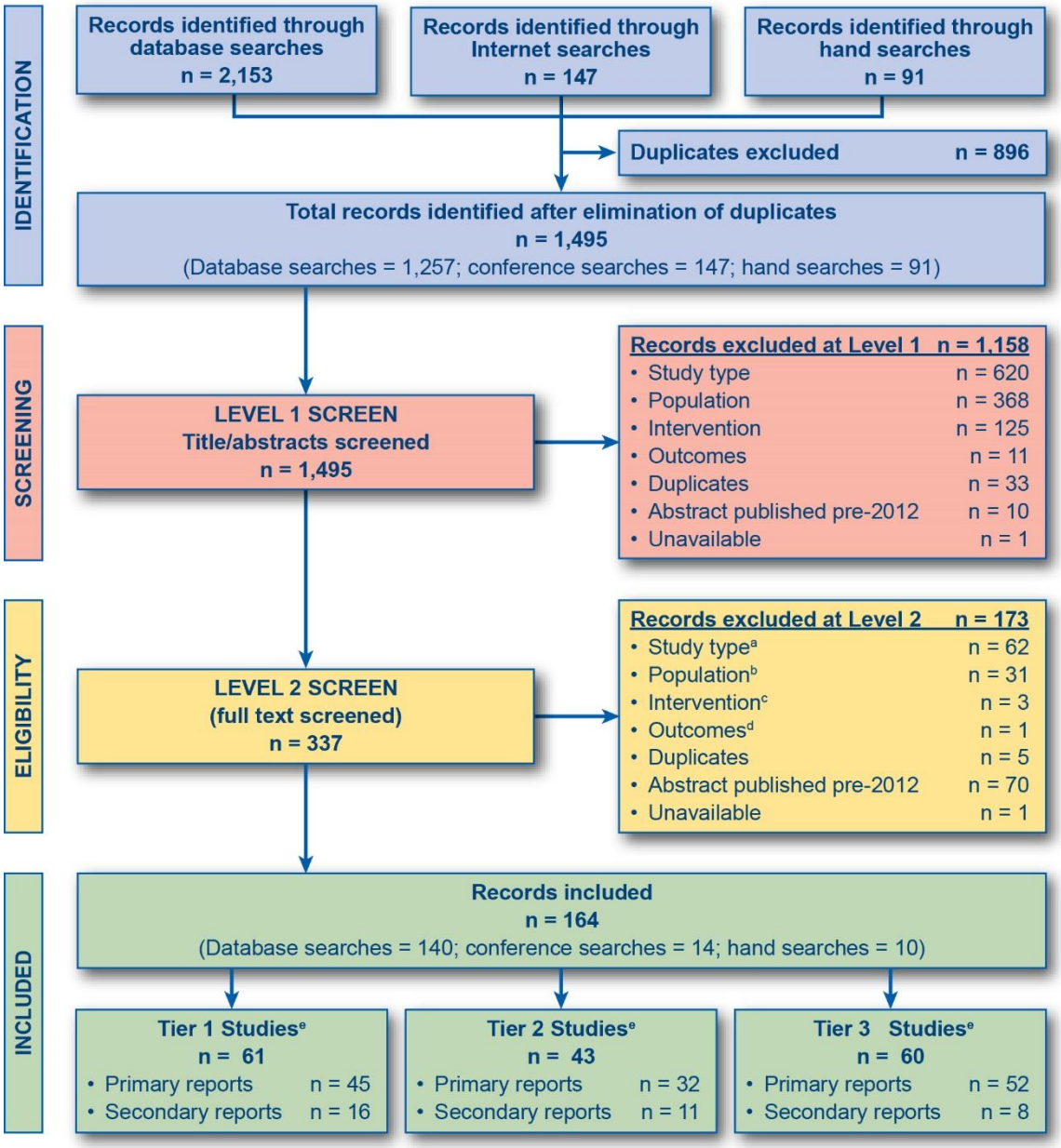
Study selection – original search June 2014

In the original search conducted on 26th June 2014, a total of 1,495 records were selected for manual screening following de-duplication (Figure 16). After screening, 164 publications were selected for inclusion in the review. Due to the large number of studies included in the review, the studies were divided into categories in order to prioritise them in terms of the importance of the comparators in the trial. Tier 1 studies included those that had one of the following interventions in both of the treatment arms: docetaxel, erlotinib, gemcitabine, nintedanib (in combination with docetaxel), nivolumab, pemetrexed, ramucirumab (in combination with docetaxel), and vinorelbine. In total, 61 articles were categorised as tier 1; these reported data on 45 trials (hence, there were 45 primary studies and 16 secondary reports). These studies formed the initial treatment network for the meta-analysis. The volume of studies included and excluded at each stage of screening is shown in Figure 16.

Five of the Tier 1 studies were written in Chinese (4 studies) or Japanese (1 study); two of these (52, 53) appeared to be relevant for the meta-analysis, so they were translated and extracted. The three remaining non-English-language (Chinese) articles (54-56) were not fully translated, as the interventions investigated did not fit the treatment network for the meta-analysis. Details of the included studies may be found in Appendix 4.

The extracted studies were examined for outcomes and completeness of the data presented. Within Tier 1, of the 45 studies described in 61 records, 27 studies in 31 records were excluded from consideration in the NMA (see Appendix 4). Within Tier 1, a total of 18 studies in 30 articles were included in the NMA. In addition, a total of 4 studies in 6 articles considered as Tier 2 studies, in which gefitinib was investigated, were included in order to allow this comparator to inform the network. Thus a total of 22 studies in 36 articles were included in the full NMA. Study design for the included studies, along with the baseline and results data extracted from the studies and used in the NMA analyses are summarised in Appendix 4.

Figure 16 PRISMA Diagram for Clinical Study Inclusion and Exclusion – original search June 2014



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Note: Some studies were reported in multiple publications; in such cases, the main study report was classed as the "primary" publication and any other articles reporting on the same trial were classed as "secondary reports." Therefore, the primary reports are all unique trials.
[a] Meta-analysis or systematic review = 33; single-arm trial or only presents results for one study arm = 7; non-systematic review = 5; phase 1 study = 4; ongoing study with no results = 3; nonrandomized trial = 3; errata = 2; pooled analysis = 2; phase 4 study = 1; consensus statement = 1; retrospective analysis = 1.
[b] First-line = 23; third-line (or greater) = 3; consolidation therapy in patients NOT progressing after first-line treatment = 2; perioperative = 1; stage 2 non-small cell lung cancer = 1; cancer stage unclear = 1.
[c] Radiotherapy = 1; drug not of interest = 1; maintenance treatment = 1.
[d] Tumour shrinkage, no other data = 1.
[e] Tier 1 studies have one of the following interventions in both treatment arms: docetaxel, erlotinib, gemcitabine, nintedanib, nivolumab, pemetrexed, ramucirumab, and vinorelbine. Tier 2 studies included the studies in which the 24 interventions listed in Table 28, but not included in Tier 1, were included in both study arms (including combination treatments). The remaining studies were classed as Tier 3 studies; these consisted of the studies

that had 1 of the 24 interventions of interest in one of the study arms and could be compared with various other interventions.

Study selection – updated search September 2015

In the updated search conducted on 2nd September 2015, a total of 209 records were identified. Of these, 54 had been identified in the 2014 search due to the overlap in search dates with the previous search (this updated search went back to 26th March 2014). As in the original search, the electronic database searches were not limited by date, language, or geographical location. A total of 218 records (titles and abstracts) were selected for manual screening (databases = 155; internet searches = 61; hand searches = 2) to identify all relevant studies.

After screening 41 articles were included comprising 30 unique studies, of which 10 were unique Tier 1 studies; full study details are provided in Appendix 4. The comparisons reported in these studies are shown in Table 29. Three of the studies identified in Table 29 had already been identified and included in the original SLR, and likewise two of the new studies had already been included in abstract form in the original SLR.

The new studies identified were not relevant for informing the relative efficacy of the comparators identified in the decision problem presented in this submission which covers RAM+DOC, ERL, DOC and NIN+DOC only (see Section 1). The one newly identified trial which included relevant comparators in both arms, Hosomi et al. (2015) (57), considered RAM+DOC vs PBO+DOC in a Japanese population using a lower dose of docetaxel (60 mg/m^2, as recommend in Japan). This trial would not therefore inform the relative efficacy of the comparators at the dose of docetaxel used in the UK (75 mg/m^2) and therefore is not relevant to the decision problem.

In conclusion, the SLR update results demonstrate that the results of the original NMA are still valid and are presented in this submission.

Table 29 Treatment Comparisons in Included Tier 1 Studies from Update Search, Focusing on Studies Assessing the Eight Main Comparators (Docetaxel, Erlotinib, Gemcitabine, Nintedanib, Nivolumab, Pembrolizumab, Pemetrexed, and Vinorelbine)

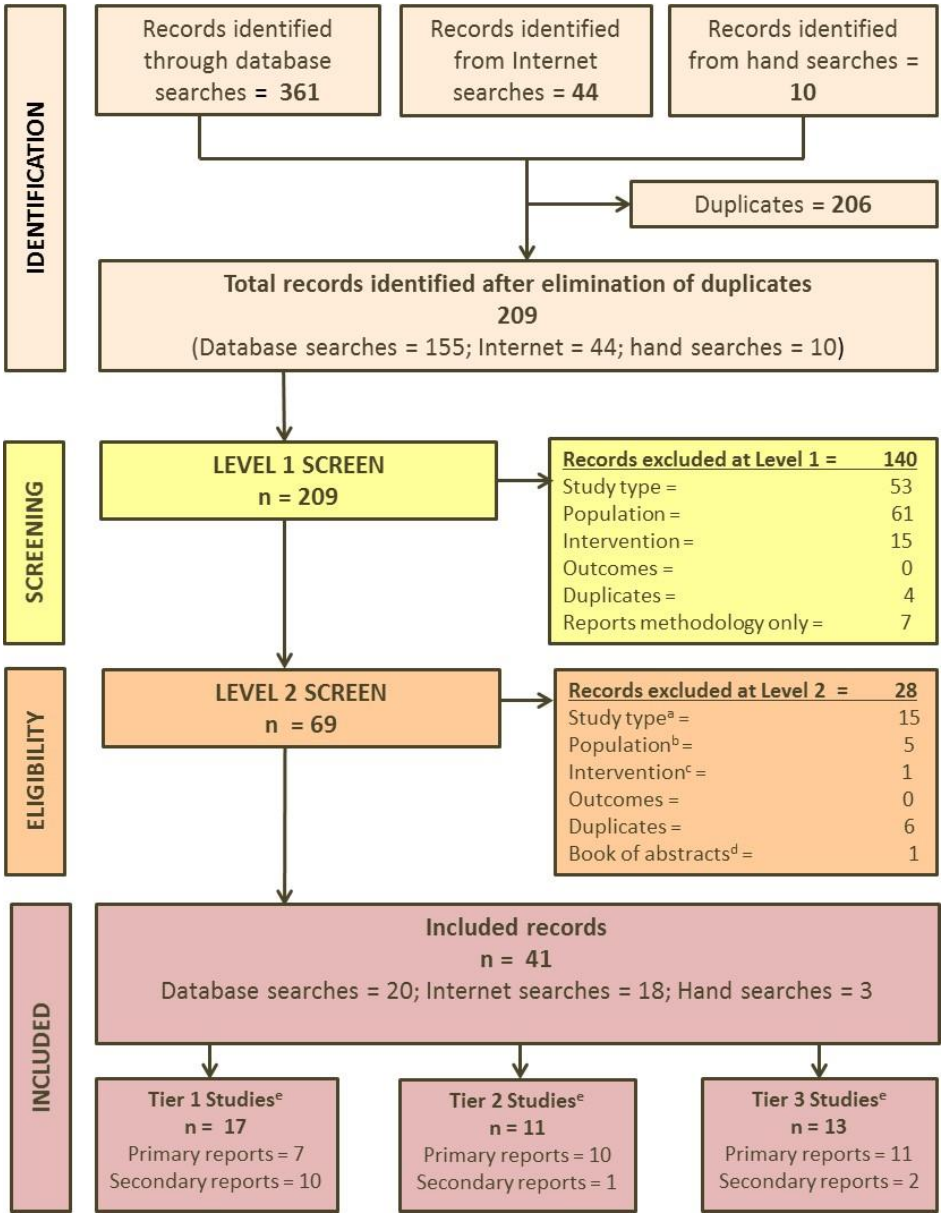
Comparison	Number of publications (number of trials)
Erlotinib + docetaxel versus docetaxel	1 (1) [a]
Erlotinib + docetaxel versus erlotinib	1 (1) [a]
Erlotinib versus pemetrexed versus erlotinib + pemetrexed	1 (1) [b]
Pemetrexed + erlotinib versus pemetrexed	1 (1)
Nintedanib + docetaxel versus docetaxel + placebo	3 (1) [b]
Nivolumab versus docetaxel	6 (2)
Pemetrexed or docetaxel versus erlotinib + pemetrexed or docetaxel	1 (1)
Ramucirumab + docetaxel versus placebo + docetaxel	3 (2) [c]
Total number of publications (unique studies)	17 (10)

[a] Abstract identified in original review.

[b] Primary study identified in original review.

[c] Primary study for one trial (REVEL) identified in original review; in addition one new trial was identified (Hosomi et al., 2015)

Figure 17 PRISMA Diagram for Clinical Study Inclusion and Exclusion – updated search September 2015



[a] Commentary = 1; HTA report = 1; meta-analyses = 9; non-randomised trial = 1; systematic reviews = 3.

[b] Mixed population (results not reported by line of therapy) = 3; previously untreated patients = 1; not clear if second-line = 1.

[c] Tivantinib plus erlotinib versus single-agent chemotherapy.

[d] The abstracts were manually searched and any which appeared to be relevant were included in the review as Internet searches.

[e] Tier 1 studies have one of the following interventions in both treatment arms: docetaxel, erlotinib, gemcitabine, nintedanib, nivolumab, pembolizumab, pemetrexed, ramucirumab, and vinorelbine. Tier 2 studies included the studies in which the 25 interventions of interest were included in both study arms (including combination treatments). The remaining studies were classed as tier 3 studies; these consisted of the studies that had 1 of the 25 interventions of interest in one of the study arms and could be compared with various other interventions.

Statistical analyses

Analyses for the NMA were performed in a Bayesian framework using JAGS, full details of which are provided in Appendix 5. A similar frequentist model was also fitted for validation purposes. Both fixed effect and random effects models were applied. Although ramucirumab is licensed across histologies, some of the comparators in the NMA are only used in specific subgroups. A comprehensive set of heterogeneity and inconsistency analyses were conducted for each endpoint that provided evidence of complex treatment-by-covariate interactions; this made simply subgrouping the data in the network inappropriate, and it was also not possible to fit the standard meta-regression models recommended by NICE. Consequently, in order to deal with the specific treatment-by-covariate interactions, it was necessary to conduct analyses that allowed different interaction between treatment and population type, although these different subgroups are not clinically relevant to ramucirumab itself. The main populations of interest were squamous and non-squamous, as some interventions in the network have indications only for non-squamous or adenocarcinoma patients (pemetrexed and nintedanib, respectively) in line with the evidence presented for licensing; studies including either or both squamous and non-squamous NSCLC patients were included in the NMA. In addition, the available evidence in the literature indicates that both erlotinib and gefitinib have considerably different outcomes in EGFR-negative and EGFR-positive patients (58). After consultation with Leicester University, models using a hierarchical exchangeable structure were used in the analyses. This is believed to be the first time such an approach has been used in the analyses of NSCLC data.

In NMAs which contain a large number of interventions but relatively few trials, it is known that sparsity of data can cause parameter uncertainty. Where class effects are known to exist in such a scenario, a three-level hierarchical NMA structure may be applied allowing exchangeability between interventions within a class whilst still predicting their effect estimate individually (59). This approach allows strength to be borrowed within classes with the potential to reduce uncertainty and also allows order constraints to be applied where appropriate. Given the features of the evidence base for NSCLC described above in this analysis the models presented below incorporate the hierarchical exchangeable structure to allow pemetrexed and nintedanib to vary by histology and gefitinib and erlotinib to vary by EGFR status. The JAGS code is specific to covariates in the data for the appropriate study arm. A class effect was used for treatments of the same class that contained different dose regimens. Order constraints were applied to pemetrexed and proportion of squamous

patients and erlotinib and gefitinib for proportion of EGFR mutation-positive patients, as these effects have been identified in other studies (58). Nintedanib was left unconstrained as there is no evidence yet that this treatment differs significantly by histology. Erlotinib and gefitinib studies that did not report the proportion of EGFR positive patients were excluded from the network of evidence. Results for all other treatments did not differ according to histology or EGFR status.

It was possible to perform NMAs for OS, PFS and ORR. These outcomes were selected for inclusion in the systematic review and NMA as they represent the key clinical outcomes for patients and are in line with EMA guidance on outcome measures appropriate for RCTs in cancer (60). There were insufficient data on quality of life outcomes to form a network due to different instruments and analyses utilised across studies. For adverse events, networks for neutropenia, thrombocytopenia, fatigue and nausea were considered. However, due to low counts of events, high zero rates and inconsistencies in the definition of the endpoints between trial reports, the data did not allow robust NMAs to be conducted and any ability to interpret these would have been limited.

Analysis of OS and PFS

To conduct a meta-analysis of OS and PFS data using hazard ratios, it was necessary to adopt the assumption of proportional hazards. This assumes that the effect of each treatment is constant over time and uses the trial-reported HRs for each comparator. On visual inspection, two of the reported Kaplan–Meier charts indicated that the proportional hazard assumption had not been met and this was confirmed by formal testing (61, 62), these studies have all been indicated on the appropriate network diagrams in red. Of the two studies, Sheppard *et al*. compared to BSC which was not an intervention of interest while for Reck *et al*. it was found that lack of PH was primarily in the squamous data which was not relevant to the comparison as nintedanib is licensed only for the adenocarcinoma population (a non-squamous subgroup). Taking all this together it seemed reasonable to use the PH approach.

A number of studies did not report hazard ratios but did publish Kaplan–Meier charts. In such cases, the Kaplan–Meier charts were digitized using the DigitizeIt software (63), patient level data simulated (64), and then hazard ratios estimated.

Fixed or random effects

Duplicated comparisons (closed loops) are required to accurately estimate the random study effect. If the information needed to estimate the random effect is sparse, Bayesian models will tend to overestimate the error. Many of the networks of evidence have only a few closed loops, and therefore the random effects models will likely be overestimating the error and producing greatly inflated credible intervals. Therefore unless the DIC indicated that the random effects models fit the data considerably better than the fixed effect models, the fixed effect model was selected preferentially. As discussed below, results and conclusions were highly consistent between fixed and random effects. However, caution is needed when interpreting small differences, since they may be attributable to the model choice.

Presentation of results

The network meta-analysis included treatments cited in guidelines or used in clinical practice. However only results for the relevant comparators for the submission (see Section 1.1) are reported here:

- Ramucirumab (10 mg/kg) + docetaxel (75 mg/m^2), both given intravenously in succession on day 1 of a 21 day cycle (RAM+DOC)
- Docetaxel (75 mg/m^2), given intravenously on day 1 of a 21 day cycle (DOC) (NB: other, unlicensed, regimens for the dosing and administration of docetaxel that were identified in the SLR and NMA are not presented as these are not used in UK clinical practice)
- Erlotinib (150 mg), taken orally, 150 mg once daily (ERL)
- Nintedanib (200 mg) + docetaxel (75 mg/m^2), docetaxel given intravenously on day 1 of a 21 day cycle and nintedanib taken orally, 200 mg twice daily on days 2-21 of the cycle (NIN+DOC)

For NIN+DOC, results are only presented for the non-squamous population. NIN+DOC is licensed for adenocarcinoma tumour histology (65). In the REVEL trial 79.50% of non-squamous patients had confirmed adenocarcinoma histology consistent with the generally accepted proportions reported and quoted in the literature (21). Therefore non-squamous and adenocarcinoma histologies are presumed to be synonymous to allow for full use of the available data in the evidence network. This includes pemetrexed, which is licensed for the non-squamous histology (66).

For ERL, the results of the EGFR-negative population are presented. The ongoing review of TA162 and TA175 for erlotinib and gefitinib (post chemotherapy) [ID620] discussed the use

of EGFR-TK inhibitors in EGFR-TK mutation positive populations. The clinical specialists stated that most patients receive an EGFR-TK inhibitor as first-line treatment in line with NICE guidance. They also concluded that the use of EGFR-TK inhibitors for re-treating NSCLC after the failure of first-line EGFR-TK inhibitor treatment is not common in clinical practice in England because of reduced sensitivity of the tumour to these treatments. Results for ERL as a second-line treatment option for the EGFR-positive patients were therefore not considered relevant to this submission. EGFR testing was confirmed by UK clinical experts to be routinely commissioned and available in 10 working days (which is usually how long it takes to schedule in the chemotherapy). ERL or another EGFR-TK inhibitor would likely have been given earlier in the treatment pathway for these patients and they would therefore not be rechallenged. These results in EGFR-positive patients are presented in Appendix 6, along with the results for other comparators not included in the scope (pemetrexed, pemetrexed plus erlotinib, gefitinib, best supportive care and other doses of docetaxel) for completeness.

Pairwise results are presented for each outcome, with hazard ratios and 95% credible intervals for survival outcomes (OS, PFS) and odds ratios and 95% credible intervals for ORR.

- RAM + DOC gave significantly greater OS, PFS and ORR than both DOC (in all populations) and ERL (in EGFR-negative patients).
- RAM+DOC was shown to have similar efficacy to NIN+DOC (in the non-squamous subpopulation) for all outcomes.
- An additional separate analysis using only adenocarcinoma subgroups from the RAM+DOC and NIN+DOC trials confirmed the finding of highly similar efficacy for both OS and PFS (HR = 1.00 for both OS and PFS in adenocarcinoma patients)

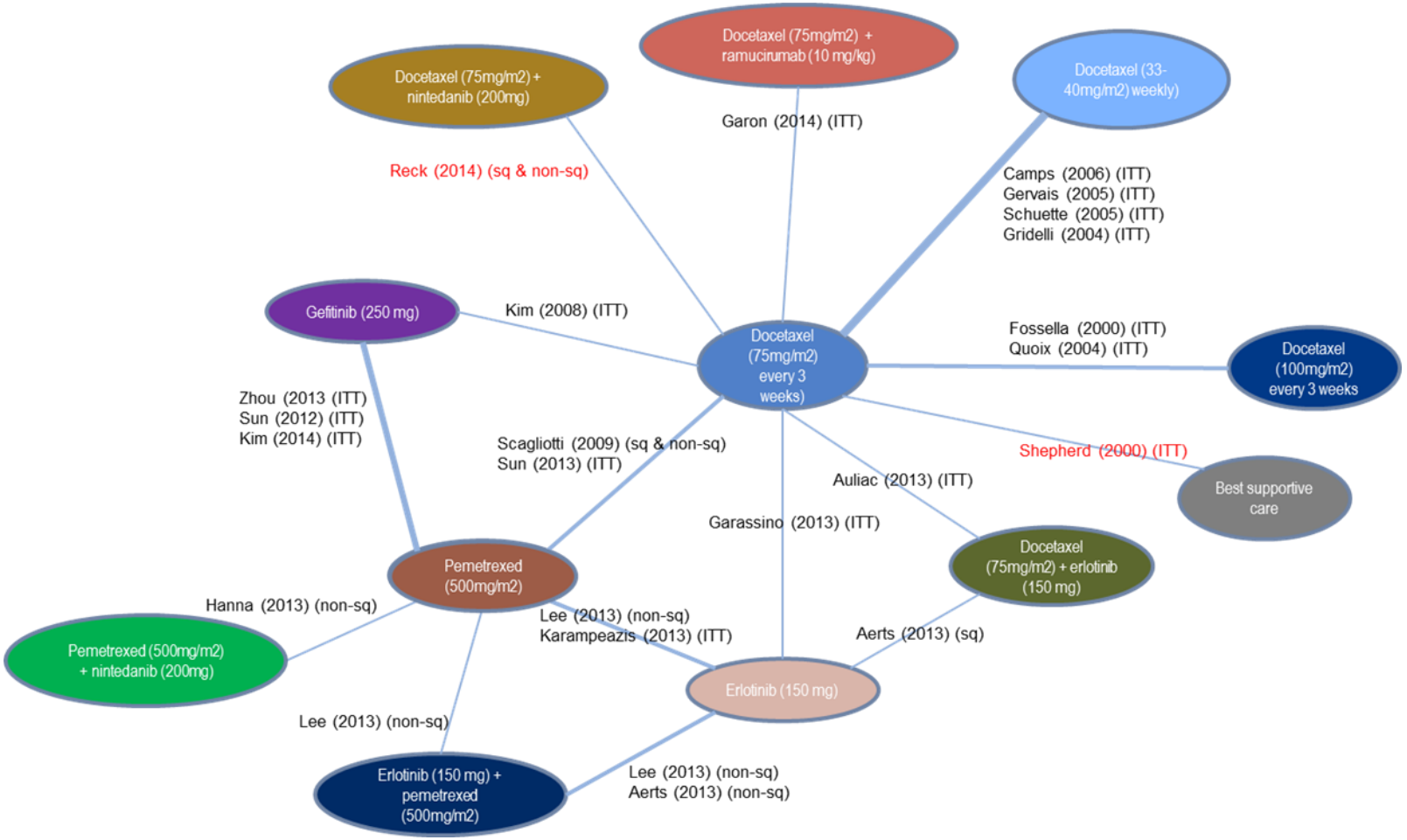
Results

The following sections present the results of the Bayesian MTC. Frequentist and Bayesian results were broadly consistent.

Overall survival

The full network analysed for OS is presented in Figure 18. Results from the network, for the relevant comparators only, are summarised in Table 30. The fixed-effect model was selected as this had a lower DIC (-8.1) than the random effects model (-6.6). The standard deviation of the heterogeneity parameter was bounded very close to zero, which suggested that this model largely explained the heterogeneity and inconsistency in the network. The incorporation of adjustment for covariates into the model was tested but gave inconclusive results, therefore the fixed-effects model of OS with the hierarchical exchangeable effects is the model presented.

Figure 18 Network of evidence for OS



Abbreviations: non-sq = non-squamous; sq = squamous; ITT = intention-to-treat
Red indicates that from the formal testing of the KM plots, the assumption of proportional hazards may not hold

Table 30 OS NMA results, pairwise comparisons, Bayesian fixed effects model, relevant comparator results only, HR (95% CrI)

Intervention	Comparator		
	DOC (all populations)	ERL (EGFR-negative)	NIN+DOC (non-squamous)
ERL (EGFR-negative)	1.22 (0.98, 1.61)		
NIN+DOC (non-squamous)	0.85 (0.71, 1.00)	0.69 (0.50, 0.92)	
RAM+DOC (all populations)	0.86 (0.75, 0.98)	0.70 (0.52, 0.91)	1.01 (0.82, 1.25)

Abbreviations = HR: hazard ratio; CrI = credible interval

HR less than 1 favours the intervention over the comparator.

Summary of OS NMA results

In all populations:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater OS compared to docetaxel (75 mg/m^2 every 3 weeks) alone—this result simply reflects the one trial (REVEL) that informs this link of the network.

In the EGFR-negative subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater OS compared to erlotinib (150 mg).

In the non-squamous subpopulation:

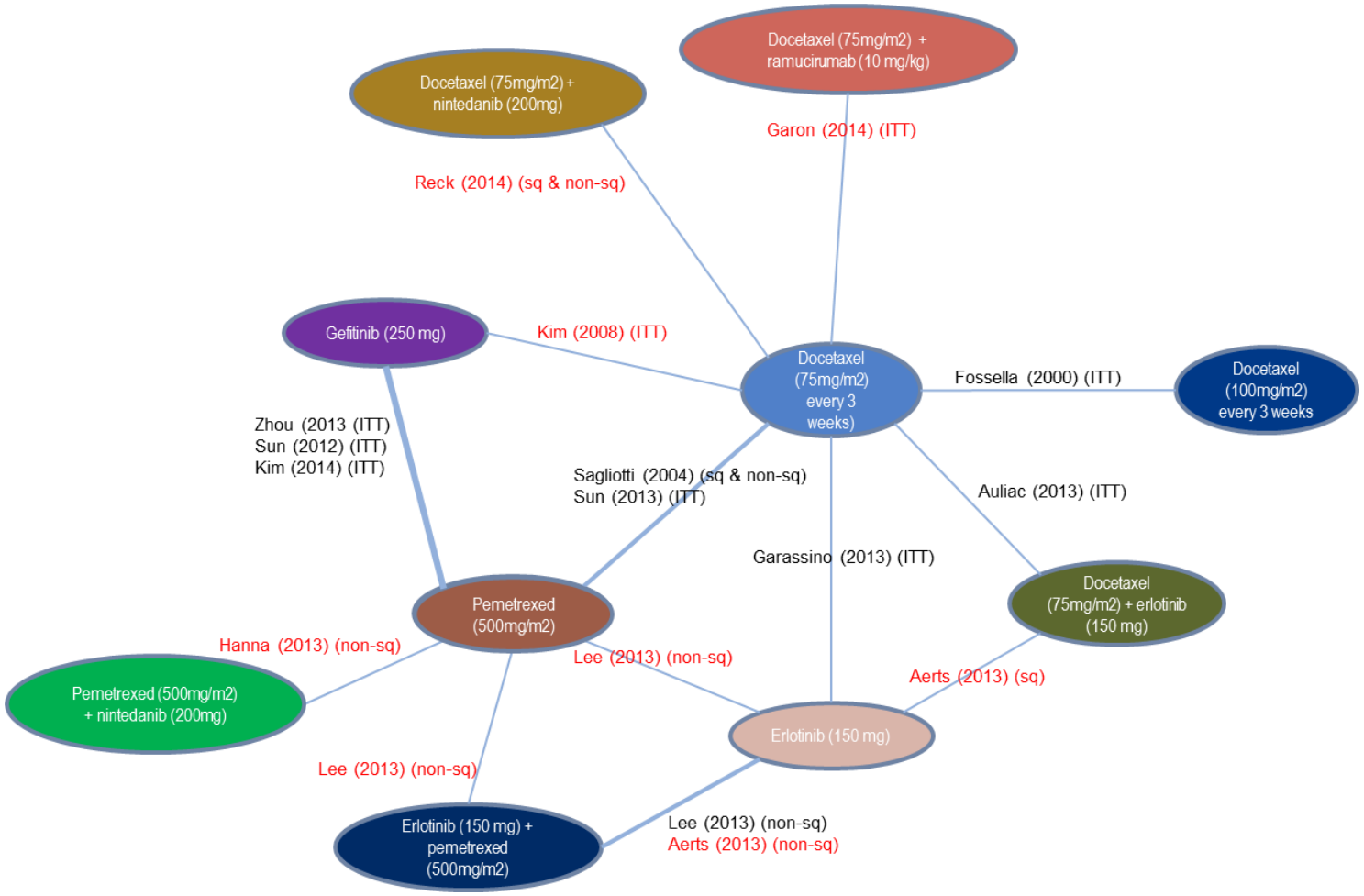
- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) was shown to be similar to nintedanib (200 mg) plus docetaxel (75 mg/m^2) in terms of OS.

Progression-free survival

The full network analysed for PFS is presented in Figure 19. Results from the network, for the relevant comparators only, are summarised in Table 31. For the hierarchical exchangeable model, the fixed-effect model gave a similar fit compared with the random-effects model, showing no significant difference between them. Therefore the fixed-effect model was selected as this had a lower DIC (-3.1) than the random effects model (-3.0). The standard deviation of the heterogeneity parameter was bounded very close to zero, which suggested that this model largely explained the heterogeneity and inconsistency in the network. Similarly to the OS network, the incorporation of adjustment for covariates into the

model was tested but gave inconclusive results, thus again the fixed-effects model of PFS with the hierarchical exchangeable effects is the model presented.

Figure 19 Network of evidence for PFS



Abbreviations: non-sq = non-squamous; sq = squamous; ITT = intention-to-treat
Red indicates that from the formal testing of the KM plots, the assumption of proportional hazards may not hold

Table 31 PFS NMA results, pairwise comparisons, Bayesian fixed effects model, relevant comparator results only, HR (95% CrI)

Intervention	Comparator		
	DOC (all populations)	ERL (EGFR-negative)	NIN+DOC (non-squamous)
ERL (EGFR-negative)	1.33 (1.04, 1.72)		
NIN+DOC (non-squamous)	0.77 (0.62, 0.95)	0.58 (0.42, 0.79)	
RAM+DOC (all populations)	0.76 (0.68, 0.86)	0.57 (0.43, 0.75)	0.99 (0.78, 1.26)

Abbreviations: HR = hazard ratio; CrI = credible interval

HR less than 1 favours the intervention over the comparator.

Summary of PFS NMA results

In all populations:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater PFS compared to docetaxel (75 mg/m^2 every 3 weeks) alone—this result simply reflects the one trial (REVEL) that informs this link of the network.

In the EGFR-negative subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater PFS compared to erlotinib (150 mg).

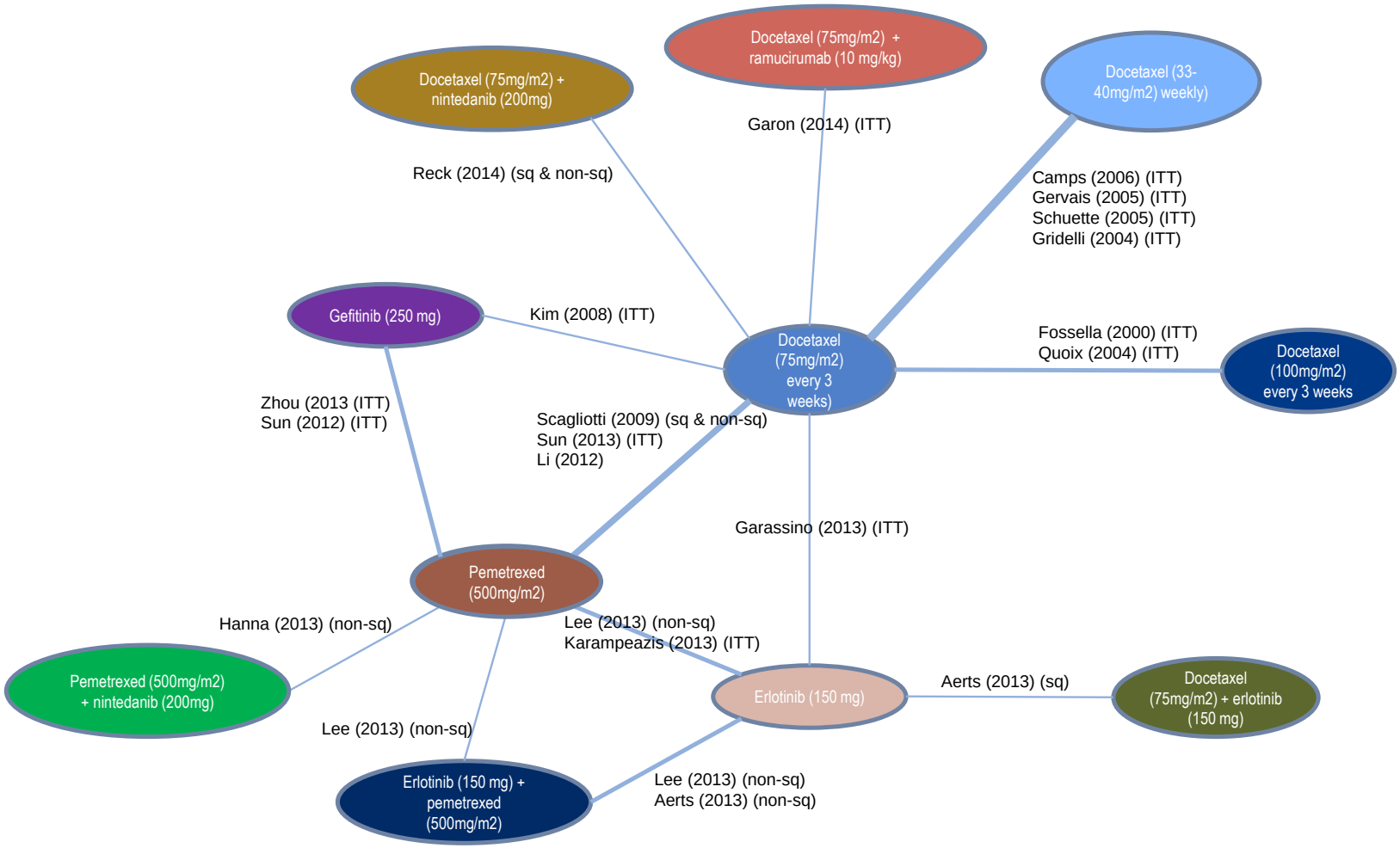
In the non-squamous subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) was shown to be similar to nintedanib (200 mg) plus docetaxel (75 mg/m^2) in terms of PFS.

Objective response rate

The full network analysed is presented in Figure 20. Results from the network, for the relevant comparators only, are summarised in Table 32. For the hierarchical exchangeable model, the fixed-effect model gave a similar fit compared with the random-effects model (DIC for fixed effect model: 761.8; DIC for random effects model: 762.2). The standard deviation of the heterogeneity parameter was bounded very close to zero, which suggested that this model largely explained the heterogeneity and inconsistency in the network. The further inclusion of covariates to the fixed-effect hierarchical exchangeable model did not improve model fit. Therefore, the fixed-effect model with the hierarchical exchangeable effects was the model from which results are presented.

Figure 20 Network of evidence for ORR



Abbreviations: non-sq = non-squamous; sq = squamous; ITT = intention-to-treat

Table 32 ORR NMA results, pairwise comparisons, Bayesian fixed effects model, relevant comparator results only, differences in probit scores (95% CrI)

Intervention	Comparator		
	DOC (all populations)	ERL (EGFR-negative)	NIN+DOC (non-squamous)
ERL (EGFR-negative)	-0.56 (-0.9, -0.25)		
NIN+DOC (non-squamous)	0.35 (0.17, 0.53)	0.91 (0.55, 1.31)	
RAM+DOC (all populations)	0.41 (0.27, 0.54)	0.96 (0.62, 1.34)	0.05 (-0.18, 0.28)

Abbreviations: HR = hazard ratio; CrI = credible interval

Probit score difference greater than zero favours the intervention over the comparator.

Summary of ORR NMA results

In all populations:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater ORR compared to docetaxel (75 mg/m^2 every 3 weeks) alone—this result simply reflects the one trial (REVEL) that informs this link of the network.

In the EGFR-negative subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) showed significantly greater ORR compared to erlotinib (150 mg).

In the non-squamous subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) was shown to be similar to nintedanib (200 mg) plus docetaxel (75 mg/m^2) in terms of ORR.

Subgroup NMA analysis – adenocarcinoma subpopulation

As NIN+DOC is only indicated for the adenocarcinoma subpopulation, a separate subgroup comparison was additionally undertaken using the adenocarcinoma subpopulation results from REVEL in order to further validate the results of the main NMA presented above. Figure 21 presents the network of evidence for the subgroup analysis of studies explicitly providing results for the adenocarcinoma subpopulation. Results from the network, for the relevant comparators only, are summarised in Table 33 and Table 34.

Figure 21 Adenocarcinoma subpopulation network

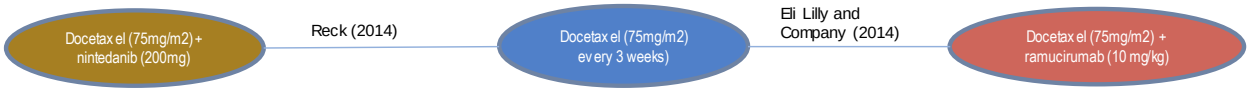


Table 33 OS NMA results for adenocarcinoma, pairwise comparisons, Bayesian fixed effects model, HR (95% CrI)

Intervention	Comparator	
	DOC	NIN+DOC
NIN+DOC	0.83 (0.70, 0.99)	
RAM+DOC	0.83 (0.72, 0.96)	1.00 (0.60, 1.25)

Abbreviations: HR = hazard ratio; CrI = credible interval

HR less than 1 favours the intervention over the comparator.

Table 34 PFS NMA results for adenocarcinoma, pairwise comparisons, Bayesian fixed effects model, HR (95% CrI)

Intervention	Comparator	
	DOC	NIN+DOC
NIN+DOC	0.83 (0.69, 0.98)	
RAM+DOC	0.83 (0.72, 0.96)	1.00 (0.81, 1.25)

Abbreviations: HR = hazard ratio; CrI = credible interval

HR less than 1 favours the intervention over the comparator.

These results are not used in the economic model, where the non-squamous subgroup is used for the comparison with NIN+DOC for the reasons highlighted above. However, the findings from this supporting analysis support the conclusions regarding the relative efficacy of RAM+DOC versus NIN+DOC.

Summary of adenocarcinoma NMA results

In the adenocarcinoma subpopulation:

- Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) was shown to be highly similar to nintedanib (200 mg) plus docetaxel (75 mg/m^2) in terms of both OS and PFS.

Data considerations

Quality Assessment

Full results of the quality assessment for each trial are provided in Appendix 7. The majority of studies were of reasonable quality, although for some the reporting of quality assessment items was unclear.

Size of the evidence networks

The overall networks for all three outcomes were relatively large and generally similar across the three outcomes of interest. The links in the network for the main RCTs assessing relevant comparators did not rely on any very small trials, with 222 patients in the smallest (67) up to 1253 patients in the largest (8).

The section of the network containing the relevant comparators formed a small star-shaped network centred on DOC. Whilst there were no closed loops within the relevant comparators, the estimates for ERL did form part of closed loops in the wider network. Links for RAM+DOC and NIN+DOC were each based on one trial comparing to DOC. As noted above, the lack of closed loops overall precluded the robust estimation of a random effects model.

Heterogeneity

Heterogeneity was investigated using three methods: comparing the results of studies that investigate the same treatment comparison; investigating consistency between direct and indirect comparisons in closed loops; exploring heterogeneity using meta-regression techniques.

For the meta-regression, the following covariates were explored based on clinical considerations and data availability:

- Median age
- Publication date
- Proportion of Asian patients
- Proportion of patients with ECOG PS ≥ 1

- Proportion of patients with stage IV NSCLC

These covariates were in addition to the treatment-specific covariates defined in the hierarchical exchangeable model for histology for pemetrexed and nintedanib and EGFR mutation-positive for gefitinib and erlotinib.

The covariates used in the analysis were included in the fixed-effects NMA models. The DIC model-fit statistic, the beta for each covariate, and the credible intervals for the beta were recorded. This type of technique assumes that there are no important missing variables in the analysis. If this assumption does not hold and there is significant variation in the network, this can produce misleading results by falsely attributing significance to included covariates when, in fact, significant differences are due to unknown factors. Therefore, results from meta-regression analyses always need to be treated with caution, as they can give misleading results due to the problems of dealing with aggregate data.

Heterogeneity in the OS network

For OS, the frequentist model, which was fitted without any attempt to model covariates, showed evidence of substantial heterogeneity (I^2 = 54.2%), which was significant (*P* = 0.0065). Decomposition of Cochran's Q and pairwise meta-analyses for the duplicate comparisons revealed that there was some heterogeneity between the 2 studies that compared docetaxel 100 mg with docetaxel 75 mg. Additionally, the relative difference between pemetrexed and docetaxel was found to be significant (p = 0.0090). This appeared to be mainly due to the Scagliotti et al. (2009) study that presented the results separately for non-squamous and squamous patients. The results from this study showed that pemetrexed was significantly more effective in the non-squamous patient population compared with the squamous population. A similar pattern was also reported by Karampeazis (68) who compared pemetrexed with erlotinib. It is also worth noting the difference between the pemetrexed non-squamous patient population of Karampeazis (68) and the results from Lee (69), which were also from a non-squamous population. The results from Lee (69) were more favourable for erlotinib. One reason for this might be that, in the Karampeazis (68) study, 9% of patients were EGFR mutation-positive compared with the Lee (69) study where 56% of patients were EGFR mutation-positive.

For the hierarchical exchangeable models, the fixed-effects model gave a better fit compared with the random-effects model, and the standard deviation of the heterogeneity parameter was bounded very close to zero, which suggested that this model largely explained the heterogeneity and inconsistency in the network.

Heterogeneity in the PFS network

For PFS, the frequentist model, which was fitted without any attempt to model covariates, also showed evidence of considerable heterogeneity (I^2 = 73.5%), which was significant (*P* < 0.0001). Decomposition of Cochran's Q and pairwise meta-analyses for the duplicate comparisons revealed that there was heterogeneity between the studies that compared pemetrexed (500 mg/m2) with docetaxel (75 mg/m2) (p = 0.028). This appeared to be mainly due to the Scagliotti (70) study that presented the results separately for non-squamous and squamous patients. The results from this study showed that pemetrexed was significantly more effective in the non-squamous patient population compared with the squamous population. In addition, there was heterogeneity between the three studies comparing pemetrexed (500 mg/m2) with gefitinib (250 mg) (P < 0.0001). Sun (71) gave more favourable results for gefitinib (250 mg) compared with Zhou (72) and Kim (73). This may be because Sun (71) contained a large proportion of individuals who were EGFR mutation-positive, whereas Zhou (72) had none and Kim (73) had only a small proportion.

For the hierarchical exchangeable models, a similar fit was found between the fixed-effects model and the random-effects model, as was the case for OS; the standard deviation of the heterogeneity parameter was bounded very close to zero, suggesting that the model largely explained the heterogeneity and inconsistency in the network.

Heterogeneity in the ORR network

The frequentist model, which was fitted without any attempt to model covariates, showed evidence of substantial heterogeneity (I2 = 60.6%), which was significant (P = 0.037). Decomposition of Cochran's Q and pairwise meta-analyses for the duplicate comparisons revealed that there was some heterogeneity between the 3 studies that compared pemetrexed (500 mg/m^2) with docetaxel (75 mg/m^2) (P = 0.0004), the 2 studies that compared pemetrexed (500 mg/m^2) with gefitinib (250 mg) (P = 0.0455), and the 2 studies that compared pemetrexed (500 mg/m^2) with erlotinib (150 mg) (P = 0.0936).

The heterogeneity between pemetrexed (500 mg/m^2) and docetaxel (75 mg/m^2) is likely due to the Scagliotti (70) study, in which results were presented separately for non-squamous and squamous patients and showed that pemetrexed was significantly more effective in the non-squamous patient population compared with the squamous population. The heterogeneity between pemetrexed (500 mg/m^2) and gefitinib (250 mg) is likely because Sun (71) contained a large proportion of individuals who were EGFR mutation-positive (52%), whereas Zhou (72) had none. Similarly, the heterogeneity between pemetrexed (500 mg/m^2) and erlotinib (150 mg) may be because the population reported in Karampeazis (68) study contained 9% of patients who were EGFR mutation-positive compared with 56% in Lee (69).

Proportional hazards (PH) assumption

For OS and PFS, analyses were based on HRs which typically make an assumption of PH. However, as previous stated, there were some studies included in the OS and PFS networks where this assumption may not hold (studies highlighted in red in Figure 18 and Figure 19). For the comparators of interest, only the results for nintedanib are affected by this for OS and as noted previously, this violation primarily affected the squamous subgroup results which were not relevant to the NMA and economic analysis presented in this submission. For PFS, the results for ramucirumab, nintedanib and some for erlotinib were affected. As only the REVEL trial informs the RAM+DOC to DOC comparison, data from the REVEL trial is used directly in the economic model rather than using the outputs of the NMA (see Section 5). The violation of PH for erlotinib may be a limitation but as erlotinib can be considered as a secondary comparator this has a limited impact on the overall decision problem and the conclusions drawn. Again the violation of PH in the nintedanib trial primarily affected the squamous subpopulation as noted above. The application of the assumption of PH was therefore considered appropriate for the decision problem considered in the economic model.

Hierarchical exchangeable models

Previous NMAs (74) have typically only presented the total patient population and may therefore have produced some potentially misleading results due to the analytic methods applied. Although there is a growing evidence base for these treatment-covariate interactions, these are often found within observational data or clinical trials designed specifically to look for these effects, meaning they could not be included in the network of evidence presented without

biasing the results. Certain limitations of the current approach need to be considered. The network was restricted to only those studies that provided patient characteristics for the relevant treatment-covariate interaction. Therefore, the network contains fewer studies in some parts compared with previously published network meta-analyses. This has resulted in networks with less information on which to estimate the heterogeneity; the presented models found that fixed-effects models appeared to work better than the random-effects models. However, it should be noted that the hierarchical exchangeable model does take into account a lot of heterogeneity that would have been present in previously published NMAs. Thus, a random-effects model may no longer be the best option due to less heterogeneity being present in the network and due to the difficulties involved in getting such a model to converge when there are only a small number of duplicate comparisons and closed loops in the network.

4.11 Non-randomised and non-controlled evidence

No non-RCT evidence has been presented in this submission.

4.12 Adverse reactions

- The REVEL safety population consisted of 627 patients in the RAM+DOC arm and 618 patients in the PBO+DOC arm
- Rates of TEAEs were similar between treatment arms with 97.8% of patients treated with RAM+DOC experiencing a TEAE versus 96.1% of patients treated with PBO+DOC
- TEAEs of any grade with incidence ≥ 5% in the RAM+DOC arm than the PBO+DOC arm were neutropenia, stomatitis, epistaxis, oedema peripheral, mucosal inflammation, febrile neutropenia, lacrimation increased and hypertension
- A greater incidence of Grade ≥3 hypertension was observed in patients receiving RAM+DOC (5.4%) than in patients receiving PBO+DOC (2.1%) although it was managed adequately with standard anti-hypertensive medication
- Grade ≥ 3 TEAEs with incidence ≥ 5% in the RAM+DOC arm than the PBO+DOC were neutropenia (34.9% vs. 28.0%, respectively) and febrile neutropenia (15.9% vs. 10.0%, respectively).
- The percentages of patients who were hospitalised were similar in both treatment arms (41.9% in the RAM+DOC arm and 42.6% in the PBO+DOC arm)
- The incidence of deaths due to AEs was low and similar in the RAM+DOC arm and the PBO+DOC arm (4.9% vs. 5.7%, respectively)
- Deaths during and up to 30 days after the last dose of study treatment occurred at a similar frequency in both treatment arms (8.5% in the RAM+DOC arm vs. 9.4% in the PBO+DOC arm).

The safety profile of RAM+DOC was assessed in the placebo controlled pivotal phase 3 trial REVEL. The REVEL safety population consisted of 627 patients in the RAM+DOC arm and 618 patients in the PBO+DOC arm. Overall, ramucirumab was well tolerated with manageable toxicities when used in combination with docetaxel for the 2nd line treatment of advanced or metastatic NSCLC. The percentage of patients who experienced at least one treatment emergent adverse event (TEAE) of any grade was similar between treatment arms: 97.8% in the RAM+DOC arm vs. 96.1% in the PBO+DOC arm. While a higher percentage of patients in the RAM+DOC than the PBO+DOC arm experienced Grade ≥3 TEAEs (78.9% vs 71.8%

respectively), the percentage of patients who experienced at least 1 serious adverse event (SAE) (42.9% vs. 42.4%, respectively) or TEAE leading to death (5.4% vs. 5.7%, respectively) was similar between treatment arms (Table 35). This suggests that the adoption of ramucirumab into NHS clinical practice for NSCLC patients is unlikely to result in a toxicity burden that is significantly above what is experienced by patients currently treated with docetaxel monotherapy.

Table 35 Overview of Treatment-Emergent Adverse Events

	RAM+DOC N = 627	**PBO+DOC N = 618**
TEAEs with Outcome of Death, n (%)	34 (5.4)	35 (5.7)
Treatment-Emergent Serious Adverse Events, n (%)	269 (42.9)	262 (42.4)
Patients with ≥1 Grade 3/4/5 TEAE	495 (78.9)	444 (71.8)
Discontinued due to TEAE, n (%)	58 (9.3)	32 (5.2)
Patients with ≥1 TEAE leading to discontinuation of ramucirumab/placebo	9 (1.4)	6 (1.0)
Patients with ≥1 TEAE leading to discontinuation of docetaxel	49 (7.8)	26 (4.2)
TEAE, n (%)	613 (97.8)	594 (96.1)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

The most frequently reported TEAE (occurring in at least 10% of participants and regardless of grade) where the incidence was ≥ 5% in the RAM+DOC arm than the PBO+DOC arm, respectively were neutropenia (38.9% vs. 33.2%), stomatitis (23.3% vs. 12.9%), epistaxis (18.5% vs. 6.5%), oedema peripheral (16.3% vs. 8.6%), mucosal inflammation (16.1% vs. 7.0%), febrile neutropenia (15.9% vs. 10.0%), lacrimation increased (13.4% vs. 4.5%), and hypertension (10.2% vs. 4.2%) – see Table 36. Grade ≥3 TEAEs occurring in more than 10% of patients in either treatment arm were fatigue, neutropenia, and febrile neutropenia (Table 36). Of these, neutropenia (34.9% vs. 28.0%, respectively) and febrile neutropenia (15.9% vs. 10.0%, respectively) occurred more frequently (≥5%) in the RAM+DOC arm than in the PBO+DOC arm. There were no Grade 5 events of neutropenia and febrile neutropenia (75). Consolidated terms of neutropenia, any grade (55.0% vs. 46.0%, respectively) and Grade ≥3 (48.8% vs. 39.8%, respectively), and thrombocytopenia, any grade (13.4% vs. 5.2%, respectively), were reported with a higher (≥5%) incidence in the RAM+DOC arm than the

PBO+DOC arm. Additional analyses examining the association between treatment-emergent thrombocytopenia and bleeding indicated that the higher incidence of thrombocytopenia was not associated with an increased risk of bleeding. The most frequently reported (≥1%) treatment-emergent serious adverse event with a higher incidence (≥5%) in the RAM+DOC arm than the PBO+DOC arm was febrile neutropenia.

Table 36 Treatment-Emergent Adverse Events (any grade) occurring in at least 10% of patients in the RAM+DOC arm, by MedDRA preferred term events

Regardless of Causality				
	Ramucirumab N = 627, n (%)		**Placebo N = 618, n (%)**	
Preferred Term	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Patients with ≥1 TEAE	613 (97.8)	495 (78.9)	594 (96.1)	444 (71.8)
Fatigue	289 (46.1)	71 (11.3)	258 (41.7)	50 (8.1)
Neutropenia	244 (38.9)	219 (34.9)	205 (33.2)	173 (28.0)
Diarrhoea	199 (31.7)	29 (4.6)	171 (27.7)	19 (3.1)
Decreased appetite	182 (29.0)	14 (2.2)	154 (24.9)	8 (1.3)
Nausea	169 (27.0)	7 (1.1)	170 (27.5)	9 (1.5)
Alopecia	162 (25.8)	0	156 (25.2)	0
Stomatitis	146 (23.3)	27 (4.3)	80 (12.9)	10 (1.6)
Dyspnoea	138 (22.0)	24 (3.8)	149 (24.1)	51 (8.3)
Cough	133 (21.2)	3 (0.5)	128 (20.7)	5 (0.8)
Anaemia	131 (20.9)	18 (2.9)	171 (27.7)	34 (5.5)
Epistaxis	116 (18.5)	2 (0.3)	40 (6.5)	1 (0.2)
Neutrophil count decreased	113 (18.0)	0	91 (14.7)	0
Pyrexia	104 (16.6)	3 (0.5)	80 (12.9)	2 (0.3)
Oedema peripheral	102 (16.3)	0	53 (8.6)	2 (0.3)
Constipation	101 (16.1)	1 (0.2)	108 (17.5)	6 (1.0)
Mucosal inflammation	101 (16.1)	18 (2.9)	43 (7.0)	3 (0.5)
Febrile neutropenia	100 (15.9)	100 (15.9)	62 (10.0)	62 (10.0)
Vomiting	87 (13.9)	8 (1.3)	88 (14.2)	12 (1.9)
Lacrimation increased	84 (13.4)	1 (0.2)	28 (4.5)	0

Regardless of Causality				
	Ramucirumab N = 627, n (%)		**Placebo N = 618, n (%)**	
Leukopenia	81 (12.9)	53 (8.5)	73 (11.8)	47 (7.6)
Myalgia	78 (12.4)	4 (0.6)	65 (10.5)	4 (0.6)
Peripheral sensory neuropathy	73 (11.6)	13 (2.1)	59 (9.5)	4 (0.6)
Arthralgia	72 (11.5)	7 (1.1)	49 (7.9)	4 (0.6)
Back pain	71 (11.3)	7 (1.1)	53 (8.6)	2 (0.3)
Asthenia	70 (11.2)	20 (3.2)	61 (9.9)	16 (2.6)
Dysgeusia	67 (10.7)	0	46 (7.4)	0
Insomnia	67 (10.7)	3 (0.5)	51 (8.3)	1 (0.2)
Headache	66 (10.5)	3 (0.5)	67 (10.8)	6 (1.0)
Hypertension	64 (10.2)	34 (5.4)	26 (4.2)	12 (1.9)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients; TEAE = treatment-emergent adverse event.

Overall, deaths that occurred while on treatment and up to 30 days after the last dose of study treatment occurred at a similar frequency in both treatment arms (8.5% in the RAM+DOC arm vs. 9.4% in the PBO+DOC arm). The incidence of deaths due to AEs (including both TEAEs and non-TEAEs) was low and similar in the RAM+DOC arm and the PBO+DOC arm (4.9% vs. 5.7%, respectively). An evaluation of the patients who died due to AEs showed no specific pattern of AEs leading to death.

The percentages of patients who were hospitalised were also similar in both treatment arms (41.9% in the RAM+DOC arm and 42.6% in the PBO+DOC arm). The median duration (range) of hospitalisation was 9.0 days (1-128) in the RAM+DOC arm and 8.0 days (1-56) in the PBO+DOC arm. The mean duration (standard deviation) of hospitalisation per patient was 14.5 days (16.5) in the RAM+DOC arm and 11.3 days (9.9) in the PBO+DOC arm. Febrile neutropenia, pneumonia, and neutropenia were the most common adverse events leading to a hospitalisation in both treatment arms.

Adverse Events of Special Interest (AESI)

Due to the anti-angiogenic mechanism of action of ramucirumab, a number of adverse events were considered to be of special interest (AESI) including hypertension, bleeding/haemorrhagic

events, venous thromboembolic events and GI perforation. Adverse events of special interest (AESIs) with a similar incidence between treatment arms were infusion-related reactions (4% in both the RAM+DOC and PBO+DOC arms), arterial thromboembolic events (2% in both arms), GI perforations (1% in the RAM+DOC arm vs <1% in the PBO+DOC arm), congestive heart failure (1% in both treatment arms), and fistula (0.5% in both treatment arms). Venous thromboembolic events occurred at a lower frequency in the RAM+DOC arm than the PBO+DOC arm. No events of reversible posterior leukoencephalopathy syndrome (RPLS) or wound healing complications were observed in the study. A greater incidence of Grade ≥3 hypertension was observed in patients receiving RAM+DOC (5.4%) than in patients receiving PBO+DOC (2.1%) although it was managed adequately with standard anti-hypertensive medication. Patients in the RAM+DOC arm also had more bleeding or haemorrhage events of any grade (29% vs 15% in the control arm), although most of these bleeding events were epistaxis and rates of grade 3 or worse events were much the same (six grade 3 events in each group and one grade 4 event (intracranial tumour haemorrhage) in the RAM+DOC group). Incidence of epistaxis of any grade was significantly higher in the RAM+DOC group than in the control group, but few grade 3 or worse events occurred. Gastrointestinal and respiratory tract bleeding events, including haemoptysis and pulmonary haemorrhage, did not differ between groups or according to histological disease type (76).

Table 37 Adverse Events of Special Interest, Safety Population

	RAM+DOC N = 627 n (%)		**PBO+DOC N = 618 n (%)**	
AESI	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Bleeding or haemorrhage	181 (29)	15 (2)	94 (15)	14 (2)
Epistaxis	116 (19)	2 (<1)	40 (6)	1 (<1)
Gastrointestinal haemorrhage	17 (3)	4 (1)	10 (2)	2 (<1)
Pulmonary haemorrhage	49 (7.8)	8 (1.3)	46 (7.4)	8 (1.3)
Haemoptysis	36 (6)	4 (1)	32 (5)	4 (1)
Hypertension	68 (11)	35 (6)	30 (5)	13 (2)
Proteinuria	21 (3)	1 (<1)	5 (1)	0
Venous thromboembolic events	16 (3)	11 (2)	36 (6)	18 (3)

Abbreviations: AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category.

4.13 Interpretation of clinical effectiveness and safety evidence

There are currently few agents routinely used in England for the second-line treatment of advanced NSCLC post-platinum. Docetaxel has been the NHS standard of care for the broad NSCLC patient population for over a decade, independent of their tumour histology or molecular subtype. Clinical outcomes in this second-line population are poor with ORR of less than 10%, median PFS of less than 4 months and median OS of 7-9 months (42). There is therefore a high unmet need in the NHS to improve treatment options for NSCLC patients that have progressed after first-line chemotherapy. New treatment options that improve survival and PFS, without adding significant toxicity while maintaining QoL, are essential to advancing care for these patients. This is particularly the case with patients with squamous NSCLC who currently have very limited NICE recommended second line treatment options, in part due to the lack of oncogenic drivers in squamous tumours.

REVEL was a global, randomised, placebo-controlled, double-blind, multi-centre Phase III study designed for unbiased assessment of the efficacy of RAM+DOC in patients with stage IV NSCLC who had progressed during or after one prior first-line platinum-based therapy for locally advanced/metastatic disease.

REVEL is the first study to demonstrate a clinically meaningful improvement in OS and PFS for a novel monoclonal antibody VEGFR inhibitor in combination with a standard chemotherapy in advanced NSCLC patients with progression after platinum-based chemotherapy. Unlike other therapies approved on the basis of subset analysis of OS in NSCLC, ramucirumab improved OS when compared with an active comparator and the OS benefit was consistent in patients with non-squamous and squamous NSCLC. RAM+DOC also conferred relevant and robust benefits consistently across all other efficacy endpoints, with an acceptable and manageable safety profile.

REVEL trial Internal and external validity

The large sample size of 1253 patients decreased the risk of an imbalance in the distribution of prognostic biomarkers. The risk of bias was assessed to be low due to randomisation via IVRS, treatments that were identical in appearance and adequate blinding of investigators and

outcome assessors. Furthermore the baseline characteristics of participants on both arms of the study were similar.

The study patient population was generally representative of the broad NSCLC population in the second-line setting with regard to sex, histology, disease characteristics, and prior therapy for lung cancer. The majority of patients had Stage IV disease at initial diagnosis and more than 2 metastatic sites (including metastases to the liver and CNS). Histologies, including squamous cell disease, were adequately represented.

The Systemic Anti-cancer Therapy (SACT) England chemotherapy dataset provides a report of the most frequently administered regimens for NSCLC across all lines of therapy (77). For the calendar year ending December 2014, the most frequently administered regimens were pemetrexed/platinum, vinorelbine/platinum and gemcitabine/platinum accounting for 22%, 17% and 14% of total chemotherapy cycles administered to patients in England respectively (77). In the REVEL trial, the most common prior platinum-based treatment regimens were pemetrexed/platinum and gemcitabine/platinum, which mirrors the SACT data distribution and is thus generalisable to England.

Other baseline demographic characteristics were reflective of the NSCLC clinical trial population. The median age for randomised patients was 62 years (range, 21 to 86 years), which is younger than the median age (70 years; (78)) at diagnosis in the general NSCLC population but in the middle of the range reported for advanced NSCLC patients enrolled in recent large clinical trials ((61, 79, 80)). National Lung Cancer Audit Data (LUCADA 2013) data showed that 77% of patients aged less than 65 years received active treatment for NSCLC compared to 63% of patients aged 65-80 years and 28% of patients aged over 80 years (1). This reflects the clinical reality that patients in the second line setting which are suitable for active treatment are likely to be younger and fitter. The ECOG PS at study entry was restricted to 0 or 1, with the majority of patients having a PS of 1 (67.4%), which is representative of the baseline PS reported for this population in clinical trials. Furthermore, since ramucirumab was evaluated in combination with docetaxel, PS 0 and 1 reflects those patients who are candidates in clinical practice to receive docetaxel in a post platinum progression setting.

The reported race of patients in the trial was broadly in line with the England cancer incidence by major ethnic group. The vast majority of participants were White at 83.8% with Asian and

Black/African American participants representing 11.8% and 2.7% respectively. This compares with age standardised lung cancer incidence rates for White, Asian and Black males of 61.1 to 62.6 per 100,000, 23.1 to 37.2 per 100,000 and 30.1 to 48.9 per 100,000 respectively (81). The corresponding age standardised lung cancer incidence rates for females is 35.2 to 36.0 per 100,000, 6.9 to 12.4 per 100,000 and 8.5 to 15.1 per 100,000 respectively (81).

Survival outcomes

OS is the gold standard for establishing clinical benefit in oncology but other endpoints such as PFS, response rate, patient-reported outcomes and toxicity help to inform an overall assessment of benefit-risk profile. REVEL demonstrated an improvement in OS with RAM+DOC over PBO+DOC. Median OS was 10.5 months for RAM+DOC and 9.1 months for PBO+DOC. RAM+DOC prolonged median survival by 15.4% (1.4 months) and reduced the risk of death by 14.3% (HR = 0.857; 95% CI: 0.751, 0.979; p=0.024).

Although the study was not powered for subgroup analysis, REVEL showed consistent results across multiple pre-specified patient subgroups for both OS and PFS, including patients with squamous and nonsquamous histology. The size of the OS benefit observed in REVEL should be viewed in the context of the very limited current survival profile of the second-line NSCLC overall patient population. Currently the median survival for lung cancer in England is 192 days (just under 7 months) across all stages (1). Furthermore, the survival rates in England are worse than those in some comparative European countries (6). The 15.4% increase in median OS over current standard of care, demonstrated in REVEL is thus a very valuable survival gain for patients with few options.

Clinically meaningful improvements were also observed across the efficacy endpoints of PFS, ORR and DCR. Treatment with ramucirumab significantly reduced the risk of disease progression or death by 23.8% (HR = 0.762; 95% CI: 0.677, 0.859; p<0.001), with a 1.5-month longer median PFS in the RAM+DOC arm than the PBO+DOC arm (4.5 months vs. 3.0 months, respectively). This represents a 50% increase in median PFS over standard of care. The duration of benefit in PFS (1.5 months) and OS (1.4 months) was much the same, suggesting that the additional survival benefit was spent in the pre-progression period where health related QoL is better and patients know that their tumour is not getting bigger (8). The ORR was significantly improved for the RAM+DOC arm as compared to the PBO+DOC arm (22.9% vs.

13.6%, respectively; p<0.001). This shows that the percentage of patients whose cancer shrinks or completely disappears is significantly higher when treated with RAM+DOC. This can also have important health related QoL benefits for patients, including reduced tumour burden and improvements in symptomatic disease. This ORR benefit observed was consistent across non-squamous and squamous patients.

By demonstrating a significant OS, PFS and ORR advantage compared to PBO+DOC in the overall study population, the clinical benefit of RAM+DOC is clear. RAM+DOC provides a clinically meaningful option for NHS patients, irrespective of histology, who currently only have access to standard treatment options with limited clinical benefit.

The NMA followed the NICEDSU technical guides for evidence synthesis and allowed for clinical and economic comparisons of RAM+DOC with other comparators identified in the NICE scope. RAM+DOC gave significantly greater OS, PFS and ORR than both docetaxel (in all populations) and erlotinib (in EGFR-negative patients). Furthermore the results of the NMA for all three outcomes were similar to the REVEL trial results. There was no evidence to suggest differences between RAM+DOC and NIN+DOC in the non-squamous population.

QoL outcomes

REVEL collected LCSS, EQ-5D and TTD in ECOG performance status data and demonstrated that OS and PFS gains were not achieved at the expense of QoL. The QoL analysis showed similar time to deterioration (TTD) for all LCSS scores between treatment arms. There were minimal changes from baseline in EQ-5D index or VAS scores while on study therapy, regardless of treatment arm. The time to deterioration of ECOG PS to 2 or worse was also similar between treatment arms (HR = 1.03; 95% CI: 0.85, 1.26). Additional analyses found no consistent or clinically meaningful differences between treatment arms, suggesting that QoL was maintained by treatment with RAM+DOC relative to PBO+DOC. This is very important given the limited survival of patients with metastatic NSCLC. Extending PFS and OS compared to the SoC docetaxel, without impacting QoL, underlines the importance and benefit to patients of ramucirumab as a treatment option.

It is noteworthy that the treatment schedule of ramucirumab (once every three weeks) is the same as that of docetaxel. Therefore no additional hospital visits are required for ramucirumab administration and this may have a positive impact on patient convenience, compliance and

QoL. Docetaxel monotherapy has been used as the standard of care, post-platinum for over a decade. Therefore patients and clinicians alike may be familiar with docetaxel and have established beliefs or perceptions of it as an appropriate choice to reduce symptoms and slow tumour growth while extending survival. The addition of ramucirumab to docetaxel may serve to increase positive perceptions of therapy, which may be an added value to patients.

Adverse event outcomes

The safety population of REVEL (N=1253) provides a large dataset for assessing the safety of ramucirumab in advanced NSCLC (82). RAM+DOC was generally well tolerated in the advanced nonsquamous and squamous NSCLC population, with expected risk of toxicities and manageable side effects. The safety profile observed was consistent with the established individual safety profiles for ramucirumab and docetaxel. The percentage of patients who experienced at least one treatment emergent adverse event (TEAE) of any grade was similar between treatment arms. The most frequently reported TEAEs of any grade observed at a higher (≥5%) incidence in the RAM+DOC arm than in the PBO+DOC arm were: neutropenia, stomatitis, epistaxis, oedema peripheral, mucosal inflammation, febrile neutropenia, lacrimation increased, and hypertension.

While a higher percentage of patients in the RAM+DOC arm than the PBO+DOC arm experienced Grade ≥3 TEAEs, the percentage of patients who experienced at least 1 serious adverse event (SAE) or TEAE leading to death was similar between treatment arms (83). In addition the percentage of patients who had at least 1 hospitalisation was similar in both treatment arms (76).

Overall the benefit-risk assessment of RAM+DOC in locally advanced or metastatic NSCLC patients with progression after platinum-based chemotherapy has been shown to be favourable, based on the proven benefit, manageable safety profile, and lack of apparent detriment to QoL. Ramucirumab thus represents a significant new therapeutic option for patients with metastatic NSCLC with progression after platinum-based chemotherapy. This technology can provide meaningful health-related benefits, irrespective of histology to a very sick population who currently have limited options.

End of life criteria

RAM+DOC fulfils the three criteria specified in section 6.2.10 of the NICE guide to the methods of technology appraisal under 'life-extending treatment at the end of life' and so should qualify under the end of life criteria. Please see below for a detailed explanation of how these criteria are met.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The prognosis and survival rate for patients with NSCLC is poor. As with most cancers better prognosis is largely dependent on early diagnosis. Unfortunately due to the non-specificity or absence of symptoms, 55% of patients with histologically confirmed NSCLC have advanced or metastatic (stage IIIB or stage IV tumours) cancer at the time of presentation (1). Nationally, the median survival for lung cancer is 192 days, i.e. just under 7 months (Interquartile range is 58 – 315 days) and the three-month, one-year and five-year survival rates are 67%, 35% and 9% respectively (1).

Criterion 2: 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 treatment

The economic model demonstrates that RAM+DOC increases mean OS by 3.06 months compared to the standard of care, docetaxel. This is a significant improvement in OS for patients with metastatic NSCLC.

Criterion 3: The treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England

Ramucirumab is currently licensed and available in England for the second-line treatment of gastric cancer (GC) and gastro-oesophageal junction cancer (GOJ). It has been designated orphan status by the EMA as GC affects not more than 3 in 10,000 people in the EU (19). An estimated 657 patients diagnosed with advanced GC/GOJ would be eligible for second-line treatment following first-line chemotherapy in England (84).

Due to the very poor prognosis for patients with NSCLC, the number of patients that will be alive and eligible to receive second-line treatment is small. It is expected that there would be approximately 1052 patients newly eligible for ramucirumab each year in England using data from the most recent national lung cancer audit (1) and applying the proportion of patients

currently eligible for second-line therapy in England. Therefore the total number of patients eligible for ramucirumab treatment across all licensed indications in England is estimated to be 1709.

Table 38 Annual NSCLC patient numbers and second-line eligibility

Description	% patients	Number	References
Cases submitted to NCLA	-	32,364	NCLA 2014 (1)
Patients with NSCLC (All lung cases excluding small cell and mesothelioma)	84%	27,186	NCLA 2014 (1)
Patients with performance status 0-1 and stage IIIB/IV NSCLC	23.12%	6,285	NCLA 2014 (1)
Patients receiving 1St line chemotherapy	59.8%	3,759	NCLA 2014 (1)
Patients receiving 2nd line chemotherapy	28%	1052	Brown 2013 (38)
Patients eligible for second-line chemotherapy	-	1052	

Table 39 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median survival for lung cancer is 192 days, i.e. just under 7 months (Interquartile range is 58 – 315 days) (1)
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 treatment	The economic model demonstrates that RAM+DOC increases mean OS by 3.06 months compared to docetaxel
The treatment is licensed or otherwise indicated for small patient populations	Patient population with previously treated, advanced GC/GOJ who are eligible for treatment is estimated to be 657 (84). Patient population with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy who are eligible for treatment is estimated to be 1,052 Total estimated eligible population across all indications = 1,709

4.14 Ongoing studies

There are no additional studies involving ramucirumab in advanced or metastatic NSCLC expected to report in the next 12 months

5. Cost effectiveness

- The cost-effectiveness model has been designed and populated based on rigorous systematic reviews and has undergone extensive internal and external validation. This, along with the robust results as demonstrated by the sensitivity analysis, shows that the model produces highly reliable results.
- The results of the model show that ramucirumab in combination with docetaxel extends mean time in PFS (by 1.45 months) and progressed disease (by 1.61 months) compared to docetaxel alone, thus providing an undiscounted life-year gain of 3.06 months compared with docetaxel alone. The QALY gain associated with ramucirumab plus docetaxel versus docetaxel alone is 0.124, 64% of which is accrued in the pre-progression phase. The additional benefit comes at an incremental cost of £24,294.
- There is clear evidence that society has a preference for allocating resources to patients with severe diseases and a high unmet need (11). NSCLC is one such condition, given that patient prognosis is so poor and even a small QALY gain is extremely valuable to patients and their families. Ramucirumab should also be considered under the end-of-life criteria.

5.1 Published cost-effectiveness studies

Identification of studies

A systematic literature review was conducted to collate in a transparent, reproducible manner, the evidence from economic analyses and cost studies of advanced or metastatic NSCLC. This search strategy was also used to identify any relevant sources to inform the resource requirements of the economic model.

The search strategy included searches of the following electronic databases: MEDLINE, MEDLINE In-Process, EconLit, Embase, BIOSIS, and The Cochrane Library. The database searches were performed from 1 January 1999 to 17 June 2014; no language or geographical restrictions were placed on the searches. The eligibility criteria used in the level 1 screen of titles/abstracts and in the first level 2 screen of full texts are presented in Table 40; the full search strategy used can be found in Appendix 8.

Due to the volume of studies identified for inclusion after completion of the original level 2 screening, the decision was made to undertake an additional level of screening (level 2b), applying the following additional exclusion criteria:

- Studies published prior to 2004 (as the cost data may be considered to be out of date or less relevant than more recent studies)
- Studies with unclear lines of therapy or combined first- and second-line therapies (as the population would not necessarily be relevant)
- Studies performed in countries not of interest for the purpose of this search (the countries of interest were the United Kingdom along with France, Germany, Italy, Spain, the Netherlands, Australia, Canada, United States, Brazil, Mexico, China, Taiwan, Korea, Japan)
- Publications that were not in the English language
- Studies whose primary objective was an assessment of methods
- Studies that compared different treatment administration routes for the same intervention (e.g., erlotinib standard therapy compared with erlotinib clinically guided therapy, or biologically guided therapy)
- Studies solely focused on caregiver costs (which were not relevant to the economic model)

Table 40 Criteria for the inclusion and exclusion of studies

Criteria	Included	Excluded
Population	Adult patients with advanced or metastatic NSCLC [a] Adult patients with squamous NSCLC Adult patients with non-squamous NSCLC Adult patients with advanced or metastatic NSCLC [a] with disease progression and undergoing second-line therapy	Children Adult patients with advanced or metastatic NSCLC undergoing first-line therapy
Interventions	All pharmacological treatments Palliative care	None
Study type	Economic evaluations Cost-effectiveness analyses Cost-benefit analyses Cost-utility analyses Prospective studies reporting costs or resource utilisation (e.g., observational studies, clinical trials) Retrospective studies reporting costs or resource utilisation (e.g., cost-of-illness, cross-sectional studies) Systematic reviews of economic analyses, resource-use, or cost studies [b]	Commentaries and letters (publication type) Consensus reports Non-systematic reviews Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden)

Abbreviations: NSCLC = non-small cell lung cancer.

[a] Patients with recurrent disease, distant metastases or locally advanced (unresectable) NSCLC were included.

[b] Systematic reviews were included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening.

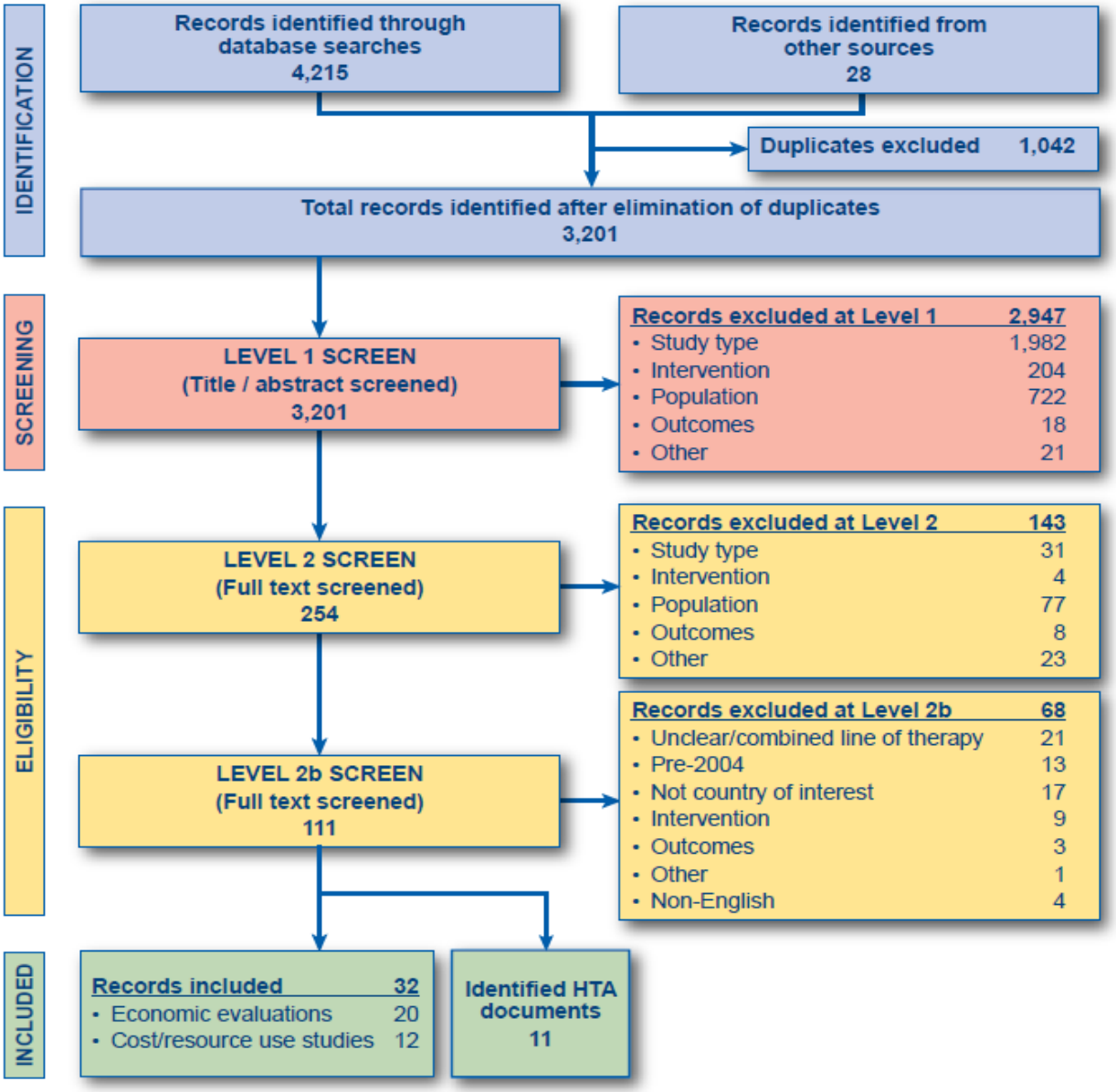
In addition to searching the published literature, targeted research was performed to identify relevant HTA documents from NICE, the Scottish Medicines Consortium, the Canadian Agency for Drugs and Technologies in Health, the Australian Pharmaceutical Benefits Advisory Committee, and the International Network of Agencies for Health Technology Assessment.

Systematic Review Results

The systematic review identified 20 relevant economic evaluations for treatments used in second-line advanced or metastatic NSCLC (Figure 22). Of the 20 economic evaluations, which are summarised in Appendix 8, 2 were from the UK (85, 86); the remainder comprised 3 Brazilian analyses (87-89), 6 Canadian analyses(90-95), 1 Chinese analysis (96), 3 French analyses (97-99), 1 Mexican analysis (100), 1 Spanish analysis (101), and 3 US analyses (102-104). In addition, a summary of the HTA documents identified is presented in Table 41.

Subsequent to the conduct of the SLR, two recent NICE appraisals were published and were referred to in the preparation of this submission – final guidance on nintedanib TA347 (10) and the final appraisal determination for erlotinib and gefitinib (ID620; a review of TA162 and TA175) (41). None of the economic evaluations included ramucirumab and therefore a *de novo* economic evaluation was undertaken and is reported in Section 5.2.

Figure 22 PRISMA diagram for the economic evaluations and cost/resource use systematic review



Abbreviations: HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Level 2 screening applied the inclusion and exclusion criteria listed in Table 40.
Level 2b screening additionally excluded: studies published prior to 2004, studies with unclear lines of therapy or combined first- and second-line therapies, studies performed in countries not of interest, publication not in the English language, studies whose primary objective was an assessment of methods, studies that compared different treatment administration routes for the same intervention, studies solely focused on caregiver costs.

Table 41 Summary of identified HTA documents

Agency	Ref ID	Full Reference
NICE	CG121	Lung Cancer: The diagnosis and treatment of lung cancer
NICE	TA162	Erlotinib for the treatment of non-small-cell lung cancer
NICE	TA310	Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer
NICE	TA124	Pemetrexed for the treatment of non-small-cell lung cancer
NICE	TA175	Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal)
NICE	TA184	Topotecan for the treatment of relapsed small-cell lung cancer
NICE	TA296	Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene
SMC	SMC920/13	afatinib (Giotrif)
SMC	SMC865/13	crizotinib (Xalkori)
SMC	SMC342/07	pemetrexed (Alimta)
CADTH	CADTH1	Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines

Abbreviations: NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; CADTH = Canadian Agency for Drugs and Technologies in Health

5.2 De novo analysis

Patient population

The cost-effectiveness model considers patients with locally advanced or metastatic NSCLC whose disease progressed during or after one prior platinum-based chemotherapy, with or without maintenance therapy, for advanced disease. This is the patient population investigated in the REVEL trial, which is the primary evidence base for this decision problem. It is also in line with the expected licence wording for ramucirumab (18) and the scope specified by NICE for this appraisal (105).

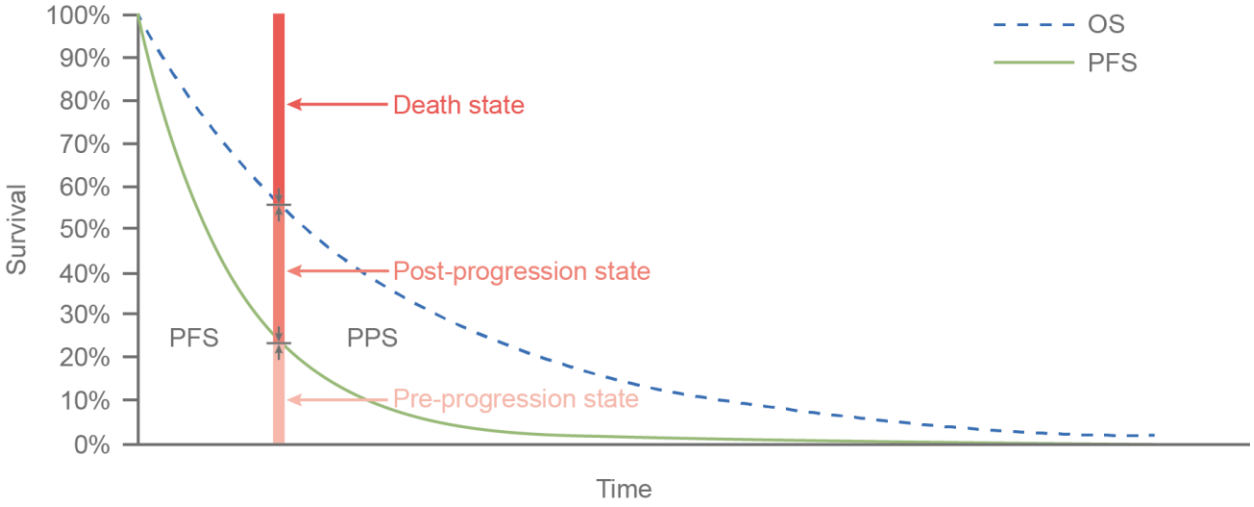
Other comparators included in the economic model are indicated for treatment after first-line chemotherapy (nintedanib, (65)) or after failure of at least one prior chemotherapy regimen (erlotinib, (106)). The standard of care in England is first-line treatment with chemotherapy-platinum doublet therapy, therefore for the purposes of this economic appraisal the definitions post-platinum and 'second-line' are assumed to be clinically equivalent.

Model structure

De novo model structure

A partitioned survival (area under the curve) model is presented for the economic evaluation of RAM+DOC vs relevant comparators. This model type has been commonly used in previous appraisals in NSCLC (9, 10), and other cancer types, and has analogies to a cohort Markov model in estimating the costs and benefits of the proportion of the cohort in each state using a fixed cycle length. Proportions of the cohort in each state over time are estimated from the pivotal clinical trials and the network meta-analysis presented in Section 4.10. The model structure is presented in Figure 23, which shows how the model captures patient cohort progression from treatment initiation through to death.

Figure 23 States included in the *de novo* partitioned survival economic model and schematic representation of how the modelled cohort partitions between them at a given time



Abbreviations: PFS: Progression-free survival; PPS: Post-progression survival; OS: Overall survival

Clinical pathway of care

The treatment pathway in England has been discussed in detail in Section 3.3. Standard of care first-line treatment consists of four cycles of third-generation chemotherapy platinum doublet or a targeted therapy for patients with a relevant tumour mutation. Patients of a non-squamous histology may be treated with pemetrexed maintenance monotherapy if they have not progressed following their first four cycles.

This decision problem however relates to the use of second-line therapies (*i.e.* post platinum chemotherapy). All patients therefore enter the economic model at initiation of second-line treatment, in the progression-free state. Patients in the model remain in this initial state until such point as they experience disease progression or death.

Of the patients in the progressed state, 70% continue to receive best supportive care in line with current clinical practice, 25% receive subsequent third-line anticancer therapy with vinorelbine and carboplatin and 5% with erlotinib, based on the assumptions used in the recent NICE appraisal of nintedanib (TA347, (10)) for second-line adenocarcinoma. Patients remain in the progressed state until death, which forms an absorbing state.

Health States

The model aims to capture all relevant benefits and costs associated with each comparator in the evaluation. QALYs and costs are accrued over time in the pre- and post-progression states, as described below. At each time point the patient cohort is partitioned between the three states.

Pre-progression

All patients enter the model in the pre-progression state and are allocated to treatment with RAM+DOC or one of the relevant comparators. Patients remain in this state until disease progression or death. Patients continue to receive active treatment whilst in this state until disease progression or treatment cessation for other reasons (for example adverse events).

Post-progression

Over time as patients' disease progresses increasing proportions of the cohort are modelled in the post-progression state where their second-line treatment is stopped and they receive either

BSC or third-line treatment. This state captures the decreased HRQoL associated with progressed disease.

Death

Death is an absorbing state, with no QALYs or costs accruing. The proportion of the cohort in the death state at each time was based on all-cause trial mortality from REVEL; as the patients in the model have advanced terminal cancer, the risk of death from other causes was assumed to be negligible.

Other features of the de novo model

The cycle length was set to 21 days as this fitted with the treatment regimens of the relevant comparators in the model, which comprised daily oral therapies or infusions administered on a 21-day cycle (except for erlotinib which is generally administered on a continuous daily basis). A 15 year time horizon was used, in keeping with the recent TA347 and the appraisal committee's conclusions that this was appropriate for this disease (10).

A half-cycle correction, using the life table method, was applied in order to minimise any bias in the cost-effectiveness estimates.

Table 42 presents the features of the *de novo* model.

Table 42 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	15 years	This covers the expected lifetime of all patients in the model allowing the model to capture all costs and benefits of intervention and comparators
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case (107)
Discount of 3.5% for utilities and costs	Yes	NICE reference case (107)
Perspective (NHS/PSS)	NHS/PSS	NICE reference case (107)

Abbreviations: PSS = personal social services; QALYs = quality-adjusted life years

Intervention technology and comparators

Intervention

The intervention assessed in the model is RAM+DOC. In this regimen ramucirumab (10 mg/kg) is administered following docetaxel (75 mg/m^2) infusion during the same hospital visit on day 1 of a 21-day cycle, as per the REVEL study and in line with the anticipated marketing authorisation for ramucirumab for NSCLC (18).

Treatment continuation rules

No treatment continuation rules were applied beyond the anticipated marketing authorisation for ramucirumab. RAM+DOC is recommended to be continued until disease progression or unacceptable toxicity has occurred (18). It has been noted in previous appraisals in similar indications that typically only 4 cycles of docetaxel are given in the UK and on rare occasions up to 6 (10) due to associated toxicities. The median number of cycles of docetaxel in REVEL was 4 for both the RAM+DOC and PBO+DOC arms but some patients received considerably more (mean = 5.5 cycles in RAM+DOC arm and 4.9 cycles in PBO+DOC arm). Whilst it would be possible to cap the number of cycles of docetaxel in the model, such an adjustment could only be made for costs, leaving the efficacy and AE profile unchanged thus introducing unknown bias into the results.

Comparators

As previously noted, the relevant comparators for the submission (see Section 1.1) are:

- Docetaxel (75 mg/m^2 every 21 days) (DOC).
- Nintedanib (200 mg twice daily on days 2–21 of the cycle) + docetaxel (75 mg/m^2 every 21 days) (NIN+DOC). NIN+DOC is licensed only for use in patients with adenocarcinoma tumour histology (65).
- Erlotinib (150 mg daily) (ERL). ERL is licensed for NSCLC after the failure of at least one prior chemotherapy regimen. However, the recent NICE multiple technology appraisal (MTA) included evidence that its use in English second-line clinical practice is generally restricted to EGFR-negative patients, as EGFR-positive patients would be expected to receive an EGFR-TK inhibitor first-line and not be re-challenged (41).

In each case, the modelled comparators are in accordance with their licensed indications, their expected use in English clinical practice and the NICE decision problem specified in the scope.

The NICE scope additionally specified nivolumab in squamous NSCLC and crizotinib in ALK mutation positive NSCLC as comparators but these have not been included in the analysis for the reasons set out in Section 1.1.

5.3 Clinical parameters and variables

As described above, the model partitions patients between three states: pre-progression, post-progression and death. The proportion of patients in the states at each cycle is based on the REVEL clinical trial and the NMA presented in Section 4.10. The approach taken to apply these data to the model is presented below in more detail.

Methodology: parameter estimation and selection

Based on the nature of NSCLC and its standard of care, as well as the needs of the model, the following endpoints were assessed:

- OS, defined as the interval of time between the date of randomisation and the date of death due to any cause
- PFS, defined as the interval of time between the date of randomisation and the earlier of the date of disease progression or the date of death due to any cause

To arrive at the best-fitting model, the principles outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 (108) were adhered to. The following five parametric models were estimated and considered for goodness of fit to PFS and OS data from REVEL; exponential, Weibull, lognormal, log-logistic and Gamma. The Gompertz distribution is not supported by the PROC LIFEREG procedure in SAS, the software used for all the survival regression analyses described here. An attempt was made to use a macro to fit the Gompertz model but there were significant concerns regarding the validity of the outputs generated and so it was decided that this distribution should not be considered further.

A robust selection process was used to evaluate the internal and external validity of each function to the observed data. Both aspects are important to ensure that the parametric model not only provides a suitable fit to the observed data, but also provides long term predictions which are clinically plausible. The following methodology was applied in modelling PFS and OS.

1. Assess the functional form of the underlying hazard, including if the proportional hazards (PH) assumption holds
2. Conduct goodness of fit tests and assess suitability of each parametric distribution
3. Select the most appropriate distribution

The specific methods used to assess each distribution are presented in Table 43.

Table 43 Methods for assessing the suitability of parametric survival models

Criteria	Method	Description
Observed trial period	AIC & BIC statistics	Assess the relative fit of parametric models whilst accounting for the number of parameters
	Cox-Snell residuals	Assess how closely a parametric function follows the Kaplan-Meier function
	Log-log hazard plot	Assess the behaviour of the hazard function over time and the plausibility of the proportional hazards assumption
	Visual inspection	Assess how closely a parametric function follows the Kaplan-Meier function and the clinical plausibility of the prediction in relation to other endpoints
Extrapolation period	Visual inspection	Assess how closely the tail of the parametric function fitted to the active treatment arm(s) concur with any available external longer term data or clinically expected outcomes

Abbreviations: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion

The survival functions were fit to the KM data in both unadjusted models and in adjusted models with covariates included to improve fit and to facilitate key subgroup analyses.

OS and PFS modelling summary

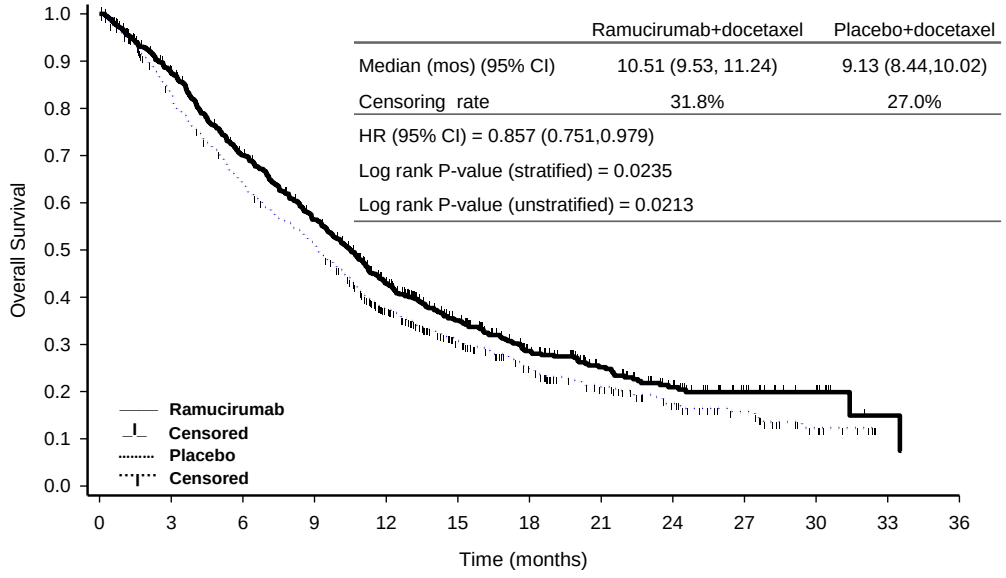
OS was estimated using a multivariate model assuming a log-logistic distribution in the base case economic model. PFS was estimated using multivariate models (one per treatment) assuming a generalised gamma distribution in the base case economic model.

Overall survival

The model uses OS data from the REVEL trial, the Kaplan–Meier curves for which are presented in Figure 24. Because not all REVEL trial patients (68.2% of RAM+DOC patients;

73.0% of PBO+DOC patients) had died as of the end of the trial follow-up period (approximately 33 months), the OS parametric curves require extrapolation from the end of the trial follow-up until all patients are estimated to have died.

Figure 24 Kaplan–Meier Plots: overall survival



Patients at Risk

Ramucirumab+docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

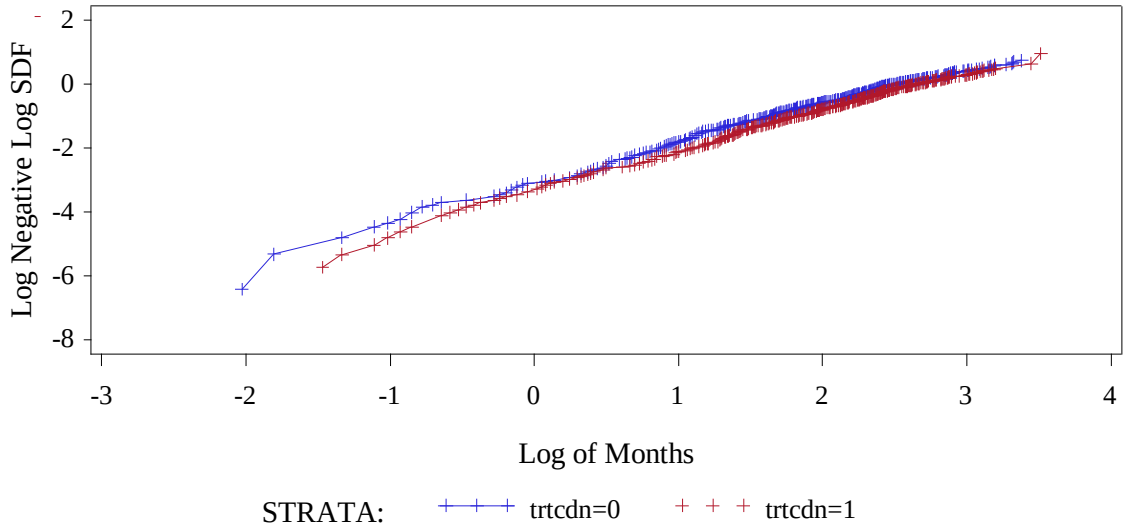
Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months. (109)

Assessment of hazards

A visual inspection of the Kaplan–Meier (KM) curves shows that they remain reasonably parallel throughout the length of the trial, implying no clear violation of the proportional hazards assumption.

The log-log plot of OS for the treatment arms from the REVEL trial is shown in Figure 25. Again the lines are approximately parallel, supporting the assumption of proportional hazards. The coefficient for the time-dependent covariate of treatment in the Cox regression model showed no evidence that non-PH is present (*i.e.* not statistical significant different from zero, P=0.1).

Figure 25 Log-log hazard plot of OS in REVEL – RAM+DOC and PBO+DOC arms



Program Location: \lillyce\prd\ly3009806\i4t_mc_jvba\csr1\programs_nonsdd\test_prophazard_os.sas
Abbreviations: SDF: survival distribution function; trtcdn=0: PBO+DOC; trtcdn=1: RAM+DOC

Based on the results of this assessment, proportional hazards was assumed to hold. Parametric survival functions were fitted for OS which included treatment as a covariate.

Goodness of fit

To assess the goodness of fit the following distributions were tested:

- Exponential
- Weibull
- log-normal
- log-logistic
- generalized gamma

Both unadjusted (*i.e.* with only treatment as a covariate) and covariate-adjusted parametric survival models were fitted for OS and assessed for goodness of fit. These are furthermore referred to as the unadjusted and multivariate parametric models. For both OS and PFS, the covariates included in the multivariate parametric models were taken from the significant

prognostic factors identified from a pre-defined set of baseline factors using Cox proportional hazard model that had been used to derive the trial HR results (8). These variables had been selected using a stepwise selection method using a p-value <0.05 as the criterion for adding a variable and p-value ≥0.10 for dropping a variable; the treatment arm factor was not included in the stepwise selection but was added to the final model. The HR for treatment effect and the corresponding 95% CI were then estimated from this final Cox model.

The multivariate parametric model for OS included the following covariates, in addition to treatment:

- Age (≤65 years vs > 65 years)
- Histology (non-squamous vs squamous)
- Time since initiation of prior therapy (< 9 months vs ≥ 9 months)
- Prior maintenance therapy (yes vs no)
- Pemetrexed first-line (yes vs no)
- Sex (female vs male)
- Geographic region (Japan/East Asia vs rest-of-world [ROW])
- Best response to platinum therapy (complete response [CR]/partial response [PR]/stable disease [SD] vs progression)
- Eastern Cooperative Group (ECOG) performance status (0 vs 1)

Generally, the multivariate OS models provided a better fit than the unadjusted OS models (see Table 44; see Appendix 9 for goodness-of-fit plots). In addition, the multivariate models provide slightly more conservative estimates of overall survival compared to the unadjusted models for almost every distribution and across both arms (see Table 45). Therefore only the multivariate OS models are considered further.

Table 44 AIC and BIC for Unadjusted and Multivariate Overall Survival Functions

Distribution	AIC (Unadjusted)	AIC (Multivariate)	BIC (Unadjusted)	BIC (Multivariate)
Exponential	3405.83	3109.34	3416.10	3190.57
Weibull	3391.11	3073.96	3406.51	3160.27
Log-normal	3386.94	3083.27	3402.34	3169.58
Log-logistic	3361.03	3052.43	3376.43	3138.73
Generalized gamma	3367.06	3055.51	3387.59	3146.89

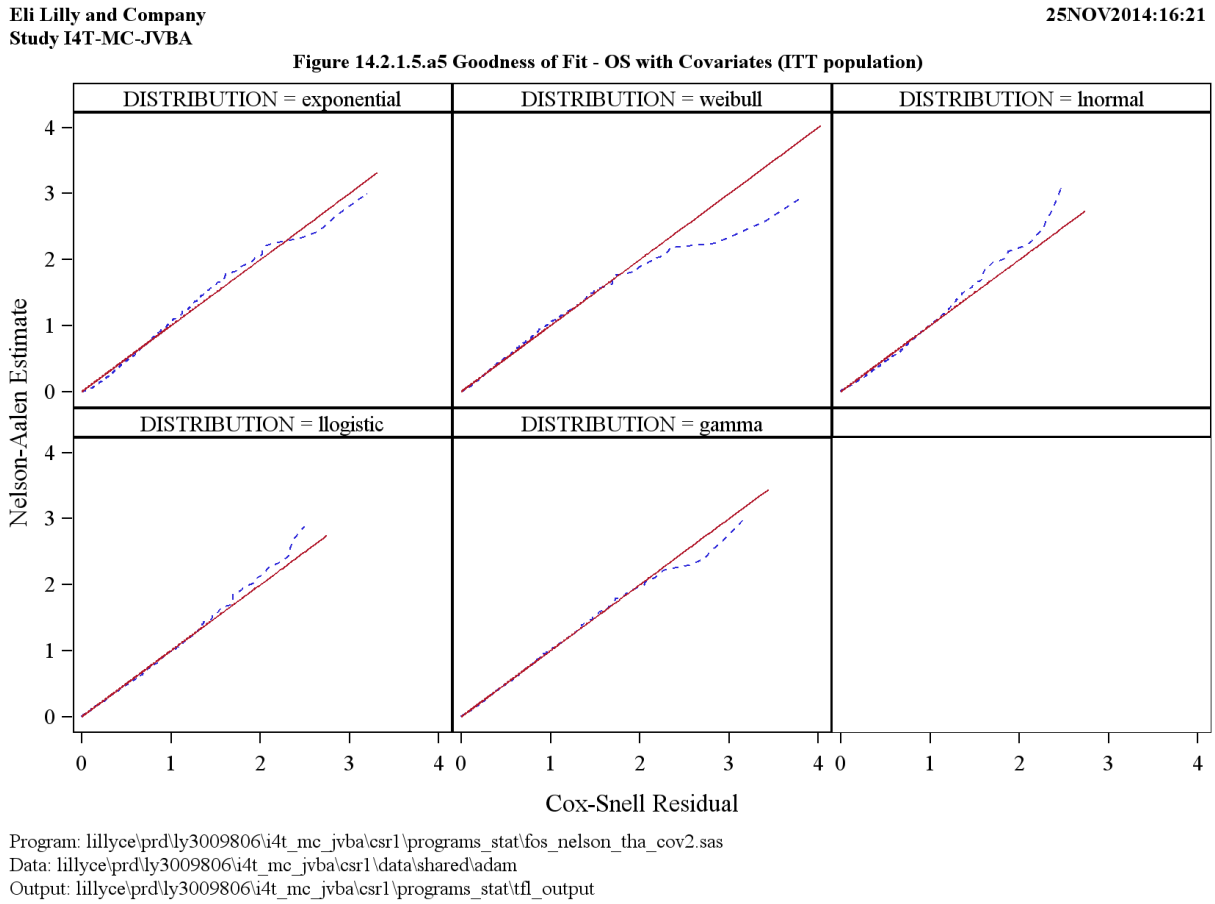
Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

Table 45 Expected overall survival life-years for REVEL study treatments generated using the model using unadjusted and adjusted parametric models for overall survival, by distribution

	RAM+DOC		PBO+DOC	
Distribution	**Mean OS (years) (Unadjusted)**	**Mean OS (years) (Multivariate)**	**Mean OS (years) (Unadjusted)**	**Mean OS (years) (Multivariate)**
Exponential	1.278	1.289	1.116	1.080
Weibull	1.216	1.198	1.068	1.012
Lognormal	1.615	1.527	1.396	1.285
Log-logistic	1.659	1.574	1.437	1.319
Generalized gamma	1.345	1.279	1.166	1.073

Among the distributions tested in the multivariate model, the log-logistic provided the best fit (on the basis of the AIC and BIC statistics). Goodness of fit plots and comparison with trial Kaplan–Meier curves for each distribution are presented in Figure 26 and Figure 27.

Figure 26 Goodness of fit plots for multivariate OS models



Program: lillyce\prd\ly3009806\i4t_mc_jvba\csr1\programs_stat\fos_nelson_tha_cov2.sas
Data: lillyce\prd\ly3009806\i4t_mc_jvba\csr1\data\shared\adam
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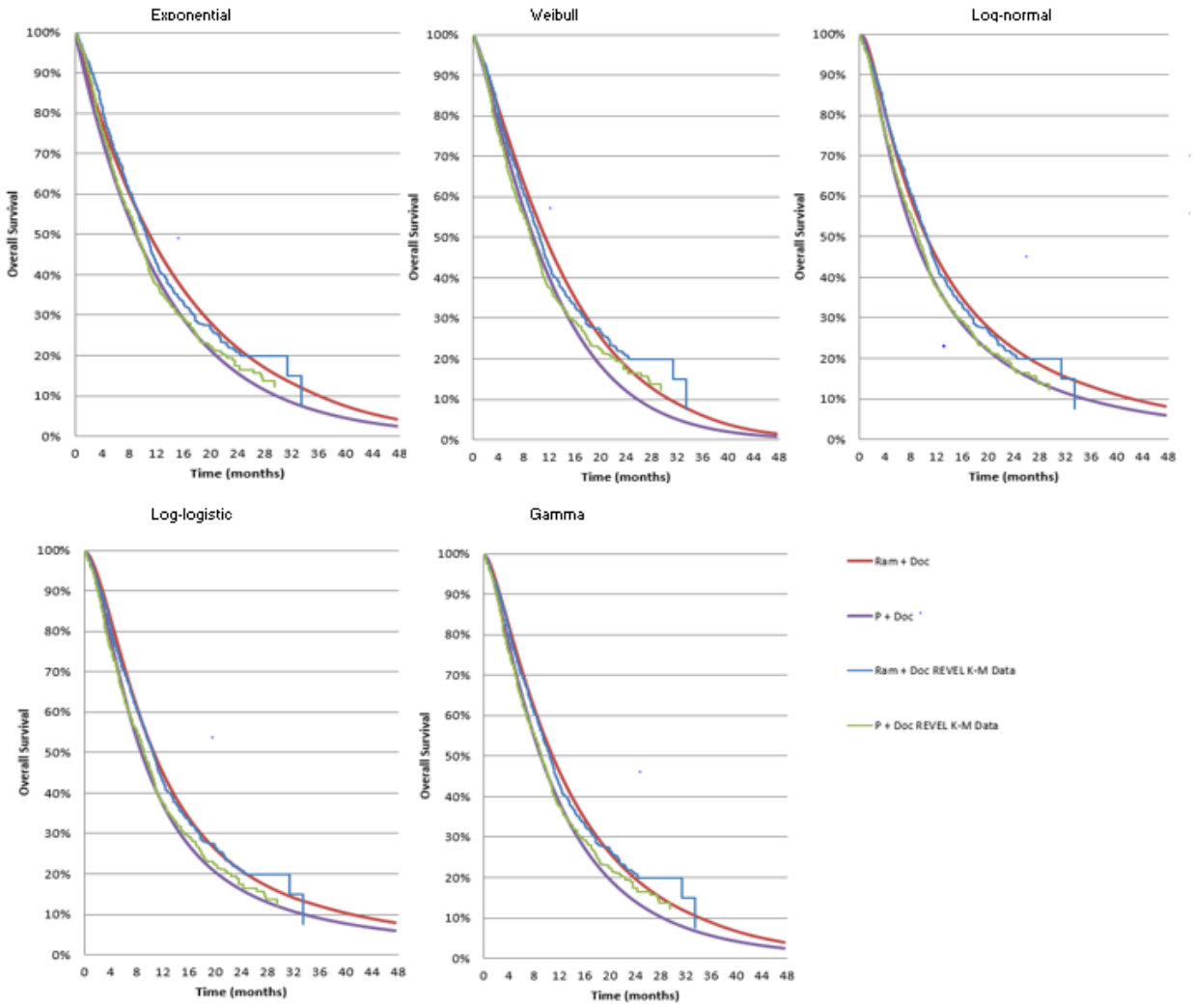
Figure 27 Overall survival Kaplan–Meier and multivariate parametric survival curves



Choice of distribution for OS

OS was therefore estimated using a multivariate model assuming a log-logistic distribution in the base case economic model. This decision was based on consideration of the AIC and BIC statistics, a comparison of nested distributions by fitting the generalized gamma function, face validity with respect to estimates of overall survival in another recent second-line NSCLC NICE appraisal (10), and visual fit to the KM data. The validation of the modelling of OS against available UK data is detailed in Section 5.10.

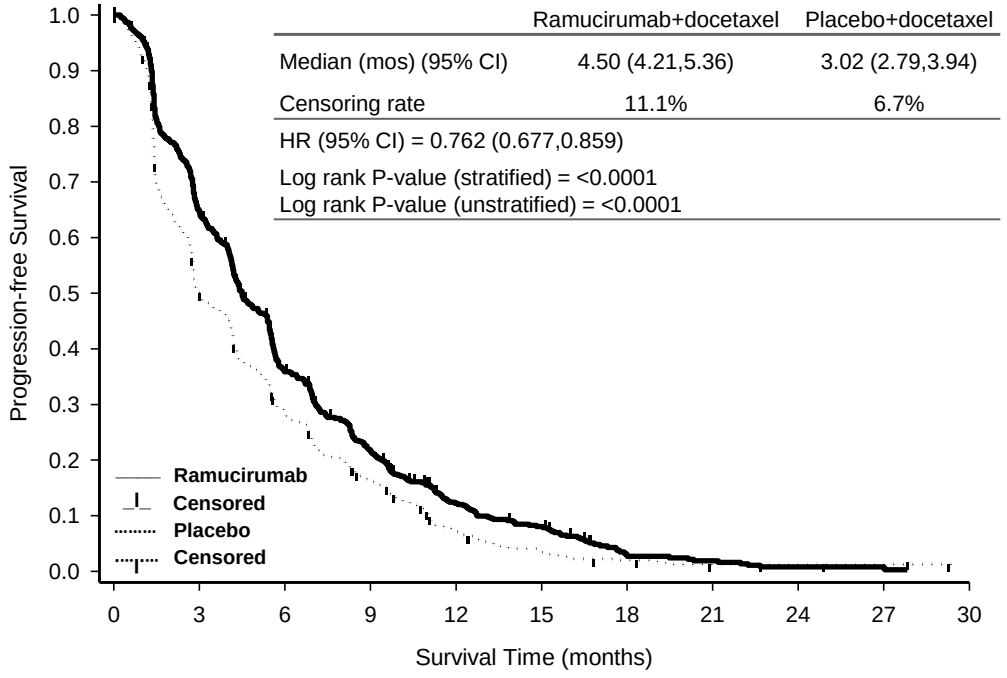
Continuation of treatment effect

The base case cost-effectiveness analysis assumes that the ramucirumab treatment effect tapers to nil over a period of 6 months. Alternative assumptions where treatment effect for OS is applied indefinitely and where no treatment is assumed at end of trial follow-up were also tested as scenario analyses.

Progression-free survival

The model uses PFS data from the REVEL trial, the Kaplan–Meier curves for which are presented in Figure 28.

Figure 28 Kaplan–Meier Plot of PFS in REVEL – RAM+DOC and PBO+DOC arms



Patients at Risk

Ramucirumab +docetaxel	628	383	204	120	59	38	11	7	3	3	0
Placebo + docetaxel	625	301	172	95	37	17	9	4	3	2	0

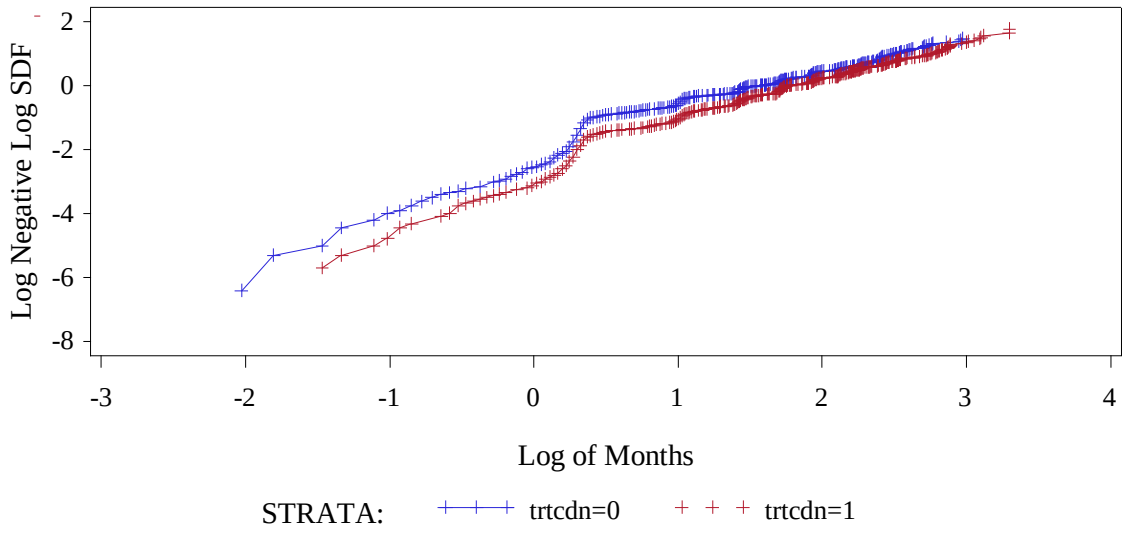
Abbreviations: CI = confidence interval; HR = hazard ratio; mos. (110)

Assessment of hazards

The log-log plot of PFS for the treatment arms from the REVEL trial is shown in Figure 29. The lines converge and the coefficient for the time-dependent covariate of treatment in the Cox regression has shown evidence that non-PH is present (*i.e.* statistical significant different from

zero, P=0.003), indicating that the proportional hazards assumption is violated. Therefore all parametric survival models were generated separately for RAM+DOC and DOC.

Figure 29 Log-log hazard plot of PFS in REVEL – RAM+DOC and PBO+DOC arms



Program Location: \lillyce\prd\ly3009806\i4t_mc_jvba\csr1\programs_nonsdd\test_prophazard_pfs.sas
Abbreviations: SDF: survival distribution function; trtcdn=0: PBO+DOC; trtcdn=1: RAM+DOC

Goodness of fit

Again, the five parametric distributions were fitted to the PFS data and assessed for goodness of fit.

Chosen using the methodology noted above for OS, the multivariate parametric models (one per treatment) for PFS included the same set of covariates as OS, with the exception of sex and ECOG performance status:

- Treatment
- Age (≤65 years vs > 65 years)
- Histology (non-squamous vs squamous)
- Time since initiation of prior therapy (< 9 months vs ≥ 9 months)
- Prior maintenance therapy (yes vs no)

- Pemetrexed first-line (yes vs no)
- Geographic region (Japan/East Asia vs rest-of-world [ROW])
- Best response to platinum therapy (complete response [CR]/partial response [PR]/stable disease [SD] vs progression)

Again the multivariate progression-free survival models for RAM+DOC and for PBO+DOC provided a better fit than the unadjusted progression survival models (see Table 46 and Table 47; see Appendix 10 for goodness-of-fit plots for all unadjusted and multivariate survival functions).

Table 46 AIC and BIC for Unadjusted and Multivariate PFS Functions: RAM+DOC

Distribution	AIC (Unadjusted)	AIC (Multivariate)	BIC (Unadjusted)	BIC (Multivariate)
Exponential	1627.63	1601.76	1632.08	1637.21
Weibull	1584.58	1548.45	1593.46	1588.34
Log-normal	1569.46	1532.91	1578.35	1572.79
Log-logistic	1585.97	1547.31	1594.86	1587.19
Generalized gamma	1561.9	1526.00	1575.23	1570.32

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

Table 47 AIC and BIC for Unadjusted and Multivariate PFS Functions: PBO+DOC

Distribution	AIC (Unadjusted)	AIC (Multivariate)	BIC (Unadjusted)	BIC (Multivariate)
Exponential	1732.84	1655.98	1737.27	1691.38
Weibull	1717.79	1619.73	1726.66	1659.56
Log-normal	1667.32	1581.24	1676.19	1621.06
Log-logistic	1687.86	1586.23	1696.73	1626.06
Generalized gamma	1668.15	1576.92	1681.46	1621.17

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

Among the distributions estimated using the multivariate model, the generalised gamma seems to provide the best fit across both arms (on the basis of AIC and BIC). In addition, the multivariate models provide slightly more conservative estimates of progression-free survival compared to all other parametric models (see Table 48). Goodness of fit plots by distribution for each trial arm are presented in Figure 30 and Figure 31, while Figure 32 presents each distribution compared with the KM plots from the trial results.

Table 48 Expected progression-free life-years for REVEL study treatments generated using core cost-effectiveness model using unadjusted and adjusted parametric models for progression-free survival, by distribution

	RAM+DOC		PBO+DOC	
Distribution	**Mean PFS (years) (Unadjusted)**	**Mean PFS (years) (Multivariate)**	**Mean PFS (years) (Unadjusted)**	**Mean PFS (years) (Multivariate)**
Exponential	0.516	0.511	0.409	0.386
Weibull	0.505	0.502	0.407	0.384
Lognormal	0.539	0.531	0.426	0.400
Log-logistic	0.605	0.585	0.471	0.432
Generalized gamma	0.513	0.507	0.417	0.386

Figure 30 PBO+DOC: Goodness of fit charts for multivariate model for progression-free survival, by distribution

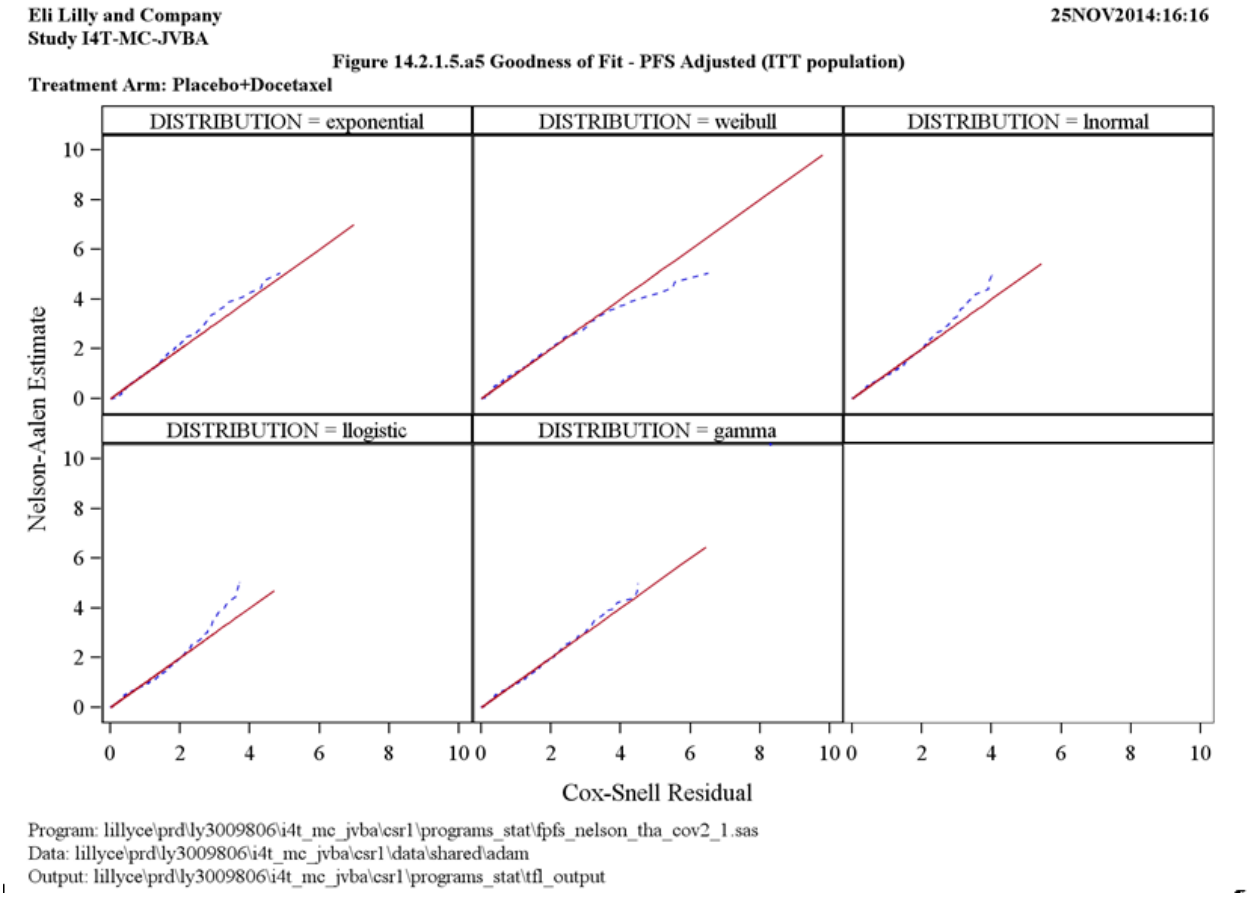


Figure 31 RAM+DOC: Goodness of fit charts for multivariate model for progression-free survival, by distribution

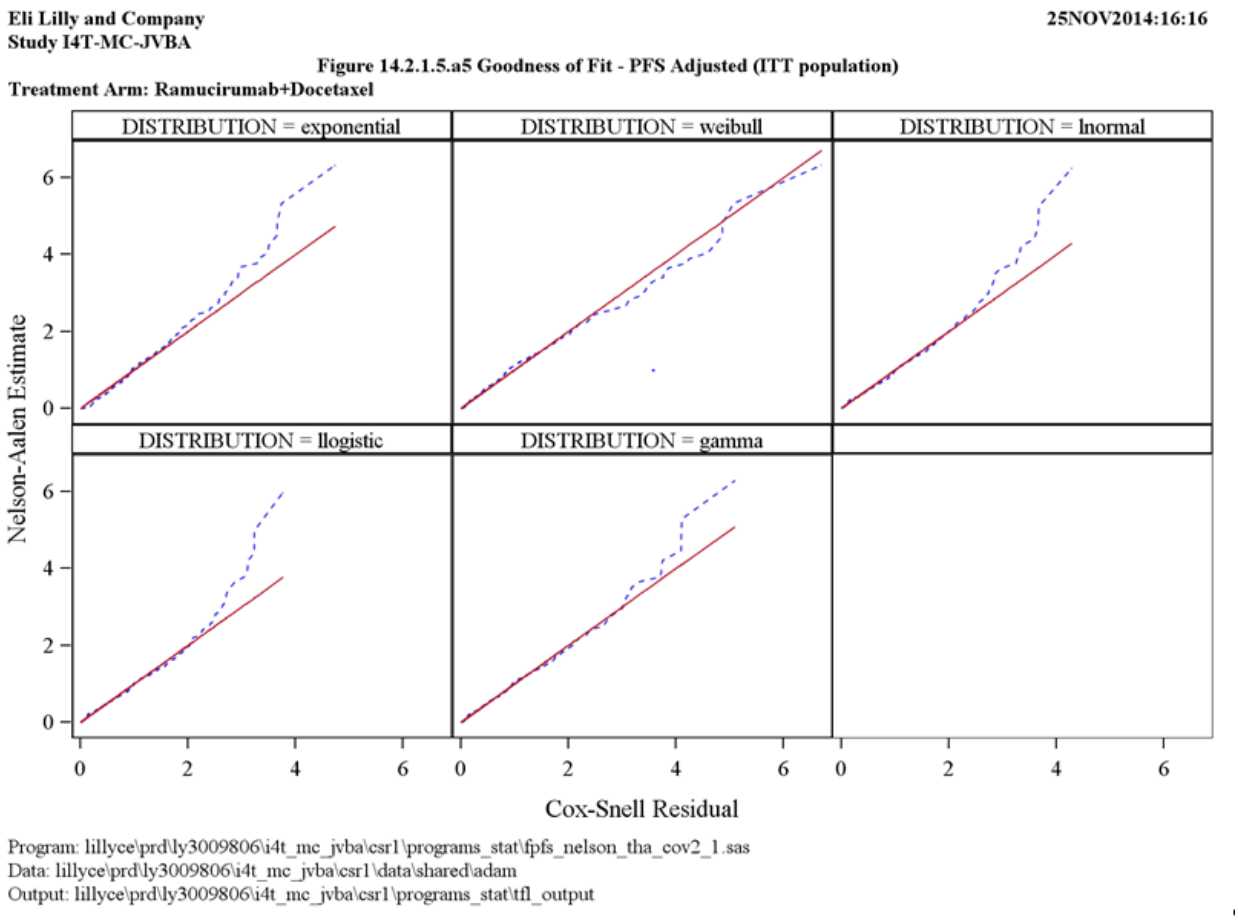
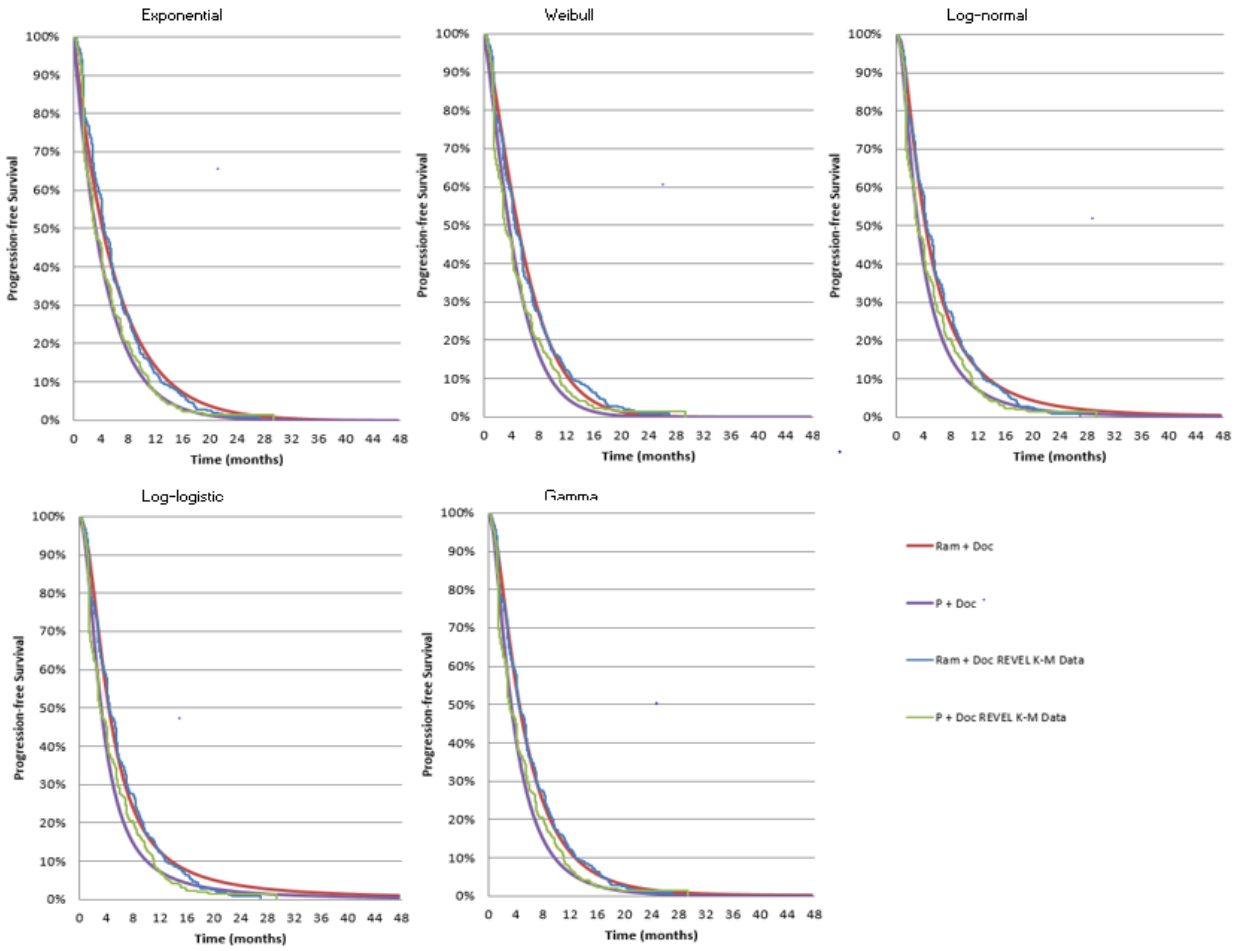


Figure 32 RAM+DOC and PBO+DOC: PFS Kaplan-Meier and multivariate parametric survival curves



Choice of distribution for PFS

PFS was therefore estimated separately for each arm, using multivariate models and assuming a generalised gamma distribution in the base case economic model. This decision was based on consideration of the AIC and BIC statistics, a comparison of nested distributions by fitting the generalized gamma function, and visual fit to the KM data.

Application of treatment effect for indirect comparison

To allow comparison with NIN+DOC and ERL, the HR estimates for the key clinical parameters, PFS and OS, were estimated using a NMA, which is presented in Section 4.10. To implement these relative treatment effects in the model, the HR estimates were applied to the baseline curves for PBO+DOC. This relies on the assumption of proportional hazards, previously discussed in Section 4.10.

Indirect treatment comparison for overall survival

The evidence network for OS was presented in Figure 18, Section 4.10. The corresponding OS indirect HRs used in the model are presented in Table 49. For ERL, the HR for the EGFR negative subgroup, as presented in Section 4.10, was used to compare ERL to PBO+DOC in the overall REVEL trial results. The HR for NIN+DOC from the non-squamous population was applied to the PBO+DOC curve estimated from the non-squamous subgroup of the REVEL trial; in comparing to NIN+DOC, the model also compares RAM+DOC to PBO+DOC in the REVEL trial non-squamous subgroup directly through the OS parametric model (which has treatment as a covariate) fit to the trial subgroup data in the same way as those for the overall REVEL population.

Table 49 HRs (95% CrIs) for OS obtained from NMA (vs. DOC)

Treatment regimen	HR (95% CrI)
ERL (EGFR-ve patients)	1.22 (0.98, 1.61)
NIN+DOC (non-squamous patients)	0.85 (0.75, 1.00)

95% credible interval: 95% probability that true value lies within the interval

Indirect treatment comparison for progression-free survival

The evidence network for PFS was presented in Figure 19, Section 4.10. The corresponding PFS indirect HRs used in the model are presented in Table 50. As noted, for PFS the parametric models were fit to each treatment arm independently; the PFS HR for ERL in the EGFR-negative subpopulation was applied to the PBO+DOC curve in the overall REVEL results and the NIN+DOC HR was applied to the PBO+DOC curve from the non-squamous subgroup of REVEL. Comparison to RAM+DOC was made through use of the PFS curves fit to the RAM+DOC arm in the overall REVEL trial or the non-squamous subpopulation of the REVEL trial, as appropriate.

Table 50 HRs (95% CrIs) for PFS obtained from NMA (vs. DOC)

Treatment regimen	HR (95% CrI)
ERL (EGFR-ve patients)	1.33 (1.04, 1.72)
NIN+DOC (non-squamous patients)	0.77 (0.62, 0.95)

95% credible interval: 95% probability that true value lies within the interval

Patients in the model

The proportion of patients in each health state at each time point was estimated from the parametric survival functions described above. These functions were used to estimate the proportion of the modelled cohort that remained free of the endpoints that define each health states, *viz.* pre-progression, post-progression and death. Time in the 'pre-progression' state was estimated directly from the PFS curve. Time in the 'post-progression' state was therefore estimated by the difference between the PFS and the OS curve at each time point (see Figure 23).

PFS and OS curves were modelled independently, with no mathematical relationship linking them. The functions used were tested to ensure that the PFS curve did not lie above the OS curve, which would yield a negative number of patients in the 'post-progression' health state. In such cases the PFS curve was set equal to the OS curve to retain face validity.

Together these parameters, OS and PFS, determined the rate at which patients progressed and died and therefore the costs and benefits accruing to each intervention and comparator in the model.

Adverse events

The model considers the effects of AEs that were observed at grade 3 or higher in at least 5 percent of patients in either the RAM+DOC or the PBO+DOC treatment arms of the REVEL trial (8). In addition, the model includes two AEs (nausea/vomiting and rash [assumed to be reported as "infusion-related reaction" in REVEL (8)]) that were included in a study that elicited utilities associated with metastatic NSCLC and key AEs resulting from systemic anticancer treatment (111).

Table 51 presents the AEs and their incidence rates considered by the model in the comparison of RAM+DOC versus DOC. These estimates are used in the base case comparison of

RAM+DOC to DOC in the overall NSCLC population, and in all subgroup analyses. Table 51 also presents the AEs used for the indirect comparators, ERL and NIN+DOC. The method used to derive the frequency for the AEs associated with the indirect comparators was:

Step 1. Identify all trials that were considered for the NMA for neutropenia for each indirect comparator (as this was the largest potential network for AEs).

Step 2: Record the incidence rates for each AE occurring at grade 3 or higher.

Step 3: Pool the incidence rates for each AE occurring at grade 3 or higher.

Step 4: Identify those AEs occurring at grade 3 or higher that occurred in at least 5 percent of patients, based on the pooled rates.

It is noted that the definitions of neutropenia reported by Garon *et al*. (RAM+DOC) (8) and Reck *et al*. (NIN+DOC) (112) trials were different – Garon reports consolidated neutropenia and decreased neutrophils (*i.e.* includes wider pool of events), whereas Reck reports neutropenia only (a subset of the Garon definition). The effect of this is evident in the incidence rates for the PBO+DOC arm for both trials, which were reported as 39% and 12% respectively. It is clear from these differing PBO+DOC rates that the use in the model of the Garon definition for the RAM+DOC input and the Reck definition for the comparator NIN+DOC input will bias the model in favour of NIN+DOC and thus the use of these rates is a conservative approach for the consideration of RAM+DOC.

Based on internal clinical input, the AEs are assumed to occur once, and are assumed to occur in the first cycle. The AE rates were varied in the probabilistic sensitivity analysis assuming a beta distribution and informed by the number of patients experiencing (alpha) and not experiencing (beta) the AE. To simplify the presentation of the one-way sensitivity analyses, rather than varying the individual AE rates, costs to treat AEs were varied as a unit, to maximise the opportunity to detect an influence of AEs on total costs.

Table 51 Grade 3 or 4 Adverse Events and Incidence Rates Included in the Model

AEs Considered in the Model for Ramucirumab + Docetaxel and Indirect Comparators	Incidence Rates			
	Ramucirumab + Docetaxel (%)	Docetaxel (%)	Erlotinib (%)	Nintedanib + Docetaxel (%)
Neutropenia	48.80	39.81	0.00	12.10
Febrile neutropenia	15.95	10.03	0.00	7.00
Fatigue	14.04	10.52	0.60	5.70
Nausea/Vomiting	1.28[a]	1.94	0.00	0.00
Diarrhoea	4.63[b]	3.07	0.00	6.70
Hair loss (any grade)	25.84	25.24	0.00	32.90
Rash	0.80[c]	0.65	8.15	0.00
Dyspnoea	3.83	8.25	0.00	0.00
Leukopenia	13.72	12.46	0.00	2.90
Anaemia	2.87	5.66	0.00	0.00
Hypertension	5.58	2.10	0.00	0.00

Abbreviations: AE = adverse event; n/a = not applicable (i.e., adverse event did not occur at grade 3 or higher in at least 5% of patients for ramucirumab + docetaxel or indirect comparator).

[a] Nausea and vomiting were reported separately in Garon et al. (2014) (8); the model presents the higher of the two incidence rates.

[b] Although not quite reaching 5% of patients at grade 3/4 in Garon et al. (2014) (8), diarrhoea was included based on rounding upwards.

[c] Garon et al. (2014) (8) did not report “rash” as an AE, however, they reported “infusion-related reaction.” The model assumes that “infusion-related reaction” is “rash” for the purposes of consideration of the analysis.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

In the REVEL trial, HRQoL data were collected using EQ-5D and LCSS, as described in Section 4.7 and summarised briefly below.

EQ-5D

The EQ-5D was collected in the REVEL trial. The EQ-5D is the preferred elicitation tool for utilities as stipulated in the NICE reference case and is therefore suitable for use within the cost-effectiveness model.

The EQ-5D instrument was administered at the following time points: at baseline, at approximately day 21 of each treatment cycle; at a summary assessment up to 7 days after discontinuation of treatment; and at a follow-up safety assessment at 30 days (± 7 days) after treatment discontinuation. EQ-5D utility index scores were calculated from the descriptive system based upon UK weights. In the REVEL trial over 60% of patients in both arms completed the 30-day post discontinuation EQ-5D questionnaire (Table 52).

Table 52 Summary of patient compliance for EQ-5D intent-to-treat population

Compliance, n (%)	RAM+DOC N=628	PBO+DOC N=625
Overall	4553 (80.6) / 5651	4041 (79.2) / 5104
Patients completing baseline EQ-5D	521 (83.0)	532 (85.1)
Patients completing end of treatment (30-day follow-up visit) EQ-5D	310 (63.9)	322 (65.7)

Descriptive statistics are presented in Appendix 11. It should be noted that the presence of minimum values below 0.0 (even those that may appear to be extreme negative values) have been verified as correct, checking both the REVEL individual patient-level data and the application of the weighting algorithm for the UK. Exploratory multivariate regression analyses (see Appendix 11) were conducted including a variety of covariates for potential model health states and baseline characteristics (e.g., geographical group, potential economic model subgroups, and baseline EQ-5D utility index). In addition, the independent effect of treatment on change in EQ-5D score was explored. Results of these analyses suggested that health status

(progressive disease vs progression-free), baseline EQ-5D utility, and treatment are the most important factors influencing utility (see Appendix 11). In some models, baseline ECOG performance status (0 vs 1) and age seemed to have a significant (although perhaps modest) influence; however, after adjusting for other factors, they lost their significance. For the sake of transparency and simplicity in the cost-effectiveness model, the base case utility estimates consist of mean post-baseline EQ-5D scores for progression-free disease and for progressive disease (see Table 53).

To facilitate incorporation of indirect comparators from beyond the REVEL trial into the model, rather than use treatment-arm specific utilities from the REVEL trial, the model takes the PFS and PD utilities across the whole trial; this approach of pooling trial arms to generate utilities was also taken in the recent NICE appraisal in NSCLC, TA347 (10). From these, AE disutilities from published literature are deducted from total QALYs based on the AE rates specific to the treatments (as described further below). Table 53 presents the overall REVEL EQ-5D utilities, estimated using UK tariffs (113), for the PFS and PD model health states.

Table 53 Mean post-baseline REVEL EQ-5D utility weights (for UK), by model health state across both treatment arms

Health State	Overall [both arms], mean (SD)
PFS	0.706 (0.251)
PD	0.599 (0.334)

Abbreviations: PD = progressive disease; PFS = progression-free survival, SD = standard deviation

LCSS

The REVEL trial additionally collected HRQoL data using the lung cancer-specific measure LCSS. However, as EQ-5D data had been collected directly, this outcome was not investigated for use in the economic model.

Mapping

No mapping of HRQoL data was conducted, as the EQ-5D was collected in the REVEL trial.

Health-related quality-of-life studies

To inform the cost-effectiveness model, a systematic literature review (SLR) was undertaken to identify health state utility values. This systematic review extracted utility values specific to

different health states and provides literature context to utility measurements from the REVEL trial.

The objective of this SLR was to identify utility values and associated health states for advanced and metastatic NSCLC reported in the literature, including the disutility associated with adverse events.

The systematic literature search was conducted from August 31 to September 2, 2015. Full details of the study search strategy for full papers and conference abstracts are provided in Appendix 12. The eligibility criteria used are given in Table 54.

The review process is summarised in Figure 33, resulting in 27 studies being included, which are detailed in Appendix 12. The SLR identified a number of studies used in previous HTA appraisals in this disease area (98, 111, 114). Rather than using the results from the SLR however, the EQ-5D data from the REVEL trial were chosen to estimate health benefits in the states in the economic model. This was due to the appropriateness of the patient population to the decision problem and the fact that the EQ-5D meets the requirements of the NICE reference case. These results from the SLR are however used to validate the observed trial values and to conduct sensitivity analyses in the economic model.

Table 54 Eligibility criteria

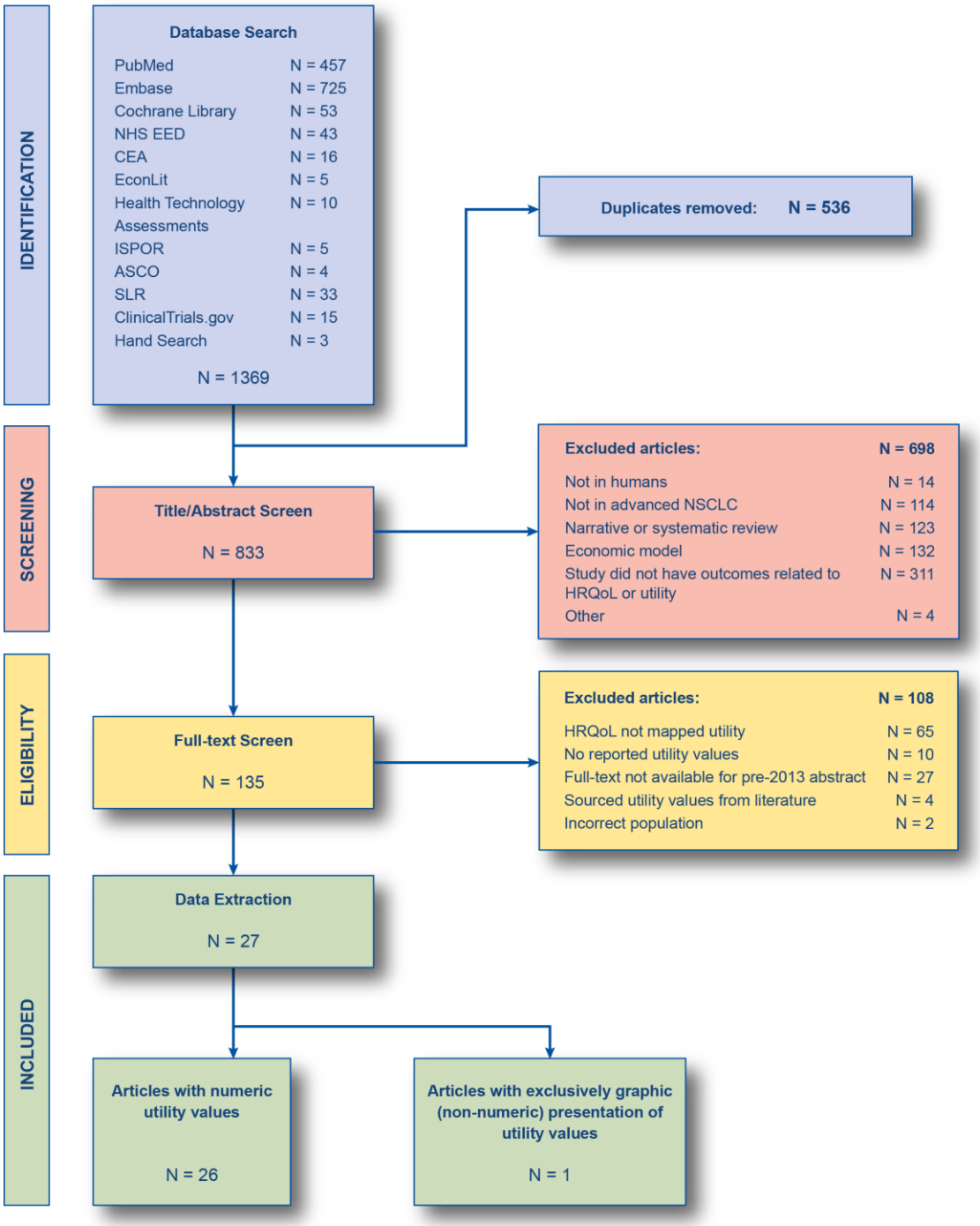
	Inclusion criteria	Exclusion criteria
Population	Advanced, metastatic, Stage IIIb or Stage IV NSCLC [a]	Small-cell lung cancer; not advanced or metastatic; stage I, II, III only
Intervention	Not restricted	
Comparator	Not restricted	
Outcomes	Any metric of utility, with the following instruments included in the search strategy: EQ-5D SF-36 SF-6D SF-12 HUI2 HUI3	Any measurement of health-related quality of life not converted to utility values
Study Design	Interventional and observational studies	Non-human, pre-clinical studies; case reports; studies exclusively sourcing secondary data (i.e., review articles, meta-analyses, economic models)
Time	Any timeframe of follow-up; when multiple time points available in graphic format, only first and last will be recorded for each health state	
Language	English	Non-English
Date	January 1, 2000 and onwards [b]	Prior to January 1, 2000 [b]

SF-36: Short Form 36 Health Survey; SF-6D: Abbreviated Short Form 36 Health Survey; SF-12: 12-Item Short Form Health Survey; HUI2: McMaster Health Utilities Indexes Mark 2; HUI3: McMaster Health Utilities Indexes Mark 3

[a] Stage IIIb with pleural effusion was the most relevant patient subpopulation within Stage IIIb. After January 2010 in accordance with the release of the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition, stage IIIb with pleural effusion was upgraded to stage IV cancer (115). Therefore, articles published prior to January 2010, or articles published after January 2010 but with reference to earlier data and/or methodologies will be included if referencing Stage IIIb with pleural effusion and Stage IV. Later articles will only be included if referencing Stage IV.

[b] Abstracts published prior to the January 1, 2013 were excluded to focus on the high-quality literature published in peer-reviewed journals with a desire to include results from newly completed trials. The abstracts from 2012 and earlier that reflect high-quality research were likely published as full reports in a peer-reviewed journal within 2.5 years of conference presentation and thus captured by the full-text search strategy.

Figure 33 PRISMA Diagram for the utility value SLR



Abbreviations: NHS EED: National Health Service Economic Evaluations Database; CEA: Cost Effectiveness Analysis Registry from the Center for the Evaluation of Value and Risk in Health; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; ASCO: American Society for Clinical Oncology; SLR: Systematic Literature Reviews; NSCLC: non-small cell lung cancer; HRQoL: health-related quality of life.

The health state utilities from another published paper by Chouaid et al. (98) were investigated in a scenario analysis (Table 55), as this was the largest study that used EQ-5D, the UK value set and reported appropriate health states. The results from Chouaid et al. 2013 do not differ considerably from those from the REVEL trial that are used in the base case (Table 53).

Table 55 Alternative Health State Utilities: Chouaid et al., 2013 (98)

Health State	Mean Utility[a]	SD[a]	95% CI[a]
PFS	0.74	0.18	0.68-0.80
PD	0.46	0.34	0.42-0.77

Abbreviations: CI = confidence interval; PD = progressive disease; PFS = progression-free survival; SD = standard deviation.

Adverse reactions

The approach taken to incorporate the HRQoL effects of AEs was the application of overall health state utilities, with an adjustment to QALYs based on disutilities associated with treatment-specific AEs meeting the model inclusion criteria (applied for a specified duration). AEs that occurred at grade 3 or higher in >5% of patients receiving either RAM+DOC or the comparator were included in the analysis comparing those two treatments. The AE disutilities were sourced from one of the papers included in the SLR, Nafees et al. (111). Table 56 presents AE-specific disutilities, their sources and assumptions, and their corresponding assumed durations.

Health-related quality-of-life data used in cost-effectiveness analysis

The utility values used in the base case are displayed in Table 56.

Pre-progression health state

HRQoL was assumed to be constant in the model for the pre-progression health state. HRQoL was adjusted for important treatment-related AEs to more accurately reflect the patient experience. AEs were considered to be clinically meaningful events which would have a time-limited impact on patient HRQoL but not be captured in the overall health state utility values used.

Post-progression health state

Disease progression is associated, as expected, with a notable decline in patient HRQoL as observed in the REVEL trial. There is, however, limited HRQoL data collected for patients who have experienced disease progression given the ethical difficulties associated with assessing HRQoL in patients who are receiving end-of-life care. Given the lack of further data in the post-progression health state, the base case does not attempt to change HRQoL close to death, which is in line with the approach taken in the recent nintedanib NICE appraisal (10). A QALY penalty applied to the last cycle before death has been investigated as a scenario analysis to reflect the predicted sudden decline in HRQoL just before death.

Table 56 Summary of utility values for cost-effectiveness analysis

Health State	**Utility value: mean (standard error)**		**Reference**	**Justification**
Progression-free	0.706 (0.003)		Table 53	EQ-5D using UK value set from the REVEL trial
Progressive disease	0.599 (0.015)		Table 53	
Decrement	**Disutility value: mean (standard error)**	**Duration (days)[a]**	**Reference**	**Justification**
Neutropenia	-0.08973 (0.01543)	7	Nafees et al. (111)	This study reported disutilities for the widest range of AEs and it was deemed important to source all disutilities from a single study. This was the same source as used in the nintedanib NICE appraisal(116)
Febrile Neutropenia	-0.09002 (0.01633)	4	Nafees et al. (111)	
Fatigue	-0.07346 (0.01849)	21	Nafees et al. (111)	
Nausea/Vomiting	-0.04802 (0.01618)	3	Nafees et al. (111)	
Diarrhoea	-0.0468 (0.01553)	3	Nafees et al. (111)	
Hair Loss (Any Grade)	-0.04495 (0.01482)	21	Nafees et al. (111)	
Rash	-0.03248 (0.01171)	21	Nafees et al. (111)	
Dyspnoea	-0.07346 (0.01849)	21	Assumed to be same as fatigue	Based on expert clinical guidance
Leukopenia	-0.08973 (0.01543)	7	Assumed to be same as neutropenia	Based on expert clinical guidance
Anaemia	-0.08973 (0.01543)	21	Assumed to be same as neutropenia	Based on expert clinical guidance
Hypertension	-0.07346 (0.01849)	21	Assumed to be same as fatigue	Based on expert clinical guidance

[a] Assumed durations for application of disutilities based on clinical guidance

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

Systematic literature review

The systematic literature review reported in Section 5.1 included resource use and cost data publications as well as economic models. The review identified 12 relevant cost/resource-use studies, of which none were from the UK; six were from Europe (one multicentre European study, two from Spain, one from the Netherlands, one from France, and one from Germany), five studies from the US and one study from China. Details of the identified studies are provided in Appendix 13.

The recent technology appraisal TA347 provided a detailed summary of the resource use and costs used in key submissions to NICE for second-line NSCLC. These NICE appraisals (TA162, TA310, TA124, and TA296) were all included within those identified in the systematic literature review (Table 41). For consistency within the same disease area, the resource assumptions from TA347 are used in this submission, where appropriate. Resources were costed using the most recent cost year available and taken from NHS reference costs, PSSRU unit costs of health and social care, or inflated from TA347 where required.

NHS Reference Costs

The unit costs for many parameters were taken from the most recent NHS reference costs at the time of preparation of this submission (2013/14) (117). These are described in more detail below.

Intervention and comparators' costs and resource use

The cost of ramucirumab and the comparators are comprised of the premedication cost, drug acquisition cost and drug administration cost.

In the model, all patients are assumed to receive premedication, and the costs of premedication for the comparators considered in the model are listed in Table 57 below.

Table 57 Premedication costs

Comparator	Premedication cost	Source
RAM+DOC	£35.54	Ramucirumab premedication: chlorphenamine (10 mg administered once per cycle, 1 1mL vial at £3.36 per vial) Docetaxel premedication: dexamethasone (20 mg administered thrice, 16 vials of 3.8 mg per vial at £1.99 per vial). (17, 118)
DOC	£32.11	Premedication: dexamethasone (20 mg administered thrice, 16 vials of 3.8 mg per vial at £1.99 per vial). (118)
NIN+DOC	£32.11	Oral medication (nintedanib) assumed to not require premedication; (65) Docetaxel premedication: dexamethasone (20 mg administered thrice, 16 vials of 3.8 mg per vial at £1.99 per vial). (118)
ERL	£00.00	Oral medication (erlotinib) assumed to not require premedication. (106)

The costs of the comparator drugs themselves are estimated separately from time spent in the pre-progression health state. Table 58 shows the unit costs of the comparator drugs. Table 59 shows the mean dose per administration of the comparator drugs. Unit costs of comparator drugs are varied in the one-way sensitivity analysis by +/-20% of their base case value.

Table 58 Unit costs of the comparator drugs

Comparator	Strength (mg/ml or mg/tablet)	Number of ml/vial or tablets/pkg	Cost per package	Source
Ramucirumab	10 mg/ml	10 ml/vial	£500.00	Monthly Index of Medical Specialties (MIMS), 2015.
Docetaxel	20 mg/ml	8 ml/vial	£35.35	Electronic Market Information Tool (eMIT), (12 month period to end December 2014, accessed June 2015).
Nintedanib	100 mg/tablet	120 tablets/pkg	£2151.10	MIMS, 2015.
Erlotinib	150 mg/tablet	30 tablets/pkg	£1631.53	MIMS, 2015.

Abbreviations: mg = milligram; ml = millilitre; pkg = package.

Table 59 Mean dose and frequency of comparator drugs

Comparator	Mean Dose	Frequency	Source
RAM+DOC (REVEL)			
Ramucirumab	9.5 mg/kg	Once every 21 days	REVEL trial intended dose (10 mg/kg, Garon et al., 2014(8)) multiplied by mean relative dose intensity (94.6%, SD 10.00%) from REVEL (119).
Docetaxel	68.3 mg/m^2	Once every 21 days	REVEL trial intended dose (75 mg/m^2, Garon et al., 2014(8)) multiplied by mean relative dose intensity (91.1%, SD 23.07%) from REVEL (119).
DOC (REVEL)	70.2 mg/m^2	Once every 21 days	REVEL trial intended dose (75 mg/m^2, Garon et al., 2014(8)) multiplied by mean relative dose intensity (93.6%, SD 24.21%) from REVEL (119).
ERL	150 mg	Once per day	Tarceva: EPAR – product information.(106) Dose intensity adjustments not made for erlotinib.
NIN+DOC			
Nintedanib	200 mg	Twice per day on days 2 to 21 of a cycle	Reck et al., 2014.(61) Dose intensity adjustments not made for nintedanib.
Docetaxel	73.7 mg/m^2	Once every 21 days	Dose in Reck et al., 2014, adjusted by relative dose intensity (98.33%) from Reck et al., 2014.(61)

Abbreviations: mg = milligram; ml = millilitre; pkg = package; SD = standard deviation.

For ramucirumab the average total dose required was based on the recommended dose of 10 mg/kg and weighted 33.4% for females to 66.6% for male (120) using an average weight of 67.17 kg (SD 14.960) for females and 76.79 kg (SD 15.773) for males (121). Unlike BSA (see below) no UK-specific source of weight data for lung cancer patients was available to externally validate these figures.

For docetaxel the average total dose required was based on the recommended dose of 75 mg/m^2 and weighted 33.4% for females to 66.6% for male (8) using an average body surface area of 1.72 m^2 (SD 0.200) for females and 1.91 m^2 (SD 0.220) for males (121). This data is validated against UK-specific data for lung cancer patients which shows that these values from REVEL are similar to the UK (males: 1.89m^2 [CI: 1.81, 1.88], females: 1.65m^2 [CI: 1.64, 1.67]) (122), even slightly higher, and therefore a conservative assumption of body surface area.

Table 60 provides the total number of administrations for each comparator, and the duration of time over which the comparator drugs are administered. Together, for comparators

administered via IV infusion, these parameters permit the estimate of the cost of the drugs for the duration of treatment.

Table 60 Number of administrations and duration of treatment

Comparator	Mean Number of Administrations	Source	Duration of Treatment (weeks)	Source
RAM+DOC (REVEL)				
Ramucirumab	6.10	REVEL (119).	19.70	REVEL (119).
Docetaxel	5.50			
DOC (REVEL)				
Docetaxel	4.90	REVEL (119).	16.90	REVEL (119).
NIN+DOC				
Docetaxel	4.79	Number of infusions of docetaxel in the ramucirumab plus docetaxel arm of REVEL among nonsquamous patients (5.6) multiplied by a ratio of 0.8545.[a]	17.09	Reported as 3.93 months in the nintedanib NICE submission (116). Months were converted into weeks.

Abbreviations: CSR = clinical study report; n/a = not applicable.

[a] Factor of 0.8545 was derived as the ratio of the mean treatment duration of nintedanib plus docetaxel among adenocarcinoma patients (17.09 weeks, (116)) to that of ramucirumab plus docetaxel among non-squamous patients (20.00 weeks, (123)).

For orally administered treatments (erlotinib and nintedanib) the percentage of oral medication taken during the PFS period is used in lieu of treatment duration and dose intensity to estimate drug costs. Table 61 presents the percentage of oral medication taken for the oral comparators erlotinib and nintedanib.

Table 61 Percentage of oral comparators taken

Oral Comparator	Percentage Taken During PFS	Source
Erlotinib	98.0%	Assumption based on 2% of erlotinib-treated patients discontinuing due to AEs in the trial described in Ciuleanu et al. (2012) (124).
Nintedanib	95.7%	The rate of patients discontinuing from the last study drug due to AEs is reported as 20.9% in the nintedanib + placebo arm in Reck et al. (2014) (61), and the median treatment duration is reported as 3.4 months. The parameter estimates were used to derive the expected percentage of patients discontinuing per 3-week cycle, and this was used as the estimate of the percentage of oral nintedanib taken during the PFS period.

Abbreviations: AE = adverse event; PFS = progression-free survival.

In the model, all comparators were assumed to be administered on an outpatient basis, so there are assumed to be no inpatient administration costs. Table 62 provides the base case costs of outpatient administration for oral, monotherapy and combination therapy comparator drugs.

Table 62 Cost of outpatient administration of comparator drugs

Cost	Cost per cycle (2015 £)	Source	Drug
Monotherapy administration	£164.81	Monotherapy IV administration cost was based on the cost of "Deliver simple parenteral chemotherapy at first attendance - SB12Z (outpatient)", and was obtained from NHS Reference Costs 2013/2014 (117).	Docetaxel Nintedanib + docetaxel
Combination therapy administration	£218.60	Combination IV therapy administration cost (applied when all treatments in the combination regimen are IV therapies) was based on the cost of "Deliver more complex parenteral chemotherapy at first attendance - SB13Z (outpatient)", and was obtained from NHS Reference Costs 2013/2014 (117).	Ramucirumab + docetaxel Vinorelbine + carboplatin [third line treatment in the progressed state]
Erlotinib dispensation cost	£41.26	The cost of the outpatient visit (applied as a dispensation cost for oral medication) was obtained from NHS Reference Costs 2013/2014 (117), with the following code: NCLFUFFA 370. The dispensation cost associated with erlotinib is applied using a frequency estimate of 0.46 per cycle (hence the dispensation cost is adjusted by a multiplier of 0.46). The frequency estimate was estimated as the frequency of oncologist visits during the stable disease period when patients were treated by monotherapy erlotinib, as reported in the submission to NICE for nintedanib (10).	Erlotinib
Nintedanib dispensation cost	£89.69	The dispensation cost associated with nintedanib (source information provided above) is applied every cycle.	Nintedanib + docetaxel

Health-state unit costs and resource use

In addition to costs specific to the drugs (premedication, administration, AE treatment, and the drugs themselves), the model captures other costs related to the management of metastatic NSCLC. Table 63 presents the resources used, their unit costs and corresponding sources included in the model.

Table 63 Costs associated with management of metastatic NSCLC (general physician visits, oncologist visits, procedures, best supportive care, and terminal care)

Resource Use	Cost	Source	Frequency per cycle
General physician visit	£68.94	Physician visit cost obtained as "general practitioner unit costs" from PSSRU (125).	None, during PFS and PD
Oncologist visit	£136.08	NHS Reference Cost codes and frequency for each monitoring procedure were based on the costs in the manufacturer's submission for nintedanib to the National Institute for Health Care Excellence (NICE) (116). Oncologist visit cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code WF01A (outpatient).	Every 3 weeks, during PFS and PD
CT scan (thorax/abdominal)	£94.90	Source as above. CT scan cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code RA08A (outpatient).	Every 0.28 cycles, during PFS and PD
Urinalysis	£1.22	Urinalysis cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code DAPS04 (x1).	Every 3 weeks, during PD
Complete blood count	£3.09	NHS Reference Cost codes and frequency for each monitoring procedure were based on the costs in the manufacturer's submission for nintedanib to the National Institute for Health Care Excellence (NICE) (116). Complete blood count cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code DAPS05 (x3)	
Renal function test	£12.18	Source as above. Renal function test cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code DAPS04 (x10)	
Hepatic function test	£8.52	Source as above. Hepatic function test cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code DAPS04 (x7)	
Electrolytes	£4.87	Source as above. Electrolytes test cost estimates obtained from NHS Reference Costs 2013/2014 (117) using the currency code DAPS04 (x4)	
Systemic anticancer treatment (post-progression)	£473.78	Approximately 25% of patients post-progression receive subsequent anticancer treatment with vinorelbine and carboplatin and 5% with erlotinib. Cost of carboplatin estimated as follows: dose of 750mg administered once per cycle, using 2 vials of 45 mL vial containing 10 mg/mL carboplatin (£20.17 per vial). Cost of vinorelbine estimated as follows: dose of 30mg/m^2 administered thrice per cycle, using vials of 1 mL vial containing 10 mg/mL vinorelbine (£4.51 per	Every 3 weeks, during PD

Resource Use	Cost	Source	Frequency per cycle
		vial). Vial-sharing was not taken into consideration. The cost of administering combination IV therapy is also applied along with the cost of vinorelbine + carboplatin (). Cost of erlotinib estimated using the same assumptions as for second-line treatment (150 mg tablet taken daily).	
Best supportive care	£429.16	Approximately 70% of patients in the PD health state receive only best supportive care. Cost of best supportive care estimated based on the cost of BSC during progressed disease obtained from the manufacturer's submission for nintedanib to NICE (116). The resource use costs included within the BSC cost per cycle are: palliative visit (£74 per visit; 3 visits/cycle, 100% of patients), blood transfusion (£140.36 per unit use, used once/cycle, 50% of patients), radiotherapy (£126.17 per visit, one visit/cycle, 50% of patients), oxygen (£14.24 per unit use, used once/cycle, 50% of patients), 99Tc scintigraphy bone scan (£232.08 per unit use, used once/cycle, 20% of patients), X-ray (£29.60 per unit use, used 0.28 times/cycle, 100% of patients). Estimates inflated to 2014 costs using CPIs from the Office of National Statistics (ONS, 2015) (126), where applicable.	Every 3 weeks, during PD
End-of-life care	£0.00	End-of-life cost assumed to be £0, based on the fact that terminal care costs not applied in the manufacturer's submission for nintedanib to NICE (116).	Once, at cycle in which death occurs

Abbreviations: NICE: National Institute for Health Care Excellence; BSC: best supportive care; PD = progressive disease; PFS = progression-free survival.

Adverse reaction unit costs and resource use

Table 64 presents hospitalisation costs to treat Grade 3 or Grade 4 AEs. The model assumes that the impact and costs associated with Grade 1 and 2 AEs are minimal, and in keeping with other HTA appraisals (10) these are not included within the model. Costs are multiplied by the incidence of each adverse event (Table 51) to calculate expected AE costs for each regimen. For simplicity, these costs are included in the first cycle of treatment although they may occur at other times during the treatment period. Only the costs of a single hospitalisation episode due to AEs are included within the model. This is because it is assumed that hospitalisations due to AEs occur only once during treatment, and that no two AEs are treated during the same hospitalisation. This assumption that no two AEs are treated during the same hospitalisation may overestimate the AE costs. The influence of uncertainty in the costs to treat AEs is therefore evaluated in both one-way (by +/- 20%) and probabilistic (based on gamma distribution, informed by standard errors) sensitivity analyses. Further details regarding parameter uncertainty and inclusion in sensitivity analyses can be found in the economic model.

Table 64 Hospitalisation costs to treat grade 3/4 adverse events

AE	Cost (2015 £)	Source
Neutropenia	£356.01	The hospitalisation costs to treat grade 3/4 AEs were based on the costs in the manufacturer's submission for nintedanib to the National Institute for Health Care Excellence (NICE) (116). Estimates inflated to 2014 costs using CPIs from the Office of National Statistics (126) to align with the cost year used for the NHS Reference Costs.
Febrile neutropenia	£2,070.23	
Fatigue	£380.71	
Nausea/vomiting	£1,974.53	
Diarrhoea	£1,847.97	
Hair loss (Any Grade)	£0.00	
Rash	£657.49	
Dyspnoea	£571.06	
Leukopenia	£435.24	
Anaemia	£1,006.30	
Hypertension *	£420.54	

Abbreviation: AE = adverse event.

* The cost of hypertension was not taken from the nintedanib submission but was estimated from the NHS reference costs directly using EB04Z.

Miscellaneous unit costs and resource use

No other resource use items or costs were used in the model.

Summary of costs incurred by health state

Table 65 summarises the costs described above by the health states in which they may occur.

Table 65 List of health states and associated costs in the economic model

Health states	Items	Reference in submission
Pre-progression	Drug acquisition	Table 58, Table 59, Table 60, Table 61
	Premedication	Table 57
	Treatment administration/dispensation	Table 62
	Adverse event management	Table 64
	Physician visits and monitoring	Table 63
Post-progression	Subsequent systemic anticancer treatment and BSC	Table 62, Table 63
	Physician visits and monitoring	Table 63
Death	End of Life care	Table 63

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case *de novo* analysis inputs and probabilistic distributions

A summary of the inputs and probabilistic sensitivity analysis parameters used in the base case analysis is presented in the tables that follow.

Table 66 Key disease progression variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Overall survival	Median RAM+DOC 10.6 months (Figure 24)	NR (log-logistic curve)	Clinical parameters and variable
Progression free survival	Median RAM+DOC 4.5 months (Figure 28)	NR (generalized gamma curve)	Clinical parameters and variable

Abbreviations: CI = confidence interval

Table 67 Hazard Ratios vs. Docetaxel Alone for Progression-free and Overall Survival. The Gamma distribution was used in the PSA

	Mean		Standard Error	
Regimen	OS	PFS	OS	PFS
Erl (EGFR mutation -ve)	1.222	1.333	0.127	0.128
Nin + Doc	0.847	0.769	0.085	0.108

Table 68 AE Incidence Rates from REVEL Trial. The Beta distribution was used in the PSA

			Ram + Doc (REVEL)		P + Doc (REVEL)	
AE	**Mean: Ram + Doc (REVEL)**	**Mean: P + Doc (REVEL)**	**alpha**	**beta**	**alpha**	**beta**
Neutropenia	0.488	0.398	306	321	246	372
Febrile neutropenia	0.159	0.100	100	527	62	556
Fatigue	0.140	0.105	88	539	65	553
Nausea/vomiting	0.013	0.019	8	619	12	606
Diarrhoea	0.046	0.031	29	598	19	599
Hair loss (Any Grade)	0.258	0.252	162	465	156	462
Rash	0.008	0.006	5	622	4	614
Dyspnoea	0.038	0.083	24	603	51	567
Leukopenia	0.137	0.125	86	541	77	541
Anaemia	0.029	0.057	18	609	35	583
Hypertension	0.056	0.021	35	592	13	605

Table 69 AE Incidence Rates for Indirect Comparators. The Beta distribution was used in the PSA

AE	Mean: Erl (EGFR mutation -ve)	SE: Erl (EGFR mutation -ve)	Mean: Nin + Doc	SE: Nin + Doc
Neutropenia	0.0000	0.0000	0.1210	0.0242
Febrile neutropenia	0.0000	0.0000	0.0700	0.0140
Fatigue	0.0060	0.0012	0.0570	0.0114
Nausea/vomiting	0.0000	0.0000	0.0000	0.0000
Diarrhoea	0.0000	0.0000	0.0670	0.0134
Hair loss (Any Grade)	0.0000	0.0000	0.1640	0.0328
Rash	0.0815	0.0163	0.0000	0.0000
Dyspnoea	0.0000	0.0000	0.0000	0.0000
Leukopenia	0.0000	0.0000	0.0290	0.0058
Anaemia	0.0000	0.0000	0.0000	0.0000
Hypertension	0.0000	0.0000	0.0000	0.0000

Table 70 Per cycle Costs of Drug Administration. The Gamma distribution was used in the PSA

Component	Mean	SE
Chemotherapy administration (inpatient setting, cost per stay)	£164.81	£32.96
Chemotherapy administration (outpatient setting)	£218.60	£43.72
Erlotinib dispensation cost	£41.26	£8.25
Nintedanib dispensation cost	£89.69	£17.94

Table 71 Number of Infusions Received. The Gamma distribution was used in the PSA

Regimen	Mean	SE
Ram + Doc (REVEL - overall)		
Ramucirumab	6.1	0.211
Docetaxel	5.5	0.178
P + Doc (REVEL - overall)	4.9	0.168
Ram + Doc (REVEL - non-squamous)		
Ramucirumab	6.3	0.249
Docetaxel	5.6	0.210
P + Doc (REVEL - non-squamous)	5.1	0.204
Erl (EGFR mutation -ve)	n/a	n/a
Nin + Doc		
Nintedanib	n/a	n/a
Docetaxel	4.785	0.180

Table 72 Treatment Duration. The Gamma distribution was used in the PSA.

Regimen	Mean	SE
Ram + Doc (REVEL - overall)	19.7	0.675
P + Doc (REVEL - overall)	16.9	0.642
Ram + Doc (REVEL - non-squamous)	20.0	0.785
P + Doc (REVEL- non-squamous)	17.6	0.757
Erl (EGFR mutation -ve)	n/a	n/a
Nin + Doc	17.088	0.783

Table 73 Percentage of Oral Medication Taken during Progression-free Survival Period. The Beta distribution was used in the PSA.

Drug	Mean	alpha	beta
Erl (EGFR mutation -ve)	98.0%	192	4
Drug	**Mean**	**SE**	
Nintedanib	95.7%	0.075	

Note that since one of the parameters used to derive the nintedanib estimate does not report uncertainty information, an assumption of 20% of the mean was made to estimate the SE.

Table 74 Premedication Utilisation. The Beta distribution was used in the PSA.

Regimen	Mean	alpha	beta
Ram + Doc (REVEL)	97.6%	612	15
P + Doc (REVEL)	98.1%	606	12
Erl (EGFR mutation -ve)	0.0%	0	0
Nin + Doc	98.1%	606	12

Table 75 Inpatient Costs for AE Treatment and Management. The Gamma distribution was used in the PSA.

AE	Mean	SE
Neutropenia	£356.01	71.20
Febrile neutropenia	£2,070.23	414.05
Fatigue	£380.71	76.14
Nausea/vomiting	£1,974.53	394.91
Diarrhoea	£1,847.97	369.59
Hair loss (Any Grade)	£0.00	0.00
Rash	£657.49	131.50
Dyspnoea	£571.06	114.21
Leukopenia	£435.24	87.05
Anaemia	£1,006.30	201.26
Hypertension	£420.54	84.11

Table 76 Physician Visits, Disease Monitoring, Subsequent Therapy, Best Supportive Care, and End-of-Life Costs. The Gamma distribution was used in the PSA.

Resource	Mean	Standard Error
Physician visit	£68.94	13.79
Oncologist visit	£136.08	27.22
CT scan (thorax or abdominal)	£94.90	18.98
Urinalysis	£1.22	0.24
Complete blood count	£3.09	0.62
Renal function test	£12.18	2.44
Hepatic function test	£8.52	1.70
Electrolytes	£4.87	0.97
Subsequent therapy and supportive care per cycle	£473.78	94.76
BSC per cycle	£429.16	85.83
End-of-life	£0.00	0.00

Table 77 Utility Weights. The Beta distribution was used in the PSA.

Health State/AE	Mean	SE
Progression-free (overall REVEL)	0.706	0.003
Progressive disease (overall REVEL)	0.599	0.015
Neutropenia	-0.090	0.015
Febrile neutropenia	-0.090	0.016
Fatigue	-0.073	0.018
Nausea/vomiting	-0.048	0.016
Diarrhoea	-0.047	0.016
Hair loss (Any Grade)	-0.045	0.015
Rash	-0.032	0.012
Dyspnoea	-0.073	0.018
Leukopenia	-0.090	0.015
Anaemia	-0.090	0.015
Hypertension	-0.073	0.018

One way sensitivity analysis – summary of inputs

The parameters varied in the OSA are listed in Table 78, along with the associated lower and upper bounds used in the OSA. Note that certain input parameters change based on the selection of the comparator for the OSA.

Table 78 One-way sensitivity analysis inputs.

Parameter	Variation	Default Estimate	Lower Bound	Upper Bound
Discount rate, costs	+/-50% of Total	3.50%	1.75%	5.25%
Discount rate, health outcomes	+/-50% of Total	3.50%	1.75%	5.25%
OS HR: ERL vs. P + Doc (REVEL)	95% CI	1.222	1.159	1.285
PFS HR: ERL vs. P + Doc (REVEL)	95% CI	1.333	1.269	1.397
OS HR: NIN + DOC vs. P + Doc (REVEL - nonsquamous)	95% CI	0.847	0.681	1.012
PFS HR: NIN+DOC vs. P + Doc (REVEL - nonsquamous)	95% CI	0.769	0.558	0.981
Ram + Doc (REVEL) adverse event costs	+/-20% of Total	£807.19	£645.75	£968.63
P + Doc (REVEL) adverse event costs	+/-20% of Total	£656.05	£524.84	£787.26
Ramucirumab vial price	+/-20%	£500.00	£400.00	£600.00
Docetaxel vial/package price	+/-20%	£35.35	£28.28	£42.42
Ram + Doc (REVEL) ramucirumab infusions	95% CI	6.1	5.686	6.514
Ram + Doc (REVEL) docetaxel infusions	95% CI	5.5	5.152	5.848
P + Doc (REVEL) docetaxel infusions	95% CI	4.9	4.571	5.229
Ram + Doc (REVEL - nonsquamous) ramucirumab infusions	95% CI	6.3	5.811	6.789
Ram + Doc (REVEL - nonsquamous) docetaxel infusions	95% CI	5.6	5.188	6.012
P + Doc (REVEL - nonsquamous) docetaxel infusions	95% CI	5.1	4.701	5.499
% erlotinib taken during trt period	95% CI	98.0%	95.6%	99.4%
% nintedanib taken during trt period	95% CI	95.7%	72.9%	100.0%
Nin + Doc docetaxel infusions	95% CI	4.785	4.433	5.137
Subsequent therapy and supportive care per cycle	+/-20%	£473.78	£288.06	£659.50
BSC cost per cycle	+/-20%	£429.16	£260.94	£597.39
End of life cost	+/-20%	£0.00	£0.00	£0.00
PF health state utility value (REVEL)	95% CI	0.706	0.700	0.712
PD health state utility value (REVEL)	95% CI	0.599	0.570	0.628

Assumptions

Assumptions specific to the model itself are listed below:

- The OS parametric models assume proportional hazards which has been tested and justified as described in Section 5.3.
- Placebo + docetaxel as observed in the REVEL trial is representative of treatment with monotherapy docetaxel. External clinical advisors confirmed the generalisability of the REVEL trial to patients suitable for docetaxel treatment in the NHS (127).
- Only grade 3 and above AEs are considered, and are assumed to occur once, and are assumed to occur in the first cycle. Costs associated with Grade 1 and 2 AEs, and costs other than hospitalization costs are similar between regimens; therefore, costs to treat Grade 1 and 2 AEs and costs other than hospitalization costs are not included within the model. It is also assumed that hospitalizations due to AEs occur only once during treatment, and that no two AEs are treated during the same hospitalization. This was considered a reasonable simplifying assumption.
- The efficacy of post-progression systemic anticancer treatment is not considered explicitly in the model. This was expected to be a conservative assumption given that RAM+DOC extends the time in the post-progression state.
- The utility associated with PFS is not explicitly influenced by the percentage of patients in each arm experiencing complete or partial response versus stable disease. This was considered reasonable due to data availability and comparability concerns; furthermore given the efficacy of RAM+DOC in ORR it was considered to be a conservative assumption.

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

Table 79, Table 80 and Table 81 present the deterministic results for the base case in the REVEL ITT population, in the EGFR negative population (to allow comparison to erlotinib) and in the non-squamous population (to allow comparison to nintedanib plus docetaxel), respectively.

Table 79 Base-case results in the ITT REVEL population (overall NSCLC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
DOC	£10,995	1.093	0.692	-	-	-	-
RAM+DOC	£35,283	1.282	0.816	£24,288	0.188	0.125	£194,919

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Note: Numbers may not compute due to rounding; all results are discounted

Table 80 Base case results vs ERL in the EGFR-ve population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER RAM+ DOC vs ERL
DOC	£10,995	1.093	0.692	-	-	-	-	
ERL	£13,562	0.895	0.567	£2567	-0.199	-0.125	Dominated	
RAM+DOC	£35,283	1.282	0.816	£21,721	0.387	0.250	£194,919	£86,985

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Note: Numbers may not compute due to rounding; all results are discounted

Table 81 Base-case results vs NIN+DOC in the non-squamous subpopulation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER RAM+ DOC vs NIN+ DOC
DOC	£11,534	1.146	0.724	-	-	-	-	
NIN+DOC	£25,064	1.338	0.852	£13531	0.192	0.128	£105,621	
RAM+DOC	£36,789	1.357	0.863	£11,724	0.020	0.011	£182,082	£1,106,497

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Note: Numbers may not compute due to rounding; all results are discounted

Clinical outcomes from the model

A comparison of the outputs of the economic model to the clinical data from the REVEL trial is provided in Table 82. The model estimated median values for RAM+DOC are shown to be a reasonable representation of the clinical trial data.

Table 82 Summary of model results compared with clinical data

Outcome	Clinical trial result (8)			Model result		
	RAM+DOC	PBO+DOC	Incremental	RAM+DOC	DOC	Incremental
Median PFS, months (95% CI)	4·5 (4·2–5·4)	3·0 (2·8–3·9)	1.5	4.518	3.327	1.192
Median OS, months (95% CI)	10·5 (9·5–11·2)	9·1 (8·4–10·0)	1.4	10.604	8.693	1.911

The mean reported health benefits by health state show that patients receiving RAM+DOC spend a greater proportion of their remaining life expectancy in the pre-progression state where HRQoL is better compared to patients receiving DOC (Table 83).

Table 83 Summary of time spent in PFS and PD health states

Technology	Outcome	Discounted LYs	% of overall LYs
DOC	Progression-free survival	0.371	34%
	Progressed disease	0.722	66%
RAM+DOC	Progression-free survival	0.483	38%
	Progressed disease	0.799	62%

Disaggregated results of the base case incremental cost effectiveness analysis

RAM+DOC vs DOC: disaggregated results in the overall REVEL trial population

The disaggregated QALYs demonstrate that the majority of the QALYs accrued from treatment with RAM+DOC are accrued in the pre-progression health state (Table 84).

Table 84 Summary of discounted QALY gain by health state

Health state	RAM+DOC	DOC	Increment	Absolute increment	% absolute increment
Before progression (second line)	0.341	0.262	0.079	0.079	63%
Disutility due to AEs	*-0.003*	*-0.003*	*0*	*0*	*0*
After progression	0.478	0.433	0.046	0.046	37%
Total	0.816	0.692	0.125	0.125	100%

Abbreviation: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

The disaggregated costs by health state demonstrate that the majority of incremental costs are associated with treatment prior to progression while the disaggregated costs by categories of resource use demonstrate that the majority of incremental costs are associated with the acquisition cost of ramucirumab (Table 85). Importantly, treatment with RAM+DOC increases the life expectancy of patients with a resource-intensive disease, reflected in increases in post-progression costs and total non-drug costs.

Table 85 Summary of predicted (discounted) resource use by category of cost

Item	RAM+DOC	DOC	Increment	Absolute increment	% absolute increment
Before progression					
Drug acquisition	£22,729	£324	£22,405	£22,405	92%
Treatment administration	£1,308	£794	£514	£514	2%
AE management	£807	£656	£151	£151	1%
Physician visits and monitoring	£1,618	£1,242	£375	£375	2%
After progression					
Subsequent systemic anticancer treatment & BSC	£6,147	£5,560	£588	£588	2%
Physician visits and monitoring	£2,674	£2,419	£256	£256	1%
Total	£35,283	£10,995	£24,288	£24,288	100%

Abbreviations: BSC, best supportive care.

RAM+DOC vs. ERL: results in the EGFR-ve subpopulation

The disaggregated results demonstrate that the QALYs accrued from treatment with RAM+DOC are gained across all health states, although with a greater proportion of the incremental QALYs accrued prior to disease progression (Table 86).

Table 86 Summary of QALY gain by health state (RAM+DOC vs. ERL)

Health state	RAM+DOC	ERL	Increment	Absolute increment	% absolute increment
Before progression (second line)	0.341	0.204	0.137	0.137	54%
Disutility due to AEs	*-0.003*	*0.000*	*-0.003*	*0.003*	*1%*
After progression	0.478	0.363	0.115	0.115	45%
Total	0.816	0.567	0.250	0.256	100%

Abbreviation: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

The disaggregated costs by health state demonstrate that the majority of incremental costs are associated with treatment prior to progression while the disaggregated costs by

categories of resource use demonstrate that the majority of incremental costs are associated with the acquisition cost of ramucirumab (Table 87). Treatment with RAM+DOC increases time in the pre-progression state as reflected by the increase in non-drug costs before progression and increases the overall life expectancy of patients with a resource-intensive disease, reflected in increases in post-progression costs and total non-drug costs.

Table 87 Summary of predicted resource use by category of cost (RAM+DOC vs. ERL)

Item	RAM+DOC	ERL	Increment	Absolute increment	% absolute increment
Before progression					
Drug acquisition	£22,729	£5,616	£17,113	£17,113	79%
Treatment administration	£1,308	£228	£1,080	£1,080	5%
AE management	£807	£56	£751	£751	3%
Physician visits and monitoring	£1,618	£966	£651	£651	3%
After progression					
Subsequent systemic anticancer treatment & BSC	£6,147	£4,666	£1,481	£1,481	7%
Physician visits and monitoring	£2,674	£2,030	£644	£644	3%
Total	£35,283	£13,562	£21,721	£21,721	100%

Abbreviations: BSC, best supportive care.

RAM+DOC vs NIN+DOC: Disaggregated results in the non-squamous subpopulation

As expected due to their similar effectiveness, the disaggregated QALYs demonstrate that the very small differences in QALYs accrued from treatment with RAM+DOC in comparison to NIN+DOC are spread across health states (Table 88).

Table 88 Summary of QALY gain by health state (RAM+DOC vs. NIN+DOC)

Health state	RAM+DOC	NIN+DOC	Increment	Absolute increment	% absolute increment
Before progression (second line)	0.351	0.344	0.006	0.006	42%
Disutility due to AEs	*-0.003*	*-0.001*	-0.002	0.002	*14%*
After progression	0.515	0.509	0.006	0.006	44%
Total	0.863	0.852	0.011	0.015	100%

Abbreviation: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

The disaggregated costs by pre- and post-progression and by categories of resource use demonstrate that the majority of incremental costs are associated with the acquisition cost of ramucirumab in the pre-progression state (Table 89). RAM+DOC was associated with slightly lower administration costs but as treatment with RAM+DOC provides similar effectiveness to NIN+DOC, little change in the other costs was apparent.

Table 89 Summary of predicted resource use by category of cost (RAM+DOC vs. NIN+DOC)

Item	RAM+DOC	NIN+DOC	Increment	Absolute increment	% absolute increment
Before progression					
Drug acquisition	£23,462	£12,112	£11,350	£11,350	93%
Treatment administration	£1,350	£1,585	-£235	£235	2%
AE management	£807	£346	£461	£461	4%
Physician visits and monitoring	£1,663	£1,634	£30	£30	0%
After progression					
Subsequent systemic anticancer treatment & BSC	£6,624	£6,541	£83	£83	1%
Physician visits and monitoring	£2,882	£2,846	£36	£36	0%
Total	£36,789	£25,064	£11,724	£12,194	100%

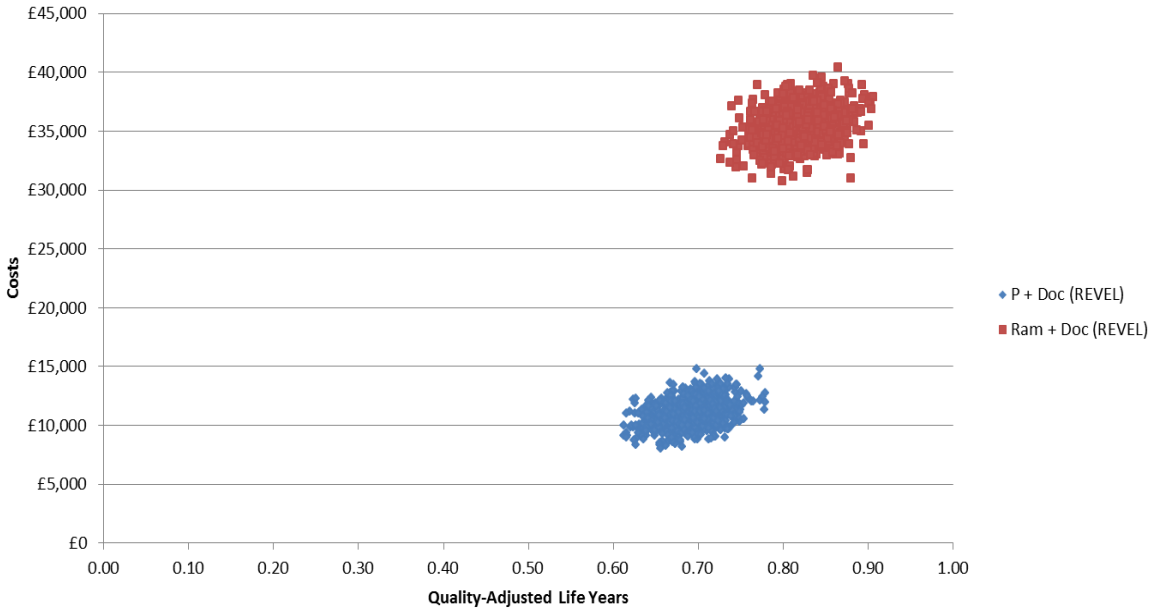
Abbreviations: BSC, best supportive care.

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

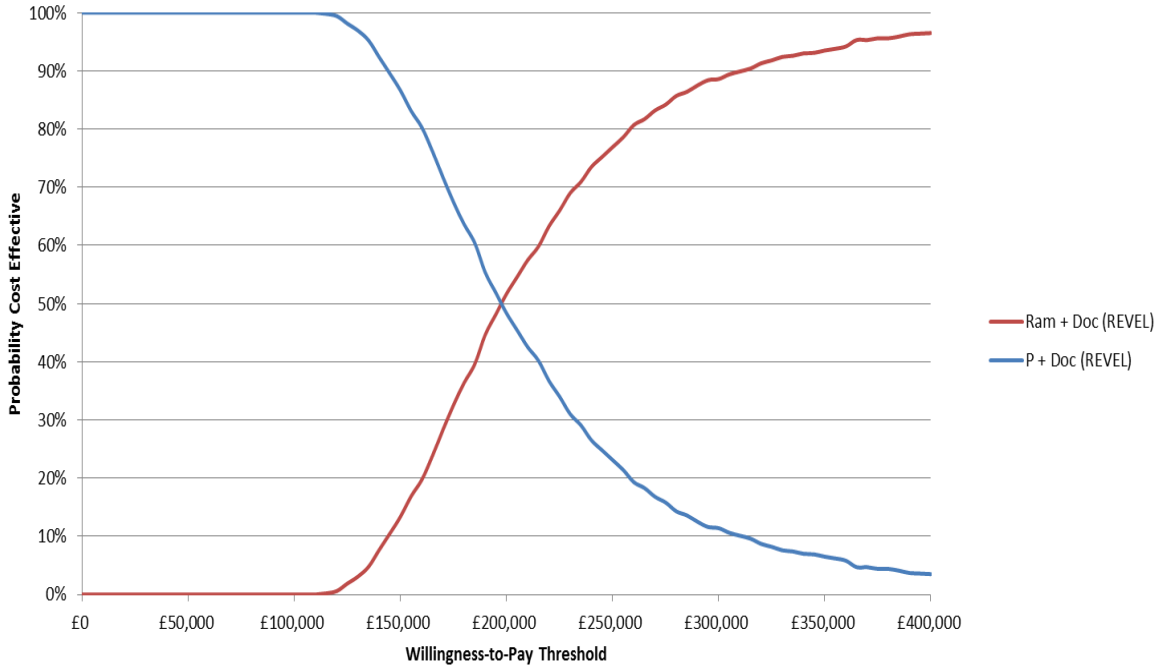
Figure 34 presents the scatterplot of 1000 simulations of the cost-effectiveness analysis of RAM+DOC compared with DOC, based on the overall REVEL population. It can clearly be seen that RAM+DOC provides an unambiguous QALY gain with good separation between the results for RAM+DOC and PBO+DOC. The increased costs of treatment with RAM+DOC are also apparent and Figure 35 presents the associated cost-effectiveness acceptability curve.

Figure 34 Base-case PSA scatterplot: Cost-effectiveness of RAM+DOC vs. DOC, REVEL overall population



Abbreviations: Doc = docetaxel; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; Ram = ramucirumab

Figure 35 Base-case PSA CEAC: REVEL overall population



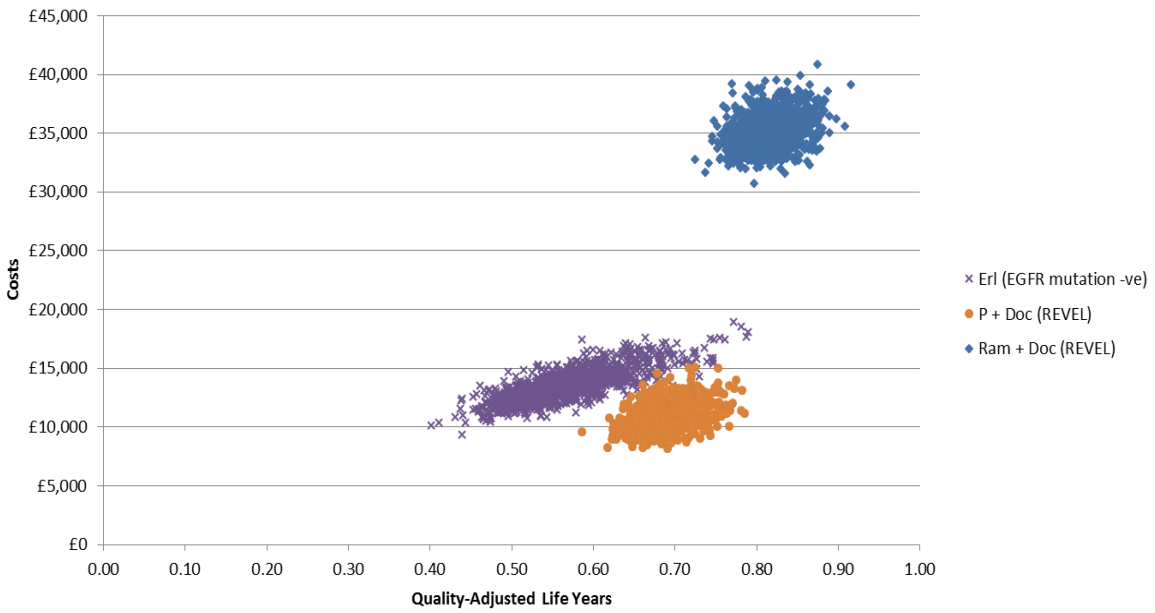
Abbreviations: CEAC = cost-effectiveness acceptability curve; Doc = docetaxel; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; Ram = ramucirumab.

Note: The non-smoothness of the CEAC is an artefact of the step-size by which the willingness-to-pay threshold for the ICER is increased in the CEAC calculations, and does not convey any meaningful information. Using smaller step-sizes increases the smoothness of the CEAC.

The equivalent scatter plot and CEAC curve for the comparison with ERL in the EGFR-ve subpopulation are presented in Figure 36 and Figure 37. These show that ERL in the EGFR-ve subpopulation is more costly and less effective than PBO+DOC, leaving the comparison between RAM+DOC and PBO+DOC in line with the main base case result discussed above.

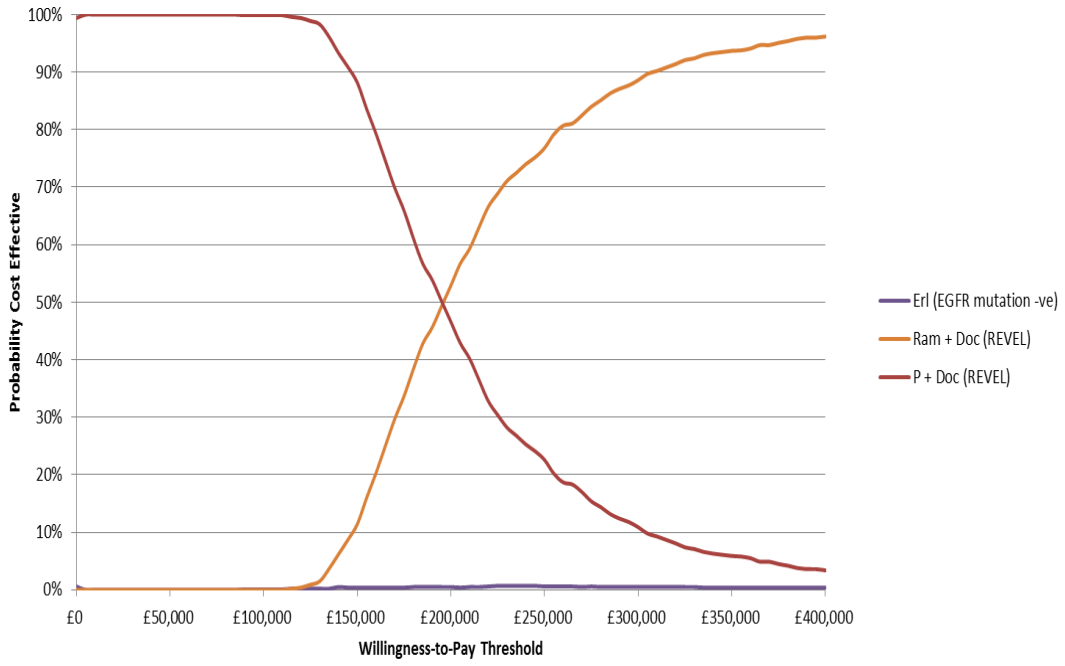
In the non-squamous subpopulation, comparing to NIN+DOC, it is expected that RAM+DOC and NIN+DOC will provide similar effectiveness in terms of QALYs but with a separation in costs. As presented in Figure 38, this is seen to be the case; it is notable that the results for NIN+DOC demonstrate a greater spread along the QALY axis, reflecting the greater uncertainty in its clinical inputs derived from the NMA. Given the greater cost of RAM+DOC, the associated cost-effectiveness acceptability curve presented in Figure 39 is as expected.

Figure 36 Base-case PSA scatterplot: Cost-effectiveness of RAM+DOC vs. ERL, EGFR-ve subpopulation



Abbreviations: Doc = docetaxel; Erl = erlotinib; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; Ram = ramucirumab

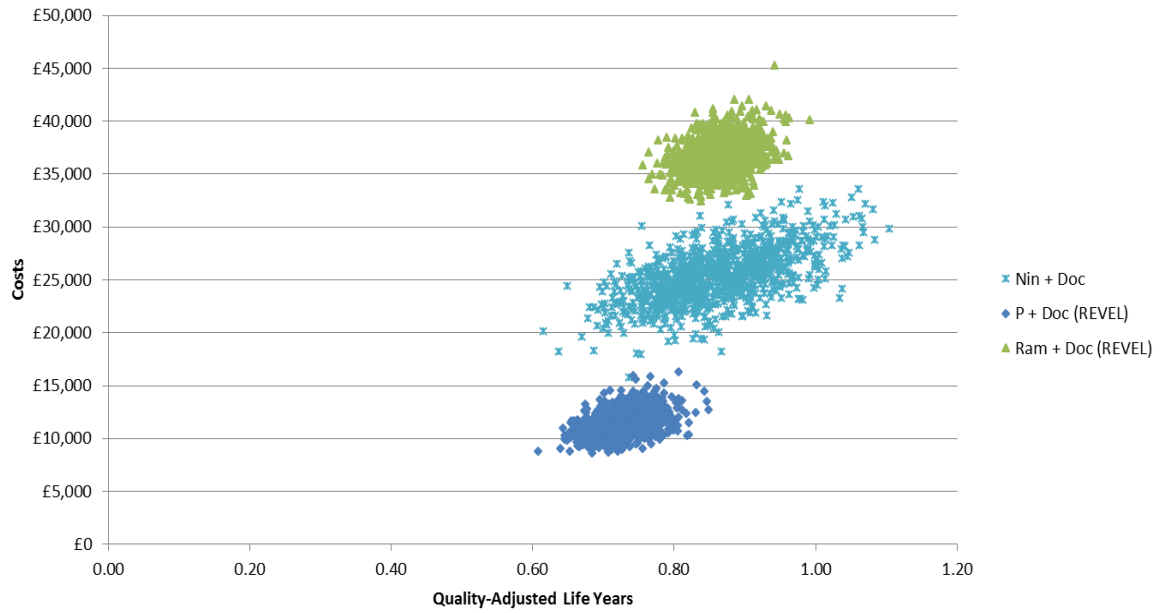
Figure 37 Base-case PSA CEAC: EGFR-ve subpopulation



Abbreviations: CEAC = cost-effectiveness acceptability curve; Doc = docetaxel; Erl = erlotinib; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

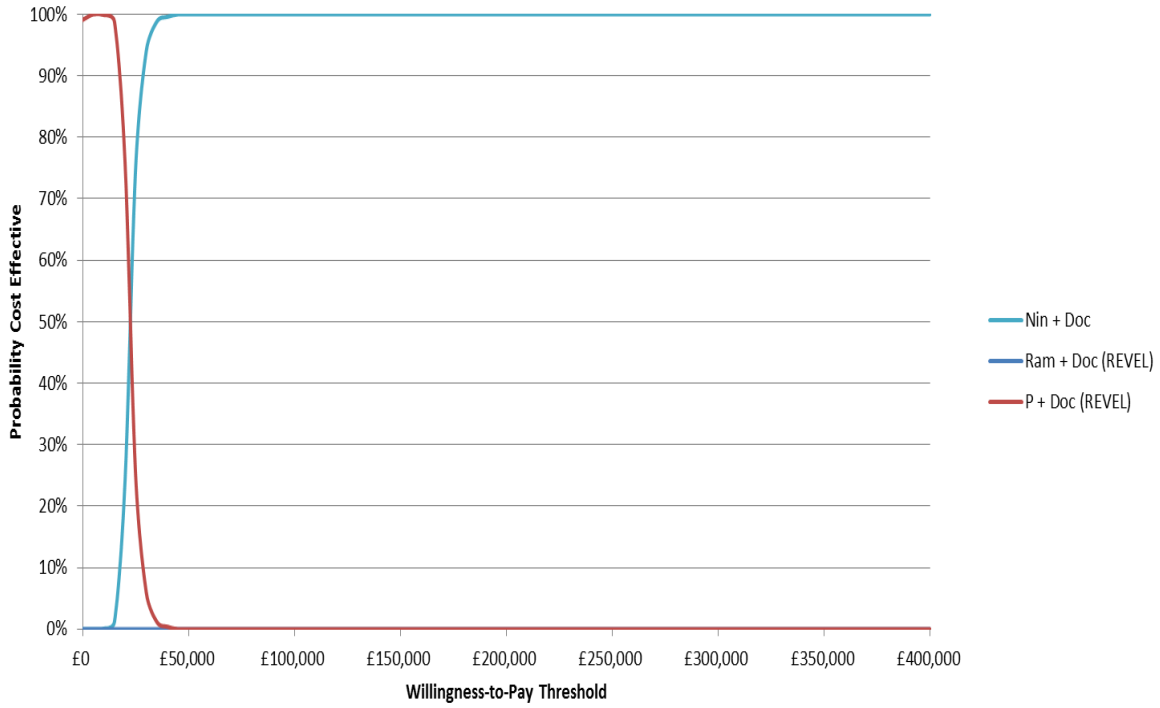
Note: The non-smoothness of the CEAC is an artefact of the step-size by which the willingness-to-pay threshold for the ICER is increased in the CEAC calculations, and does not convey any meaningful information. Using smaller step-sizes increases the smoothness of the CEAC.

Figure 38 Base-case PSA scatterplot: Cost-effectiveness of RAM+DOC vs. NIN+DOC, non-squamous subpopulation



Abbreviations: Doc = docetaxel; Nin = nintedanib; Erl = erlotinib; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; Ram = ramucirumab

Figure 39 Base-case PSA CEAC: non-squamous subpopulation



Abbreviations: CEAC = cost-effectiveness acceptability curve; Doc = docetaxel; Nin = nintedanib; Erl = erlotinib; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Note: The non-smoothness of the CEAC is an artefact of the step-size by which the willingness-to-pay threshold for the ICER is increased in the CEAC calculations, and does not convey any meaningful information. Using smaller step-sizes increases the smoothness of the CEAC.

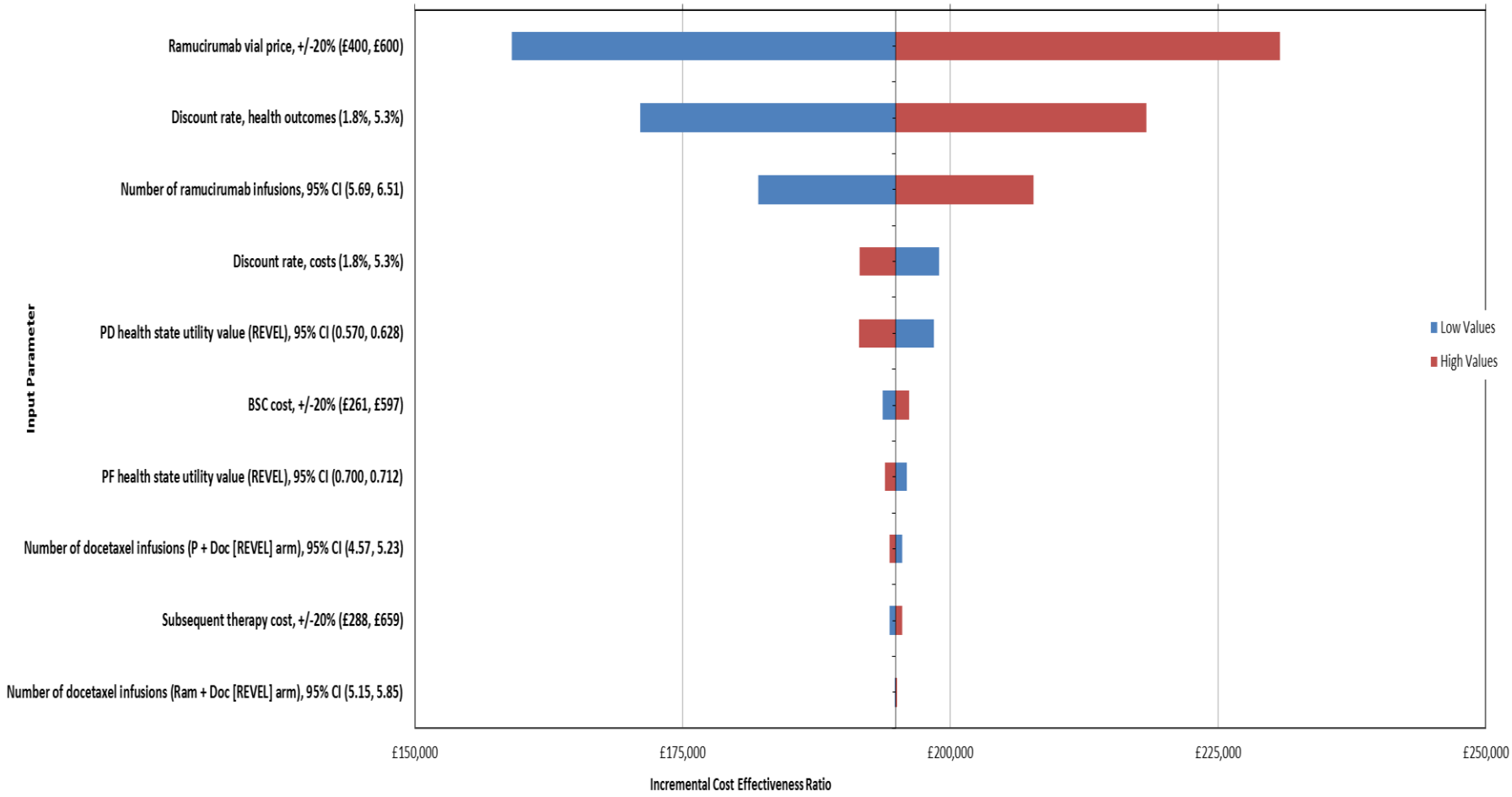
Deterministic sensitivity analysis

Figure 40 presents the graphical results of the one-way sensitivity analysis for the base-case analysis of the cost-effectiveness analysis of RAM+DOC compared with DOC, based on the overall REVEL population. The main drivers of the economic model are ramucirumab acquisition cost, the number of ramucirumab infusions and the discount rates for health outcomes and costs.

The results for comparisons with ERL in the EGFR-ve subpopulation and are presented in Figure 41. The most influential parameters are again the price of ramucirumab and the discount rate for health outcomes, then followed by the HR for OS for ERL and the number of ramucirumab infusions.

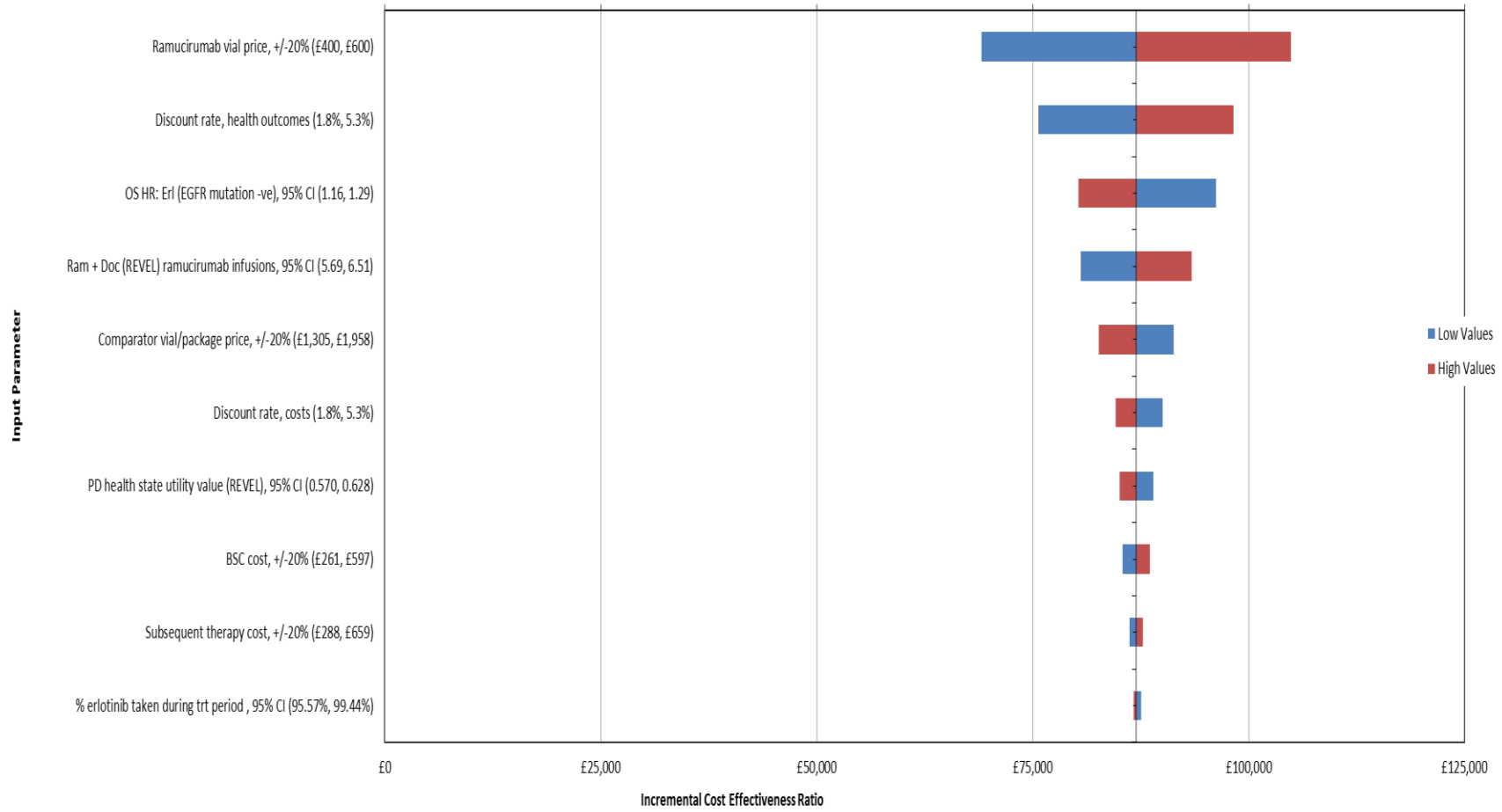
For NIN+DOC in the non-squamous subpopulation, the one-way sensitivity analysis results are shown in Figure 42. Given the similar effectiveness results for RAM+DOC and NIN+DOC in this subpopulation, it is unsurprising that the most influential parameters are the PFS and OS HR, followed by the price of each of ramucirumab and nintedanib.

Figure 40 Base-case tornado diagram for RAM+DOC vs DOC: REVEL overall population



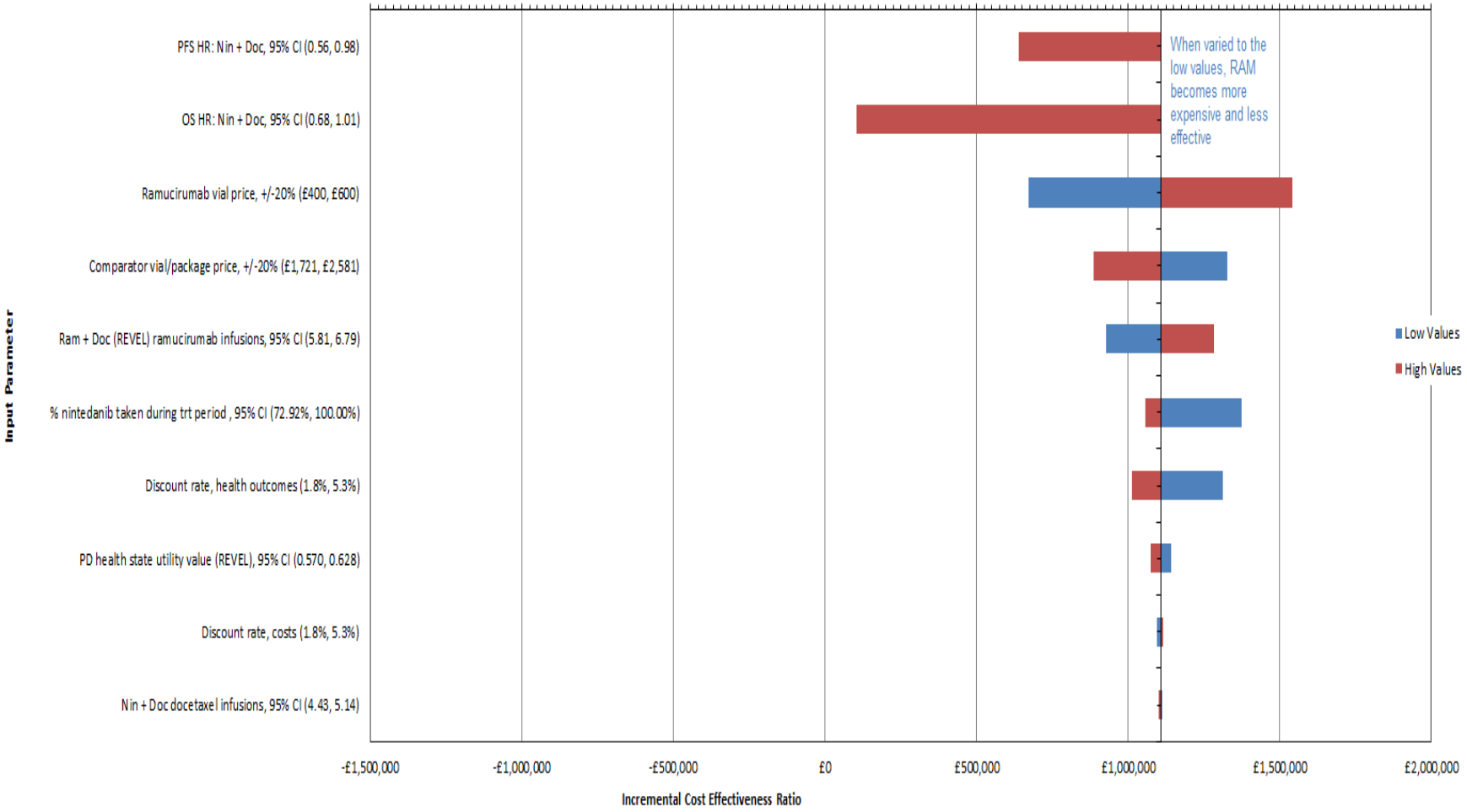
Abbreviations: CI = confidence interval; Doc = docetaxel; P = placebo; PF = progression free; Ram = ramucirumab.

Figure 41 **Base-case tornado diagram for RAM+DOC vs ERL: EGFR-ve subpopulation**



Abbreviations: OS: overall survival; HR: hazard ratio; Erl: erlotinib; CI = confidence interval; Ram = ramucirumab; Doc = docetaxel; PD: progressed disease; BSC: best supportive care.

Figure 42 **Base-case tornado diagram for RAM+DOC vs NIN+DOC: non-squamous subpopulation**



PFS: progression-free survival; HR: hazard ratio; Nin: nintedanib; Doc: docetaxel; CI: confidence interval; OS: overall survival; PD: progressed disease.

Scenario analysis

Table 90 summarises the scenario analyses conducted around the base case comparison of RAM+DOC compared to DOC in the overall REVEL ITT population. For each scenario, only the setting indicated in the table differs from those laid out in Table 79. None of the scenarios differ drastically from the base case. It is notable that even when the key parameters of the survival analyses, such as the time horizon, choice of distribution used to fit the survival curves and the assumptions used to extrapolate the treatment effect beyond the trial data were varied to the extremes, the model results remained stable. This highlights the robustness of the model results and the maturity of the trial data available for ramucirumab.

The scenario results for the comparison against ERL in the EGFR-ve subpopulation are presented in Table 91 and again reaffirm the stability of the model to changes in key parameters, reinforcing the robustness of the results.

The results against NIN+DOC in the non-squamous subpopulation are given in Table 92. As expected, given the extremely similar clinical effectiveness of RAM+DOC and NIN+DOC in this subpopulation, some scenarios do dramatically alter the ICER but this is driven by very small changes in incremental QALYs, simply reflecting how close the modelled QALY results for these two comparators are.

For the indirect comparators two scenarios were not analysed – the use of an unadjusted parametric survival curve and the application of a QALY penalty in the last cycle before death. The results of the QALY penalty scenario had barely changed from the base case in the overall REVEL population so it was not considered relevant to estimate them for the indirect comparators.

Table 90 Scenario analyses conducted on the base-case overall REVEL cost-effectiveness analysis (RAM+DOC vs DOC)

Scenario	Incremental Life-Years (Undiscounted)	Incremental Costs (Discounted)	Incremental QALYs (Discounted)	ICER (Cost/QALY Gained, Discounted)
Base case	0.188	£24,288	0.125	£194,919
1. Unadjusted parametric survival functions for OS and PFS	0.221	£24,140	0.105	£230,272
2: Generalized gamma for OS	0.206	£24,066	0.113	£213,803
3. Time horizon 10 years	0.239	£24,236	0.122	£198,997
4. Time horizon lifetime (20 years)	0.265	£24,306	0.126	£193,580
5. Treatment effect for OS applied indefinitely	0.272	£24,367	0.129	£189,068
6. No treatment effect upon end of trial follow-up	0.253	£24,275	0.124	£195,909
7. Published health state utilities (Chouaid et al., 2013 (98); see Table 55)	0.255	£24,288	0.118	£206,175
8. QALY penalty applied to last cycle before death	0.255	£24,288	0.125	£194,617

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 91 Scenario analyses conducted on the base-case EGFR-ve subpopulation cost-effectiveness analysis (RAM+DOC vs ERL)

Scenario	Incremental Life-Years (Undiscounted)	Incremental Costs (Discounted)	Incremental QALYs (Discounted)	ICER (Cost/QALY Gained, Discounted)
Base case	0.387	£21,721	0.250	£86,985
1. Unadjusted parametric survival functions for OS and PFS	NA	NA	NA	NA
2: Generalized gamma for OS	0.388	£20,966	0.209	£100,435
3. Time horizon 10 years	0.495	£21,605	0.243	£88,747
4. Time horizon lifetime (20 years)	0.553	£21,760	0.252	£86,408
5. Treatment effect for OS applied indefinitely	0.583	£21,966	0.263	£83,524
6. No treatment effect upon end of trial follow-up	0.524	£21,676	0.247	£87,667
7. Published health state utilities (Chouaid et al., 2013 (98); see Table 55)	0.532	£21,721	0.230	£94,614
8. QALY penalty applied to last cycle before death	NA	NA	NA	NA

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 92 Scenario analyses conducted on the base-case non-squamous subpopulation cost-effectiveness analysis (RAM+DOC vs NIN+DOC)

Scenario	Incremental Life-Years (Undiscounted)	Incremental Costs (Discounted)	Incremental QALYs (Discounted)	ICER (Cost/QALY Gained, Discounted)
Base case	0.020	£11,724	0.011	£1,106,497
1. Unadjusted parametric survival functions for OS and PFS	NA	NA	NA	NA
2: Generalized gamma for OS	0.067	£12,128	0.032	£373,633
3. Time horizon 10 years	0.016	£11,735	0.011	£1,049,964
4. Time horizon lifetime (20 years)	0.011	£11,721	0.010	£1,127,055
5. Treatment effect for OS applied indefinitely	-0.049	£11,439	-0.005	Dominated
6. No treatment effect upon end of trial follow-up	0.019	£11,765	0.013	£918,030
7. Published health state utilities (Chouaid et al., 2013 (98); see Table 55)	0.013	£11,724	0.009	£1,246,442
8. QALY penalty applied to last cycle before death	NA	NA	NA	NA

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Summary of sensitivity analyses

The overall conclusion of the sensitivity and scenario analyses is that the model is robust to changes in key parameters and assumptions. As would be expected from the disaggregated cost results, the one-way sensitivity analyses showed that the price of ramucirumab is a main driver of the model, along with the discount rate. For the comparison of RAM+DOC to NIN+DOC in the non-squamous subgroup the model became sensitive to the clinical efficacy inputs and assumptions. This reflects the highly similar clinical efficacy of the two drugs. With this comparison small absolute incremental changes to costs and QALYs lead to large changes to the ICER which does not reflect the robustness of the model.

5.9 Subgroup analysis

The EGFR negative and non-squamous subgroups have been presented as part of the base case to allow for comparison to ERL (Table 80) and NIN+DOC (Table 81), respectively; note that data for RAM+DOC do not vary by EGFR status from the REVEL results in the comparison to ERL, whereas for the comparison to NIN+DOC the non-squamous subgroup data from REVEL were used. No other subgroup analyses were performed.

5.10 Validation

Validation of de novo cost-effectiveness analysis

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision-Making (SMDM) Joint Task Force for Modeling Good Research Practices describes model validity simply, as “how well the model reproduces reality” (128). The guidelines define the following 5 elements of model validation:

1. Face validity: experts evaluate model structure, data sources, assumptions, results, e.g., consultation with clinical advisors before and (perhaps) after model development
2. Verification or internal validity: check accuracy of coding, e.g., “quality control” checks
3. Cross validity: comparison of results with other models analysing the same problem
4. External validity: comparing model results with real-world results
5. Predictive validity: comparing model results with prospectively observed events

To ensure the face validity of the model, external clinical and economic advisors in the UK were consulted during development of the model. An advisory board was attended by 4 NHS consultant oncologists, 3 UK academic health economists and 2 UK academic statisticians. Additionally, expert clinical advisors were consulted at multiple points in the model development process, including after completion of the draft model plan and after completion of the draft model.

The ISPOR-SMDM Joint Task Force refers to verification of a model as internal validity, and offers, as an example, checking the accuracy of programming code. The model development process employed an extensive quality control procedure to conduct model verification. This quality-control process sought to avoid errors in the model's logical structure, equations, and

programming and to ensure accuracy of data entry. For example, prior to finalisation of the model, the following activities were completed:

- Fully documented program code.
- Conducted a series of diagnostic tests to confirm that the model is correctly applying all formulas.
- Conducted a complete quality review of the model. A researcher not involved in the original model design performed the review.

To address cross validity and/or external validity, a selection of benchmark health outcomes from the literature were compared with model predictions at multiple time points. For example, the modelled median PFS and OS was compared with that observed in the REVEL trial (Table 82) and the health-state utility estimates generated from the REVEL EQ-5D data were compared to literature-based estimates (see Section 5.4 'Health-related quality of life studies'). The validation of OS extrapolation assumptions is described in detail below.

Predictive validity refers to comparing the model results with prospectively observed events. At this time, predictive validity in terms of RAM+DOC cannot be assessed.

Validation of OS extrapolation assumptions

To cross-validate the model assumptions on the extrapolation of OS beyond the trial data against a recent UK model, outcomes in the non-squamous subgroup were compared against those in the updated company and ERG base cases in the recent NICE appraisal of nintedanib for adenocarcinoma NSCLC, which had formed the basis of the decision by NICE to recommend nintedanib be accepted for use in the NHS (10). As can be seen in Table 93, the life year results for the model presented in this submission are clearly in line with the previous appraisal, being in fact slightly lower than those presented in the updated company base case while slightly above those in the updated ERG base case. Given that it is noted in the previous appraisal that "The Committee concluded that the ERG's updated base case for a mean extension to life of 2.69 months was implausible" (10) the results presented in this submission have clear cross validity with those previously used for NICE decision making.

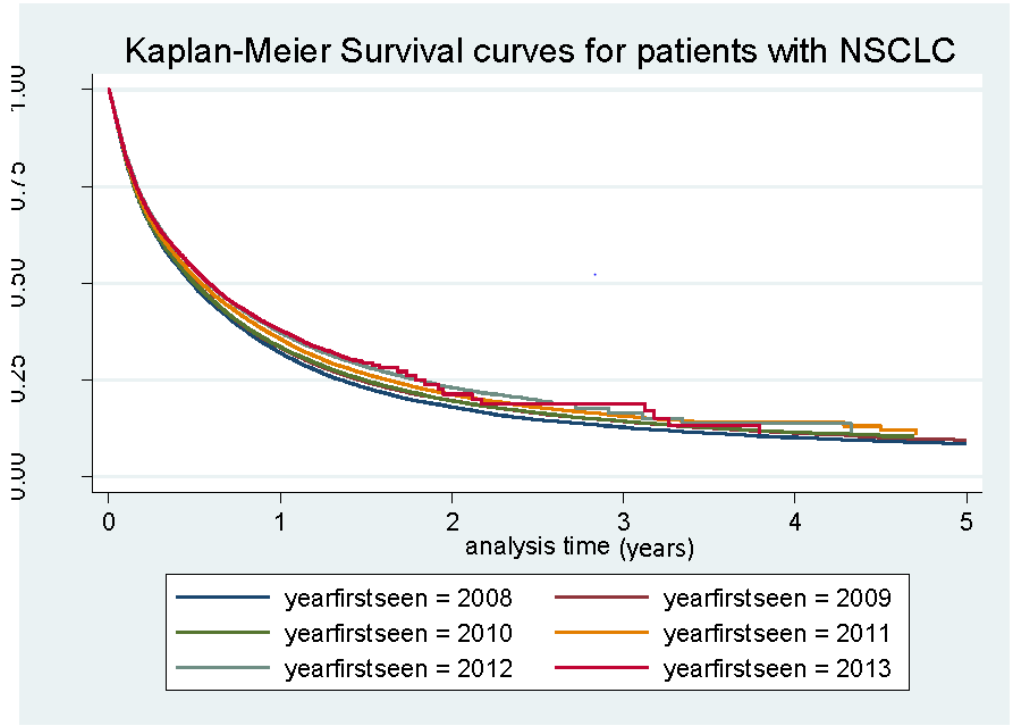
Table 93 Cross validation of non-squamous results against TA347

	LY – NIN+DOC	LY – DOC	LY – incremental
Updated company base case – TA347	1.709	1.411	0.298
Updated ERG base case – TA347	1.604	1.380	0.224
This submission – non-squamous subgroup	1.666	1.390	0.276

Abbreviations: LY: life year (undiscounted); NIN: nintedanib; DOC: docetaxel; TA: technology appraisal

A further attempt was made to validate the model OS results against real world data for NSCLC from a UK population. The only viable long-term UK data on NSCLC outcomes identified were those collected by the Royal College of Physicians (RCP) as part of the National Lung Cancer Audit (LUCADA). Unfortunately however these data were not available in the ideal format for model validation, as they were not available by stage of disease or line of therapy. The publicly available summary data from LUCADA are included here to provide a basis for consideration of the OS extrapolation in the model. Figure 43 reproduces a figure included in a presentation available on the RCP website for LUCADA (129). It appears that the survival curves were for all patients with NSCLC regardless of stage of diagnosis and whether systemic anticancer treatment was provided. This data will therefore include patients who received treatment with curative intent, and also those who were too unwell to receive any form of anticancer treatment (i.e. PS 2 and greater), which clearly has limitations for validation purposes.

Figure 43 NSCLC Kaplan-Meier survival curves (unadjusted), by year first seen, from LUCADA (129)



Unadjusted

Source: Peake, 2015, p. 72. (129)

Based on visual inspection of the completion of the Kaplan-Meier curves, the data for patients first seen in 2011, 2012 and 2013 were not as mature as the data for patients first seen earlier. Consequently, a comparison of survival percentages from LUCADA for patients first seen in 2010 was made to survival estimates in the cost-effectiveness model. Table 94 provides a comparison of the survival percentages from LUCADA (approximated from Peak, (129); see Figure 43) and from the cost-effectiveness model for each of the first four years of follow-up.

Table 94 Comparison of survival estimates: LUCADA and economic model, by year of follow-up

Data Source	1 Year	2 Years	3 Years	4 Years
LUCADA[a]	~35%	~20%	~14%	~12%
Model[b]	37%	16%	9%	6%

LUCADA = (UK National) Lung Cancer Audit.

[a] Peake, 2015 (129), p. 72. Data for NSCLC patients first seen in 2009. Percentages approximated based on visual inspection of the Kaplan-Meier curves (see Figure 43).

[b] Estimated using the cost-effectiveness model for PBO+DOC assuming the log-logistic multivariate overall survival function.

Given the limitations discussed above no conclusions will be made from the comparison. As the data were available, however, and provide the only source of long-term outcomes data for NSCLC in the UK, they have been included as an important reference source.

In conclusion, given that the model shows good cross validity with a recent NICE appraisal in second-line NSCLC, it is reasonable to conclude that the modelling approach and results are presented here are suitable for decision making.

5.11 Interpretation and conclusions of economic evidence

The results of the model show that RAM+DOC extends PFS (by 1.45 months) and survival in progressed disease (by 1.61 months) to give an undiscounted life-year gain of 3.06 months compared to DOC alone. The discounted QALY gain associated with RAM+DOC versus DOC alone is 0.124, 64% of which is accrued in the pre-progression phase. Compared to ERL in the EGFR-ve subpopulation, RAM+DOC extends PFS (2.52 months) and survival in progressed disease (3.86 months) to give an undiscounted life-year gain of 6.38 months compared to ERL, with a resulting discounted QALY gain of 0.250 vs. ERL, 55% of which was accrued before progression. In the non-squamous subpopulation, RAM+DOC provides similar OS benefit to NIN+DOC, with RAM+DOC giving an undiscounted life-year gain of 3.47 months versus DOC alone and NIN+DOC giving an undiscounted life-year gain of 3.32 months versus DOC alone; similar QALY benefits were also observed for these comparators, although RAM+DOC was more costly.

There is clear evidence that society has a preference for allocating resources to patients with severe diseases and a high unmet need (11). NSCLC is one such condition, given that patient prognosis is so poor and even a small QALY gain is extremely valuable to patients and their families. As such, it has been stated by NICE that: “The Institute recognises that the public, generally, places special value on treatments that prolong life – even for a few months – at the end of life, as long as that extension of life is of reasonable quality” (130). Ramucirumab should be considered under the end-of-life criteria, as:

- Nationally, the median survival for lung cancer is just under 7 months (see Section 4). Patients with advanced or metastatic NSCLC whose disease has progressed on platinum-based therapies have an expected median survival of only 9 months under current treatment with docetaxel (8); this is far below the 2 years stipulated in the end-of-life criteria.
- Due to the high fatality rate of NSCLC, the number of patients that will be alive to receive second-line treatment is small. It is expected that there would be approximately 1000 patients newly eligible for ramucirumab each year (see Section 6). The total eligible patient population across all licensed indications is estimated to be approximately ~1700 (see Section 4).
- Ramucirumab in combination with docetaxel is shown in the economic model to give an extension in OS of 3.06 months compared to docetaxel alone in the overall NSCLC population combining squamous and non-squamous, meeting the criterion for OS benefit. Furthermore, this is a substantial proportional improvement in a disease where the overall survival with the standard of care (DOC) is estimated to be

only 15.83 months. The proportional improvement in mean overall survival in this case (~21%) is similar in magnitude to that in the recent nintedanib appraisal in adenocarcinoma (10).

- Indirect comparisons confirm that ramucirumab in combination with docetaxel has equivalent overall survival benefit to nintedanib in combination with docetaxel in the non-squamous subpopulation. The recent NICE appraisal of nintedanib, TA347 (10), concluded that the end-of-life criteria were met in that appraisal. Ramucirumab and nintedanib, both in combination with docetaxel, are modelled to give an OS benefit of 3.47 months and 3.32 months compared to docetaxel alone in the non-squamous subpopulation analysis, respectively. It would therefore be appropriate and consistent to consider the end of life criteria met in the present appraisal.

The results of the model were extensively tested in deterministic, probabilistic and scenario analyses, all of which found the model to be robust to change. Even in the most extreme scenario analyses tested—making fundamental changes to the assumptions on modelling survival and treatment effect—the ICER change against DOC in the primary analysis reached a maximum of 18%. This robustness to change is due in part to the mature data available for RAM+DOC, which provides further confidence in the results.

The model inputs were generalisable to England, with clinical inputs primarily comprising a phase III, randomised, double blind clinical trial (REVEL) comparing RAM+DOC to PBO+DOC. External clinical advisors consulted considered it generalisable to second-line NSCLC patients suitable for docetaxel therapy in the NHS (127). The NMA was well-performed and allowed for a robust indirect comparison to ERL and NIN+DOC in this increasingly complex treatment landscape. The model structure and inputs were chosen to follow closely the economic model which informed the recent successful NICE appraisal of nintedanib and which was judged to be a suitable basis for NICE decision making (10). Consequently, the limitations of the analysis presented here are largely those of every analysis of treatment in NSCLC and are not specific to this submission; in particular the inherent limitation in such models of extrapolation of OS and PFS beyond the end of the observed trial results has been thoroughly explored in this submission and a variety of alternative parametric models tested for fit and presented as scenario analyses.

Overall reassurance is provided by the similarity of the modelled estimates for extension to OS in the non-squamous subpopulation for both DOC and NIN+DOC, which lie between the updated company base case and the updated ERG base case from TA347 (10). Given that the appraisal committee in that submission preferred the updated company OS estimate, stating that the updated ERG OS estimate was implausibly low, the model presented here is

seen to be suitably conservative in its approach and very much in line with previous appraisals.

The structure and assumptions used throughout the model were consistent with those used in previous NICE appraisals in this area in order to allow a consistent approach to decision making. Combined with the results of the sensitivity analyses that indicate that the results are robust to changes in the most uncertain parameters and the comprehensive validation process undertaken, the model presented clearly demonstrates the benefits of RAM+DOC and provides a reliable basis for decisions on clinical and cost-effectiveness.

6. Assessment of factors relevant to the NHS and other parties

Patient population

Based on statistics from the National Lung Cancer Audit (LUCADA) 2014 (1) and the proportion of patients who are estimated to receive second-line therapy from Brown et al 2013 (38), it is estimated that there are 1052 new cases of NSCLC that would be eligible for ramucirumab each year (Table 95). Of these, approximately 33% would be squamous and 67% would be non-squamous (38). The incidence of NSCLC and the proportion that are expected to require second-line therapy is not expected to change over the next 5 years, based on the overall trend of lung cancer incidence over time from Cancer Research UK (131).

Table 95 Eligible patient population

Population	Value	Source
Incident cases of lung cancer	32,364	Cases submitted to the National Lung Cancer Audit; LUCADA 2014 (1)
NSCLC (All lung cases excluding small cell and mesothelioma)	84%	LUCADA 2014 (1)
Performance status 0–1 and Stage IIIB/IV	23.12%	LUCADA 2014 (1)
Receive 1st line chemotherapy	59.80%	LUCADA 2014 (1)
Receive 2nd line chemotherapy	28%	Brown, 2013 (38)
Squamous proportion	33%	Brown, 2013 (38)
Non-squamous proportion	67%	Brown, 2013 (38) (assumed to be 100% minus % of squamous)
Total eligible patient population	1,052	
Total squamous proportion	347	
Total non-squamous patient population	705	

Market share

The current market shares are based on market research (Lilly data on file) and internal forecasts (Table 96). In a situation without ramucirumab, the current market shares are assumed not to change over the next 5 years (Table 96). This assumption was made because of current uncertainty regarding the approval and availability of new second-line lung cancer treatment. This picture is expected to dramatically change if newer agents were to be made available for routine use in the NHS. In both the squamous and non-squamous populations, ramucirumab is predicted take up 12% of the market in 2016 and 2017, and

then 15% of the market in 2018-20 (Table 97). In the squamous population, ramucirumab market share is expected to come entirely from docetaxel and in the non-squamous population, ramucirumab market share is expected to be taken proportionally from docetaxel and nintedanib plus docetaxel, based on their relative market share. Ramucirumab is not expected to displace erlotinib, which is in established use in the UK for patients who do not wish to receive docetaxel.

Table 96 Current market share

	2016	2017	2018	2019	2020
Squamous population					
DOC	67%	67%	67%	67%	67%
ERL	33%	33%	33%	33%	33%
Non-squamous population					
DOC	47%	47%	47%	47%	47%
ERL	33%	33%	33%	33%	33%
NIN+DOC	20%	20%	20%	20%	20%

Table 97 Future market share with ramucirumab

	2016	2017	2018	2019	2020
Squamous population					
RAM+DOC	12%	12%	15%	15%	15%
DOC	55%	55%	52%	52%	52%
ERL	33%	33%	33%	33%	33%
Non-squamous population					
RAM+DOC	12%	12%	15%	15%	15%
DOC	39%	39%	36%	36%	36%
ERL	33%	33%	33%	33%	33%
NIN+DOC	17%	17%	17%	17%	17%

Costs

Treatment acquisition cost is the main driver of cost differences between therapies in the cost-effectiveness model. Premedication and administration costs have also been included as these differ between the comparators. No other costs were considered to be relevant to commissioners, as ramucirumab is administered alongside docetaxel and therefore monitoring costs are not expected to change. The annual drug acquisition costs are

presented in Table 98 and were derived from the unit costs previously presented in Table 57 and Table 58 in Section 5.

Table 98 Annual drug acquisition costs used in the budget impact model

	RAM+DOC	DOC	NIN+DOC	ERL
Drug acquisition				
Non-docetaxel treatment	£22,769	--	£12,329	£5,787
Docetaxel	£198	£179	£183	--
Premedication	£212	£154	£302	£0
Second-line administration	£1,363	£825	£806	£0
Subtotal	**£24,541**	**£1,158**	**£13,620**	**£5,787**

Budget impact results

The introduction of ramucirumab is expected to result in a budget impact of £2,636,686 in each of the first two years after introduction and of £3,295,858 in years 3–5 after introduction (Table 99).

Table 99 Budget impact results

	2016	2017	2018	2019	2020
Total without RAM	£4,591,301	£4,591,301	£4,591,301	£4,591,301	£4,591,301
Total with RAM	£7,227,988	£7,227,988	£7,887,159	£7,887,159	£7,887,159
Net budget impact	**£2,636,686**	**£2,636,686**	**£3,295,858**	**£3,295,858**	**£3,295,858**

Discussion

The budget impact model does not include costs associated with disease state, nor take into account that patients receiving ramucirumab plus docetaxel remain in the progression-free state for longer than those receiving docetaxel alone. Therefore the savings associated with not moving to a more severe health state have not been captured here.

The main limitations of the budget impact model are that it has not been possible to accurately predict any change in the NSCLC population over the next 5 years and that the market shares are forecast-based only, rather than based on current prescribing data. This is especially the case for nintedanib which was only made available for use in the NHS in the three months from the publication of TA347 (10). The assumption that ramucirumab does not displace erlotinib is also a conservative one, seeing as erlotinib is more expensive than

docetaxel and therefore any assumption of displacement would have decreased the overall budget impact associated with ramucirumab.

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Single Technology Appraisal

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Dear Bemi and James,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 11th December 2015 from Lilly. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **1st February 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Caroline Hall, Technical Lead (caroline.hall@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.morre@nice.org.uk).

Yours sincerely

Helen Knight
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION:** In the company submission, the comparison with erlotinib is presented for the EGFR negative subgroup. However the final recommendation for erlotinib in the NICE technology appraisal 374 is for people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR positive or of unknown mutation status. Please comment on whether you consider the analyses you have presented for the EGFR negative subgroup an appropriate analyses, given the recommendation in TA374.

A2. **PRIORITY QUESTION.** Nivolumab is a comparator intervention identified in the NICE final scope for which relevant randomised controlled trial data is published. We acknowledge that you do not consider nivolumab a suitable comparator. However please reconsider if it is suitable to include the nivolumab evidence in your network meta-analysis.

A3. **PRIORITY QUESTION.** The Company Submission (Figure 19, page 90) indicates that nearly all studies used in the progression-free survival network meta-analysis failed the test for proportional hazards (including those studies most relevant to the comparators of interest). Please explain why the network meta-analysis approach was still used and why alternative approaches were not considered.

A4. **PRIORITY QUESTION.** Please supply the following patient number data for the REVEL trial in the table below. Please note that within a cycle the number eligible for treatment is better considered as being on day 1 of the cycle, whereas the number of patients receiving treatment may not exactly correspond with day 1 of the cycle if treatments are delayed. This should instead be considered as the number of patients receiving treatment during the cycle. If eligibility for treatment is not recorded, progression-free survival data can be provided, but please note this in the response.

	RAM+DOC			DOC	
	Eligible for Tx	RAM received	DOC received	Eligible for Tx	DOC received
1st cycle	N=???	N=???	N=???	N=???	N=???
2nd cycle	N=???	N=???	N=???	N=???	N=???
3rd cycle	N=???	N=???	N=???	N=???	N=???
etc…	N=???	N=???	N=???	N=???	N=???

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A5. **PRIORITY QUESTION.** In table JVBA.12.1.1. (page 137 of the CSR) a mean number of ramucirumab infusions of 6.1 and a mean cumulative dose of 61.0mg/kg has been included. However, the dose intensity is given as 94.6%. Please explain the calculation of each of the mean cumulative doses and the dose intensity, using patient level data. If it is simpler the full calculation of these quantities can be presented within an excel spreadsheet.

A6. **PRIORITY QUESTION.** Please present the overall survival Kaplan Meier data for both arms of the REVEL trial for all patients, and also separately for each of the three subgroups (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet.

Time	N events	N censored	N at risk	OS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A7. **PRIORITY QUESTION** Please present the investigator assessed progression-free survival Kaplan Meier data for both arms of the REVEL trial for all patients, and for each of the three subgroups of (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet if it is easier.

Time	N events	N censored	N at risk	PFS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A8. **PRIORITY QUESTION.** If the REVEL trial included an independent review committee (IRC) assessment of progression, please present the IRC assessed progression-free survival Kaplan Meier data for both arms of REVEL for all patients, and separately for each of the three subgroups of (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet if it is easier.

Time	N events	N censored	N at risk	PFS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A9. **PRIORITY QUESTION.** For table 24 (page 65 of the company submission) please present the patient numbers underlying each of the columns.

A10. **PRIORITY QUESTION.** To follow

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A11. In Table 10 (page 37 of company submission) it states that for trials to be eligible they had to report overall survival or progression-free survival as primary outcomes. Were trials that reported overall survival or progression-free survival as secondary outcome measures excluded? If so please provide details.

A12. In the company submission (page 53, figure 5), please explain what is meant by an investigator decision and a sponsor decision for reasons for treatment discontinuation.

A13. In the company submission (page 54, table 18) please provide more details for the 11 participants (5 ramucirumab and 6 placebo) included in the REVEL trial with 'other diagnoses, not lung cancer'. Please report the numbers of patients with other diagnosis in each arm that were alive, dead and censored by month 30 for the overall survival analysis.

A14. In the company submission (pages 59 and 60) the results of four sensitivity analyses for overall survival and progression-free survival are presented. Please provide details of the sensitivity analyses, including what they were determining, and also provide the 95% confidence intervals for the results reported.

A15. In the company submission (figure 6, pages 59 and 60) please report the number of censorings in each arm for overall survival and progression-free survival and indicate the reasons for censoring.

A16. Please list all hazard ratio inputs for the network meta-analysis, indicating whether each hazard ratio was an adjusted or unadjusted value. If adjusted values are presented please identify the covariates used in the adjustment. Please also confirm from which study the hazard ratio for erlotinib in the EGFR positive subgroup was sourced (Appendix 6).

A17. Please provide the results from the frequentist network meta-analysis.

A18. Fixed and random effects models were estimated in the network meta-analysis, however only the results of fixed effects were presented. Please provide the results of the random effects model.

A19. In the company submission (table 29, page 80) an excluded study of pemetrexed + erlotinib compared with pemetrexed is detailed but this appears to meet the network criteria for tier 1. Please explain the reason for this exclusion.

A20. As gefitinib findings were the only tier 2 data included in the network meta-analysis, it would be helpful to understand the effects of this evidence on the network meta-analysis. Please provide a sensitivity analysis excluding this data from the network?

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A21. The addition of the data for the other tier 2 interventions should provide more evidence and help reduce uncertainty. Please provide an additional sensitivity analysis to allow an assessment of all the tier 2 evidence and comparators?

A22. The company submission states that the network meta-analysis, incorporating meta-regression, was estimated to account for potentially influential covariates. Please provide these results?

A23. In the statistical analyses section of the company submission (page 82) describes a 'full set of inconsistency analyses' that were undertaken. Please clarify what these were. We also note that issues of heterogeneity are included, however direct and indirect outcomes do not appear to be reported for those in the closed loops so please provide these.

A24. Please provide a sensitivity analysis including the study (Hosomi 2015) that was excluded from the network meta-analysis because the dose of docetaxel was lower (60mg) than is typically used in the UK.

A25. Please present the patient numbers underlying the patient distributions within the economic model separately for the ramucirumab+docetaxel and the docetaxel groups for overall survival and progression-free survival for:

a. the REVEL trial as a whole

b. the patient subgroups for which there is data within the economic model

c. the squamous subgroup

d. the adenocarcinoma subgroup

Please also supply the age range and the median age for each subgroup. This data can be presented within an excel spreadsheet (see example below).

	OS		PFS	
	RAM+D	DOC	RAM+D	DOC
Total N	N=???	N=???	N=???	N=???
Age group >= 65	N=???	N=???	N=???	N=???
ECOG PS 0	N=???	N=???	N=???	N=???
Gender - F	N=???	N=???	N=???	N=???
Geographic region - Japan/East Asia	N=???	N=???	N=???	N=???
Histology - nonsquamous	N=???	N=???	N=???	N=???
Best Response to Plat. Tx - CR/PR/SD	N=???	N=???	N=???	N=???
Time since prior therapy < 9 months	N=???	N=???	N=???	N=???
Prior maintenance therapy (Y)	N=???	N=???	N=???	N=???
Prior 1st line pemetrexed (Y)	N=???	N=???	N=???	N=???

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A26. Please supply the following count data for patient baseline weights across all patients within REVEL.

	N female	N male
weight <= 40kg	N=???	N=???
40kg < weight <= 50kg	N=???	N=???
50kg < weight <= 60kg	N=???	N=???
60kg < weight <= 70kg	N=???	N=???
70kg < weight <= 80kg	N=???	N=???
80kg < weight <= 90kg	N=???	N=???
90kg < weight <= 100kg	N=???	N=???
100kg < weight <= 110kg	N=???	N=???
110kg < weight <= 120kg	N=???	N=???
120kg < weight <= 130kg	N=???	N=???
130kg < weight <= 140kg	N=???	N=???
140kg < weight <= 150kg	N=???	N=???
150kg < weight <= 160kg	N=???	N=???
weight > 160kg	N=???	N=???

A27. Table JVBA.12.1.1 of the CSR suggests a mean number of ramucirumab infusions of 6.1 and a mean number of docetaxel infusions of 5.5. We understand that ramucirumab and docetaxel are administered on the same day of a 21 week cycle. Please provide an account of why the mean numbers of infusions differed for ramucirumab and docetaxel in the ramucirumab+docetaxel group of the REVEL trial.

A28. Please provide details of any analyses undertaken using fitted curves to the subgroup specific data underlying, for example, the data in figure 12, page 72 of the company submission, rather than estimating one overarching multivariate overall survival analysis with patient covariates, and then using the REVEL trial non-squamous patient characteristics to model non-squamous overall survival curves for ramucirumab+docetaxel and docetaxel groups. Please supply these even if only available as exploratory analyses?

A29. Please provide details of how the explanatory variables for the multivariate analyses were selected for each analysis. For example, why did the overall survival analysis include region and best response to platinum therapy whereas the progression-free survival analysis did not? How was the list of interaction variables for ramucirumab+docetaxel in the overall survival analysis determined? Please also supply the details and results of any statistical tests underlying this.

A30. In the company submission EQ-5D was assessed among all patients for whom there was a valid translation. Please itemise which regions had a valid EQ-5D translation (for the geographic regions specified in table 14, page 44 of company submission). Please specify what number of patients in each arm had valid EQ-5D translations at

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baseline, and the number of EQ-5D questionnaires that were administered (not necessarily completed) at baseline, if this differs.

Section B: Clarification on cost-effectiveness data

B1. Please clarify why table 66 (page 156 in company submission) presents medians but is titled *Key disease progression variables applied in the economic model*. Please provide more detail on how the values presented in Table 66 are applied in the economic model as key disease progression variables.

B2. Please explain why the administration costs of erlotinib are calculated as being 46% of those of nintedanib, with reference to each of the products' Summary of Product Characteristics and pack sizes.

B3. The arithmetic underlying cell M241 of the Model Mechanics worksheet is not clearly explained. Please provide a more detailed account of the information such as an annotated spreadsheet with an exploded version of the arithmetic of cell M241 of the Model Mechanics worksheet.

B4. Please provide scenario analyses with subsequent/post-progression treatments removed for all patients, and also separately for each of the three subgroups (1) squamous, (2) non-squamous and (3) adenocarcinoma.

B5. Please provide the 95% confidence intervals for the cited 3.06 month life-year gain (discussion of end of life, page 110 of company submission).

Section C: Textual clarifications and additional points

C1. **PRIORITY QUESTION.** The network meta-analyses hazard ratios for nintedanib plus docetaxel in Tables 30 and 31 (page 88 and 91 of company submission) appear to be the preferred data used in the company submission rather than those in Tables 33 and 34 (page 94 of company submission). Please provide a more detailed explanation account for this.

C2. **PRIORITY QUESTION.** We have noted that some of the confidentiality marking is not in line with the instructions on marking confidential information sent with the invitation to submit and the directions in the NICE Guide to the processes of technology appraisals (sections 3.1.24 – 3.1.29). Please update the following:

a. Please ensure that any 'academic in confidence' data such as the network meta-analyses results are accompanied by an estimated date and place of publication in the checklist.

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b. Titles of figures (for example figure 40, 41 and 42 page 174 onwards of company submission) cannot be marked as confidential because this prevents readers from determining the context of the information included in the submission. Please update accordingly.

c. Any confidential information in your submission must also be marked appropriately in your model. Please update your model reflecting any changes you make to your written submission and highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow within the excel model.

d. We note that the mean number of docetaxel infusions of 5.5 in the main submission, is very similar to the median number of infusions presented in the draft EPAR. As the data will be released as soon as marketing authorisation has been granted and the EPAR will be publicly available, please confirm the date, in the confidentiality checklist, that this data will be released and please inform NICE as soon as this confidential marking can be removed.

e. Please remove the 'commercial in confidence' marking from the tornado diagrams in the company submission (figures 40, 41 and 42) because details of the ICERs cannot be marked as confidential.

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1st February 2016

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RE: Lilly response to STA clarification questions: ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Dear Helen

Please find enclosed the clarification requested by the ERG and the NICE technical team in relation to the clinical and cost effectiveness data of ramucirumab.

Please contact me if you have any further queries, either by email or telephone (01256 775022).

Kind regards

James Parnham
Head of Health Outcomes & HTA

Section A: Clarification on effectiveness data

A1. ***PRIORITY QUESTION:*** *In the company submission, the comparison with erlotinib is presented for the EGFR negative subgroup. However the final recommendation for erlotinib in the NICE technology appraisal 374 is for people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR positive or of unknown mutation status. Please comment on whether you consider the analyses you have presented for the EGFR negative subgroup an appropriate analyses, given the recommendation in TA374.*

TA374 states that "erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that doesn't test positive for the EGFR-TK mutation." This removes erlotinib as a comparator in the EGFR negative population and therefore the comparisons that were submitted for this can now be disregarded.

For EGFR positive patients, it is believed that very few patients now have a delayed or problematic test result. Clinical expert opinion from a recent UK advisory board was that newly diagnosed NSCLC patients usually receive their EGFR test results before any prescribed chemotherapy regimen has been initiated and therefore the recommendations made in TA374 apply to very few patients. If it is the case that an EGFR-positive patient (or suspected EGFR-positive patient if there is a problem with the test result) has progressed on chemotherapy, then it is expected that they would receive targeted therapy with erlotinib prior to being considered for ramucirumab. As noted in the submission, it is not expected that EGFR-positive patients who have progressed on erlotinib would be rechallenged.

Given all of the above, we therefore no longer consider erlotinib to be a relevant comparator for this appraisal.

A2. ***PRIORITY QUESTION.*** *Nivolumab is a comparator intervention identified in the NICE final scope for which relevant randomised controlled trial data is published. We acknowledge that you do not consider nivolumab a suitable comparator. However please reconsider if it is suitable to include the nivolumab evidence in your network meta-analysis.*

Nivolumab is currently undergoing NICE appraisal and has not been launched in the UK. Therefore it is not part of established clinical practice and does not comply with the definition of a comparator as laid out in the NICE Guide to Methods of Technology Appraisal:

"The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology."[1]

Furthermore, NICE has not recommended nivolumab for squamous cell NSCLC in their draft guidance.[2] This calls into question whether nivolumab will ever become routinely used in the UK. Therefore it is not an appropriate comparator for ramucirumab.

Given that nivolumab is not a comparator in this appraisal, its addition to the NMA would only be of use if its phase III trials were to create additional loops or otherwise inform the existing network. However, the pivotal phase III trials of nivolumab in NSCLC only provide a comparison of nivolumab to docetaxel and are therefore unlikely to strengthen or improve the overall network.[3, 4] We have not, therefore, added nivolumab to the NMA.

A3. ***PRIORITY QUESTION.*** *The Company Submission (Figure 19, page 90) indicates that nearly all studies used in the progression-free survival network meta-analysis failed the test for proportional hazards (including those studies most relevant to the comparators of interest).*

Please explain why the network meta-analysis approach was still used and why alternative approaches were not considered.

The tests for significant non-proportional hazards are given below.

Study	rho	Chi-sq	P	Rx1	Rx2	Rx3
Aerts.2013.n	-0.14	2.67	0.1023	Erlotinib (150 mg)	Erlotinib (150 mg) + pemetrexed (500 mg/m²)	
Aerts.2013.s	0.20	2.89	0.0894	Docetaxel (75 mg/m²) + erlotinib (150 mg)	Erlotinib (150 mg)	
Fossella.2000	0.00	0.00	0.9485	Docetaxel (100 mg/m² every 3 weeks)	Docetaxel (75 mg/m² every 3 weeks)	
Garassino.2013	0.00	0.00	0.9828	Docetaxel (75 mg/m² every 3 weeks)	Erlotinib (150 mg)	
Garon.2014	-0.07	4.88	0.0271	Docetaxel (75 mg/m² every 3 weeks)	Docetaxel (75 mg/m²) + ramucirumab (10 mg/kg)	
Hanna.2004	-0.03	0.42	0.5148	Docetaxel (75 mg/m² every 3 weeks)	Pemetrexed (500 mg/m²)	
Hanna.2013	-0.09	3.85	0.0499	Pemetrexed (500 mg/m²)	Pemetrexed (500 mg/m²) + nintedanib (200 mg)	
Kim.2008	-0.07	6.22	0.0126	Docetaxel (75 mg/m² every 3 weeks)	Gefitinib (250 mg)	
Lee.2013	0.10	2.42	0.1200	Erlotinib (150 mg)	Erlotinib (150 mg) + pemetrexed (500 mg/m²)	Pemetrexed (500 mg/m²)
Quoix.2004	-0.05	0.41	0.5210	Docetaxel (100 mg/m² every 3 weeks)	Docetaxel (75 mg/m² every 3 weeks)	
Reck.2014.n	-0.08	2.39	0.1223	Docetaxel (75 mg/m² every 3 weeks)	Docetaxel (75 mg/m²) + nintedanib (200 mg)	
Reck.2014.s	-0.11	4.16	0.0415	Docetaxel (75 mg/m² every 3 weeks)	Docetaxel (75 mg/m²) + nintedanib (200 mg)	
Sun.2012	-0.01	0.01	0.9126	Gefitinib (250 mg)	Pemetrexed (500 mg/m²)	
Sun.2013	0.00	0.00	0.9805	Docetaxel (75 mg/m² every 3 weeks)	Pemetrexed (500 mg/m²)	

There were only a few studies that gave significant non-proportional hazards. Docetaxel plus nintedanib was one of the main comparators of interest. However, for this intervention only the squamous data were found to be significant whereas it was the comparison with the non-squamous data that was of primary interest.

Work has just been completed using fractional polynomial NMAs on re-constructed patient level data for overall survival and progression-free survival. Whist there were a number of studies that did not meet the proportional hazard assumption a further issue has been identified which is that a number of early studies only reported Kaplan-Meier charts for time to treatment failure and time to treatment progression. These were not included in the NMA due to not being the same as progression-free survival. There were also studies in the network that did not achieve the desired results and from which only abstracts published which only reported summary data such as median survival times and hazard ratios and so these studies were also not included in the fractional polynomial NMA. The network of evidence based on re-constructed data for progression-free survival therefore suffered from publication bias. The hazard ratio results for progression free survival were consistent to the results from previously published NMAs on overall survival based on hazard ratios and from the NMA for overall survival based on re-constructed patient level data. This suggests that despite the problem of non-proportional hazards the current NMA based on summary data is probably the best estimate we can give for relative differences for progression-free survival.

A4. ***PRIORITY QUESTION.*** *Please supply the following patient number data for the REVEL trial in the table below. Please note that within a cycle the number eligible for treatment is better considered as being on day 1 of the cycle, whereas the number of patients receiving treatment may not exactly correspond with day 1 of the cycle if treatments are delayed. This should instead be considered as the number of patients receiving treatment during the cycle. If eligibility for treatment is not recorded, progression-free survival data can be provided, but please note this in the response.*

	RAM+DOC			*DOC*	
	Eligible for Tx	*RAM received*	*DOC received*	*Eligible for Tx*	*DOC received*
1st cycle	*N=???*	*N=???*	*N=???*	*N=???*	*N=???*
2nd cycle	*N=???*	*N=???*	*N=???*	*N=???*	*N=???*
3rd cycle	*N=???*	*N=???*	*N=???*	*N=???*	*N=???*
etc…	*N=???*	*N=???*	*N=???*	*N=???*	*N=???*

We have provided the number of patients receiving treatment during the cycle in the table below. Patients have delays for various reasons but they do get treatment eventually so are eligible.

	Ramucirumab + Doctexel (N=627)			DOC (N=618)		
	Eligible for Tx[a]	RAM received	DOC received	Eligible for Tx[a]	Placebo received	DOC received
1st cycle	626	626	625	618	618	618
2nd cycle	553	551	552	538	529	530
3rd cycle	426	420	424	372	364	364
4th cycle	385	379	379	327	319	321
5th cycle	317	313	302	255	248	247
6th cycle	292	287	267	236	229	226
7th cycle	215	210	162	169	167	146
8th cycle	199	195	148	154	153	125
9th cycle	152	150	105	117	116	96
10th cycle	130	128	87	105	102	86
11th cycle	102	100	68	77	76	59
12th cycle	91	88	59	71	70	53
13th cycle	74	72	47	59	58	43
14th cycle	63	59	41	51	49	37
15th cycle	47	44	31	41	39	28
16th cycle	40	39	26	39	37	27

*a – Number of patient randomized that received some study drug and were alive at beginning of each cycle
Source: S107exp.r1 and S107cmpl.r1

Section 9.1 of the REVEL study protocol states that patients will receive study treatment every 3 weeks until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision. It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions precisely 3 weeks following a prior infusion (because of holidays, travel difficulties, or other circumstances). **Accordingly, infusions administered within 3 days before or after the planned 3-week time point will be considered acceptable**. Deviations beyond this window are strongly discouraged, and require Sponsor or designee approval.

9.5.1.1. Criteria for Starting Next Cycle

To start next cycle, the following criteria must be fulfilled:

- Total bilirubin less than or equal to ULN
- AST and ALT ≤2.5 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- ANC ≥1.5 x 103/µL (≥
- 1.5 x 109/L), platelets ≥100 x 103/µL (≥100 x 109/L)
- NCI-CTCAE v 4.0 Grade < 2 (except for alopecia; for hypertension, see Section 9.5.1.2.1.2, and for proteinuria, see Section 9.5.1.2.1.5)

If these criteria are not met, the start of next cycle should be delayed for up to 2 weeks to allow for recovery. If a delay of more than 2 weeks due to unresolved toxicity is necessary, one or both of the drugs should be discontinued (depending on the causality of the drug). The other agent should be continued, with the patient remaining on study, if clinically indicated. If the start of the next cycle is delayed due to either chemotherapy or ramucirumab/placebo related toxicity, the start of the other compound should also be postponed to maintain synchronized administration. However, if either docetaxel or ramucirumab/placebo dosing is permanently discontinued, dosing should be continued with the remaining compound according to the schedule, if clinically indicated.

A5. ***PRIORITY QUESTION.*** *In table JVBA.12.1.1. (page 137 of the CSR) a mean number of ramucirumab infusions of 6.1 and a mean cumulative dose of 61.0mg/kg has been included. However, the dose intensity is given as 94.6%. Please explain the calculation of each of the mean cumulative doses and the dose intensity, using patient level data. If it is simpler the full calculation of these quantities can be presented within an excel spreadsheet.*

The cumulative dose (mg/kg) is determined for each patient by summing up the total dose in mg/kg at each infusion. To determine the mean cumulative dose of ramucirumab you would calculate the cumulative dose (mg/kg) for each patient in the ramucirumab arm and then take the mean. The dose intensity (mg/kg/week) is determined for each patient by first determining the cumulative dose (mg/kg) that the patient received divided by the number of weeks the patient received the drug. The relative dose intensity is the actual dose intensity divided by the planned dose intensity X 100 percent.

For example, Pt 1000 received 11 infusions as shown below

Cycle	Dose (mg/kg)	Calculation
1	10.00	• The cumulative dose is 113.37mg/kg • The patient started the first infusion on 26/01/2012 and had the last infusion on 20/09/2012 therefore the treatment duration was 37 weeks. • The dose intensity for this patient would be 113.37 mg/kg divided by 37 weeks = 3.06 mg/kg/week. • The relative dose intensity for this patient would be 3.06mg/kg/week divided by 3.34 mg/kg/week = 91.7%. • Please note that the planned ramucirumab dose is 10 mg/kg every 3 weeks
2	9.91	
3	10.23	
4	10.25	
5	10.18	
6	10.09	
7	10.40	
8	10.29	
9	10.47	
10	10.70	
11	10.85	
Total	**113.37**	

A6. ***PRIORITY QUESTION.*** *Please present the overall survival Kaplan Meier data for both arms of the REVEL trial for all patients, and also separately for each of the three subgroups (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet.*

Time	*N events*	*N censored*	*N at risk*	*OS S(t)*
0	*0*	*0*	*???*	*100%*
???	*???*	*???*	*???*	*???*
etc.	*???*	*???*	*???*	*???*

Please see the attached excel spreadsheets named

- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (1 of 5) g107kmos*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (2 of 5) g107kmps*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (3 of 5) OS_overall*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (4 of 5) PFS_overall*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (5 of 5) km_tte_hist_adeno*

A7. ***PRIORITY QUESTION*** *Please present the investigator assessed progression-free survival Kaplan Meier data for both arms of the REVEL trial for all patients, and for each of the three subgroups of (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet if it is easier.*

Time	*N events*	*N censored*	*N at risk*	*PFS S(t)*
0	*0*	*0*	*???*	*100%*
???	*???*	*???*	*???*	*???*
etc.	*???*	*???*	*???*	*???*

Please see the attached excel spreadsheets named

- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (1 of 5) g107kmos*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (2 of 5) g107kmps*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (3 of 5) OS_overall*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (4 of 5) PFS_overall*
- *Ramucirumab, NSCLC Nice ERG Clarification Question 6 & 7 (5 of 5) km_tte_hist_adeno*

A8. ***PRIORITY QUESTION.*** *If the REVEL trial included an independent review committee (IRC) assessment of progression, please present the IRC assessed progression-free survival Kaplan Meier data for both arms of REVEL for all patients, and separately for each of the three subgroups of (1) squamous, (2) non-squamous and (3) adenocarcinoma. This data can be presented within an excel spreadsheet if it is easier.*

Time	*N events*	*N censored*	*N at risk*	*PFS S(t)*
0	*0*	*0*	*???*	*100%*
???	*???*	*???*	*???*	*???*
etc.	*???*	*???*	*???*	*???*

Since OS is the primary endpoint for REVEL trial, IRC assessment of progression was not done

A9. ***PRIORITY QUESTION.*** *For table 24 (page 65 of the company submission) please present the patient numbers underlying each of the columns.*

Table 24 REVEL: EQ-5D Results

	RAM+DOC N=628	PBO+DOC N=625
Compliance, n (%)		
Overall	4553 (80.6) / 5651	4041 (79.2) / 5104
Patients completing baseline EQ-5D	521 (83.0)	532 (85.1)
Patients completing end of treatment (30-day follow-up visit) EQ-5D	310 (63.9)	322 (65.7)
EQ-5D Index Score, mean (SD) (patient numbers)		
Baseline	0.714 (0.232)(521)	0.687 (0.259)(532)
Cycle 2	0.707 (0.248)(483)	0.692 (0.273)(473)
Cycle 3	0.704 (0.251)(377)	0.707 (0.258)(320)
Cycle 4	0.700 (0.250)(357)	0.721 (0.255)(293)
Cycle 5	0.678 (0.250)(295)	0.752 (0.221)(228)
Cycle 6	0.697 (0.246)(251)	0.740 (0.238)(208)
Cycle 7	0.712 (0.244)(195)	0.741 (0.213)(155)
Cycle 8	0.699 (0.235)(179)	0.727 (0.213)(129)
Cycle 9	0.738 (0.228)(138)	0.698 (0.264)(105)
Cycle 10	0.741 (0.200)(117)	0.700 (0.265)(92)
Cycle 11	0.706 (0.221)(95)	0.743 (0.232)(67)
Cycle 12	0.717 (0.240)(81)	0.725 (0.260)(60)
Cycle 13	0.690 (0.241)(70)	0.719 (0.249)(53)
Cycle 14	0.698 (0.212)(57)	0.746 (0.236)(45)
Cycle 15	0.714 (0.201)(47)	0.802 (0.155)(39)
Cycle 16	0.745 (0.209)(39)	0.763 (0.196)(35)
Summary Visit	0.611 (0.285)(383)	0.579 (0.360)(379)
30-day follow up	0.612 (0.201)(310)	0.595 (0.340)(322)

A10. ***PRIORITY QUESTION.*** *Please provide any other analyses of the REVEL EQ-5D data (other than simple means and medians of quality of life data as presented in the company submission and appendix 11) which have been undertaken or commissioned*

As noted on pages 140–141, the submission has already provided the further analyses of EQ-5D that were performed during the preparatory work for the economic model building but not used in the final model, in Appendix 11.

Lilly confirms that no further analyses of the REVEL EQ-5D data are available

A11. *In Table 10 (page 37 of company submission) it states that for trials to be eligible they had to report overall survival or progression-free survival as primary outcomes. Were trials that reported overall survival or progression-free survival as secondary outcome measures excluded? If so please provide details*.

We can confirm that trials that reported overall survival or progression-free survival as secondary outcome measures were included.

A12. *In the company submission (page 53, figure 5), please explain what is meant by an investigator decision and a sponsor decision for reasons for treatment discontinuation.*

Investigator/Physician Decision: The investigator/physician decides that the patient should be withdrawn from the study or study drug. If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication; in this event, discontinuation from the study drug must occur prior to introduction of the new agent

Sponsor Decision: The investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice

A13. *In the company submission (page 54, table 18) please provide more details for the 11 participants (5 ramucirumab and 6 placebo) included in the REVEL trial with 'other diagnoses, not lung cancer'. Please report the numbers of patients with other diagnosis in each arm that were alive, dead and censored by month 30 for the overall survival analysis.*

REVEL CSR Table JVBA.14.1.17. Additional information on patient without cytologically/histologically confirmed NSCLC at study entry (Intent to treat population)

Patient ID	Initial Dx (Stage)	Study Entry Dx	Treatment	Treatment Start-End Dates	Death Date	Cause of Death
681-6813	Adenocarcinoma, lung (IV)	Ascites	Placebo	9/15/2011 - 10/27/2011	1/4/2012	study disease
689-6896	Large cell carcinoma, lung (IV)	Esophageal diverticulum	RAM	9/1/2011 - 9/23/2011	3/31/2012	study disease
100-1001	Adenocarcinoma, lung (IIIB)	Brain anomaly	RAM	2/14/2012 - 2/14/2012	3/28/2012	study disease
695-8251	Squamous cell carcinoma, lung (IIIB)	CNS metastasis	Placebo	11/9/2011 - 11/13/2013	alive*	
526-5263	Lung disease (IV)	[none provided]	RAM	1/23/2012 - 3/26/2012	6/8/2012	study disease
801-8010	Neuroendocrine carcinoma (IV)	[none provided]	Placebo	12/6/2011 - 11/23/2012	alive*	
810-8106	CNS anomaly (IV)	[none provided]	Placebo	10/8/2012 - 12/31/2012	1/25/2013	adverse event(other causes)
176-1762	CNS anomaly (IV)	[none provided]	RAM	3/27/2012 - 4/16/2012	6/15/2012	adverse event(other causes)
490-8961	CNS anomaly (IV)	[none provided]	RAM	1/16/2013 - 1/16/2013	2/15/2013	study disease
687-7052	CNS anomaly (IV)	[none provided]	Placebo	7/17/2012 - 9/17/2012	alive*	
674-6748	CNS anomaly (IV)	CNS anomaly	Placebo	7/2/2012 - 11/27/2012	alive*	
750-7504	CNS metastasis (IV)	[none provided]	Placebo	6/11/2012 - 8/22/2012	6/21/2013	study disease
494-4941	[none provided]	[none provided]	RAM	randomized but not treated	alive*	

*alive at study data cut-off
Sources:
/data1/projects/li/li2107/tr201402lock/final/list/s107demo.r1
/data1/projects/li/li2107/tr201402lock/final/list/s107dth.r1
/data1/projects/li/li2107/tr201402lock/final/list/s107sda.r1

Thirteen patients did not have histologically or cytologically confirmed NSCLC at study entry (Inclusion Criterion #5) (CSR Table JVBA 10.2.1) Two patients had an initial diagnosis of Stage IV NSCLC and 2 patients had an initial diagnosis of Stage IIB and IIIB NSCLC, but study entry diagnosis was not NSCLC (CSR Table JVBA. 14.1.17). One patient had unspecified Stage IV lung disease at initial diagnosis only. The remaining 8 patients did not have NSCLC at initial diagnosis nor at study entry, including 1 patient (Patient 4941) who was randomized but not treated. Additional information on these 13 patients is provided in (CSR Table JVBA.14.1.17)

A14. *In the company submission (pages 59 and 60) the results of four sensitivity analyses for overall survival and progression-free survival are presented. Please provide details of the sensitivity analyses, including what they were determining, and also provide the 95% confidence intervals for the results reported.*

Sensitivity Analyses for Overall Survival (11.5.1.2) (Page 101 – 104 in CSR)

The statistical significance, magnitude of effect, and robustness of the primary OS analysis results were supported by prespecified sensitivity analyses, as demonstrated by consistent HRs between 0.81 and 0.86, all with p≤0.027 (CSR Table JVBA.11.5.2) The following analyses were prespecified in the SAP

Using IVRS (interactive voice recognition system) data for stratified analysis: A prespecified analysis was conducted to assess the sensitivity of the primary analysis to the source of data for the stratification factors (Note: the primary analysis was based on the case report form (CRF) data). The stratified log-rank test using the stratification factors based on the data as recorded on the IVRS has an HR of 0.86 (95% CI: 0.75, 0.98) that was statistically significant (p=0.027).

Adjusting for potential prognostic factors: Despite randomization, small imbalances in potential prognostic factors could impact the analysis of survival. Hence, an analysis was conducted to assess the sensitivity of the primary analysis to any imbalances in potential prognostic factors. The list of factors to be included in this analysis was prespecified in the SAP. The stepwise Cox regression analysis selected baseline factors that were significantly associated with OS using the pooled (ramucirumab plus docetaxel and placebo plus docetaxel) data, and then adjusted for these factors in a Cox proportional hazards model that included a term for treatment arm. The factors that were significantly associated with OS (p<0.05), and therefore included in the final model were geographical region, ECOG performance status, gender, histology, best response to platinum-based chemotherapy, and time since prior therapy. The analyses indicated a HR of 0.81 (95% CI: 0.70, 0.92) and a p-value of 0.002.

An unstratified analysis: The unstratified Cox proportional hazards model indicated a HR of 0.86 (95% CI: 0.75, 0.98) and an unstratified log-rank test that was statistically significant (p=0.021).

Per protocol population analysis: This analysis was conducted to assess the impact on the ITT analysis by excluding patients with specific major protocol deviations (identified as: no histologically or cytologically confirmed NSCLC or concurrent prohibited therapies prior to study treatment discontinuation. This analysis was performed because the numbers of patients with these specific major protocol deviations met the threshold for performing this analysis (5.6%; ≥5% of total ITT population). The HR was 0.82 (95% CI: 0.71, 0.94) and a p-value of 0.004.

Table JVBA.11.5.2. Sensitivity Analyses for Overall Survival Time Intent-to-Treat Population

Overall Survival	HR (95% CI)	Log-rank p-value (unless otherwise specified)
Primary Analysis		
Stratified by CRF, 884 events	0.86 (0.75, 0.98)	0.024
SAP-specified		
Stratified by IVRS	0.86 (0.75, 0.98)	0.027
Multivariate Cox regression[a]	0.81 (0.70, 0.92)	0.002[b]
Unstratified Cox regression	0.86 (0.75, 0.98)	0.021
Per Protocol Analysis	0.82 (0.71, 0.94)	0.004

Abbreviations: CI = confidence interval; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; IVRS = interactive voice recognition system; SAP = statistical analysis plan.

Note: Overall survival is the duration from randomization to death. For patients who are alive, overall survival is censored at the last contact.

a Cox proportional hazard model: stepwise selection of significant prognostic factors:
Significant factors: geographical region, ECOG performance status, gender, histology, best response to platinum-based chemotherapy, and time since prior therapy.
Variables included in model selection: geographical region, ECOG performance status, prior maintenance therapy, gender, smoking history, histology, best response to platinum-based chemotherapy, prior taxane treatment, prior bevacizumab, EGFR status, age, race, and time since prior therapy; these factors are defined in the SAP.

b Wald's p-value.

Sources: CSR (Table JVBA.14.2.1; Table JVBA.14.2.2; Table JVBA.14.2.3; Table JVBA.14.2.4.)

Sensitivity Analyses for PFS (11.5.2.1.1.) (page 106-107 in CSR)

The robustness of the main PFS analysis results was supported by prespecified sensitivity analyses, as demonstrated by consistent HRs between 0.75 and 0.80, all with p<0.001 (CSR Table JVBA.11.5.5). Collectively, the sensitivity analyses support the finding of an improvement in PFS associated with ramucirumab plus docetaxel versus placebo plus docetaxel.

The sensitivity analyses performed were defined in the SAP. Full results for PFS sensitivity analyses are presented in CSR Table JVBA.14.2.8.

Table JVBA.11.5.5 Sensitivity Analysis of Progression-Free Survival
Intent-to-Treat Population

Progression-free Survival	HR (95% CI)[a]	p-value[b]
Primary Analysis		
Stratified, 1141 events	0.76 (0.68, 0.86)	<0.001
Sensitivity Analyses		
Progressed at date of earlier of 2 visits if documented progression between visits and censored at date of later of 2 visits if censored between visits (1141 events)	0.76 (0.68, 0.86)	<0.001
Censored at date of new anticancer therapy (1067 events)	0.75 (0.66, 0.85)	<0.001
Censored at date of last adequate radiological assessment before missed assessments if death or documented progression was reported after >2 missed assessments (1028 events)	0.75 (0.66, 0.84)	<0.001
Worst case analysis: Progressed at date of next scheduled radiological assessment at or after becoming lost to follow-up without death or documented progression (1186 events)	0.78 (0.69, 0.88)	<0.001
Worst case analysis & least favoring the experimental arm: Progressed for treatment arm or censored for the control arm at date of next scheduled radiological assessment at or after becoming lost to follow-up without death or documented progression (1174 events)	0.80 (0.71, 0.89)	<0.001

Abbreviations: CI = confidence interval; HR = hazard ratio.

a Ramucirumab versus placebo.

b p-value based on log-rank test.

Source: CSR Table JVBA.14.2.8.

A15. *In the company submission (figure 6, pages 59 and 60) please report the number of censorings in each arm for overall survival and progression-free survival and indicate the reasons for censoring.*

This information can be found in Table JVBA.14.2.1 and 14.2.7 in the REVEL CSR

A16. *Please list all hazard ratio inputs for the network meta-analysis, indicating whether each hazard ratio was an adjusted or unadjusted value. If adjusted values are presented please identify the covariates used in the adjustment. Please also confirm from which study the hazard ratio for erlotinib in the EGFR positive subgroup was sourced (Appendix 6).*

Only unadjusted hazard ratios were used in NMA. The interaction effects for EGFR mutation positive and proportion of non-squamous with pemetrexed were derived from the studies that varied in the proportion of these tumour types with the relevant treatments. The estimates were therefore derived from multiple studies with Lee et al. (2013) having the highest proportion of patients with EGFR mutation positive tumours for erlotinib. The estimates for 100% EGFR mutation positive were extrapolated from all of the estimates from the NMA based on linear regression for each of the Bayesian draws.

A17. *Please provide the results from the frequentist network meta-analysis.*

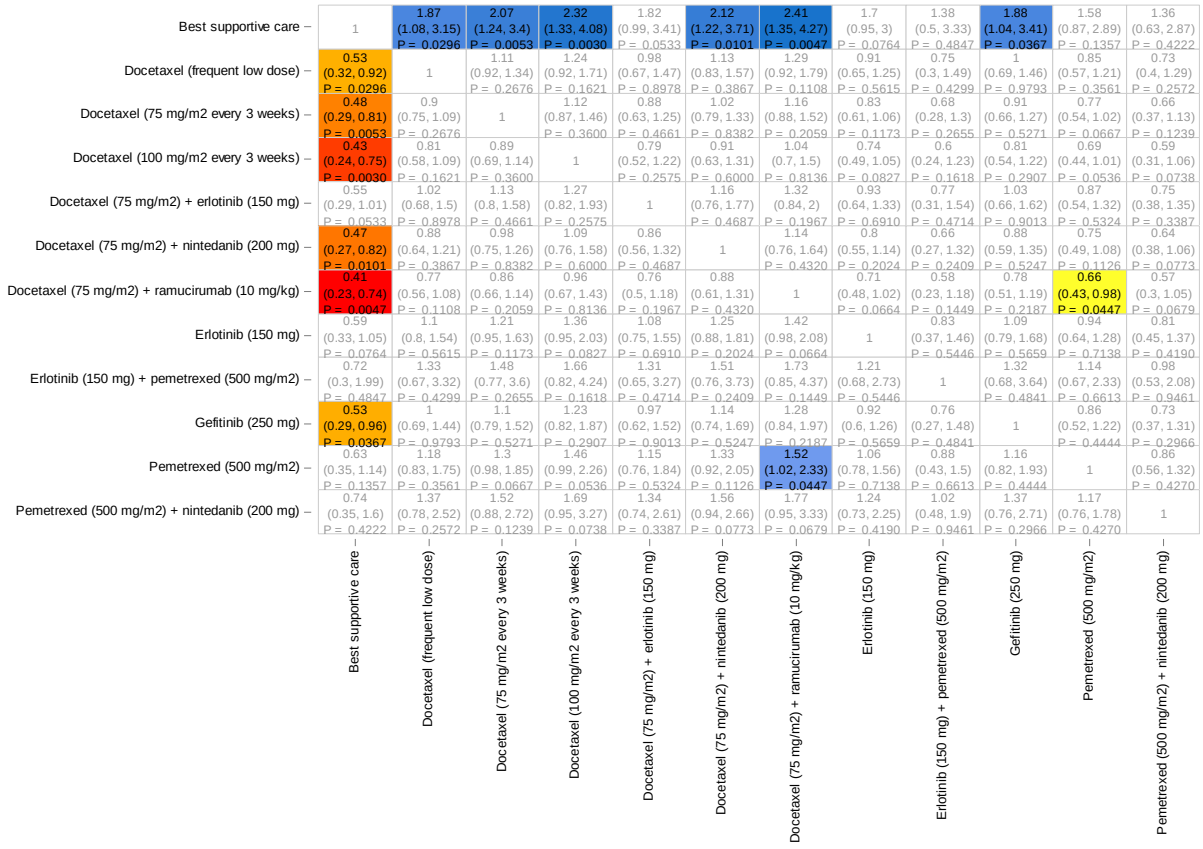
The frequentist NMAs were only conducted to help validate the Bayesian NMA. Only forest plots were produced which were plotted alongside the Bayesian results. The frequentist models do not adjust for correlations in multi-arm trials and although similar are not quite the same as the models in the NICE guidelines or cited in the NICE guidelines. The NICE DSU 2 document states that "When multi-arm trials are involved, it is essential to take account of both the correlation in parameters in random effect models, but also the correlations in the likelihood, which affect both fixed and random effect models." We therefore consider that the Bayesian NMAs should be considered to give the most robust results and do not feel that the frequentist NMA results will add anything to this work.

A18. *Fixed and random effects models were estimated in the network meta-analysis, however only the results of fixed effects were presented. Please provide the results of the random effects model.*

The pairwise difference charts derived from the random effects models for overall survival, progression-free survival and best response are as follows:

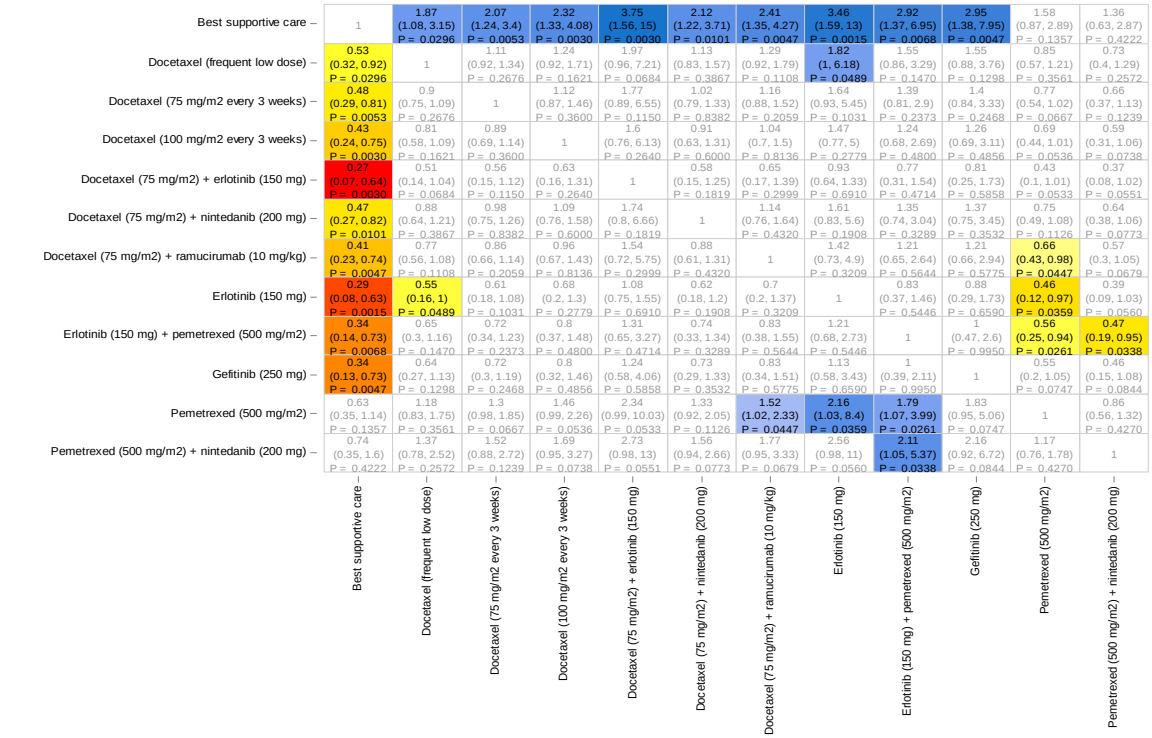
Overall Survival: Hazard Ratios

1) Squamous, EGFR mutation negative



Endpoint: Overall survival; MTC: Random effects; Prediction: Squamous , EGFR -ve; Other covariates: None

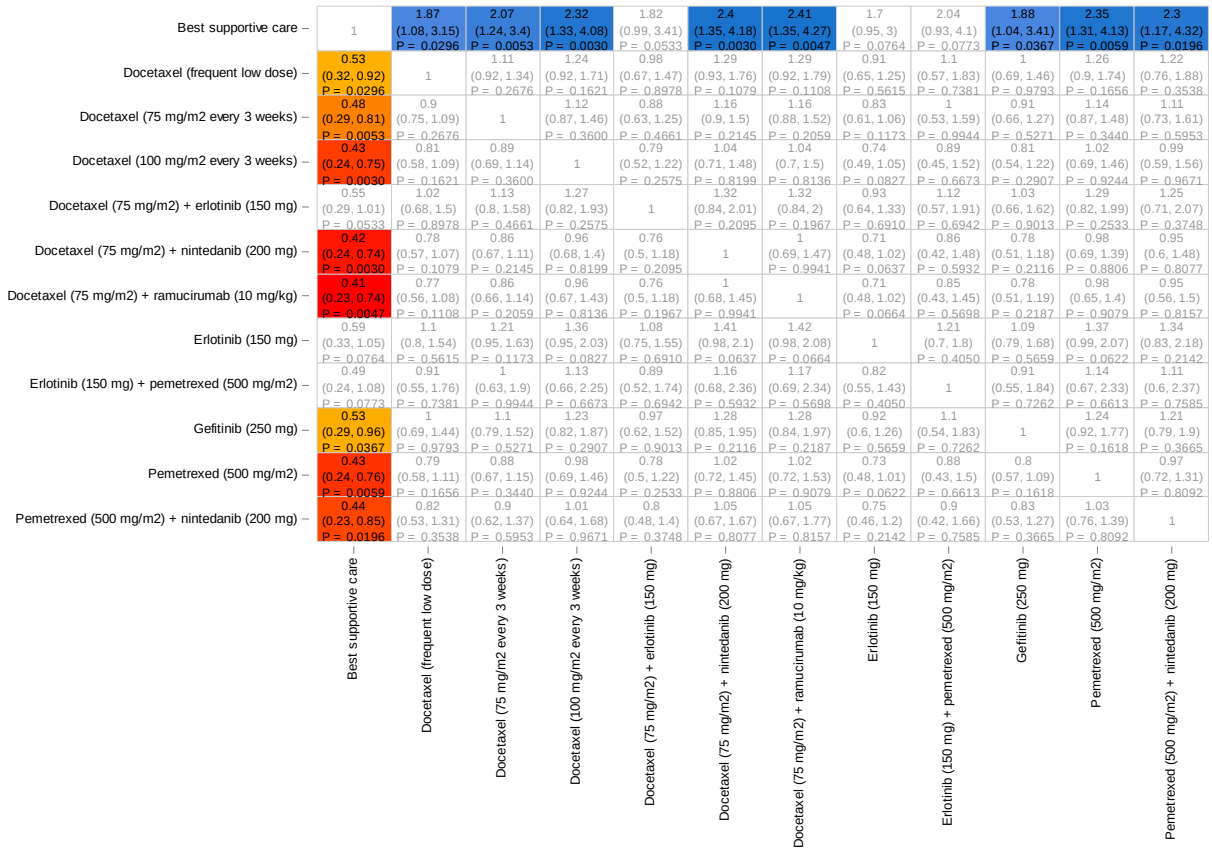
2) Squamous, EGFR mutation positive



	Best supportive care	Docetaxel (frequent low dose)	Docetaxel (75 mg/m2 every 3 weeks)	Docetaxel (100 mg/m2 every 3 weeks)	Docetaxel (75 mg/m2) + erlotinib (150 mg)	Docetaxel (75 mg/m2) + nintedanib (200 mg)	Docetaxel (75 mg/m2) + ramucirumab (10 mg/kg)	Erlotinib (150 mg)	Erlotinib (150 mg) + pemetrexed (500 mg/m2)	Gefitinib (250 mg)	Pemetrexed (500 mg/m2)	Pemetrexed (500 mg/m2) + nintedanib (200 mg)
Best supportive care	1	1.87 (1.08, 3.15) P = 0.0296	2.07 (1.24, 3.4) P = 0.0053	2.32 (1.33, 4.08) P = 0.0030	3.75 (1.56, 15) P = 0.0030	2.12 (1.22, 3.71) P = 0.0101	2.41 (1.35, 4.27) P = 0.0047	3.46 (1.59, 13) P = 0.0015	2.92 (1.37, 6.95) P = 0.0068	2.95 (1.38, 7.95) P = 0.0047	1.58 (0.87, 2.89) P = 0.1357	1.36 (0.63, 2.87) P = 0.4222
Docetaxel (frequent low dose)	0.53 (0.32, 0.92) P = 0.0296	1	1.11 (0.92, 1.34) P = 0.2676	1.24 (0.92, 1.71) P = 0.1621	1.97 (0.96, 7.21) P = 0.0684	1.13 (0.83, 1.57) P = 0.3867	1.29 (0.92, 1.79) P = 0.1108	1.82 (1, 6.18) P = 0.0489	1.55 (0.86, 3.29) P = 0.1470	1.55 (0.88, 3.76) P = 0.1298	0.85 (0.57, 1.21) P = 0.3561	0.73 (0.4, 1.29) P = 0.2572
Docetaxel (75 mg/m2 every 3 weeks)	0.48 (0.29, 0.81) P = 0.0053	0.9 (0.75, 1.09) P = 0.2676	1	1.12 (0.87, 1.46) P = 0.3600	1.77 (0.89, 6.55) P = 0.1150	1.02 (0.79, 1.33) P = 0.8382	1.16 (0.88, 1.52) P = 0.2059	1.64 (0.93, 5.45) P = 0.1031	1.39 (0.81, 2.9) P = 0.2373	1.4 (0.84, 3.33) P = 0.2468	0.77 (0.54, 1.02) P = 0.0667	0.66 (0.37, 1.13) P = 0.1239
Docetaxel (100 mg/m2 every 3 weeks)	0.43 (0.24, 0.75) P = 0.0030	0.81 (0.58, 1.09) P = 0.1621	0.89 (0.69, 1.14) P = 0.3600	1	1.6 (0.76, 6.13) P = 0.2640	0.91 (0.63, 1.31) P = 0.6000	1.04 (0.7, 1.5) P = 0.8136	1.47 (0.77, 5) P = 0.2779	1.24 (0.68, 2.69) P = 0.4800	1.26 (0.69, 3.11) P = 0.4856	0.69 (0.44, 1.01) P = 0.0536	0.59 (0.31, 1.06) P = 0.0738
Docetaxel (75 mg/m2) + erlotinib (150 mg)	0.27 (0.07, 0.64) P = 0.0030	0.51 (0.14, 1.04) P = 0.0684	0.56 (0.15, 1.12) P = 0.1150	0.63 (0.16, 1.31) P = 0.2640	1	0.58 (0.15, 1.25) P = 0.1819	0.65 (0.17, 1.39) P = 0.2999	0.93 (0.64, 1.33) P = 0.6910	0.77 (0.31, 1.54) P = 0.4714	0.81 (0.25, 1.73) P = 0.5858	0.43 (0.1, 1.01) P = 0.0533	0.37 (0.08, 1.02) P = 0.0551
Docetaxel (75 mg/m2) + nintedanib (200 mg)	0.47 (0.27, 0.82) P = 0.0101	0.88 (0.64, 1.21) P = 0.3867	0.98 (0.75, 1.26) P = 0.8382	1.09 (0.76, 1.58) P = 0.6000	1.74 (0.8, 6.66) P = 0.1819	1	1.14 (0.76, 1.64) P = 0.4320	1.61 (0.83, 5.6) P = 0.1908	1.35 (0.74, 3.04) P = 0.3289	1.37 (0.75, 3.45) P = 0.3532	0.75 (0.49, 1.08) P = 0.1126	0.64 (0.38, 1.06) P = 0.0773
Docetaxel (75 mg/m2) + ramucirumab (10 mg/kg)	0.41 (0.23, 0.74) P = 0.0047	0.77 (0.56, 1.08) P = 0.1108	0.86 (0.66, 1.14) P = 0.2059	0.96 (0.67, 1.43) P = 0.8136	1.54 (0.72, 5.75) P = 0.2999	0.88 (0.61, 1.31) P = 0.4320	1	1.42 (0.73, 4.9) P = 0.3209	1.21 (0.65, 2.64) P = 0.5644	1.21 (0.66, 2.94) P = 0.5775	0.66 (0.43, 0.98) P = 0.0447	0.57 (0.3, 1.05) P = 0.0679
Erlotinib (150 mg)	0.29 (0.08, 0.63) P = 0.0015	0.55 (0.16, 1) P = 0.0489	0.61 (0.18, 1.08) P = 0.1031	0.68 (0.2, 1.3) P = 0.2779	1.08 (0.75, 1.55) P = 0.6910	0.62 (0.18, 1.2) P = 0.1908	0.7 (0.2, 1.37) P = 0.3209	1	0.83 (0.37, 1.46) P = 0.5446	0.88 (0.29, 1.73) P = 0.6590	0.46 (0.12, 0.97) P = 0.0359	0.39 (0.09, 1.03) P = 0.0560
Erlotinib (150 mg) + pemetrexed (500 mg/m2)	0.34 (0.14, 0.73) P = 0.0068	0.65 (0.3, 1.16) P = 0.1470	0.72 (0.34, 1.23) P = 0.2373	0.8 (0.37, 1.48) P = 0.4800	1.31 (0.65, 3.27) P = 0.4714	0.74 (0.33, 1.34) P = 0.3289	0.83 (0.38, 1.55) P = 0.5644	1.21 (0.68, 2.73) P = 0.5446	1	1 (0.47, 2.6) P = 0.9950	0.56 (0.25, 0.94) P = 0.0261	0.47 (0.19, 0.95) P = 0.0338
Gefitinib (250 mg)	0.34 (0.13, 0.73) P = 0.0047	0.64 (0.27, 1.13) P = 0.1298	0.72 (0.3, 1.19) P = 0.2468	0.8 (0.32, 1.46) P = 0.4856	1.24 (0.58, 4.06) P = 0.5858	0.73 (0.29, 1.33) P = 0.3532	0.83 (0.34, 1.51) P = 0.5775	1.13 (0.58, 3.43) P = 0.6590	1 (0.39, 2.11) P = 0.9950	1	0.55 (0.2, 1.05) P = 0.0747	0.46 (0.15, 1.08) P = 0.0844
Pemetrexed (500 mg/m2)	0.63 (0.35, 1.14) P = 0.1357	1.18 (0.83, 1.75) P = 0.3561	1.3 (0.98, 1.85) P = 0.0667	1.46 (0.99, 2.26) P = 0.0536	2.34 (0.99, 10.03) P = 0.0533	1.33 (0.92, 2.05) P = 0.1126	1.52 (1.02, 2.33) P = 0.0447	2.16 (1.03, 8.4) P = 0.0359	1.79 (1.07, 3.99) P = 0.0261	1.83 (0.95, 5.06) P = 0.0747	1	0.86 (0.56, 1.32) P = 0.4270
Pemetrexed (500 mg/m2) + nintedanib (200 mg)	0.74 (0.35, 1.6) P = 0.4222	1.37 (0.78, 2.52) P = 0.2572	1.52 (0.88, 2.72) P = 0.1239	1.69 (0.95, 3.27) P = 0.0738	2.73 (0.98, 13) P = 0.0551	1.56 (0.94, 2.66) P = 0.0773	1.77 (0.95, 3.33) P = 0.0679	2.56 (0.98, 11) P = 0.0560	2.11 (1.05, 5.37) P = 0.0338	2.16 (0.92, 6.72) P = 0.0844	1.17 (0.76, 1.78) P = 0.4270	1

Endpoint: Overall survival; MTC: Random effects; Prediction: Squamous , EGFR +ve; Other covariates: None

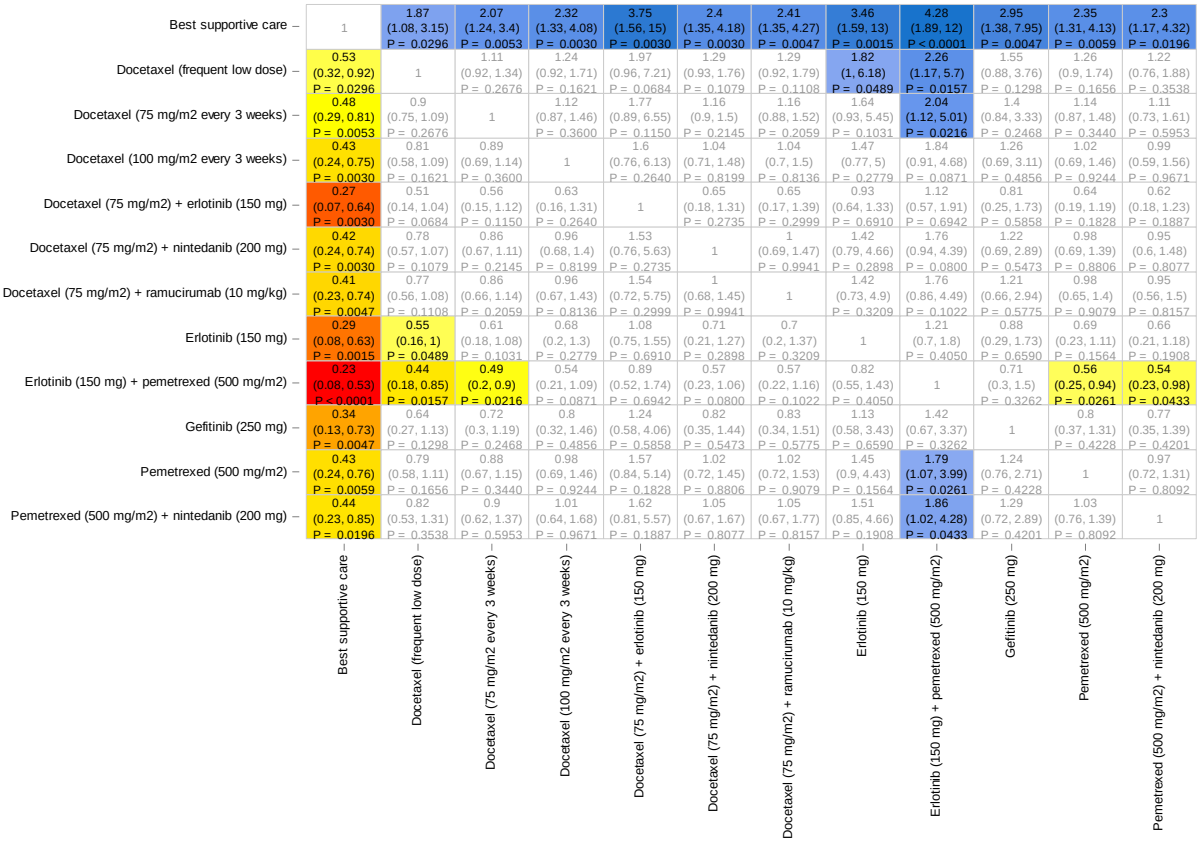
3) Non-squamous, EGFR mutation negative



	Best supportive care	Docetaxel (frequent low dose)	Docetaxel (75 mg/m2 every 3 weeks)	Docetaxel (100 mg/m2 every 3 weeks)	Docetaxel (75 mg/m2) + erlotinib (150 mg)	Docetaxel (75 mg/m2) + nintedanib (200 mg)	Docetaxel (75 mg/m2) + ramucirumab (10 mg/kg)	Erlotinib (150 mg)	Erlotinib (150 mg) + pemetrexed (500 mg/m2)	Gefitinib (250 mg)	Pemetrexed (500 mg/m2)	Pemetrexed (500 mg/m2) + nintedanib (200 mg)
Best supportive care	1	1.87 (1.08, 3.15) P = 0.0296	2.07 (1.24, 3.4) P = 0.0053	2.32 (1.33, 4.08) P = 0.0030	1.82 (0.99, 3.41) P = 0.0533	2.4 (1.35, 4.18) P = 0.0030	2.41 (1.35, 4.27) P = 0.0047	1.7 (0.95, 3) P = 0.0764	2.04 (0.93, 4.1) P = 0.0773	1.88 (1.04, 3.41) P = 0.0367	2.35 (1.31, 4.13) P = 0.0059	2.3 (1.17, 4.32) P = 0.0196
Docetaxel (frequent low dose)	0.53 (0.32, 0.92) P = 0.0296	1	1.11 (0.92, 1.34) P = 0.2676	1.24 (0.92, 1.71) P = 0.1621	0.98 (0.67, 1.47) P = 0.8978	1.29 (0.93, 1.76) P = 0.1079	1.29 (0.92, 1.79) P = 0.1108	0.91 (0.65, 1.25) P = 0.5615	1.1 (0.57, 1.83) P = 0.7381	1 (0.69, 1.46) P = 0.9793	1.26 (0.9, 1.74) P = 0.1656	1.22 (0.76, 1.88) P = 0.3538
Docetaxel (75 mg/m2 every 3 weeks)	0.48 (0.29, 0.81) P = 0.0053	0.9 (0.75, 1.09) P = 0.2676	1	1.12 (0.87, 1.46) P = 0.3600	0.88 (0.63, 1.25) P = 0.4661	1.16 (0.9, 1.5) P = 0.2145	1.16 (0.88, 1.52) P = 0.2059	0.83 (0.61, 1.06) P = 0.1173	1 (0.53, 1.59) P = 0.9944	0.91 (0.66, 1.27) P = 0.5271	1.14 (0.87, 1.48) P = 0.3440	1.11 (0.73, 1.61) P = 0.5953
Docetaxel (100 mg/m2 every 3 weeks)	0.43 (0.24, 0.75) P = 0.0030	0.81 (0.58, 1.09) P = 0.1621	0.89 (0.69, 1.14) P = 0.3600	1	0.79 (0.52, 1.22) P = 0.2575	1.04 (0.71, 1.48) P = 0.8199	1.04 (0.7, 1.5) P = 0.8136	0.74 (0.49, 1.05) P = 0.0827	0.89 (0.45, 1.52) P = 0.6673	0.81 (0.54, 1.22) P = 0.2907	1.02 (0.69, 1.46) P = 0.9244	0.99 (0.59, 1.56) P = 0.9671
Docetaxel (75 mg/m2) + erlotinib (150 mg)	0.55 (0.29, 1.01) P = 0.0533	1.02 (0.68, 1.5) P = 0.8978	1.13 (0.8, 1.58) P = 0.4661	1.27 (0.82, 1.93) P = 0.2575	1	1.32 (0.84, 2.01) P = 0.2095	1.32 (0.84, 2) P = 0.1967	0.93 (0.64, 1.33) P = 0.6910	1.12 (0.57, 1.91) P = 0.6942	1.03 (0.66, 1.62) P = 0.9013	1.29 (0.82, 1.99) P = 0.2533	1.25 (0.71, 2.07) P = 0.3748
Docetaxel (75 mg/m2) + nintedanib (200 mg)	0.42 (0.24, 0.74) P = 0.0030	0.78 (0.57, 1.07) P = 0.1079	0.86 (0.67, 1.11) P = 0.2145	0.96 (0.68, 1.4) P = 0.8199	0.76 (0.5, 1.18) P = 0.2095	1	1 (0.69, 1.47) P = 0.9941	0.71 (0.48, 1.02) P = 0.0637	0.86 (0.42, 1.48) P = 0.5932	0.78 (0.51, 1.18) P = 0.2116	0.98 (0.69, 1.39) P = 0.8806	0.95 (0.6, 1.48) P = 0.8077
Docetaxel (75 mg/m2) + ramucirumab (10 mg/kg)	0.41 (0.23, 0.74) P = 0.0047	0.77 (0.56, 1.08) P = 0.1108	0.86 (0.66, 1.14) P = 0.2059	0.96 (0.67, 1.43) P = 0.8136	0.76 (0.5, 1.18) P = 0.1967	1 (0.68, 1.45) P = 0.9941	1	0.71 (0.48, 1.02) P = 0.0664	0.85 (0.43, 1.45) P = 0.5698	0.78 (0.51, 1.19) P = 0.2187	0.98 (0.65, 1.4) P = 0.9079	0.95 (0.56, 1.5) P = 0.8157
Erlotinib (150 mg)	0.59 (0.33, 1.05) P = 0.0764	1.1 (0.8, 1.54) P = 0.5615	1.21 (0.95, 1.63) P = 0.1173	1.36 (0.95, 2.03) P = 0.0827	1.08 (0.75, 1.55) P = 0.6910	1.41 (0.98, 2.1) P = 0.0637	1.42 (0.98, 2.08) P = 0.0664	1	1.21 (0.7, 1.8) P = 0.4050	1.09 (0.79, 1.68) P = 0.5659	1.37 (0.99, 2.07) P = 0.0622	1.34 (0.83, 2.18) P = 0.2142
Erlotinib (150 mg) + pemetrexed (500 mg/m2)	0.49 (0.24, 1.08) P = 0.0773	0.91 (0.55, 1.76) P = 0.7381	1 (0.63, 1.9) P = 0.9944	1.13 (0.66, 2.25) P = 0.6673	0.89 (0.52, 1.74) P = 0.6942	1.16 (0.68, 2.36) P = 0.5932	1.17 (0.69, 2.34) P = 0.5698	0.82 (0.55, 1.43) P = 0.4050	1	0.91 (0.55, 1.84) P = 0.7262	1.14 (0.67, 2.33) P = 0.6613	1.11 (0.6, 2.37) P = 0.7585
Gefitinib (250 mg)	0.53 (0.29, 0.96) P = 0.0367	1 (0.69, 1.44) P = 0.9793	1.1 (0.79, 1.52) P = 0.5271	1.23 (0.82, 1.87) P = 0.2907	0.97 (0.62, 1.52) P = 0.9013	1.28 (0.85, 1.95) P = 0.2116	1.28 (0.84, 1.97) P = 0.2187	0.92 (0.6, 1.26) P = 0.5659	1.1 (0.54, 1.83) P = 0.7262	1	1.24 (0.92, 1.77) P = 0.1618	1.21 (0.79, 1.9) P = 0.3665
Pemetrexed (500 mg/m2)	0.43 (0.24, 0.76) P = 0.0059	0.79 (0.58, 1.11) P = 0.1656	0.88 (0.67, 1.15) P = 0.3440	0.98 (0.69, 1.46) P = 0.9244	0.78 (0.5, 1.22) P = 0.2533	1.02 (0.72, 1.45) P = 0.8806	1.02 (0.72, 1.53) P = 0.9079	0.73 (0.48, 1.01) P = 0.0622	0.88 (0.43, 1.5) P = 0.6613	0.8 (0.57, 1.09) P = 0.1618	1	0.97 (0.72, 1.31) P = 0.8092
Pemetrexed (500 mg/m2) + nintedanib (200 mg)	0.44 (0.23, 0.85) P = 0.0196	0.82 (0.53, 1.31) P = 0.3538	0.9 (0.62, 1.37) P = 0.5953	1.01 (0.64, 1.68) P = 0.9671	0.8 (0.48, 1.4) P = 0.3748	1.05 (0.67, 1.67) P = 0.8077	1.05 (0.67, 1.77) P = 0.8157	0.75 (0.46, 1.2) P = 0.2142	0.9 (0.42, 1.66) P = 0.7585	0.83 (0.53, 1.27) P = 0.3665	1.03 (0.76, 1.39) P = 0.8092	1

Endpoint: Overall survival; MTC: Random effects; Prediction: Non-squamous , EGFR -ve; Other covariates: None

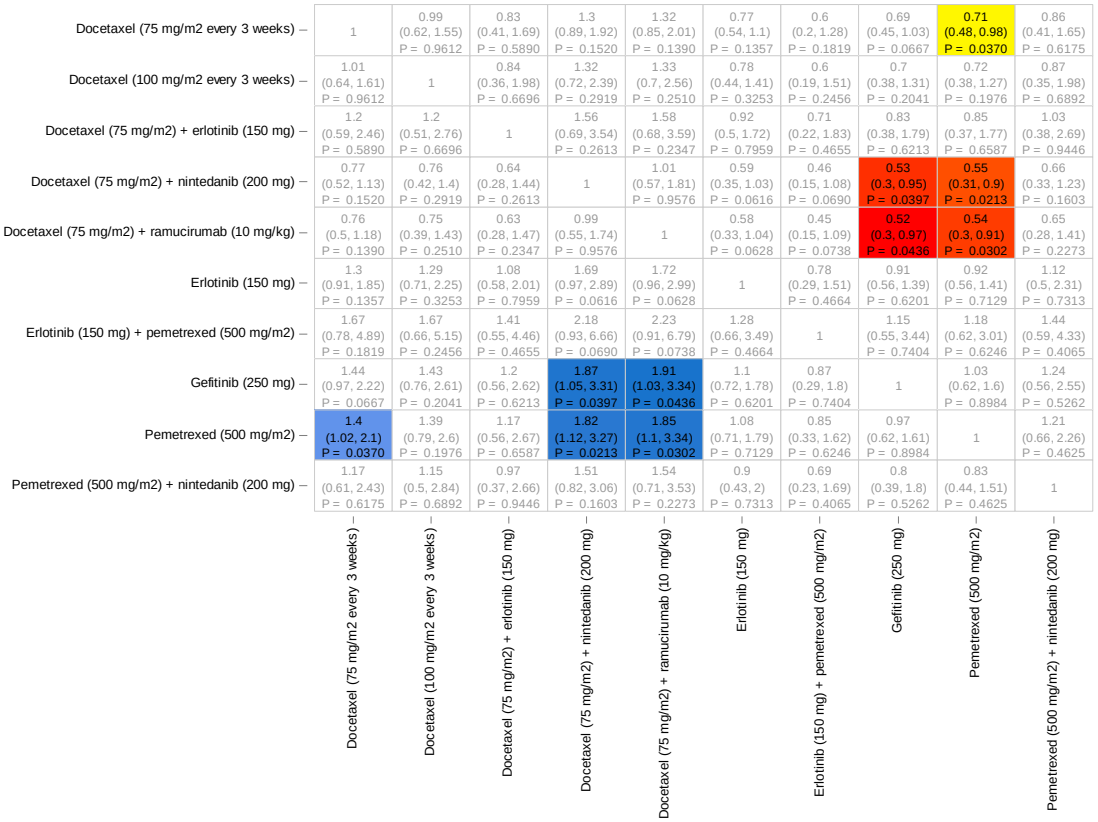
4) Non-squamous, EGFR mutation positive



Endpoint: Overall survival; MTC: Random effects; Prediction: Non-squamous , EGFR +ve; Other covariates: None

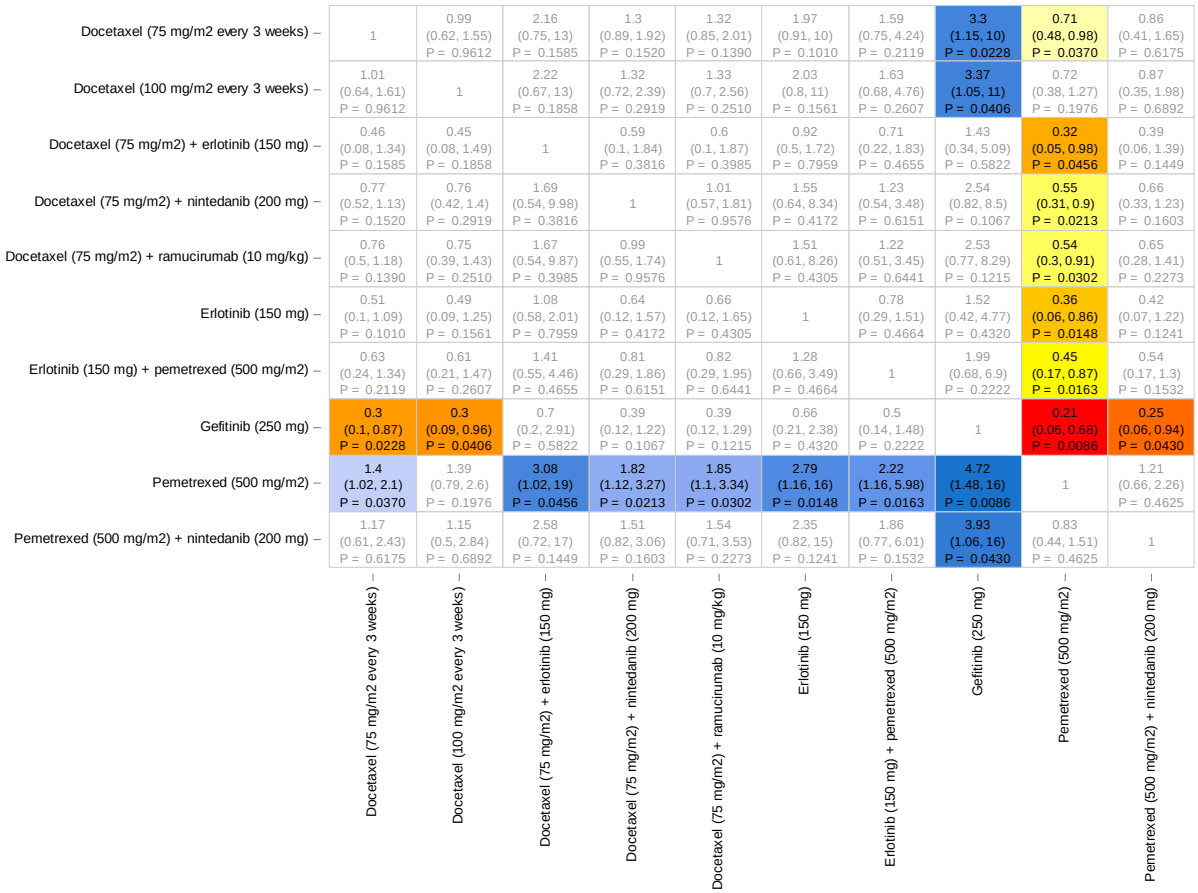
Progression-free Survival: Hazard Ratios

1) Squamous, EGFR mutation negative



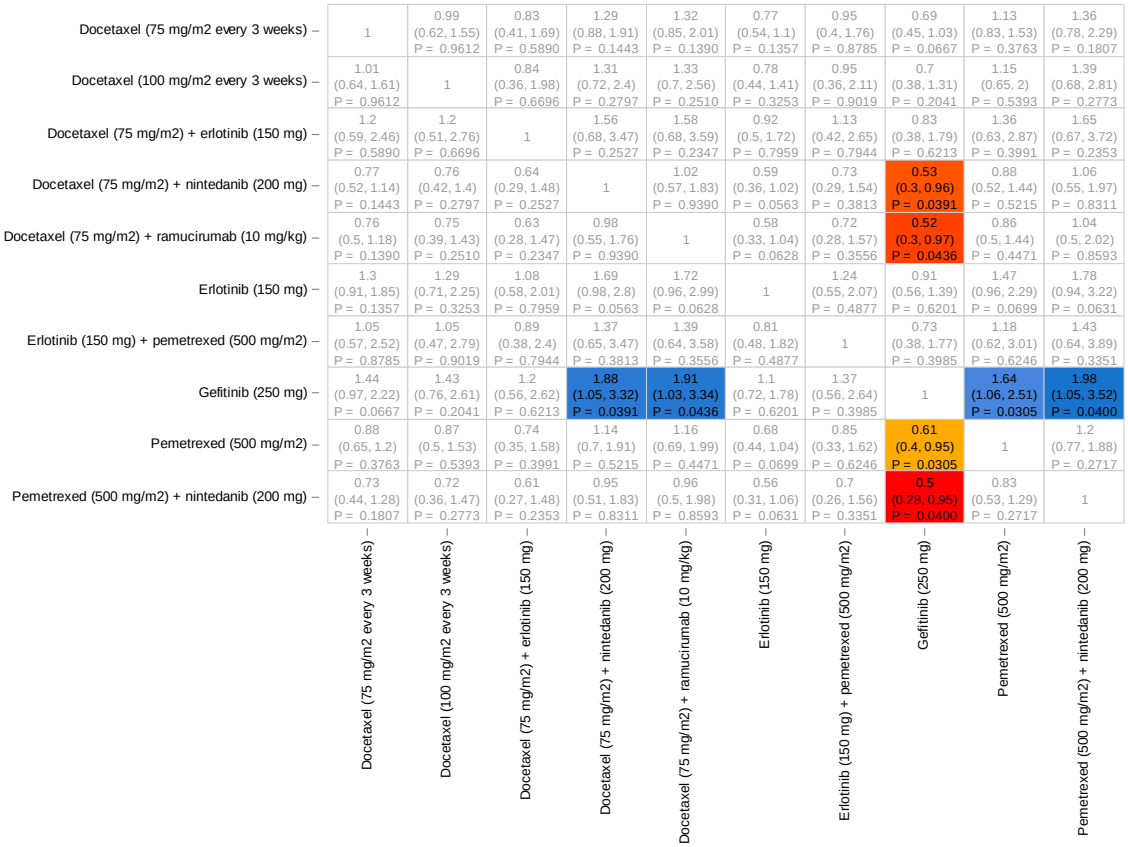
Endpoint: Progression free survival; MTC: Random effects; Prediction: Squamous , EGFR -ve; Other covariates: None

2) Squamous, EGFR mutation positive



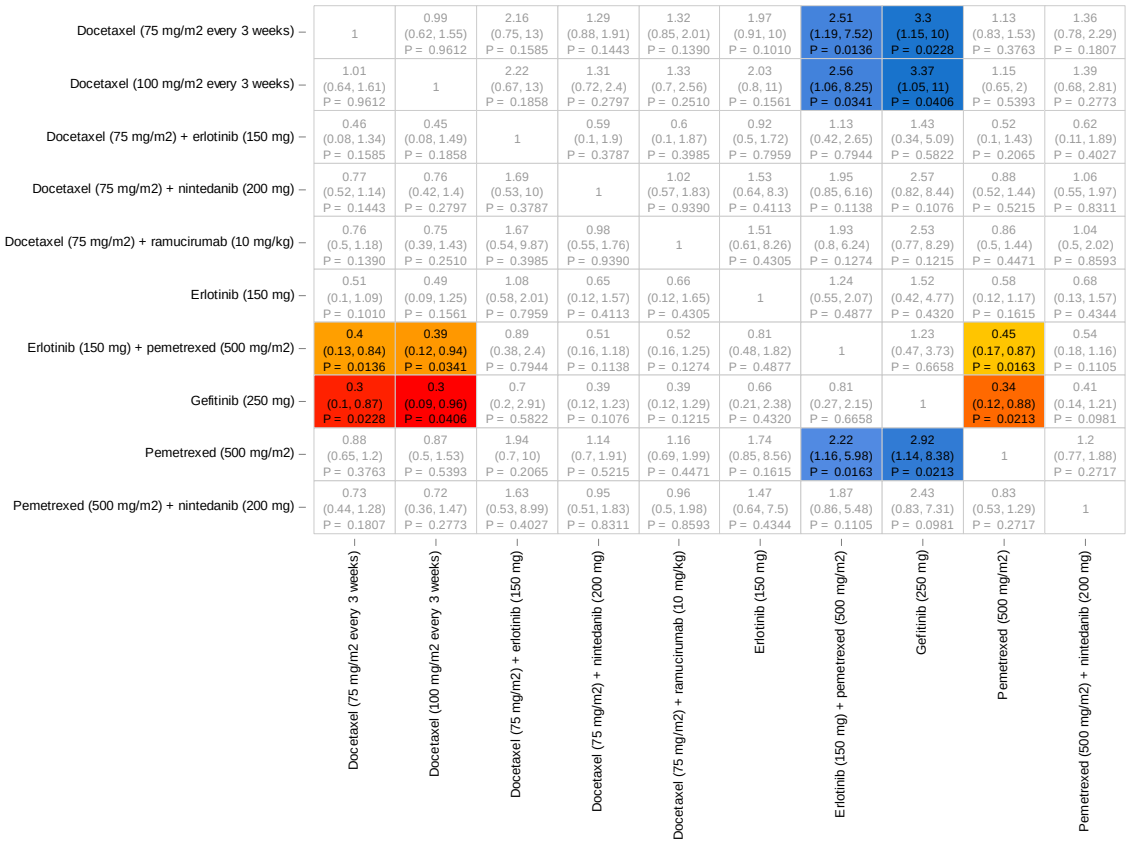
Endpoint: Progression free survival; MTC: Random effects; Prediction: Squamous , EGFR +ve; Other covariates: None

3) Non-squamous, EGFR mutation negative



Endpoint: Progression free survival; MTC: Random effects; Prediction: Non-squamous , EGFR -ve; Other covariates: None

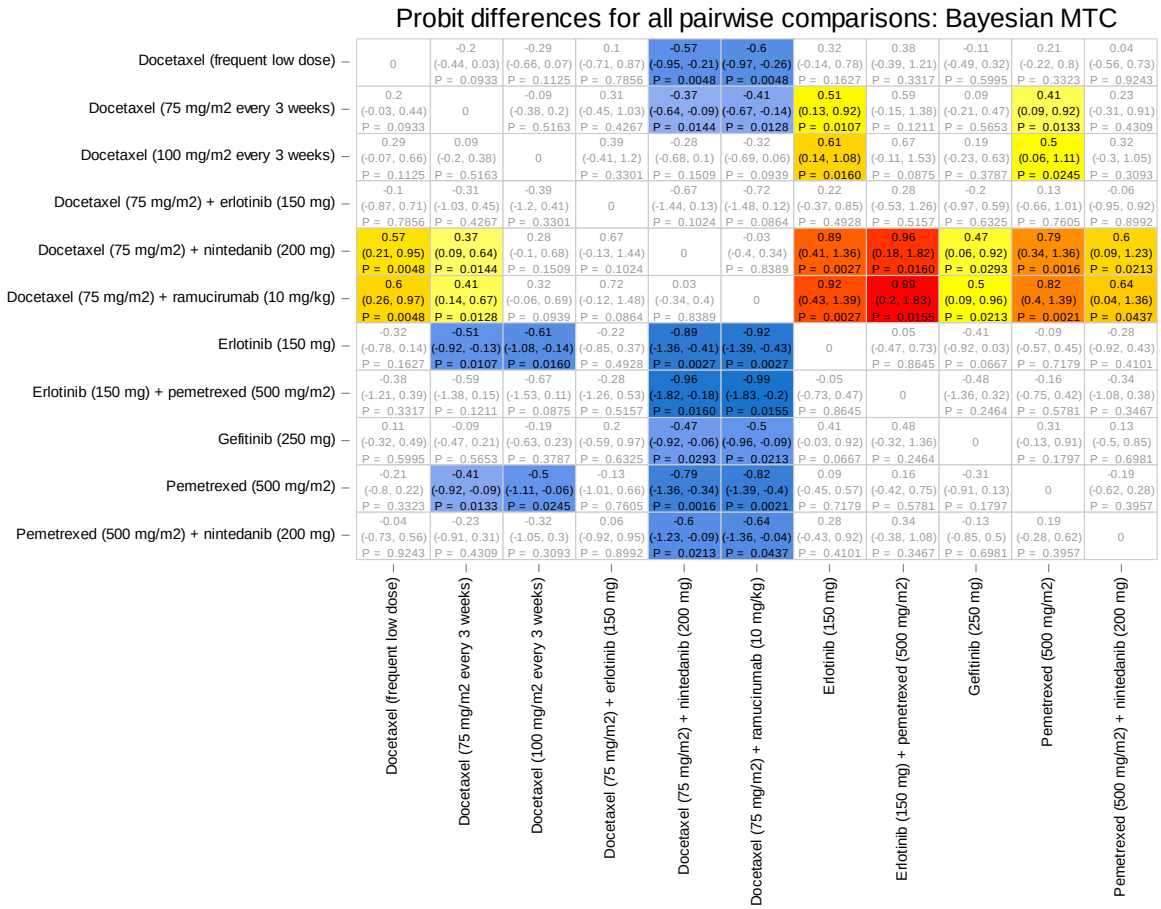
4) Non-squamous, EGFR mutation positive



Endpoint: Progression free survival; MTC: Random effects; Prediction: Non-squamous , EGFR +ve; Other covariates: None

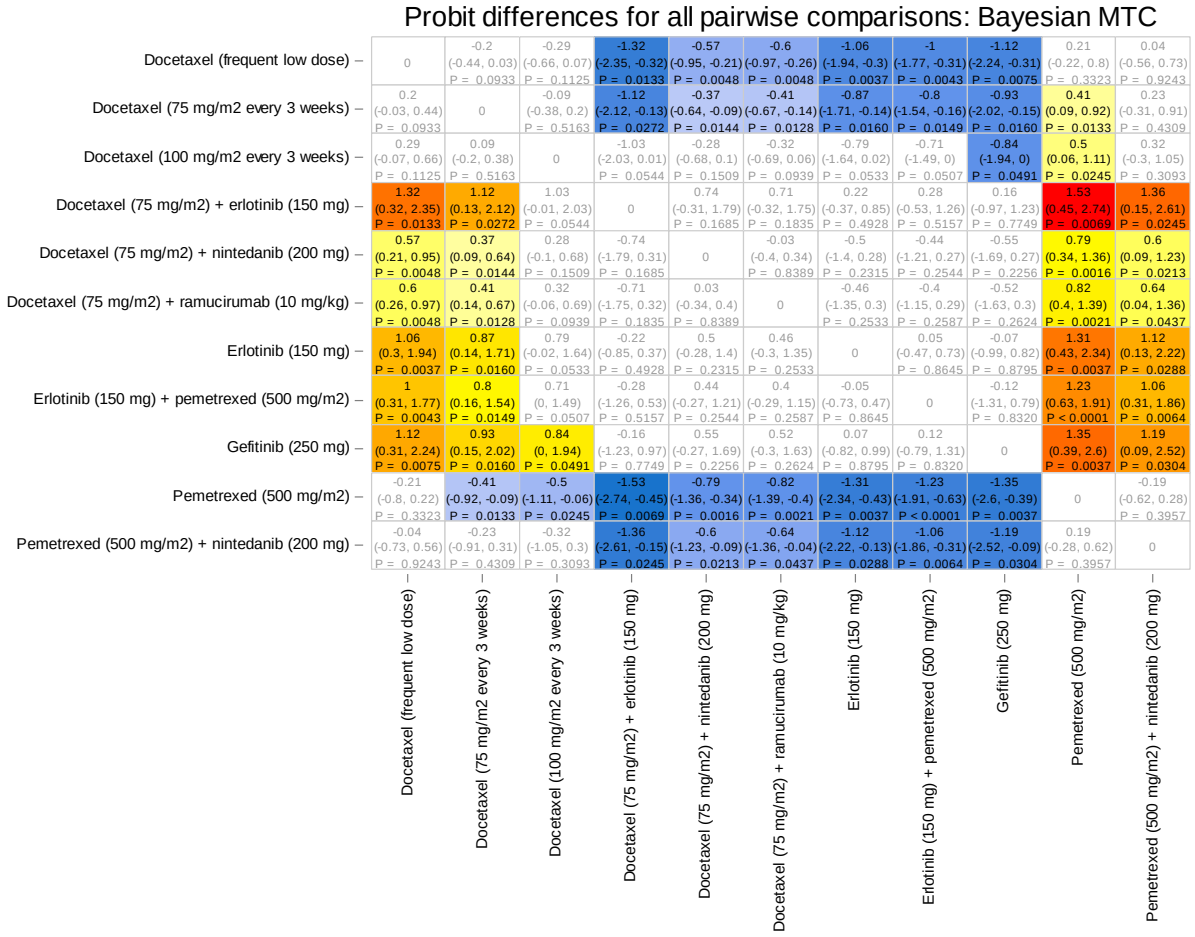
Best Response: Probit differences

1) Squamous, EGFR mutation negative



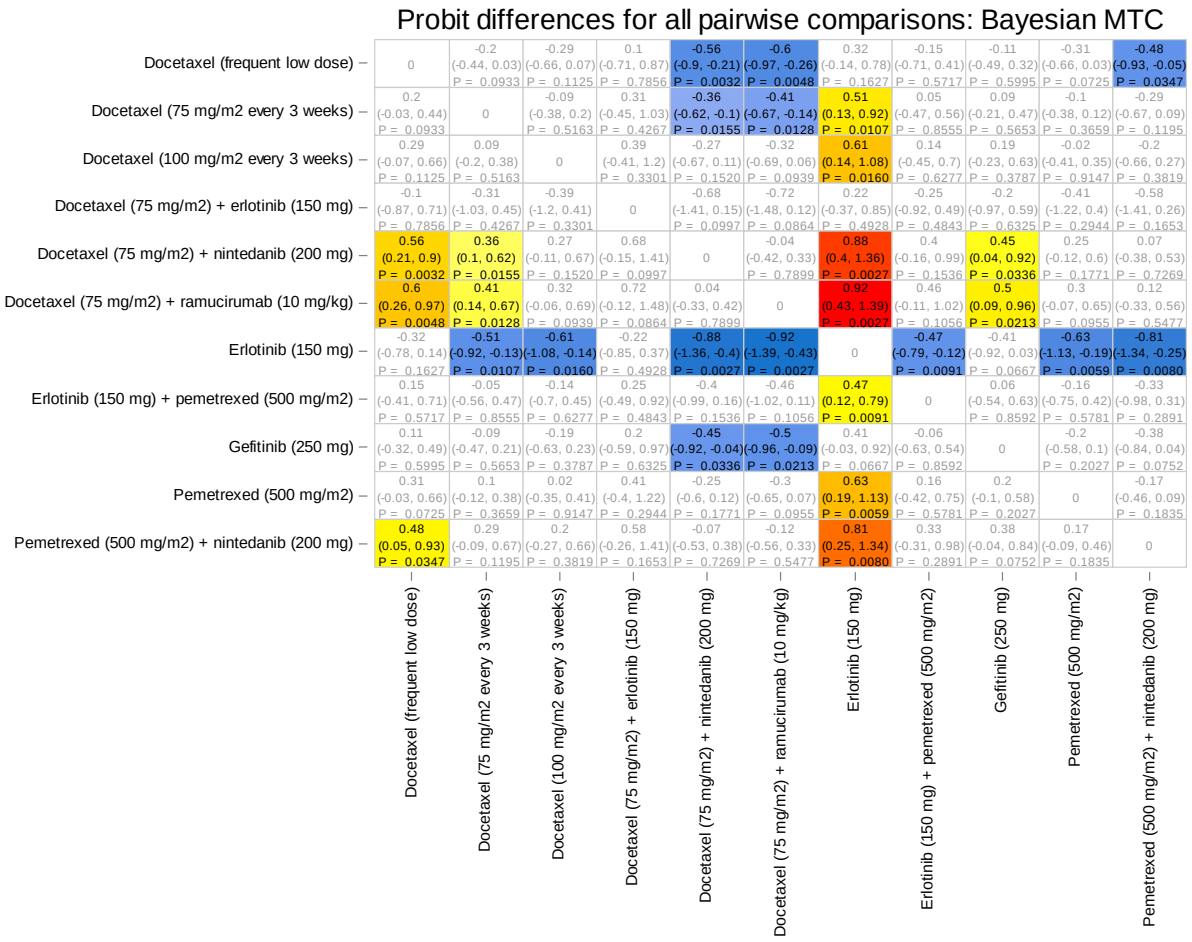
Endpoint: Disease status; MTC: Random effects; Prediction: Squamous , EGFR -ve; Other covariates: None

2) Squamous, EGFR mutation positive



Endpoint: Disease status; MTC: Random effects; Prediction: Squamous , EGFR +ve; Other covariates: None

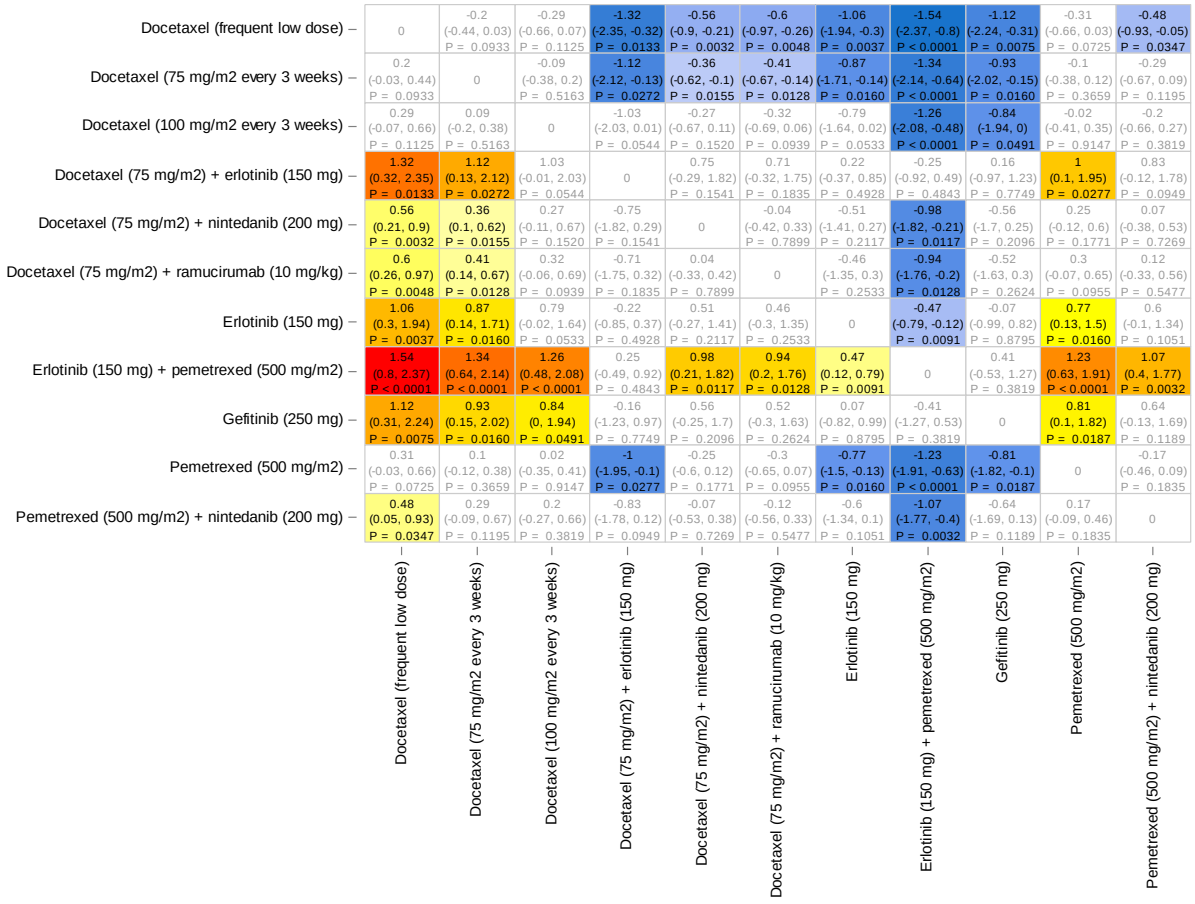
3) Non-squamous, EGFR mutation negative



Endpoint: Disease status; MTC: Random effects; Prediction: Non-squamous , EGFR -ve; Other covariates: None

4) Non-squamous, EGFR mutation positive

Probit differences for all pairwise comparisons: Bayesian MTC



Endpoint: Disease status; MTC: Random effects; Prediction: Non-squamous , EGFR +ve; Other covariates: None

A19. *In the company submission (table 29, page 80) an excluded study of pemetrexed + erlotinib compared with pemetrexed is detailed but this appears to meet the network criteria for tier 1. Please explain the reason for this exclusion.*

Table 29 presents results from the updated search for SLR and no data from any of the detailed studies has been included in the original NMA. The new studies identified were not relevant for informing the relative efficacy of the comparators identified in the decision problem presented in this submission as stated on page 79 of the submission.

A20. *As gefitinib findings were the only tier 2 data included in the network meta-analysis, it would be helpful to understand the effects of this evidence on the network meta-analysis. Please provide a sensitivity analysis excluding this data from the network?*

Gefitinib should have been included in tier 1. We had a meeting with a statistics expert from Leicester University who advised us that gefitinib should be included in the network because it was included in previously published NMAs and adds a closed loop to the network which would make the NMA more robust. We therefore don't see that excluding key studies from the NMA will help in assessing the NMA. If the gefitinib studies are removed and a difference is observed we would suggest that the

NMA that includes all the evidence should be used. We feel that removing the gefitinib studies from the network will only make the results less robust.

A21. *The addition of the data for the other tier 2 interventions should provide more evidence and help reduce uncertainty. Please provide an additional sensitivity analysis to allow an assessment of all the tier 2 evidence and comparators?*

These studies only add appendages to the network. They don't add any duplicate comparisons or closed loops. So although inclusion of these other tier 2 studies will make it possible to estimate other treatments which are not standard therapies they won't add to the robustness of the network or provide additional information to estimate heterogeneity in the random effects model. We therefore don't have a reason to suspect this will impact the NMA or warrant the need for sensitivity analyses.

A22. *The company submission states that the network meta-analysis, incorporating meta-regression, was estimated to account for potentially influential covariates. Please provide these results?*

The following covariates were included to the hierarchical exchangeable fixed effects model that included EGFR mutation status and histology: mean age, publication date, proportion stage IV, proportion ECOG ≥1 and proportion of Asian patients. The DIC scores of these NMAs are presented below, as well as those for no covariates and no hierarchical exchangeable structure and also just the hierarchical exchangeable structures alone for fixed and random effects models.

Table H-1. Model-Fit Statistics: All Patients (OS)

Covariate	DIC	Parameter	Median	Lower 95 cr	Lower 95 cr
FE - No covariates	9.3				
RE - No covariates	7.5	sd	0.205	0.073	0.367
FE - Exchangeable model	-8.1				
RE - Exchangeable model	-6.6	sd	0.091	0.005	0.225
FE - Exchangeable model + Age	-5.0	beta	0.008	-0.044	0.056
FE - Exchangeable model + Publication date	-5.5	beta	0.056	-0.523	0.579
FE - Exchangeable model + Asian	-6.1	beta	-0.205	-0.672	0.257
FE - Exchangeable model + ECOG ≥ 1	-5.7	beta	-0.160	-1.360	1.112
FE - Exchangeable model + STAGE IV	-8.2	beta	-0.620	-1.414	0.153

Table I-1.Model-Fit Statistics: All Patients (PFS)

Covariate	DIC	Parameter	Median	Lower 95 cr	Lower 95 cr
FE - No covariates	21.5				
RE - No covariates	2.9	sd	0.302	0.157	0.524
FE - Exchangeable model	-3.1				
RE - Exchangeable model	-3.0	sd	0.154	0.007	0.451
FE - Exchangeable model + Age	-4.4	beta	0.044	-0.022	0.109
FE - Exchangeable model + Publication date	-1.3	beta	-0.006	-0.051	0.041

Covariate	DIC	Parameter	Median	Lower 95 cr	Lower 95 cr
FE - Exchangeable model + Asian	-2.1	beta	-0.193	-0.737	0.338
FE - Exchangeable model + ECOG ≥ 1	-4.8	beta	-1.307	-3.317	0.803
FE - Exchangeable model + STAGE IV	-5.2	beta	-1.509	-3.923	0.538

Table J-1. Model-Fit Statistics: All Patients (ORR)

Covariate	DIC	Parameter	Median	Lower 95 cr	Upper 95 cr
FE - No covariates	769.3				
RE - No covariates	772.0	SD	0.193	0.024	0.431
FE - Exchangeable model	761.8				
RE - Exchangeable model	762.2	SD	0.086	0.004	0.256
FE - Exchangeable model + Age	763.7	beta	-0.169	-1.050	0.505
FE - Exchangeable model + Publication date	762.2	beta	-0.324	-1.060	0.368
FE - Exchangeable model + Asian	762.9	beta	-0.450	-0.891	0.110
FE - Exchangeable model + ECOG ≥ 1	763.1	beta	-0.287	-1.399	0.559
FE - Exchangeable model + STAGE IV	764.6	beta	0.126	-0.516	0.738

cr = credible interval; ECOG = Eastern Cooperative Oncology Group; FE = fixed effects; RE = random effects; SD = standard deviation.

A23. *In the statistical analyses section of the company submission (page 82) describes a 'full set of inconsistency analyses' that were undertaken. Please clarify what these were. We also note that issues of heterogeneity are included, however direct and indirect outcomes do not appear to be reported for those in the closed loops so please provide these.*

The following analyses were performed that investigated heterogeneity/inconsistency.

- Higgin's I^2 to give the proportion of variance that could be explained by heterogeneity/inconsistency
- Cochran's Q to give an overall significance test for heterogeneity/inconsistency
- Meta-analyses of all duplicate comparisons and decomposition of Conchran's Q for these comparisons
- Node-splitting

- Experimental version of node-splitting

Direct results are reported below (meta-analyses for duplicate comparisons). Indirect analyses such as separate Bucher tests are likely to be uninformative. Node-splitting is far more informative. The experimental node-splitting analyses presented below also gave the results of these closed loops and the heterogeneity values for them. Bucher tests do not provide any further information than that presented using the experimental node-splitting technique. These results have shown a high degree of inconsistency which can be explained by the treatment covariate interactions. However, the evidence for these interaction effects could not be tested for in the NMA due to the limited amount of information available which caused confounding errors in the NMA when standard meta-regression techniques were applied. The choice to include the interaction effects as hierarchical exchangeable effects mainly came from external data sources which are listed below.

Pemetrexed and Histology (Scaglitotti et al. (2009) was in the network of evidence)

- Kubota K, Niho S, Enatsu S, Nambu Y, et al. Efficacy differences of pemetrexed by histology in pretreated patients with stage IIIB/IV non-small cell lung cancer. J Thorac Oncol. 2009;4(12):1530-6.

- Scagliotti G, Hanna N, Fossela, Sugarman K, et al. The differential efficacy of pemetrexed accordinf to NSCLC histology: a revew of two phase III studies. The Oncologist. 2009;14:253-63.

Erlotininb and gefitnib with EGFR mutation status (Sun et al. (2012) was in the network of evidence)

- Lim SH, Lee JY, Sun JM, Ahn JS, Park K, Ahn MJ. Comparison of clinical outcomes following gefitinib and erlotinib treatment in non–small-cell lung cancer patients harboring an epidermal growth factor receptor mutation in either exon 19 or 21. J Thorac Oncol. 2014;9:506-11.

- Sun JM, Lee KH, Kim SW, Lee DH, Min YJ, Yun HJ, et al. Gefitinib versus pemetrexed as second-line treatment in patients with nonsmall cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01): an open-label, phase 3 trial. Cancer. 2012 Dec 15;118(24):6234-42.

- Wang F, Fu S, Zhou Y-B, Zhang X, Zhang X, Xue C, et al. High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR. J Trans Med. 2013;11:90:1-10.

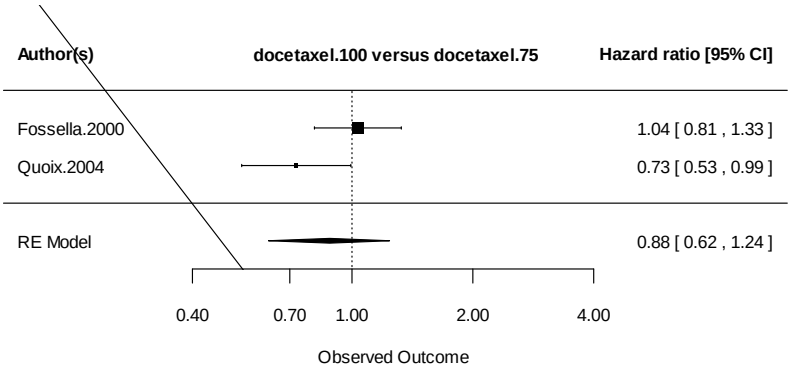
We had a discussion with a statistics expert from Leicester University on how these interactions effects could be modelled in the NMA. Alternative methods were discussed such as fitting meta-regression models with informative priors based on the information in the publications above. However, Keith Abrams considered that this was not yet an accepted method and preferred that we tried the hierarchical exchangeable approach.

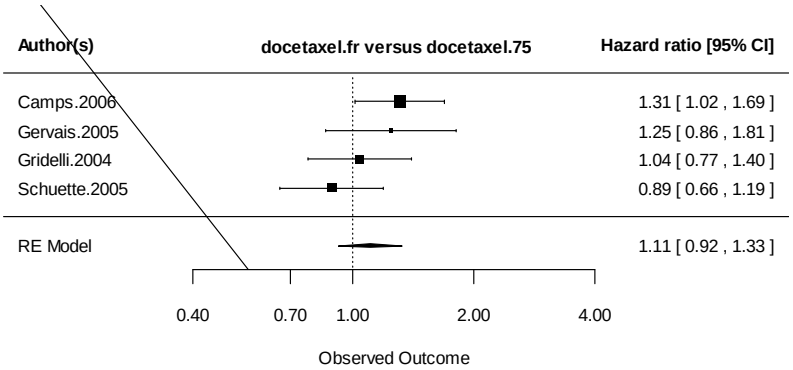
Table H-2. Exploring Heterogeneity: All Patients (OS)

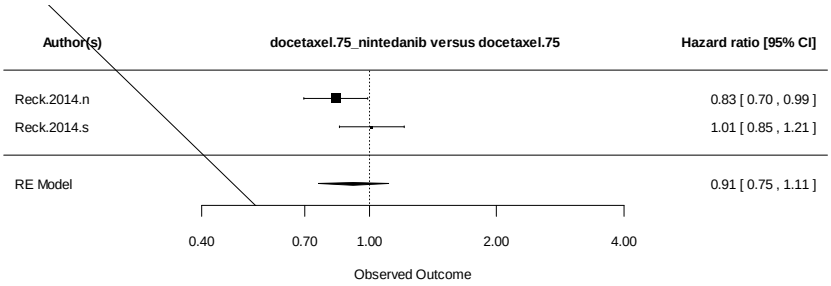
Treatment 1	Treatment 2	df	Q	*P* Value
Overall		14	30.49	0.0065
Docetaxel 100 mg/m^2 every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks	1	3.04	0.0812

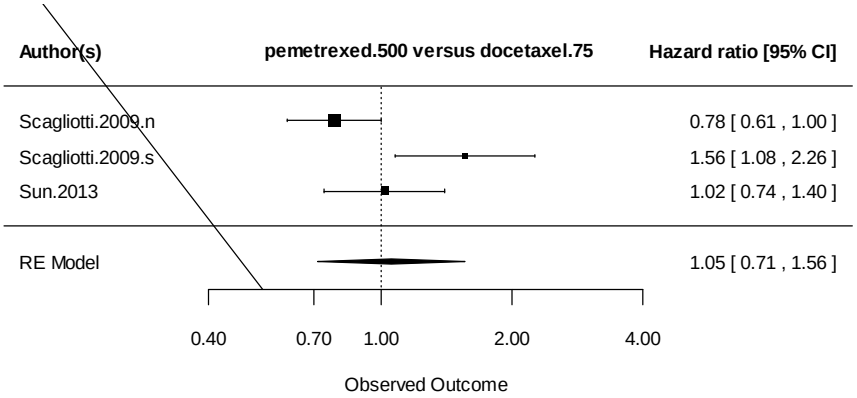
Treatment 1	Treatment 2	df	Q	*P* Value
Docetaxel frequent low dose	Docetaxel 75 mg/m^2 every 3 weeks	3	4.42	0.2197
Docetaxel 75 mg/m^2 every 3 weeks + nintedanib 200 mg	Docetaxel 75 mg/m^2 every 3 weeks	1	2.42	0.1199
Pemetrexed 500 mg	Docetaxel 75 mg/m^2 every 3 weeks	3	9.43	0.0090
Erlotinib 150 mg + pemetrexed 500 mg	Erlotinib 150 mg	1	1.25	0.2639
Pemetrexed 500 mg	Erlotinib 150 mg	2	5.61	0.0605
Pemetrexed 500 mg	Gefitinib 250 mg	2	3.47	0.1766

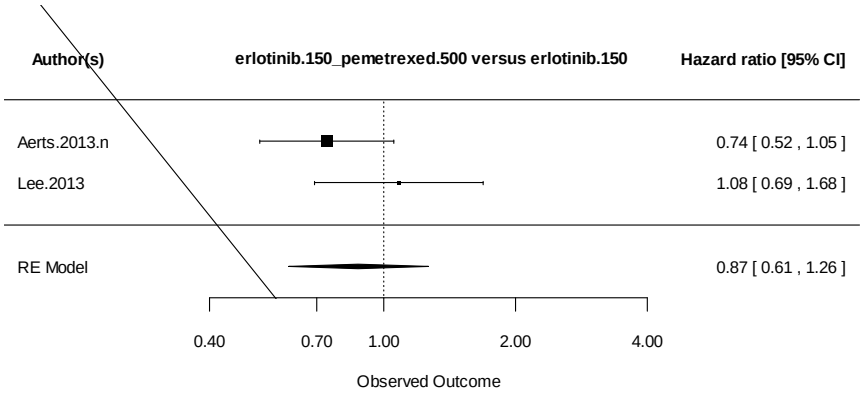
Figure H-1. Pairwise Meta-Analysis Where Duplicate Comparisons Exist: All Patients (OS)

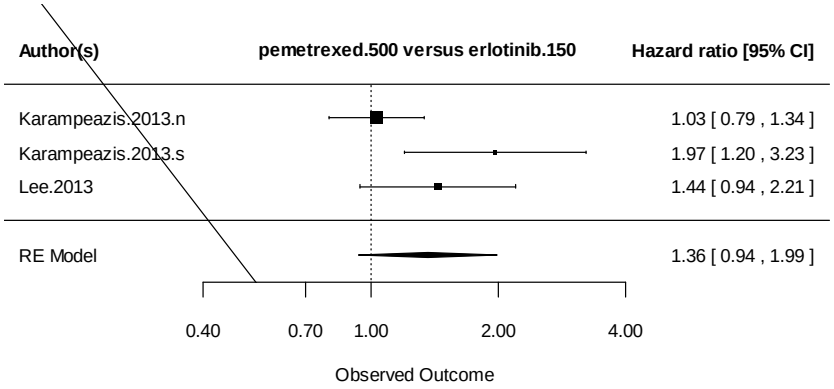





Author(s)
docetaxel.75_nintedanib versus docetaxel.75
Hazard ratio [95% CI]
Reck.2014.n
0.83 [0.70 , 0.99]
Reck.2014.s
1.01 [0.85 , 1.21]
RE Model
0.91 [0.75 , 1.11]
0.40
0.70
1.00
2.00
4.00
Observed Outcome


Author(s)
pemetrexed.500 versus docetaxel.75
Hazard ratio [95% CI]
Scagliotti.2009.n
0.78 [0.61 , 1.00]
Scagliotti.2009.s
1.56 [1.08 , 2.26]
Sun.2013
1.02 [0.74 , 1.40]
RE Model
1.05 [0.71 , 1.56]
0.40
0.70
1.00
2.00
4.00
Observed Outcome


Author(s)
erlotinib.150_pemetrexed.500 versus erlotinib.150
Hazard ratio [95% CI]
Aerts.2013.n
0.74 [0.52 , 1.05]
Lee.2013
1.08 [0.69 , 1.68]
RE Model
0.87 [0.61 , 1.26]
0.40
0.70
1.00
2.00
4.00
Observed Outcome


Author(s)
pemetrexed.500 versus erlotinib.150
Hazard ratio [95% CI]
Karampeazis.2013.n
1.03 [0.79 , 1.34]
Karampeazis.2013.s
1.97 [1.20 , 3.23]
Lee.2013
1.44 [0.94 , 2.21]
RE Model
1.36 [0.94 , 1.99]
0.40
0.70
1.00
2.00
4.00
Observed Outcome

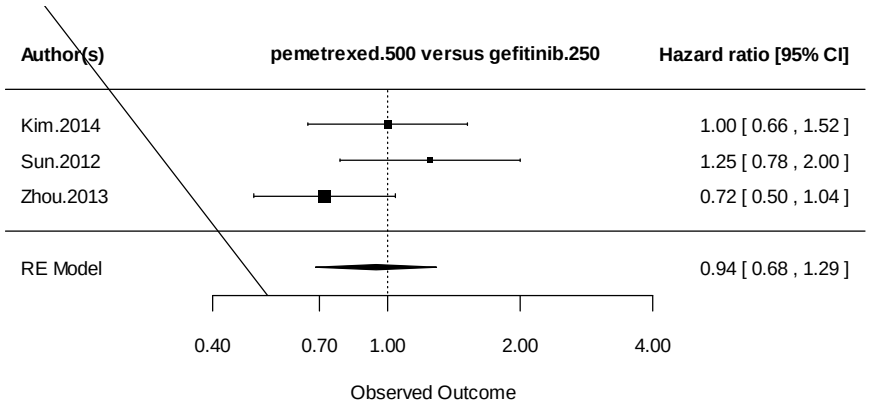

Author(s)
pemetrexed.500 versus gefitinib.250
Hazard ratio [95% CI]
Kim.2014
1.00 [0.66 , 1.52]
Sun.2012
1.25 [0.78 , 2.00]
Zhou.2013
0.72 [0.50 , 1.04]
RE Model
0.94 [0.68 , 1.29]
0.40
0.70
1.00
2.00
4.00
Observed Outcome

Figure H-2. Node-Splitting: Continuous Model Based on Log Hazard Ratios: All Patients (OS)

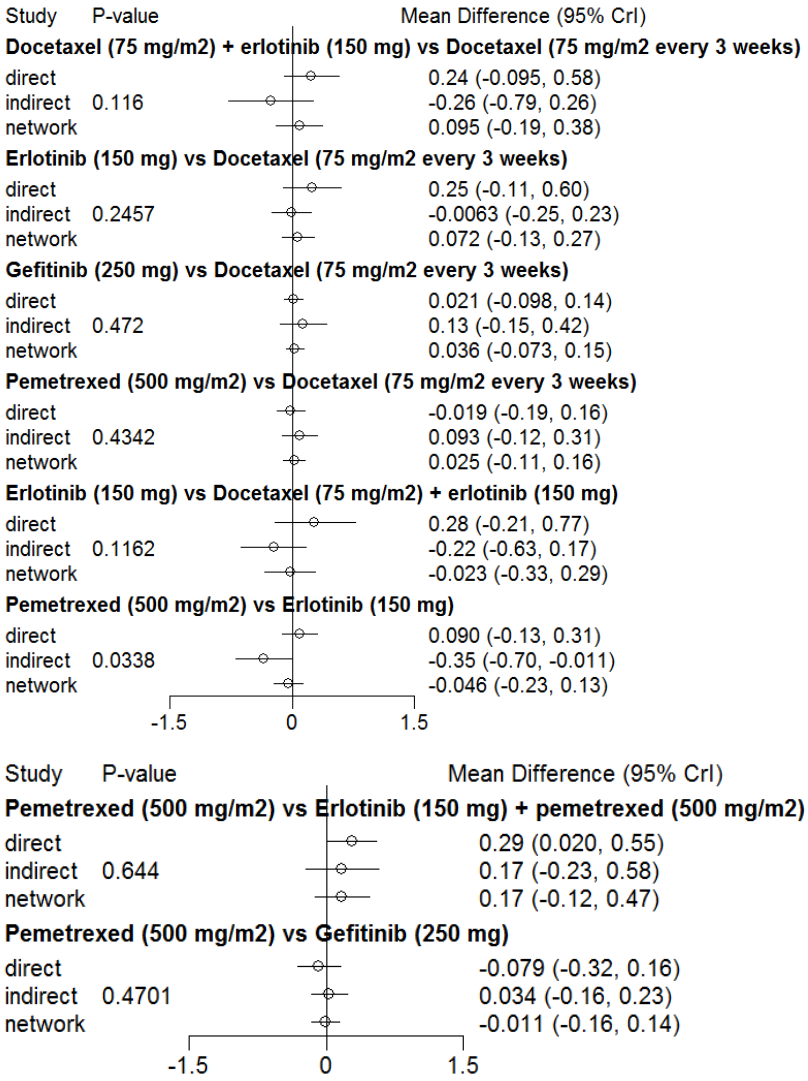


Figure H-3. Node-Splitting: Continuous Model Based on Log Hazard Ratios: All Patients (OS)

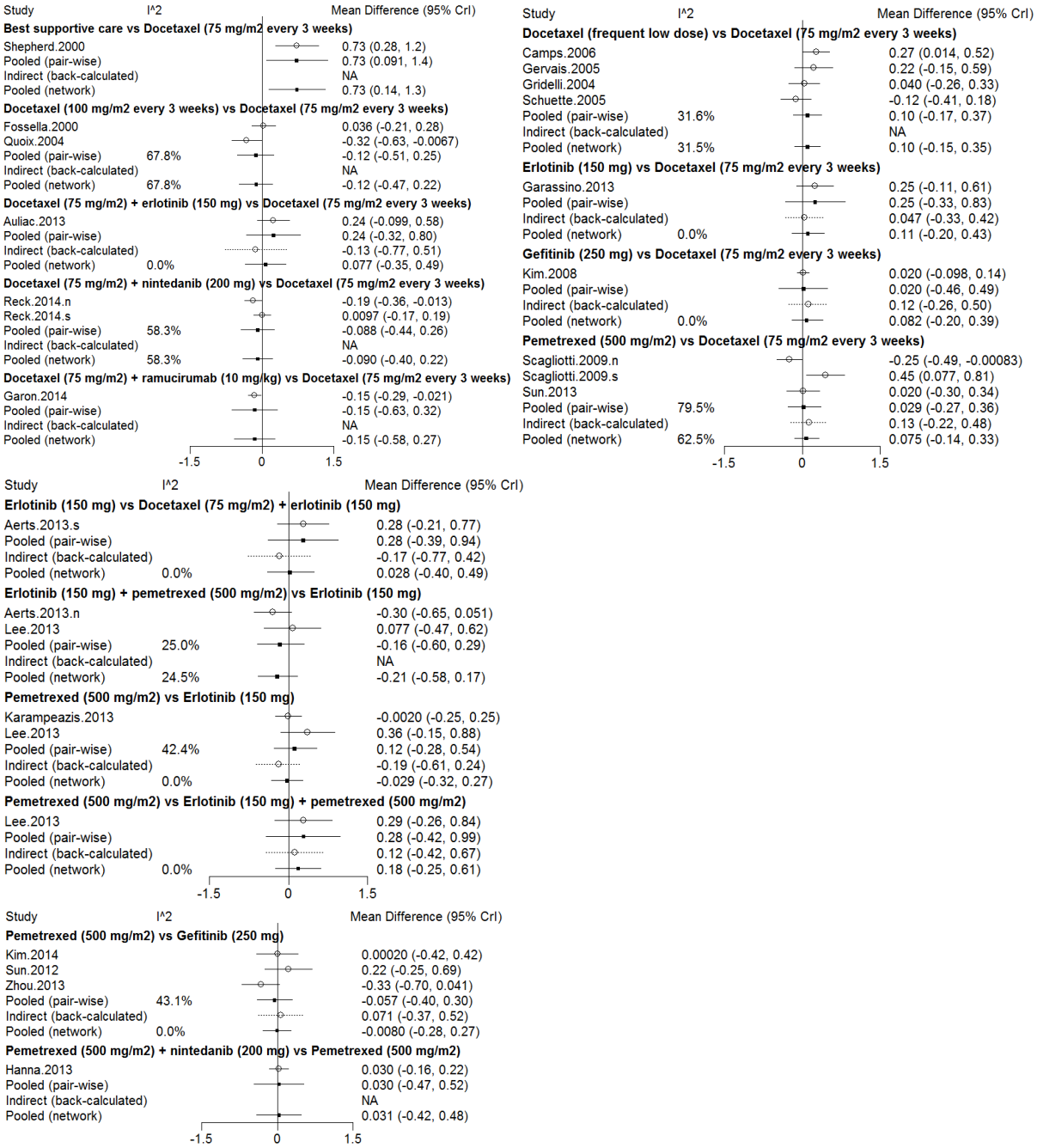
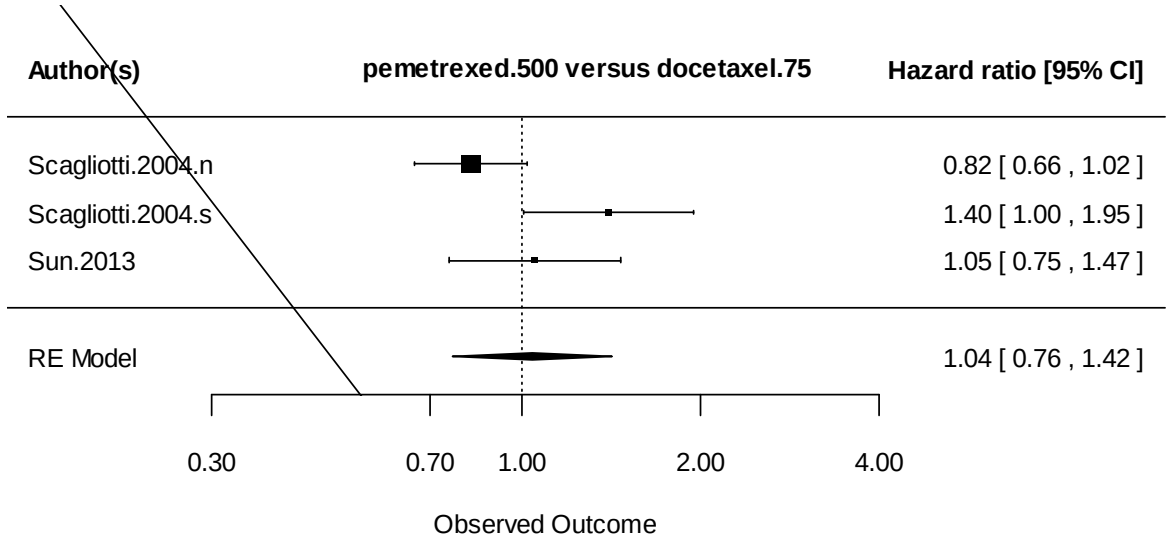


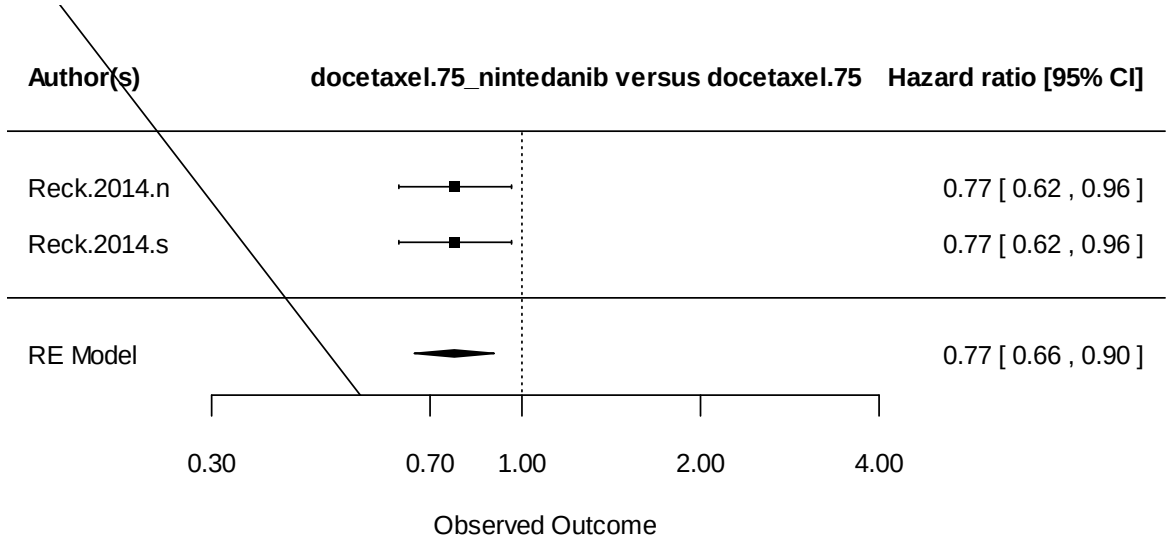
Table I-2. Exploring Heterogeneity: All Patients (PFS)

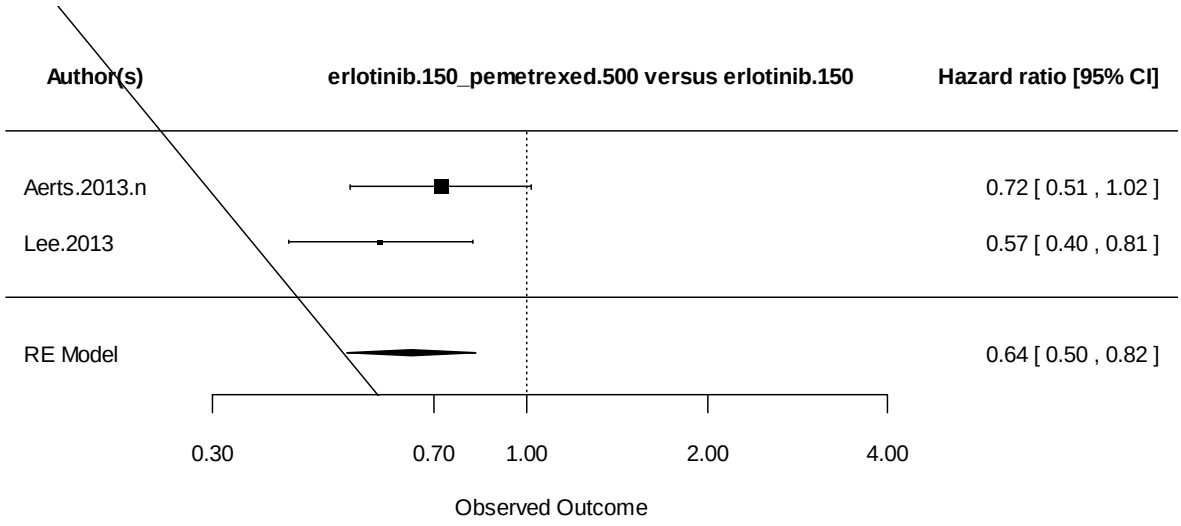
Treatment 1	Treatment 2	df	Q	*P* Value
Overall		7	34.02	< 0.0001
Docetaxel 75 mg/m^2 every 3 weeks + nintedanib 200 mg	Docetaxel 75 mg/m^2 every 3 weeks	1	0.00	1.000
Pemetrexed 500 mg	Docetaxel 75 mg/m^2 every 3 weeks	2	7.17	0.0277

Treatment 1	Treatment 2	df	Q	*P* Value
Erlotinib 150 mg + pemetrexed 500 mg	Erlotinib 150 mg	1	0.71	0.3994
Pemetrexed 500 mg	Gefitinib 250 mg	2	23.27	< 0.0001

Figure I-1. Pairwise Meta-Analysis Where Duplicate Comparisons Exist: All Patients (PFS)






Author(s)
erlotinib.150_pemetrexed.500 versus erlotinib.150
Hazard ratio [95% CI]
Aerts.2013.n
0.72 [0.51 , 1.02]
Lee.2013
0.57 [0.40 , 0.81]
RE Model
0.64 [0.50 , 0.82]
0.30
0.70
1.00
2.00
4.00
Observed Outcome

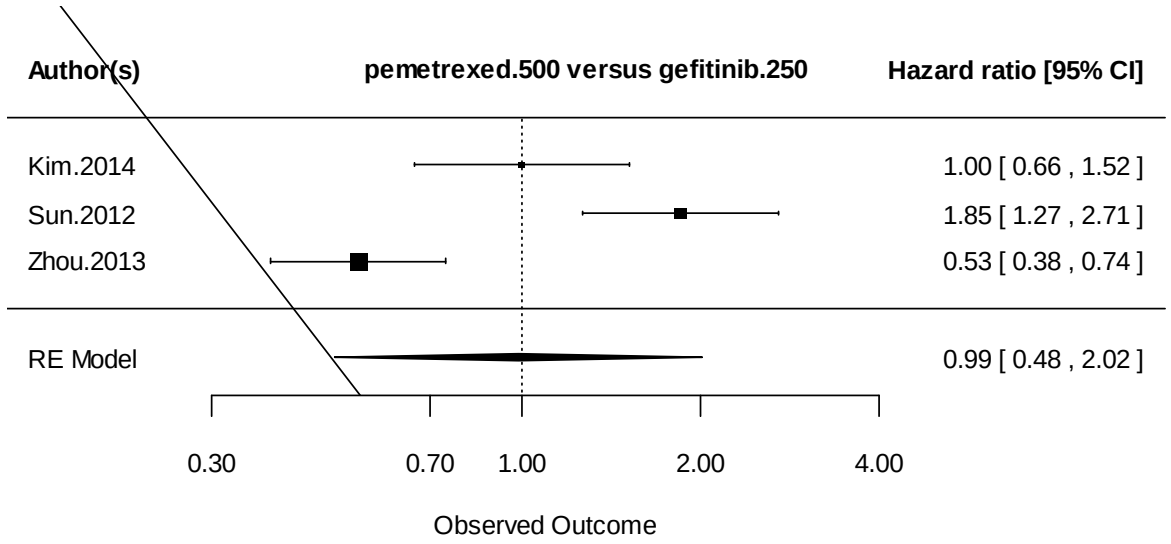
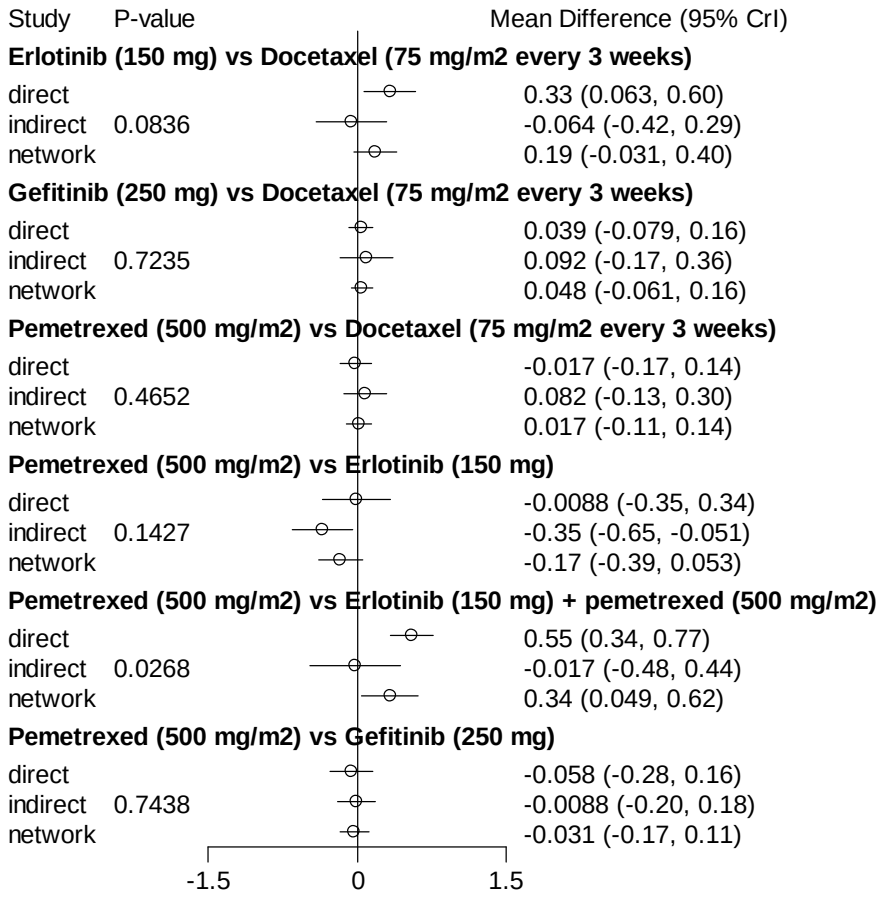
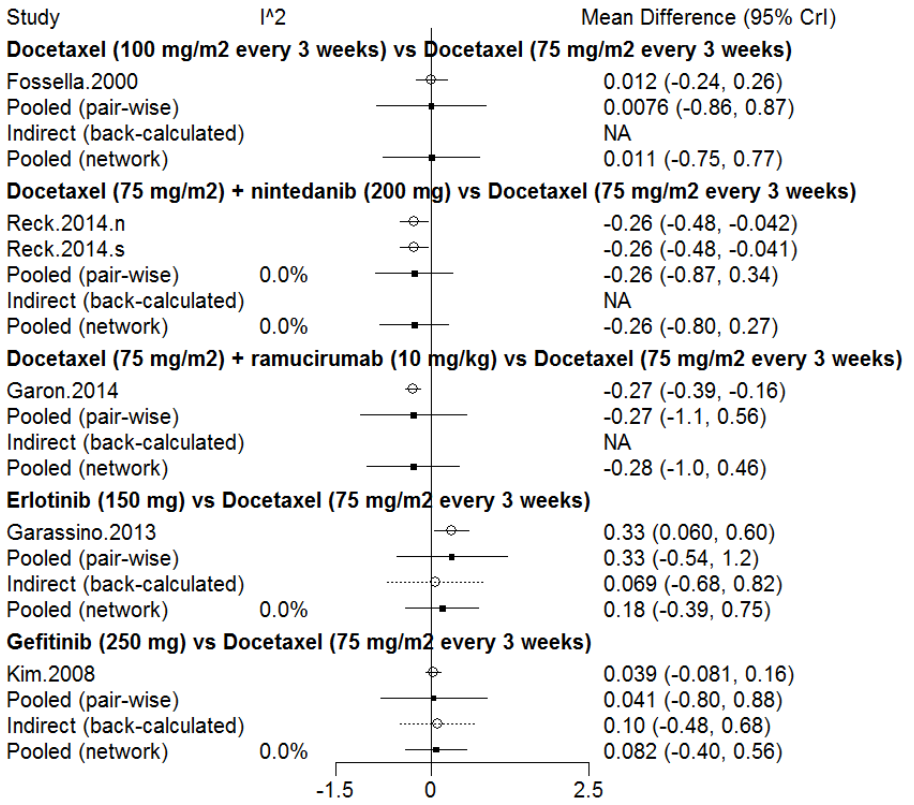

Author(s)
pemetrexed.500 versus gefitinib.250
Hazard ratio [95% CI]
Kim.2014
1.00 [0.66 , 1.52]
Sun.2012
1.85 [1.27 , 2.71]
Zhou.2013
0.53 [0.38 , 0.74]
RE Model
0.99 [0.48 , 2.02]
0.30
0.70
1.00
2.00
4.00
Observed Outcome

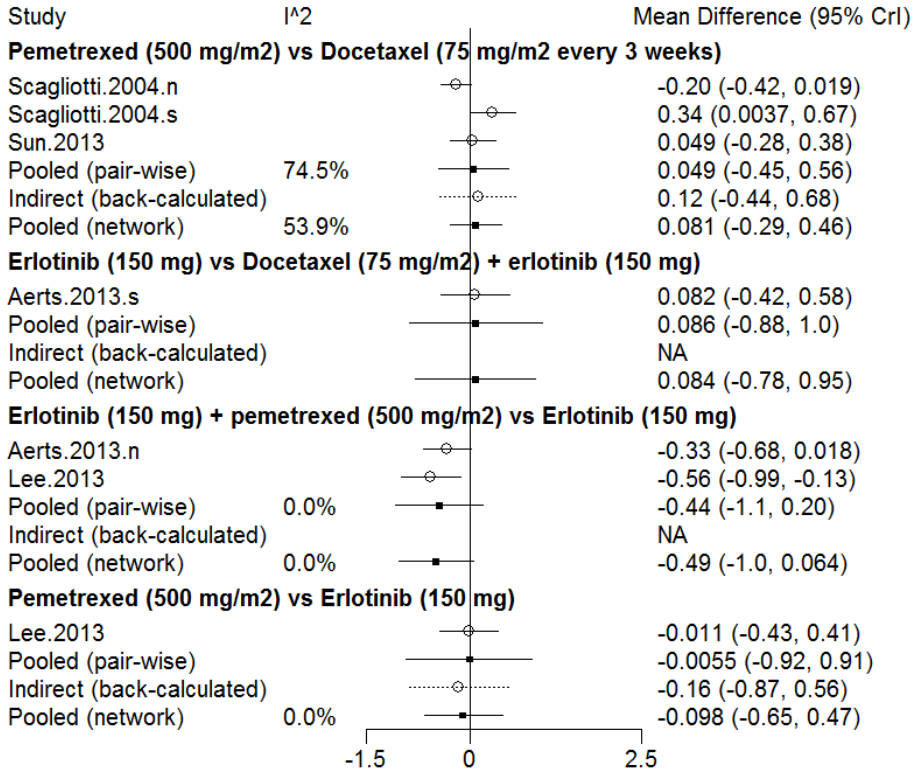
Figure I-2. Node-Splitting: Continuous Model Based on Log Hazard Ratios: All Patients (PFS)

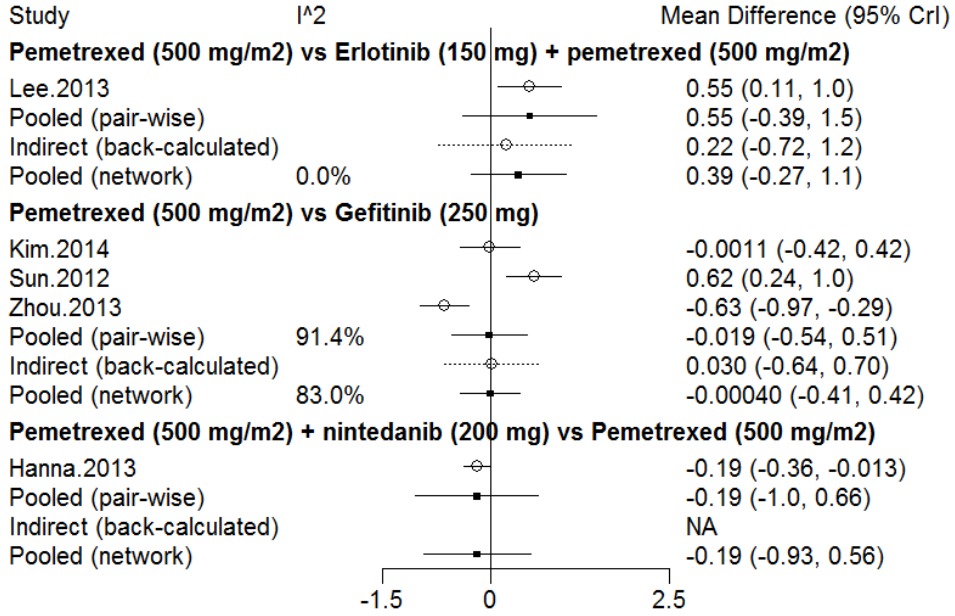


Indirect evidence is not consistent with direct evidence.

Figure I-3. Node-Splitting: Continuous Model Based on Log Hazard Ratios: All Patients (PFS)





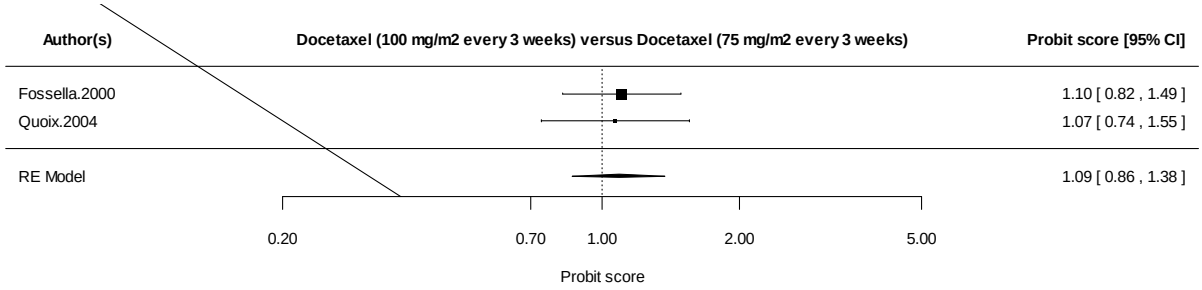


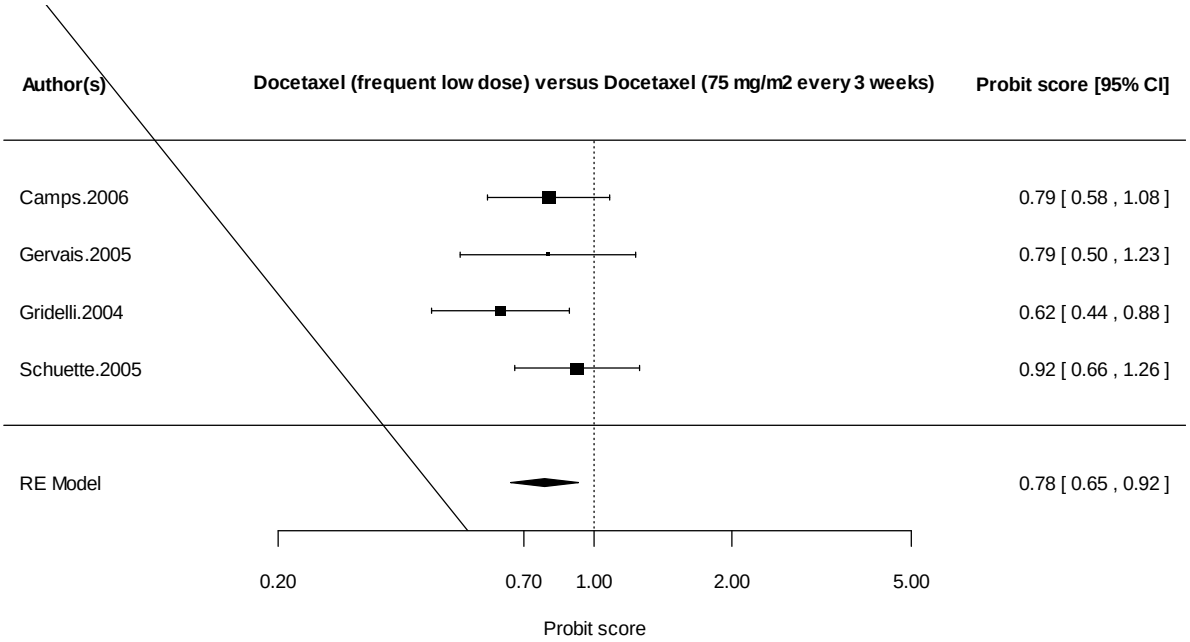
High I^2 values can be seen for pemetrexed, docetaxel and erlotinib, and gefitinib.

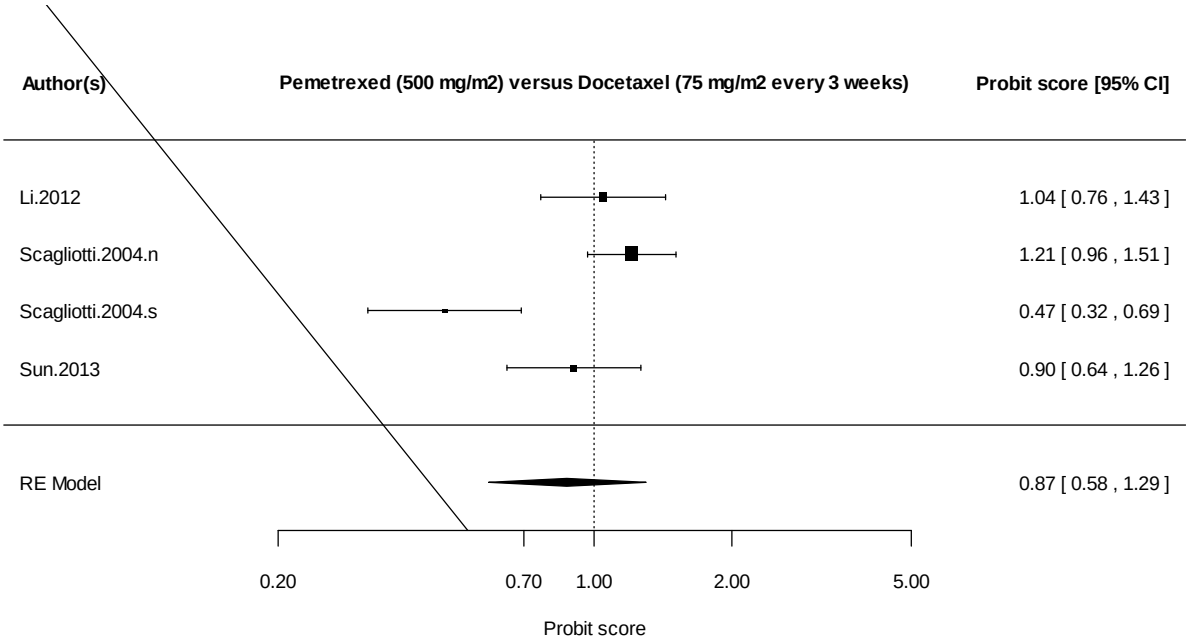
Table J-2.Exploring Heterogeneity: All Patients (ORR)

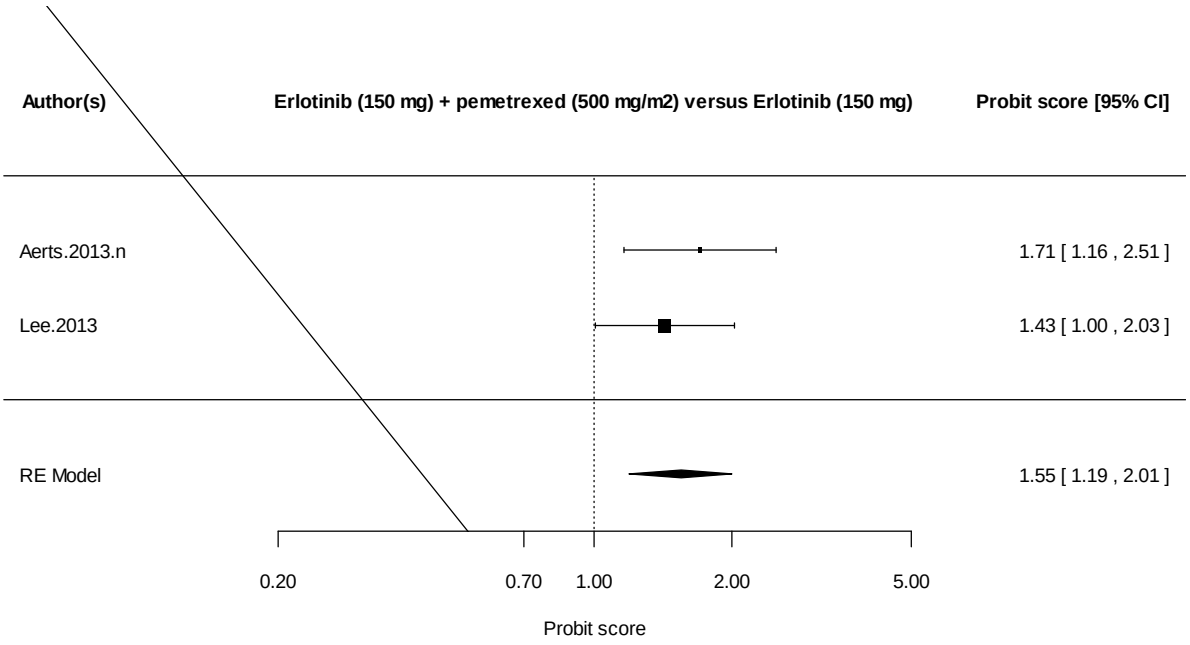
Treatment 1	Treatment 2	df	Q	*P* Value
Overall		13	33.02	0.0017
Docetaxel 100 mg/m2 every 3 weeks	Docetaxel 75 mg/m2 every 3 weeks	1	0.02	0.8983
Docetaxel (frequent low dose)	Docetaxel 75 mg/m2 every 3 weeks	3	2.80	0.4242
Docetaxel 75 mg/m2 every 3 weeks + nintedanib 200 mg	Docetaxel 75 mg/m2 every 3 weeks	1	0.00	0.9730
Pemetrexed 500 mg	Docetaxel 75 mg/m2 every 3 weeks	3	17.99	0.0004
Erlotinib 150 mg + pemetrexed 500 mg	Erlotinib 150 mg	1	0.37	0.5404
Pemetrexed 500 mg	Erlotinib 150 mg	1	2.81	0.0936
Pemetrexed 500 mg	Gefitinib 250 mg	2	4.00	0.0455

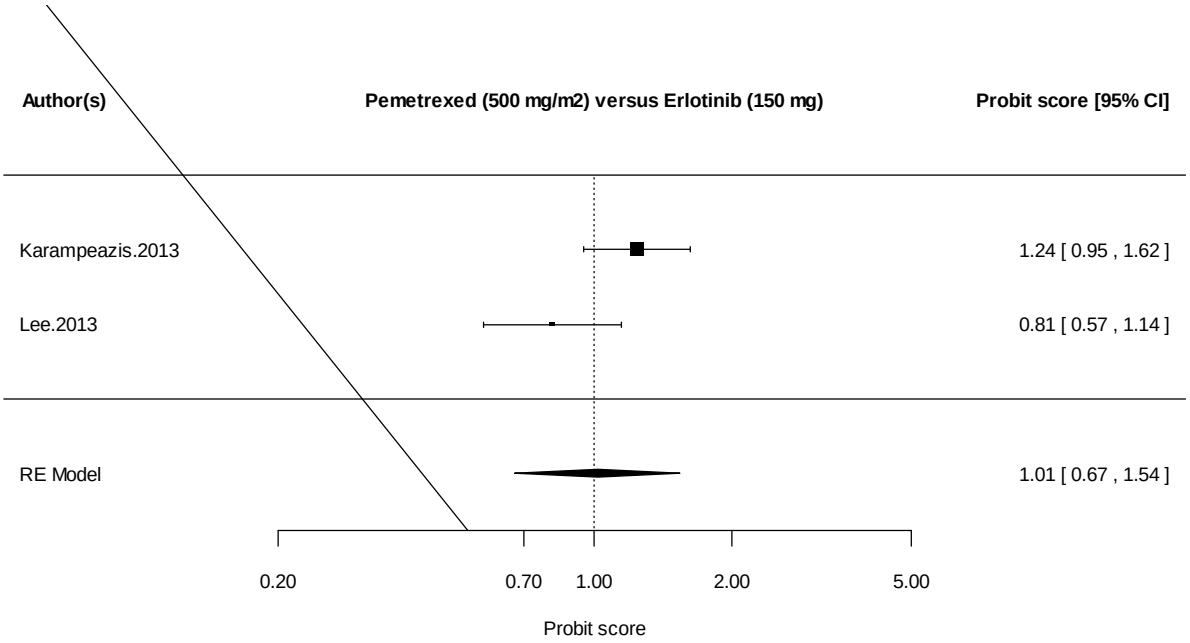
Figure J-1. Pairwise Meta-Analysis Where Duplicate Comparisons Exist: All Patients (ORR)






Author(s)
Pemetrexed (500 mg/m2) versus Docetaxel (75 mg/m2 every 3 weeks)
Probit score [95% CI]
Li.2012
1.04 [0.76 , 1.43]
Scagliotti.2004.n
1.21 [0.96 , 1.51]
Scagliotti.2004.s
0.47 [0.32 , 0.69]
Sun.2013
0.90 [0.64 , 1.26]
RE Model
0.87 [0.58 , 1.29]
0.20
0.70
1.00
2.00
5.00
Probit score


Author(s)
Erlotinib (150 mg) + pemetrexed (500 mg/m2) versus Erlotinib (150 mg)
Probit score [95% CI]
Aerts.2013.n
1.71 [1.16 , 2.51]
Lee.2013
1.43 [1.00 , 2.03]
RE Model
1.55 [1.19 , 2.01]
0.20
0.70
1.00
2.00
5.00
Probit score


Author(s)
Pemetrexed (500 mg/m2) versus Erlotinib (150 mg)
Probit score [95% CI]
Karampeazis.2013
1.24 [0.95 , 1.62]
Lee.2013
0.81 [0.57 , 1.14]
RE Model
1.01 [0.67 , 1.54]
0.20
0.70
1.00
2.00
5.00
Probit score

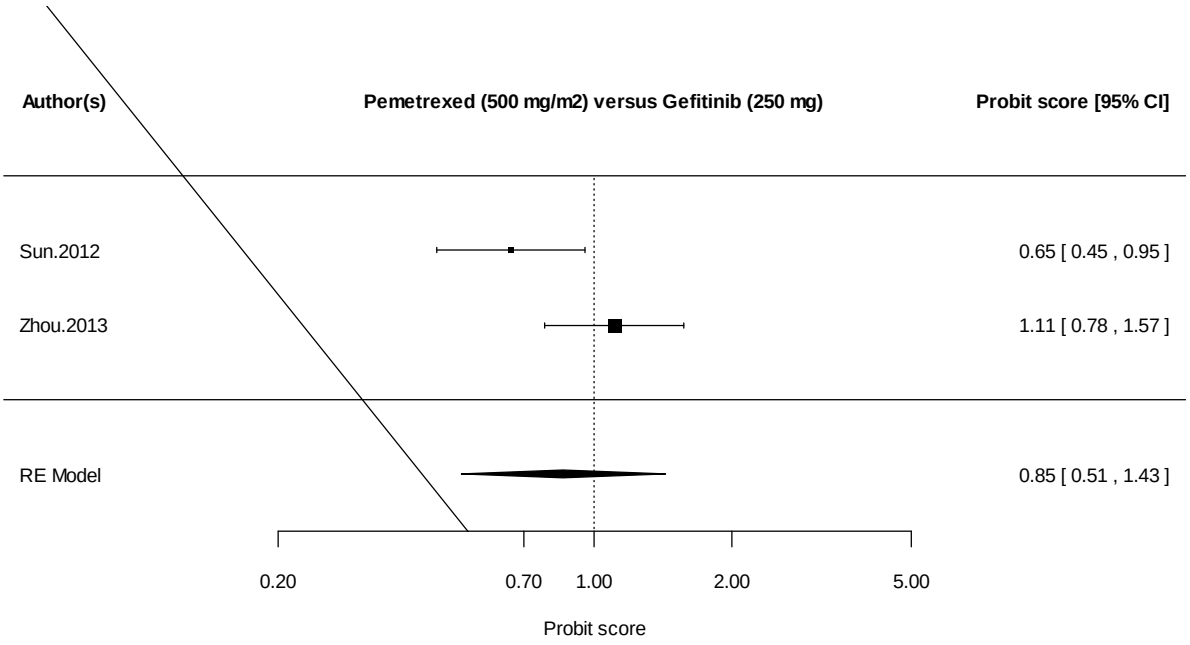
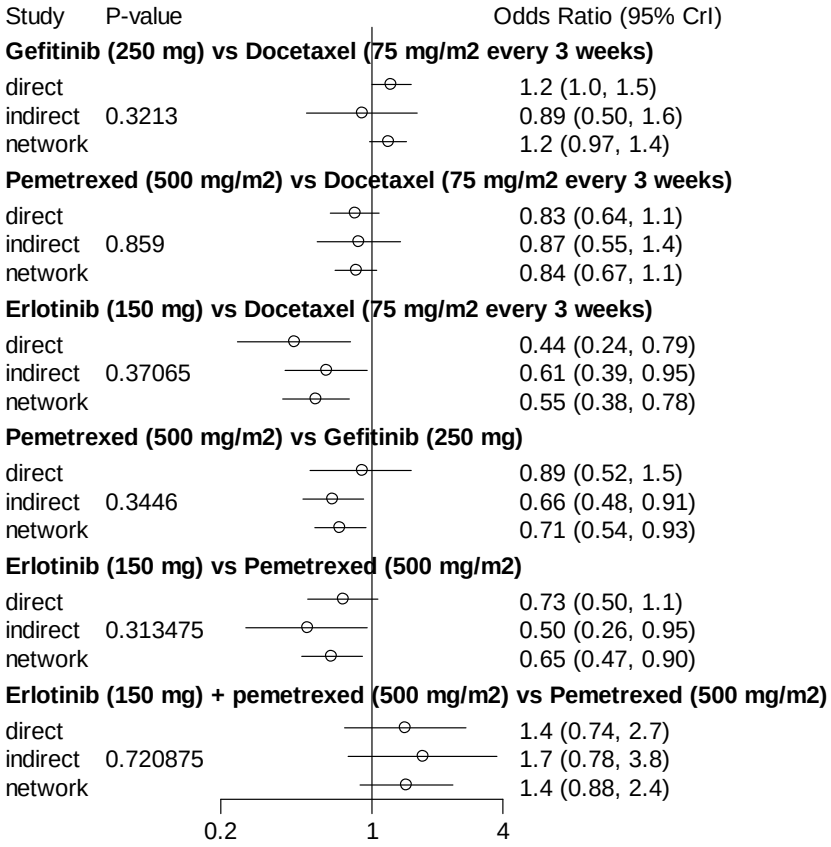
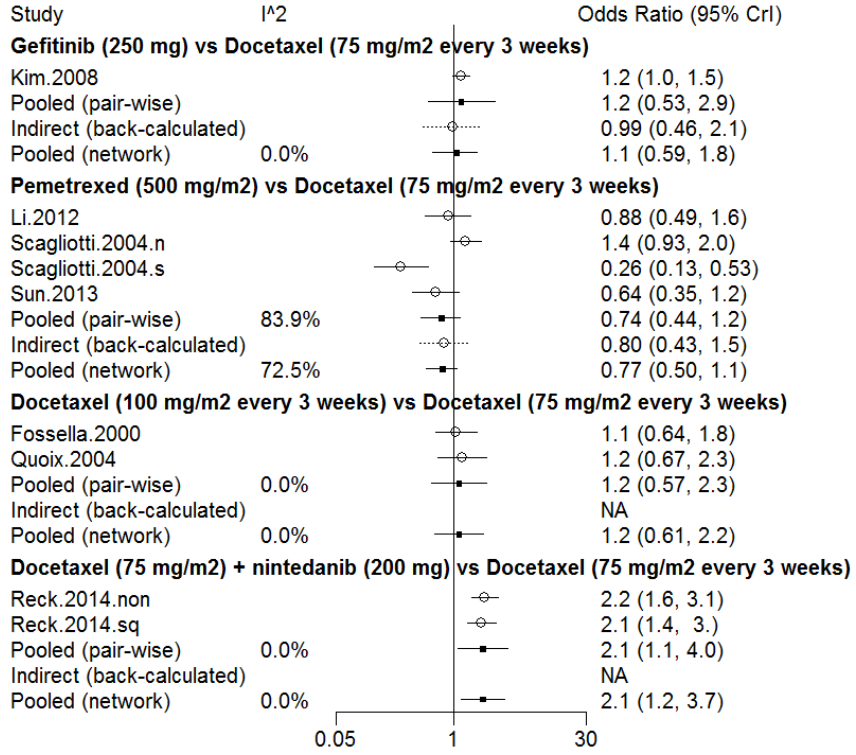

Author(s)
Pemetrexed (500 mg/m2) versus Gefitinib (250 mg)
Probit score [95% CI]
Sun.2012
0.65 [0.45 , 0.95]
Zhou.2013
1.11 [0.78 , 1.57]
RE Model
0.85 [0.51 , 1.43]
0.20
0.70
1.00
2.00
5.00
Probit score

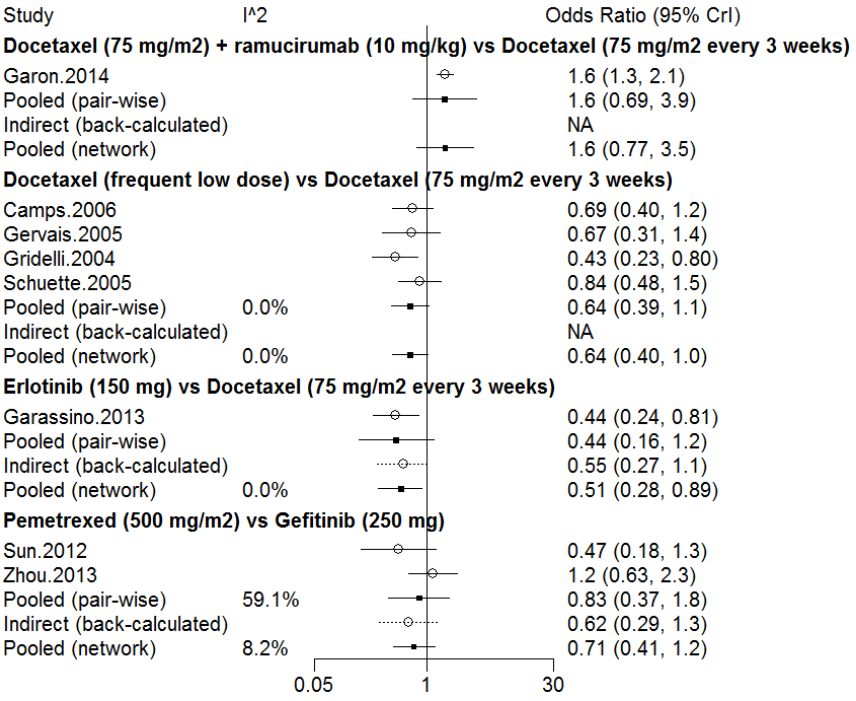
Figure J-2. Node-Splitting: Continuous Model Based on Log Hazard Ratios: All Patients (ORR)

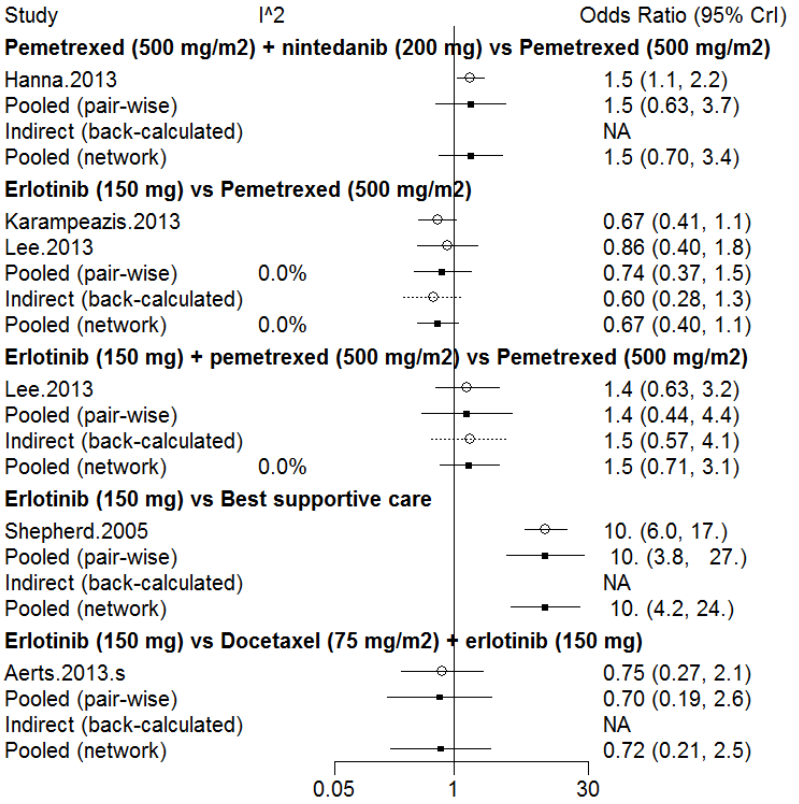


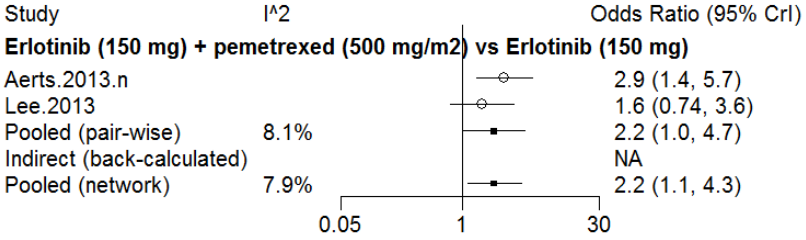
Odds ratio = odds of stable disease.

Figure J-3. New Experimental Method for Node-Splitting: Binomial Model: Random-Effects Model (ORR)









High I^2 values can be seen for pemetrexed, and gefitinib. Odds ratio = odds of stable disease.

A24. *Please provide a sensitivity analysis including the study (Hosomi 2015) that was excluded from the network meta-analysis because the dose of docetaxel was lower (60mg) than is typically used in the UK.*

The results for this study were only available after the date constraints of the current SLR. However, it is unlikely that this study will be easy to connect to the network, especially for overall survival due to the lack of studies that connect docetaxel 60mg with the rest of the network. Only one study forms a connection which had a high degree of treatment switching.

A25. *Please present the patient numbers underlying the patient distributions within the economic model separately for the ramucirumab+docetaxel and the docetaxel groups for overall survival and progression-free survival for:*

a. the REVEL trial as a whole

b. the patient subgroups for which there is data within the economic model

c. the squamous subgroup

d. the adenocarcinoma subgroup

Please also supply the age range and the median age for each subgroup. This data can be presented within an excel spreadsheet (see example below).

	OS		*PFS*	
	RAM+D	*DOC*	*RAM+D*	*DOC*
Total N	*N=???*	*N=???*	*N=???*	*N=???*
Age group >= 65	*N=???*	*N=???*	*N=???*	*N=???*
ECOG PS 0	*N=???*	*N=???*	*N=???*	*N=???*
Gender - F	*N=???*	*N=???*	*N=???*	*N=???*
Geographic region - Japan/East Asia	*N=???*	*N=???*	*N=???*	*N=???*
Histology - nonsquamous	*N=???*	*N=???*	*N=???*	*N=???*
Best Response to Plat. Tx - CR/PR/SD	*N=???*	*N=???*	*N=???*	*N=???*
Time since prior therapy < 9 months	*N=???*	*N=???*	*N=???*	*N=???*
Prior maintenance therapy (Y)	*N=???*	*N=???*	*N=???*	*N=???*
Prior 1st line pemetrexed (Y)	*N=???*	*N=???*	*N=???*	*N=???*

The data requested is in the table below. Please also refer to columns BQ to BW, rows 34 to 54 in the PSA sampling sheet of the economic model

	OS		PFS	
	R+D	D	R+D	D
Total N (ITT)	N=628	N=625	N=628	N=625
Age group >= 65	N=237	N=218	N=237	N=218
ECOG PS 0	N=207	N=199	N=207	N=199
Gender - F	N=209	N=210	N=209	N=210
Geographic region - Japan/East Asia	N=43	N=46	N=43	N=46
Histology - squamous	N=157	N=171	N=157	N=171
Histology - nonsquamous	N=465	N=447	N=465	N=447
Histology - adenocarcinoma	N=377	N=348	N=377	N=348
Best Response to Plat. Tx - CR/PR/SD	N=420	N=417	N=420	N=417
Time since prior therapy < 9 months	N=400	N=374	N=400	N=374
Prior maintenance therapy (Y)	N=135	N=143	N=135	N=143
Prior 1st line pemetrexed (Y)	N=220	N=229	N=220	N=229

	OS and PFS	
Median Age (RANGE)	R+D	D
Total N (ITT)	62.0 (21-85)	61.0 (25-86)
Age group >= 65	70.0 (65-85)	70.0 (65-86)
ECOG PS 0	61.0 (33 - 81)	62.0 (26 - 86)
Gender - F	62.0 (21 - 85)	59.5 (28 - 84)
Geographic region - Japan/East Asia	62.0 (35-81)	57.5 (25-78)
Histology - squamous	64.0 (41-80)	63.0 (43-78)
Histology - nonsquamous	62.0 (21-85)	61.0 (25-86)
Histology - adenocarcinoma	61.0 (21 - 85)	60.0 (26 - 86)
Best Response to Plat. Tx - CR/PR/SD	62.0 (21 - 85)	62.0 (25 - 84)
Time since prior therapy < 9 months	62.0 (21 - 85)	61.0 (25 - 86)
Prior maintenance therapy (Y)	61.0 (31 - 85)	62.0 (26 - 79)
Prior 1st line pemetrexed (Y)	61.0 (23-85)	60.0 (25-84)

A26. *Please supply the following count data for patient baseline weights across all patients within REVEL.*

	N female	*N male*
weight <= 40kg	*N=???*	*N=???*
40kg < weight <= 50kg	*N=???*	*N=???*
50kg < weight <= 60kg	*N=???*	*N=???*
60kg < weight <= 70kg	*N=???*	*N=???*
70kg < weight <= 80kg	*N=???*	*N=???*
80kg < weight <= 90kg	*N=???*	*N=???*
90kg < weight <= 100kg	*N=???*	*N=???*
100kg < weight <= 110kg	*N=???*	*N=???*
110kg < weight <= 120kg	*N=???*	*N=???*
120kg < weight <= 130kg	*N=???*	*N=???*
130kg < weight <= 140kg	*N=???*	*N=???*
140kg < weight <= 150kg	*N=???*	*N=???*
150kg < weight <= 160kg	*N=???*	*N=???*
weight > 160kg	*N=???*	*N=???*

Summary of Baseline Weight (Kg) by Gender
ITT population

	Females (N=419)	**Males (N=834)**
weight <= 40 kg	8 (1.9)	0
40 kg < weight <= 50 kg	30 (7.2)	23 (2.8)
50 kg < weight <= 60 kg	122 (29.1)	91 (10.9)
60 kg < weight <= 70 kg	105 (25.1)	201 (24.1)
70 kg < weight <= 80 kg	75 (17.9)	224 (26.9)
80 kg < weight <= 90 kg	52 (12.4)	151 (18.1)
90 kg < weight <= 100 kg	16 (3.8)	80 (9.6)
100 kg < weight <= 110 kg	5 (1.2)	35 (4.2)
110 kg < weight <= 120 kg	2 (0.5)	20 (2.4)
120 kg < weight <= 130 kg	4 (1.0)	6 (0.7)
130 kg < weight <= 140 kg	0	1 (0.1)
140 kg < weight <= 150 kg	0	2 (0.2)
150 kg < weight <= 160 kg	0	0
weight > 160 kg	0	0

A27. *Table JVBA.12.1.1 of the CSR suggests a mean number of ramucirumab infusions of 6.1 and a mean number of docetaxel infusions of 5.5. We understand that ramucirumab and docetaxel are administered on the same day of a 21 week cycle. Please provide an account of why the mean numbers of infusions differed for ramucirumab and docetaxel in the ramucirumab+docetaxel group of the REVEL trial.*

As per REVEL protocol, it is possible for patients to discontinue a component of RAM+Doc but continue on the other component in the study design section. Patients were randomized to receive ramucirumab in combination with docetaxel administered once every 3 weeks versus docetaxel and placebo administered once every 3 weeks. Patients underwent radiographic assessment of disease status (computed tomography [CT] or magnetic resonance imaging [MRI]) according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, v 1.1), every 6 weeks, as calculated from the first dose of study therapy (± 3 days), until there is radiographic documentation of progressive disease (PD). Patients were treated until there was

radiographic or symptomatic PD, toxicity requiring cessation, withdrawal of consent, or until other withdrawal criteria were met. If toxicity leads to an interruption of one or both components of therapy, the administration of both components will be delayed for a maximum of 5 weeks from the last administered dose (i.e., a delay of a maximum of 14 days from start of the next cycle). If a patient cannot be treated with the respective component for more than 5 weeks, that component will be permanently discontinued. The other component of the combination should be continued, with the patient remaining on-study, if clinically indicated. Therefore, the mean numbers of infusions differed for Ram and Doc in the Ram+Doc group.

A28. *Please provide details of any analyses undertaken using fitted curves to the subgroup specific data underlying, for example, the data in figure 12, page 72 of the company submission, rather than estimating one overarching multivariate overall survival analysis with patient covariates, and then using the REVEL trial non-squamous patient characteristics to model non-squamous overall survival curves for ramucirumab+docetaxel and docetaxel groups. Please supply these even if only available as exploratory analyses?*

We are not aware that NICE expresses a preference for either (1) an adjusted model (including covariates that represent all subgroups of interest) of the ITT population or (2) a separate unadjusted model (perhaps including only treatment as a covariate) for each subgroup of interest within the overall ITT population. There are advantages and disadvantages to each approach. The first approach was taken in our analysis, as the advantages of including multiple covariates in a model are that one may generate a better fitting model where more of the variability in the data is explained. We did, however, also undertake some exploratory analyses in the non-squamous patient subgroup; the details of these analyses for OS and PFS have been provided as Excel files alongside this response:

- *Ramucirumab, NSCLC Nice ERG Clarification Question A28 (1 of 2) and*
- *Ramucirumab, NSCLC Nice ERG Clarification Question A28 (1 of 2)*

The attached exploratory analyses show that the best fit distributions chosen from both approaches were the same (log-logistic for OS and generalised gamma for PFS), based on the AIC/BIC and visual investigation. The curves of the non-squamous patient subgroup generated from both approaches are very close when one compares the probability at various time points for different distributions and we are therefore content that the approach taken in our primary analysis was valid.

A29. *Please provide details of how the explanatory variables for the multivariate analyses were selected for each analysis. For example, why did the overall survival analysis include region and best response to platinum therapy whereas the progression-free survival analysis did not? How was the list of interaction variables for ramucirumab+docetaxel in the overall survival analysis determined? Please also supply the details and results of any statistical tests underlying this.*

(Please note that the response to A14 is also pertinent to this question)
For the primary efficacy comparison of OS between the assigned study treatment arms in REVEL CSR, a stratified log-rank test was performed using the CRF stratification factors. Hazard ratio (HR) for treatment effect was estimated using a Cox proportional hazards (PH) model stratified identically to the primary log-rank test with assigned treatment as the only covariate, reported with 2-tailed 95% CIs and Wald's test p-value. The hazard ratio for treatment effect was also estimated using a multivariate Cox PH model as supportive analyses of OS. This was estimated using a multivariate Cox PH model incorporating covariates selected using a prespecified stepwise selection method, from among all the variables listed below. The stepwise selection used p-value <0.05 as the criterion for adding a variable and p-value ≥0.10 for dropping a variable. The treatment factor (RAM or PBO) was not used for stepwise selection, but was added to the final model. The hazard ratio for the treatment effect and corresponding 95% CI were estimated from the final model.

For PFS, the same set of analyses used for the analyses of the primary endpoint OS were performed and the same approach to stepwise selection of covariates taken. The explanatory variables for the multivariate analyses were selected for each analysis listed in the tables provided below.

Adjustments for Covariates

As explained above, in the supportive analysis, the primary and secondary efficacy endpoints in CSR were analysed adjusting for prespecified potential prognostic factors chosen from the variables listed below, with * indicating the reference level. The list of factors to be included in this analysis was prespecified in the SAP.

- Randomization stratification factors:
    - ECOG performance status (0 versus 1*)
    - gender (females versus males*)
    - prior maintenance therapy (yes versus no*)
    - geographic region (Japan/East Asia versus ROW*)
- Other factors of interest:
    - smoking history (never* versus ever)
    - histology (nonsquamous versus squamous*)
      Note. It was defined based on pathological diagnosis at study entry, or initial pathological diagnosis if pathological diagnosis at study entry was missing.
    - best response to platinum-based chemotherapy (CR/PR/SD versus progressive disease*)
    - prior taxane treatment (no* versus yes)
    - prior bevacizumab treatment (no* versus yes)
    - EGFR status (wild-type versus mutation* versus unknown)
    - age (<65 years versus ≥65 years*)
    - race (White* versus Black versus Other)
    - age (<70 years versus ≥70 years*)
    - time since prior therapy (<9 months versus ≥9 months*), with time since prior therapy defined as the time from the start of the prior therapy to randomization. **Note**. This factor was identified to be prognostic and predictive for treatment of nintedanib in combination with second-line chemotherapy in NSCLC patients (Kaiseret al. 2013).

Multivariate Cox Regression Analysis of Overall Survival Time

Intent-to-Treat Population

Factor	N for Alternative Level	N for Reference Level	Hazard Ratio (95% CI)	p-value*a
Treatment				
Ramucirumab vs. Placebo (reference)	593	591	0.81 (0.70, 0.92)	0.002
ECOG Performance Status				
0 vs. 1 (reference)	383	801	0.67 (0.58, 0.78)	<0.001
Gender				
Female vs. Male (reference)	397	787	0.84 (0.73, 0.98)	0.026
Geographic Region				
Japan/East Asia vs. ROW (reference)	83	1101	0.66 (0.50, 0.87)	0.003
Histology				
Nonsquamous vs. Squamous (reference)	869	315	0.79 (0.68, 0.92)	0.002
Best Response To Platinum-Based Chemotherapy				
CR/PR/SD vs. PD (reference)	828	356	0.83 (0.71, 0.96)	0.015
Time since prior therapy				
<9 months vs. >=9 months (reference)	733	451	1.65 (1.41, 1.93)	<0.001

Abbreviations: N = total population size; CI = Confidence Interval.
Note: Overall survival is the duration from randomization to death. For patients who are alive, overall survival is censored at the last contact.
Hazard Ratio was estimated using a multivariate Cox Proportional Hazard model by stepwise selection method. The stepwise selection used p-value <0.05 as the criterion for adding a variable and p-value >= 0.10 for dropping a variable. The treatment factor was not used for stepwise selection but was added in the final model. HR for treatment effect and corresponding 95% CI estimated from the final model.
***a - Wald's p-value.**
Program Location: /data1/projects/li/li2107/displaysf/final/code/s107mcrs.sas
Output Location: /data1/projects/li/li2107/tr201402lock/final/list/s107mcrs.r2
Data Set Location: /data1/projects/li/li2107/tr201402lock/final/data/adsl.xpt adtte.xpt

Factor	N for Alternative Level	N for Reference Level	Hazard Ratio (95% CI)	p-value*a
Treatment				
Ramucirumab vs. Placebo (reference)	626	624	0.73 (0.65, 0.82)	<0.001
ECOG Performance Status				
0 vs. 1 (reference)	406	844	0.79 (0.70, 0.90)	<0.001
Gender				
Female vs. Male (reference)	417	833	0.86 (0.76, 0.98)	0.021
Time since prior therapy				
<9 months vs. >=9 months (reference)	774	476	1.60 (1.41, 1.81)	<0.001

Abbreviations: N = total population size; CI = Confidence Interval.
Note: Progression free survival is the duration from randomization to objective progressive disease (OPD) or death, whichever is first. Patients without OPD were censored at last adequate post baseline radiological assessment or randomization date (whichever is last).
Hazard Ratio was estimated using a multivariate Cox Proportional Hazard model by stepwise selection method. The stepwise selection used p-value <0.05 as the criterion for adding a variable and p-value >= 0.10 for dropping a variable. The treatment factor was not used for stepwise selection but was added in the final model. HR for treatment effect and corresponding 95% CI estimated from the final model.
*a - Wald's p-value.
Program Location: /data1/projects/li/li2107/displaysf/final/code/s107mcrs.sas
Output Location: /data1/projects/li/li2107/tr201402lock/final/list/s107mcrs.r1
Data Set Location: /data1/projects/li/li2107/tr201402lock/final/data/adsl.xpt adtte.xpt

A30. *In the company submission EQ-5D was assessed among all patients for whom there was a valid translation. Please itemise which regions had a valid EQ-5D translation (for the geographic regions specified in table 14, page 44 of company submission). Please specify what number of patients in each arm had valid EQ-5D translations at baseline, and the number of EQ-5D questionnaires that were administered (not necessarily completed) at baseline, if this differs.*

We do not have the data to answer the first part of the question regarding which regions had a valid EQ-5D translation. However we can confirm that 'translation not available' data was collected and this was not a common reason for lack of completion of EQ-5D. Please see REVEL CSR table JVBA.14.2.18 - Summary of Patient Compliance for EuroQoL EQ-5D Intent-to-Treat Population (Page 526 of the CSR)

Section B: Clarification on cost-effectiveness data

B1. *Please clarify why table 66 (page 156 in company submission) presents medians but is titled Key disease progression variables applied in the economic model. Please provide more detail on how the values presented in Table 66 are applied in the economic model as key disease progression variables.*

We apologise for any confusion caused by wording in this table; the OS and PFS outcomes are clearly the key disease progression variables and the NICE template requests that this table, with the column "Value (reference to appropriate table or figure in submission)", be provided. In the User Guide for the NICE template an example of this table is shown where Overall Survival is a Weibull model but the Value column contains an illustrative value in months.

To be clear, both OS and PFS are modelled from the parametric curves as described in detail on pages 123–135 of the submission. The median values provided in Table 66 were intended merely to be illustrative within the context of the specified template and the example given in the User Guide. We confirm that these illustrative values are not themselves used in any way in the model.

B2. *Please explain why the administration costs of erlotinib are calculated as being 46% of those of nintedanib, with reference to each of the products' Summary of Product Characteristics and pack sizes.*

The resource use costs were taken primarily from the recent nintedanib appraisal TA347 for consistency with other appraisals in the second-line NSCLC setting. However, TA347 did not include any administration costs for the oral therapies erlotinib and nintedanib so a non-consultant led outpatient visit (medical oncology), i.e. £89.69, was assumed for the purpose of preparing and dispensing the tablets.

Nintedanib tablets are assumed to be administered every 21 days in line with the administration of the docetaxel infusion for patient convenience. Erlotinib is assumed to be administered every 30 days in line with the available pack size for erlotinib, and without the constraints of a concomitant therapy on a different administration schedule.

The per model cycle (i.e. 21 day) administration cost of erlotinib should therefore be 70% (= 21/30) of the total administration cost *per treatment cycle (i.e. 30 day), not 46% as stated in the model (Cost Inputs sheet, cell I69)*, i.e. the administration cost for erlotinib should be £62.78 (£89.69*70%) rather than £41.26 (£89.69*46%) in cell G71 of the cost Inputs sheet. All other monitoring costs are assumed in line with those provided in TA347.

B3. *The arithmetic underlying cell M241 of the Model Mechanics worksheet is not clearly explained. Please provide a more detailed account of the information such as an annotated spreadsheet with an exploded version of the arithmetic of cell M241 of the Model Mechanics worksheet.*

Cell M241 of the Model Mechanics worksheet in the model contains the calculations that yield the cost per cycle of systemic anticancer treatment provided after patients enter the progression health state.

Based on the manufacturer's submission to NICE for nintedanib (BI, 2014), 30% of patients receive systemic anticancer treatment after progression. 25% of patients received treatment with vinorelbine and carboplatin, and the remaining 5% are treated with erlotinib. The costs of subsequent systemic anticancer treatment per cycle are estimated as the weighted average of the costs per cycle of providing these treatments.

The formula in cell M241 of the Model Mechanics worksheet is as follows:

(0.25/0.3)*20.17*2 + (0.25/0.3)*(CEILING(30*'Model Mechanics'!$M$159/10, 1)*3*4.51*(1-'Model Mechanics'!$M$152) + CEILING(30*'Model Mechanics'!$M$155/10,1)*3*4.51*'Model Mechanics'!$M$152) + (0.25/0.3)*'Model Mechanics'!$M$185 + (0.05/0.3)*'Markov - Erlotinib'!$E$15

The first term - (0.25/0.3)*20.17*2 – calculates the cost per cycle of carboplatin (in combination with vinorelbine), weighted by the proportion of patients receiving carboplatin + vinorelbine among those who receive subsequent systemic anticancer treatment (0.25/0.3). The cost per 45 mL vial containing 10 mg/mL of carboplatin is £20.17, and 2 vials are used to deliver the recommended dose of 750 mg of carboplatin administered once per cycle.

The second term - (0.25/0.3)*(CEILING(30*'Model Mechanics'!$M$159/10,1)*3*4.51*(1-'Model Mechanics'!$M$152) + CEILING(30*'Model Mechanics'!$M$155/10,1)*3*4.51*'Model Mechanics'!$M$152) – calculates the cost per cycle of vinorelbine (in combination with carboplatin), weighted by the proportion of patients receiving carboplatin + vinorelbine among those who receive subsequent systemic anticancer treatment (0.25/0.3). The cost per 1 mL vial containing 10 mg/mL of vinorelbine is £4.51, and the recommended dose per administration is 30 mg/m^2 administered thrice per cycle. The number of vials required to administer this dose to male and female patients is calculated based on estimates of their respective mean body surface area (mean body surface area, male patients: 'Model Mechanics'!$M$159; mean body surface area, female patients: 'Model Mechanics'!$M$155). Note that in the estimation of the costs of providing carboplatin + vinorelbine per cycle, we assume that vial-sharing is not practiced, so we round up (not down) to the next 1 ml vial using the CEILING function. The costs of the number of vials required for male and female patients are weighted by the proportion of male and female patients (proportion of male patients: 1 - 'Model Mechanics'!$M$152, proportion of female patients: 'Model Mechanics'!$M$152).

The third term - (0.25/0.3)*'Model Mechanics'!$M$185 – calculates the cost of intravenously administering the combination therapy of carboplatin + vinorelbine ('Model Mechanics'!$M$185), weighted by the proportion of patients receiving carboplatin + vinorelbine among those who receive subsequent systemic anticancer treatment (0.25/0.3).

The fourth term - (0.05/0.3)*'Markov - Erlotinib'!$E$15 – calculates the cost per cycle of providing 150 mg of erlotinib daily ('Markov - Erlotinib'!$E$15), weighted by the proportion of patients receiving erlotinib among those who receive subsequent systemic anticancer treatment (0.05/0.3).

The step-by-step estimation of these costs is detailed in the attached Excel worksheet named: *Ramucirumab, NSCLC Nice ERG Clarification Question B3*

B4. *Please provide scenario analyses with subsequent/post-progression treatments removed for all patients, and also separately for each of the three subgroups (1) squamous, (2) non-squamous and (3) adenocarcinoma.*

In order to run the scenario analyses requested as part of this question, we set the cost of subsequent systemic anticancer treatment per cycle in the model (Cost Inputs worksheet, cell E178) to £0 per cycle.

The results of running this scenario analysis among the overall population of patients with metastatic NSCLC (post-platinum progression) are provided in Table 1 below.

Table 1. Scenario Analysis Tabular Results: REVEL Overall Population

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Costs (per person, discounted)			
Progression-free	£26,462	£3,017	£23,445
Drug acquisition	£22,729	£324	£22,405
Treatment administration	£1,308	£794	£514
Toxicity management	£807	£656	£151
Physician visits and monitoring	£1,618	£1,242	£375
Progression	£6,847	£6,193	£655
~~Subsequent systemic anticancer treatment and~~ best supportive care	£4,173	£3,774	£399
Physician visits and monitoring	£2,674	£2,419	£256
Total	£33,309	£9,210	£24,099
Health outcomes (per person)			
Total life-years (undiscounted)	1.574	1.319	0.255
Median PFS (months)	4.518	3.327	1.192
Median OS (months)	10.604	8.693	1.911
Discounted life-years			
Progression-free	0.483	0.371	0.112
Progression	0.799	0.722	0.076
Total	1.282	1.093	0.188
Total QALYs (undiscounted)	0.994	0.828	0.166
Discounted QALYs			

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Progression-free	0.341	0.262	0.079
Progression	0.478	0.433	0.046
Due to adverse events	−0.003	−0.003	0.000
Total	0.816	0.692	0.125
Incremental results			
ICER (£/progression-free life-year gained)		£215,107	—
ICER (£/life-year gained)		£127,930	—
ICER (£/QALY gained)		£193,405	—

The results of running this scenario analysis among the patients with squamous metastatic NSCLC (post-platinum progression) are provided in Table 2 below.

Table 2. Scenario Analysis Tabular Results: Squamous Population

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Costs (per person, discounted)			
Progression-free	£26,320	£2,910	£23,410
Drug acquisition	£22,713	£324	£22,389
Treatment administration	£1,307	£793	£513
Toxicity management	£807	£656	£151
Physician visits and monitoring	£1,493	£1,136	£357
Progression	£5,511	£5,288	£223
~~Subsequent systemic anticancer treatment and~~ best supportive care	£3,359	£3,223	£136
Physician visits and monitoring	£2,153	£2,066	£87
Total	£31,831	£8,198	£23,633
Health outcomes (per person)			
Total life-years (undiscounted)	1.312	1.136	0.175
Median PFS (months)	4.156	3.032	1.124

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Median OS (months)	8.665	7.398	1.267
Discounted life-years			
Progression-free	0.446	0.339	0.107
Progression	0.643	0.617	0.026
Total	1.089	0.956	0.133
Total QALYs (undiscounted)	0.832	0.715	0.117
Discounted QALYs			
Progression-free	0.315	0.240	0.081
Progression	0.385	0.369	0.058
Due to adverse events	−0.003	−0.003	0.000
Total	0.697	0.606	0.091
Incremental results (discounted)			
ICER (£/progression-free life-year gained)		£221,547	—
ICER (£/life-year gained)		£178,129	—
ICER (£/QALY gained)		£260,663	—

The results of running this scenario analysis among the patients with nonsquamous metastatic NSCLC (post-platinum progression) are provided in Table 3 below.

Table 3. Scenario Analysis Tabular Results: Nonsquamous Population

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Costs (per person, discounted)			
Progression-free	£27,283	£3,099	£24,184
Drug acquisition	£23,462	£337	£23,125
Treatment administration	£1,350	£826	£524
Toxicity management	£807	£656	£151
Physician visits and monitoring	£1,663	£1,280	£383

Results	Ramucirumab + Docetaxel	Placebo + Docetaxel	Difference
Progression	£7,378	£6,547	£831
~~Subsequent systemic anticancer treatment and~~ best supportive care	£4,497	£3,990	£507
Physician visits and monitoring	£2,882	£2,557	£325
Total	£34,661	£9,646	£25,015
Health outcomes (per person)			
Total life-years (undiscounted)	1.679	1.390	0.289
Median PFS (months)	4.652	3.429	1.222
Median OS (months)	11.403	9.204	2.198
Discounted life-years			
Progression-free	0.497	0.382	0.115
Progression	0.861	0.764	0.097
Total	1.357	1.146	0.211
Total QALYs (undiscounted)	1.059	0.872	0.186
Discounted QALYs			
Progression-free	0.351	0.270	0.081
Progression	0.515	0.457	0.058
Due to adverse events	−0.003	−0.003	0.000
Total	0.863	0.724	0.139
Incremental results (discounted)			
ICER (£/progression-free life-year gained)		£218,468	—
ICER (£/life-year gained)		£118,292	—
ICER (£/QALY gained)		£180,353	—

The scenario analysis in the adenocarcinoma subgroup is not presented because the adenocarcinoma subgroup analysis is not included in the cost-effectiveness model. This subgroup analysis was not included in the cost-effectiveness model based on the assumption that adenocarcinoma and nonsquamous histology could be considered comparable in terms of clinical outcomes, because adenocarcinomas are the most common form of nonsquamous NSCLC (National Cancer Institute, 2015). This assumption was made based on inputs from internal RTI-HS and Lilly clinical advisors.

B5. *Please provide the 95% confidence intervals for the cited 3.06 month life-year gain (discussion of end of life, page 110 of company submission).*

The cited figure of 3.06 months is taken from the undiscounted life-year gain outcome from the deterministic economic model, as noted in Section 5.11 (page 186) of the submission. As such, this value is not associated with 95% CIs and therefore we are unable to provide these. We would further note that the use of life-year gain outcomes from the economic model without 95% CIs was the approach taken in the recent NICE appraisal of nintedanib when considering the criterion of 3-month extension to life, as discussed in paragraph 4.19 of the final guidance for appraisal TA347.[5] We therefore believe that consideration of the figure cited, a 3.06 month life-year gain, would represent a consistent approach to this issue.

Section C: Textual clarifications and additional points

C1. ***PRIORITY QUESTION.*** *The network meta-analyses hazard ratios for nintedanib plus docetaxel in Tables 30 and 31 (page 88 and 91 of company submission) appear to be the preferred data used in the company submission rather than those in Tables 33 and 34 (page 94 of company submission). Please provide a more detailed explanation account for this.*

The results in Tables 33 and 34 are based on a non-stratified *post hoc* subgroup analysis of the REVEL trial and a very limited network informed by only two trials. This sub-analysis was exploratory in nature and provides further reassurance that the overall NMA conclusion for this comparison, that NIN+DOC and RAM+DOC provide equivalent efficacy, was robust. It was considered most appropriate, however, to use the results from the full NMA to inform the economic analysis, in line with best practice and for consistency with the other comparisons in the economic model, rather than apply the results of the separate exploratory analysis. Furthermore, given that the estimated HRs of RAM+DOC vs NIN+DOC for OS and for PFS vary by no more than ±0.01 between the two sets of NMA results, it seemed unlikely that further investigation of the exploratory NMA results was justified.

C2. ***PRIORITY QUESTION.*** *We have noted that some of the confidentiality marking is not in line with the instructions on marking confidential information sent with the invitation to submit and the directions in the NICE Guide to the processes of technology appraisals (sections 3.1.24 – 3.1.29). Please update the following:*

a. *Please ensure that any 'academic in confidence' data such as the network meta-analyses results are accompanied by an estimated date and place of publication in the checklist.*

We have marked the confidentiality checklist accordingly.

b. *Titles of figures (for example figure 40, 41 and 42 page 174 onwards of company submission) cannot be marked as confidential because this prevents readers from determining the context of the information included in the submission. Please update accordingly.*

The titles of figures have been updated to remove the confidential marking, which had in any case been intended to denote that some of the figure content was confidential rather than the title itself.

c. *Any confidential information in your submission must also be marked appropriately in your model. Please update your model reflecting any changes you make to your written submission and highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow within the excel model.*

d. *We note that the mean number of docetaxel infusions of 5.5 in the main submission, is very similar to the median number of infusions presented in the draft EPAR. As the data will be released as soon as marketing authorisation has been granted and the EPAR will be publicly available, please confirm the date, in the confidentiality checklist, that this data will be released and please inform NICE as soon as this confidential marking can be removed.*

The mean number of docetaxel infusions *5.5* has been marked up as CIC in the main submission and remains so. [Confidential marking was superseded as of 4 April 2016].

On January 27 2016, Ramucirumab received Commission Decision for the following indication: "Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy." We would expect the EPAR to be published by the end of February 2016 on the EMA website and will inform NICE as soon as the confidential marking on the EPAR can be removed. The confidentiality checklist has been updated accordingly.

e. *Please remove the 'commercial in confidence' marking from the tornado diagrams in the company submission (figures 40, 41 and 42) because details of the ICERs cannot be marked as confidential.*

As noted under point (b) above the intention had not been to mark the ICERs as confidential but reflected that the data labels in the tornado diagrams contain some input parameter ranges which are marked as confidential elsewhere. We have now adjusted the figure labels to highlight and underline the confidential values.

References cited in the response

1. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Section 6.2.3. Available at: http://www.nice.org.uk/article/pmg9/chapter/6-The-appraisal-of-the-evidence-and-structured-decision-making#appraisal-of-the-evidence (accessed 20.01.16).
2. National Institute for Health and Care Excellence. Appraisal consultation document: Nivolumab for previously treated locally advanced or metastatic squamous nonsmall-cell lung cancer. Available at: http://www.nice.org.uk/guidance/GID-TAG506/documents/appraisal-consultation-document (accessed 20.01.16). 2015.
3. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
5. NICE. Nintedanib for previously treated, locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). Available at: http://www.nice.org.uk/guidance/ta347 (accessed October 20, 2015). 2015.

Other reference

National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1975-2012: Table 15.28. Cancer of the lung and bronchus (invasive): percent distribution and counts by histology among histologically confirmed cases, 2008-2012. Available at: http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.28.html. Accessed October 8, 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Independent Cancer Patients' Voice

Your position in the organisation: Trustee

Brief description of the organisation: ICPV is a patient advocate group independent of established UK cancer charities and aware of the value of medical research to both public health and to the national economy. Our aim is to improve existing treatments for every cancer patient and develop new treatments by bringing the patients' voice into clinical research.

Our funds are used, in the main, for education for members, including study days and the VOICE course, and attending conferences and meetings. We have been fortunate in that so far all our speakers and meeting organisers have donated their time and the costs incurred were put to ensuring volunteers are able to attend. Our income in our first five years has come from a variety of sources, including Pharmaceutical companies (31%), members' fundraising (18%), cancer charities (17%) and clinical trial units (11%).

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

With a range of professional backgrounds and of patient/carer experiences, most of our members are involved with cancer charities and many of us are members of NCRI Clinical Study Groups and sit on a number of cancer & health related research bodies.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ✓ No (specialist comment will be given by our expert nomination)

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

NO

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Being used by more than one tumour group – good use of known knowledge on side effects and tolerance

Are there any other issues that you would like the Appraisal Committee to consider?

Already approved by the FDA

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Our expert nominated member will highlight these points.
-
-
-
-

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of Ramucirumab in the treatment of previously treated locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC), [ID838].

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (NSCLC).

General Points

1. For patients with advanced or metastatic NSCLC, in this second line setting, cure is not a treatment option. Only three second-line therapy options are currently NICE approved – Docetaxel (monotherapy), Erlotinib (note, this is currently undergoing a NICE MTA, so, this may change) and Docetaxel in combination with Nintedanib (adenocarcinoma histology). Nivolumab is currently undergoing NICE assessment.

In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. As available active treatment options are limited in second line NSCLC and as overall outcomes remain poor, the availability of new choices, offer 'hope' for patients

3. The issue of "inverse weighting for duration of life" must be stressed. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

5. The potential of improving quality of life brings obvious benefits. These patients, in general, have quite limited life expectancy. It is of paramount importance, both to them and their families, that they are able to function as fully as is possible, for as long as possible.

This Product

1. Administration
   Ramucirumab is administered intravenously, in combination with Docetaxel.

2. Side effect profile
   In the anecdotal patient experience reported to us, patients report side effects associated with Docetaxel – neutropenia, hair loss, fatigue, stomatitis, nausea. We understand that the addition of Ramucirumab can cause severe bleeding, blood clots, elevation of blood pressure and may impair wound healing.

3. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available. However, we note the Phase III Study of 1,253 patients, with previously treated locally advanced or metastatic NSCLC. Results showed that participants who received Ramucirumab plus Docetaxel survived an average 10.5 months from the start of treatment, compared to an average of about 9 months for participants who received only Docetaxel.

4. As noted above, for this patient group, prognosis is very poor. Thus, even relatively small benefits of extension to life can be disproportionately large for patients.

   Our observations come from a combination of one-to-one discussion with lung cancer patients, published research and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer, who have progressed after first line therapy, are in a particularly devastating situation. There is a need for new improved therapy options.

[redacted], **RCLCF.**

December 2015.

Professional Organisation Statement

Single Technology Appraisal:
Ramicirumab for treating non-small cell lung cancer of adenocarcinoma subtype that has progressed following prior chemotherapy (ID838)

Prepared by [redacted]
Organisation: RCP/NCRI/BTOG

Role:

- Specialist in the treatment of people with the condition for which NICE is considering this technology
- Specialist in the clinical evidence base that is to support the technology (involved in clinical trials for the technology)

What is the expected place of the technology in current practice?

Background

Lung cancer is one of the most common cancers in the UK with over 41 thousand new cases being diagnosed each year. In 2010, there were 34,859 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients[1] (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung). Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths and constitutes almost a quarter (24%) of all male deaths from cancer and is also the most common cause of cancer death in women (21%).

The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, an average of 55% of patients who have good performance status (PS 0-1) receive first line chemotherapy[2] (http://www.hscic.gov.uk/lung) with approximately 25% of all patients undergoing systemic treatment. Palliative chemotherapy modestly improves in median survival from 6 months to 8-11 months compared to best supportive care alone[3] for patients with stage IV NSCLC.

NICE guidance on the diagnosis and treatment of lung cancer (CG121) suggests that patients of good performance status (PS 0-1) diagnosed with stage III or IV disease should be offered platinum doublet chemotherapy (cisplatin or carboplatin plus one of the third generation drugs {docetaxel, gemcitabine, paclitaxel or vinorelbine}) in addition to supportive care.

More recently pemetrexed was shown to improve outcomes for patients with NSCLC other than those with predominantly squamous cell histology[4,5]. The guidance goes on to recommend that patients who have progressed following initial chemotherapy should be considered for 2nd line treatment. Approximately 25% of patients who are treated with 1st line chemotherapy go on to receive 2nd line treatment in the UK.

NICE guidance recommends that patients who are suitable for 2nd line treatment can receive Docetaxel. Pemetrexed, although licensed for the 2nd line treatment of non-squamous NSCLC, was not deemed to be cost effective (TA124) and erlotinib has recently been reviewed and is no longer a 2nd line option for patients without an EGFR activating mutation (MTA, review of TA 62 and TA175 {ID620}).

Most recently, nintedanib[6] has been recommended as a possible treatment for patients with NSCLC of adenocarcinoma subtype in combination with docetaxel after 1st line chemotherapy (TA347). This recommendation has resulted in nintedanib being available in clinical pracitce in this indication since October 2015. Data on nintedanib usage is not yet available.

Clinical practice is standarised according to NICE guidance in England and with regard to 2nd line treatment there is very little geograpghical variation. However socio-economic variability means that in some areas patients are fitter with fewer co-morbidities and are more likely to access 2nd line treatment, either as standard care or as part of a clinical trials.

Clinical Practice

In UK clinical practice docetaxel is now the only NICE approved 2nd line chemotherapy treatment, and can be used in combination with nintedanib for those patients with an adenocarcinoma subtype. Docetaxel treatment is only suitable for the fittest patients (PS 0-1) due to the burden of toxicity associated with therapy, in particular myelosuppression and neutropaenic sepsis rates are high, but nausea, vomitting, lethargy, alopecia and arthralgia are also common. The toxicity associated with docetaxel limits the number of patients who are suitable for currently available 2nd line therapy.

The Technology

The REVEL study[7] reported on outcomes of patients who received ramicirumab plus docetaxel compared to placebo plus docetaxel and is the basis of the NICE submission. The study was a well designed, large, randomised phase III trial which recruited 1253 patients with NSCLC. The trial recruited patients in the UK and the overall population in the trial was similar to the UK population who would be eligible for treatment.

The major finding of the trial is that ramicirumab improves overall survival (HR 0.86, CI 0.75-0.98) without any deterioration in quality of life compared to docetaxel plus placebo. The

degree of benefit is similar to that seen with the addition of nintedanib to docetaxel in the adenocarcinoma population of the LUME Lung 1 study (HR 0.83 [CI 0.70-0.99])[6].
The technology is a monoclonal antibody which binds to VEGFR2 and inhibits angiogenesis. Consequently there are a number of toxicities of special interest which are associated with antiangiogenic therapy that require scrutiny, however, ramicirumab was generally well tolerated. Of note the study reported increased bleeding events of any grade (15% to 29%) but there was no difference in grade 3 or higher events. There was no difference in haemoptysis, gastrointestinal haemorrrhage or perforation. Hypertension of all grades was more common (5% versus 11%), but was generally managable.

A number of hypothesis-generating subgroup analyses of the REVEL study have been carried out, including exploration of histological subtype and age. The hazard ratio for squamous disease was 0.88 (CI 0.69-1.13) compared to 0.83 (CI 0.71-0.97) for non-squamous disease, but the study was not powered for subgroup analysis. The only subgroup which did not seem to benefit from therapy was patients >70 years (HR 1.07, CI 0.80-1.43). Older patients have demonstrated relatively less benefit from a variety systemic treatments in different clinical senarios which may be related to increased toxicity and less exposure to drug.

Ramicirumab is not currently used in clinical practice although clinicians may have experience using the drug from clinical trials and other disease areas (eg gastric cancer). It could be used for patients of all histologies and no subgroups of patients deriving greater benefit have been robustly identified.

Where is the technology used?

The technology is used in secondary care and administered through oncology out-patient chemotherapy suites.
The majority of patients recieving ramicirumab in combination with docetaxel would have the same frequency of visits to the chemotherapy suite, oncology outpatient clinic and CT scan department, as patients receiving docetaxel alone and would be very similar to current standard care. However, there is potential for a small proportion of patients to go on to receive a longer duration of therapy than would be usual in standard UK practice. These patients would have additional visits to the chemotherapy suite (x1 every 3 weeks), oncology outpatient clinics (x1 every 3 weeks), blood tests (x2 every 3 weeks) and potentially an average of 1 extra CT scan.

Guidelines

At present the NCCN guidelines version 2.2016[8] recommends ramicirumab with docetaxel as a 2nd line treatment option for patients with NSCLC of all histologies.
ESMO and ASCO guidelines have not yet been updated.

The advantages and disadvantages of the technology

The main advantages of the technology under appraisal are:

1. Ramicirumab in combination with docetaxel compared to docetaxel alone improves median overall survival from 9.1 to 10.5 months (HR 0.86, CI 0.75-0.98) and progression free survival from 3.0 to 4.5 months (HR 0.76, CI 0.68-0.86)
2. Ramicirumab can be used in patients with all NSCLC histologies, whereas other 2nd line treatments eg nintedanib are restricted to adenocarcinoma.
3. There is no significant increase in grade 3-5 bleeding, proteinuria or gastrointestinal perforation (adverse events of special interest with antiangiogenic therapy)
4. There was no detriment to patient reported QoL by adding ramicirumab to docetaxel

The main disadvantages of the technology under appraisal are:

1. There is a 6% increase in febrile neutropaenia with ramicirumab plus docetaxel compared to docetaxel alone (10% to 16%) and a 10% increase in grade 3-5 neutropaenia (39% to 49%)
2. There is a 4% increase in grade 3-5 hypertension (2% to 6%) with ramicirumab and docetaxel compared to docetaxel alone

3. The technology is administered by iv infusion, thereby increasing chairtime for treatment on the chemotherapy suite.

Any additional sources of information

None identified

Implementation issues

The majority of patients who receive 2nd line treatment in the UK are treated with 4 cycles of docetaxel. The addition of ramicirumab would increase the chair time for a patient on the chemotherapy suite for approximately 1 hour every 3 weeks. There would be no additional visits to clinic, chemotherapy suite or extra pathology or radiology tests in this period. However, in the REVEL study patients were allowed to continue treatment until disease progression and were allowed to continue ramicirumab if deemed to be still deriving clinical benefit, after stopping docetaxel.
The median and mean number of cycles of docetaxel received was 4.0 and 5.5 respectively and the median and mean number of ramicirumab cycles received was 4.5 and 6.1 respectively[7]. If translated into clinical practice this would mean that a small number of patients would have a longer duration of therapy, resulting in a modest but additional burden for the chemotherapy suite, out-patient clinic and CT scanning department.

Equality

There are no equality issues identified, however the technology under assessment does represent an advancement for patients with squamous cell histology. Patients with squamous NSCLC have an enormous unmet clinical need, as outcomes for this group are poorer and no new therapies have been available for this group of patients for more than 10 years.

References

1. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung
2. http://www.hscic.gov.uk/lung
3. Ramalingam S, Belani CP. Systemic chemotherapy for advanced NSCLC: recent advances and future directions Oncologist 2008: 13 (suppl 1) 5-13
4. Scagliotti G, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy naive patients with advanced NSCLC. J Clin Oncol 2008; 26:3543-51
5. Ciuleanu T, Brodowicz T, Zielinski, C. et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for NSCLC: a randomised double blind phase 3 study. Lancet 2009; 374:1432-40
6. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib in patients with previously treated NSCLC (LUME-Lung 1). Lancet 2014; 15:143-155
7. Garon E, Ciuleanu T, Arrieta O, et al. Ramicirumab plus docetaxel versus placebo plus docetaxel for second line treatment of stage IV NSCLC after disease progression on platinum-based therapy (REVEL). Lancet 2014; 384:665-73
8. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NLCFN
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- Yes an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Treatment would be in secondary care in specialist clinic
Patient group numbers low as for those patients previously treated, performance status would need to be good

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Unable to answer as no experience of this drug

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
Nil to add

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nil to add

Professional Organisation Statement

Single Technology Appraisal:
Ramicirumab for treating non-small cell lung cancer of adenocarcinoma subtype that has progressed following prior chemotherapy (ID838)

About you

Your name: Dr [redacted] [redacted] submitting on behalf of:

Name of your organisation:NCRI-RCR-RCP-ACP

Comments coordinated by [redacted] [redacted]

What is the expected place of the technology in current practice?

Background

Lung cancer is one of the most common cancers in the UK with over 41 thousand new cases being diagnosed each year. In 2010, there were 34,859 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients[1] (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung). Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths and constitutes almost a quarter (24%) of all male deaths from cancer and is also the most common cause of cancer death in women (21%).

The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, an average of 55% of patients who have good performance status (PS 0-1) receive first line chemotherapy[2] (http://www.hscic.gov.uk/lung) with approximately 25% of all patients undergoing systemic treatment. Palliative chemotherapy modestly improves in median survival from 6 months to 8-11 months compared to best supportive care alone[3] for patients with stage IV NSCLC.

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More recently pemetrexed was shown to improve outcomes for patients with NSCLC other than those with predominantly squamous cell histology[4,5]. The guidance goes on to recommend that patients who have progressed following initial chemotherapy should be considered for 2nd line treatment. Approximately 25% of patients who are treated with 1st line chemotherapy go on to receive 2nd line treatment in the UK.

NICE guidance recommends that patients who are suitable for 2nd line treatment can receive Docetaxel. Pemetrexed, although licensed for the 2nd line treatment of non-squamous NSCLC, was not deemed to be cost effective (TA124) and erlotinib has recently been reviewed and is no longer a 2nd line option for patients without an EGFR activating mutation (MTA, review of TA 62 and TA175 {ID620}).

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Clinical Practice

In UK clinical practice docetaxel is now the only NICE approved 2nd line chemotherapy treatment, and can be used in combination with nintedanib for those patients with an adenocarcinoma subtype. Docetaxel treatment is only suitable for the fittest patients (PS 0-1) due to the burden of toxicity associated with therapy, in particular myelosuppression and neutropaenic sepsis rates are high, but nausea, vomitting, lethargy, alopecia and arthralgia are also common. The toxicity associated with docetaxel limits the number of patients who are suitable for currently available 2nd line therapy.

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The major finding of the trial is that ramicirumab improves overall survival (HR 0.86, CI 0.75-0.98) without any deterioration in quality of life compared to docetaxel plus placebo. The

degree of benefit is similar to that seen with the addition of nintedanib to docetaxel in the adenocarcinoma population of the LUME Lung 1 study (HR 0.83 [CI 0.70-0.99])[6].
The technology is a monoclonal antibody which binds to VEGFR2 and inhibits angiogenesis. Consequently there are a number of toxicities of special interest which are associated with antiangiogenic therapy that require scrutiny, however, ramicirumab was generally well tolerated. Of note the study reported increased bleeding events of any grade (15% to 29%) but there was no difference in grade 3 or higher events. There was no difference in haemoptysis, gastrointestinal haemorrrhage or perforation. Hypertension of all grades was more common (5% versus 11%), but was generally managable.

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Ramicirumab is not currently used in clinical practice although clinicians may have experience using the drug from clinical trials and other disease areas (eg gastric cancer). It could be used for patients of all histologies and no subgroups of patients deriving greater benefit have been robustly identified.

Where is the technology used?

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Guidelines

At present the NCCN guidelines version 2.2016[8] recommends ramicirumab with docetaxel as a 2nd line treatment option for patients with NSCLC of all histologies.
ESMO and ASCO guidelines have not yet been updated.

The advantages and disadvantages of the technology

The main advantages of the technology under appraisal are:

1. Ramicirumab in combination with docetaxel compared to docetaxel alone improves median overall survival from 9.1 to 10.5 months (HR 0.86, CI 0.75-0.98) and progression free survival from 3.0 to 4.5 months (HR 0.76, CI 0.68-0.86)
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The main disadvantages of the technology under appraisal are:

1. There is a 6% increase in febrile neutropaenia with ramicirumab plus docetaxel compared to docetaxel alone (10% to 16%) and a 10% increase in grade 3-5 neutropaenia (39% to 49%)
2. There is a 4% increase in grade 3-5 hypertension (2% to 6%) with ramicirumab and docetaxel compared to docetaxel alone

3. The technology is administered by iv infusion, thereby increasing chairtime for treatment on the chemotherapy suite.

Any additional sources of information

None identified

Implementation issues

The majority of patients who receive 2nd line treatment in the UK are treated with 4 cycles of docetaxel. The addition of ramicirumab would increase the chair time for a patient on the chemotherapy suite for approximately 1 hour every 3 weeks. There would be no additional visits to clinic, chemotherapy suite or extra pathology or radiology tests in this period. However, in the REVEL study patients were allowed to continue treatment until disease progression and were allowed to continue ramicirumab if deemed to be still deriving clinical benefit, after stopping docetaxel.
The median and mean number of cycles of docetaxel received was 4.0 and 5.5 respectively and the median and mean number of ramicirumab cycles received was 4.5 and 6.1 respectively[7]. If translated into clinical practice this would mean that a small number of patients would have a longer duration of therapy, resulting in a modest but additional burden for the chemotherapy suite, out-patient clinic and CT scanning department.

Equality

There are no equality issues identified, however the technology under assessment does represent an advancement for patients with squamous cell histology. Patients with squamous NSCLC have an enormous unmet clinical need, as outcomes for this group are poorer and no new therapies have been available for this group of patients for more than 10 years.

References

1. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung
2. http://www.hscic.gov.uk/lung
3. Ramalingam S, Belani CP. Systemic chemotherapy for advanced NSCLC: recent advances and future directions Oncologist 2008: 13 (suppl 1) 5-13
4. Scagliotti G, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy naive patients with advanced NSCLC. J Clin Oncol 2008; 26:3543-51
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8. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Raffaele Califano

Name of your organisation

The Christie NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

The current standard of care for EGFR/ALK wild type patients with stage IIIB/IV non-small cell lung cancer (NSCLC) who progress after platinum-based doublet chemotherapy is docetaxel. This drug is approved for squamous and non-squamous histology. Only about 50% of patients who progress after first-line chemotherapy is fit enough to tolerate second-line docetaxel.
Response rate, median progression-free survival and median overall survival with second line docetaxel are 9%, 3-4 months and 8-9 months, respectively.

Very recently nintedanib has been recommended by NICE in combination with docetaxel for treating locally advanced or metastatic adenocarcinoma NSCLC (NICE technology appraisal 347). Nintedanib is an oral drug that is given together with docetaxel chemotherapy (usually 4 cycles) and then continued as a single agent until progressive disease or intolerable toxicity.

Patients with anaplastic-lymphoma-kinase (ALK) positive non-small-cell lung cancer may receive second-line treatment with crizotinib (not recommended by NICE but funded via the Cancer Drugs Fund)

There are some discrepancies across the country regarding the use of second-line docetaxel. The efficacy of docetaxel in terms of overall survival (OS) advantage versus best supportive care is modest and some clinicians use docetaxel rarely. Since NICE recommendation on nintedanib, a number of clinicians have started to use nintedanib in association with docetaxel for fit patients with stage IIIB/IV or recurrent adenocarcinoma NSCLC. On average the prognosis of patients with adenocarcinoma histology is slightly better than patients with squamous histology, this is also due to the fact that patients with squamous histology are usually less fit and have more comorbidities due to the association with smoking.

Nivolumab, an anti PD-1 antibody (immunotherapy) is currently approved by EMA as second-line treatment for patients with advanced squamous NSCLC who progressed after first-line platinum based chemotherapy but is currently not recommended by NICE.

Ramucirumab was investigated in the REVEL study, published on The Lancet in June 2014. The study enrolled patients with advanced NSCLC who progressed after first-line platinum based chemotherapy.
Ramucirumab is an intravenous anti-angiogenic drug that was given together with docetaxel and then continued as a single agent until progressive disease or intolerable toxicity. Notably patients in the study had squamous and non-squamous (eg: adenocarcinoma and large cell) histology but patients with involvement of major blood vessels by the tumor, poorly controlled hypertension, gastrointestinal perforation, arterial thromboembolic events during the previous 6 months, gross haemoptysis and sever gastrointestinal bleeding during the previous 3 months were excluded from the study. Benefit in OS was seen in both squamous and non-squamous histology.

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Ramucirumab should be prescribed by a thoracic oncologist who is experienced in the use of systemic anticancer treatment.

NICE clinical guideline 121 recommends chemotherapy with a platinum drug (carboplatin or cisplatin) in combination with a third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine). Alternatively, people may receive pemetrexed in combination with cisplatin if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (NICE technology appraisal 181). If subsequent treatment is appropriate, docetaxel monotherapy should be considered for people with locally advanced or metastatic non-small-cell lung cancer that has relapsed after previous chemotherapy (NICE clinical guideline 121)

Ramucirumab would be used within its licensed indication.
Guidelines on metastatic NSCLC from the European Society for Medical Oncology (ESMO) (Reck et al, Ann Onc 2014) also recommend docetaxel as second line treatment for patients without an ALK gene rearrangement and with a performance status of 0-2. At the time the ESMO guidelines were published, data on nintedanib, nivolumab or ramucirumab was not available.

The advantages and disadvantages of the technology

Ramucirumab is associated with increased response rate, longer progression free survival and OS over docetaxel. Patients treated with ramucirumab experienced higher incidence of febrile neutropenia, fatigue and hypertension but there was no difference in treatment-related deaths between the two arms. Adding ramucirumab to docetaxel did not worsen quality of life compared to docetaxel alone.

Ramucirumab is administered IV every 3 weeks, with a maintenance phase after docetaxel has been discontinued (usually 4-6 cycles). For this reason, there will be a requirement for extra capacity in treatment units and oncology clinics. Docetaxel is given IV every 3 weeks, usually for up to 6 cycles.

There is no current data on activity of ramucirumab in routine clinical practice compared to that from the clinical trial.

The outcomes measured in the REVEL study (Overall survival, Progression free survival, response rates, adverse events and quality of life) were all appropriate

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

I cannot identify any equality issues.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any other additional sources of evidence

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The infrastructure to deliver ramucirumab already exists.

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Single Technology Appraisal (STA)

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Patient/carer expert statement (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Tom Haswell
Name of your nominating organisation: Independent Cancer Patients Voice
Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☑ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?

☑ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☑ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with NSCLC in 1993 and told there was no treatment which would have any effect on my lung cancer and I was given a very short life expectancy. I took part in an early phase clinical trial of gemcitibine and cisplatin which proved to have a positive effect and this was followed by radiotherapy. The outcome was/is I am registered disabled, medically retired unable to work, but alive and with a quality of life acceptable to me considering the prognosis I was given. The impact of lung cancer totally changed my life, my background was in engineering and I worked overseas for many years, in fact my diagnosis was in Jeddah, Saudi Arabia and was picked up at a routine employment medical. What made it more surprising was the fact that I had no outward symptoms that would have indicated to me that I should present to a doctor yet I had a 7cm. by 4cm tumour and infected nodes. As you can imagine, the impact of the diagnosis on my family was severe but made many times worse when we were told of my short life expectancy, so you can see how lung cancer can affect people other than the patient. The side/after effects of lung cancer and the treatments can be considerable, in my own case pneumonitis, pulmonary fibrosis and bronciectasis. I have been very fortunate and without being melodramatic, if I had not been given the opportunity of taking part in the clinical trial I would not be around today. Taking part in the clinical trial created an interest in me in medical research and for many years I have been involved in patient issues, service delivery and research with the emphasis on research and in particular lung cancer. I am involved in various committees, organisations and groups which have included membership of the NICE GDG which reviewed and updated the lung cancer guidelines in 2011 and I was also a member of a NICE Expert Diagnostic Advisory Group which reported on EGFR test

equipment for lung cancer patients and patient " expert " on the NICE STA for ceritinib for ALK+ lung cancer patients. I was a member of the NCRI Lung Clinical Studies Group from 2006 until 2012 and have recently been reappointed to that CSG. I am also involved as co-applicant, collaborator, advisor on various research studies, many involving lung cancer and am and have been a member of TMG's and TSC's.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Cure and overall survival are the most important outcomes in my opinion, but being realistic and being aware of the condition, quality of life is a major factor and unfortunately some patients have got to decide in certain circumstances if they prefer a shorter life expectancy with good quality of life, or longer life expectancy with not so good quality of life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

My understanding is that not all approved treatments are available to all patients.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)

- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Ramucirumab in combination with docetaxel would appear to improve overall survival with no loss of quality of life compared to docetaxel alone.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Can be a treatment for all non small cell lung cancer patients whose illness has progressed after platinum based treatment. Potential for some patients to receive additional cycles of treatment.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not known.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Availability of treatments locally.

Please list any concerns you have about the treatment being appraised.

Possibility of slight increase in some side effects but suggest these would be tolerable and acceptable to patients.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not known

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

It would appear to benefit all NSCLC patients including subtypes and mutations.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not certain but perhaps older patients with additional serious co-morbidities, but this would not be unique to ramucirumab+docetaxel.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

N/A

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Improved overall survival with no apparent loss of quality of life is important to patients.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but

have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☑ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Not aware of any equality issues.

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Would appear to be a beneficial treatment for all NSCLC patients after 1st line platinum treatment.

Is there anything else that you would like the Appraisal Committee to consider?

Please place emphasis on clinical benefit over cost.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- No detriment to quality of life.
- Treatment suitable for all NSCLC patients.
- Improvement in overall survival.
- Improvement in progression free survival.
- To NSCLC patients all of above are immeasureable.

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

Produced by ERG: Warwick Evidence

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Date completed: 24/02/2016

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/69/07

Declared competing interests of the authors:
Adam Dangoor has previously received consultancy fees from Boehringer Ingelheim

Acknowledgements

We thank Michael Crowther, University of Leicester, for statistical advice.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer: A Single Technology Appraisal. Warwick Evidence, 2016.

Contributions of authors

Emma Loveman (Senior Researcher) co-ordinated and conducted the critique of clinical effectiveness evidence; Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence; Martin Connock (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and undertook additional analyses; Xavier Armoiry (Senior Visiting Fellow) conducted the critique of clinical effectiveness; Pam Royle (Research Fellow) conducted the critique of the company searches; Jill Colquitt (Senior Researcher) conducted the critique of clinical effectiveness, Jeremy Rodrigues (NIHR fellow) and Adam Dangoor (Medical Oncologist) provided comment on the report and clinical input respectively; Andy Clegg (Senior Researcher) provided methodological support to the network meta-analysis critique, and Aileen Clarke (Professor of Public Health and Health Services Research) co-ordinated the project and provided comment on the report.

Word count: 50049.

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

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AIC	Akaike Information Criterion
ALK+	Anaplastic Lymphoma Kinase Positive
ALT	Alanine Amino Transferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BSA	Body Surface Area
BSC	Best Supportive Care
CEAF	Cost-effectiveness Acceptability Frontier
CI	Confidence Interval
CMU eMIT	Commercial Medicines Unit electronic market information tool
CR	Complete Response
CS	Company Submission
CT	Computerised Tomography
DCR	Disease Control Rate
DOC	Docetaxel
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol – 5 Dimensions
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FDA	Food and Drug Administration
HRQoL	Health Related Quality of Life
KM	Kaplan Meier
LUCADA	Lung Cancer Audit Data Set
LCSS	Lung Cancer Symptom Scale
LL	Log logistic
LYG	Life Years Gained
ICER	Incremental Cost-Effectiveness Ratio
IV	Intravenous

MV	Multivariate
NCIN	National Cancer Intelligence Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIN	Nintedanib
NIV	Nivolumab
NLCA	National Lung Cancer Audit
NMA	Network Meta-Analysis
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PBO	Placebo
PFS	Progression-Free Survival
PPS	Post-Progression Survival
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RAM	Ramucirumab
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response rates
SD	Standard Deviation
SPC	Summary of Product Characteristics
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor
WTP	Willingness To Pay

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The CS decision problem matches the population, interventions and outcomes described in the final NICE scope, as seen in Box 1. The CS decision problem differs from the NICE scope on the comparators, with nivolumab and crizotinib being excluded from the decision problem.

Ramucirumab is indicated in patients with gastric cancer and is currently awaiting marketing authorisation to be used intravenously in combination with docetaxel for non-small cell lung cancer. A positive opinion recommending changes to the marketing authorisation of ramucirumab was adopted by the Committee for Medicinal Products for Human Use in December 2015 to include adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy.

Box 1: NICE final scope

	Final scope issued by NICE
Population	People with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed after platinum based chemotherapy.
Intervention	Ramucirumab in combination with docetaxel
Comparator (s)	Docetaxel Erlotinib (subject to ongoing NICE review) Nintedanib in combination with docetaxel (adenocarcinoma tumour histology) Nivolumab (squamous tumour histology), subject to ongoing NICE appraisal Crizotinib for people with anaplastic-lymphoma-kinase (ALK)-positive NSCLC
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life

1.2 Summary of submitted clinical effectiveness evidence

The CS undertook a systematic review to search for evidence of relevance to the decision problem, including searches for studies on the intervention and separate searches for comparator studies for a network meta-analysis.

The CS includes direct evidence of ramucirumab in combination with docetaxel compared with placebo and docetaxel from one phase 3 RCT. The CS presents outcomes of survival (overall survival and

progression free survival), response rates, health-related quality of life (HRQoL) and adverse events. The REVEL trial was of good quality, with a low risk of bias in most domains although there is the potential for attrition bias and selective reporting bias. Participants with disease progression following first line chemotherapy were eligible for inclusion in the trial if they were in stage IV NSCLC with a performance status of 0-1 indicating minimal impact on day to day activities.

- The hazard ratio (HR) for overall survival (OS) indicated significantly better survival in those treated with ramucirumab + docetaxel compared with placebo + docetaxel (HR 0.86, 95% CI 0.75, 0.98) suggesting a 14.3% reduction in risk.
- For progression-free survival (PFS), defined as time to disease progression or death, the HR from the trial suggested a 24% reduction in risk (HR 0.76, 95% CI 0.68, 0.86) with ramucirumab + docetaxel.
- Objective response rate (ORR) was higher with ramucirumab + docetaxel than with placebo + docetaxel. ORR was 22.9% (95% CI, 19.7, 26.4) in the ramucirumab and docetaxel group and 13.6 % (95% CI, 11.0, 16.5) in the docetaxel group ($p<0.001$).
- There were no significant differences observed between groups on measures of HRQoL.
- A high proportion of patients in both groups experienced adverse events of any grade and the proportion of participants who experienced at least one serious adverse event was similar between groups. A higher proportion of the ramucirumab + docetaxel group experienced adverse events of Grade 3 or above than the placebo + docetaxel group (78.9% vs. 71.8%). Grade 3+ adverse events with a higher incidence (≥5%) in the ramucirumab + docetaxel group were neutropenia and febrile neutropenia.

The CS presented indirect evidence for comparisons with erlotinib (in EGFR mutation negative NSCLC) and nintedanib + docetaxel (in non-squamous NSCLC) via a network meta-analysis (NMA). The network included a wider range of comparator treatments for second line NSCLC and was undertaken using a fixed-effect hierarchical exchange model which enables the inclusion of study level variables such as the relevant sub-populations of interest. The ERG has a number of concerns about the NMA, its reporting, methodology and outcomes as discussed subsequently. Results presented by the CS are:

- Ramucirumab + docetaxel showed a significantly greater OS than placebo + docetaxel in line with the results of the REVEL trial. The comparison of ramucirumab + docetaxel with combination nintedanib + docetaxel in the non-squamous subpopulation shows no significant

difference in OS (HR 1.10 (95% CI 0.82, 1.25). The comparison with erlotinib showed greater OS with ramucirumab + docetaxel.

- Similar results were observed for PFS and ORR.
- A post-hoc subgroup analysis comparing ramucirumab + docetaxel with nintedanib + docetaxel in the adenocarcinoma population, in which nintedanib is indicated, were similar for OS and PFS.

1.3 Summary of the ERG's critique of submitted clinical evidence

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial that compared ramucirumab with one of the scoped comparators, docetaxel. The outcomes and analytical approach to the phase 3 trial were appropriate. The population in the trial appear to be relevant to those treated in the NHS and the ERG do not have any reason to consider the results of the trial to be significantly biased.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of a scoped comparator, nivolumab, from the decision problem. Nivolumab in the squamous NSCLC population is currently being considered by NICE in an ongoing appraisal. For this reason the CS consider that nivolumab is not a relevant comparator as it is not currently used in NHS practice. The ERG has considered the clinical effectiveness evidence for this potential comparator.
- The evaluation of the NMA is restricted, in part owing to the limited details provided as regards some aspects of the analysis and results.
- The ERG agrees with the rationale presented in the CS for using hierarchical models for the NMA. Comprehensive heterogeneity and inconsistency analyses revealed complex treatment-by-covariate interactions and limited trial evidence which could result in uncertainty in the analysis which was accommodated through exchangeability.
- The assumption of similarity in the NMA is not stated or justified in the CS. The ERG note any known differences between the studies of relevance to the scope but have not been able to assess similarity between the wider studies included in the NMA.
- Assumptions of the survival data compared in the NMA are questioned by the ERG, in particular the assumption of proportional hazards and the potential for adjusted HRs to result in double counting of variables.

1.4 Summary of submitted cost effectiveness evidence

The company presents a model that partitions patients to be in one of three health states:

- Progression free survival;
- Post progression survival; and,
- Dead.

A three week cycle is used in order to be aligned with the ramucirumab dosing frequency. The time horizon is 15 years with perspectives being as per the NICE methods guide.

For the all patient modelling ramucirumab + docetaxel is compared with:

- Docetaxel

For the EGFR negative modelling ramucirumab + docetaxel is compared with:

- Erlotinib
- Docetaxel

The company argues that given the recent NICE recommendation for erlotinib that this comparison is now irrelevant. The ERG agrees with this. While the body of the ERG report presents these results in full they are not considered in this summary.

For the non-squamous modelling ramucirumab + docetaxel is compared with:

- Nintedanib + docetaxel
- Docetaxel

Parameterised curves are estimated from REVEL for OS and PFS with a number of covariates. A pooled analysis is undertaken for OS, while for PFS separate curves are fitted for ramucirumab + docetaxel and for docetaxel. The non-squamous covariate coupled with the application of the non-squamous subgroup baseline characteristics yields the subgroup specific curves. Based largely upon information criteria the company chooses the log logistic for OS and the generalised gamma for PFS.

To derive the curves for nintedanib + docetaxel the hazard ratios of the company NMA are applied to the docetaxel curves.

The REVEL EQ-5D post baseline on treatment values are pooled between the arms to yield the quality of life value for PFS. Similarly, the post end of treatment REVEL EQ-5D quality of life values are pooled between the arms to yield the quality of life value for post progression survival (PPS).

The number of drug administrations for ramucirumab and docetaxel are drawn from the REVEL trial, with the number of ramucirumab vials and docetaxel vials that are required per administration being further conditioned by a drug utilisation percentage. The number of drug administrations for nintedanib is based upon the inferred PFS curve, with this also being conditioned by a drug utilisation percentage.

Patients are assumed to receive ongoing monitoring, with an outpatient visit every three weeks in both progression free and post progression survival.

For the all patient modelling, compared to docetaxel this results in estimates of net costs of £24,288, net gains of 0.125 QALYs and a cost effectiveness of £195k per QALY.

For the non-squamous modelling, compared to docetaxel this results in estimates of net costs of £25,255, net gains of 0.139 QALYs and a cost effectiveness of £182k per QALY.

For the non-squamous modelling, compared to nintedanib + docetaxel this results in estimates of net costs of £11,724, net gains of 0.011 QALYs and a cost effectiveness of £1.1mn per QALY.

1.5 Summary of the ERG's critique of submitted cost effectiveness evidence

The ERG views the model structure as appropriate to the decision problem.

Most of the ERG critique of the economic evidence submitted by the company is summarised in Section 1.6 and as a consequence is not repeated here.

1.5.1 Strengths

The CS had several strengths.

- Overall, quality of the systematic review was deemed to be reasonable, and assessment of risk of bias of the pivotal RCT was generally appropriate.
- The quality of the included trial was good with a low risk of bias.

- Results for the trial were accurately presented and showed the risks and benefits from the addition of ramucirumab to docetaxel, one of the scoped comparators.
- The model is generally well constructed and transparent. While there are elements of disagreement between the company and the ERG, the ERG does not have the impression that the economic modelling has been heavily influenced by the company. What disagreements there are are largely transparent. The company is to be commended for presenting data in its submission and electronic model that permits an exploration of much of this; e.g. including the unadjusted models.
- Standard sources for costs are used and are well documented.

1.5.2 Weaknesses and areas of uncertainty

The CS excluded two scoped comparators from their decision problem. The ERG agrees with the exclusion of crizotinib, however, does not believe that the exclusion of nivolumab is justified, not least because there was RCT evidence identified by the CS that could have allowed this comparison to be made.

There is only one comparative study of ramucirumab, therefore, the assessment of the treatment effects of ramucirumab compared with comparators other than docetaxel relied on indirect comparisons via a NMA. There are a number of areas of uncertainty with the NMA which lead to the ERG to recommend the results be interpreted with caution:

- The NMA appears to adequately meet the assumption of homogeneity and partly the assumption of consistency. The assumption of similarity is not stated or justified in the CS.

- Results were presented for the Bayesian NMA for the fixed-effect hierarchical models with no covariates only. Those for the random-effects hierarchical models with no covariates and the fixed-effects hierarchical model with covariates were presented in clarifications from the company. There was little difference in terms of the model fit but the random effects model produced wider credible intervals with many outputs no longer being significant.

- Although the fixed effect hierarchical model appears to have accounted for some heterogeneity, it is evident that there was inconsistency in the analyses.

- The CS notes that the NMAs may have contained fewer studies than previous analyses of these interventions, due to a requirement to include patients' characteristics. These may have reduced the information available to estimate the heterogeneity.

- The CS produced NMAs using hazard ratio and count data. Few details for the methods are presented. The NMA appears to assume that treatment baselines and treatment effects on the log hazard scale were normally distributed. For the count data, a binomial model was used. Bayesian vague priors (when the value of a parameter is unknown) were specified for the baseline treatment effects, treatment effects and class effects in the NMAs but although these are often used there does not appear to be any sensitivity analyses around the priors. No results of tests assessing convergence were presented.

- The NMAs of OS and PFS used hazard ratios, assuming proportional hazards. Although a visual inspection was used to assess this assumption, formal testing was only conducted on those where it was felt the assumption was not met. No further details are provided.

The log logistic curves of the adjusted analysis for OS have quite a long tail that might not be justified during extrapolation.

There is a lack of exploration of fitting separate curves to the different arms of REVEL and the different subgroups of REVEL and what might be an over reliance upon the multivariate analyses.

There is some lack of consideration of the REVEL EQ-5D data used within the model and how this tallies with that presented in appendix 11 of the submission. The ERG is confused by elements within appendix 11 of the submission. The mean values are statistically different at baseline and during PFS between the arms with the mean values crossing over in favour of docetaxel. But the changes from baseline are not statistically significantly different despite their standard errors.

It is assumed that those in post progression survival do not experience any decline in their quality of life over time. The literature and the REVEL EQ-5D data suggest otherwise.

There may be some uncertainty as to whether, given the parameterised PFS curves, the mean administrations during REVEL are most appropriate for costing purposes. Since ramucirumab is

administered until progression or unacceptable toxicity some consideration of the parameterised PFS curve in part determining the number of administrations might be warranted.

The drug utilisation percentage applied for ramucirumab does not appear to be justified, while nintedanib might not have its drug utilisation percentage reduced sufficiently to reflect the nintedanib trial.

It may be questionable for the balance between the survival gains to be broadly equally divided between that pre and that post progression. If so, this may call into question either the OS curves, the PFS curves or both.

There is an unfortunate error in the discounting applied within the model. Correcting this improves the cost effectiveness estimates for ramucirumab + docetaxel compared to docetaxel and worsens it for the comparison of ramucirumab + docetaxel with nintedanib + docetaxel.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has made a number of revisions to the company base case. The overall impact of these is to tend to improve the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel in the all patient modelling, but to worsen it for ramucirumab + docetaxel compared to nintedanib + docetaxel in the non-squamous patient modelling.

Briefly summarising these, for the comparison of ramucirumab + docetaxel with docetaxel across the all patients group a net cost of £26,161 is associated with a net gain of 0.150 QALYs resulting in a cost effectiveness estimate of £175k per QALY. Central probabilistic estimates are in line with this and there is no probability of ramucirumab + docetaxel being cost effective for willingness to pay values up to £100k per QALY.

In the all patient modelling, the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel shows some sensitivity to:

- The use of the unadjusted company curves which worsens it to £204k per QALY
- Applying the Weibull rather than the log logistic for OS which worsens it to £217k per QALY
- Applying the Kaplan-Meier (KM) PFS curve rather than the parameterised curve which worsens it to around £182k per QALY

- Reinstating the company drug utilisation percentage for ramucirumab which improves it to £167k per QALY
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve which worsens it to £247k per QALY.
- Revising the REVEL PFS QoL values to be treatment specific as might be implied by appendix 11 of the company submission which worsens it to £218k per QALY

The scenario analysis of applying the ERG linear trend curves to the squamous subgroup results in a cost effectiveness estimate for the squamous subgroup that is approximately £10k per QALY better than the corresponding estimate for all patients. The smaller net patient gain is more than offset by a reduction in the net costs. But it should be stressed that the reduction in net costs arises from an ERG estimate of reduced drug use among the squamous subgroup, and that this estimate has not been confirmed with the company.

For the comparison of ramucirumab + docetaxel with docetaxel in the non-squamous population the revised ERG base case results in net costs of £27,268 and a net gain of 0.167 QALYs and so a cost effectiveness estimate of £163k. The comparison with nintedanib + docetaxel has net costs of £12,899 and net gains of 0.008 QALYs and a cost effectiveness estimate of £1.6mn. Probabilistic modelling suggests that there is no probability of ramucirumab being cost effective for willingness to pay values up to £100k per QALY.

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS which worsens it to £188k per QALY
- Applying the ERG linear trends OS curves improves it to £114k per QALY.
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £156k per QALY
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £232k per QALY.
- Revising the REVEL PFS QoL values to be treatment specific as might be implied by appendix 11 of the company submission worsens it to £199k per QALY

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to nintedanib + docetaxel typically suggests small QALY gains or losses which render the cost effectiveness estimate unstable. The base case net cost estimate of £12,899 shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS worsens it to £13,563
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £11,660
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £24,374
- Assuming a febrile neutropenia cost of £7,352 worsens it to £13,372

Not tapering the OS hazard ratio and applying the company hazard ratio for ramucirumab + docetaxel both cause the model to estimate that nintedanib + docetaxel provides small patient gains and so dominates nintedanib + docetaxel.

The scenario analysis of applying the ERG linear trends curves to the adenocarcinoma subgroup results in a cost effectiveness estimate for the adenocarcinoma subgroup that is approximately £14k per QALY worse than the corresponding estimate for the non-squamous subgroup. Within this the ERG retained the drug use estimates for the non-squamous subgroup.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company states on CS page 27 that the predominant form of lung cancer is NSCLC which accounts for 85% to 90% of all cancers, this estimate was extracted from an European Society for Medical Oncology guideline published in 2012.[1] More recent data from the National Lung Cancer Audit (NLCA), published in 2015 for the period 2014,[2] states that NSCLC represent 88.1% of all form of lung cancers (excluding mesothelioma).

On CS pages 12 and 27, the company states that lung cancer survival has not shown much improvement in the last 40 years. The ERG agrees with this statement when compared to other cancer types. Data from the National Cancer Intelligence Network (NCIN)[3] has, however, emphasized that lung cancer survival has improved over the past two decades and more so among women than men. Whereas 17% of male and female lung cancer patients were alive one year after diagnosis in 1990, 29% of men and 33% of women diagnosed with lung cancer in 2010 survived one year (Figure 1). [3]

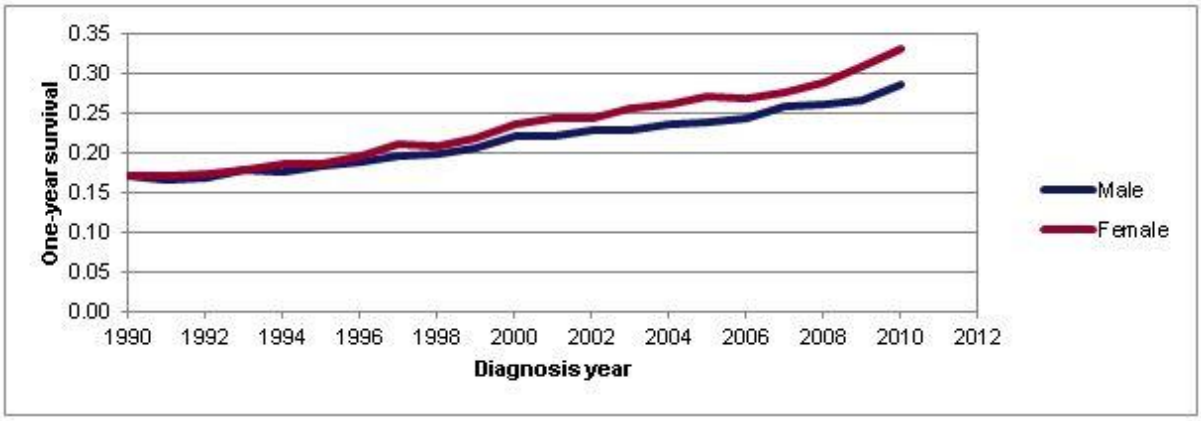


Figure 1: Lung cancer survival 1990 to 2012

On CS pages 12 and 27, the company states that lung cancer survival lags behind those in some comparative European countries. While this is true, it is thought that the poorer survival is predominantly due to larger numbers of patients being diagnosed with late stage disease (therefore excluding them from potentially curative surgery)[4] and does not seem related to a restricted access to anticancer therapies. Consequently, the statement is not linked to the population of patients potentially eligible to ramucirumab which is mainly patients with stage IV NSCLC.

On CS page 28, the company emphasizes the key role of histology and molecular testing both as prognostic factor and as determinant for treatment choice among NCSLCs. According to histology, there are three main subtypes of NSCLCs: squamous cell carcinoma (about 25-30% of lung cancers), adenocarcinoma (about 40%), and large cell (undifferentiated) carcinoma (about 10-15%). Adenocarcinoma and large cell carcinoma combined are classified as non-squamous NSCLCs. For a same disease stage, squamous NSCLCs have a poorer prognosis compared to adenocarcinomas.

It is also known that tumour susceptibility varies depending on the chemotherapy agent. Two main gene mutations are now recommended for molecular testing as they are strong predictors for response to targeted therapies. The first is epidermal growth factor receptor (EGFR) mutation which predicts response to EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, and afatinib. Overexpression of EGFR by mutation is found in about 10-16% of adenocarcinoma in European patients but rarely found in squamous cell carcinomas.[5] EGFR mutation testing is consequently recommended in non-squamous NSCLCs.

The second oncogenic driver is the anaplastic lymphoma kinase (ALK) fusion gene which is a predictor for ALK-targeted inhibitors response like crizotinib. The ALK fusion is encountered more frequently in never smokers, the adenocarcinoma subtype, and in younger patients, representing an incidence of 3-5% in adenocarcinomas.[5] There is no molecular biomarker to predict patient response to therapies targeted to Vascular Endothelial Growth Factor (VEGF) receptors like ramucirumab.

2.2 Critique of company's overview of current service provision

The CS presents a treatment pathway for NSCLC on page 32 and corresponding text on pages 33-35. The treatment pathway for first line and maintenance therapy is in line with current standards.

When the company prepared its submission there was an ongoing NICE appraisal for EGFR TK inhibitors in patients that have progressed after prior therapy. The CS reflected on the appraisal consultation document and reasoned that for second line therapy those with EGFR negative mutations were the likely eligible population which the CS states is in line with clinical practice following advice from UK clinical experts. Subsequent to the submission NICE published guidance on the use of erlotinib as a second-line therapy (Section 3.3) and as such the inclusion of erlotinib in the EGFR negative population is not appropriate (as confirmed in clarifications from the company).

The company justifies the non-inclusion of nivolumab by its current non-availability in routine use in UK clinical practice and does not consider this agent as an appropriate comparator. The ERG considers that nivolumab should be considered (see Section 3.3).

The company states on CS page 189 that based on incident cases of lung cancer (about 32,000 out of which 84% are NSCLCs based on statistics from the period 2013[6] and the estimated proportion of patients receiving second-line therapy (about 28%),[7] the total eligible patient population is 1,052. The proportion of 84% (CS Table 95, page 189) corresponds to all lung cancer cases excluding SCLC and mesothelioma. Of these 20,409 were histologically confirmed NSCLCs and 8,389 were categorised as 'other'. Consequently, based on the LUCADA statistics, the proportion of confirmed NSCLCs is lower than 84%. In addition, the proportion of 84% that is stated in the LUCADA statistics are actually for the overall England and Wales cases of lung cancers (34,468 in total) and not solely for England cases. The calculations by which the total eligible population is found to be 1,052 is therefore unclear. Furthermore, the proportion (23.12%) of patients with performance status 0-1 and stage IIIB/IV NSCLCs extracted from the LUCADA data cannot be easily verified within the audit. However, assuming this proportion is valid, 23.12% of 19,198 patient's leads to 4,438 cases with performance status 0-1 and stage IIIB/IV NSCLCs and if 28% receive second line treatment, the estimated eligible population is 1,242 which slightly differs compared to the CS.

The pages 190-191 of the CS present the budget impact analysis based on projections on future market share with ramucirumab. With the exclusion of nivolumab from the submission it is not possible to apply much confidence to these budget impact projections. The CS notes that the picture is expected to change as newer agents are made available in routine NHS use.

2.3 Changes to service provision

The company notes that the only additional tests that are required during the course of treatment with ramucirumab are blood pressure and urinalysis. Furthermore, ramucirumab is administered on the same hospital outpatient stay as docetaxel on day 1 of a 21 day cycle. The CS states that as such, there is no expectation that ramucirumab will increase resource use apart from drug costs. The ERG agrees with this statement in cases where ramucirumab is discontinued concomitantly to docetaxel. However, the mean number of administrations for ramucirumab and docetaxel that was reported on REVEL was 6.1 and 5.5 respectively for the treatment arm and 4.9 administrations for the docetaxel alone group (CS Table 60).

This indicates that patients are likely to receive more ramucirumab infusions compared to docetaxel which will also necessitate more hospital stays compared to patients treated with docetaxel alone.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population in the decision problem, and subsequent clinical evidence, matches the population described in the final scope. The population of relevance is people with locally advanced or metastatic NSCLC who have progressed after platinum based chemotherapy.

3.2 Intervention

The intervention in the decision problem is ramucirumab in combination with docetaxel and this matches the final scope. The company provides a description of the technology and the mechanism of action of ramucirumab (CS page 22) which the ERG clinical advisor has confirmed is accurate. Ramucirumab is an intravenously administered medication already authorised for use in patients with gastric cancer. On 17 December 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinions recommending changes on the marketing authorisation of ramucirumab in two new indications:1) the treatment in combination with docetaxel of adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy; 2) the treatment in combination with FOLFIRI of adult patients with metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.[8] Consequently, EMA authorisation is anticipated end-February 2016. According to the summary of product characteristics of ramucirumab in gastric cancer, ramucirumab is a human receptor-targeted antibody that specifically binds Vascular Endothelial Growth Factor (VEGF) Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells.

The indication of ramucirumab in NSCLC, which is the target of NICE scope, has already been approved by the U.S. Food and Drug Administration (FDA) (gained on 12th December 2014).[9] The conclusions of the FDA was that ramucirumab given in combination with docetaxel meets the criteria for approval and has a favourable risk-benefit profile for the treatment of patients with metastatic NSCLC who have

progressed on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.

The FDA has emphasized some areas of uncertainties on the risk/benefit analysis of ramucirumab. First, the safety and efficacy of ramucirumab have not been adequately evaluated in patients with EGFR mutation or ALK rearrangement-positive NSCLC. Second, the benefit of adding ramucirumab to docetaxel in older patients is unclear.

Ramucirumab will be assessed by the Scottish Medicines Consortium in 2016.

Table 7 in the CS (page 24-5) summarises administration and costs of ramucirumab, and information provided in this table regarding the treatment administration concur with those in the REVEL trial. The cost of a course of treatment was calculated based on data on drug wastage and patient weight in the REVEL trial. The calculated cost is consistent with data provided on patients' weight and men/women proportions stated on CS page 149. In Table 7, the dose adjustments section specifies that the mean relative dose intensity of ramucirumab was 94.6% in the REVEL trial (mean dose of 9.5mg/kg, Table 59, page 149). Ramucirumab is given in combination with docetaxel (intended dose 75mg/m^2). For docetaxel the dose intensity varied in the REVEL trial, in those treated with ramucirumab and docetaxel this was a mean dose of 68.3mg/m^2 and in those treated with placebo and docetaxel this was a mean dose of 70.2mg/m^2.

3.3 Comparators

The comparators described in the decision problem are docetaxel, erlotinib in EGFR-negative patients only, nintedanib in combination with docetaxel for adenocarcinomas only. This differs substantially compared to the NICE final scope as follows:

The company has excluded nivolumab and crizotinib from the list of comparators. The reason for excluding nivolumab is because a STA is being undertaken by NICE on nivolumab (on the licensed population of squamous NSCLC) and the CS states it is therefore not currently available for patients within the NHS. The ERG notes that erlotinib was also subject to ongoing NICE review but this wasn't excluded from the list of comparators in the decision problem. In addition, ramucirumab is currently not available within the NHS but its clinical effectiveness is being reviewed. Consequently, the ERG

considers that the exclusion of nivolumab is not justified and that nivolumab should be included. The ERG considers that the exclusion of crizotinib is reasonable. People with NSCLC that is anaplastic-lymphoma-kinase (ALK) positive would be unlikely to receive ramucirumab given a targeted therapy (crizotinib) is available through the cancer drug fund. In addition, ALK mutation was not collected routinely in the REVEL trial.

The target population of erlotinib has been restricted in the CS to EGFR-negative patients only. Following NICE technology appraisal guidance (TA374) published on December 2015, erlotinib is not recommended in EGFR-negative patients and as confirmed in clarification request A1 the comparison of ramucirumab to EGFR-negative patients is not appropriate. Erlotinib is recommended as second-line therapy in a small population who have delayed confirmation that their tumour is EGFR positive or are of unknown mutation status and who received non-targeted first-line chemotherapy.

3.4 Outcomes

The outcomes reported in the decision problem match the NICE scope. These are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects and health-related quality of life (HRQoL).

4 CLINICAL EFFECTIVENESS

4.1 Critique of company's approach to systematic review

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included a search for studies on the intervention and separate searches for any comparator studies for a network meta-analysis (NMA).

The ERG's quality assessment of the CS, based on CRD quality assessment questions for systematic reviews,[10] is summarised in Table 1 below. The quality of the company's systematic review is reasonable, although the ERG had concerns regarding the exclusion of some studies from the decision problem and reporting of some variables from the studies in the NMA was minimal.

The process for study selection was not described in the CS and the ERG is therefore unable to assess whether this was adequate.

The submitted evidence generally reflects the decision problem, although summary baseline characteristics and data from the comparator trials were not consistently reported. In addition, a scoped comparator, nivolumab, was not included in the decision problem.

Overall, the chance of systematic error in the systematic review is uncertain owing to limited details of the primary studies being reported for the NMA.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. However, the CS excluded one study of ramucirumab that has some relevance to the decision problem (lower dose docetaxel) and for the NMA a second stage of inclusion into the model was applied with little description or justification.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes, although there were no searches for ongoing studies.
3. Is the validity of included studies adequately assessed?	Yes the CS uses the NICE recommended criteria and applies to all studies in the NMA, although comment or discussion is provided for REVEL only. The quality of the included RCTs is generally good and in most cases (for trials of comparators relevant to the decision problem) the ERG agrees with the company's assessment.
4. Is sufficient detail of the individual	Uncertain. Details of the RCT of the intervention were described

studies presented?	in sufficient detail. Details of the RCTs included in the NMA were focused on key variables only and were not always presented for each study arm.
5. Are the primary studies summarised appropriately?	Uncertain. Results for the pivotal RCT are presented in narrative form with tabulation of data and appropriate statistics. For the comparator studies and additional studies in the NMA there were no HR inputs presented. The ERG requested these from the company (clarification A16) but these were not provided in the response.

4.1.1 Description of company's search strategy

The searches to identify RCTs of ramucirumab appeared appropriate. Our independent searches identified only one additional relevant study,[11] a secondary publication of HRQoL data from the pivotal RCT, but this was published after the CS searches were completed (results incorporated in Section 4.2.4). Also, the searches to identify studies for the NMA appeared systematic and comprehensive, and would have resulted in all relevant studies being retrieved for manual screening. The ERG were satisfied that the search strategy for identification of studies for economic analyses was appropriate. Our independent searches for UK based resources use studies found six articles of potential relevance).

In summary, all searches appeared systematic and sufficiently comprehensive, and were clearly reported.

The ERG undertook searches for ongoing studies. None were identified of relevance to the decision problem.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The eligibility criteria are listed in CS Table 10, CS page 37. The eligible population is adults with advanced or metastatic NSCLC being treated with second-line therapy, the intervention is ramucirumab. These match the decision problem and NICE scope and the anticipated licensed indication. The comparators are stated as 'not restricted'. In the NICE scope there are five stated comparators (docetaxel, erlotinib, nintedanib, nivolumab, crizotinib). In the company decision problem three comparators are stated as relevant (docetaxel, erlotinib, nintedanib), discussed in Section 3. For outcomes, the eligibility criteria for the company systematic review states that trials with primary outcome measures of either progression free survival (PFS) or overall survival (OS) are eligible. Trials with other primary outcome measures were excluded, however, the ERG does not consider that this would have led to the exclusion of relevant studies and the company confirmed in clarification (A11) that trials reporting OS and PFS as

secondary outcomes were included. Other outcomes in the NICE scope were response rates, adverse effects and HRQoL. Non-randomised trials and phase 1/2 trials were excluded; only phase 3 RCTs were eligible. The ERG considered that there may be phase 2 RCTs that included the scoped outcomes that were missed, however, no phase 2 RCTs of ramucirumab as second-line therapy were identified in our searches. Two phase 2 RCTs of ramucirumab were identified, these were both in the first-line setting and had different co-interventions.

Eligibility criteria for studies to include in the NMA are listed in CS Table 28 (CS page 76). In this systematic review, studies that were phase 2 or phase 3 RCTs were eligible; also long-term extension studies were reported to be eligible. The interventions (comparators for the purpose of the CS) included a broader range of treatments (CS Table 28) than the scoped comparators, however, the NICE scoped comparators (of docetaxel, erlotinib, nintedanib, crizotinib and nivolumab) were all included. The CS does not state why a broader range of interventions were eligible, the ERG assumes this was to ensure appropriate linkages through the network for the scoped comparators. The eligible interventions were divided into three tiers according to the interventions. In tier one studies had to include one of docetaxel, erlotinib, gemcitabine, nintedanib, nivolumab, pemetrexed, ramucirumab and vinorelbine. Tier 2 studies included any other of the fuller list of interventions if included in both study arms, tier 3 studies included any other interventions if included in one study arm. The NMA for the submission was predominately focused on the Tier 1 studies (discussed further below). For the NMA studies were not restricted on eligibility according to outcomes of OS and PFS only, all outcomes in the decision problem were eligible. No limits were placed on inclusion of studies to either systematic review that related to the quality of the RCTs.

A flow diagram with the numbers included and excluded at each stage, as per PRISMA statement is provided on CS page 38 for the systematic review of ramucirumab studies. Only 88 records were identified through database searches. After deduplication 78 records were screened, and of these, 74 studies were excluded at the title and abstracts screenings stage, because they were not phase 3 studies. Four publications of one trial were ultimately included (2 full publications, 2 abstracts). The CS provides RCT reports for the full publications but does not provide reference details for the two abstracts. The ERG has identified four abstracts with outcomes from REVEL.[12-15] With the exception of differences in HRs likely to be related to rounding, none of these studies appear to have additional data than presented in the CS.

Flow diagrams for the NMA searches are provided in CS figure 16 (page 78) for searches until June 2014 and CS figure 17 (CS page 81) for updated searches to September 2015.

Non-randomised studies or phase 2 RCTs were not eligible for the systematic review of ramucirumab, but phase 2 RCTs were eligible for inclusion in the systematic review for the network meta-analysis. The inclusion criteria for the NMA was broader and no additional ramucirumab studies appear to have been identified. The company has not been explicit about potential bias in their selection of studies that may have occurred owing to this eligibility criteria.

4.1.3 Identified studies

One phase 3 RCT (4 publications, 2 conference abstracts), the REVEL trial[16] was included for the systematic review of ramucirumab (see Section 4.1.3.1 for discussion of the NMA included RCTs). This RCT compared ramucirumab and docetaxel (10mg/kg and 75mg/m^2 on day 1 of a 21-day cycle) with placebo and docetaxel (equivalent volume placebo, same dose docetaxel and same scheduling) thereby providing evidence for the intervention against one comparator of the scope / decision problem. The RCT was sponsored by Eli Lilly.

Summary details of the REVEL trial[16] were provided in the CS. Trial design was reported on CS page 40 and Figure 4 and protocol amendments were reported on CS page 41-2. REVEL was a multi-centre, double-blind RCT. Randomisation was stratified on Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); sex (male or female); prior maintenance therapy (yes or no); and geographic region (East Asia or rest of world). A protocol amendment to reduce the docetaxel dose to 60mg/m^2 in those from East Asia based on high rates of neutropenia and febrile neutropenia was made in May 2012 (first participant had been enrolled on 3rd December 2010).

There were 8 study centres in the UK which included 38 (3.0%) of the 1253 trial participants.

The details of the intervention dose and administration were provided on CS page 44-45 (described above in decision problem Section 1.1). Radiographic investigator-assessment of disease status was completed every 6 weeks using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 until there was evidence of progressive disease. Participants continued treatment until documented progressive disease, symptomatic progressive disease, toxicity, withdrawal of consent or other withdrawal criteria

were met. Dose modifications for ramucirumab and docetaxel were permitted and these were summarised in CS page 45. There was no independent review committee assessment of disease status.

Participants were those who had progressed during or after platinum-based chemotherapy for advanced / metastatic disease; summary eligibility criteria were provided in CS Table 13 (page 42) and in full in CS Appendix 2. All participants had Stage IV NSCLC, an ECOG status of 0 (Fully active) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature). Those with evidence of major blood vessel invasion, and those with untreated or clinically unstable central nervous system metastases were excluded.

Participant flow through the RCT is summarised on CS pages 52-53, including a flow chart of participant disposition in CS Figure 5. From the 1:1 randomisation schedule 628 participants were randomised to ramucirumab + docetaxel and 625 to placebo + docetaxel. Four participants in each arm were not treated (2 in the ramucirumab + docetaxel arm did not meet the trial entry criteria). Three participants randomised to placebo + docetaxel received 1 dose of ramucirumab instead of placebo, in error. Rates of treatment discontinuation appeared to differ between groups for progressive disease (ramucirumab + docetaxel 54.3%; placebo + docetaxel 68.6%); adverse events (ramucirumab + docetaxel 15.0%; placebo + docetaxel 8.8%); participant decision (ramucirumab + docetaxel 14.3%; placebo + docetaxel 8.5%); investigator decision (ramucirumab + docetaxel 5.9%; placebo + docetaxel 3.0%). At data cut-off 21 participants were still receiving study treatment. A small number of participants were classified as discontinuing treatment because of a sponsor decision (2 in the ramucirumab and docetaxel arm, 1 in the docetaxel arm). The ERG requested details of what constitutes a sponsor decision in clarification A12. The company responded that this was defined as when '*the investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice*'.

Summary details of outcomes were reported on CS page 47 and 48; power analysis, trial statistics and subgroup analyses were reported in CS page 48-51. For critique of outcomes and statistical analyses see below.

No non-randomised studies were included.

4.1.3.1 Identified studies for the NMA

The CS includes a systematic review to allow a network-meta analysis of studies including comparator evidence, to fulfil the decision problem. As described above, a broad range of interventions were eligible, however, the studies were divided into three tiers, with tier one studies (and four tier 2 studies) being included in the CS as having interventions that were most relevant to the decision problem. These were docetaxel, erlotinib, gemcitabine, nintedanib + docetaxel, nivolumab, pemetrexed, ramucirumab + docetaxel, vinorelbine (and gefitinib from tier 2). From the searches the CS identified 45 tier 1 studies that met the inclusion criteria. Three of these were not reported in English language publications and were deemed irrelevant to the decision problem, 24 other studies (therefore 27 in total) were excluded from the final NMA. Four studies from tier 2 were also included, the intervention was gefitinib and these were reported to be included to inform the network. Update searches were undertaken in September 2015.

There are discrepancies in the CS between the flow-chart on page 81, the text on page 79 and Table 29 on page 80. The flow-chart shows that 7 additional tier 1 studies were included (the text states 10). The CS says these were unique studies but 5 had already been identified, 2 of which were previously published abstracts, however, all of these studies were excluded. There were 5 unique studies, one of these was a phase 2 RCT of ramucirumab versus docetaxel. The study was undertaken in a Japanese population and the dose of docetaxel was 60mg/m^2 which the CS states is therefore not relevant to the UK setting (see Section 4.1.5). The other four studies were of pemetrexed + erolotinib, nivolumab (2 studies) and pemetrexed or docetaxel. It is unclear to the ERG why the pemetrexed + erlotinib trial was excluded as this had a comparator of pemetrexed and would appear to meet the network for tier 1, and the two nivolumab studies were of potential relevance to the NICE scope. The CS states (p79) that the excluded studies were not relevant to informing the relative efficacy of the comparators in the decision problem, however, tier 1 of the NMA did not only include studies of relevance to the decision problem and therefore this study should have been included in the NMA for completeness. The company confirmed at clarification that no studies identified from the update searches were included. It is also unclear whether the studies reported only in abstract form at the initial searches were updated. The ERG considers that nivolumab is a relevant comparator and two RCTs of nivolumab were identified in the company update searches for the NMA but were not included, although nivolumab was listed in the CS as a tier 1 intervention. One of these RCTs of nivolumab is in the licensed population of squamous NSCLC and therefore relevant to the scope.

The ERG requested the company to reconsider adding nivolumab into the NMA as tier 1 studies. The company reiterated their position that nivolumab is not part of established clinical practice and does not

comply with the definition of a comparator as laid out in the NICE Guide to Methods of Technology Appraisal. Although the ERG acknowledge that the company do not consider nivolumab a suitable comparator for the decision problem, the NMA included other comparators in tier 1 that were not directly relevant to the decision problem but were presumed to have been included to reduce uncertainty. Therefore, the studies identified at the update search, including those for nivolumab, should have been included in the NMA.

The CS states, therefore, that there were 22 studies in the network. These are summarised in Tables 9 -12 in the CS Appendix document and in the network diagrams as appropriate (CS page 87, 90, 92). On checking the ERG noted that there are only 21 trials in total (although in Table 9 there are 22 studies listed, one study (Ardizzoni 2012[17]) appears to be listed in error as it is not of an eligible treatment and comparator for Tier 1 and is noted as such in Appendix Table 6). Of relevance to the decision problem there were three RCTs: REVEL for ramucirumab + docetaxel;[16] Reck et al (2014)[18] for nintedanib + docetaxel; Garassino et al (2013)[19] for erlotinib. In addition the ERG considers that one of the two RCTs of nivolumab is relevant to the NICE scope for this appraisal (Brahmer et al 2015[20]) and is therefore considered hereafter. Subsequent to submission NICE published guidance on erlotinib for second-line therapy and the company confirmed that the erlotinib study in EGFR-negative populations was no longer relevant to the decision problem. As erlotinib in a second-line treatment setting is relevant for a small population only (Section 3.3) and the ERG are not aware of any evidence in this small population, the evidence for erlotinib is considered in Appendix 1.

Summary details of the included RCTs are provided in CS Appendix Table 11 which summarises the country, intervention, participant numbers and characteristics, follow-up details, outcomes and subgroups of these studies. Study design was also reported for all studies (all phase 2 or 3 RCTs) except for two gefitinib studies.

4.1.4 Participant characteristics

The CS states on page 53 that demographic and baseline disease characteristics were generally well balanced between arms (the trial publication says groups were 'much the same') and the ERG agrees that there were not any notable differences in those presented. Smoking status (see below), time since previous therapy, disease: measureable/ non-measurable, and EGFR mutation status were not reported by CS table 18 (CS page 53) which summarises key characteristics (all have been checked with the publication and CSR). Smoking status may be different between study arms with 82% ever smoked, 17% never smoked in the ramucirumab + docetaxel arm compared with 77% ever smoked and 23% never

smoked in the placebo + docetaxel arm. Eleven participants (5 in ramucirumab + docetaxel, 6 in placebo + docetaxel) were recorded in CS Table 18 as having 'other diagnoses, not lung cancer'. The ERG requested clarity on these diagnoses in clarification question A13. The response shows that these participants (and one other that was not treated) did not have NSCLC at study entry. Eight of these did not have a diagnosis of NSCLC at initial diagnosis. The ERG is not clear how these participants were eligible for the study and were randomized to treatment. It is unclear if these participants would contribute to any difference in outcomes between the two treatments. The rate of these non NSCLC diagnoses was approximately 1% in each study group. Two participants (0.3%) in the ramucirumab arm had not received any prior systemic therapy; eight participants (5 ramucirumab + docetaxel, 3 placebo + docetaxel) had not received prior platinum chemotherapy and were noted as protocol deviators.

4.1.4.1 Participant characteristics in the studies included in the NMA

Key baseline characteristics (age, % Asian, % ECOG ≥1, % stage IV, % non-squamous, % EGFR mutation positive) were presented for the NMA included studies in CS Appendix Table 12. The data presented is for the total population in the studies (and by squamous / non-squamous subgroup for the nintedanib + docetaxel study) rather than by treatment arm. The ERG has checked baseline characteristics from the publications of the one study of relevance to the NICE scope and CS updated decision problem (Reck et al 2014 nintedanib + docetaxel), Table 2 (for Garassino et al 2013, erlotinib see Appendix 1). Baseline characteristics were well balanced between the two treatment groups in the nintedanib + docetaxel study. As discussed previously, the ERG considers that nivolumab in the squamous population is an eligible comparator. In the nivolumab RCT publication (Brahmer et al 2015[20]) for squamous populations it is noted that groups were generally balanced but with slight imbalance in some characteristics. These were the percentages of female patients (nivolumab 18%, docetaxel 29%), patients 75 years of age or older (nivolumab 8%, docetaxel 13%), and patients with an ECOG performance-status score of 1 (nivolumab 79%, docetaxel 73%). The ERG also notes slight imbalance in proportion with prior gemcitabine therapy (nivolumab 44%, docetaxel 52%).

There appear to be some differences in patient characteristics between the two studies the ERG consider of relevance to the scope. The proportion who were Asian was 18% in the nintedanib study and 13% in the ramucirumab study (although this stated as not reported in appendix table 12). For other key characteristics (stage of NSCLC, EGFR mutation positive) it is unclear from CS Appendix Table 12 whether participants were similar across studies because one or more study did not report rates. From the

study of nivolumab participants ages were similar to those of the ramucirumab and nintedanib studies (approximately 62 years) but the proportion of Asian participants was 2%.

Eligibility criteria differed between studies in terms of the stage of NSCLC for ramucirumab (stage IV) and nintedanib (stage IIIB or IV). In the nivolumab RCT 80% of participants were Stage IV NSCLC.

Table 2: Key Baseline characteristics from the trials of relevance to the scope

	REVEL		Reck 2014[18]		Brahmer 2015[20]	
Characteristic n (%) unless stated	**RAM + DOC (n=628)**	**PBO + DOC (n=625)**	**NIN + DOC (n=655)**	**PBO + DOC (n=659)**	**NIV squamous (n=135)**	**DOC squamous (n=137)**
Age, years (median, range)	62 (21–85)	61 (25-86)	60 (53–67)	60 (54–66)	62 (39-85)	64 (42-84)
Male sex	419 (67)	415 (66)	476 (73)	479 (73)	111 (82)	97 (71)
Ethnicity						
White	526 (84)	503 (81)	533 (81)	530 (80)	122 (90)	130 (95)
Asian	74 (12)	86 (14)	116 (18)	123 (19%)	4 (3)	2 (1)
Black	17 (3)	16 (3%)	4 (<1)	5 (<1)	6 (4)	2 (1)
ECOG PS						
0	207 (33)	199 (32)	187 (29)	189 (29)	27 (20)	37 (27)
1	420 (67)	425 (68)	467 (71)	470 (71)	106 (79)	100 (73)
Smoking history						
Current and former	518 (82)	483 (77)	490 (75)	498 (76)	121 (90)	129 (94)
Never	109 (17)	141 (23)	165 (25)	161 (24)	10 (7)	7 (5)
Unknown	1 (<1)	1 (<1)	0 (0)	1 (0)	4 (3)	1 (1)
Clinical stage at inclusion						
Stage IIIB	0	0	148 (23)	146 (22)	29 (21)	24 (18)
Stage IV	628 (100)	625 (100)	399 (61)	408 (62)	105 (78)	112 (82)
Histological subtype						
Non-squamous	465 (74)	447 (72)	347 (53)	352 (53)	0	0
Squamous	157 (25)	171 (27)	276 (42)	279 (42)	135 (100)	137 (100)
Prior platinum-based therapy	623 (99)	622 (99)	628 (97)	636 (98)	135 (100)	138 (100)
First-line bevacizumab	88 (14)	92 (15)	27 (4)	23 (4)	1 (1)	2 (1)
Prior maintenance treatment	135 (21)	143 (23%	NA	NA	NA	NA

Previous taxane	153 (24)	152 (24)	NA	NA	46 (34)	46 (34)
Best response to first-line therapy						
Complete response	420 (67)	417 (67)	13 (2·0%)	19 (2·9%)	48 (36)	43 (31)
Partial response			214 (33)	177 (27)		
Stable disease			249 (39)	249 (38)	33 (24)	47 (34)
Progressive disease	178 (28)	182 (29)	127 (20)	139 (21)	44 (33)	41 (30)
EGFR status						
Wild type	207 (33)	197 (32)	NA	NA	NA	NA
Mutant	15 (2)	18 (3)	NA	NA	NA	NA
Unknown or missing	406 (65)	410 (66)	NA	NA	NA	NA

DOC: docetaxel; NA: Not available; NIN + DOC: nintedanib + docetaxel; NIV: nivolumab; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

4.1.5 Relevant studies not included in the submission

A phase 2 study of ramucirumab and docetaxel compared with docetaxel alone and undertaken in Japan was excluded by the company because the dose of docetaxel was lower than the standard dose used in the UK (60mg versus 75mg). The ERG asked in a clarification request (A24) that this study be included in a sensitivity analysis in the NMA. The company stated that connecting the study to the network would likely be difficult owing to the lack of studies connecting docetaxel 60mg with the rest of the network. The ERG considers that this study could have been included as a sensitivity analysis in the ramucirumab and docetaxel versus docetaxel arm, regardless of the different dose of docetaxel used. Hosomi et al[21] conducted a phase 2 RCT (sponsored by Eli Lilly) in Japan comparing ramucirumab and docetaxel with placebo and docetaxel, using the lower dose of docetaxel (60mg/m^2) as recommended in Japan. The study is currently reported in an abstract and poster presentation only. Results from this study can be seen in Appendix 2.

As discussed above, the ERG considers that one RCT of nivolumab is relevant to the NICE scope and has been summarised in the relevant sections of the ERG report.

4.1.6 Description and critique of the approach to validity assessment

The CS provided quality assessment for the included REVEL study[16] (CS Table 20) and for 45 studies identified for the NMA (CS Appendix 7), using criteria recommended by NICE. The ERG has checked the company's QA for the REVEL trial and the comparator trial of relevance to the decision problem versus docetaxel: Reck et al 2014[18] (nintedanib + docetaxel vs docetaxel) see Table 3. For the erlotinib versus docetaxel trial, Garassino et al 2013[19] see Appendix 1). In addition, the ERG has provided quality assessment of the trial of nivolumab in the squamous population (Brahmer et al 2015[20]).

The ERG QA mostly agrees with the company assessment of study quality for REVEL, which has a low risk of selection bias or bias due to lack of blinding (performance bias or detection bias). However the ERG notes that there were some imbalances in reasons for treatment discontinuations between groups, which are suggestive of attrition bias. In addition, a secondary outcome specified in the clinical trial record (https://clinicaltrials.gov/ct2/show/NCT01168973)[22] and relevant to the decision problem, maximum improvement on LCSS, was not reported in the publication or CS. Therefore there is a high risk of selective reporting bias in the trial.

The ERG agrees with the company assessment of study quality for Reck et al 2014[18] which was judged to be a reasonably good quality study with a risk of selective reporting bias. Methods to account for missing data were not reported.

The relevant study of nivolumab (Brahmer 2015[20]) was an open label study and therefore had a high risk of performance bias and detection bias. In addition, the method of randomisation was unclear. Patient reported outcomes have not (yet) been reported for the study.

Table 3: Company and ERG assessment of trial quality

		Ramucirumab (Garon 2014)	Nintedanib (Reck 2014[a])	Nivolumab (Brahmer 2015)
1. Was randomisation carried out appropriately?	CS:	Yes	Yes	-
	ERG:	Yes	Yes	Unclear
Comment: Brahmer 2015: method of sequence generation not reported, randomization stratified according to prior treatment with paclitaxel-based doublet vs. other doublet, and region (US vs. Europe vs. Rest of World).				
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes	-
	ERG:	Yes	Yes	yes
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes	-
	ERG:	Yes	yes	yes
Comment: Brahmer 2015: groups were balanced with slight imbalances in the percentages of female patients (nivolumab 18%, docetaxel 29%) patients 75 years of age or older (nivolumab 8%, docetaxel 13%), and patients with an ECOG performance-status score of 1 (nivolumab 79%, docetaxel 73%). ERG also notes slight imbalance in proportion with prior gemcitabine therapy (nivolumab 44%, docetaxel 52%)				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes	-
	ERG:	Yes	Yes	No
Comment: outcome assessors were blinded, however, there was no independent review of PFS in trials except in Reck et al for nintedanib.				
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No	-
	ERG:	Yes	No	No
Comment: REVEL: CS Figure 5, p. 53 suggests there were no losses to follow-up from the study, however Figure 1 of the publication states losses to follow-up were included in the 'other category' but the numbers are unclear. There were some imbalances in treatment discontinuations between groups due to adverse events (ramucirumab 14.9%, placebo 8.8%), subject decision (ramucirumab 14.3%, placebo 8.5%), investigator decision (ramucirumab 5.9%, placebo 3.0%)				
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No	Yes	-
	ERG:	Yes	Yes	Yes
Comment: REVEL: Maximum improvement on LCSS was a specified secondary outcome (NCT01168973) but not reported in the trial publication (states additional analysis will be reported elsewhere but not identified) or CS which states (p63) in a general way only that 'most pre-specified analyses suggest QOL was maintained by treatment'. Also CSR has change from baseline LCSS and percentage improved, stable or deteriorated. Reck 2014: The CS notes that: *The study stated, "Patient-reported quality of life, clinical improvement, and pharmacokinetics of nintedanib were also secondary endpoints; these results are being analyzed and will be reported separately." Quality of life data were reported in Novello et al. (2013) (conference abstract), which*				

is included in this review. The ERG also notes that the clinical trial record (NCT00805194) lists the following secondary outcomes not reported in the publication: duration of and time to confirmed objective tumour response, duration of disease control and change from baseline in tumour size (these may have been reported in secondary publications not identified by the ERG). Brahmer 2015: publication states that analyses for patient reported outcomes (EQ-5D and Lung Cancer Symptom Scale) are ongoing.				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes, Yes	Yes, Not clear	-
	ERG:	Yes, Yes	Yes, Not clear	Yes, yes
Comment: REVEL: states that ITT analyses used and the numbers reported suggest this is correct. CS also states 'unless otherwise specified, observed data was used and missing data were not imputed or carried forward.' Also, 'data were imputed for partial dates concerning pivotal efficacy or safety parameter according to rules specified in the statistical analysis plan', although these rules were not specified in the CS. Reck 2014: methods used to account for missing data were not reported.				

[a] CS Appendix 7, Table 33, p. 86
[b] CS Appendix 7, Table 41, p. 96

4.1.7 Description and critique of company's outcome selection

The NICE scoped outcomes were OS, PFS, response rates, adverse effects and HRQoL. The company notes on CS p.14 that the outcomes in the decision problem addressed by the company are the same as the NICE scope. The primary outcome in the REVEL trial was OS, with secondary endpoints including PFS, objective response rate (ORR), disease control rate (DCR), safety and HRQoL (CS page 47).

Overall survival was measured from date of randomisation to date of death from any cause, and PFS was defined as the time from randomisation until objectively determined (radiographically documented) disease progression or death. PFS, ORR and DCR were assessed by investigators according to RECIST v 1.1 every 6 weeks. As confirmed in clarification question A8 there was no independent review committee assessment of PFS in the REVEL trial. ORR is the proportion of patients achieving a best overall response of partial response or complete response. DCR is the proportion of patients achieving a best overall response of partial response, complete response or stable disease.

HRQoL was assessed at baseline, the end of each cycle, and at the end of therapy, using the Lung Cancer Symptom Scale (LCSS) and EQ-5D index and visual analogue scale (VAS). For the LCSS, the CS reported Time to Deterioration (TTD), defined *a priori* as the time from randomisation to the first 15mm increase, for each of 11 items. LCSS scores are not reported.

The CS also presented TTD in ECOG status, defined as the time from date of randomisation to the first date observing a change in ECOG PS to ≥2 (not a scoped outcome)

Adverse events were coded using MedDRA version 16.1 and graded using National Cancer Institute - Common Terminology Criteria for Adverse Events V 4.0. Adverse events were collected until at least 30 days after discontinuing study treatment. After this point, only new and ongoing serious adverse events (SAEs) related to study treatment were collected.

4.1.8 Description and critique of the company's approach to trial statistics

The CS reports trial results for all relevant outcome measures (other than LCSS as noted above). Data from REVEL were final data and included all randomised patients (intention-to-treat analysis, ITT) for the efficacy outcomes. The safety population comprised of people who received the study treatment (4 ramucirumab and 4 placebo patients were randomised but not treated). Three people randomised to

placebo received ramucirumab in error for one cycle, and were included in the ramucirumab group for safety analysis.

The study was adequately powered to detect a treatment difference.

OS data were censored for analysis on the last date the patient was known to be alive. In the case of patients without objectively determined progressive disease who were alive at the follow-up period, or lost to follow-up, data for PFS were censored on the date of the patient's last complete radiographic tumour assessment (or date of randomisation if no baseline or post baseline radiologic assessment was available).

OS and PFS in the treatment groups were compared using a stratified (ECOG status, sex, prior maintenance therapy and geographic region) log-rank test at a two-sided 5% level of significance. The HR was determined using a Cox regression model stratified identically to the primary log-rank test with assigned treatment as the only covariate. Survival curves were estimated by the Kaplan-Meier method.

The CS states that observed data were used and missing data were not imputed or carried forward, unless otherwise specified. Data were imputed for partial dates concerning pivotal efficacy or safety parameter according to rules specified in the statistical analysis plan.

The ERG considers the trial statistics to be appropriate, although notes that a statistical comparison of EQ-5D data were not provided.

Subgroup analyses were reported in the CS, although subgroups were not identified in the NICE scope. The CS states that REVEL was not powered for subgroup analyses and that the analyses were undertaken to assess internal consistency and to assess treatment heterogeneity across the subgroups. OS and PFS HRs were estimated using the Cox regression model for 13 pre-specified variables: four stratification factors of ECOG, sex, prior maintenance therapy and geographic region, and nine other pre-specified factors (smoking history, histology, best response to platinum chemotherapy, prior taxane therapy, prior bevacizumab therapy, EGFR mutation status, age, race, time since prior therapy). These are described in CS Table 17 (page 52) and results in CS Section 4.8 (page 67 – 74).

4.1.9 Description and critique of the company's approach to the evidence synthesis

The evidence synthesis presented in the CS focused on a narrative review of reported outcomes from the REVEL trial and a NMA of data for the comparators in the decision problem. Where possible the ERG has checked key data presented in the CS against those in the publications and CSR provided by the company and summaries of the evidence can be seen in Section 4.2. The narrative results presented in the CS reflects the data in the trials.

The CS undertook an NMA as there was no direct evidence comparing ramucirumab with all of the comparators listed in the decision problem. The NMA was divided into three tiers of evidence based on the interventions and the study characteristics (whether both study arms were of relevance, or just one study arm was of relevance). Tier 1 studies were the main focus of the NMA that is reported in the CS. The NMA was undertaken assessing the outcomes of OS, PFS and ORR. The NMA uses a hierarchical structure which allows the introduction of specific subgroups such as the NSCLC histology and EGFR mutation status. Where appropriate data are available, hierarchical models using exchangeable structures allow different interactions between treatments and population sub-groups within the network through order constraints (i.e. studies of sub-groups can be accommodated within NMAs where other studies do not examine the sub-group). It was thought that these could not be accounted for through sub-group and meta-regression. Bayesian NMA and frequentist models were used. Although the approach outlined appears appropriate, limited details are provided as regards some aspects of the analysis and results and the ERG has considered two aspects of the NMA for their critique, a) the methodology of the NMA itself, b) the assumptions of the data included in the NMA.

4.1.9.1 Methodology of the NMA

The ERG has critically appraised the methodology of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency.

Homogeneity was considered in the CS. CS page 95 states that heterogeneity was investigated using three methods: comparing results of studies that investigate the same treatment comparison; investigating consistency (see below); using meta-regression (covariates median age, publication date, proportion Asian participants, proportion with ECOG PS $\geq$ 1, proportion with stage IV NSCLC). Although the CS presents limited details or results for these analyses, clarifications were presented subsequently. The method used to determine the presence of statistical heterogeneity was adequate. For OS the frequentist model showed evidence of substantial heterogeneity (I^2 54%) and investigation showed that two studies

comparing docetaxel doses (100mg and 75mg) were heterogeneous and one study contributed to significant differences between pemetrexed and docetaxel. For PFS, there was considerable heterogeneity (I^2 74%) and investigation showed that there was heterogeneity between the three studies comparing pemetrexed and docetaxel, which was mostly attributable to one study, and heterogeneity between three studies comparing pemetrexed with gefitinib. Similar findings were observed in the ORR network. Heterogeneity and inconsistency were also reflected in the comparisons presented through node-splitting and from the results of the NMAs and pairwise-comparisons. These were presented as part of clarification with the company and suggest that the results of the NMA should be interpreted with caution.

The model used by the CS was a Bayesian hierarchical model and both fixed-effect and random-effects models were estimated. The CS reports only the results for fixed-effects analyses, with the rationale provided that the hierarchical model had accounted for any heterogeneity and random-effects models were not necessary. Given that fixed-effect models have more conservative credible intervals, it is helpful to compare both fixed- and random-effects models. The results of random-effects models were made available as part of the clarifications from the company. These were for the hierarchical and non-hierarchical models without covariates, highlighting limited differences between the fixed- and random-effects hierarchical models, indicating that the hierarchical models accounted for the heterogeneity. The credible intervals for the random-effects model that were presented in response to clarification request A18 differ for a number of comparisons from those for the fixed-effects model (many cross unity). Results for the fixed-effect hierarchical model with each covariate included separately showed that none added significantly to the explanation provided, with differences in the deviance information criteria (DIC) <5 points. No results were presented for the random-effects hierarchical models with covariates.

The CS acknowledges that heterogeneity does affect the studies included in the NMA, outlining approaches that are taken to identify, and accommodate, it (p.82 and p.95-98). Clinical heterogeneity was noted in several studies that focused on comparator interventions that were used in specific clinical sub-groups. The CS identified the existence of heterogeneity through frequentist NMA, which did not take the heterogeneity into account through meta-regression, presenting I^2 and Cochrane Q statistics. Bayesian 3-level hierarchical NMAs were estimated to take account of the heterogeneity, with results presented for fixed-effects rather than random-effects models as they appeared to account for the heterogeneity. Clarifications from the company provided results for both the fixed- and random-effects hierarchical models without the covariates, highlighting limited differences between them when assessed in terms of the DIC.

The assumption of similarity is not stated or justified in the CS. Studies are divided into categories of evidence, however this is based on an assessment of the relevance of the interventions included rather than the relative effect. The included studies all had similar study designs, being phase II or phase III RCTs. However, minimal discussion of homogeneity of participants across the included studies was presented in the CS. Tables 11 and 12 in the CS Appendix list key characteristics, however, little discussion is made of how similar or different these are. The ERG notes that follow-up, median age, proportion ECOG ≥1 vary across the included studies, although it is unclear whether differences observed are clinically relevant. Many studies did not report all of the characteristics, for example the proportion of participants who were Asian, the proportion with stage IV NSCLC and therefore similarity cannot be adequately assessed.

The NMA assumed proportional hazards for OS and PFS hazard ratios. The CS states that two studies did not meet the assumption for proportional hazards and these were indicated by the CS in the respective network plots. One study was not relevant to the scope. In the nintedanib study the CS reports that the assumption for proportional hazards was primarily in the squamous NSCLC data which was not relevant to the scope. This statement appears to relate to OS. For PFS the network diagram suggests that the assumption may not hold for six studies. In response to clarification request A3 the company stated that there was a significant non-proportional hazard for PFS in four studies (one was the REVEL trial) and that additional work had indicated that results were consistent with results from published NMAs and a reconstructed individual patient data for overall survival (see Section 4.2.8 for ERG analysis). A number of studies did not report hazard ratios and data were estimated from Kaplan-Meier charts. There was no discussion of similarity in the treatment effects for the NMA of ORR.

The CS reports that it assesses consistency to establish whether the indirect evidence is consistent with the direct evidence. CS page 95 states that consistency between direct and indirect comparisons in closed loops was investigated. Although results of the comparisons of direct and indirect evidence are not presented in the CS, these have been presented in clarifications by the company. In addition, there is no explicit reporting of patient or trial characteristics being compared between indirect and direct evidence.

In addition, the ERG has considered a number of other indices of the methodological reporting of the NMA in the CS as summarised in Table 4.

Table 4: Appraisal of methodological reporting of the NMA

Rationale and searches 1. Is the rationale for the NMA and the study objectives clearly stated?	Yes
2. Are searches stated and do they appear appropriate?	Yes
3. Are inclusion/exclusion criteria adequately reported?	Yes although the CS provides little detail of the choice of interventions in the criteria or why Tier 1 studies were chosen, and why Tier 2 and 3 studies were excluded. One comparator, nivolumab, is excluded but is relevant to the NICE scope.
4. Is the quality of the included studies assessed?	Yes, using CRD questions (CS Appendix 7) although it is not stated how many reviewers assessed quality.
Model methods 1. Is the statistical model described?	Yes
2. Is there a justification for the choice of outcome measure provided?	Yes
4. Has a structure of the network been provided?	Yes for Tier 1 studies and 1 comparator from Tier 2.
3. Has the choice of fixed or random effects model been justified?	Yes
5. Is any of the programming code used in the statistical programme provided?	Yes
6. Is a sensitivity analysis presented, is this appropriate?	No, one study of a lower dose of docetaxel was excluded, which the ERG consider could have been included in a sensitivity analysis. A subgroup analysis for the nintedanib vs docetaxel vs ramucirumab was presented for those with adenocarcinoma only, the CS states this confirmed the conclusions regarding the relative efficacy of ramucirumab versus nintedanib in the non-squamous subgroup that was used in the main NMA using the hierarchical exchange model. The ERG agrees that outcomes appear to be similar for OS and PFS for the nintedanib vs ramucirumab comparisons but considers it more appropriate to consider the adenocarcinoma subgroup. As there is little justification provided regarding the choice of Tier 1 and Tier 2 studies, and one Tier 2 study was included in the presented NMA, the ERG consider sensitivity analyses could have been presented to test the inclusion and exclusion of these studies to assess the effect on reducing uncertainty (see clarification request A20 and A21).
Results 1. Are the results of the NMA presented?	Yes

2. Does the study describe an assessment of the model fit?	Although DIC's are presented, there is no discussion about model convergence or the effects of autocorrelation.
3. Is the evidence combined and the results presented?	Yes
4. Has there been any discussion around the model uncertainty?	No
5. Are the point estimates of the relative treatment effects accompanied by some measure of variance?	Yes

Summary of ERG assessment of the methodology of the NMA

The NMA appears to adequately meet the assumption of homogeneity and in part consistency. The assumption of similarity is not stated or justified in the CS.

The evaluation of the NMA is restricted owing to the limited details provided as regards some aspects of the analysis and results. The CS provides an appropriate justification for using hierarchical models. First, comprehensive heterogeneity and inconsistency analyses were indicated to have revealed complex treatment-by-covariate interactions thought to be the result of differences in the licensing for the interventions and suggested differences in terms of effectiveness for particular sub-groups of patients. Second, sparse evidence in the NMA was thought to be a potential concern, which can result in uncertainty in the analysis. Where trial evidence is limited, the posterior distribution of the standard deviation may be poorly identified and likely to include extreme values. This results in unexpectedly wide credible intervals, showing greater uncertainty. Hierarchical models can accommodate problems associated with sparse data through exchangeability, borrowing strength from across the evidence (i.e. allows class effects to be included without lumping of data). Issues of sparse evidence may also result in non-convergence of models, particularly random-effects models. The CS does not discuss issues regarding non-convergence and indicates that comparable models were estimated using both fixed- and random-effects models.

Although results were presented for the Bayesian NMA for the fixed-effect hierarchical models with no covariates only in the CS, those for the random-effects hierarchical models with no covariates and the fixed-effects hierarchical model with covariates were presented in clarifications from the company. These showed that the random-effects hierarchical models differed little from the fixed-effects hierarchical models when no covariates were included in terms of the model fit (i.e. DIC). The fixed-effect hierarchical models with covariates showed that the covariates had limited effect on improving the explanation provided by the models (i.e. in terms of DIC). No random-effects hierarchical models with covariates were presented. Random-effects models tend to have wider credible intervals, as evident in the

reporting of the results of the NMA from the random effects models without covariates in response to clarification request A18 where it can be seen that a number of credible intervals include unity for both OS and PFS estimates. Although the fixed effect hierarchical model appears to have accounted for some of the heterogeneity, it is evident that there was inconsistency in the analyses and the results should be interpreted with caution. In addition, the CS notes that the NMAs may have contained fewer studies than previous analyses of these interventions, due to a requirement to include patients' characteristics. These may have reduced the information available to estimate the heterogeneity. This may, in part, underlie the rationale for using fixed- rather than random-effects models and resulted in more conservative outcomes.

4.1.9.2 Assumptions of the data in the NMA

The ERG has critically considered the assumptions of the data included in the NMA.

There is a potential risk of bias in most trials reporting PFS because there was no independent review of disease progression, with the exception of the nintedanib trial[18] which had a centralised review of PFS.

The CS produced NMAs using hazard ratio and count data. Details for the methods are only presented as part of the JAGS code in the CS, although an appropriate reference is provided.[23] It appears that the NMA assumes that treatment baselines and treatment effects on the log hazard scale were normally distributed. For the count data, a binomial model was used. Bayesian vague priors were specified for the baseline treatment effects, treatment effects and class effects in the NMAs. The CS did not appear to undertake any sensitivity analyses around the priors. Although the CS indicates that convergence was assessed using the Gelman-Rubin diagnostic, iteration plots and frequentist validation models, no specific findings were presented. Information was presented on the iterations, burn-in, thin rate and differential initial values used, however it does not indicate the rationale for the approach or whether sensitivity analyses were undertaken.

The NMA outputs were "pooled" HR estimates (and credible intervals) for paired treatment comparisons in various NSCLC populations. The company's submitted appendix lists > 500 output HRs for overall survival comparisons. The ERG has the following concerns in regard to the use of the NMA output for estimating life-years gained (LYG), used in the CS economic evaluation (see Section 5):

A) The NMAs of OS and PFS used hazard ratios, assuming proportional hazards. Although a visual inspection was used to assess this assumption, formal testing was only conducted on those where it was

felt the assumption was not met. No further details are provided. The ERG considers this assumption was violated by a number of studies especially relevant for the decision problem (e.g. for nintedanib,[18] erlotinib,[19] and nivolumab[20]). Consequently the output HR estimates may be less robust than desirable.[24]

B) Although the NMA was designed for binary outcomes[25] and HRs may be regarded as ORs of risk,[26] the extraction of only HRs from the published survival analyses does not use most of the survival information in the constituent studies, specifically information embodied in the shape of the survival curves and their disposition along the time axis. When only HRs are used to estimate LYG (area under the survival curve (AUC)) they can fail to provide useful information since identical HRs for pairs of survival curves with proportional hazards deliver different LYG depending on their shape and dispersion on the time axis (illustrative examples are provided in Appendix 3).

C) The ERG is concerned that the use of adjusted HRs as output from the NMA might result in double counting of variables (e.g. tumour histology) when used in conjunction with an adjusted baseline loglogistic model for the placebo + docetaxel arm from REVEL.[16] The ERG requested values for the HR inputs to the NMA and whether these were adjusted or unadjusted (the submission appendix provides log HR inputs to 2 decimal places) in clarification request A16. The requested values were not supplied, however, the company stated that all input HRs were unadjusted.

D) To model OS for comparator treatments the company has applied NMA HRs (generated under the assumption of proportional hazards; see above) to a loglogistic model for the docetaxel arm of REVEL that was developed under assumed proportional hazards between REVEL trial arms (treatment as a covariate); both "adjusted" and "unadjusted" models were generated with and without patient level variables respectively. Unfortunately loglogistic models used in this way are not consistent with the assumption of proportional hazards because the resulting hazard ratio is not invariant through time (see examples in Section 4.2.8). Royston and Lambert (2011)[27] explain that unlike parametric models with monotonic hazard functions (e.g. Weibull, exponential), log logistic models allow for a turning point in the underlying hazard function, but that it is not possible to use them in a proportional hazards model. The ERG believes that if the choice of parametric model is to be loglogistic then this should be fit separately to each trial arm (i.e. no assumption of proportional hazards).

E) Although the log logistic models of OS developed in the CS may fit reasonably well to the observed data from the REVEL trial, their extrapolation in modelling survival beyond the observed data from about 3 years to the time horizon of 15 years (see Section 5) may not be appropriate. Firstly, the models were

developed under a proportional hazards assumption inappropriate for log logistic models. Secondly, beyond the observed data, these models predict continuously decreasing hazard for death for the diminishing population of survivors (Figure 2). As noted elsewhere (STA of nivolumab for NSCLC) such decreasing hazard implies that a few months intervention with docetaxel or ramucirumab confers a lifelong reduction in risk from all causes of death for which there is no obvious biological explanation. In the ongoing STA of nivolumab for squamous NSCLC the ERG remark that the company's extrapolated loglogistic model eventually results in a lower probability of death for nivolumab treated NSCLC patients with progressed disease than for similarly aged members of the general population.

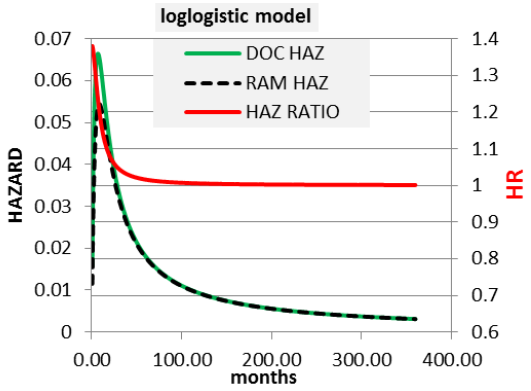


Figure 2 Log logistic hazard plots for all patients in REVEL; note decreasing hazard in both arms from ~8 months onwards

When data is incomplete (i.e. patients not followed up until all are dead) a likely consequence of using loglogistic models for extrapolation is that the estimated proportion of mean survival due to extrapolation may represent an appreciable proportion of the estimated total mean survival. Data for PFS is more complete than for OS and when combined with a decreasing hazard loglogistic model for OS may result in the apparent benefit of treatment accruing well after progression and cessation of treatment. For example the ERG for the nintedanib STA remarked that the company's loglogistic model results in only 15% of mean survival being attributable to the pre-progression phase.

On CS pages 182-183 (Table 93) the company considers the validity of their loglogistic extrapolation by comparing estimates of LYG for non-squamous patients in the REVEL trial with that modelled by the manufacturer of nintedanib (Boehringer) for adenocarcinoma patients in the Reck et al (2014)[18] nintedanib trial that was recently assessed by NICE in a completed STA appraisal. The ERG are unclear how this supports the company's approach to modelling overall survival because the Boerhringer approach for nintedanib was very substantially different; it did not apply proportional hazards loglogistic

modelling but employed direct Kaplan-Meier estimates observed in the trial up to a pre-determined point and then applied to each arm "per cycle" mortality risks based on an unadjusted log-normal model fit to an extract of data from LUCADA (UK National Lung Cancer Audit) encompassing various unspecified treatments.

The ERG considers the implementation of the NMA HRs to estimate LYG in more detail in Section 4.2.8.

4.2 Summary of submitted evidence

The primary outcome of REVEL was overall survival (OS). Clinical secondary outcomes included progression-free survival (PFS) and objective response rate (ORR). PFS was defined as the time from randomisation until disease progression or death. Progression/objective response was judged based on radiographic assessment according to RECIST criteria every 6 weeks. Radiographic assessment was performed by onsite investigators and not by an independent central review. All the endpoints were analysed using the ITT population.

4.2.1 Overall Survival (OS)

Overall survival was longer with ramucirumab + docetaxel than with docetaxel. Median OS was 10.5 months (95% CI, 9.5,11.2) among 628 patients in the ramucirumab and docetaxel group and 9.1 months (95% CI, 8.4,10.0) in the docetaxel group (hazard ratio (HR) for death 0.86, 95% CI, 0.75,0.98) suggesting a 14.3% reduction in risk. At 1 year, the overall survival rate was 43% (95% CI, 39 to 47) with ramucirumab and docetaxel versus 38% (95% CI, 34 to 41.5) with docetaxel. At 2 years, the overall survival rate was 21% (95% CI, 17 to 25) with ramucirumab and docetaxel versus 17.5% (95% CI, 14 to 21.5) with docetaxel. Table 5 summarises results on OS of REVEL.

Table 5: REVEL overall survival results

Outcome	RAM+DOC	PBO+DOC
Number of Patients	628	625
Number of Deaths, n (%)	428 (68.2)	456 (73.0)
Number censored, n (%)	200 (31.8)	169 (27.0)
Median Survival, months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)
Treatment difference	1.4 (p=0.024[a])	
Stratified Hazard ratio (95% CI)	0.86 (0.75, 0.98)	

12 month survival rate, % (95% CI)[b]	42.9 (38.9, 46.9)	37.7 (33.8, 41.5)
24 month survival rate,% (95% CI)[b]	20.9 (17.0, 25.1)	17.5 (13.8, 21.5)

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
[a]stratified Log-Rank; [b]the ERG was unable to check survival rates with published data

The company states that four sensitivity analyses were conducted and confirmed the robustness of the hazard ratio (range, 0.81 to 0.86). No dedicated table with hazard ratios and their 95% CI was provided in the CS for the prespecified sensitivity analyses. However, the company statement is consistent with the results on the table 3S (page 5/41) published in the supplementary appendix of the paper by Garon et al 2014.[16] This table presents sensitivity analyses on three parameters: the use of unstratified Cox regression, the use of multivariate Cox regression, and the stratification by interactive voice recognition system strata. The forth parameter for sensitivity analyses was confirmed in clarification request to be a per protocol population analysis. The HRs, 95% CI and p-values for these sensitivity analyses can be seen in clarification response A14.

The company indicates that the percentage of patients who received post-discontinuation systemic anticancer therapy (PDT) and the types of PDT used were similar between treatment arms, suggesting that the observed prolongation of OS is due to a treatment effect of the combination of ramucirumab with docetaxel. The ERG was unable to find the corresponding data in the CS to check the statement but this is consistent with the results on the table 1S (page 3/41) in the supplementary appendix of the paper by Garon et al 2014.[16]

4.2.2 Progression-free Survival (PFS)

Progression-free survival was longer with ramucirumab and docetaxel than with docetaxel. Median PFS was 4.5 months (95% CI, 4.2,5.3) in the ramucirumab and docetaxel group and 3.0 months (95% CI, 2.8,3.9) in the docetaxel group (HR for progression or death 0.76, 95% CI, 0.68,0.86). At 1 year, the PFS rate was 12.2% (95% CI, 9.6 to 15) with ramucirumab and docetaxel versus 7.1% (95% CI, 5 to 9.5) with docetaxel. Table 6 summarises results on PFS of REVEL.

Table 6: REVEL progression free survival

Outcome	RAM+DOC	PBO+DOC
Number of Patients	628	625
Number of events, n (%)	558 (88.9)	583 (93.3)
Number censored, n (%)	70 (11.1)	42 (6.7)

Median PFS, months (95% CI)	4.5 (4.2, 5.3)	3.0 (2.8, 3.9)
Treatment difference	1.5 ($p<0.0001$[a])	
Stratified hazard ratio (95% CI)	0.76 (0.68, 0.86)	
3 months PFS rate (%) (95% CI)[b]	64.7 (60.7, 68.3)	50.1 (46.1, 54.0)
6 months PFS rate (%) (95% CI)	35.9 (32.0, 39.8)	29.1 (25.5, 32.7)
9 months PFS rate (%) (95% CI)	21.8 (18.5, 25.3)	16.6 (13.8, 19.7)
12 months PFS rate (%) (95% CI)	12.2 (9.6, 15.1)	7.1 (5.2, 9.5)

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
[a]Log-rank stratified; [b]the ERG was unable to check survival rates with published data

The company states that sensitivity analyses were conducted and confirmed the robustness of the hazard ratio (range, 0.75, 0.80). As was the case for OS, no dedicated table with hazard ratios and their 95% CI was provided in the CS for the prespecified sensitivity analyses (however, see clarification response A14). However, the company statement is consistent with the results on the table 3S (page 5/41) published in the supplementary appendix of the paper by Garon et al (2014)[16]. In this table, it can be noted that four sensitivity analysis were conducted and found that the range of HR was 0.75 to 0.78. In the clarification response two other sensitivity analyses are presented, both with HRs within the range 0.75 – 0.80).

The CS says that the statistical significance of the improvement in PFS can be considered inferential because the sensitivity analyses support the finding of an improvement in PFS associated with ramucirumab and docetaxel versus docetaxel, and also the type I error for evaluation of PFS as a secondary endpoint was controlled using gatekeeping methodology. The ERG is unable to verify this.

4.2.3 Objective Response Rate (ORR)

Objective response rate (ORR) was higher with ramucirumab and docetaxel than with docetaxel. ORR was 22.9% (95% CI, 19.7, 26.4) in the ramucirumab and docetaxel group and 13.6 % (95% CI, 11.0, 16.5) in the docetaxel group ($p<0.001$). Table 7 summarises results on ORR of REVEL. The CS says that the statistical significance of the improvement in ORR can be considered inferential because the type I error for evaluation of ORR as a secondary endpoint was controlled using gatekeeping methodology. The ERG is unable to verify this.

Table 7: REVEL objective response rate results

ITT population	RAM+DOC	PBO+DOC
Number of Patients	628	625
Complete response (CR)	3 (0.5)	2 (0.3)

Partial response (PR)	141 (22.5)	83 (13.3)
Stable disease (SD)	258 (41.1)	244 (39.0)
Progressive disease (PD)	128 (20.4)	206 (33.0)
Unknown/Not done	98 (15.6)	90 (14.4)
Objective response (CR+PR) rate (%) (95% CI)	22.9 (19.7, 26.4)	13.6 (11.0, 16.5)
p-value (based on the Cochran-Mantel-Haenszel test adjusting for the stratification variables)	<0.001	

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

4.2.4 Health-related quality of life (HRQoL)

The CS presents data from the REVEL trial on the Lung Cancer Symptom Score (LCSS) and the EQ-5D. For the LCSS the CS presents the time to deterioration on each of the 6 symptom questions (appetite loss, fatigue, cough, dyspnoea, haemoptysis, pain) together with the Average Symptom Burden Score (ASBI); the 3 global items (symptom distress, difficulties with daily activities, quality of life) together with the total score (all nine items). Each item is assessed with a 100-mm visual analogue scale with higher ratings equating to poorer quality of life. The definition of time to deterioration was predefined as the time from randomisation to the first 15mm increase. No reference was provided for this definition in the CS; the ERG's clinical advisor agrees this is a reasonable definition for this measure. Compliance rates for completion of the LCSS questionnaire was reported to be 78% at baseline in both treatment groups, at 30-day follow-up (post treatment discontinuation) this was reported to be 61% in the ramucirumab and docetaxel group and 62.2% in the docetaxel group. The data for the time to deterioration was presented in a figure (CS Figure 8, p64), where it was seen that none of the 11 items were significantly different between groups (all confidence intervals for the reported HRs crossed 1.0).

A recent publication of the quality of life results from the REVEL trial has been identified by the In this publication the mean scores on the LCSS at baseline and at 30-days follow-up (post discontinuation) were presented by treatment group and have been reproduced in

Table 8. As reported in the Perol 2016[11] paper the symptom burden was similar between the treatment arms across the LCSS throughout treatment (no p-values were reported). Quality of life in the areas of fatigue, activity level, and global QoL had the highest scores at baseline, most scores had worsened by the 30-day follow-up.

Table 8: LCSS mean scores at baseline and 30-days post treatment discontinuation

LCSS, mean (SD), mm		RAM+DOC	PBO+DOC
Loss of appetite	baseline	27.8 (26.8), n=510	29.3 (26.2), n=514
	30-days	32.2 (27.7), n=315	33.9 (28.0), n=315
Fatigue	baseline	38.6 (26.3), n=510	39.4 (26.9), n=518
	30-days	44.8 (28.2), n=316	44.1 (28.6), n=319
Cough	baseline	26.2 (27.5), n=513	30.9 (27.6), n=517
	30-days	23.8 (25.0), n=317	28.9 (28.0), n=314
Dyspnoea	baseline	28.9 (28.1), n=509	30.4 (28.0), n=520
	30-days	34.6 (28.6), n=319	30.6 (28.9), n=318
Haemoptysis	baseline	2.4 (8.8), n=513	2.7 (7.8), n=519
	30-days	3.5 (9.0), n=319	4.5 (11.8), n=317
Pain	baseline	24.5 (27.5), n=514	27.1 (28.7), n=519
	30-days	26.2 (27.6), n=319	29.2 (28.9), n=318
Symptom distress	baseline	27.9 (26.3), n=512	31.3 (28.5), n=516
	30-days	34.3 (27.2), n=319	34.0 (28.1), n=315
Activity level	baseline	34.9 (27.6), n=510	36.1 (27.8), n=517
	30-days	43.9 (29.4), n=319	43.8 (29.6), n=318
Global quality of life	baseline	36.0 (25.6), n=503	37.2 (25.5), n=513
	30-days	43.1 (26.3), n=317	44.0 (27.2), n=312
ASBI	baseline	24.6 (16.3), n=493	26.8 (16.3), n=501
	30-days	27.6 (17.7), n=300	28.4 (18.7), n=311
Total LCSS	baseline	27.3 (17.1), n=484	29.6 (17.6), n=491
	30-days	32.0 (19.0), n=296	32.5 (19.9), n=305

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

The mean maximum improvement in scores and the proportion of patients' improved, stable, or deteriorated for all LCSS scores were also presented in the Perol et al (2016) paper.[11] The mean maximum improvement from baseline was similar between treatment arms. The proportion of patients who were improved, stable, or deteriorated were similar across treatment groups with the exception of fatigue and haemoptysis.

EQ-5D

Summary outcomes of the EQ-5D at baseline, each cycle and at 30-day follow-up were presented as academic-in-confidence data in CS Table 24 (p 65). At baseline the EQ-5D index score was reported to be 0.714 (SD 0.232), n=521 in the ramucirumab and docetaxel group and 0.687 (SD 0.259), n=532 in the docetaxel group. At follow-up these were 0.612 (SD 0.201), n=310 and 0.595 (SD 0.340), n=322 for the

two groups respectively. Compliance was reported in the CS as 83% at baseline for the ramucirumab and docetaxel and 85.1% at baseline for the docetaxel group. At follow-up compliance was reported to be 63.9% and 65.7% for the two groups respectively. The CS states that there were minimal changes from baseline while on study treatment, regardless of treatment arm, and that scores decreased in both arms at the follow-up assessment.

4.2.5 Subgroup analysis

Thirteen subgroup analyses had been pre-specified including outcomes by histology. The company states that a statistically significant and clinically meaningful improvement in OS and PFS was consistently observed across squamous and non-squamous histology, in male and female patients, in patients from different geographies, in patients with different smoking status, in patients with different EGFR status and in patients with or without prior taxane, prior maintenance, or prior bevacizumab treatment. This sentence is not in line with the forest plots for subgroup analysis of OS and PFS (CS figure 10 on page 69 and figure 11 on page 70 respectively). Indeed, according to those plots, a statistically significant improvement occurred only in the following pre-specified subgroups:

- Analyses on OS: age <65 years, female, white patients, ever smoking history, staging of IV, nonsquamous histology, best response (complete response/partial response/stable disease) to platinum-based chemotherapy, no prior bevacizumab treatment, prior maintenance therapy, and time since prior therapy <9months
- Analyses on PFS: PS 0-1, age <65 years, male and female, white patients and 'other' patients, geographic region as 'rest of world', ever smoking history, staging of IV, squamous and non-squamous histology, wild type or unknown EGFR status, all responses to platinum-based chemotherapy, no prior taxane treatment, no prior bevacizumab treatment, prior or no prior maintenance therapy, time since therapy <9months.

On pages 67-68, the Company provides interpretations of the findings from subgroup analyses. The absence of benefit on OS and PFS in patients ≥65 years (OS HR: 1.10 (0.89, 1.36), PFS HR : 0.98 (0.81,1.19) is questionable, but the explanations of the company that this may be related to the inflexibility of the dichotomy and owing to variability given the number of subgroup analyses undertaken, seem to be plausible.

The subgroup analyses of OS and PFS by histology are summarised in Table 9 and Table 10 for the nonsquamous and squamous histologies (for other histologies see CS Table 26 and 27).

Table 9: REVEL subgroup analyses for OS

Outcome by histology	RAM+DOC	PBO+DOC
Nonsquamous subpopulation		
Number of Patients	465	447
Median Survival, months (95% CI)	11.1 (9.9, 12.3)	9.7 (8.5, 10.6)
Unstratified hazard ratio (95% CI)	0.83 (0.71,0.97)	
p-value (Unstratified Log rank)	0.02	
Squamous subpopulation		
Number of Patients	157	171
Median Survival, months (95% CI)	9.5 (8.0, 10.8)	8.2 (6.3, 9.4)
Unstratified hazard ratio (95% CI)	0.88 (0.69,1.13)	
p-value (Unstratified Log rank)	0.319	

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
NB: nonsquamous includes: 'Adenocarcinoma', 'Large Cell', 'Other'

Table 10: REVEL subgroup analyses for PFS

Outcome by histology	RAM+DOC	PBO+DOC
Nonsquamous subpopulation		
Number of Patients	465	447
Median PFS, months (95% CI)	4.6 (4.3, 5.5)	3.7 (2.8, 4.1)
Unstratified hazard ratio (95% CI)	0.77 (0.67,0.88)	
p-value (Unstratified Log rank)	<0.001	
Squamous subpopulation		
Number of Patients	157	171
Median PFS, months (95% CI)	4.2 (3.6, 5.4)	2.7 (2.5, 2.9)
Unstratified hazard ratio (95% CI)	0.76 (0.61,0.96)	
p-value (Unstratified Log rank)	0.019	

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
NB: nonsquamous includes: 'Adenocarcinoma', 'Large Cell', 'Other'

The company indicates on page 70 that a consistent treatment effect was observed in patients regardless of squamous or nonsquamous histology. In the squamous subgroup, the difference on OS is not statistically different (0.88, 95% CI, 0.69, 1.13) but this may be related to smaller samples (328 patients overall versus 912 patients in the nonsquamous subgroup).

Erlotinib is a potential comparator to ramucirumab in those with unknown mutation status or in those with a positive mutation status who did not have first line treatment with erlotinib. In the REVEL trial

testing for EGFR mutation status was undertaken in only 437 patients (35.1%), thereby limiting the analysis of the pre-specified subgroup analysis of EGFR mutation positive, wild-type or unknown. The CS states that a consistent treatment effect was observed in the ramucirumab and docetaxel arm compared to the docetaxel, across those with EGFR-mutated, wild type, or unknown mutation status. However, as stated above, there was only a significant benefit seen for PFS for EGFR wild-type or unknown. The CS also states that it is unlikely that imbalance in the EGFR mutation status between groups has an impact on survival, or that imbalance in those treated with EGFR TKI's post discontinuation impacts on the survival seen.

4.2.6 NMA results

The results of the NMA for OS for ramucirumab and docetaxel versus the comparators in the CS decision problem are summarised in Table 11. Ramucirumab and docetaxel showed a significantly better OS than docetaxel alone (HR 0.86 (95% CI 0.75, 0.98)) in line with the results of the REVEL trial. The comparison with erlotinib is in the EGFR negative subpopulation and is not considered to be an appropriate comparator but is presented in Appendix 1 for completeness. The comparison of ramucirumab and docetaxel with combination nintedanib and docetaxel in the non-squamous subpopulation shows no significant difference in OS (HR 1.10 (95% CI 0.82, 1.25)).

The CS undertook a separate subgroup NMA for the comparison of ramucirumab and docetaxel with nintedanib and docetaxel (Table 12). This was for the adenocarcinoma subpopulation because nintedanib and docetaxel is indicated in this subgroup only. The HRs seen were similar to those seen for the comparison with the ramucirumab and docetaxel in Table 11. The company confirmed in clarification C1 that these analyses were post hoc comparisons.

Table 11: Overall survival NMA HR results, fixed effect model

Intervention	**Comparator**	
	Docetaxel (all populations)	Nintedanib and docetaxel (non-squamous)
Ramucirumab and docetaxel (all populations)	0.86 (95% CI 0.75, 0.98)	1.01 (95% CI 0.82, 1.25)
Nintedanib and docetaxel (non-squamous)	0.85 (95% CI 0.71, 1.00)	

CS Table states Ramu + doc is for all populations, the ERG believes the population differs in relation to the comparison of relevance.

Table 12: Overall survival NMA HR results for the adenocarcinoma subpopulations

Intervention	Comparator	
	Docetaxel (all populations)	Nintedanib and docetaxel
Ramucirumab and docetaxel	0.83 (95% CI 0.72, 0.96)	1.00 (95% CI 0.60, 1.25)
Nintedanib and docetaxel	0.83 (95% CI 0.70, 0.99)	

For PFS the results of the NMA showed that ramucirumab and docetaxel was significantly better compared with docetaxel alone in line with the results from the REVEL trial: HR 0.76 (95% CI 0.68, 0.86) (Table 13). PFS was similar between ramucirumab and docetaxel and nintedanib and docetaxel in the non-squamous subpopulation (HR 0.99 (95% CI 0.78, 1.26)). Similar results were shown in the post hoc adenocarcinoma subpopulation NMA (Table 14). The comparison with erlotinib is in the EGFR negative subpopulation and is not considered to be an appropriate comparator but is presented in Appendix 1 for completeness.

Table 13: Progression free survival NMA HR results, fixed effect model

Intervention	Comparator	
	Docetaxel (all populations)	Nintedanib and docetaxel (non-squamous)
Ramucirumab and docetaxel (all populations)	0.76 (95% CI 0.68, 0.86)	0.99 (95% CI 0.78, 1.26)
Nintedanib and docetaxel (non-squamous)	0.77 (95% CI 0.62, 0.95)	

CS Table states Ramu + doc is for all populations, the ERG believes the population differs in relation to the comparison of relevance.

Table 14: PFS NMA HR results for the adenocarcinoma subpopulations

Intervention	Comparator	
	Docetaxel (all populations)	Nintedanib and docetaxel
Ramucirumab and docetaxel	0.83 (95% CI 0.72, 0.96)	1.00 (95% CI 0.81, 1.25)
Nintedanib and docetaxel	0.83 (95% CI 0.69, 0.98)	

NMA results for ORR are seen in Table 15. Similarly to the results for OR and PFS the NMA outputs show that ramucirumab and docetaxel are significantly better than docetaxel alone and similar to nintedanib and docetaxel in the non-squamous subpopulation. No NMA was undertaken for ORR in the adenocarcinoma subgroup. The comparison with erlotinib is in the EGFR negative subpopulation and is not considered to be an appropriate comparator but is presented in Appendix 1 for completeness.

Table 15: Overall response rate NMA results, fixed effect model, difference in probit scores

Intervention	Comparator	
	Docetaxel (all populations)	Nintedanib and docetaxel (non-squamous)
Ramucirumab and docetaxel (all populations)	0.41 (95% CI 0.27, 0.54)	0.05 (95% CI -0.18, 0.28)
Nintedanib and docetaxel (non-squamous)	0.35 (95% CI 0.17, 0.53)	

Probit score difference greater than zero favours the intervention over the comparator. CS Table states Ramu + doc is for all populations, the population differs in relation to the comparison of relevance.

4.2.7 Adverse events

The CS reported treatment-emergent adverse events (TEAEs) by MeDRA Preferred Term. In contrast, the trial publication presented some adverse events where clinically synonymous Preferred Terms were consolidated to allow clearer interpretation of the data, and where applicable these have been reported in the tables below.

Deaths that occurred on treatment and up to 30 days after the last dose of study treatment (ramucirumab + docetaxel 8.5% vs placebo + docetaxel 9.4%) and deaths due to TEAEs (ramucirumab + docetaxel 5.4% vs placebo + docetaxel 5.7%, Table 16) were similar between groups. CS p103 also states deaths due to adverse events (including treatment-emergent and non-treatment-emergent adverse events) was similar, at 4.9% vs 5.7% (checked in CSR p. 157-158). The ERG notes that there is an inconsistency in the reporting, with the number of deaths in the ramucirumab + docetaxel arm (31, 4.9%) being lower than the TEAE numbers reported in CS page 101 (34, 5.4%).

The proportion of participants who experienced at least one treatment-emergent serious adverse event was also similar between ramucirumab + docetaxel and placebo + docetaxel (42.9% vs 42.4%, Table 16). The most frequently reported (≥1%) treatment-emergent serious adverse event with a higher incidence (≥5%) in the ramucirumab arm was febrile neutropenia ([redacted] Table 17).

Table 16: Summary of treatment-emergent adverse events REVEL trial

	RAM+DOC **N = 627**	**PBO+DOC** **N = 618**
At least one TEAE, n (%)	613 (97.8)	594 (96.1)
TEAEs with outcome of death, n (%)	34 (5.4)	35 (5.7)
Treatment-Emergent Serious Adverse Events, n (%)	269 (42.9)	262 (42.4)
Patients with ≥1 Grade 3/4/5 TEAE	**495 (78.9)**	**444 (71.8)**
Discontinued any study drug due to ≥1 TEAE, n (%)	58 (9.3)	32 (5.2)
- Discontinued ramucirumab/placebo	9 (1.4)	6 (1.0)
- Discontinued docetaxel	49 (7.8)	26 (4.2)

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
CS Table 35 p. 101. Bold font indicates adverse events occurring ≥5% in ramucirumab group. Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

Table 17: Serious adverse events with a higher incidence (≥5%) in ramucirumab versus placebo, REVEL

Serious adverse event, n (%)	**RAM+DOC** **N = 627**	**PBO+DOC** **N = 618**
Febrile neutropenia	[redacted]	[redacted]

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
[redacted]

A higher proportion of the ramucirumab group experienced TEAEs of Grade 3 or above (78.9% vs. 71.8%, Table 16). Grade ≥3 TEAEs with a higher incidence (≥5%) in the ramucirumab + docetaxel group were neutropenia (consolidated term: 48.8% vs 39.8%) and febrile neutropenia (15.9% vs 10.0%) (Table 18). There was no grade 5 of these two events.

The proportion of participants who experienced at least one TEAE of any grade was similar between ramucirumab + docetaxel and placebo + docetaxel (97.8% vs 96.1%, Table 16). Adverse events of special interest were specified due to the anti-angiogenic mechanism of action of ramucirumab and are presented in Table 19. Bleeding or haemorrhage was more common with ramucirumab + docetaxel than placebo + docetaxel (28.9% vs 15.2%), mainly due to increased epistaxis (18.5% vs 6.5%). Hypertension was also more common with ramucirumab + docetaxel than placebo + docetaxel (consolidated term 10.8% vs 4.9%). Other TEAEs of any grade with a higher incidence (≥5%) in the ramucirumab + docetaxel group were neutropenia (consolidated term: 55.0% vs 46.0%), stomatitis (23.0% vs 12.9%), peripheral oedema (16.3% vs 8.6%), mucosal inflammation (16.1% vs 7.0%), febrile neutropenia (15.9% vs 10.0%), increased lacrimination (13.4% vs 4.5%), and thrombocytopenia (13.4% vs 5.2%) (Table x to x).

Anaemia was more common in the placebo + docetaxel group (ramucirumab + docetaxel 20.9% vs 228.2% placebo + docetaxel) (Table 18).

A similar proportion of participants in each group was hospitalised (ramucirumab + docetaxel 41.9% vs placebo + docetaxel 42.6%) and the duration of stay was also similar (ramucirumab + docetaxel median 9.0 days (range 1 to 128) vs placebo + docetaxel median 8.0 days (range 1 to 56); hospitalisation per patient: ramucirumab + docetaxel mean 14.5 days (SD 16.5) vs placebo + docetaxel mean 11.3 days (SD 9.9)).

Table 18: Haematological adverse events

Haematological adverse events, n (%)	**RAM+DOC N = 627**		**PBO+DOC N = 618**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia[a]	**345 (55.0)**	**306 (48.8)**	**284 (46.0)**	**246 (39.8)**
Leukopenia [a]	134 (21.4)	86 (13.7)	117 (18.9)	77 (12.5)
Anaemia [a]	131 (20.9)	18 (2.9)	174 (28.2)	35 (5.7)
Febrile neutropenia	**100 (15.9)**	**100 (15.9)**	**62 (10.0)**	**62 (10.0)**
Thrombocytopenia [a]	**84 (13.4)**	18 (2.9)	**32 (5.2)**	4 (0.6)

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
Garon 2014[16]. Bold font indicates adverse events occurring ≥5% in ramucirumab group. [a] Consolidated term.

Table 19: Adverse events of special interest

Adverse event, n (%)	**RAM+DOC N = 627 n (%)**		**PBO+DOC N = 618 n (%)**	
	Any Grade	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Bleeding or haemorrhage	**181 (28.9)**	15 (2.4)	**94 (15.2)**	14 (2.3)
Epistaxis	**116 (18.5)**	2 (0.3)	**40 (6.5)**	1 (0.2)
Gastrointestinal haemorrhage	17 (2.7)	4 (0.6)	10 (1.6)	2 (0.3)
Pulmonary haemorrhage	49 (7.8)	8 (1.3)	46 (7.4)	8 (1.3)
Haemoptysis	36 (5.7)	4 (0.6)	32 (5.2)	4 (0.7)
Hypertension[a]	**68 (10.8)**	35 (5.6)	**30 (4.9)**	13 (2.1)
Infusion-related reaction	23 (3.7)	5 (0.8)	28 (4.5)	4 (0.7)
Proteinuria	21 (3.3)	1 (0.2)	5 (0.8)	0
Venous thromboembolic events	16 (2.6)	11 (1.8)	36 (5.8)	18 (2.9)
Renal failure	14 (2.2)	3 (0.5)	14 (2.3)	2 (0.3)

Arterial thromboembolic	10 (1.6)	6 (1.0)	13 (2.1)	8 (1.3)
Congestive heart failure	6 (1.0)	5 (0.8)	4 (0.7)	1 (0.2)
Gastrointestinal perforation	6 (1.0)	5 (0.8)	2 (0.3)	2 (0.3)

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
Garon 2014[16]. Bold font indicates adverse events occurring ≥5% in ramucirumab group. [a] Consolidated term.

Table 20: Treatment-emergent adverse events by preferred term (unless stated otherwise)

TEAE, n (%)	**RAM+DOC N = 627**		**PBO+DOC N = 618**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Fatigue [a]	343 (54.7)	88 (14.0)	309 (50.0)	65 (10.5)
Diarrhoea	199 (31.7)	29 (4.6)	171 (27.7)	19 (3.1)
Decreased appetite	182 (29.0)	14 (2.2)	154 (24.9)	8 (1.3)
Nausea	169 (27.0)	7 (1.1)	170 (27.5)	9 (1.5)
Alopecia	162 (25.8)	NA	156 (25.2)	NA
Stomatitis	**146 (23.0)**	27 (4.3)	**80 (12.9)**	10 (1.6)
Neuropathy [a]	145 (23.1)	17 (2.7)	126 (20.4)	10 (1.6)
Dyspnoea	138 (22.0)	24 (3.8)	149 (24.1)	51 (8.3)
Cough	133 (21.2)	3 (0.5)	128 (20.7)	5 (0.8)
Pyrexia	104 (16.6)	3 (0.5)	80 (12.9)	2 (0.3)
Peripheral oedema	**102 (16.3)**	0	**53 (8.6)**	2 (0.3)
Constipation	101 (16.1)	1 (0.2)	108 (17.5)	6 (1.0)
Mucosal inflammation	**101 (16.1)**	18 (2.9)	**43 (7.0)**	3 (0.5)
Vomiting	87 (13.9)	8 (1.3)	88 (14.2)	12 (1.9)
Lacrimation increased	**84 (13.4)**	1 (0.2)	**28 (4.5)**	0
Myalgia	78 (12.4)	4 (0.6)	65 (10.5)	4 (0.6)
Arthralgia	72 (11.5)	7 (1.1)	49 (7.9)	4 (0.6)
Back pain	71 (11.3)	7 (1.1)	53 (8.6)	2 (0.3)
Abdominal pain [a]	68 (10.8)	5 (0.8)	61 (9.9)	8 (1.3)
Dysgeusia	67 (10.7)	NA	46 (7.4)	NA
Insomnia	67 (10.7)	3 (0.5)	51 (8.3)	1 (0.2)
Headache	66 (10.5)	3 (0.5)	67 (10.8)	6 (1.0)

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
Garon 2014.[16] Bold font indicates adverse events occurring ≥5% in ramucirumab group. [a] Consolidated term.

4.2.8 Additional work on clinical effectiveness undertaken by the ERG

For summary results from Hosomi et al[21] see

Appendix 2.

Implementation of NMA hazard ratios to estimate LYG

In the CS the HRs from the NMA are used to generate estimates of LYG by different treatments. To generate the survival curve for comparator treatment 'X' (a treatment other than ramucirumab + docetaxel) the CS takes the HR estimates from the NMA (e.g. X versus docetaxel) and applies this to a multivariate loglog distribution fit for OS of the placebo + docetaxel arm of the REVEL trial. The LYG estimate for X is the area under this newly generated survival curve. This procedure: (a) imposes proportional hazards between compared treatments; in the opinion of the ERG there is no *a piori* reason to expect proportional hazards to hold for two treatments that differ in their mode of action[1]; (b) forces a loglogistic curve shape on the comparator which is unlikely to reflect that observed in studies of that treatment (there is no a priori reason to expect that the observed curve will conform to a loglgog distribution); (c) anchors the generated curve on the time axis according to the position of the REVEL docetaxel survival curve (again there is no a priori reason that this is appropriate); (d) if the loglogistic model for the REVEL docetaxel arm is an overestimate or underestimate of survival then it follows that all NMA-dependent comparator treatment estimates may also be over or underestimated (Section 4.1.9.2)

The resulting survival curves from this procedure may be implausible and/or bear little relationship to the observed curves found in published studies. For example if the NMA HRs for erlotinib in an EGFR positive non squamous NSCLC population are used the resulting curves may be considered clinically implausible.

The primary source of survival data for each treatment specified in the NICE scope comes from a single trial: REVEL for ramucirumab, Reck et al (2014)[18] for nintedanib in the adenocarcinoma subgroup, Brahmer et al 2015[20] for nivolumab in the squamous subgroup, and Garassino et al (2013)[19] for erlotinib in the EGFR wild type populations. Two other trials of marginal relevance are considered in Appendix 4; these are Borghaei et al. 2015[28] for nivolumab in the non-squamous subgroup and Kawaguchi et al. 2014[29] who analysed erlotinib versus docetaxel in a subgroup of EGFR positive patients. When single clinical trials are the primary source for cost-effectiveness assessment, the ERG believes it important to report the observed evidence. Replacing trial results with NMA-dependent fitted models imposes "uncertainty of modelling assumptions to the unavoidable data sampling uncertainty"[24] so that despite the advantage of introducing study level variables offered by the NMA, the resulting models may bear a poor

[1]For example ramucirumab binds to VEGFR and EGFR and blocks other ligands, whereas nintedanib prevents ATP binding to the tyrosine kinase domain of EGFR, and nivolumab interacts with the programmed cell death pathway.

relationship to the observed survival seen in the relevant trials. The extent of such incongruity is difficult to judge from the CS because of the lack of information provided about observed survival in RCTs other than REVEL; the only information provided was log HR NMA inputs (see above) and hazard ratio outputs from the NMA. Therefore the ERG has attempted to provide more detailed survival information for these important trials.

In view of the concerns outlined above, the ERG has estimated LYG and progression-free life months gained (PFLMG) using, as far as possible, the observed data from the relevant trials (thereby retaining the properties of shape and temporal dispersion of the survival curves observed in the trial). Differences in the observed survival in the control arms of the trials were also examined (Appendix 5). The RCT for ramucirumab, nintedanib and nivolumab interventions were REVEL, Reck et al (2014)[18], and Brahmer et al 2015[20]. These studies and their published median OS, median PFS and HRs are summarised in Table 21.

Table 21: Survival estimates from key studies of relevance to the NICE scope

Study	Intervention comparator	Median Φ	Difference in medians	Population	HR	Comment
Brahmer 2015 CHECKMATE 017	nivolumab docetaxel	9.2 6.0	3.2	Squamous	0.59	Monotherapy one RCT
Garon 2014 REVEL	Ram+doc docetaxel	10.5 9.1	1.4	All	0.86	Dual therapy One RCT
	Ram+doc docetaxel	8.2 9.5	1.3	Squamous	0.88	Dual therapy One RCT
	Ram+doc docetaxel	11.1 9.7	1.4	Non squamous	0.83	Dual therapy One RCT
Paz-Arez 2015 (abs)	Ram+doc docetaxel	11.2 9.8	1.4	Adenocarcinoma	0.83	Dual therapy One RCT
Kasahara 2015 (abs)§§	Ram+doc docetaxel	NR	NR	ERGF +ve	NR	Dual therapy One RCT
Reck 2014 LUME1-Lung	Nin+doc docetaxel	12.6 10.3	2.3	Adenocarcinoma	0.83	Dual therapy One RCT
	Nin+doc docetaxel	10.1 9.1	1.0	All *	0.94	Dual therapy One RCT

Φ months. * NICE do not recommend nintedanib for this Population. **analysis of a very small subgroup at risk of imbalance. § unadjusted hazard ratio.

Estimation of mean LYG and mean PFLMG using observed trial data

In clarification response A6+7 the company supplied detailed information of OS and PFS for patients in the REVEL trial (for all patients and for subgroups according to tumour histology). For the other trials the ERG digitised published KM plots from published studies (Table 21) and used the method of Guyot et al. (2012)[30] to reconstruct individual patient data. Kaplan Meier plots were constructed in Stata and parametric models obtained using the commands streg and stgenreg (Crowther and Lambert, 2013[31]).

To be consistent with the company's use of loglogistic models for OS the ERG fit separate loglogistic models for intervention and control arms and estimated mean LYG over 15 years (the time horizon of the economic model). Because patient level covariates were unavailable to the ERG the models are unadjusted. Additionally the mean LYG from interventions was estimated directly from Kaplan Meier plots over the observed period. Figure 3 summarises the OS KM plots for nintedanib, ramucirumab, and nivolumab in patients subgroups categorised by tumour histology (other potentially relevant KM plots are provided in Appendix 4).

Estimates of LYG based on the AUC of reconstructed KM plots are summarised in Table 22. These estimates indicate that the observed LYG from ramucirumab (relative to docetaxel) is likely less than that observed in the nivolumab trial but similar to that in the nintedanib trial; the similarity of observed survival for adenocarcinoma patients in the intervention and control arms of the REVEL and LUME 1 trials is shown in Appendix 6.

Table 22: LYG over observed period estimated from AUC of the Kaplan-Meier plots

STUDY	**Population**	**Intervention LYG**	**Control LYG**	**Intervention Gain**	**Observation Period Φ**
REVEL	Non squamous	RAM **1.22**	DOC **1.07**	0.154	32.5
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab **0.94**	DOC **0.66**	0.281	22
REVEL	Squamous	RAM **0.96**	DOC **0.86**	0.070	32.4
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib **1.28**	DOC **1.11**	0.166	36
REVEL	Adenocarcinoma	RAM **1.25**	DOC **1.09**	0.158	32.5
REVEL	All	RAM **1.15**	DOC**1.03**	0.121	32.5
Φ months, the KM observation period used was kept the same for both arms. DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab					

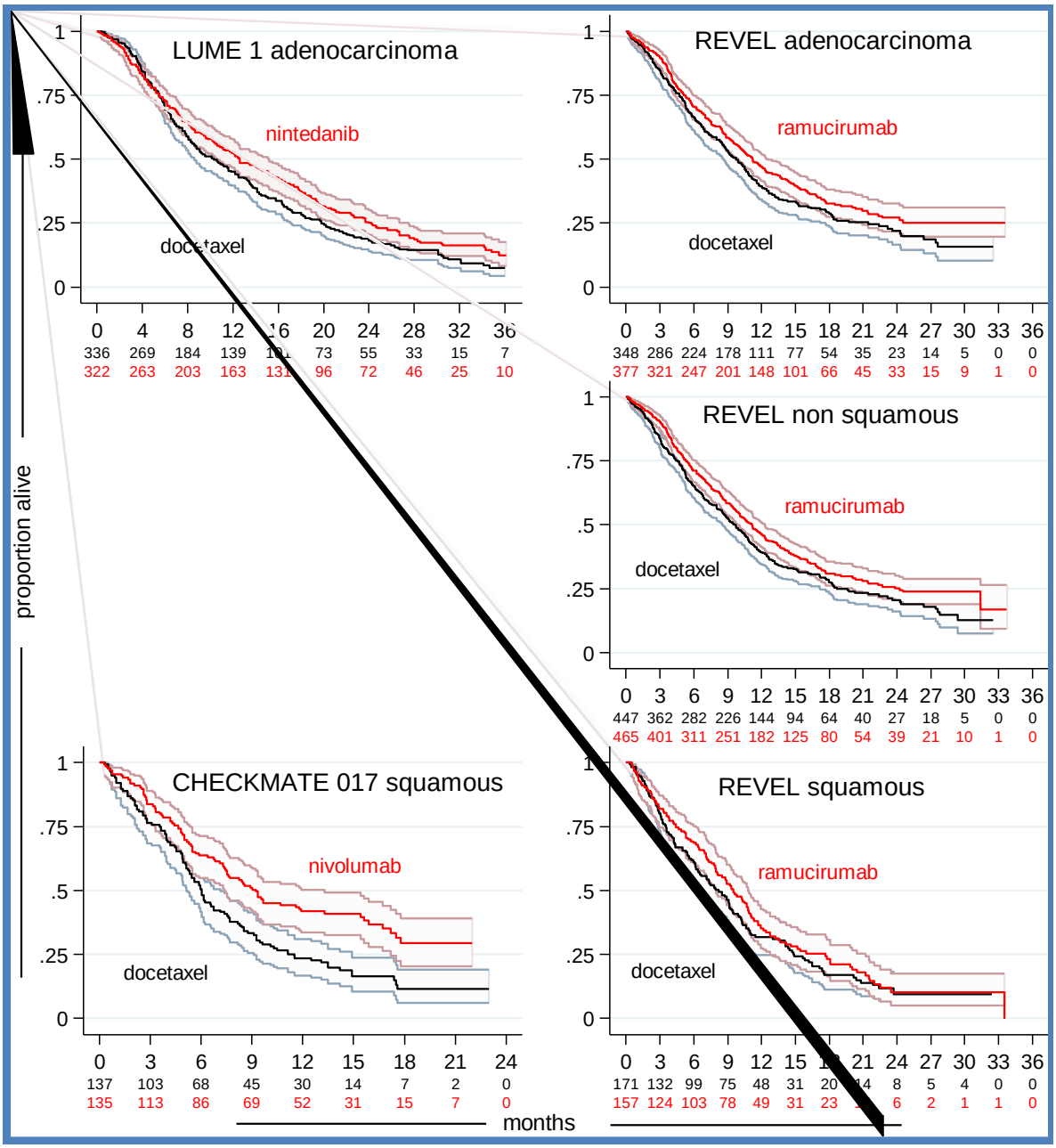


Figure 3: Kaplan Meier plots for overall survival

The published studies used were: LUME 1 lung for nintedanib in adenocarcinoma ; REVEL for ramucirumab in each histology subgroup; CHECKMATE 017 for nivolumab in squamous tumours; TAILOR for erlotinib in wild type EGFR.

Table 23 summarises the estimated LYG by each trial treatment after applying the loglogistic models to each arm of each trial over the lifetime horizon of 15 years. These estimates indicate that the LYG from ramucirumab (relative to docetaxel) may be less than that observed in the trials for the comparator treatments.

Table 23: Estimated LYG over a 15 year time horizon estimated using separate unadjusted loglogistic models for each arm¥

STUDY	Population	Intervention LYG	Control LYG	Intervention Gain
REVEL	Non squamous	RAM **1.805**	DOC **1.589**	**0.216**
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab **2.14**	DOC **1.36**	**0.780**
REVEL§	Squamous	RAM **1.371**	DOC **1.205**	**0.166**
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib **1.891**	DOC **1.436**	**0.455**
REVEL	Adenocarcinoma	RAM **1.947**	DOC **1.649**	**0.298**
REVEL*	All	RAM **1.67**	DOC **1.48**	**0.186**

¥ estimates do not include discounting or tapering of the drug effect beyond the observed data. § Data from CS Table 93 for the REVEL non-squamous population indicates 1.666 and 1.390 LYG for Ramu and Doce arms respectively providing an intervention gain of 0.276 LY . * Data from CS Table 45 using multivariate adjusted model intervention provides LYG estimates of 1.574 and 1.319 for Ramu and Doce arms respectively with an intervention gain of 0.255 LY.
DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab

Based on the estimates in Table 22 and Table 23 the proportion of mean LYG that accrues from log logistic model extrapolations is between 31% and 36% for the REVEL trial populations, more than 50% for the squamous Brahmer et al 2015[20] population, and 33% and 23% respectively for the adenocarcinoma nintedanib and docetaxel populations in Reck et al (2014)[18].

Figure 4 summarises the PFS KM plots for nintedanib, ramucirumab, and nivolumab in patients subgroups categorised by tumour histology (other potentially relevant KM plots are provided in Appendix 7). To be consistent with the manufacturer's approach gamma models of progression fee survival were fit separately for each trial arm and PFLMG were estimated.

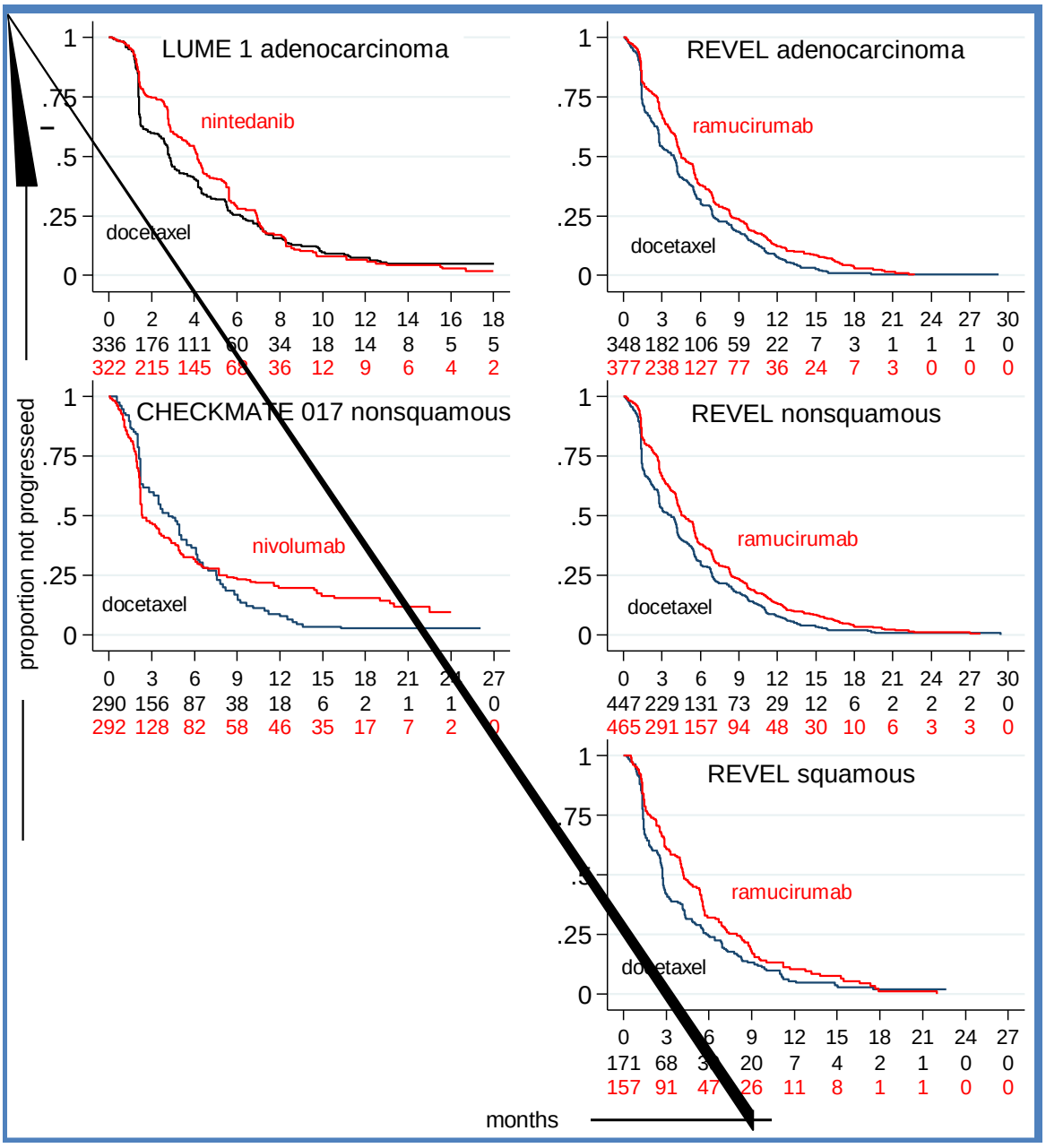


Figure 4: Kaplan Meier plots for PFS.

The published studies used were: LUME 1 lung for nintedanib in adenocarcinoma ; CHECKMATE 057 for nivolumab in non-squamous tumours; REVEL for ramucirumab in each histology subgroup; CHECKMATE 017 for nivolumab in squamous tumours; TAILOR for erlotinib in wildtype EGFR. For greater clarity the 95% CI have been excluded.

Table 24 and Table 25 provide estimates of PFLMG based on the AUC of reconstructed KM plots and on gamma models of PFS. It should be noted that visual inspection of the gamma models indicates that fit the observed data poorly and may generate anomalous results.

Table 24: PFLMG over observed period estimated from AUC of the Kaplan-Meier plots

STUDY	Population	Intervention PFLMG	Control PFLMG	Intervention Gain	Observation Period Φ
REVEL	Non squamous	RAM **6.22**	DOC **4.94**	1.29	27.8
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab **6.41**	DOC **3.99**	2.42	18
REVEL	Squamous	RAM **5.49**	DOC **4.30**	1.20	22
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib **4.89**	DOC **4.44**	0.45	18
REVEL	Adenocarcinoma	RAM **6.12**	DOC **4.94**	1.18	22.7
REVEL	All	RAM **6.00**	DOC **4.85**	1.15	27.8
Φ months, the KM observation period used was kept the same for both arms. DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab					

Table 25: Estimated PFLYMG over a 15 year time horizon estimated using separate unadjusted gamma models for each arm¥

STUDY	Population	Intervention PFLMG	Control PFLMG	Intervention Gain
REVEL	Non squamous	RAM **6.69**	DOC **5.42**	**1.270**
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab **12.17**	DOC **4.55**	**7.626**
REVEL	Squamous	RAM **6.05**	DOC **5.08**	**0.966**
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib **5.20**	DOC **4.71**	**0.00**
REVEL	Adenocarcinoma	RAM **6.58**	DOC **5.44**	**1.142**
REVEL *****	All	RAM **6.46**	DOC **5.31**	**1.146**
¥ estimates do not include discounting or half cycle adjustment. * Data from CS Table 48 using multivariate adjusted model intervention PFLMG = 1.45 and unadjusted of 1.152 DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab				

LYG by RAM+DOC versus DOC

The company developed parametric models for OS under the assumption of proportional hazards (i.e. treatment was a covariate). In the opinion of the ERG this assumption is unnecessary and the preferred option would be to model each arm separately. The ERG recognises that the company's procedure allows the introduction of patient level variables into the development of models (multivariate adjusted models). The company has selected loglogistic models for implementation in the economic model; unfortunately these models do not fulfil the proportional hazards assumption since with these models the HR between

treatments varies through time. The covariates included in the multivariate models did not encompass consideration of post progression treatments.

Table 26 shows the data from CS Table 45 in which estimates of the modelled LYG are presented according to various parametric models (either unadjusted or adjusted for patient covariates). The ERG has inserted extra columns showing the gain from ramucirumab + docetaxel relative to placebo + docetaxel for each model. The adjusted multivariate loglogistic models generate the greatest gain for ramucirumab + docetaxel. These models are the only ones to meet the three months survival gain suggested by NICE as an end of life criterion. On the basis that the adjusted loglogistic models provided the best fit to the observed data they were selected by the company for input to the economic analysis.

Table 26: LYG according to adjusted and unadjusted parametric models

	RAM+DOC	**PBO+DOC**		**RAM+DOC**	**PBO+DOC**	
Distribution	**Mean OS (years) (Unadjusted)**	**Mean OS (years) (Unadjusted)**	**RAM+DOC MINUS PBO+DOC**	**Mean OS (years) (Multivariate)**	**Mean OS (years) (Multivariate)**	**RAM+DOC MINUS PBO+DOC**
Exponential	1.278	1.116	0.162	1.080	1.289	0.209
Weibull	1.216	1.068	0.148	1.012	1.198	0.186
Lognormal	1.615	1.396	0.219	1.285	1.527	0.242
Log-logistic	1.659	1.437	0.222	1.319	1.574	0.255
Generalized gamma	1.345	1.166	0.179	1.073	1.279	0.206
It is unclear if these estimates involve implementation of tapering treatment effect to zero after 6 months as is used in the economic model; in practice the difference between tapered and non-tapered estimates are extremely small DOC: Docetaxel; PBO: placebo; RAM: ramucirumab						

Figure 27 of the CS, p129) shows the fit for each of the multivariate adjusted parametric models superimposed on the observed KM plot for each arm of REVEL (all patients). The loglogistic model (CS Figure 27, reproduced as Figure 5) provides a good fit for the ramucirumab + docetaxel arm but the fit is poorer for the placebo + docetaxel arm (Figure 5). From about 10 months onward the placebo + docetaxel loglog fit underestimates the observed survival seen in the KM plot. This underestimate of survival for placebo + docetaxel arm relative to ramucirumab + docetaxel would be continued in extrapolation; with these models about 44% of the gain from ramucirumab over PBO + docetaxel is accrued beyond the observed data (estimated with no discounting or "tapering" of drug effect). Since this placebo + docetaxel arm fit is used in the economic model for calculating OS for any comparators (using

NMA HRs) it appears these will be underestimated relative to ramucirumab + docetaxel arm. In employing these methods any comparator may tend to lose out relative to ramucirumab + docetaxel. In the opinion of the ERG, if loglog models are adopted, the preferred option would be to fit separate models for each arm.

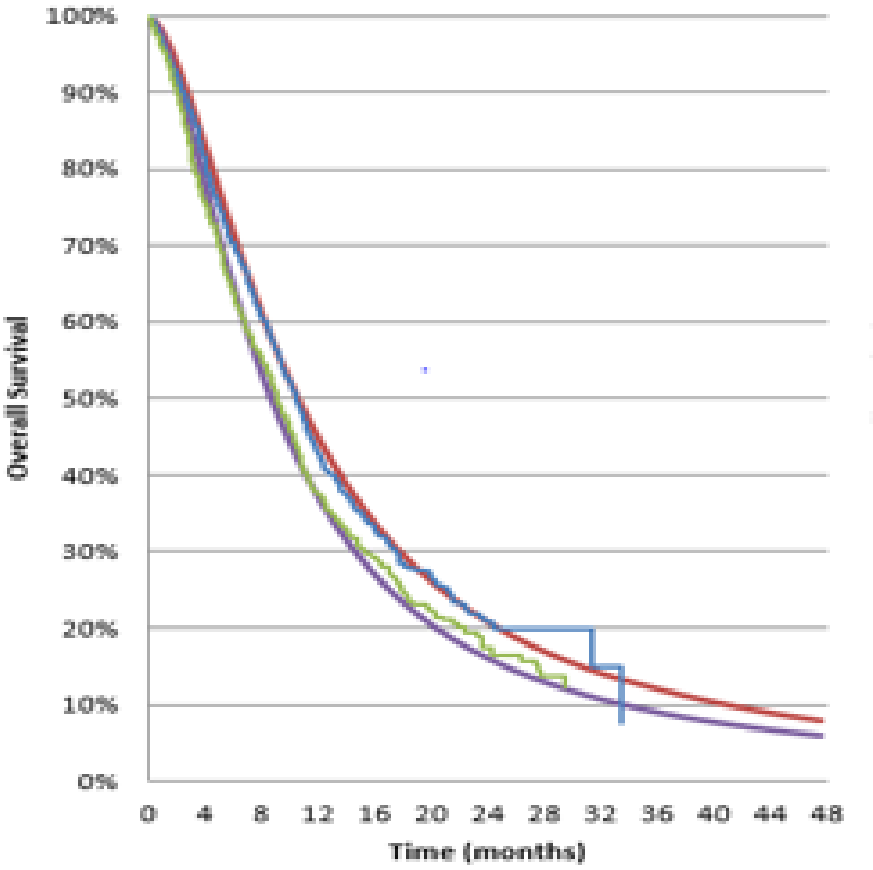


Figure 5: Loglogistic OS (from Figure 27 CS p129)

Two difficulties with the company log logistic models are: they do not provide good fits for the observed trial data and they violate the assumption of proportional hazards. When trial cumulative hazard plots are examined it is evident that beyond about 11 months there is linear trend for each arm, suggesting that from this time a constant hazard fits the observed data. Figure 6 compares the trial cumulative hazard from 11 months onward with modelled cumulative hazard in each arm (company loglogistic models right, linear trend models left).

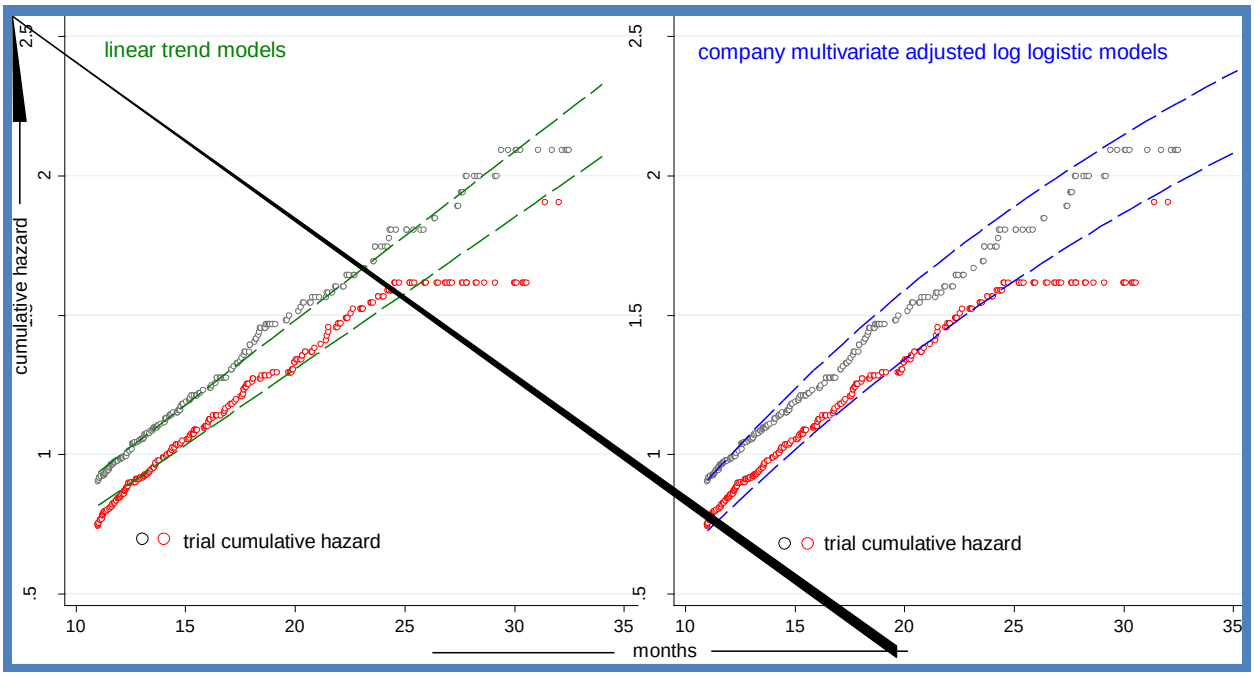


Figure 6: Observed cumulative hazard compared to company and linear trend models (REVEL trial all patients; linear trend was obtained by regression of observed data from 11 months onward).

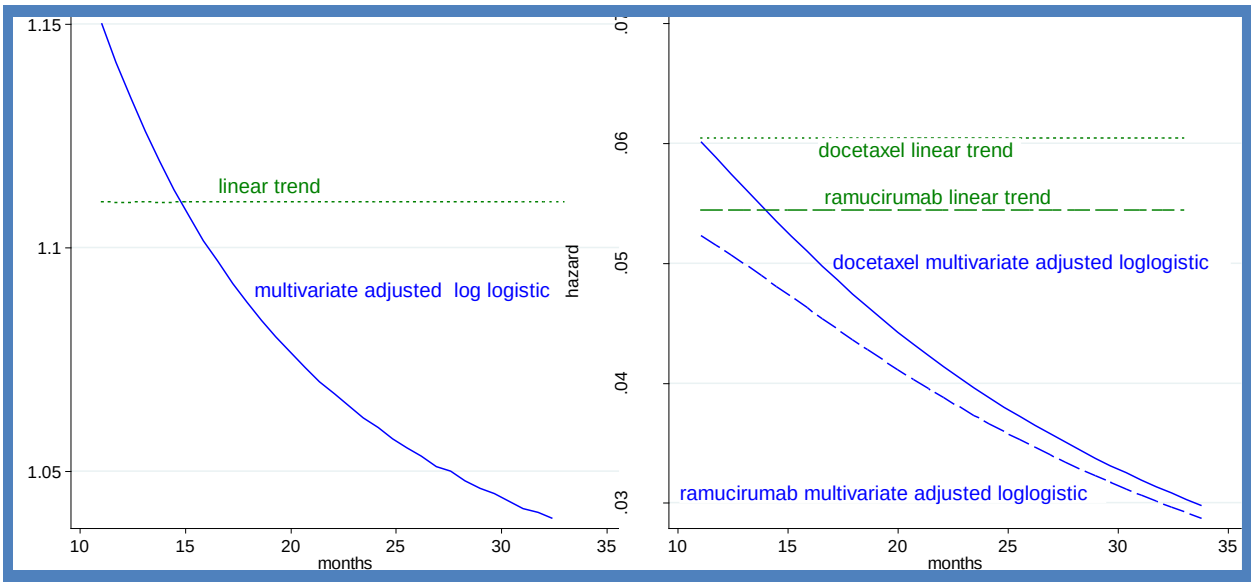


Figure 7: Hazard for each trial arm and hazard ratios of linear trend and log logistic models

The ERG considers the linear trend models superior if a proportional hazards option is desired because they provide a better fit and retain proportional hazards (Figure 7). When mean survival is calculated from AUC of the KM plot to 13 months and from AUC under the linear trend model from 13 months to

the economic model time horizon (15 years) the placebo + docetaxel arm delivers about 14.3 months and the ramucirumab + docetaxel arm about 16.5 months providing a gain from ramucirumab of approximately 2.2 months. This reduction relative to the company multivariate log logistic model's 3.06 months is due to far less accrual of survival benefit beyond the observed trial data and beyond the cessation of ramucirumab treatment.

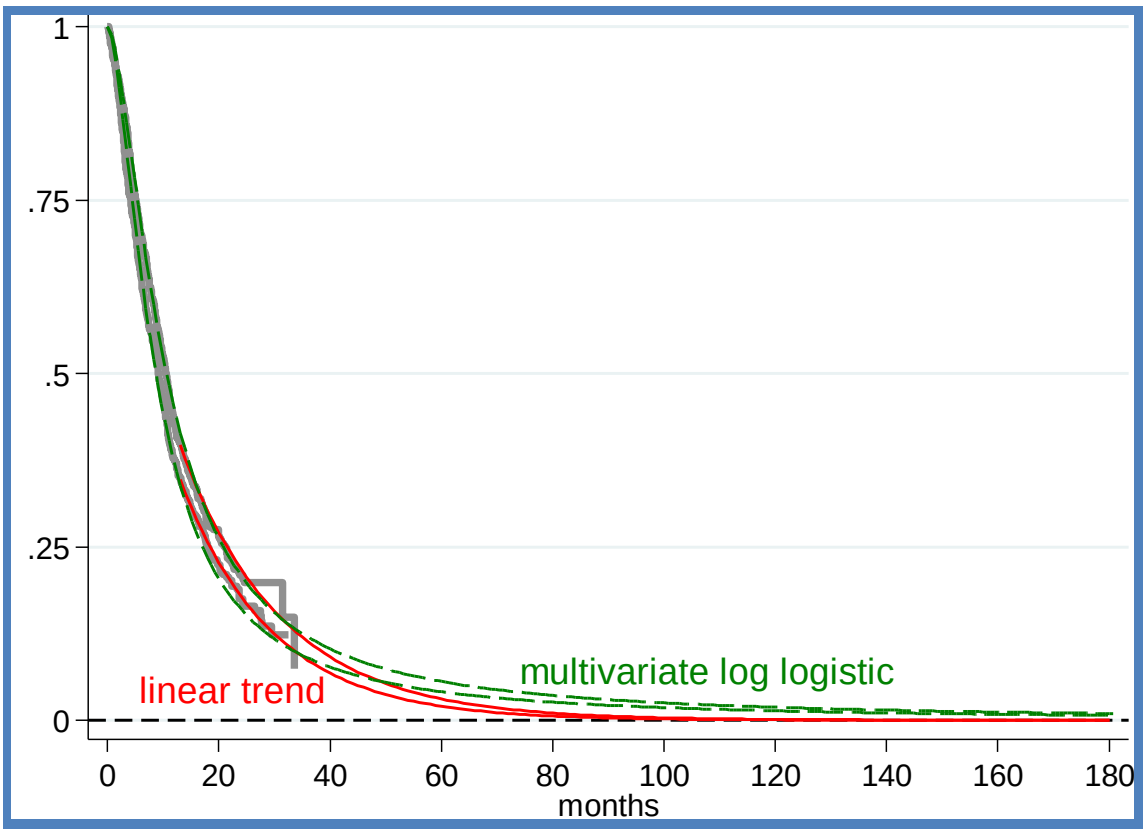


Figure 8: Projected survival according to extrapolation modelling (all patients REVEL)

Figure 9 shows the linear trend and multivariate log logistic cumulative hazard and survival plots for the non-squamous REVEL population. For this histological subgroup the linear trend model delivers an estimated 3.9 months mean survival gain compared with 3.6 months from the multivariate model. With both models the accrual of benefit beyond the observed data is substantial.

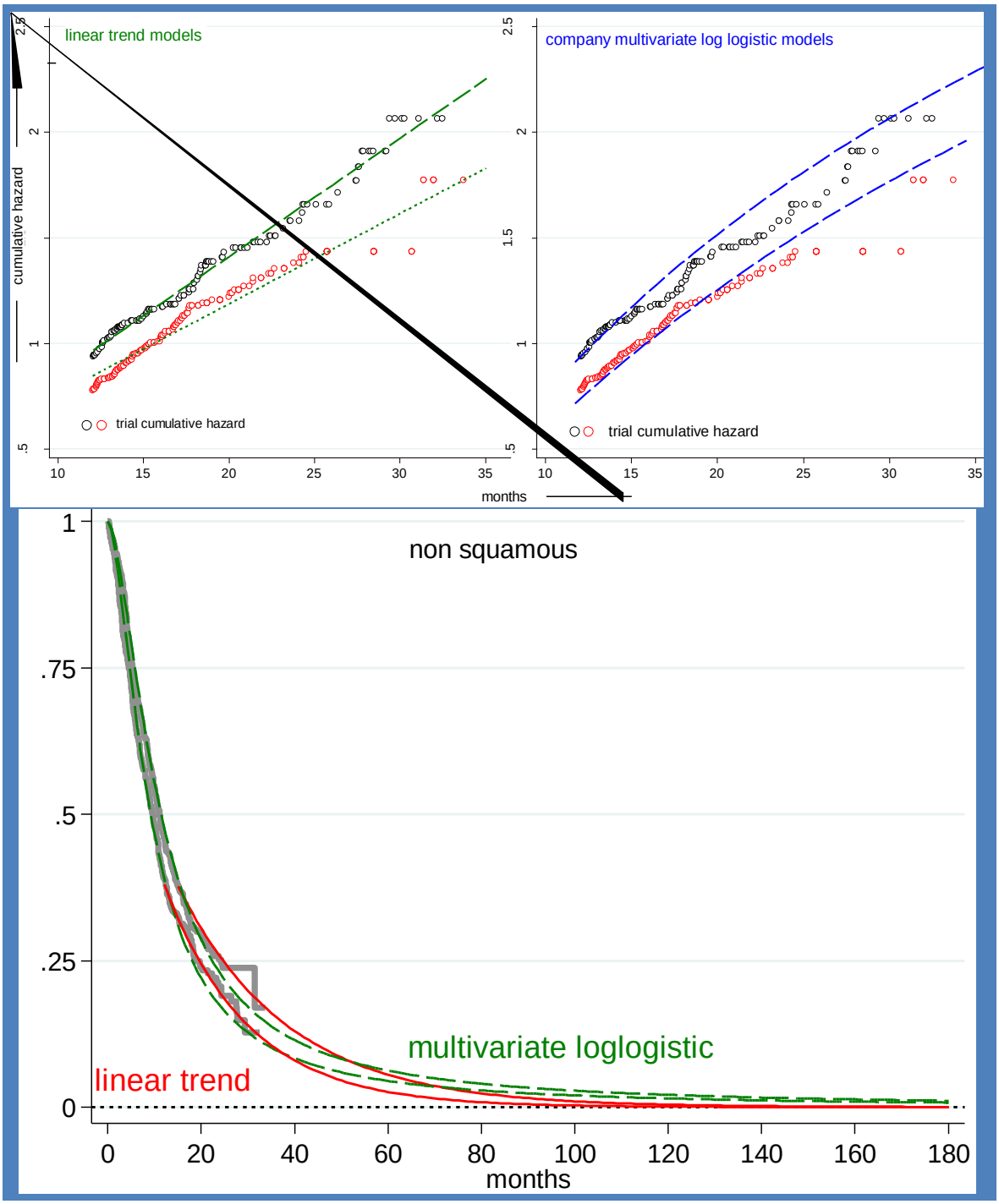


Figure 9: Projected survival according to extrapolation modelling (non-squamous pts REVEL)

Figure 10 shows the linear trend and multivariate log logistic cumulative hazard and survival plots for the squamous population (REVEL). For this histological subgroup the multivariate model underestimates observed cumulative hazard from about 10 months for the ramucirumab + docetaxel arm and from 15 months in the placebo + docetaxel arm. Linear trends in cumulative hazard were less clear cut than for

the other subgroups. A linear trend was fit from 14 to 24 months and used to model survival beyond the observed data. The linear trend models delivers an estimated mean 1.5 months survival benefit from ramucirumab treatment compared with 2.15 months from the company model.

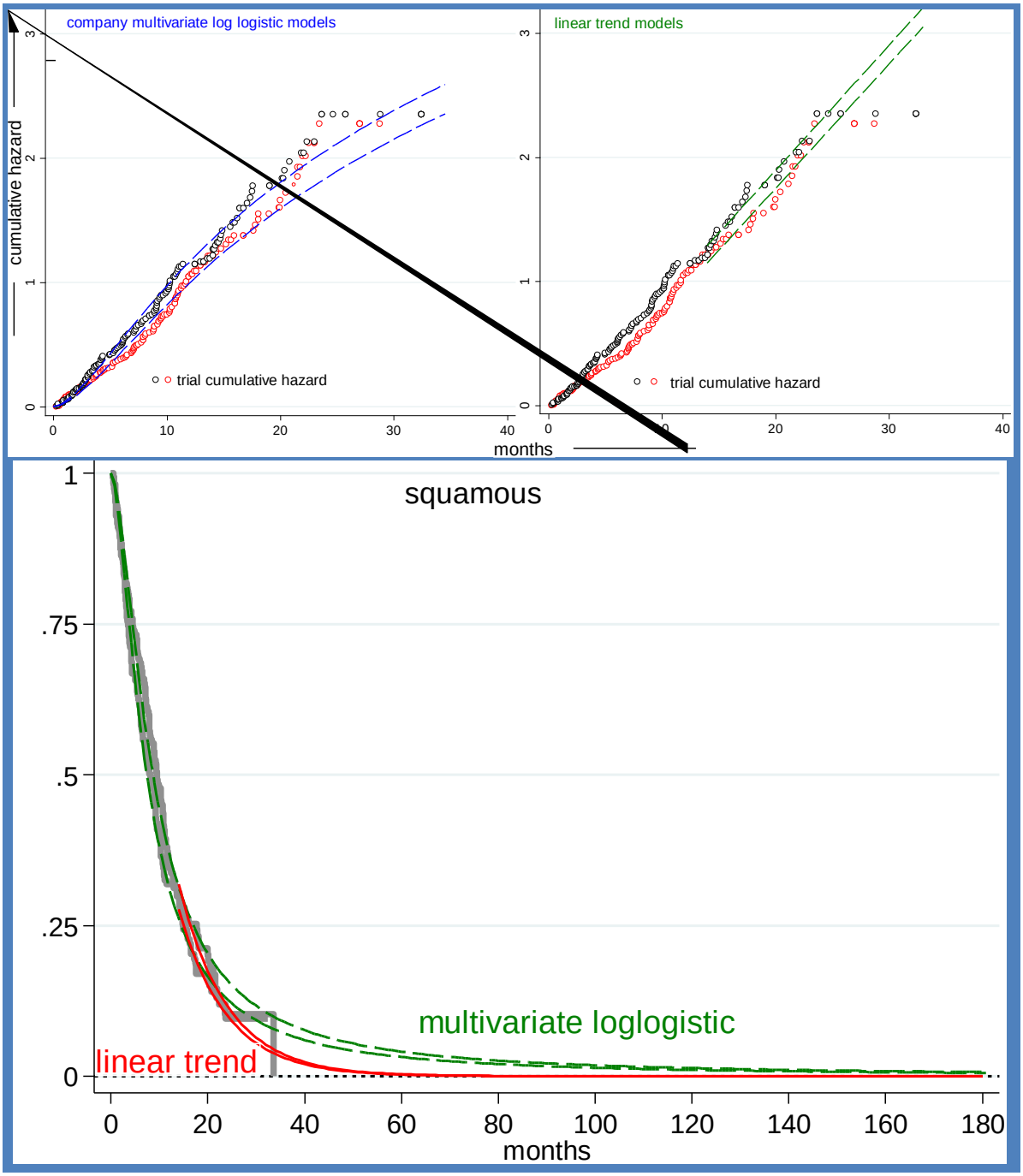


Figure 10: Projected survival according to extrapolation modelling (squamous pts REVEL)

The company did not submit a multivariate loglogistic model of OS for the adenocarcinoma subgroup. Loglogistic models fit separately to each arm (Figure 11) delivered an estimated mean 3.6 months survival benefit from ramucirumab treatment, compared with 2.6 months from a linear trend model (based on the observed cumulative hazard between 13 and 25 months).

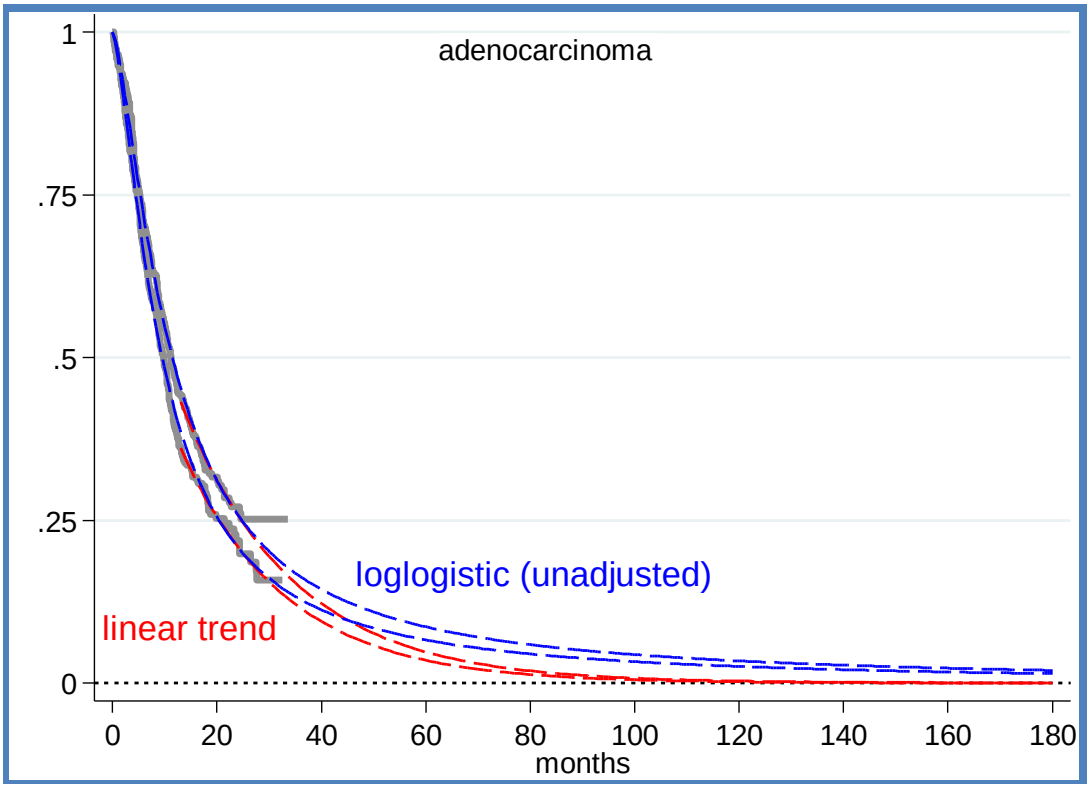


Figure 11: Projected survival according to extrapolation modelling (adenocarcinoma patients REVEL)

Table 27 summarises estimates of the mean OS gain from ramucirumab + docetaxel treatment relative to placebo + docetaxel according to different patient populations in REVEL. For most models in most patient groups the estimates of gain are less than 3 months. For squamous patients all model estimates are less than 3 months. Except for the non-squamous subgroup the linear trend models reduce the contribution of extrapolation beyond the observed data and estimates are well short of three months.

Table 27: Estimates of mean months gain in OS from ramucirumab¶ in REVEL according to patient group and model

Patient group	Treatment	MV ADJUSTED LL	Linear trend ¥	Separate LL to each arm ¥
All patients	RAM + DOC PBO + DOC	18.89 15.83 Net gain 3.06 Φ	16.6 14.4 Net gain 2.2	20.05 17.83 Net gain 2.23

Non-squamous	RAM + DOC PBO + DOC	20.148 16.68 Net gain 3.47 §	19.23 15.32 Net gain 3.91	21.66 19.07 Net gain 2.59
Squamous	RAM + DOC PBO + DOC	16.13 13.99 Net gain 2.15 §	12.28 11.19 Net gain 1.08	16.45 14.46 Net gain 1.99
Adenocarcinoma	RAM + DOC PBO + DOC	NM	18.95 16.40 Net gain 2.55	23.36 19.78 Net gain 3.58
¶ Results apply for a 15 year time horizon. DOC: docetaxel; LL: log logistic models; MV: multivariate; NM: no multivariate model was supplied in the CS; PBO: placebo; RAM: ramucirumab. Φ From CS table 45. § not reported in the CS, estimates based on ERG analysis of Kaplan Meier data supplied by the company. ¥ estimates based on ERG analysis of Kaplan Meier data supplied by the company.				

Progression free life months gained by RAM + DOC versus PBO + DOC

The company modelled PFS using multivariate adjusted gamma distributions fit separately to each trial arm of REVEL. The ERG estimated the progression free life months gained by ramucirumab + docetaxel versus placebo + docetaxel using the observed KM data and compared this with that derived using the company multivariate model. The results are summarised in Table 28. For all groups for which data was available the multivariate adjusted gamma model delivered greater gain (by about 18 to 22%) than estimates from the KM data. Since greater utility is attached to the progression free state in the economic model the choice of multivariate adjusted gamma or KM based data may influence the estimate of cost effectiveness of ramucirumab + docetaxel versus docetaxel alone.

Table 28: Estimates of progression free survival gain for ramucirumab according to estimation method and patient subgroup.

Patient group	MV adjusted gamma	Observed KM ¥
All patients	1.45 §	1.11
Non-squamous	1.49 §	1.16
Squamous	1.38 §	1.14
adenocarcinoma	NM	1.09
¶ results apply for a 15 year time horizon. MV: multivariate; NM = no multivariate model was supplied in the CS. § not reported in the CS report, estimates based on data in the submitted economic model. ¥ estimates based on ERG analysis of Kaplan Meier data supplied by the company.		

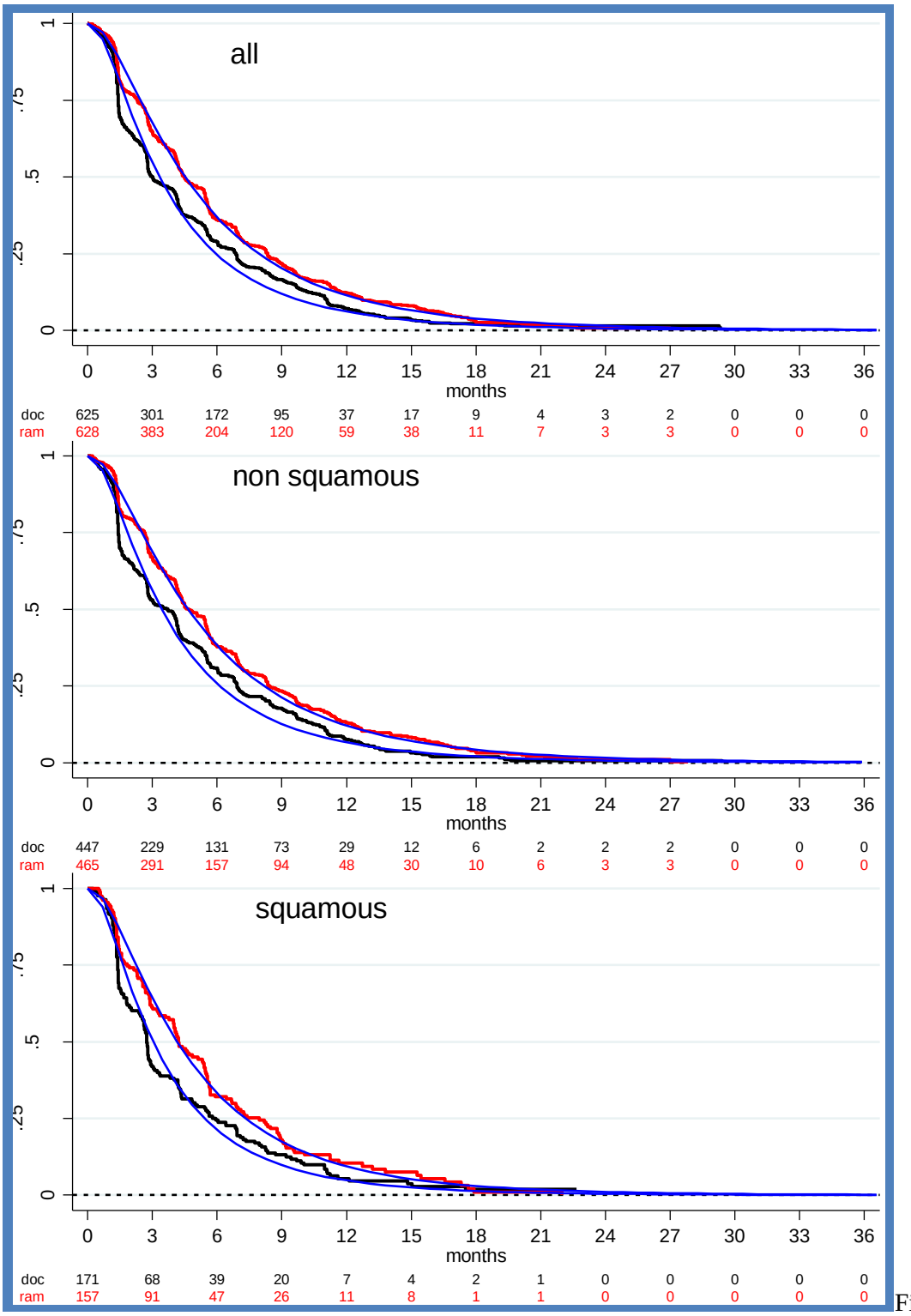


Figure 12 compares the multivariate gamma models with the KM plots for PFS for the squamous, and non-squamous subgroups and for all patients in REVEL. On visual inspection the gamma models do not fit the observed data well. In each case the model fit for the ramucirumab + docetaxel arm is somewhat

superior to that for the placebo + docetaxel arm with the latter tending to indicate lower accumulative PFS than the corresponding KM plot. Corresponding unadjusted gamma models are shown in Appendix 8.

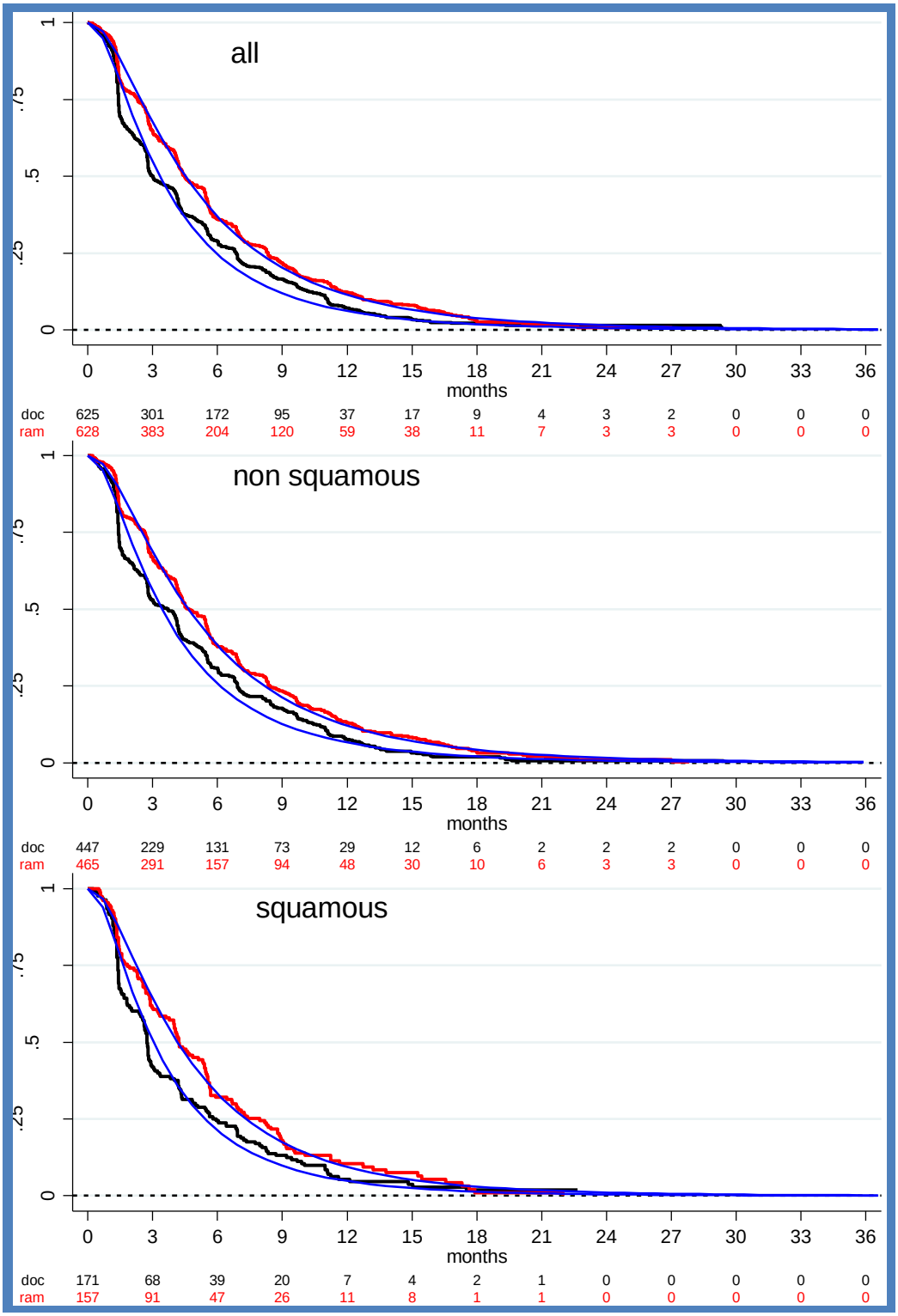


Figure 12: Kaplan Meier PFS and predicted PFS according multivariate gamma models and patient group

4.3 Conclusions of the clinical effectiveness section

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial that compared ramucirumab with one of the scoped comparators, docetaxel. The ERG has concerns regarding the exclusion of a scoped comparator, nivolumab, from the decision problem. The evaluation of the NMA is restricted, in part owing to the limited details provided as regards some aspects of the analysis and results, and the ERG believe there are several issues which mean the results of the NMA should be interpreted with caution. For non-squamous, squamous and adenocarcinoma patients, and for patients overall, ramucirumab + docetaxel provides OS and PFS benefit relative to docetaxel alone. The results of the NMA suggest that ramucirumab + docetaxel are likely equivalent, in terms of efficacy, to nintedanib + docetaxel in the non-squamous population. The CS modelling of overall survival using multivariate log logistic models violates the company's assumption of proportional hazards. Except for the non-squamous subgroup, linear trend models that obey a proportional hazards assumption for most of the modelled time horizon deliver less benefit for ramucirumab + docetaxel over docetaxel alone than do the company's multivariate log logistic models. Under the company's multivariate log logistic models a substantial proportion of OS benefit from ramucirumab + docetaxel over docetaxel alone accrues after disease progression and in the modelled extrapolation beyond the observed data. Except for the non-squamous subgroup the mean extra survival benefit from ramucirumab + docetaxel over docetaxel alone for other subgroups appears to be substantially less than three months irrespective of the survival modelling used. This also applies for the whole trial population except in the case of the company's multivariate log logistic model. The company's multivariate adjusted gamma models of PFS deliver approximately 20% more benefit from ramucirumab + docetaxel over docetaxel alone than estimates based on the observed data.

5 ECONOMIC EVALUATION

5.1 ERG comment on company's review of cost-effectiveness evidence

The ERG considers the search strategy for the review of cost-effectiveness studies to be appropriate (Section 4.1.1). The inclusion criteria seen in CS Table 40 appear reasonable. The ERG agrees with the justification for producing a de novo economic evaluation for ramucirumab.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 29: NICE reference case

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	The NICE scope specifies for all patient modelling: • Docetaxel • Erlotinib (subject to STA, which recently approved it only for EGFR positive) For those with adenocarcinoma: • Nintedanib + docetaxel For the squamous: • Nivolumab (subject to STA, which the Dec 2015 ACD did not recommend) For those with ALK +ve: • Crizotinib (not recommended but in Cancer drugs fund)	For all patient modelling: • Docetaxel For EGFR negative: • Erlotinib • Docetaxel For the non-squamous: • Nintedanib + docetaxel • Docetaxel
Patient group	The patient group is locally advanced or metastatic NSCLC patients who have progressed after platinum based chemotherapy. This is further divided into a number of subgroups as outlined above.	The patient group is based upon the REVEL trial which recruited stage IV patients with ECOG 0 or 1 that had progressed during or after platinum based chemotherapy. The non-squamous subgroup of

		REVEL is used and not the adenocarcinoma group for the comparison with nintedanib.
Perspective costs	NHS & Personal Social Services (PSS)	Yes. The model contains the direct drug and drug administration costs, monitoring costs and adverse event costs. There may be a question about whether other outpatient and inpatient resource use might apply.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility.
Time horizon	Sufficient to capture differences in costs and outcomes	15 years which is sufficient.
Synthesis of evidence on outcomes	Systematic review	For the comparisons with erlotinib and nintedanib the economics relies upon hazard ratios for PFS and OS drawn from the company NMA. This is in turn based upon a systematic review.
Outcome measure	Quality adjusted life years (QALYs)	QALYs.
Health states for QALY	Described using a standardised and validated instrument	For the main model health states the EQ-5D. For the adverse events values were drawn from Nafees et al (2008)[32]. Expert opinion guided the development of health state vignettes.
Benefit valuation	Time trade-off or standard gamble	For the main model health states the time trade-off of the standard UK EQ-5D tariff. For the adverse events standard gamble.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	For the main model health states yes. For the adverse events a sample of 100 members of the UK public.

Discount rate	An annual rate of 3.5% on both costs and health effects	The intention within the model was to discount at 3.5%. But due to a modelling error the applied rate appears to be 10.9%.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity analyses and scenario analyses are presented.

5.2.2 Model Structure

The company presents a model that partitions patients to be in one of three health states:

- Progression free survival;
- Post progression survival; and,
- Dead.

A three week cycle is used in order to be aligned with the ramucirumab dosing frequency.

The model structure applies half cycle correction to calculate health state costs and QALYs. Half cycle correction is not applied to the direct drug costs or the drug administration cost of ramucirumab and docetaxel, but is applied to the direct drug costs of erlotinib and nintedanib.

5.2.3 Population

The patient population reflects that of the REVEL trial.

The all patient data of REVEL has been analyses in a multivariate analysis. For the all patient modelling the REVEL baseline patient characteristics are applied to this.

For the non-squamous modelling the subgroup specific patient characteristics are applied to the multivariate analysis. The multivariate analysis includes a histology covariate.

5.2.4 Interventions and comparators

For the all patient modelling ramucirumab + docetaxel is compared with:

- Docetaxel

For the EGFR negative modelling ramucirumab + docetaxel is compared with:

- Erlotinib
- Docetaxel

For the non-squamous modelling ramucirumab + docetaxel is compared with:

- Nintedanib + docetaxel
- Docetaxel

To arrive at the OS and PFS curves for erlotinib HRs are applied to the docetaxel all patient hazards. Erlotinib is estimated to be inferior to docetaxel in the EGFR negative population.

To arrive at the OS and PFS curves for nintedanib + docetaxel HRs are applied to the docetaxel non-squamous hazards. Nintedanib + docetaxel is estimated to be superior to docetaxel in the non-squamous population.

The values below (Table 30) for erlotinib in the EGFR negative population and nintedanib + docetaxel in the non-squamous/adenocarcinoma population correspond with CS tables 30 and 31 of the clinical effectiveness section of the company submission.

Table 30: Erlotinib and nintedanib + docetaxel hazards ratios vs docetaxel

	OS (s.e.)	PFS (s.e.)
Erlotinib EGFR -ve	1.222 (0.127)	1.333 (0.128)
Erlotinib EGFR +ve	0.487 (0.374)	0.447 (0.592)
Nintedanib + docetaxel	0.847 (0.085)	0.769 (0.108)

Note that the company modelling for the comparison with erlotinib is restricted to the EGFR negative and there is no consideration of the EGFR positive.

5.2.5 Perspective, time horizon and discounting

The perspective for health effects is that of the patient while for costs it is that of the NHS/PSS. A 15 year time horizon is applied.

The model intention is to discount costs and benefits at an annual rate of 3.5%. But as reviewed later due to a modelling error the effective annual discount rates within the submitted model are 10.9%.

5.2.6 Treatment effectiveness and extrapolation

Unadjusted and multivariate adjusted REVEL OS analyses

Relatively little is presented in the company submission on the unadjusted and adjusted analyses. In the light of this the ERG report presents what detail there is of this in the electronic model below. For many readers much of this will be of little interest and they may wish to skip to the graphical presentations towards the end of the section.

The company concludes that there is no clear violation of the proportionate hazards function, in part based upon the log-log plot of figure 25 of the submission, and also upon the time covariate of the Cox regression model not being significantly different from zero, though its p-value was 0.1. As a consequence it estimates the OS curves using analyses that pool the data between the arms of REVEL and include a covariate for the treatment arm.

The company undertakes two analyses of the REVEL OS data. One that is a simple unadjusted fitting of curves to the REVEL OS data and another that uses a multivariate analysis to fit curves to the REVEL OS data.

The unadjusted analyses result in the following estimates (Table 31 and Table 32).

Table 31: REVEL OS unadjusted analysis: docetaxel covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	2.594	2.368	2.171	2.152	2.593
Treatment	..	..	..	..	..
Scale	1.000	1.047	0.663	1.180	0.889
Shape	..	0.467	..	..	..

Table 32: REVEL OS unadjusted analysis: ramucirumab covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	2.594	2.368	2.171	2.152	2.593
Treatment	0.150	0.159	0.167	0.174	0.139
Scale	1.000	1.047	0.663	1.180	0.889
Shape	..	0.467	..	..	..

Only the treatment effect differs between the two arms with this in effect being added to the intercept term in the ramucirumab arm when parameterising the curves. This results in the following (Table 33).

Table 33: REVEL OS unadjusted analysis

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept - Docetaxel	2.594	2.368	2.171	2.152	2.593
Intercept - Ramucirumab	2.744	2.527	2.338	2.326	2.732
Scale	1.000	1.047	0.663	1.180	0.889
Shape	..	0.467	..	..	..

The adjusted multivariate analyses include the following pre-planned subgroups as covariates:

- Age (≤ 65 years vs > 65 years)
- Histology (non-squamous vs squamous)
- Time since initiation of prior therapy (< 9 months vs ≥ 9 months)
- Prior maintenance therapy (yes vs no)
- Pemetrexed first-line (yes vs no)
- Sex (female vs male)
- Geographic region (Japan/East Asia vs rest-of-world [ROW])
- Best response to platinum therapy (complete response [CR]/partial response [PR]/stable disease [SD] vs progression)
- Eastern Cooperative Group (ECOG) performance status (0 vs 1)

They exclude the following pre-planned subgroups as covariates:

- Smoking history (never vs ever)
- Prior taxane treatment (yes vs no)
- Prior bevacizumab treatment (yes vs no)
- EGFR status (wild-type vs mutation vs unknown)

- Race (Black vs White vs Other)

though prior maintenance therapy may encompass some of the above.

Interaction terms with treatment and Age group, Time since prior therapy, Histology, Prior maintenance therapy and Prior 1st line pemetrexed were also included.

The CS does not provide any justification for the inclusion of covariates or for the exclusion of covariates but the company has provided some additional information at clarification. A stratified log-rank test was performed using the pre-specified stratification factors. Stepwise selection of variables using a pre-specified stepwise selection method as used. The criterion for adding a variable was a p-value of less than 5% and the criterion for dropping a variable was a p-value of at least 10%. The treatment effect was not subject to stepwise selection but was added to the final model. The determination of the treatment interaction covariates remains unclear, but the ERG assumption is that treatment interaction terms were explored for all the covariates and the same stepwise elimination undertaken.

The adjusted analyses were not presented within the CS. They are presented below. The values are drawn from the electronic copy of the economic model. Within this the ERG has collapsed the treatment specific interaction terms in the ramucirumab arm with the pooled estimates for reasons of space.

The multivariate analyses estimates for docetaxel are as seen in Table 34 and for ramucirumab as seen in Table 35.

Table 34: REVEL OS adjusted analysis: docetaxel covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	2.524	2.300	2.034	2.021	2.529
Treatment	..	..	..	..	..
Age group	-0.046	-0.061	-0.078	-0.098	-0.040
ECOG PS	0.373	0.379	0.402	0.424	0.341
Gender	0.161	0.174	0.187	0.216	0.142
Geographic region	0.452	0.437	0.444	0.442	0.425
Histology	0.258	0.243	0.264	0.223	0.233
Best Response to Platinum therapy	0.176	0.206	0.259	0.254	0.158
Time since prior therapy	-0.606	-0.563	-0.558	-0.547	-0.552
Prior maintenance therapy	-0.078	-0.083	-0.084	-0.119	-0.062
Prior 1st line pemetrexed	-0.164	-0.146	-0.157	-0.088	-0.164

Scale	1.000	0.958	0.613	1.102	0.834
Shape	..	0.537	..	..	..

Table 35: REVEL OS adjusted analysis: ramucirumab covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	2.524	2.300	2.034	2.021	2.529
Treatment	-0.306	-0.310	-0.288	-0.400	-0.269
Age group	0.226	0.232	0.223	0.296	0.196
ECOG PS	0.373	0.379	0.402	0.424	0.341
Gender	0.161	0.174	0.187	0.216	0.142
Geographic region	0.452	0.437	0.444	0.442	0.425
Histology	0.274	0.240	0.225	0.218	0.246
Best Response to Platinum therapy	0.176	0.206	0.259	0.254	0.158
Time since prior therapy	-0.295	-0.232	-0.197	-0.144	-0.277
Prior maintenance therapy	0.265	0.217	0.191	0.178	0.241
Prior 1st line pemetrexed	-0.033	-0.026	-0.050	0.010	-0.030
Scale	1.000	0.958	0.613	1.102	0.834
Shape	..	0.537	..	..	..

In the unadjusted model only the treatment effect differs between the arms, with this in effect being added to the intercept term in the ramucirumab arm. In a parallel manner in the adjusted model the treatment effect and the treatment interaction effects of the italicised values differ between the arms. The treatment effect is in effect added to the intercept, as are the other covariates' coefficients once they have been conditioned by the baseline distribution of the various covariates. For the OS analysis these baseline distributions are pooled between the arms, but are subgroup specific as Table 36.

Table 36: Baseline patient characteristics for OS adjusted analysis

	All patients	Non-Squamous
Age group	64%	66%
ECOG PS	32%	33%
Gender	33%	37%
Geographic region	7%	6%
Histology	74%	100%
Best Response to Platinum therapy	70%	70%
Time since prior therapy	62%	61%

Prior maintenance therapy	22%	26%
Prior 1st line pemetrexed	37%	48%

Applying these distributions to the covariates results in the following functional forms (Table 37 and Table 38).

Table 37: REVEL OS adjusted analysis: All patients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept - Docetaxel	2.562	2.376	2.162	2.144	2.558
Intercept - Ramucirumab	2.758	2.566	2.361	2.343	2.736
Scale	1.000	0.958	0.613	1.102	0.834
Shape	..	0.537	..	..	..

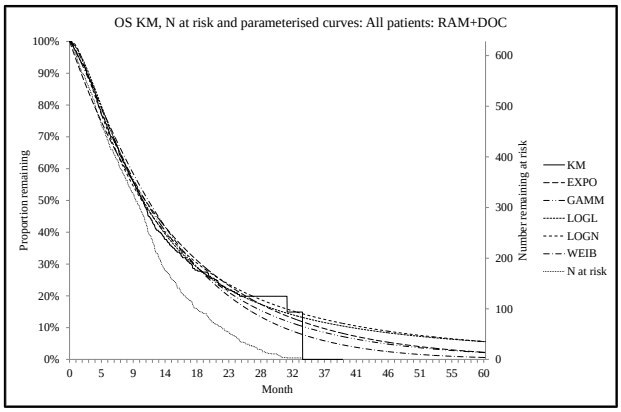
Table 38: REVEL OS adjusted analysis: Non-squamous

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept - Docetaxel	2.616	2.428	2.220	2.198	2.606
Intercept - Ramucirumab	2.847	2.645	2.434	2.422	2.815
Scale	1.000	0.958	0.613	1.102	0.834
Shape	..	0.537	..	..	..

This results in the following sets of curves[2] (

Figure 13 and Figure 14). The unadjusted curves are not presented here, due to the unadjusted and adjusted curves being considered later after the presentation of the goodness of fit statistics.

[2] These have been constructed on the assumption of each month lasting 365.25/12 days in line with the economic model. The horizontal axis also reports months rounded to the nearest month, but due to the month length these are not exact and it would have been better to have reported these correct to one decimal place to highlight this. The end period is not actually 60 months but 59.8 months.



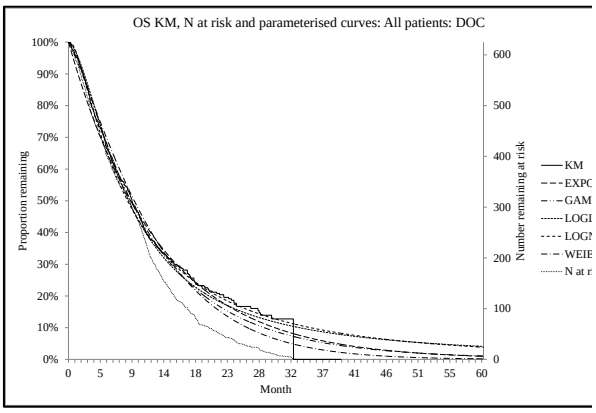
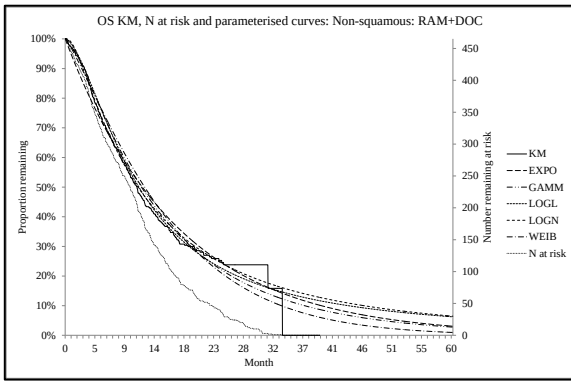


Figure 13: REVEL OS adjusted analysis: All patients

In both arms the numbers at risk start to drop below the KM curve from around the 10th month, though the drop off is not precipitous and reasonable numbers remain at risk perhaps as far as the two year point. The parameterised curves are relatively tightly grouped initially, but start to diverge at around the 16th month with the Weibull tending to be below the other curves, and the log normal and log logistic tending to be above them. For both arms the log logistic is initially below the log normal only to cross it towards the end of the period of the above graphs, it having the longest tail of the parameterised curves.



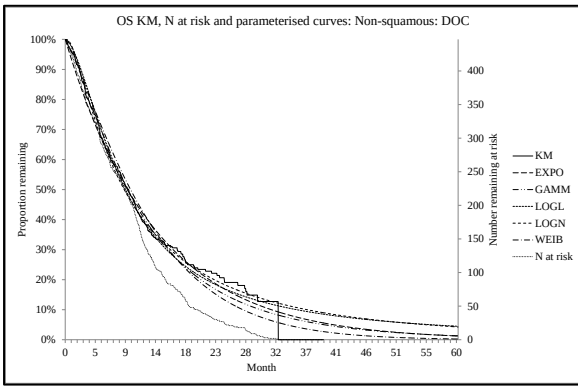


Figure 14: REVEL OS adjusted analysis: Non-squamous

For the non-squamous, the visual inspection of the curves is much as for the all patient modelling. The parameterised curves are reasonably tightly grouped until perhaps around the 16th month after which the Weibull falls to noticeably lower levels than the other curves and the log normal and the log logistic tend to rise above them. Again, the log logistic crosses the log normal to rise above it towards the end of the graphs above and has the longest extrapolated tail.

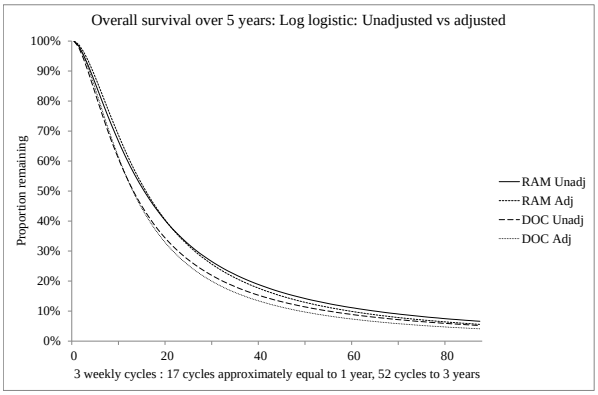
The CS provides the following goodness of fit statistics (Table 39).

Table 39: REVEL OS: Unadjusted and adjusted: Good ness of fit statistics

	AIC		BIC	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Exponential	3405.8	3109.3	3416.1	3190.6
Weibull	3391.1	3074.0	3406.5	3160.3
Log-normal	3386.9	3083.3	3402.3	3169.6
Log-logistic	**3361.0**	**3052.4**	**3376.4**	**3138.7**
Generalized gamma	3367.1	3055.5	3387.6	3146.9

On the basis of the above and the Cox-Snell residuals of figure 26 of the CS, the company prefers the multivariate adjusted analysis log-logistic fit for OS (Figure 15).

All patients and EGFR negative



Non-squamous

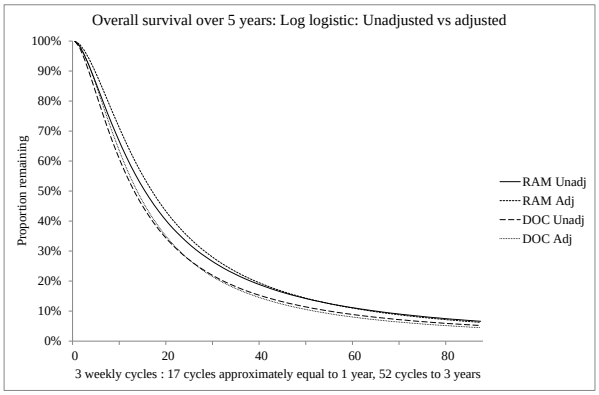


Figure 15: REVEL OS: Unadjusted vs adjusted: Log logistic

For the all patient and EGFR negative modelling the adjusted model tends to slightly raise the OS curve for ramucirumab + docetaxel until a little after the 20th cycle when it tends to slightly depress it. For docetaxel the effect is generally to slightly depress the OS curve and by slightly more than occurs in the ramucirumab + docetaxel arm.

For the non-squamous modelling the adjusted model raises the OS curve for ramucirumab + docetaxel. There is a slight raising of the docetaxel OS curve until around the 20th cycle, after which the effect is to depress it. But in reviewing the non-squamous OS curves it should be borne in mind that the unadjusted curves are those estimated from the all patient data. The relative effects are consistent with the subgroup analyses reported in figure 10 of the CS: a better central estimate for the OS hazard in the non-squamous

subgroup of 0.83 compared to 0.88 for the squamous, and 0.86 across all patients as reported in table 21 of the submission. There is a more immediate case for applying the adjusted curves for the non-squamous subgroup modelling than the unadjusted curves of the all patient modelling. How these would compare with unadjusted curves estimated from the non-squamous subgroup is not known.

The CS in table 45 also provides the following mean survival estimates from the various curves which are reproduced here in Table 40 for ease of reference with an additional presentation of the net effects.

Table 40: REVEL OS: Unadjusted and adjusted: Mean OS: All patients and EGFR negative

	RAM + Doc		DOC		Net OS gain	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Exponential	1.278	1.289	1.116	1.080	0.162	0.209
Weibull	1.216	1.198	1.068	1.012	0.148	0.186
Lognormal	1.615	1.527	1.396	1.285	0.219	0.242
Log-logistic	1.659	1.574	1.437	1.319	0.222	0.255
Generalized gamma	1.345	1.279	1.166	1.073	0.179	0.206

DOC: Docetaxel; RAM: Ramucirumab

With the exception of the exponential for the ramucirumab + docetaxel arm, the adjusted models result in lower estimates of mean OS in both arms. But this affects the docetaxel arm more than the ramucirumab + docetaxel arm. As a consequence, the adjusted models estimate a greater net gain in survival from ramucirumab + docetaxel compared to docetaxel than the unadjusted models.

For the comparison of docetaxel with ramucirumab + docetaxel and for the comparison of these with erlotinib in the EGFR negative population, the all patient adjusted log logistic OS curves are used for docetaxel and for ramucirumab + docetaxel.

For the comparison of docetaxel, ramucirumab + docetaxel and nintedanib + docetaxel, the non-squamous adjusted log logistic OS curves are used for docetaxel and for ramucirumab + docetaxel. The log logistic curve yields the largest estimate for the net OS gain for ramucirumab + docetaxel compared to docetaxel.

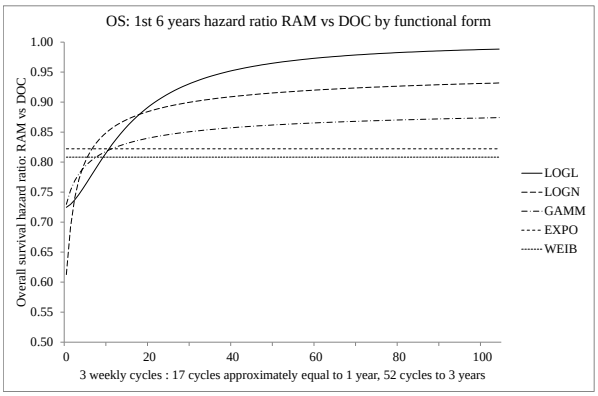
OS equalisation of hazards, extrapolation and erlotinib and nintedanib + docetaxel

The docetaxel arm is extrapolated using the parameterised adjusted log logistic OS curve.

The company notes that REVEL was of 33 months duration, and that the survival hazard ratio at the end of this period for the adjusted analyses is 0.961 for the all patient modelling and 0.954 for the non-squamous modelling. For the base case the company assumes that this hazard ratio will increase to unity over a six month period. This is implemented within the model by estimating a linear rise in the hazard ratio over six months from month 33 to month 39 at which point a hazard ratio of unity is attained and maintained. To model survival in the ramucirumab + docetaxel arm the ramucirumab + docetaxel parameterised log logistic OS curve is used up to month 33. Between month 33 and month 39 the adjusted hazard ratio is applied to the docetaxel OS hazard to derive the ramucirumab + docetaxel OS hazard. After month 39 the hazard ratio is assumed to be unity and the docetaxel OS hazard is applied in the ramucirumab + docetaxel arm.

Note that in relation to the selection of the appropriate parameterised OS curve, the tapering of the hazard ratio to unity between month 33 and month 39 has a lesser effect upon the log logistic curve and a greater effect upon the exponential and the Weibull (Figure 16).

No tapering of HRs



With tapering of HRs

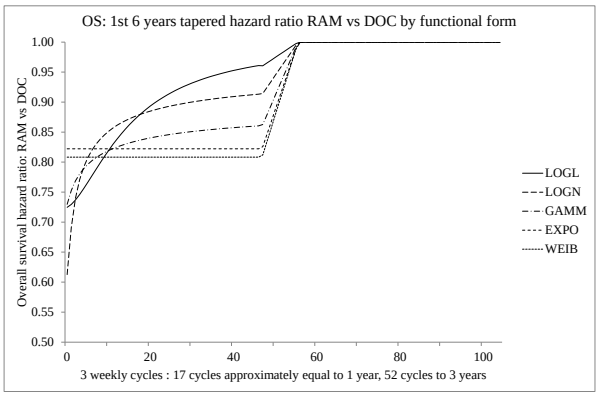


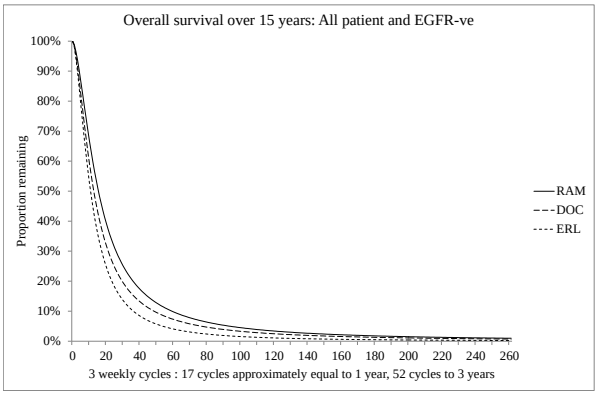
Figure 16: OS hazard ratios and tapering: 1st 6 years of the model

The tapering affects the hazard ratios of the exponential and the Weibull to a greater extent than the log logistic. The impact of the tapering of the hazard ratio for the log logistic is relatively muted. Any modelling based upon the exponential or the Weibull would be more sensitive to any tapering assumptions that are made. ERG calculations suggest that over the time horizon of the model, when the tapering is applied, the log logistic still provides the highest undiscounted and discounted overall survival estimates of the functional forms which were estimated.

For erlotinib the hazard ratio of 1.222 is applied to the all patient docetaxel hazard up to month 33. For nintedanib + docetaxel the hazard ratio of 0.847 is applied to the non-squamous docetaxel hazards up to month 33. After month 33 the same tapering to a hazard ratio of unity at and beyond month 39 is applied as in the ramucirumab + docetaxel arm as outlined above.

This adjustment to the hazard ratios will tend to reduce the patient gain from the more effective treatment, with this also rolling through to the other comparators. It results in the following base case OS curves (Figure 17 and Figure 18) with months 33 and 39 corresponding to around cycles 48 and the 57 respectively.

No equalisation of hazards



Hazards equalised between months 33 & 39

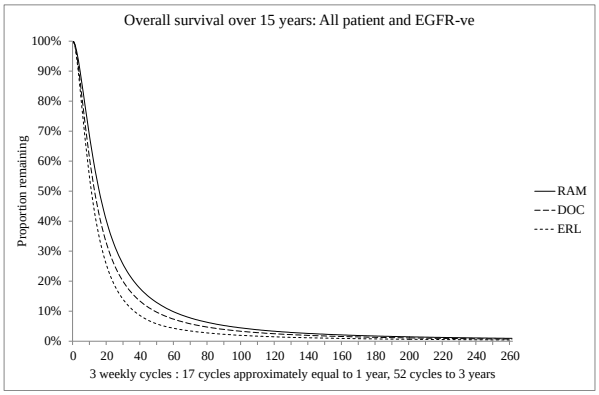
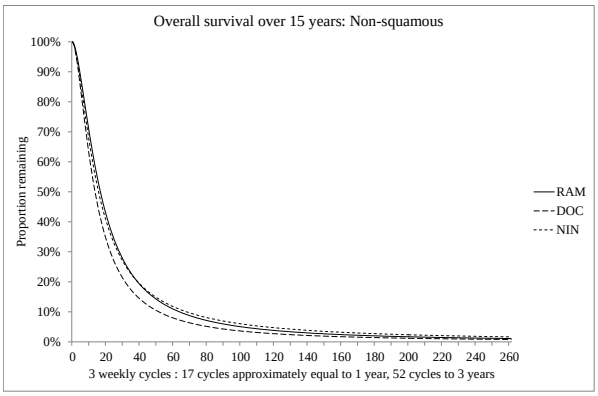


Figure 17: OS extrapolation: All patient and EGFR negative modelling

No equalisation of hazards



Hazards equalised between months 33 & 39

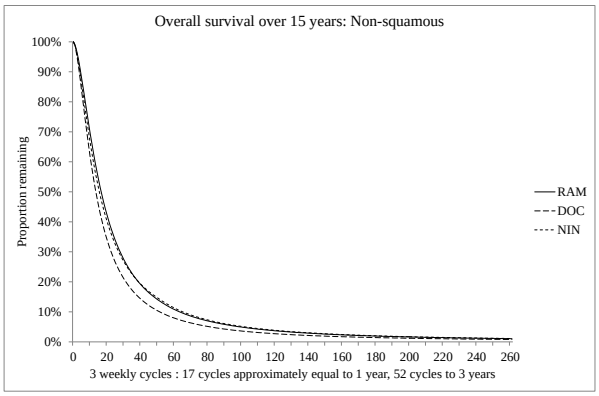


Figure 18: OS extrapolation: Non-squamous

The equalisation of the hazards between months 33 and 39 appears to have only a slight impact on the all patient and EGFR negative modelling, slightly narrowing the differences between the treatments after

month 33 to the detriment of ramucirumab + docetaxel and the benefit of erlotinib. The effect on the non-squamous modelling is again to narrow the difference between ramucirumab + docetaxel and docetaxel, but also to slightly reduce the estimated benefit from nintedanib + docetaxel after month 39.

Unadjusted and multivariate adjusted REVEL PFS analyses

As for the presentation of the OS modelling, much of what follows will be of limited interest to most readers. Many readers may wish to ignore the presentation of the unadjusted and adjusted modelling and skip to the graphical presentations towards the end of the section.

Based upon the log-log plot of figure 29 of the CS and the time covariate of the Cox regression being significantly different from zero with a p-value of 0.003, the company concludes that proportionate hazards do not hold for PFS. As a consequence it fits parameterised curves separately to the individual arms of REVEL.

As in the OS analysis, unadjusted and adjusted curves are fitted to the data for PFS analysis. Unlike the OS analysis, the adjusted PFS curves do not include the Geographic region or the Best response to platinum therapy as covariates. Again for the sake of completeness the parameters of the various analyses are presented in Table 41 and for the adjusted models in Table 42 and Table 43.

Table 41: REVEL PFS unadjusted analysis

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Docetaxel					
Intercept	1.588	1.229	1.171	1.170	1.632
Scale	1.000	0.954	0.564	0.961	0.874
Shape		0.124			
Ramucirumab + docetaxel					
Intercept	1.817	1.611	1.474	1.447	1.874
Scale	1.000	0.877	0.533	0.917	0.794
Shape		0.375			

Table 42: REVEL PFS adjusted analysis: Docetaxel covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	1.834	1.591	1.496	1.487	1.879
Treatment	n.a.	n.a.	n.a.	n.a.	n.a.
Age group	-0.164	-0.233	-0.261	-0.266	-0.145

ECOG PS	0.247	0.247	0.259	0.239	0.240
Gender	0.041	0.052	0.063	0.058	0.037
Geographic region	n.a.	n.a.	n.a.	n.a.	n.a.
Histology	0.180	0.184	0.224	0.171	0.174
Best Response to Platinum therapy	n.a.	n.a.	n.a.	n.a.	n.a.
Time since prior therapy	-0.575	-0.560	-0.610	-0.535	-0.554
Prior maintenance therapy	-0.086	-0.059	-0.040	-0.050	-0.085
Prior 1st line pemetrexed	-0.144	-0.110	-0.110	-0.096	-0.145
Scale	1.000	0.879	0.516	0.899	0.815
Shape	..	0.261	..	..	..

Table 43: REVEL PFS adjusted analysis: Ramucirumab covariate coefficients

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Intercept	1.781	1.528	1.372	1.319	1.869
Treatment	n.a.	n.a.	n.a.	n.a.	n.a.
Age group	0.042	0.073	0.076	0.105	0.031
ECOG PS	0.217	0.219	0.214	0.241	0.192
Gender	0.144	0.174	0.213	0.197	0.131
Geographic region	n.a.	n.a.	n.a.	n.a.	n.a.
Histology	0.076	0.063	0.064	0.046	0.076
Best Response to Platinum therapy	n.a.	n.a.	n.a.	n.a.	n.a.
Time since prior therapy	-0.245	-0.218	-0.216	-0.192	-0.249
Prior maintenance therapy	-0.041	-0.014	0.032	0.009	-0.061
Prior 1st line pemetrexed	-0.013	0.015	0.009	0.041	-0.015
Scale	1.000	0.854	0.516	0.890	0.772
Shape	..	0.367	..	..	..

The patient characteristics that are applied to the adjusted models differ from those of the OS analysis, and also differ by arm (Table 44).

Table 44: Baseline patient characteristics for OS and PFS adjusted analysis

	All patients			Non-Squamous		
	OS Both	PFS RAM	PFS DOC	OS Both	PFS RAM	PFS DOC
Age group	64%	62%	65%	66%	63%	68%
ECOG PS	32%	33%	32%	33%	35%	31%

Gender	33%	33%	34%	37%	37%	38%
Geographic region	7%	n.a.	n.a.	6%	n.a.	n.a.
Histology	74%	75%	72%	100%	100%	100%
Best Response to Platinum therapy	70%	n.a.	n.a.	70%	n.a.	n.a.
Time since prior therapy	62%	64%	60%	61%	63%	60%
Prior maintenance therapy	22%	21%	23%	26%	25%	27%
Prior 1st line pemetrexed	37%	36%	38%	48%	46%	49%

These patient distributions result in the following adjusted models (Table 45 and Table 46).

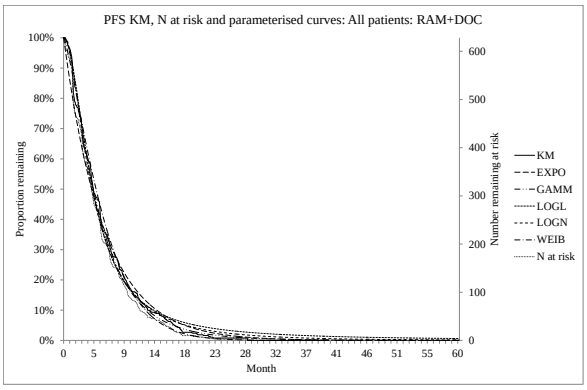
Table 45: REVEL PFS adjusted analysis: All patients and EGFR negative

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Docetaxel					
Intercept	1.532	1.278	1.176	1.165	1.594
Scale	1.000	0.879	0.516	0.899	0.815
Shape		0.261			
Ramucirumab + docetaxel					
Intercept	1.814	1.614	1.481	1.458	1.875
Scale	1.000	0.854	0.516	0.890	0.772
Shape		0.367			

Table 46: REVEL PFS adjusted analysis: Non-squamous

	Expo.	Gamma	Log Log	Log Norm.	Weibull
Docetaxel					
Intercept	1.558	1.309	1.218	1.194	1.619
Scale	1.000	0.879	0.516	0.899	0.815
Shape		0.261			
Ramucirumab + docetaxel					
Intercept	1.841	1.643	1.512	1.488	1.900
Scale	1.000	0.854	0.516	0.890	0.772
Shape		0.367			

This results in the following sets of curves (Figure 19 and Figure 20).



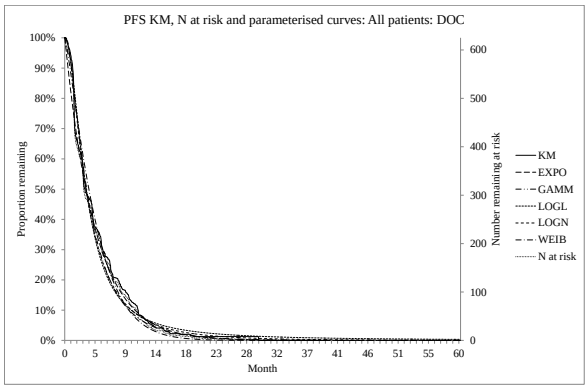
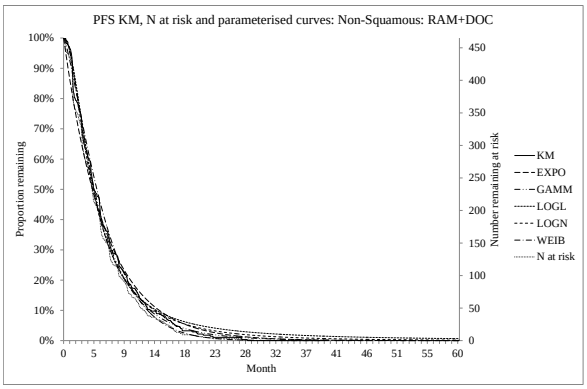


Figure 19: REVEL PFS adjusted analysis: All patients

For both arms the number at risk closely follows the KM curve. There is also relatively little to distinguish the parameterised curves during the period of the trial. By around the 14th month both the log normal and the log logistic curves have risen above the other parameterised curves, with the log logistic being the higher of the two curves. As is normal, during the extrapolation period these have more of a tail out to the right with small proportions simulated as remaining progression free when the other parameterised curves effectively simulate none remaining progression free.



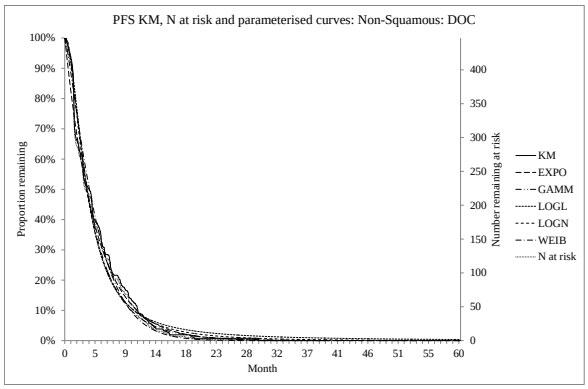


Figure 20: REVEL PFS adjusted analysis: Non-squamous

In terms of the visual inspection of the curves, the conclusions for the non-squamous are much as those for the all patient modelling.

The Cs provides the following goodness of fit statistics for the docetaxel arm (Table 47) and for the ramucirumab + docetaxel arm (Table 48).

Table 47: REVEL PFS: Unadjusted and adjusted: DOC: Good ness of fit statistics

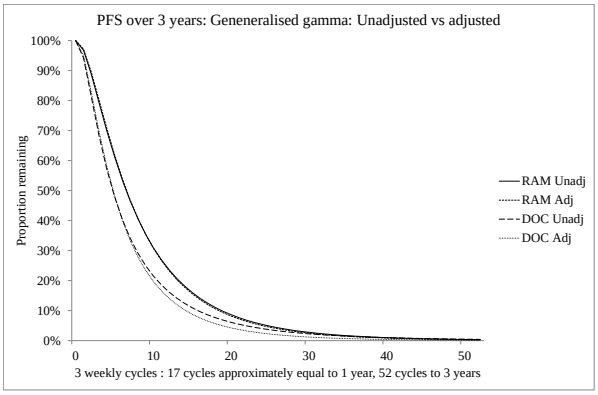
	AIC		BIC	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Exponential	1732.8	1656.0	1737.3	1691.4
Weibull	1717.8	1619.7	1726.7	1659.6
Log-normal	**1667.3**	1581.2	**1676.2**	**1621.1**
Log-logistic	1687.9	1586.2	1696.7	1626.1
Generalized gamma	1668.2	**1576.9**	1681.5	1621.2

Table 48: REVEL PFS: Unadjusted and adjusted: RAM+DOC: Good ness of fit statistics

	AIC		BIC	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Exponential	1627.6	1601.8	1632.1	1637.2
Weibull	1584.6	1548.5	1593.5	1588.3
Log-normal	1569.5	1532.9	1578.4	1572.8
Log-logistic	1586.0	1547.3	1594.9	1587.2
Generalized gamma	**1561.9**	**1526.0**	**1575.2**	**1570.3**

On the basis of the above and the Cox-Snell residuals of figure 30 and 31 of the CS, the company prefers the multivariate adjusted analysis generalized gamma fit for OS. Note that it is the docetaxel PFS curve that determines the erlotinib and the nintedanib + docetaxel PFS curves (Figure 21)

All patients and EGFR negative



Non-squamous

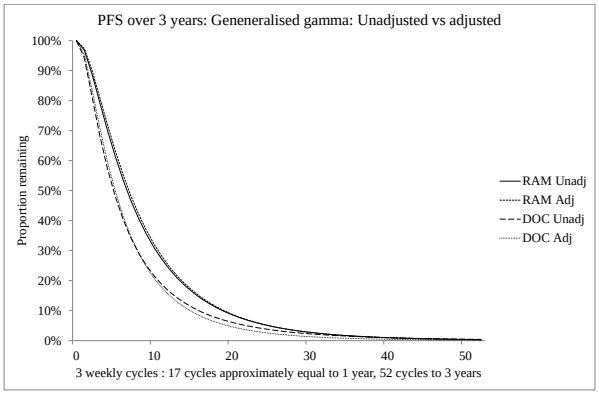


Figure 21: REVEL PFS: Unadjusted vs adjusted: Generalised gamma

For the all patient and EGFR negative modelling the adjusted model appears to have very little impact on the PFS curve for ramucirumab + docetaxel. But for the docetaxel arm, the effect is to depress the PFS curve compared to the unadjusted curve.

For the non-squamous modelling the effects of the adjusted models appear to be similar though perhaps slightly less so than those in the all patient modelling. Again, however, this is a rather meaningless comparison. A more sensible comparison would be between an unadjusted analysis estimated among the non-squamous subgroup and an adjusted analysis, either that of the above or perhaps even one estimated among the non-squamous subgroup.

Table 48 of the submission outlines the mean PFS estimates of the various curves, the ERG calculates the differences between these in Table 49.

Table 49: REVEL PFS: Unadjusted and adjusted: Mean PFS: All patients and EGFR negative

	RAM+DOC		DOC		Net PFS gain	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Exponential	0.516	0.511	0.409	0.386	0.107	0.125
Weibull	0.505	0.502	0.407	0.384	0.098	0.118
Lognormal	0.539	0.531	0.426	0.400	0.113	0.131
Log-logistic	0.605	0.585	0.471	0.432	0.134	0.153
Generalized gamma	0.513	0.507	0.417	0.386	0.096	0.121

Unlike the log logistic for OS, the chosen generalized gamma for PFS does not result in the largest PFS gain from ramucirumab + docetaxel compared to docetaxel. The generalized gamma results in the smallest PFS gain from ramucirumab + docetaxel compared to docetaxel in the unadjusted analyses and the second smallest in the adjusted analyses. The use of the log-normal has relatively little impact upon the cost effectiveness estimates.

As for the OS analysis, the adjusted analysis reduces the mean PFS in both arms but reduces it more in the docetaxel arm. As a consequence, the net gain from ramucirumab + docetaxel compared to docetaxel is greater when using the adjusted analysis than when using the unadjusted analysis.

PFS and erlotinib and nintedanib + docetaxel

Within the PFS curves there is no tapering of the hazards ratios between months 33 and 39.

A hazard ratio of 1.333 for erlotinib compared to docetaxel is applied to the docetaxel all patient hazards to derive the hazards for erlotinib. A hazard ratio of 0.769 for nintedanib + docetaxel compared to docetaxel is applied to the docetaxel non-squamous hazards to derive the hazards for nintedanib + docetaxel. This results in the following PFS curves (Figure 22).

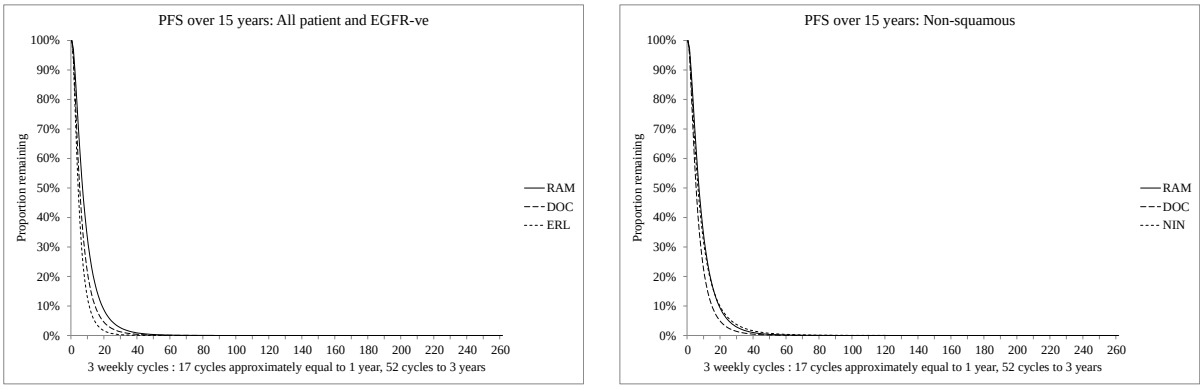


Figure 22: PFS extrapolation.

Patients progress relatively quickly. For the all patient modelling, patients progress most quickly with erlotinib and least quickly with ramucirumab + docetaxel, with docetaxel lying roughly equidistant between these. For the non-squamous patients, progression is fastest with docetaxel. Ramucirumab + docetaxel and nintedanib + docetaxel are estimated to be reasonably similar.

SAEs

The submission states that SAEs are included if they were experienced by at least 5% of patients in either the ramucirumab + docetaxel arm or the docetaxel arm. Nausea/vomiting and rash are also included due to quality of life values being available for them and them being important in other systemic anticancer treatments (Table 50).

Table 50: SAE adverse event rates

Toxicity	RAM	DOC	ERL	NIN
Neutropenia	48.8%	39.8%	0.0%	12.1%
Febrile neutropenia	15.9%	10.0%	0.0%	7.0%
Fatigue	14.0%	10.5%	0.6%	5.7%
Nausea/vomiting	1.3%	1.9%	0.0%	0.0%
Diarrhoea	4.6%	3.1%	0.0%	6.7%

Hair loss (Any Grade)	25.8%	25.2%	0.0%	16.4%
Rash	0.8%	0.6%	8.1%	0.0%
Dyspnoea	3.8%	8.3%	0.0%	0.0%
Leukopenia	13.7%	12.5%	0.0%	2.9%
Anaemia	2.9%	5.7%	0.0%	0.0%
Hypertension	5.6%	2.1%	0.0%	0.0%

5.2.7 Health related quality of life

Quality of life: PFS and PPS

The EQ-5D was administered during the REVEL trial at baseline, each cycle during treatment and at 7 days, and 30 days subsequent to the end of therapy where possible. The quality of life value for PFS is based upon the pooled mean post baseline EQ-5D value among those on treatment. The quality of life values for post-progression survival (PPS) is based upon the pooled mean post end of treatment EQ-5D values (Table 51).

Table 51: PFS and PPS quality of life values

	Mean	s.e.
PFS	0.706	(0.003)
PPS	0.599	(0.015)

Quality of life: Adverse events

The quality of life impacts of adverse events are drawn from Nafees et al (2008)[32], a study sponsored by Eli Lilly. This identified the most common SAEs reported in two trials of pemetrexed and docetaxel among NSCLC patients previously treated with chemotherapy. Health state vignettes originally used in a breast cancer study were adapted with the help of expert opinion to be relevant to the adverse events identified. After piloting these among 5 members of the general public, they were valued using the standard gamble by 100 members of the UK general public.

The resulting quality of life values are combined with company expert opinion as to their probable mean duration and the treatment specific adverse event rate profiles to arrive at an SAE QALY decrement for each treatment. Nafees et al[32] did not report values for dyspnoea or hypertension so these were assumed to have the same quality of life value as fatigue, while leukopenia and anaemia were assumed to have the same quality of life value as neutropenia (Table 52).

Table 52: SAE QALYs by treatment

Toxicity	QoL	Days	RAM+D	DOC	ERL	NIN+D
Neutropenia	-0.0897	7	48.8%	39.8%	0.0%	12.1%
Febrile neutropenia	-0.0900	4	15.9%	10.0%	0.0%	7.0%
Fatigue	-0.0735	21	14.0%	10.5%	0.6%	5.7%
Nausea/vomiting	-0.0480	3	1.3%	1.9%	0.0%	0.0%
Diarrhoea	-0.0468	3	4.6%	3.1%	0.0%	6.7%
Hair loss (Any Grade)	-0.0450	21	25.8%	25.2%	0.0%	16.4%
Rash	-0.0325	21	0.8%	0.6%	8.1%	0.0%
Dyspnoea	-0.0735	21	3.8%	8.3%	0.0%	0.0%
Leukopenia	-0.0897	7	13.7%	12.5%	0.0%	2.9%
Anaemia	-0.0897	21	2.9%	5.7%	0.0%	0.0%
Hypertension	-0.0735	21	5.6%	2.1%	0.0%	0.0%
QALY loss			-0.0031	-0.0029	-0.0002	-0.0010

DOC; docetaxel; ERL: erlotinib; Nind+D: nintedanib + docetaxel; QoL: Quality of life; RAM+D: Ramucirumab + docetaxel

5.2.8 Resources and costs

Drug costs per administration

To calculated the mean cost of ramucirumab the company estimates the distribution of female and male patient weights that can be treated with a given number of vials. These patient weights are conditioned by the 94.6% treatment utilisation percentage. For example, 5 vials of ramucirumab provide 500mg and given a dose of 10mg/kg would seem to suggest that patients up to a weight of 50kg could be treated. But this is then divided by 94.6% to suggest that patients up to a weight of 52.85kg could be treated. The mean weight (s.d.) for women is 67.2kg (15.0) and for men is 76.8kg (15.8), with the balance between men and women being 67:33. The normal distribution is used to simulate the distribution of patient weights and a floor of 40kg is also assumed.

The docetaxel costs for ramucirumab + docetaxel, docetaxel and nintedanib + docetaxel are calculated in a similar manner, based upon a dose of 75mg/m^2 and company estimates of the distribution of female and male Body surface areas (BSAs) and docetaxel drug utilisation percentages of 91.1% for ramucirumab + docetaxel, 93.6% for docetaxel and 98.3% for nintedanib + docetaxel. The mean BSA (s.d.) for women is 1.72m^2 (0.20) and for men is 1.91m^2 (0.22).

Based upon a cost of £500 per 10ml ramucirumab vial, and £35.35 per 8ml docetaxel vial, this results in the following cost calculations (Table 53).

Table 53: Mean IV drug costs per administration

	Ramucirumab doses		Docetaxel doses			
				RAM+DOC	DOC	NIN+DOC
Vials	Dose mg	% Pat	Dose mg	% Pat	% Pat	% Pat
1	100	0.0%	160	98.3%	96.8%	91.7%
2	200	0.0%	320	1.7%	3.2%	8.3%
3	300	0.0%	480	0.0%	0.0%	0.0%
4	400	2.6%	640	0.0%	0.0%	0.0%
5	500	7.4%	800	0.0%	0.0%	0.0%
6	600	16.7%	960	0.0%	0.0%	0.0%
7	700	24.6%	1120	0.0%	0.0%	0.0%
8	800	24.0%	1280	0.0%	0.0%	0.0%
9	900	15.6%	1440	0.0%	0.0%	0.0%
10	1000	6.8%	1600	0.0%	0.0%	0.0%
11	1100	2.0%	1760	0.0%	0.0%	0.0%
12	1200	0.4%	1920	0.0%	0.0%	0.0%
13	1300	0.0%	2080	0.0%	0.0%	0.0%
Cost		**£3,733**		**£36**	**£36**	**£38**

DOC: docetaxel; NIN: nintedanib; RAM: ramucirumab

The ERG considers that the application of treatment utilisation percentages to the calculation of maximum patient weights and estimates of maximum patient BSAs which can be treated with a given number of vials unusual. However, if these are instead applied to the mean cost, the results are very little different.

Erlotinib drug costs are based upon a 30 tablet pack size of 150mg tablets costing £1,632, dosed at one tablet per day. Nintedanib drug costs are based upon a 120 tablet pack size of 100mg tablets costing £2,151, dosed at 4 tablets per day for days 2 to 21 due to docetaxel being taken on the 1st day. The 1st day of the 3 week cycle does not have the nintedanib cost applied, even when treatment with docetaxel has ceased. These costs are applied pro rata to the 3 week cycle length despite the 30 day pack sizes.

Drug utilisation percentages of 98% for erlotinib and 96% for nintedanib are also applied within the model. The 98% dose adjustment for erlotinib is based upon 2% of erlotinib-treated patients discontinuing

due to adverse events as reported in Ciuleanu et al. (2012).[33] The 96% dose adjustment for nintedanib is based upon a discontinuation rate due to adverse events for nintedanib plus placebo of 20.9% as reported by Reck et al. (2014)[18] coupled with the median treatment duration of 3.4 months to give the three weekly adjustment factor.

Number of drug administrations

The number of ramucirumab administrations is assumed to be equal to that observed in the REVEL trial: 6.1 for the all patient modelling and 6.3 for the non-squamous modelling (Table 54).

The number of docetaxel administrations is also assumed to be equal to that observed in the REVEL trial, differentiated by arm: 5.5 for the all patient modelling and 5.6 for the non-squamous modelling in the ramucirumab + docetaxel arm; and, 4.9 for the all patient modelling and 5.1 for the non-squamous modelling in the docetaxel arm. For the non-squamous patients, in the nintedanib + docetaxel arm an average of 4.8 administrations are estimated from the 5.6 of the ramucirumab + docetaxel arm for the non-squamous and conditioned by the nintedanib STA which reported mean durations of 17.1 for those with adenocarcinoma compared to 20.0 for the non-squamous.

Table 54: Number of IV administrations

	RAM+DOC		DOC	NIN+DOC
	RAM	DOC	DOC	DOC
All patients	6.1	5.5	4.9	n.a.
Non-squamous	6.3	5.6	5.1	4.8

Erlotinib and nintedanib are assumed to be taken until progression. Half cycle correction is applied to the erlotinib and the nintedanib drug costs.

Administration costs

Intravenous (IV) administrations are based upon the 2013-14 NHS reference costs of £219 for a complex IV administration, which is applied to ramucirumab + docetaxel arm, and £165 for a simple IV administration, which is applied to docetaxel administrations in the docetaxel arm and the nintedanib + docetaxel arm.

The oral treatments are also associated with administration costs. Nintedanib has a three weekly cost of £90 for a non-consultant led outpatient appointment applied, though the company acknowledges that no

administration cost was included in the nintedanib STA submission. It is assumed that nintedanib would be administered on a 3 weekly, or 21 day, basis in order to be in line with the docetaxel infusions. Erlotinib has 46% of this applied resulting in a three weekly administration cost of £41. During clarification the company acknowledged that the 46% was an error and that the intended proportion is 70% based upon erlotinib being administered every 30 days, hence 21/30=70%.

Monitoring costs

Patients are assumed to have one outpatient oncologist visit every three weeks while in PFS and PPS. This is costed at £132 based upon the 2013-14 NHS reference cost as used in the nintedanib submission, with this then being inflated to £136. In addition to this, there are three weekly tests of: urinalysis, renal function, hepatic function and electrolytes which add a further £30. A CT scan is assumed to be required on average every 10 to 11 weeks, these being costed at £92 based upon the 2013-14 NHS reference cost as reported in the nintedanib submission and inflated to £95.

Premedication costs

Each docetaxel administration is assumed to also require premedication with dexamethasone, while ramucirumab requires premedication with chlorpheniramine. This adds an additional premedication cost per cycle while patients remain on IV treatment of £35.54 in the ramucirumab + docetaxel arm, and £32.11 in the docetaxel and the nintedanib + docetaxel arm.

PPS costs

The model assumes that 30% of patients receive further active therapy and that the remainder receive best supportive care (BSC) (Table 55), these values are drawn from table 78 of the company submission for the nintedanib STA. The annual costs of these are estimated to be reasonably similar at £8,240 for active therapy and £7,464 for BSC.

The annual £8,240 cost for active therapy is, given a patient BSA of a little under 2.0m^2, based upon 25% of patients receiving intravenous vinorelbine plus carboplatin and 5% of patients receiving erlotinib.

Table 55: PPS active therapy costs

	Per 3wk	Dose	Vial* ml	Vials	Unit cost	Cost
Vinorelbine	3	30mg/m2	1	6	£4.51	£81.18
Carboplatin	1	750mg	45	2	£20.17	£40.34
IV Admin				1	£218.60	£218.60

Vin+C						£340.12
			Tablets	Tablets	Unit cost	Cost
Erlotinib	21	150mg	1	21	£54.38	£1,142.07
Cost per 3wk cycle						£473.78
*10mg/ml						

Note that the above includes erlotinib. As a consequence, the erlotinib PAS inclusive cost for the above is: £340.12*(25/30) + £1,142.07 *(5/30) * (1- PAS_Erlotinib). This means that the cost effectiveness estimate for ramucirumab + docetaxel compared with docetaxel is very slightly affected by the erlotinib PAS. The effect is negligible.

The annual £7,464 cost for BSC (Table 56) is drawn from the nintedanib submission.

Table 56: PPS BSC costs

	Cost	Per 3wk cycle	% patients
Palliative visit	£74.00	3	100%
Blood transfusion	£140.36	1	50%
Radiotherapy	£126.17	1	50%
Oxygen	£14.24	1	50%
Bone scan	£232.08	1	20%
X-Ray	£29.60	0.28	100%
Cost per 3wk cycle			£417.09

SAE costs

Unit costs per SAE are drawn from the nintedanib STA and inflated by 2.9% as drawn from Consumer Prices Index data to arrive at costs in 2014 prices. As for the SAE quality of life decrements, these unit costs are modified by the estimated SAE event rates to arrive at treatment specific SAE costs (Table 57). These costs are applied once within the model during the first cycle.

Table 57: SAE costs by treatment

Toxicity	Cost	RAM+D	DOC	ERL	NIN+D
Neutropenia	£356	48.8%	39.8%	0.0%	12.1%
Febrile neutropenia	£2,070	15.9%	10.0%	0.0%	7.0%
Fatigue	£381	14.0%	10.5%	0.6%	5.7%
Nausea/vomiting	£1,975	1.3%	1.9%	0.0%	0.0%

Diarrhoea	£1,848	4.6%	3.1%	0.0%	6.7%
Hair loss (Any Grade)	£0	25.8%	25.2%	0.0%	16.4%
Rash	£657	0.8%	0.6%	8.1%	0.0%
Dyspnoea	£571	3.8%	8.3%	0.0%	0.0%
Leukopenia	£435	13.7%	12.5%	0.0%	2.9%
Anaemia	£1,006	2.9%	5.7%	0.0%	0.0%
Hypertension	£421	5.6%	2.1%	0.0%	0.0%
Cost		£807	£656	£56	£346

DOC: docetaxel; ERL: erlotinib; NIN: nintedanib; RAM: ramucirumab

5.2.9 Cost effectiveness results

The clinical inputs for ramucirumab + docetaxel and for docetaxel alone are the same for the REVEL all patient modelling and for the EGFR negative patient modelling, therefore the results of these two sets of analyses are presented alongside one another in order to economise on space (Table 58)

Table 58: Cost effectiveness: REVEL all patient and EGFR negative patients

	RAM+DOC	DOC	ERL
PFS undisc. LY	0.507	0.386	0.297
PPS undisc. LY	1.067	0.933	0.745
OS Total undisc. LY	1.574	1.319	1.042
net LY vs		0.255	0.532
PFS QALY	0.341	0.262	0.204
PPS QALY	0.478	0.433	0.363
AE QALYs	-0.003	-0.003	0.000
Total QALYs	0.816	0.692	0.567
net QALY vs		0.125	0.250
PFS Tx Drug	£22,332	..	£5,616
PFS Doc Drug	£194	£176	..
PFS Premed	£203	£148	£0
PFS admin	£1,308	£794	£228
PFS AEs	£807	£656	£56
PFS monitoring	£1,618	£1,242	£966
PPS Tx and BSC	£6,147	£5,560	£4,666
PPS monitoring	£2,674	£2,419	£2,030
Total Cost	£35,283	£10,995	£13,562

net cost vs.		£24,288	£21,721
ICER		£194,919	£86,985

DOC: docetaxel; ERL: erlotinib; RAM: ramucirumab

For the REVEL all patient modelling that compares ramucirumab + docetaxel with docetaxel, it is anticipated that ramucirumab + docetaxel results in an additional 0.255 undiscounted life years. This gain in life expectancy is estimated to be broadly equally split between PFS survival, a gain of 0.121 life years, and PPS survival, a gain of 0.134 life years. These survival gains translate into an estimated 0.125 discounted QALYs. The estimated discounted QALY gain may appear to be too low a proportion of the undiscounted additional survival, but as reviewed later this is in large part due to a quite serious error in the way the company model discounts future quantities.

Most costs are reasonably equally balanced between ramucirumab + docetaxel and docetaxel, the main differences arising due to the costs of ramucirumab and its administration. Net costs of £24,288 yield a cost effectiveness of £195k per QALY for ramucirumab + docetaxel compared to docetaxel.

Turning to the EGFR negative subgroup, erlotinib is estimated to result in somewhat fewer QALYs than docetaxel and to cost more, and so is estimated to be dominated by docetaxel. If erlotinib is compared with ramucirumab + docetaxel, ramucirumab + docetaxel yields an additional 0.532 undiscounted life years. This gain in life expectancy is estimated to be less during PFS survival, a gain of 0.210 life years, with the majority being during PPS survival, a gain of 0.322 life years. This survival gain translates into an estimated 0.250 discounted QALYs.

Due to the reduced survival, costs are lower in the erlotinib arm in general compared to ramucirumab + docetaxel. The direct drug costs are less than a quarter of those of ramucirumab + docetaxel and administration costs are also rather lower. The net cost for ramucirumab + docetaxel of £21,721 yields a cost effectiveness estimate of £86,985 per QALY for ramucirumab + docetaxel compared to erlotinib.

For the REVEL all patient population the PSA run over 5,000 iterations results in estimates of a net cost of £24,273 and a net gain of 0.124 QALYs for ramucirumab + docetaxel compared to docetaxel, and a cost effectiveness estimate of £195,385 per QALY. This is similar to the deterministic estimate of

£194,919 per QALY. The corresponding Cost-effectiveness Acceptability Frontier (CEAF[3]) is as Figure 23.

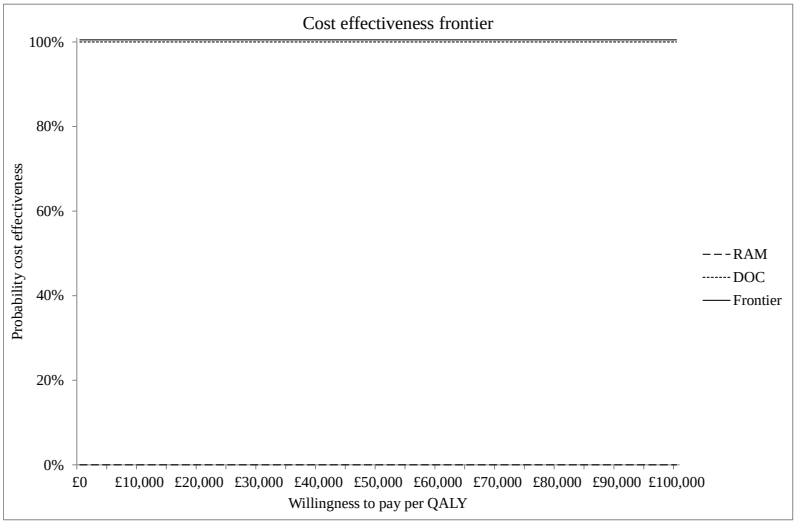


Figure 23: CEAF: REVEL all patients

Over the willingness to pay range of £0 to £100k per QALY docetaxel is estimated to be certain to be the most cost effective with the ramucirumab + docetaxel having no probability of being cost effective.

For the EGFR positive patient population the PSA run over 5,000 iterations results in estimates of a net cost of £21,558 and a net gain of 0.243 QALYs for ramucirumab + docetaxel compared to erlotinib, and a cost effectiveness estimate of £88,700 per QALY. This is similar to the deterministic estimate of £86,985 per QALY. The central estimates also suggest that erlotinib is £2,715 more expensive than docetaxel and results in a patient loss of 0.119 QALYs so is dominated by docetaxel.

As in the deterministic modelling the estimates for ramucirumab + docetaxel, and docetaxel are identical to the REVEL all patient modelling. As a consequence, due to the poor cost effectiveness estimate for erlotinib compared to docetaxel, over the willingness to pay range of £0 to £100k per QALY, docetaxel is effectively estimated to be certain to be the most cost effective with the other comparators having no probability of being cost effective. In the light of this, the CEAF and table of probabilities has not been reproduced here.

[3] Note that all CEAFs have had an arbitrary 0.5% added to them in order to ease the identification of the treatment curves which underlie them.

For the non-squamous patient population, the model outputs are as follows (Table 59).

Table 59: Cost effectiveness: Non-squamous patients

	RAM+DOC	DOC	NIN+DOC
PFS undisc. LY	0.522	0.398	0.516
PPS undisc. LY	1.157	0.991	1.150
OS Total undisc. LY	1.679	1.390	1.666
net LY vs		0.289	0.013
PFS QALY	0.351	0.270	0.344
PPS QALY	0.515	0.457	0.509
AE QALYs	-0.003	-0.003	-0.001
Total QALYs	0.863	0.724	0.852
net QALY vs		0.139	0.011
PFS Tx Drug	£23,055	..	£11,650
PFS Doc Drug	£198	£183	£181
PFS Premed	£210	£154	£281
PFS admin	£1,350	£826	£1,585
PFS AEs	£807	£656	£346
PFS monitoring	£1,663	£1,280	£1,634
PPS Tx and BSC	£6,624	£5,878	£6,541
PPS monitoring	£2,882	£2,557	£2,846
Total Cost	£36,789	£11,534	£25,064
net cost vs.		£25,255	£11,724
ICER		£182,082	£1,106,497

The estimates for the comparison of ramucirumab + docetaxel with docetaxel are much as for the all patient modelling, though the OS gains are less in PFS survival, a gain of 0.124 life years, than in PPS survival, a gain of 0.165 life years. The gains are estimated to be slightly larger at 0.139 QALYs but there is a corresponding increase in net costs to £25,255 and the cost effectiveness estimate is reasonably similar at £182k per QALY.

There are estimated to be slight survival gains from ramucirumab + docetaxel compared to nintedanib of 0.013 undiscounted life years, with these gains being equally split between PFS survival and PPS survival. These translate into a modest gain of 0.011 QALYs. The non-drug costs are generally similar between the two arms with the possible exception of the drug administration costs which are actually higher in the nintedanib + docetaxel arm despite nintedanib being orally administered. Adverse event

costs are slightly lower in the nintedanib + docetaxel arm. But the main difference is again in the direct drug costs with ramucirumab being considerably more expensive. The resulting net cost of £11,724 translates into a cost effectiveness estimate of £1.1mn per QALY. The drugs are estimated to be broadly clinically equivalent, but ramucirumab to involve slightly more than double the direct drug costs of nintedanib.

For the comparison of nintedanib + docetaxel with docetaxel, the model suggests gains of 0.128 QALYs at a cost of £13,531 yielding a cost effectiveness estimate of £105k per QALY.

For the non-squamous patient population the PSA run over 5,000 iterations results in estimates of a net cost of £25,271 and a net gain of 0.139 QALYs for ramucirumab + docetaxel compared to docetaxel, and a cost effectiveness estimate of £181,163 per QALY. This is similar to the deterministic estimate of £182,082 per QALY.

For the comparison with nintedanib + docetaxel the net costs are estimated to be £11,465 and the net gain 0.007 QALYs resulting in a cost effectiveness estimate of £1.7mn per QALY. The cost effectiveness estimate for ramucirumab + docetaxel compared to nintedanib + docetaxel is somewhat above the deterministic estimate of £1.1mn, but this is due to the small denominator and the two effectively resulting in the same patient gains, with ramucirumab + docetaxel, however, being somewhat more expensive. The corresponding CEAF is seen in Figure 24.

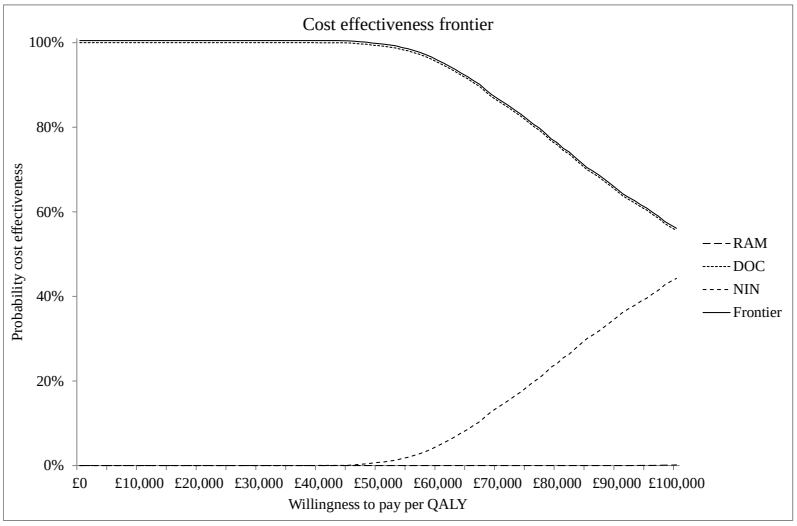


Figure 24: CEAF: Non-squamous

This has the following estimates (Table 60) for the probabilities of the treatments being the most likely to be cost effective.

Table 60: Probabilities of cost effectiveness: Non-squamous

WTP	RAM+DOC	DOC	NIN+DOC
£0	0.0%	100.0%	0.0%
£10,000	0.0%	100.0%	0.0%
£20,000	0.0%	100.0%	0.0%
£30,000	0.0%	100.0%	0.0%
£40,000	0.0%	100.0%	0.0%
£50,000	0.0%	99.3%	0.7%
£60,000	0.0%	95.3%	4.7%
£100,000	0.2%	55.6%	44.2%

DOC: docetaxel; NIN: nintedanib; RAM: ramucirumab; WTP: willingness to pay

Up to around a willingness to pay of around £60k per QALY there is effectively no likelihood of nintedanib + docetaxel being the most cost effective. It is only for willingness to pay values of over £60k per QALY that there starts to become some likelihood of nintedanib + docetaxel being the most cost effective. It appears that the two curves cross over in the region of the central estimate at around £105k per QALY.

At all willingness to pay values up to £100k per QALY there is effectively no likelihood of ramucirumab + docetaxel being the most cost effective.

5.2.10 Sensitivity analyses

The company presents a number of one way sensitivity analyses in the tornado diagram of figures 40 to 42 on pages 174 to 176 of the CS. The sensitivity analyses are generally the 95% confidence interval or where this is not available ±20% of the base case value. The values underlying these one way sensitivity analyses coupled with some others are presented in Table 61.

Table 61: Company one way sensitivity analyses

			vs DOC		vs ERL		vs NIN+DOC	
			ICER	ICER	ICER	ICER	ICER	ICER
Input Parameter	Low V.	High V.	Low V.	High V.	Low V.	High V.	Low V.	High V.
RAM vial price	£400	£600	£159k	£230k	£69,099	£104k	£671k	£1.5mn
ERL price	£1,305	£1,958			£91,330	£82,640		
NIN Price	£1,721	£2,581					£1.3mn	£886k
Benefit discount rate	1.8%	5.3%	£171k	£218k	£75,647	£98,222	£1.3mn	£1mn
RAM + DOC RAM inf.	5.69	6.51	£182k	£207k	£80,567	£93,403		
RAM + DOC RAM inf.	5.81	6.79					£927k	£1.2mn
RAM + DOC DOC inf.	5.15	5.85			£86,936	£87,034		
RAM + DOC DOC inf.	5.19	6.01					£1.1mn	£1.1mn
NIN + DOC DOC inf.	4.43	5.14					£1.1mn	£1.0mn
Cost discount rate	1.8%	5.3%	£198k	£191k	£90,041	£84,577	£1.0mn	£1.1mn
PPS QoL	0.57	0.628	£198k	£191k	£89,002	£85,058	£1.1mn	£1.0mn
BSC cost	£261	£597	£193k	£196k	£85,407	£88,564	£1.1mn	£1.1mn
PFS QoL	0.700	0.712	£195k	£193k	£87,385	£86,589	£1.1mn	£1.1mn
DOC DOC inf.	4.57	5.23	£195k	£194k				
PPS TX cost	£288	£659	£194k	£195k	£86,238	£87,732	£1.1mn	£1.1mn
RAM + DOC DOC inf.	5.15	5.85	£194k	£195k				
DOC vial cost	£28	£42	£194k	£194k				
OS HR: ERL	1.16	1.29			£96,237	£80,329		
OS HR: NIN+DOC	0.68	1.01					Nin.Dom	£104k
PFS HR: ERL	1.27	1.4			£86,828	£87,126		
PFS HR: NIN_DOC	0.56	0.98					Nin.Dom	£638k
ERL Utilisation	95.57%	99.44%			£87,543	£86,655		
NIN Utilisation	72.92%	100.00%					£1.3mn	£1.0mn
Nin. Dom: Nintedanib + docetaxel dominates ramucirumab + docetaxel								

DOC: docetaxel; ERL: erlotinib; NIN: nintedanib; RAM: ramucirumab;

Eight scenario analyses are also presented (Table 62).

- SA01: Using the unadjusted parametric curves
- SA02: Using the generalised gamma for OS
- SA03: 10 year time horizon
- SA04: 20 year time horizon
- SA05: No tapering of OS hazard ratios

- SA06: Common OS hazard with docetaxel immediately at month 33
- SA07: Chouaid et al (2013)[34] quality of life values of 0.74 for PFS and 0.46 for PPS
- SA08: A QALY penalty of 0.010 QALYs applied to the last cycle before death.

Table 62: Company scenario analyses: ICERs

	vs DOC	vs ERL	vs NIN+DOC
Base case	£195k	£86,985	£1.1mn
SA01: Unadjusted OS	£230k	..	..
SA02: OS generalised gamma	£214k	£100k	£374k
SA03: 10 year horizon	£199k	£88,747	£1.0mn
SA04: 20 year horizon	£194k	£86,408	£1.1mn
SA05: No tapering of benefits	£189k	£83,524	Nin, Dom
SA06: No HR benefit after month 33	£196k	£87,667	£918k
SA07: Chouaid QoL	£206k	£94,614	£1.2mn
SA08: Death QALY penalty	£195k	..	..

DOC: docetaxel; ERL: erlotinib; NIN: nintedanib

5.2.11 Model validation and face validity check

The company presents validation data comparing the mean OS estimates of the TA347 assessment of nintedanib with those of the current submission for the non-squamous comparison. (Table 63)

Table 63: Company model validation data: Mean OS estimates

	NIN+DOC	DOC	Net
TA347 company base case	1.709	1.411	0.298
TA347 ERG base case	1.604	1.380	0.224
Current submission	1.666	1.390	0.276

DOC: docetaxel; NIN: nintedanib

For nintedanib + docetaxel the model of the current submission is less optimistic than the company model of the TA347 assessment, but more optimistic than the ERG revised model of TA347.

The company model suggests for all patients median OS of between 10.3 and 11.0 months in the ramucirumab + docetaxel arm and between 8.3 months and 9.0 months in the docetaxel arm. This compares with medians of 10.5 months and 9.1 months in the REVEL trial. The gain from ramucirumab + docetaxel over docetaxel in terms of median OS may have been slightly exaggerated.

The company model suggests for non-squamous patients median OS of between 11.0 and 11.7 months in the ramucirumab + docetaxel arm, between 9.0 months and 9.7 months in the docetaxel arm and between 10.3 and 11.0 months in the nintedanib + docetaxel arm. This compares with medians of 11.1 months and 9.7 months in the REVEL trial.

Turning to the adenocarcinoma subgroup, medians of 11.2 months and 9.8 months were observed in the REVEL trial: a gain of 1.4 months. This compares with Reck et al (2014) reporting medians of 12.6 months for nintedanib + docetaxel and 10.3 months for docetaxel, a difference of 2.3 months. The company model suggests a better median OS gain for ramucirumab + docetaxel than for nintedanib + docetaxel, although the company NMA appears to suggest the reverse.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has rebuilt the deterministic model applying the company assumptions and gets agreement with the company model (Table 64 and Table 65).

Table 64: ERG rebuild and company model: All patients and EGFR –ve

	ERG rebuild			Company model		
	Costs	QALYs	ICER	Costs	QALYs	ICER
RAM	£35,283	0.816		£35,283	0.816	
DOC	£10,995	0.692	£194,917	£10,995	0.692	£194,919
ERL	£13,562	0.567	£86,979	£13,562	0.567	£86,985

Table 65: ERG rebuild and company model: Non-squamous

	ERG rebuild			Company model		
	Costs	QALYs	ICER	Costs	QALYs	ICER
RAM	£36,789	0.863		£36,789	0.863	
DOC	£11,534	0.724	£182,080	£11,534	0.724	£182,082
NIN	£25,064	0.852	£1,105,226	£25,064	0.852	£1,106,497

5.3.2 Data Inputs: Correspondence between written submission and sources cited

PFS and PPS quality of life

The publicly available documents of the NICE assessments listed in the scope report the following quality of life values.

- Nintedanib (TA347): Approved for treatment experienced adenocarcinoma patients. The company submission pooled EQ-5D data between the arms, estimating a baseline quality of life of 0.710, with this showing an initial improvement to 0.721 at week 3. Thereafter for those on treatment tended to decline, falling to 0.661 by week 30 with the company base case implementing a linear decline. A value of 0.64 was derived for the PPS health state. The FAD expressed the concern that the PPS value of the company base case was not much lower than that for PFS, while also expressing that concern that the value of 0.46 drawn from Chouaid et al (2013)[34] for PPS was perhaps too low and that a value between the two would be more appropriate.
- Crizotinib (TA296): Not recommended for the treatment experienced. The PMB noted that the values used were higher than previously reported in NSCLC with the ERG expressing particular concern for the value for PPS QoL value compared that used for the erlotinib STA. The FAD also expressed concern about the uncertainty around this value. The PROFILE 1007 EQ-5D quality of life values were redacted though the summary of Blackhall et al (2013),[35] as summarised below, gives the baseline values by arm.
- Erlotinib (TA374): Approved for EGFR positive but rejected for EGFR negative after progression on 1st line chemotherapy. The standard gamble survey among 100 members of the UK general public of Nafees et al (2008)[32], which the current submission uses for the SAE quality of life values, also reports quality of life values for stable, response and progressive disease of 0.6532, 0.6725 and 0.4734. The values of Nafees et al were used for TA374 with the MTA reporting treatment specific adverse event conditioned quality of life values ranging between 0.6225 and 0.6450 for PFS and 0.4734 for PPS.
- Pemetrexed (TA124): Approved for 1st line use but not locally advanced or metastatic. This also relied upon the estimates of Nafees et al (2008)[32] with values of 0.66 for stable disease, 0.67 for response and 0.47 for progressive disease.

In terms of the broader literature the ERG agrees that the most relevant study within the literature review to the current assessment is that of Chouaid et al (2013) [34]. But the values reported in the submission are

not completely aligned with those of the paper, and the submission also omits to mention data from this paper that suggests a reduction in quality of life as patient's progress towards the later lines of therapy. The broader literature may provide some additional support for the proposition that quality of life on 1st line therapy or on 2nd line therapy is not particularly different. Blackhall et al (2014)[35] suggests some general deterioration in quality of life while receiving docetaxel treatment, though there are caveats around this in terms of possible reporting bias.

The detail underlying the above summary of the literature is outlined below. The ERG found appendix 12 of the CS of only limited use in deciding which values from the literature would be useful for the current assessment. Given the summary above, most readers may prefer to briefly review the values of Chouaid et al (2013)[34] as presented below and then move on to the next section.

In appendix 12 the company presents results from a systematic review of HRQoL studies in NSCLC. But other than a brief presentation of the values of Chouaid et al (2013)[34] the results of the systematic review are not presented in the CS. Table 87 of appendix 12 reports the characteristics of these studies. Restricting attention to those that are reported as using patient reported EQ-5D and including those which either used the UK social tariff, or which did not specify the tariff used, results in the following 13 papers[4].

Bischoff et al (2010)[36] is an observational study sponsored by Eli Lilly of 975 stage IIIb/IV patients about to receive 1st line chemotherapy and only reports the mean baseline QoL value of 0.65 and standard deviation of 0.3. The valuation set to convert from the EQ-5D to QoL values is not stated.

Blackhall et al (2014)[35] report the results of the Pfizer PROFILE 1007 phase III study of crizotinib among 310 ALK positive patients with advanced or metastatic disease and had progressive disease after one platinum based chemotherapy regime. The EQ-5D was administered on the first day of each cycle until treatment discontinuation. The valuation set to convert from the EQ-5D to QoL values is not stated. The mean baseline EQ-5D quality of life was 0.73 for the crizotinib arm (n=160) and 0.70 for the chemotherapy arm (n=150), the latter being further split into 0.73 for the pemetrexed arm (n=88) and 0.67 for the docetaxel arm (n=62), resulting in an overall mean baseline value of 0.72. The EQ-5D mean VAS at baseline was 65.5 for crizotinib and 67.5 for chemotherapy, the latter being split into 68.5 for

[4] Roughley et al (2014) used the French and German tariffs for the French and German patients respectively [Personal communication: Gary Milligan, Adelhpi Group: 27 Jan 2016]. Novello et al (2013) do not appear to report any EQ-5D QoL results.

pemetrexed and 66.2 for docetaxel. The mean changes from baseline in the EQ-5D VAS based upon a repeated measures mixed-effects analysis were +4.68 for crizotinib, -6.06 for chemotherapy, -4.09 for pemetrexed and -9.46 for docetaxel, all these having a p-value < 0.05. This appears to suggest a general deterioration in quality of life among those receiving docetaxel over time. But it should be borne in mind that this is an industry sponsored study and that changes in the EQ-5D quality of life values despite being analysed do not appear to be reported.

Chouaid et al (2013),[34] supported by Boehringer Ingelheim report the results of a multinational study which included sites in Turkey among 263 patients previously diagnosed with stage IIIb/IV disease and an ECOG status of 0 to 2. At the time of the survey 18% were stage IIIb and 82% were stage IV, with 17% having squamous disease. Patients were receiving pharmacotherapy at either 1st, 2nd line or 3rd/4th line or BSC (n=6) where BSC patients were required to have failed at least 2 lines of therapy. Patients were excluded if they knew their tumour response to therapy on the grounds that this might bias questionnaire completion. Quality of life values were not reported for the small number of BSC patients. The valuation set to convert from the EQ-5D to QoL values was the UK social tariff. The quality of life values that are reported are as in Table 66.

Table 66: Chouaid et al QoL values: EQ-5D UK social tariff

	PFS patients			PPS patients		
	N	QoL	95% C.I.	N	QoL	95% C.I.
1st line	111	0.71	[0.67-0.76]	26	0.67	[0.59-0.75]
2nd line	44	0.74	[0.68-0.80]	17	0.59	[0.42-0.77]
3rd/4th line	24	0.62	[0.49-0.74]	21	0.46	[0.28-0.63]

The above values differ from those reported in table 55 of the submission in that the mean value and confidence interval for 2nd line progressive disease are confused with the values for 3rd line progressive disease.

Chouaid et al (2013)[34] also report the results of a regression analysis on the 243 patients who had complete information. This resulted in the following coefficients.

Table 67: Chouaid et al QoL coefficients: EQ-5D UK social tariff

Covariate	Value	p-value
Intercept	0.77	<0.0001
Stage IV	-0.07	0.029
1st line PPS	-0.04	0.4067
2nd line PFS	0.03	0.4697
2nd line PPS	-0.11	0.1836
3rd/4th line PFS	-0.10	0.0920
3rd/4th line PPS	-0.26	0.0022

The regression analysis suggests that there may be limited evidence for a difference in quality of life between those in 1st line PPS or 2nd line PFS compared to those in 1st line PFS. The evidence for a deterioration while in 2nd line PPS is stronger, but is still far from statistically significant. The evidence for a deterioration while in 3rd line PFS is again stronger, though only the coefficient for being in 3rd line PPS is statistically significant. The stage IV coefficient is also statistically significant and it would be anticipated that the proportion with stage IV disease would tend to increase as patients progress through lines of therapy. As a consequence, viewing the coefficients on line of therapy in isolation from the stage IV coefficient may tend to understate the deterioration in quality of life as patients move through the lines of therapy. The results of Chouaid et al appear to suggest that there is a continuing and potentially quite serious deterioration in quality of life as patients progress to the later lines of therapy.

Galetta et al (2015)[37] in an Italian study supported by Eli Lilly report the results of the phase III ERACLE trial of cisplatin followed by maintenance pemetrexed (n=60) versus carboplatin plus paclitaxel followed by maintenance bevacizumab (n=58) as 1st line treatment for stage IIIb/IV non-squamous chemotherapy naïve patients. The vast majority of patients, 96%, were stage IV. The valuation method that was used to convert the EQ-5D responses to quality of life values was the UK social tariff [Personal communication: Dr D. Galetta, Istituto Tumori IRCCS, 29 Jan 2016]. The mean baseline EQ-5D values were 0.719 [0.656-0.782] in the cisplatin arm and 0.661 [0.582-0.740] in the carboplatin arm. These seem surprisingly different but this may be due to the sample sizes and the 95% confidence intervals largely overlap, with an overall mean value of 0.690. Mean changes from baseline after 18 weeks of maintenance therapy were -0.04 in the cisplatin arm and -0.177 in the carboplatin arm. The paper does not report any analysis by PFS and PPS. The overall mean value is slightly below that of the submission value for PFS for 2nd line treatment subsequent to progressing after platinum based chemotherapy.

Gridelli et al (2012)[38] in a study sponsored by Eli Lilly report the results of the multinational, including Turkey and India, phase III PARAMOUNT study of pemetrexed maintenance therapy compared to BSC among patients with advanced non-squamous NSCLC who had previously received four cycles of cisplatin plus pemetrexed. The EQ-5D valuation method was the UK social tariff. The mean values at baseline were approximately 0.70, with there being some statistically significant improvements subsequent to baseline during induction therapy. The mean changes from baseline at the post discontinuation visits were -0.13 in the pemetrexed arm and -0.09 in the BSC arm, though reporting rates dropped from around 82% to only 44% mainly due to investigation sites not administering the questionnaire.

Grutters et al (2010) [39] undertook a postal survey of 374 Dutch patients receiving treatment for NSCLC identified through the Netherlands Cancer Registry, of whom 260 completed the questionnaire. Their health records were then linked to their responses and examined through multivariate regression analysis. Only 23% of patients were stage IIIB and 1% of patients were stage IV. The EQ-5D valuation method is not stated. The mean quality of life is stated as being 0.74, with the regression analysis suggesting a constant of 0.820 and coefficients for SAEs and radiotherapy or chemotherapy of -0.353 and -0.069 respectively with all being statistically significant. Given the distribution of patients between stages, the main element of interest is perhaps the SAE coefficient but the distribution of patients may limit the relevance of this.

Hirsh et al (2013)[40] in a study supported by Boehringer Ingelheim report the results of a multinational phase IIb/III trial, including Asian countries, of afatinib versus placebo among 585 patients who had progressed after 1-2 lines of chemotherapy and at least 12 weeks of erlotinib or gefitinib. The EQ-5D valuation was performed using the UK social tariff. Questionnaires were administered during treatment and at end of treatment, with treatment being until disease progression or withdrawal due to adverse events. The baseline quality of life appears to have been 0.727, with the mean values at median follow up being 0.71 in the afatinib arm compared to 0.67 in the placebo arm.

Iyer et al (2013)[41] in a study sponsored by Pfizer analysed data among French (n=320) and German (n=517) stage IIIb/IV patients receiving drug treatment for NSCLC in a non-trial setting identified through the Adelphi NSCLC Disease Specific Programme. 85% of patients were stage IV. 52% of patients were receiving 1st line therapy. The EQ-5D valuation was performed using the UK social tariff. The overall mean quality of life was 0.58. The mean for the French patients, all of whom were stage IV, was 0.57 and the mean for the German patients was 0.59. This could be read as suggesting quality of life

values of 0.65 for stage IIIb and 0.57 for stage IV as these tally with the German and overall mean values. The mean value for those on 1st line treatment of 0.63 was statistically significantly higher than that for those on later lines of treatment of 0.53. The value for the later lines of treatment is of only limited relevance to the current assessment given that the balance between 2nd, 3rd and possibly later lines of treatment is not presented.

Khan et al (2015)[42] estimated the cost effectiveness of 1st line erlotinib + BSC compared to BSC based upon a UK based RCT among 670 stage IIIb/IV patients unsuitable for chemotherapy. The EQ-5D valuation was performed using the UK social tariff. It appears that quality of life data was collected monthly during the first year and 6 monthly thereafter during overall survival, with a 98% completion rate at baseline and an 80% completion rate at 1 year. The PFS and PPS QoL values in the erlotinib arm were 0.648 and 0.552 and were 0.644 and 0.576 in the placebo arm, suggesting mean values of around 0.646 for PFS, 0.563 for PPS and a decrement for progression of 0.082. These values have limited relevance to the current assessment other than to suggest that progression after 1st line treatment is associated with a loss in quality of life.

Lal et al (2015),[43] supported by Eli Lilly, report the results of an exploratory phase II trial of pemetrexed maintenance therapy through home delivery among 52 UK and Swedish stage IIIB/IV non-squamous patients whose disease had not progressed after 4 cycles of platinum based chemotherapy. The EQ-5D valuation was performed using the UK social tariff. The mean baseline quality of life was 0.72 with mean changes from baseline ranging between 0.009 and 0.077 over the five cycles. These values have limited relevance to the current assessment.

Schuette et al (2012),[44] supported by Lilly Deutschland GmBH, report the results of a study among 521 stage IIIa/b or IV German patients who had previously received one cytotoxic chemotherapy regime who went on to receive 2nd line pemetrexed for up to a maximum of 9 treatment cycles. The EQ-5D valuation was performed using the UK social tariff. The mean baseline quality of life reported among 271 patients was 0.66 (s.d. 0.256 hence s.e. 0.015) with mean changes from baseline for cycle 2 among 190 patients of 0.02 (s.d. 0.214 hence s.e. 0.015) and for cycle 6 among 61 patients of 0.11 (s.d. 0.228 hence s.e. 0.029) . It is not entirely clear whether the reported improvements are compared to the overall baseline of 0.66 or to the patient group remaining on treatment, but it appears to be the latter. There may also be concerns around the EQ-5D completion rate at baseline, though if there was completion bias it might be expected to unreasonably boost the mean baseline value. The mean baseline value is somewhat below that of the submission.

Trippoli et al (2001)[45] report the results of a study among 95 NSCLC Italian patients recruited from 15 clinics by investigators each recruiting 8 respondents. 63% had metastatic disease and 86% had received chemotherapy, though it appears that chemotherapy could be ongoing. The EQ-5D valuation was performed using the UK social tariff. The mean EQ-5D quality of life was 0.58 among the 92 patients reporting (s.d. 0.33 hence s.e. 0.03). A multivariate regression analysis estimated a statistically significant decrement for metastases of -0.236. Given the selection of patients by a number of investigators it is unclear what biases may have resulted from this and the values are of questionable relevance.

Van den Hout et al (2006)[46] analysed the EQ-5D data among 303 Dutch patients of a randomised trial of short course versus long course palliative radiotherapy among stage IIIa/IIIb patients with an ECOG status of at least 2 and stage IV patients. The EQ-5D valuation was performed using the UK social tariff. Only 12% of patients had had prior chemotherapy. The median quality of life at baseline is reported as 0.62 in the long course group and 0.52 in the short course group to give an average of 0.57. The authors go on to estimate QALYs as the area under the EQ-5D utility curve, but this is irrelevant to the current assessment. The median baseline values are also not obviously relevant to the current assessment.

SAE quality of life

The values used correspond to those in Nafees et al (2008)[32] which appears to be the most reasonable source.

Erlotinib and nintedanib administrations

The ERG has not cross checked the erlotinib STA submission to see if it lists any amendments to treatment administrations since erlotinib is no longer relevant.

The company submission for the nintedanib STA reports a 3 weekly discontinuation probability of 12.5% and a mean duration of treatment with nintedanib of 5.53 months. The model simulates a mean undiscounted duration of treatment with nintedanib of 5.93 months which is qualified by the nintedanib drug utilisation percentage as derived from separate discontinuation data of 96% to imply an overall mean duration of 5.68 months. This is around 2.7% higher than the 5.53 months reported in the nintedanib submission. But it should be noted that the ERG has no further access to the nintedanib data and consequently there is uncertainty around this data.

Docetaxel costs

There are no Commercial Medicines Unit electronic Market Information Tool (CMU EMIT) entries for ramucirumab, erlotinib or nintedanib. The costs applied for erlotinib and nintedanib cross check with eMIMS. The year to the end of June 2015 CMU EMIT entry for docetaxel is as Table 68 with N being the number of items used.

Table 68: CMU EMIT docetaxel costs: 20mg/ml

ml	mg	Unit cost	mg cost	N
1	20	£4.55	£0.23	26,546
4	80	£12.39	£0.15	42,743
7	140	£20.95	£0.15	6,132
8	160	£44.84	£0.28	6,771

The CS applies a cost of £35.35 for an 8ml vial. While this is cheaper than the June 2015 CMU EMIT cost, the cost per mg of £0.22 is reasonably higher than the cost per mg of the most commonly used vial size of £0.15. The assumption of the 160 mg vial size rather than the somewhat more commonly used 80mg vial size will also have increased the costs of docetaxel wastage, on the assumption that vial use among NSCLC patients is broadly similar to that among those contributing to the CMU EMIT database.

The docetaxel drug costs are an insignificant element within the total costs that are modelled, and as a consequence the ERG has not explored reducing these in the light of the above.

Monitoring costs

The ERG derives slightly different costs for medical oncology WF01A from the 2013-14 NHS reference costs: £143 as compared with £136 in the submission. The cost per outpatient RA08A CT scan is also slightly different at £92 rather than £95. These discrepancies have negligible impact upon the cost effectiveness estimates.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

Month and cycle duration

The economic model assumes that the parameterised curves are based upon one month being equal to 1/12th of a year. It is possible that within the trial data one month related to 4 weeks or 1/13th of a year. If

this was the case it would tend to extend the modelled curves slightly, by around 1/13th or 7% as illustrated in Figure 25 for the log logistic overall survival curves.

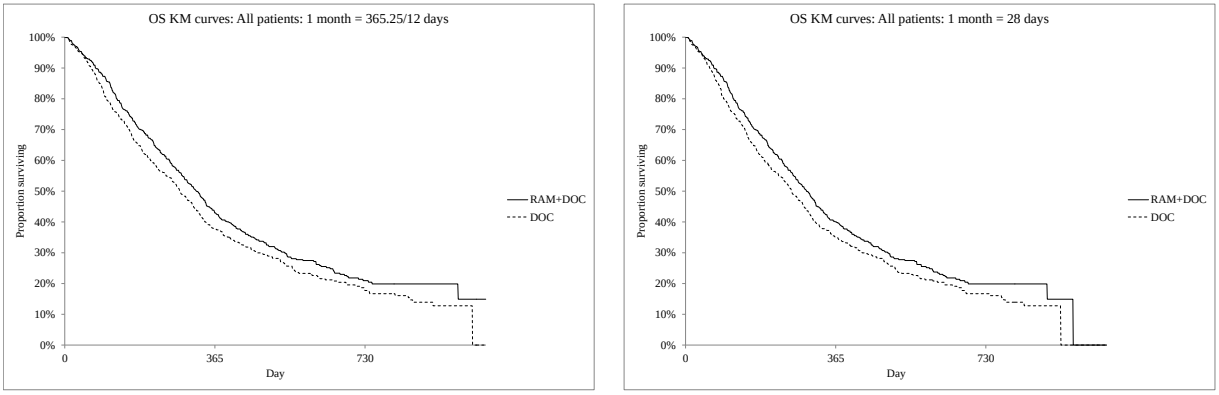


Figure 25: Month and cycle duration and OS Kaplan Meier curves: All patients

As can be seen in the above, if the definition of a month in the REVEL trial was only 28 days this compresses the KM curves, and the area between the two curves is reduced. This would naturally also flow through to the parameterised curves.

The ERG assumption is that the definitions of a month are aligned, with the trial month also being 1/12th of a year. In retrospect the ERG should have confirmed this during clarification.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Log logistic for overall survival

As already outlined the hazard ratio implied by the log logistic curves of the adjusted analysis varies considerably over time. This seems at odds with the assumptions of the NMA and there may consequently be some discomfort around the use of the log logistic for comparisons that use the results of the NMA (Figure 26).

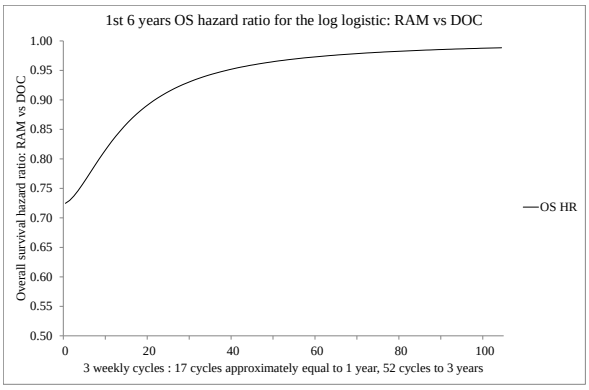


Figure 26: Log logistic OS hazard ratio for ramucirumab + docetaxel versus docetaxel

As also already outlined in

Figure 13 and Figure 14 above, the log logistic also has something of a longer tail after the end of the trial at 33 months than the other parameterisations which could have been used. This tail is not obviously justified and this may argue for an exploration of other parameterisations of the curves. Given previous NICE assessments of cancer drugs, the Weibull would seem to be an obvious choice.

Trial duration

While the REVEL trial may have lasted for around 33 months the KM data supplied by the company suggests that in practise the number at risk begins to drop off after around the 10th month, though this drop off is not precipitous. This might argue for the tapering of hazards to start earlier than the 33rd months, though any point prior to this would be arbitrary due to the lack of a precipitous drop off in the numbers at risk as often occurs in other cancer trials due to censoring before the end of the trial.

Squamous and non-squamous impact upon adjusted multivariate OS curves and KM curves

Given the focus on histology the ERG economic reviewer has anticipated that histology would be an important driver of results. A more detailed exploration of this is given below, but those with clinical experience will probably want to skip this section.

In comparison to the OS analysis the effect the histology covariate is smaller in the PFS analysis, but with this seeming to affect the ramucirumab + docetaxel arm more than the docetaxel arm (Table 69).

Table 69: Histology coefficient: OS and PFS adjusted analyses

	Expo.	Gamma	Log Log.	Log Norm.	Weibull
OS : Docetaxel	0.258	0.243	0.264	0.223	0.233
OS : Ramucirumab + docetaxel	0.274	0.240	0.225	0.218	0.246
PFS : Docetaxel	0.180	0.184	0.224	0.171	0.174
PFS : Ramucirumab + docetaxel	0.076	0.063	0.064	0.046	0.076

This appears to suggest that histology does not particularly differentiate OS between docetaxel and ramucirumab + docetaxel, but does perhaps to a greater extent differentiate PFS between docetaxel and ramucirumab + docetaxel. But this has to be coupled with the other parameters within the multivariate analyses and it also has to be borne in mind that the non-squamous made up around three quarters of the REVEL trial.

The mean OS and PFS for the docetaxel arm for all patients for the non-squamous can be derived from the above curves over the time horizon of the model. The values for the squamous can be inferred by assuming a 74:26 split in the all patient survival between non-squamous and squamous. The implied differences in mean OS and PFS between the non-squamous and the squamous can then be presented (Table 70).

Table 70: Histology coefficient: Mean docetaxel OS and PFS: Life years

	Expo.	Gamma	Log Log.	Log Norm.	Weibull
OS : Docetaxel : All patients	1.109	1.102	1.347	1.314	1.041
OS : Docetaxel : Non-Squamous	1.169	1.160	1.418	1.382	1.09
OS : Docetaxel : Squamous	0.942	0.941	1.150	1.125	0.905
OS : Docetaxel : Non-squam - Squam	0.227	0.219	0.268	0.257	0.185
PFS : Docetaxel : All patients	0.415	0.415	0.461	0.429	0.413
PFS : Docetaxel : Non-Squamous	0.425	0.427	0.479	0.441	0.422
PFS : Docetaxel : Squamous	0.387	0.382	0.411	0.396	0.388
PFS : Docetaxel : Non-squam - Squam	0.038	0.045	0.068	0.045	0.034

The above suggests that the non-squamous mean OS is greater than the squamous mean OS, with this difference ranging between 68 days under the Weibull and 98 days under the log logistic. Similarly there is a longer mean PFS for the non-squamous, the difference ranging between 12 days for the Weibull and 25 days for the log logistic. The larger absolute impacts for OS compared to PFS are consistent with the Kaplan Meier curves (Figure 27).

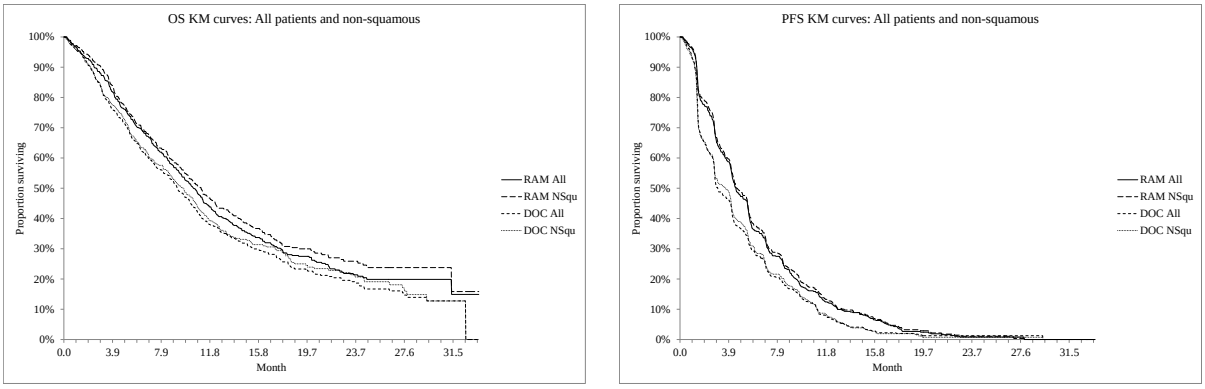


Figure 27: KM curves: All patients versus non-squamous

The above might suggest a slightly greater impact from histology upon OS within the ramucirumab + docetaxel arm than in the docetaxel arm. It is unclear whether estimating parameterised curves from the non-squamous subgroup data would have particularly affected results.

Non-squamous and adenocarcinoma patients

The comparison with nintedanib + docetaxel is based upon the non-squamous subgroup of the REVEL trial. Nintedanib + docetaxel has been approved by NICE for those with adenocarcinoma.

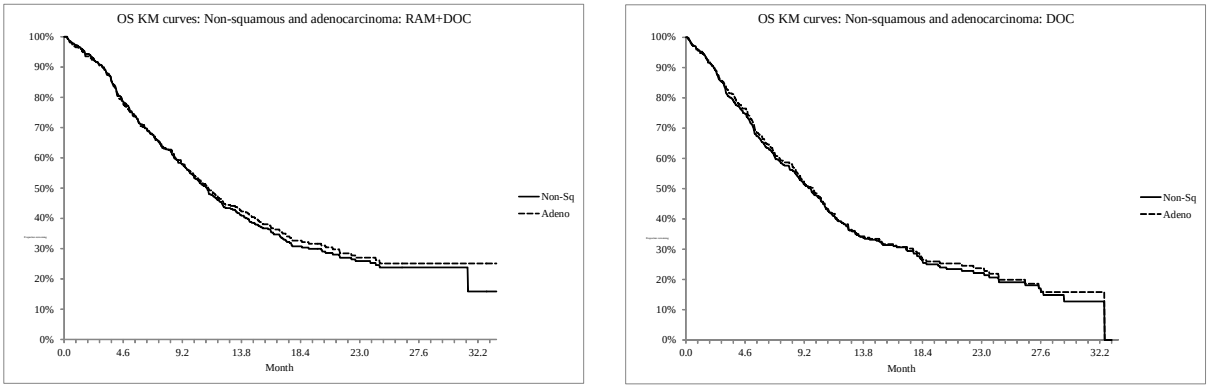


Figure 28: Kaplan Meier OS curves: Non-squamous and adenocarcinoma

The OS curves for the non-squamous and those with adenocarcinoma appear to be quite similar (Figure 28). In the ramucirumab + docetaxel arm they are virtually identical up to around the 10th month, after which the adenocarcinoma curve rises slightly above the non-squamous curve. In the docetaxel arm the adenocarcinoma curve is slightly above that of the non-squamous from an earlier point with a convergence around the 10th month and then another very slight divergence thereafter. Though not depicted in the above, the ratios between the numbers at risk remain very nearly constant until only small numbers remain at risk, meaning that the weight within the Kaplan Meier curves is distributed in much the same manner for the non-squamous and the adenocarcinoma. The differences between the curves seem slight on visual inspection.

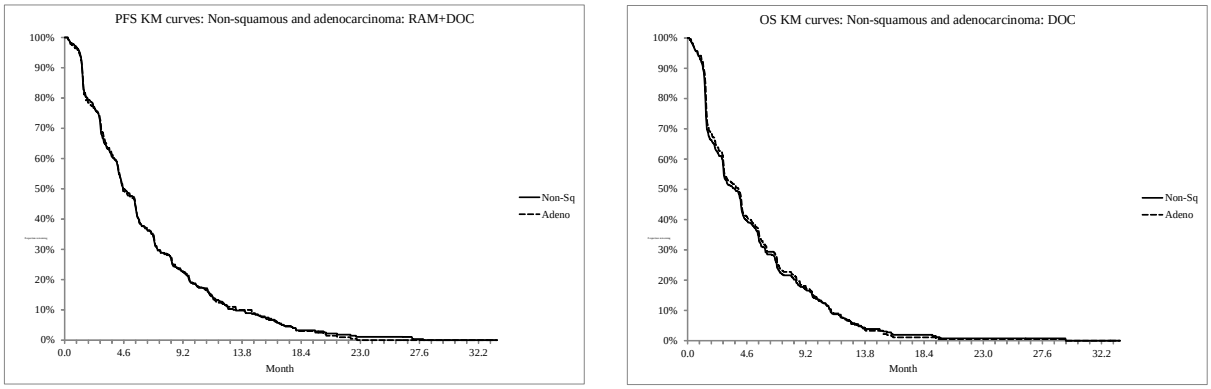


Figure 29: Kaplan Meier PFS curves: Non-squamous and adenocarcinoma

There is again a suggestion of a slight superiority for the adenocarcinoma subgroup compared to squamous subgroup, with this possibly being very marginally greater in the docetaxel arm (

Figure 29). As for the OS curves, the weight within the Kaplan Meier curves is distributed in much the same manner for the non-squamous and the adenocarcinoma. Much as for the OS curves, it is not obvious that estimates for the PFS gain from ramucirumab + docetaxel in the adenocarcinoma subgroup would be much different from that in the non-squamous subgroup.

Given the company cost effectiveness estimates for the comparison with nintedanib + docetaxel it is difficult to see the above having much impact upon the conclusion that committee is likely to draw from the modelling results.

Quality of life: PFS

The model assumes that the quality of life is the same in each arm while on treatment, aside from what are quite minor allowances for the different side effects profiles: a net worsening for ramucirumab + docetaxel compared to docetaxel of -0.0002 QALYs. The quality of life data supplied in table 24 of the submission could be read as suggesting a larger net impact. Note that the post end of treatment values have been appended to the graph below (Figure 30) as though occurring after cycle 16, which obviously does not correspond to the true timing of these values which will have been spread out throughout the cycles of REVEL.

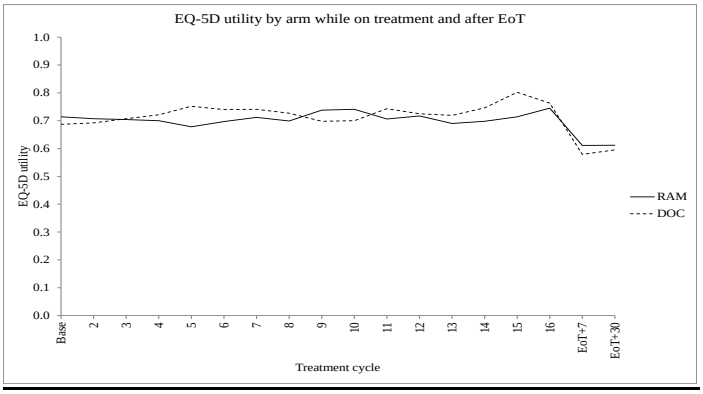


Figure 30: REVEL EQ-5D utilities by cycle

Despite the lower baseline mean value in the docetaxel arm of 0.687 compared to 0.715 for ramucirumab + docetaxel or a net difference at baseline of 0.028, the mean post baseline values for docetaxel appear to tend to be higher than those for ramucirumab + docetaxel. If the difference at baseline were simply added to the docetaxel mean values the docetaxel values would lie above those of ramucirumab + docetaxel by a reasonable margin with the exceptions of cycles 9 and 10.

Appendix 11 of the submission presents some analyses of the REVEL EQ-5D quality of life values which appear to be comparisons of the mean values and the mean changes from baseline (Table 71)

Table 71: REVEL EQ-5D analyses: Mean values and mean changes from baseline

	Ramucirumab + docetaxel				Docetaxel				
	N Pat.	N EQ5D	Mean	s.e.	N Pat.	N EQ5D	Mean	s.e.	
Mean values									p-values
Baseline	528	528	0.715	(0.010)	532	532	0.687	(0.011)	p=0.008*
PFS	587	3624	0.696	(0.004)	580	2970	0.717	(0.005)	p=0.031*
Response	114	291	0.724	(0.013)	67	177	0.782	(0.018)	p=0.161
Stable	316	720	0.706	(0.008)	292	628	0.719	(0.010)	p=0.017*
PPS	215	237	0.624	(0.019)	247	271	0.577	(0.022)	p=0.001*
Mean changes from baseline									p-values
PFS	493	2928	-0.058	(0.004)	489	2500	-0.020	(0.005)	p=0.463
Response	98	236	-0.056	(0.013)	58	152	0.011	(0.017)	p=0.560
Stable	266	584	-0.051	(0.009)	246	544	-0.015	(0.010)	p=0.079
PPS	187	209	-0.124	(0.019)	209	232	-0.109	(0.021)	p=0.019*

The mean values at baseline are statistically significantly different between the two arms with ramucirumab + docetaxel having a higher mean value at baseline. The mean values for PFS are also statistically significantly different from one another, only now the two arms have crossed over and the mean value for docetaxel is higher than that of ramucirumab + docetaxel. The mean changes from baseline among those in PFS are apparently not statistically significantly different between the arms despite the reported standard errors and the differences in the mean values. The ERG finds this surprising and cannot readily account for it.

The mean values for the changes from baseline among responders might suggest some difference between the arms and a worse experience in the ramucirumab + docetaxel arm but the standard errors are quite large and there is apparently no statistically significant difference between the arms. The picture is similar for those with stable disease with the mean values suggesting a greater worsening in the ramucirumab + docetaxel arm compared to the docetaxel arm, with this difference approaching statistical significance.

The ERG remains confused by the p-values for the mean PFS quality of life and the mean changes from baseline, given the mean baseline values.

The ERG is also confused by the large number of EQ-5D responses that enter the PFS calculations, but the very much smaller number of EQ-5D responses for the two PFS health states of response and stable disease. Unfortunately the ERG did not ask about this at clarification.

The company has confirmed at clarification that other than the data presented in the submission and appendix 11 of the submission no further analyses of the REVEL EQ-5D data are available.

In the light of the above the ERG has conducted a sensitivity analysis which applies the mean changes from baseline for PFS to the pooled mean baseline value of 0.701 to yield PFS quality of life estimates of 0.643 for ramucirumab + docetaxel and 0.681 for docetaxel.

Quality of life: PPS

The base case of the model assumes a constant quality of life for those who have progressed based upon the REVEL post end of treatment EQ-5D values. A sensitivity analysis that applies a QALY decrement to the proportion of patients modelled as dying in each cycle is applied. But as with one off terminal care costs this has little impact due to it in effect applying to all patients with only its timing differing between the arms.

Appendix 11 of the submission presents the mean quality of life for PPS as a function of the number of months prior to death (Table 72). The ERG interpretation of this is that these are the mean values for of the summary visit within 7 days of end of treatment and the follow-up visit at 30 days since end of treatment, banded by the time to patient death. The ERG has based the s.e. estimates on the s.d. estimates divided by the square root of the number reporting.

Table 72: REVEL EQ-5D analyses: Mean PPS values prior to death

Months before death	N	Mean	s.e.
<=1	59	0.442	(0.054)
>1-2	100	0.446	(0.036)
>2-3	89	0.419	(0.042)
>3-4	65	0.501	(0.040)
>4-5	61	0.600	(0.039)
>5-6	48	0.566	(0.040)

The above appears to support quality of life tending to decline among those with progressive disease during the last six months of life. The results of the company systematic literature review also provide support for an assumption of quality of life tending to be worse during subsequent lines of treatment and in particular for those having progressed after 3rd or 4th line treatment.

This may also suggest that applying the Chouaid et al (2013) quality of life decrements for initial and subsequent lines of therapy may be sensible as a sensitivity analysis, if not for the base case.

Subsequent treatments: Costs and QoL values

The model assumes that 30% of patients receive subsequent therapy with the remainder moving onto BSC. Subsequent therapy is assumed to endure for the remainder of the patient survival. The costs of these two health states are little different and there are no quality of life effects despite the company identifying the Chouaid et al (2013) paper as the most relevant within the literature and this supplying quality of life estimates for subsequent treatments' PFS and PPS health states.

Mean number of administrations and dose intensity: ramucirumab

The company applies a mean number of ramucirumab administrations of 6.1 for the all patient modelling and 6.3 for the non-squamous modelling. The company also applies subgroup specific dose intensity percentages of 92.9% for the all patient modelling and 94.5% for the non-squamous modelling. These are used to determine the timing of the ramucirumab dosing but have no impact upon the mean number of doses that are administered in the company model. As such they have little impact upon results, any impact being due to discounting which is minor.

Applying the mean number of docetaxel administrations that were observed during REVEL seems reasonable. ERG expert opinion is that due to accumulating toxicity the number of cycles of docetaxel will be limited.

It may be less reasonable to apply the number of ramucirumab administrations that were observed during REVEL if the modelling relies upon the parameterised PFS curves. ERG expert opinion is that patients will tend to continue to receive ramucirumab while remaining progression free. As a consequence it may be more reasonable to use the ramucirumab + docetaxel PFS curve to determine the number of ramucirumab administrations when the parameterised PFS curves are being used. This will be explored as a sensitivity analysis by the ERG.

Within the submission there is a lack of clarity around how the estimate for mean number of ramucirumab administrations and the estimate for the dose intensity of ramucirumab interact. At clarification the company has supplied the following data for the number of ramucirumab administrations during the REVEL trial (Table 73).

Table 73: Ramucirumab administrations by cycle

Cycle	RAM received	Cycle	RAM received
1	626	9	150
2	551	10	128
3	420	11	100
4	379	12	88
5	313	13	72
6	287	14	59
7	210	15	44
8	195	16	39

The above yields a total number of patients receiving ramucirumab across each of the three week cycles of 3,661. Given the 627 patients at baseline corresponds to an average of 5.84 administrations which is somewhat less than the 6.10 average of the submission, the latter corresponding with the value given in table JVBA12.1.1 of the CSR. The company notes that drug administrations could be administered 3 days either side of the planned 3 week time point and that doses might be delayed for up to 2 weeks due to toxicity. This might mean that some patients received more than one dose of ramucirumab during one three week cycle, but this alone seems unlikely to account for the discrepancy. The corresponding data for the number of patients receiving docetaxel during each cycle also appears to suggest mean values that are lower than those used in the model for the all patient modelling.

The data above corresponds with table JVBA14.3.1 of the CSR except that it specifies the numbers of patients experiencing at least 1, 2, 3 etc. administrations rather than it being the number of administrations per cycle. The apparent discrepancy may be due to this and a number of patients perhaps receiving more than 16 administrations.

Turning to the calculation of the drug utilisation percentage for ramucirumab, the company provides a worked example for patient 1000. This patient "*received 11 infusions*" with a dose in mg/kg as outlined in Table 74.

Table 74: Drug utilisation calculation: ramucirumab

Admin	mg/kg	Admin	mg/kg
1	10.00	7	10.40
2	9.91	8	10.29

3	10.23	9	10.47
4	10.25	10	10.70
5	10.18	11	10.85
6	10.09		
Cumulative dose			113.37
Mean dose per infusion			10.31

The mean dose per infusion over the 11 infusions was 10.31mg/kg. But due to dose delay these doses were spread out over 37 weeks rather than the 33 weeks. This results in a dose intensity per week of treatment of 10.31 * 37/33 = 91.7% for this patient.

The CSR in table JVBA 12.1.4 reports that in the ramucirumab + docetaxel arm [redacted] of patients experienced at least one dose delay and [redacted] of patients experienced at least one dose reduction. Tables JVBA14.1.19 and JVBA14.1.20 provide some data on the number of patients reducing their dose within the safety population. From this it appears that [redacted] patients reduced their dose once, [redacted] patients reduced their dose twice and [redacted] patients reduced their dose at least three times. But there does not appear to be a figure for the mean dose per administration.

The 94.6% dose intensity is not used to account for dose delays. This is separately accounted for by the 92.9% drug administration percentage as calculated from 6.10 administrations over 19.7 weeks. The dose intensity percentage is used to increase the patient weight that can be treated with a given number of vials and an assumed dose of 10mg/kg, or equivalently to assume that the mean dose per administration is 9.46mg/kg. In the opinion of the ERG this is incorrect and it should not be applied.

Removing the dose intensity percentage for ramucirumab increases the mean drug cost per ramucirumab administration at list prices from £3,733 to £3,931.

It might even be argued if patient 1000 is in any way representative that a drug utilisation percentage of more than 100% should be applied to ramucirumab. Similar considerations apply to the direct drug costs of docetaxel but as these are only around £36 per administration the ERG has not explored this further.

Mean number of vials per administration: ramucirumab

The company has supplied the distribution of patient weights in REVEL. ERG calculations suggest that applying these values rather than inferring them from means and standard errors with a floor put on the

minimum weight would reduce the average number of vials required per administration and so the ramucirumab drug costs by 0.77% or around £30 at list prices.

Drug dosing and half cycle correction

The number of doses of ramucirumab and docetaxel are calculated based upon the mean number of administrations that are reported. As a consequence, whether half cycle correction is applied or not within the model has no effect on these drug costs, other than some minor issues around discounting. The model does not apply half cycle correction and the ERG views this as the correct approach.

However, the model does apply half cycle correction to the direct drug costs of erlotinib and nintedanib. If the cycle length were in line with the pack size of erlotinib and nintedanib, the ERG thinks that the correct approach would be not to apply a half cycle correction. But there is the additional difficulty that the cycle length of 3 weeks is not in line with the 30 day pack size of erlotinib and nintedanib. Despite this the ERG thinks that the most reasonable approach is not to apply a half cycle correction to the erlotinib and nintedanib drug costs.

Administration costs

The NHS reference costs for 2013-14 outline the following costs for chemotherapy administered in the outpatient setting (Table 75).

Table 75: Chemotherapy outpatient administration reference costs 2013-14

Code	Currency description	Reference cost guidance	Cost
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance	30 minutes nurse time and 30 to 60 minutes chair time for complete cycle	£165
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	60 minutes nurse time and up to 2 hours chair time for complete cycle	£219
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at first Attendance	60 minutes nurse time and more than two hours chair time	£266
SB15Z	Deliver subsequent elements of a chemotherapy cycle	..	£314
SB97Z	Same Day Chemotherapy Admission or Attendance	..	£0

The company model applies the first attendance costs, but ignores the SB15Z cost for the delivery of subsequent cycles of chemotherapy at £314. The ERG has some sympathy with this in that it has never been entirely comfortable with subsequent cycles having the same cost regardless of their complexity. But for completeness the ERG feels that a sensitivity analysis that applies the SB15Z cost to subsequent cycles should be applied.

Turning to the administration costs for erlotinib and nintedanib it should be borne in mind that patients in all arms are modelled as having an outpatient visit every three week cycle. Administration costs for orally administered drugs are often not explicitly addressed within NICE assessments in part due to the frequency of outpatient monitoring that is assumed for drugs being assessed by NICE. This is something of a simplification and there will be pharmacy as well as other administration costs. But the reference costs for chemotherapy administration also do not include pharmacy costs. While dated, the 2005 TA93 drew pharmacy costs of £23 per simple IV infusion and £38 per complex IV infusion from expert opinion from the Christie Hospital Manchester. In current prices these would be around £29 and £48 respectively.

The FAD for the nintedanib STA notes that no administration cost was included for nintedanib. From the FAD it appears that the assessment committee did not question this and the ERG cannot find any amendment to this in the ERG report for the nintedanib STA.

In the light of this, while imperfect, the ERG prefers to exclude the administration costs for erlotinib and for nintedanib, though we present a sensitivity analysis that includes them.

PPS active treatment costs

The company response at clarification notes that vinorelbine is administered 3 times per cycle by IV, but the company costing only applied the £219 administration cost once per cycle. Applying three IV administration costs and assuming an IV administration cost of £314 results in an average annual cost of £18,725 rather than the £8,240 of the submission.

As already noted PPS active treatment includes erlotinib. As a consequence, the erlotinib PAS inclusive cost is: £1,063.52*(25/30) + £1,142.07 *(5/30) * (1- PAS_Erlotinib).

The ERG may have misunderstood the company arguments around these costs, and as a consequence only revises these costs in a sensitivity analysis.

SAE costs

The FAD for the nintedanib STA states that the ERG questioned the unit cost for febrile neutropenia doe to it being substantially less than work undertaken by the DSU and the value used in the review of TA162 and TA175. The ERG undertook a sensitivity analysis of applying a value per event of £5,240 which with an assumption of 1.4 events per patients increased this cost to £7,352. The nintedanib FAD notes that experts suggested that the original company estimate may have been reasonable and in the light of results not being particularly sensitive to this committee did not pursue the matter further.

In the light of this the ERG will undertake a sensitivity analysis that applies a £7,352 cost for febrile neutropenia.

Other costs

No other costs are included in the modelling. A longer survival might be anticipated to result in additional inpatient and outpatient costs. But the modelled OS and PFS is relatively short and the OS and PFS gains are not particularly large for the comparison of ramucirumab + docetaxel with docetaxel. Inclusion of other costs might further worsen this cost effectiveness estimate but they seem unlikely to be key drivers. There is little to no OS difference or PFS difference for the comparison of ramucirumab + docetaxel with nintedanib + docetaxel and as a consequence including other costs is unlikely to affect results.

Discounting

The discount factor for a given cycle is given as 1 / (1.035) ^ (time in weeks / n cycles per year). Given the three week cycle length the number of cycles per year is 17.4. For instance, by the 17th 3 week cycle or week 51; i.e. virtually the one year point, the discount factor for this cycle is 1 / (1.035) ^ (51/17.4) = 0.904. This is too great a degree of discounting. Given the annual discount rate of 3.5% this discount factor for the 17th cycle or week 51 should be approximately 1 / 1.035 = 0.966.

This discounting error compounds exponentially such that by say the 87th cycle; i.e. the five year point, the discount factor for this cycle is 1 / (1.035) ^ (51/17.4) = 0.597 when it should be 1 / (1.035) ^ 5 = 0.842.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

In the light of the NICE recommendation for erlotinib, the ERG has not considered it or the EGFR negative modelling in what follows.

The ERG has revised the company model to:

- Correct the errors in discounting[5].
- Apply the same patient characteristics for the PFS curves as for the OS curves[6].
- Remove half cycle correction from nintedanib drug costs[7].
- Apply a 100% drug utilisation percentage for ramucirumab[8].
- Exclude the nintedanib drug administration costs[9].

Sensitivity analyses.

- SA00: Apply the unadjusted rather than the multivariate adjusted OS and PFS curves for the all patient modelling.
- SA01: Apply the Weibull curves for OS.
- SA02: Not taper the hazard ratio for OS.
- SA03: For the non-squamous modelling for the comparison with nintedanib + docetaxel applying the company ramucirumab + docetaxel all patient OS hazard ratio of 0.86 and all patients PFS hazard ratio of 0.76 to the docetaxel OS and PFS curves for consistency of approach with nintedanib + docetaxel.
- SA04: Apply the ERG linear trends OS curves, without tapering.
- SA05: Apply the ERG linear trends OS curves, without tapering, and the KM PFS curves.
- SA06: Reinstate the ramucirumab drug utilisation percentage.
- SA07: Assume that the number of ramucirumab administrations is conditioned by the PFS curve with there being no maximum number of administrations while in PFS[10].
- SA08: Reduce the drug utilisation of nintedanib by 2.7% to reflect the mean number of treatment durations reported in the company submission for the nintedanib STA[11].

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[5] Implemented in the markov worksheets cells AF36:AG557, AJ36:AK557, AM36:AM557 and usually BA36:BJ557 and CQ36:CR557 but for the erlotinib markov sheet AX36:BE557 and CL36:CM557 by replacing the reference to xlCyclesPerYear by (365.25/7).

[6] Implemented in the *PSA_sampling* worksheet by setting cells BW264:BW265=BW39:BW40, BW266:BW267=BW37:BW38, BW268:BW269=BW41:BW42, BW270:BS271=BW45:BW46 and BW272:BW277=BW49:BW54 and BW316:BW329 equal to BW264:BW277

[7] Implemented in the erlotinib and nintedanib markov worksheets by setting cell AO35=V35*H$15 and likewise for AO36:AO557

[8] Implemented in the *Model_mechanics* worksheet by setting cell M163=10

[9] Implemented in the erlotinib and nintedanib markov worksheets by setting cell F15=0

[10] Implemented in the ramucirumab markov worksheet by setting cell G15=9999

[11] Implemented in the *Model_mechanics* worksheet by multiplying cell M204 by 97.3%.

- SA09: Assume no Japanese or far eastern patients within the company adjusted curves[12].
- SA10: Assume a PFS quality of life of 0.643 for ramucirumab + docetaxel and of 0.701 for docetaxel, while also removing the adverse event quality of life decrements[13].
- SA11: Assume a PFS quality of life of 0.74 and a PPS quality of life of 0.46[14] as drawn from Chouaid et al (2013).
- SA12: Apply the SB15Z £314 cost for subsequent infusions regardless of regime[15].
- SA13: Include the administration costs for nintedanib.
- SA14: Apply a £7,352 cost for febrile neutropenia[16].
- SA15: Revise the costs of PPS active treatment to apply three IV administrations per 3 week cycle.[17]

Scenario analyses:

- Sc01: Apply the ERG linear trends OS curves, without tapering, and the ERG PFS curves of the squamous subgroup while also setting the model subgroup to the squamous.
- Sc02: Apply the ERG linear trends OS curves, without tapering, and the ERG PFS curves of the adenocarcinoma subgroup while also setting the model subgroup to the non-squamous due to the patient characteristics of the adenocarcinoma subgroup not being available.

The ERG linear trends OS curves suggest the following mean month's survival (Table 76).

Table 76: ERG linear trends OS curves mean survival estimates (mths)

	RAM+DOC	DOC	Net
All	16.6	14.4	2.2
Non-Squamous	19.2	15.3	3.9
Adenocarcinoma	19.0	16.4	2.6

[12] Implemented in the *PSA_sampling* worksheet by setting BW43=0 and BW44=1
[13] Implemented in the ramucirumab and docetaxel markov worksheets by setting cell P14=0.643 and P14=0.701 respectively, and cells U14:U24=0 in both worksheets.
[14] Implemented in the *Model_mechanics* worksheet by setting cell M254=0.74 and M255=0.46.
[15] Implemented in the ramucirumab, docetaxel and nintedanib markov worksheets by conditioning cells AT36:AT557, AT36:AT557 and AU36:AU557 respectively by £314 rather than by the administration costs in cells F15, F15 and F16 respectively.
[16] Implemented in the *Model_Mechanics* worksheet by setting cell M212=7352
[17] Implemented in the *Model_Mechanics* worksheet by setting cell M241= (0.25/0.3)*20.17*2+(0.25/0.3)*(CEILING(30*'Model Mechanics'!$M$159/10, 1)*3*4.51*(1-'Model Mechanics'!$M$152)+CEILING(30*'Model Mechanics'!$M$155/10,1)*3*4.51*'Model Mechanics'!$M$152)+(0.25/0.3)*O241*3+(0.05/0.3)*'Markov - Erlotinib'!$E$15 where cell O241 contains the IV administration cost.

Squamous	12.3	11.2	1.1

DOC: docetaxel; RAM: ramucirumab

The ERG application of the ERG derived curves and the application of hazard ratios and tapering of hazard ratios where appropriate has required an additional worksheet to be inserted into the company model with these workings. For these sensitivity analyses the relevant values are copied into cells H35:H557 and L35:L557 of the Markov worksheets for ramucirumab + docetaxel, docetaxel and nintedanib + docetaxel. This is quite a large model revision and while the ERG has attempted to cross check its implementation, given timelines and the speed with which this has been done, the ERG does not discount the possibility of slight errors. Therefore, the ERG is happy to provide a copy of the revised company model, with comparator PASs redacted to the company upon request for error checking.

The ERG has undertaken a sensitivity analysis that applies the company all patient hazard ratios for OS and PFS to the docetaxel non-squamous curves in order to put the comparison with nintedanib + docetaxel on a more consistent basis; i.e. both treatment effects being derived by applying hazard ratios to the docetaxel hazards. This may to some extent still be mixing apples and oranges, as only the all patient hazard ratios are available for ramucirumab + docetaxel in tables 30 and 31 of the CS, though the ERG is unclear as to whether this might be a typographical error. But the hazard ratios of 0.99 for OS and 1.01 for PFS for nintedanib + docetaxel compared to ramucirumab + docetaxel among both the non-squamous patients EGFR negative subgroup and the non-squamous patients EGFR positive subgroup provide some reassurance around these sensitivity analyses. There are also the hazard ratios of tables 33 and 34 which report hazard ratios for the adenocarcinoma subgroup of unity for both OS and PFS for nintedanib + docetaxel compared to ramucirumab + docetaxel.

To model the squamous subgroup, the ERG has also calculated the number of ramucirumab and docetaxel administrations as 5.7 and 5.4 in the ramucirumab + docetaxel arm, and the number of docetaxel administrations as 4.6 in the docetaxel arm[18]. This appears to approximately align the weighted average of the squamous and the non-squamous drug administrations with the average among all patients.

The ERG implementation of the PASs is implemented by multiplying cells M173, M175 and M176 of the *Model_mechanics* worksheet respectively by (1-ERG_PAS_RAM), (1-ERG_PAS_ERL) and (1-ERG_PAS_NIN) where the ERG_PAS_ variables are the respective PAS percentages.

[18] Implemented in the *Model_mechanics* worksheet by setting M190=5.7, M191=5.4 and M192=4.6.

Given the lack of a PAS for ramucirumab and the cost effectiveness estimates, there are a number of elements within the modelling which currently have little impact upon the cost effectiveness results; e.g. administration costs for nintedanib. The choice of curves does have an impact upon the cost effectiveness estimates but not to an extent that is likely to affect the recommendation of the committee. If a PAS sufficient to affect the likely recommendation of the committee is proposed, these elements may require further consideration.

Results: All patients: Base case

The ERG revisions to the company base case result in the following estimates (Table 77).

Table 77: ERG revised base case: All patients

	RAM+DOC	DOC
PFS undisc. LY	0.509	0.385
PPS undisc. LY	1.065	0.934
OS Total undisc. LY	1.574	1.319
net LY vs		0.255
PFS QALY	0.354	0.268
PPS QALY	0.573	0.509
AE QALYs	-0.003	-0.003
Total QALYs	0.924	0.775
net QALY vs		0.150
PFS Tx Drug	£23,822	..
PFS Doc Drug	£196	£178
PFS Premed	£206	£150
PFS admin	£1,325	£803
PFS AEs	£807	£656
PFS monitoring	£1,677	£1,272
PPS Tx and BSC	£7,369	£6,543
PPS monitoring	£3,206	£2,846
Total Cost	£38,609	£12,448
net cost vs.		£26,161
ICER		£175k

The ERG revisions improve the base case cost effectiveness estimate from the £195k per QALY of the company to £175k per QALY.

For the all patient probabilistic modelling the central cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel is £175k per QALY, which is in line with the £175k per QALY of the deterministic modelling. The CEAF follows the docetaxel curve as outlined in Figure 31. Up to a willingness to pay of £100k per QALY there is effectively no probability of ramucirumab + docetaxel being cost effective.

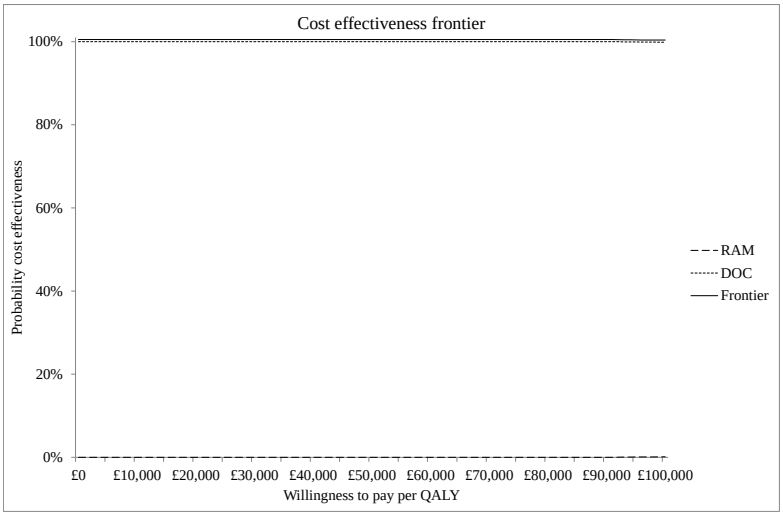

Figure 31: ERG revised base case: CEAF: All patients

Results: All patients: Sensitivity analyses

The univariate sensitivity analyses result in the following estimates (Table 78).

Table 78: ERG univariate sensitivity analyses: All patients

	RAM+DOC vs DOC		
	Δ Cost	ΔQALY	ICER
Base case	£26,161	0.150	£175k
SA00: Unadjusted curves	£26,024	0.127	£204k
SA01: Weibull OS	£25,573	0.118	£217k
SA02: No OS taper	£26,224	0.153	£171k
SA03: HRs for RAM+DOC	..	..	..
SA04: ERG LT OS	£26,124	0.148	£177k
SA05: ERG LT OS and KM PFS	£26,310	0.144	£182k
SA06: RAM drug util %	£24,961	0.150	£167k
SA07: No max RAM admins	£36,936	0.150	£247k
SA08: NIN drug util -2.7%	..	..	..

SA09: No Jap/Far East	£26,103	0.146	£178k
SA10: REVEL PFS QoL by arm	£26,161	0.120	£218k
SA11: Chouaid QoL	£26,161	0.139	£189k
SA12: Subs IV admin £314	£26,111	0.150	£175k
SA13: NIN admin cost	..	..	..
SA14: Feb neutr £7,352	£26,474	0.150	£177k
SA15: PPS weekly IV cost	£26,365	0.150	£176k

DOC: docetaxel; RAM: ramucirumab

None of the sensitivity analyses result in cost effectiveness estimates that fall below the usual NICE thresholds, including if end of life considerations are thought to apply.

The unadjusted curves somewhat reduce the net gain to 0.127 QALYs which worsens the cost effectiveness estimate to £204k. Applying the Weibull OS curve worsens the cost effectiveness estimate quite considerably to £217k per QALY, while applying the ERG linear trends OS curves and the KM PFS curves improves it to around £160k per QALY.

Applying the ramucirumab drug utilisation percentage also improves the cost effectiveness estimate to £167k per QALY, due to the net costs falling from £26,161 to £24,961.

If the number of ramucirumab administrations is based upon the parameterised PFS curve rather than the number observed during the REVEL trial, the net costs worsen quite considerable to £36,936 and the cost effectiveness estimate increases proportionately to £247k. But for this sensitivity analysis, the completeness of the REVEL KM PFS curve and the closeness with which the number at risk tracked it should be borne in mind. The focus should perhaps be less upon costs and more upon whether the balance between survival spent in PFS and in PPS appears reasonable, given the parameterised curves, and the implications of this for the overall QALY gains.

If the treatment specific PFS QoL values inferred by the ERG from appendix 11 of the submission apply the net gain falls from 0.150 QALYs to 0.120 QALYs and the cost effectiveness worsens to £218k per QALY.

The other sensitivity analyses are of limited interest, other than demonstrating a general lack of sensitivity of results to these analyses.

Results: Non-squamous patients: Base case

The ERG revisions to the company base case result in the following estimates (Table 79).

Table 79: ERG revised base case: Non-squamous

	RAM+DOC	DOC	NIN+DOC
PFS undisc. LY	0.524	0.399	0.517
PPS undisc. LY	1.155	0.991	1.149
OS Total undisc. LY	1.679	1.390	1.666
net LY vs		0.289	0.013
PFS QALY	0.364	0.278	0.358
PPS QALY	0.621	0.539	0.616
AE QALYs	-0.003	-0.003	-0.001
Total QALYs	0.981	0.814	0.973
net QALY vs		0.167	0.008
PFS Tx Drug	£24,600	..	£12,813
PFS Doc Drug	£200	£185	£182
PFS Premed	£212	£156	£277
PFS admin	£1,368	£836	£785
PFS AEs	£807	£656	£346
PFS monitoring	£1,725	£1,318	£1,699
PPS Tx and BSC	£7,977	£6,927	£7,916
PPS monitoring	£3,470	£3,014	£3,444
Total Cost	£40,359	£13,092	£27,461
net cost vs.		£27,268	£12,899
ICER		£163k	£1.6mn

DOC: docetaxel; NIN: nintedanib; RAM: ramucirumab

The ERG revisions improve the cost effectiveness of ramucirumab + docetaxel compared to docetaxel from the £182k per QALY of the company to £163k per QALY. But the cost effectiveness compared to nintedanib + docetaxel worsens from £1.1mn per QALY to £1.6mn per QALY.

For the probabilistic modelling, the central cost effectiveness estimates for ramucirumab + docetaxel are £162k per QALY compared to docetaxel, and clinical equivalence at the third decimal place but an additional cost of £12,499 compared to nintedanib + docetaxel. The probabilistic estimate for the comparison with docetaxel is in line with the deterministic estimate. The probabilistic estimate for the

comparison with nintedanib + docetaxel is not in line with the deterministic estimate, but this is probably due to the very small estimated gains making the ICER unstable.

Up to a willingness to pay of around £50k per QALY only docetaxel has any probability of being cost effective (Figure 32). Thereafter nintedanib plus docetaxel starts to have some probability of being cost effective until at a willingness to pay of around £92k per QALY nintedanib + docetaxel starts to have a greater probability of being cost effective than docetaxel. Up to a willingness to pay of £100k per QALY there is effectively no probability of ramucirumab + docetaxel being cost effective.

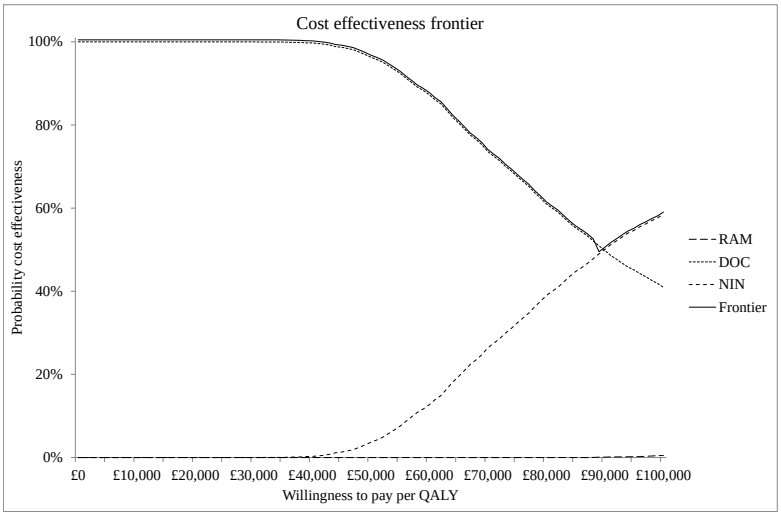

Figure 32: ERG revised base case: CEAF: Non-squamous

Results: Non-squamous patients: Sensitivity analyses

The univariate sensitivity analyses are as Table 80 below.

Table 80: ERG revised model: Non-squamous: Sensitivity analyses

	RAM+DOC vs DOC			RAM+DOC vs NIN+DOC		
	Δ Cost	ΔQALY	ICER	Δ Cost	ΔQALY	ICER
Base case	£27,268	0.167	£163k	£12,899	0.008	£1.6mn
SA01: Weibull OS	£26,808	0.142	£188k	£13,563	0.044	£307k
SA02: No OS taper	£27,350	0.172	£159k	£12,300	-0.024	Dom'td
SA03: HRs for RAM+DOC	..	..	..	£12,380	-0.020	Dom'td
SA04: ERG LT OS	£28,808	0.251	£114k	..	..	..
SA05: ERG LT OS and KM PFS	£29,012	0.248	£117k	..	..	..
SA06: RAM drug util %	£26,029	0.167	£156k	£11,660	0.008	£1.4mn

SA07: No max RAM admins	£38,743	0.167	£232k	£24,374	0.008	£3.0mn
SA08: NIN drug util -2.7%	..	..	..	£13,252	0.008	£1.6mn
SA09: No Jap/Far East	£27,210	0.164	£166k	£12,873	0.007	£1.9mn
SA10: REVEL PFS QoL by arm	£27,268	0.137	£199k	..	..	..
SA11: Chouaid QoL	£27,268	0.152	£179k	£12,899	0.007	£1.8mn
SA12: Subs IV admin £314	£27,219	0.167	£163k	£12,843	0.008	£1.6mn
SA13: NIN admin cost	..	..	..	£12,062	0.008	£1.4mn
SA14: Feb neutr £7,352	£27,580	0.167	£165k	£13,372	0.008	£1.6mn
SA15: PPS weekly IV cost	£27,527	0.167	£165k	£12,914	0.008	£1.6mn

DOC: docetaxel; NIN: nintedanib; RAM: ramucirumab

For the comparison of ramucirumab + docetaxel with docetaxel none of the sensitivity analyses result in cost effectiveness estimates that fall anywhere close to the usual NICE thresholds, even if end of life considerations apply.

The Weibull OS curves slightly reduce the net gains and cause the cost effectiveness estimate to worsen to £188k per QALY.

The ERG linear trend OS curves increase the anticipated overall survival gain, causing the patient gain to increase from 0.167 QALYs to 0.251 QALYs. This improves the cost effectiveness estimate to £114k per QALY.

As would be anticipated, assuming that patients continue with ramucirumab treatment while remaining progression free increases the net cost to £38,743 which worsens the cost effectiveness estimate to £232k per QALY.

Again, as would be anticipated applying the treatment specific PFS QoL values as may be suggested by appendix 11 of the submission reduces the gain to 0.137 QALYs with a proportionate increase in the cost effectiveness estimate to £199k per QALY.

For the comparison of ramucirumab + docetaxel with nintedanib + docetaxel none of the sensitivity analyses result in cost effectiveness estimates that fall anywhere close to the usual NICE thresholds, even if end of life considerations apply. In general both treatments are estimated to be of similar effectiveness, but ramucirumab + docetaxel is estimated to result in total costs that are around £12-13,000 higher than

those of nintedanib + docetaxel: around a 50% increase in total costs and a 90% increase in direct drug costs.

The application of the Weibull OS curve tends to increase the net benefit associated with ramucirumab + docetaxel, but it should be remembered that this is still in the context of a tapering of hazard ratios after the 33rd month. The anticipated gain increases from 0.008 QALYs to 0.044 QALYs causing the cost effectiveness estimate to fall to £307k per QALY.

Removing the tapering from the OS hazard ratio and applying the hazard ratios for ramucirumab + docetaxel both cause nintedanib + docetaxel to come to dominate ramucirumab + docetaxel.

Assuming that patients continue with ramucirumab treatment while remaining progression free increases the net cost to £24,374, worsening the cost effectiveness estimate to £3.0mn per QALY.

The other sensitivity analyses are of limited interest, other than demonstrating a general lack of sensitivity of results to these analyses.

Scenario analyses

Applying the ERG linear trends OS modelling among the squamous results in a net cost estimate of £24,528 and a net gain of 0.144 QALYs. This results in a cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel of £167k per QALY, as compared with £177k per QALY for the all patient modelling. The slight improvement in the cost effectiveness estimate arises from the reduction in the net drug costs due to the reduced number of ramucirumab administrations being slightly greater than the fall in net QALYs. Further applying the KM PFS curves results in a cost effectiveness estimates of £172k per QALY as compared to £182k per QALY for the all patient modelling.

Applying the ERG linear trends OS modelling among the adenocarcinoma subgroup results in a cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel of £128k per QALY, as compared with £114k per QALY for the non-squamous modelling. Further applying the KM PFS curves results in a cost effectiveness estimates of £131k per QALY as compared to £117k per QALY for the non-squamous modelling.

5.5 Conclusions of the cost effectiveness section

A number of the comparators that were in the scope have not been included in the company submission. In the light of the NICE recommendation for erlotinib the company also argues that it should not be considered a relevant comparator for the EGFR negative population.

The company modelling appears to present reasonably unbiased estimates with the possible exceptions of:

- The drug utilisation percentage applied to ramucirumab.
- The drug utilisation percentage applied to nintedanib.
- The quality of life values for PFS perhaps not reflecting the REVEL EQ-5D analyses presented in appendix 11 of the submission.
- The quality of life value for PPS perhaps being too high, at least for the period preceding death.
- Not exploring the separate fitting of the parameterised curves to the arms of the REVEL trial and to the subgroups of the REVEL trial.
- The balance of the survival gains typically being broadly equal between that in progression free survival and that in post progression survival.
- Whether the duration of a month within REVEL was $1/12^{th}$ of a year or 28 days.
- The application of discounting.

A PAS may alter the conclusions that would be drawn from the current cost effectiveness modelling since the cost effectiveness estimates may become sensitive to a number of inputs. Further consideration as to their most reasonable values might then be required.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has made a number of revisions to the company base case. The overall impact of these is to tend to improve the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel in the all patient modelling, but to worsen it for ramucirumab + docetaxel compared to nintedanib + docetaxel in the non-squamous patient modelling. The full disaggregate results of this modelling are presented in section 5.4 above.

Briefly summarising these, for the comparison of ramucirumab + docetaxel with docetaxel across the all patients a net cost of £26,161 is associated with a net gain of 0.150 QALYs resulting in a cost effectiveness estimate of £175k per QALY. Central probabilistic estimates are in line with this and there is no probability of ramucirumab + docetaxel being cost effective for willingness to pay values up to £100k per QALY.

In the all patient modelling, the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel shows some sensitivity to:

- The use of the unadjusted company curves worsens it to £204k per QALY
- Applying the Weibull rather than the log logistic for OS worsens it to £217k per QALY
- Applying the KM PFS curve rather than the parameterised curve worsens it to around £182k per QALY
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £167k per QALY
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £247k per QALY.
- Revising the REVEL PFS QoL values to be treatment specific as might be implied by appendix 11 of the company submission worsens it to £218k per QALY

The scenario analysis of applying the ERG linear trends curves to the squamous subgroup results in a cost effectiveness estimate for the squamous subgroup that is approximately £10k per QALY better than the corresponding estimate for all patients. The smaller net patient gain is more than offset by a reduction in the net costs. But it should be stressed that the reduction in net costs arises from an ERG estimate of reduced drug use among the squamous subgroup, and that this estimate has not been confirmed with the company.

For the comparison of ramucirumab + docetaxel with docetaxel in the non-squamous population the revised ERG base case results in net costs of £27,268 and a net gain of 0.167 QALYs and so a cost effectiveness estimate of £163k. The comparison with nintedanib + docetaxel has net costs of £12,899 and net gains of 0.008 QALYs and a cost effectiveness estimate of £1.6mn. Probabilistic modelling suggests that there is no probability of ramucirumab being cost effective for willingness to pay values up to £100k per QALY.

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS which worsens it to £188k per QALY
- Applying the ERG linear trends OS curves improves it to £114k per QALY.
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £156k per QALY
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £232k per QALY.
- Revising the REVEL PFS QoL values to be treatment specific as might be implied by appendix 11 of the company submission worsens it to £199k per QALY

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to nintedanib + docetaxel typically suggests small QALY gains or losses which render the cost effectiveness estimate unstable. The base case net cost estimate of £12,899 shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS worsens it to £13,563
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £11,660
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £24,374
- Assuming a febrile neutropenia cost of £7,352 worsens it to £13,372

Not tapering the OS hazard ratio and applying the company hazard ratio for ramucirumab + docetaxel both cause the model to estimate that nintedanib + docetaxel provides small patient gains and so dominates nintedanib + docetaxel.

The scenario analysis of applying the ERG linear trends curves to the adenocarcinoma subgroup results in a cost effectiveness estimate for the adenocarcinoma subgroup that is approximately £14k per QALY worse than the corresponding estimate for the non-squamous subgroup. Within this the ERG retained the drug use estimates for the non-squamous subgroup.

7 END OF LIFE

The CS states that it would be appropriate to consider the end of life criteria in the appraisal of ramucirumab. The ERG agrees that ramucirumab is indicated for patients with a life expectancy less than 24 months (Section 2). As discussed in Section 2.2, the number of people with NSCLC and eligible for ramucirumab is thought to be approximately 1200.

The CS states that ramucirumab gives an extension in overall survival in the economic model of 3.06 months in the all patient group, compared with docetaxel, and similar overall survival to nintedanib which has previously met the end of life criteria. The ERG's analyses suggest there may not be an extension to life of at least an additional 3 months, compared with current NHS treatment. As outlined in the clinical effectiveness section the overall survival estimates from the various possible sources are summarised in Table 81 (see also Table 27 for the values that underlie the net gains).

Table 81: Overall undiscounted survival estimates and gain¶: RAM + DOC vs DOC

Patient group	MV ADJUSTED LL	Linear trend ¥	Separate LL to each arm ¥
All patients	3.06 Φ	2.2	2.2
Non-squamous	3.6 §	3.9	2.6
Squamous	2.2 §	1.1	2.0
adenocarcinoma	NM	2.6	3.6
¶ results apply for a 15 year time horizon. LL: log logistic models; MV: multivariate; NM: no multivariate model was supplied in the CS. Φ From CS table 45. § not reported in the CS, estimates based on ERG analysis of Kaplan Meier data supplied by the company. ¥ estimates based on ERG analysis of Kaplan Meier data supplied by the company.			

8 INNOVATION

Ramucirumab is a monoclonal antibody that specifically binds VEGF receptor 2 (VEGFR-2) which is a mediator of VEGF induced angiogenesis. Other existing therapies have a neutralizing action on the VEGF pathway such as bevacizumab which binds to VEGF and thereby inhibits the binding of VEGF to its

receptors VEGFR-1 and VEGFR-2 (Bevacizumab is licensed for first line NSCLCs but is not recommended by NICE in this indication). Like bevacizumab, ramucirumab exerts its antitumoral effect in synergy with conventional cytotoxic agents but is not indicated as single agent. This differs from the emerging class of immunotherapy drugs, like nivolumab licensed as single agent in NSCLCs, whose mechanism of action consists of increasing the ability of the immune system to kill cancer cells. On CS page 25, the company states that ramucirumab offers an innovation as it is a new second-line option that brings a statistically significant improvement in response rate, progression-free survival and overall survival. While this is true, the magnitude of clinical benefit remains modest in regard to the median OS which is improved by 1.4 months (10.5 months vs 9.1 months) compared to docetaxel alone.

9 OVERALL CONCLUSIONS

9.1 Clinical effectiveness evidence

The ERG considered that the evidence presented in the CS meets the decision problem but does not meet the NICE scope as a potentially relevant comparator, nivolumab in squamous NSCLC was excluded. The systematic review presented in the CS was of reasonable quality and the presentation of evidence from the pivotal RCT comparing ramucirumab + docetaxel with placebo + docetaxel was accurate. This trial showed overall survival, progression-free survival and response rates were improved with the addition of ramucirumab. Adverse events were reported in both groups, a higher proportion of the ramucirumab + docetaxel participants experienced adverse events of Grade 3 or more. With only one main comparative study of ramucirumab, the assessment of the treatment effects of ramucirumab compared with other comparators relied on indirect comparisons via a NMA. There are a number of areas of uncertainty with the NMA which lead to the ERG to recommend the results be interpreted with caution. Results suggest that ramucirumab is similar in efficacy to nintedanib.

9.2 Cost-effectiveness evidence

The main areas of debate and uncertainty between the company and the ERG that affect the cost effectiveness estimates are:

- The drug utilisation percentage to apply to ramucirumab.
- The drug utilisation percentage to apply to nintedanib.
- The quality of life values for PFS and whether these reflect the REVEL EQ-5D data.

- The quality of life value for PPS perhaps being too high, and whether it would be maintained at a high level indefinitely.
- Whether separate curves should have been fitted to the arms and the subgroups of REVEL and if so what form these should have taken.
- Whether it is reasonable to expect the survival gains from ramucirumab + docetaxel to be roughly equally balanced between pre and post progression and if not what this implies for the curves applied within the model.
- Whether the duration of a month within REVEL was 1/12th of a year or 28 days.
- Discounting errors.

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11 APPENDICES

Appendix 1: Erlotinib comparator

Subsequent to the submission from the company NICE produced guidance on erlotinib in second-line treatment settings. The use of erlotinib is restricted to a small population who have delayed confirmation that their tumour is EGFR positive or are of unknown mutation status and who received non-targeted first-line chemotherapy. The ERG are unaware of any robust evidence in this small population. The CS present data in the submission for a comparison with erlotinib in a EGFR-negative population and at clarification confirmed that this was not an appropriate comparator. The ERG has summarised the data from this study including the outputs of the CS NMA for completeness. The ERG has also identified a study in EGFR-positive populations and estimates for overall survival and progression free survival are presented.

Garassino 2013[19] undertook a RCT of erlotinib in an EGFR-negative population. In the erlotinib study there were some baseline imbalances between arms which the study authors state were due to chance as confirmed by interaction analyses. The characteristics that appear to be unbalanced were histology (% squamous and adenocarcinoma), smoking history and previous best response to first-line treatment (see Table 82) The participants in the erlotinib trial were slightly older (67 years) than those in the ramucirumab and nintedanib studies (approximately 61 years). The proportion with an ECOG performance status of ≥1 was lower in the erlotinib trial.

Table 82: Baseline characteristics of the erlotinib RCT

Characteristic n (%) unless stated	**ERL (n=109)**	**DOC (n=110)**
Age, years (median, range)	66 (40-81)	67 (35-83)
Male sex	77 (71)	73 (66)
Ethnicity		
White	108 (99)	109 (99)
Asian	1 (1)	1 (1)
Black	0	0
ECOG PS		
0	52 (48)	53 (48)
1	48 (44)	50 (45)
Smoking history		
Current and former	90 (83)	80 (73)
Never	19 (17)	30 (27)

Unknown	0	0
Clinical stage at inclusion		
Stage IIIB	109 (100)	110 (100)
Stage IV		
Histological subtype		
Non-squamous	73 (67)	84 (76)
Squamous	31 (28)	23 (21)
Prior platinum-based therapy	109 (100)	110 (100)
First-line bevacizumab	NA	NA
Prior maintenance treatment	NA	NA
Previous taxane	0	0
Best response to first-line therapy		
Complete response	1 (1)	0 (0)
Partial response	44 (44)	36 (35)
Stable disease	24 (24)	36 (35)
Progressive disease	31 (31)	30 (29)
EGFR status		
Wild type	109 (100)	110 (100)
Mutant	0	0
Unknown or missing	0	0

There is a high risk of selection bias in the study by Garassino et al 2013 due to unclear methods of allocation concealment and some imbalances between groups at baseline. Methods to account for missing data were not reported. Patients and investigators who gave treatment and assessed outcomes were not blinded. Investigators who did tumour genotyping and analysed results were blinded. Two independent radiologists masked to treatment assignment undertook post hoc reviews of the scans of responding patients. Quality of life data was not reported in the publication (states will be reported separately). Premature withdrawals is listed as a secondary outcome on the clinical trial record (NCT00637910), but publication reports treatment-related adverse events leading to withdrawal only (these may have been reported in secondary publications not identified by the ERG).

Results for the NMA of erlotinib are seen in Tables 83-85.

Table 83: Overall survival NMA HR results, fixed effect model

Intervention	Comparator	
	Docetaxel (all populations)	Erlotinib (EGFR-negative)
Ramucirumab and docetaxel (all populations)		0.70 (95% CI 0.52, 0.91)
Nintedanib and docetaxel (non-squamous)		0.69 (95% CI 0.50, 0.92)
Erlotinib (EGFR-negative)	1.22 (95% CI 0.98, 1.61)	

CS Table states Ramu + doc is for all populations, the population differs in relation to the comparison of relevance.

Table 84: Progression free survival NMA HR results, fixed effect model

Intervention	Comparator	
	Docetaxel (all populations)	Erlotinib (EGFR-negative)
Ramucirumab and docetaxel (all populations)		0.57 (95% CI 0.43, 0.75)
Nintedanib and docetaxel (non-squamous)		0.58 (95% CI 0.42, 0.79)
Erlotinib (EGFR-negative)	1.33 (95% CI 1.04, 1.72)	

Table 85: Overall response rate NMA results, fixed effect model, difference in probit scores

Intervention	Comparator	
	Docetaxel (all populations)	Erlotinib (EGFR-negative)
Ramucirumab and docetaxel (all populations)		0.96 (95% CI 0.62, 1.34)
Nintedanib and docetaxel (non-squamous)		0.91 (95% CI 0.55, 1.31)
Erlotinib (EGFR-negative)	-0.56 (95% CI -0.9, -0.25)	

Probit score difference greater than zero favours the intervention over the comparator. CS Table states Ramu + doc is for all populations, the population differs in relation to the comparison of relevance.

Appendix 2: Hosomi et al

In the trial comparing ramucirumab + docetaxel (60mg) with placebo + docetaxel (60mg) recruitment was 16 months duration and follow-up 4 months. Randomisation was stratified by ECOG performance status, gender and prior maintenance therapy. Participants had stage IV NSCLC following disease progression during or after prior platinum-based chemotherapy and ECOG performance status of 0-1. 157 participants were randomised and treated. Baseline characteristics were similar between groups, although the proportion with ECOG performance status was slightly higher in the placebo group (Table 86).

Table 86: Selected baseline characteristics from Hosomi et al[21]

	RAM+DOC (N=76)	**PBO+DOC (N=81)**
Median age, years (min, max)	65.6 (29, 78)	64.9 (27, 79)
Male, %	77.6	76.5
Nonsquamous, %	88.2	88.9
Squamous, %	11.8	11.1
ECOG PS1, %	55.3	60.5

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

In the Hosomi et al study[21] that compared ramucirumab and docetaxel with placebo and docetaxel using a lower dose of docetaxel (60mg) than is typically used in the NHS setting, the primary outcome, PFS, was one month longer in the ramucirumab + docetaxel group than in the placebo group, but this difference was not statistically significant (HR 0.83, 95% CI 0.59 to 1.16) (Table 87). Similarly, the difference in overall survival was not statistically significant between groups (HR 0.77, 95% CI 0.48 to 1.24), although the authors note that data are immature. Response is also presented in Table 87. The ORR and DCR were 28.9% and 18.5%, respectively, for ramucirumab and docetaxel, and 18.5% and 70.4%, respectively, for placebo and docetaxel, however the overlapping confidence intervals between groups indicate no statistically significant differences for these outcomes.

Table 87: Summary of results from Hosomi et al

Outcome	**RAM+DOC (N=76)**	**PBO+DOC (N=81)**	
Primary outcome: PFS, months	5.2 (95% CI 3.52, 6.97)	4.2 (95% CI 2.83, 5.62)	HR 0.83 (95% CI 0.59, 1.16)
OS, months[a]	15.2 (95% CI 12.58, NA)	13.9 (95%CI 11.4, NA)	HR 0.77 (95% CI 0.48, 1.24)
Complete response, n (%)	0	0	
Partial response, n (%)	22 (28.9)	15 (18.5)	
Stable disease, n (%)	38 (50.0)	42 (51.9)	
Progressive disease, n (%)	13 (17.1)	23 (28.4)	
Unknown / not assessed, n (%)	3 (3.9)	1 (1.2)	
ORR, n (%)	22 (28.9)	15 (18.5)	

	(95% CI 19.1, 40.5)	(95% CI 10.8, 28.7)	
DCR, n (%)	60 (78.9) (95% CI 68.1, 87.5)	57 (70.4) (95% CI 59.2, 80.0)	

[a] Publication states that data are immature. DCR, disease control rate (complete response + partial response + stable disease); NA; Not available; ORR, objective response rate (complete response + partial response); OS, overall survival; PFS, progression-free survival; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

Adverse events

Rates of any TEAE, TEAE grade ≥3, any serious TEAE, TEAE leading to death and serious TEAE leading to discontinuation were similar between groups (Table 88). However, TEAE leading to discontinuation and dose adjustments due to TEAE were more common among the ramucirumab + docetaxel group than placebo + docetaxel.

The study presented TEAEs occurring in ≥40% of patients or ≥10% higher in the ramucirumab + docetaxel arm (Table 89). Grade 3-4 febrile neutropenia occurred more frequently (≥10%) in the ramucirumab + docetaxel group than the placebo + docetaxel group (34.2% vs 19.8%).

Table 88: Summary of adverse events Hosomi et al

n (%)	**RAM+DOC (N=76)**	**PBO+DOC (N=81)**
Any TEAE	76 (100.0)	81 (100.0)
Grade ≥ TEAE	71 (93.4)	77 (95.1)
Any serious TEAE	22 (28.9)	27 (33.3)
TEAE leading to death	1 (1.3)	1 (1.2)
TEAE leading to discontinuation	**28 (36.8)**	**14 (17.3)**
Serious TEAE leading to discontinuation	7 (9.2)	6 (7.4)
Dose adjustment due to TEAE	**43 (56.6)**	**34 (42.0)**

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
Bold font indicates events occurring 10% in ramucirumab group. TEAE = treatment-emergent adverse event.

Table 89: Selected TEAEs occurring in ≥40% of patients or ≥10% higher in the RAM+DOC arm of the Hosomi et al study

%	**RAM+DOC (N=76)**		**PBO+DOC (N=81)**	
	Grade 1-2	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
Neutropenia[a]	5.3	89.5	8.6	90.1
Leukopenia[a]	19.7	69.7	19.8	71.6
Fatigue[a]	30.3	1.3	25.9	0
Hypoalbuminemia[a]	**28.9**	2.6	**18.5**	1.2
Neuropathy[a]	**17.1**	0	**29.6**	0
Thrombocytopenia[a]	**21.1**	3.9	**11.1**	3.7
Alopecia	67.1	0	61.7	0
Decreased appetite	53.9	10.5	48.1	6.2

Malaise	48.7	0	48.1	0
Anaemia[a]	36.8	2.6	41.9	3.7
Stomatitis	**44.7**	5.3	**28.4**	0
Nausea	35.5	0	39.5	1.2
Epistaxis	**46.1**	0	**17.3**	0
Febrile neutropenia	0	**34.2**	0	**19.8**
Proteinuria	**22.4**	3.9	**9.9**	0
AST increased	**22.4**	1.3	**7.4**	1.2
ALT increased	**18.4**	0	**2.5**	1.2

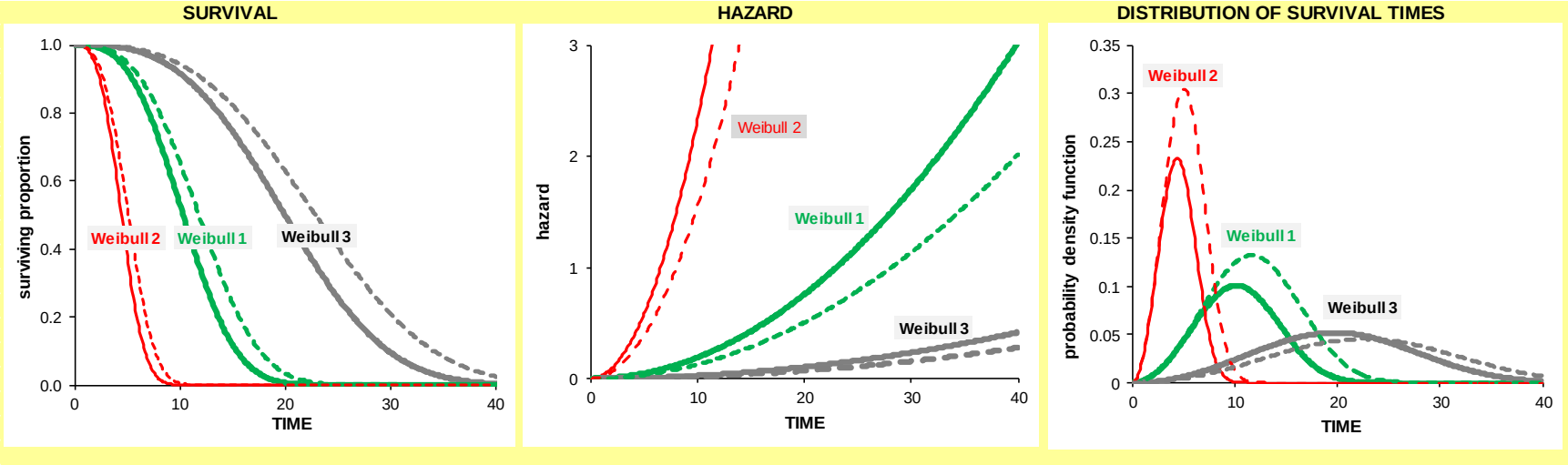
[a]MedDRA consolidated term. PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

Bold font indicates events occurring 10% in ramucirumab and docetaxel group. TEAE = treatment-emergent adverse event.

Appendix 3: Examples of survival curve pairs with identical hazard ratios but different median and mean survival values

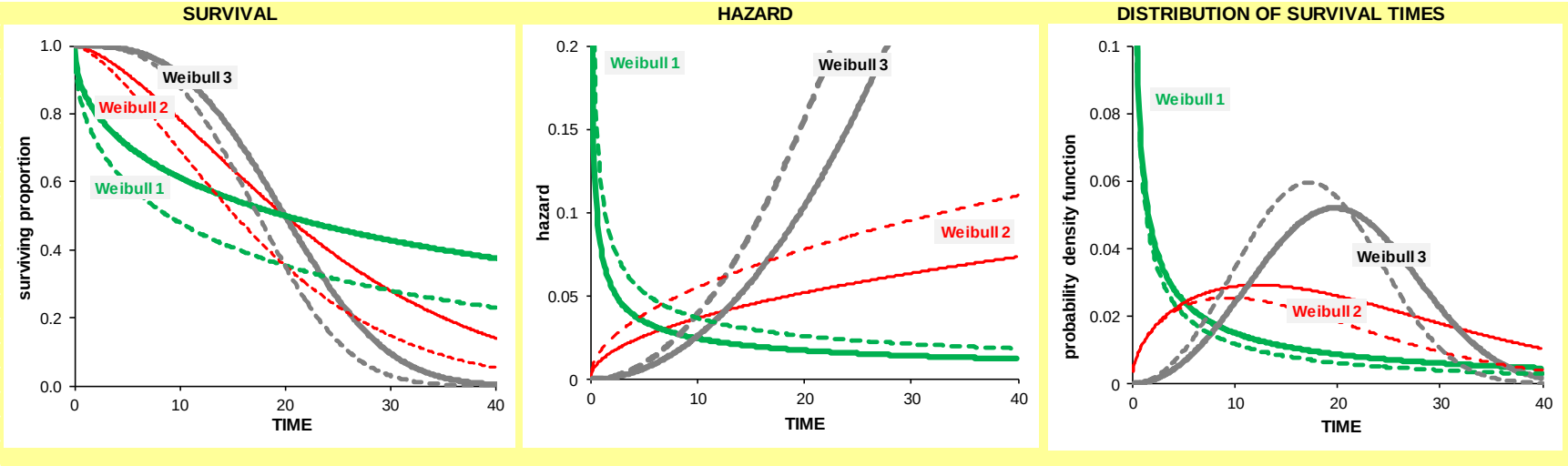
A] Three pairs of survival curves (intervention dashed lines, control solid lines) all having HR = 1.5 (control relative to intervention) and have similarl shape (sigmoid). The mean and median survival values are summarised in the table.

	Mean survival time			Median survival time		
	WEIB 1	WEIB 2	WEIB 3	WEIB 1	WEIB 2	WEIB 3
CONTROL	10.41171	4.512478	20.18039	10.32	4.47	20.00
INTERVN	11.91883	5.16567	23.10155	11.81	5.12	22.90
DIFFERENCE	*1.50712*	*0.653192*	*2.92116*	*1.49*	*0.65*	*2.90*



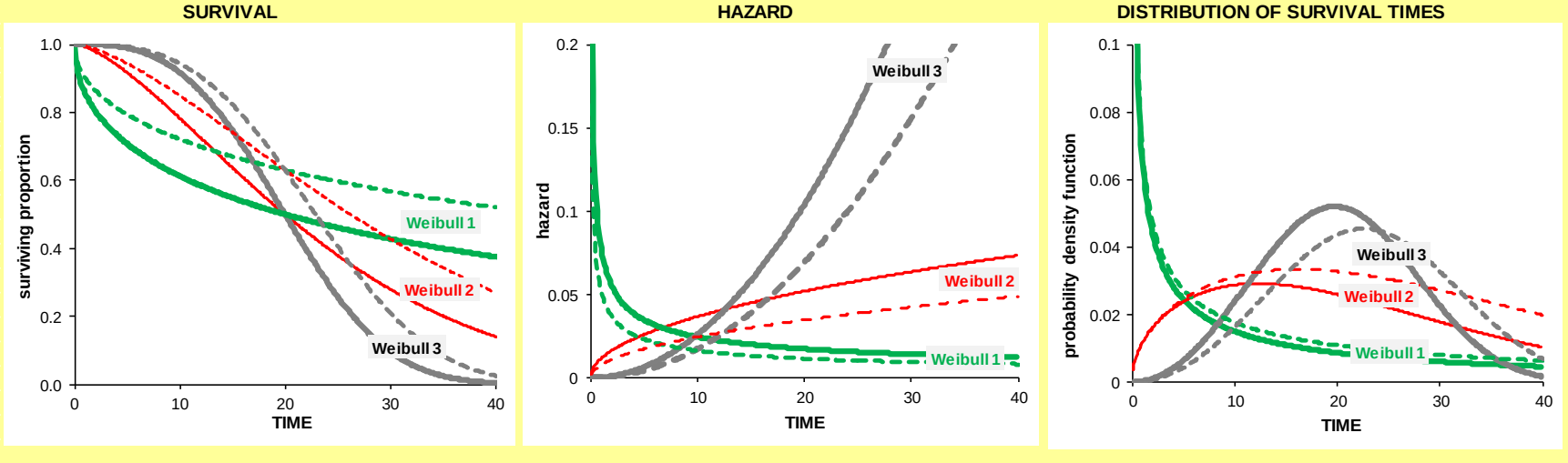
B] Three pairs of survival curves (intervention solid lines, control dashed lines) all having the same intervention median survival and the same HR = 1.5 (control relative to intervention) but dissimilar shape. The mean and median survival values are summarised in the table

	Mean survival time			Median survival time		
	WEIB 1	WEIB 2	WEIB 3	WEIB 1	WEIB 2	WEIB 3
INTERVN	83.25521	23.0522	20.18039	20.00	20.00	20.00
CONTROL	37.00232	17.59212	17.6292	8.89	15.26	17.47
DIFFERENCE	*46.2529*	*5.460079*	*2.551196*	*11.11*	*4.74*	*2.53*



C] Three pairs of survival curves (intervention dashed lines, control solid lines) all having the same control median survival and the same HR = 1.5 (control relative to intervention) but dissimilar shape. The mean and median survival values are summarised in the table

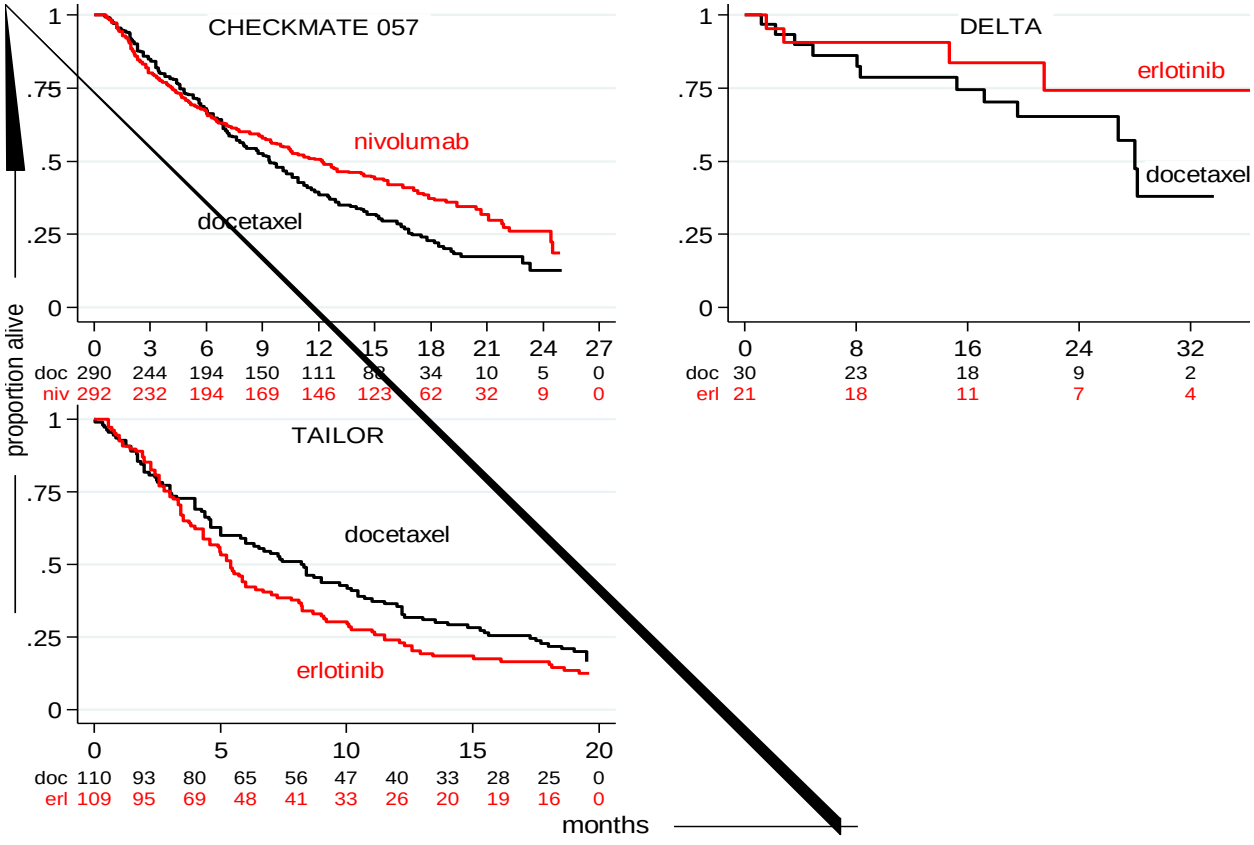
	Mean survival time			Median survival time		
	WEIB 1	WEIB 2	WEIB 3	WEIB 1	WEIB 2	WEIB 3
CONTROL	83.25521	23.0522	20.18039	20.00	20.00	20.00
INTERVN	187.3617	30.20894	23.10155	45.01	26.21	22.90
DIFFERENCE	*104.1065*	*7.156741*	*2.92116*	*25.01*	*6.21*	*2.90*



Appendix 4: Overall survival in additional trials

Published overall survival estimates from studies of marginal relevance to the NICE scope

Study	Intervention comparator	Median Φ	Difference in medians	Population	HR	Comment
Borghaei 2015 CHECKMATE 057	nivolumab docetaxel	12.2 9.4	2.8	Non squamous	0.73	Monotherapy one RCT
Kawaguchi 2014 DELTA§§	Erlotinib docetaxel	>40 27.8	> 12.2	EGFR +ve **	0.43	Monotherpay one RCT
Φ months. * NICE do not recommend Nintedanib for this Population. **analysis of a very small subgroup at risk of imbalance. § unadjusted hazard ratio. §§ docetaxel dose 60 mg/m^2 every 21 days rather than 75 mg/m^2 every 21 days.						



Kaplan Meier plots of overall survival. nb: the populations shown for DELTA and TAILOR trials were EGFR positive and EGFR wild type respectively.

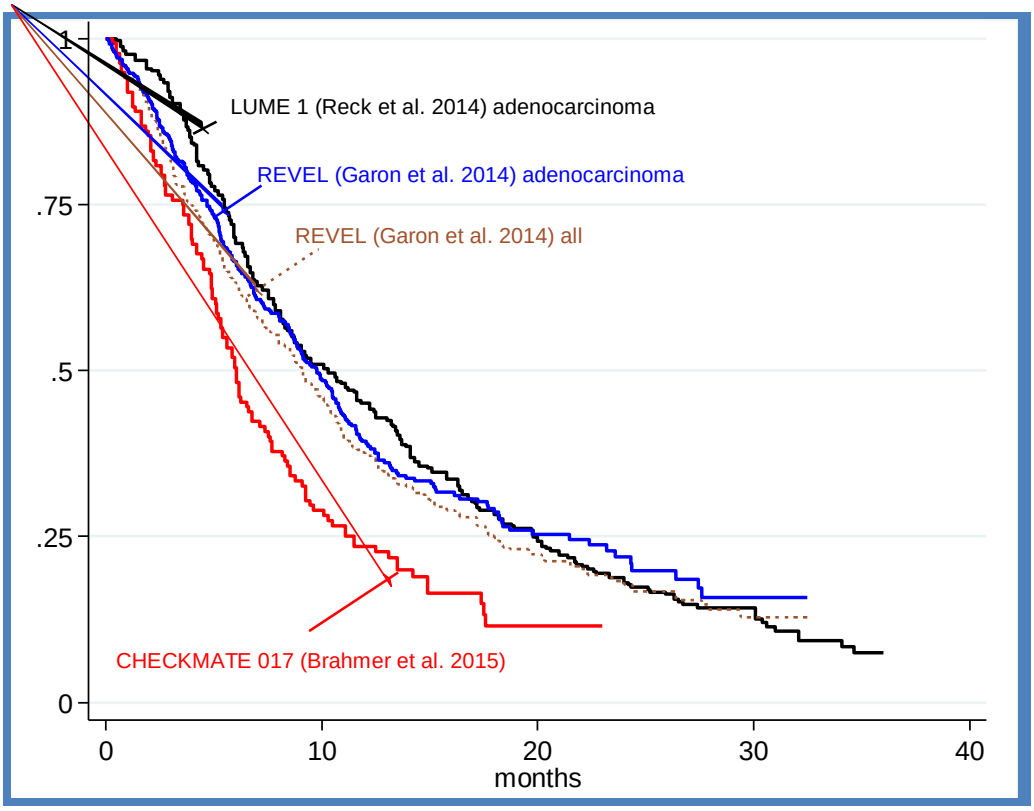
LYG over observed period estimated from AUC of the Kaplan-Meier plots

STUDY	**Population**	**Intervention LYG**	**Control LYG**	**Intervention Gain**	**Observation Period Φ**
CHECKMATE 057	Non squamous	Nivolumab **1.09**	Doce **0.91**	0.183	24.9
REVEL	All	Ramu **1.15**	Doce**1.03**	0.121	32.5
DELTA	EGFR +ve	Erlotinib **2.33**	Doce **1.90**	0.43	33.7
TAILOR	EGFR wild type	Erlotinib **0.59**	Doce **0.77**	-0.181	19.5
Φ months . All patients from REVEL and TAILOR included for cross reference.					

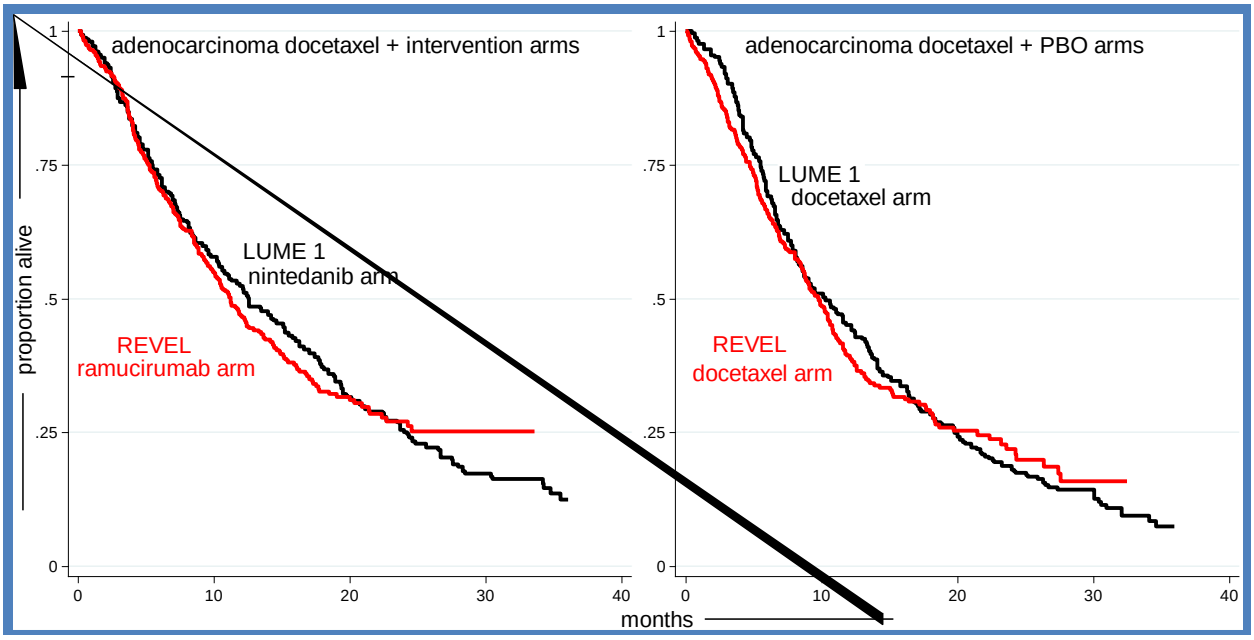
Estimated LYG over a 15 year time horizon estimated using separate unadjusted loglogistic models for each arm¥

STUDY	**Population**	**Intervention LYG**	**Control LYG**	**Intervention Gain**
CHECKMATE 057	Non squamous	Nivolumab **1.83**	Doce **1.35**	**0.477**
REVEL	Non squamous	Ramu **1.805**	Doce **1.589**	**0.216**
DELTA	EGFR +ve	Erlotinib **8.94**	Doce **4.46**	**4.450**
TAILOR	EGFR wild type	Erlotinib **0.90**	Doce **1.37**	**-0.463**
¥ estimates do not include discounting or tapering of the drug effect beyond the observed data				

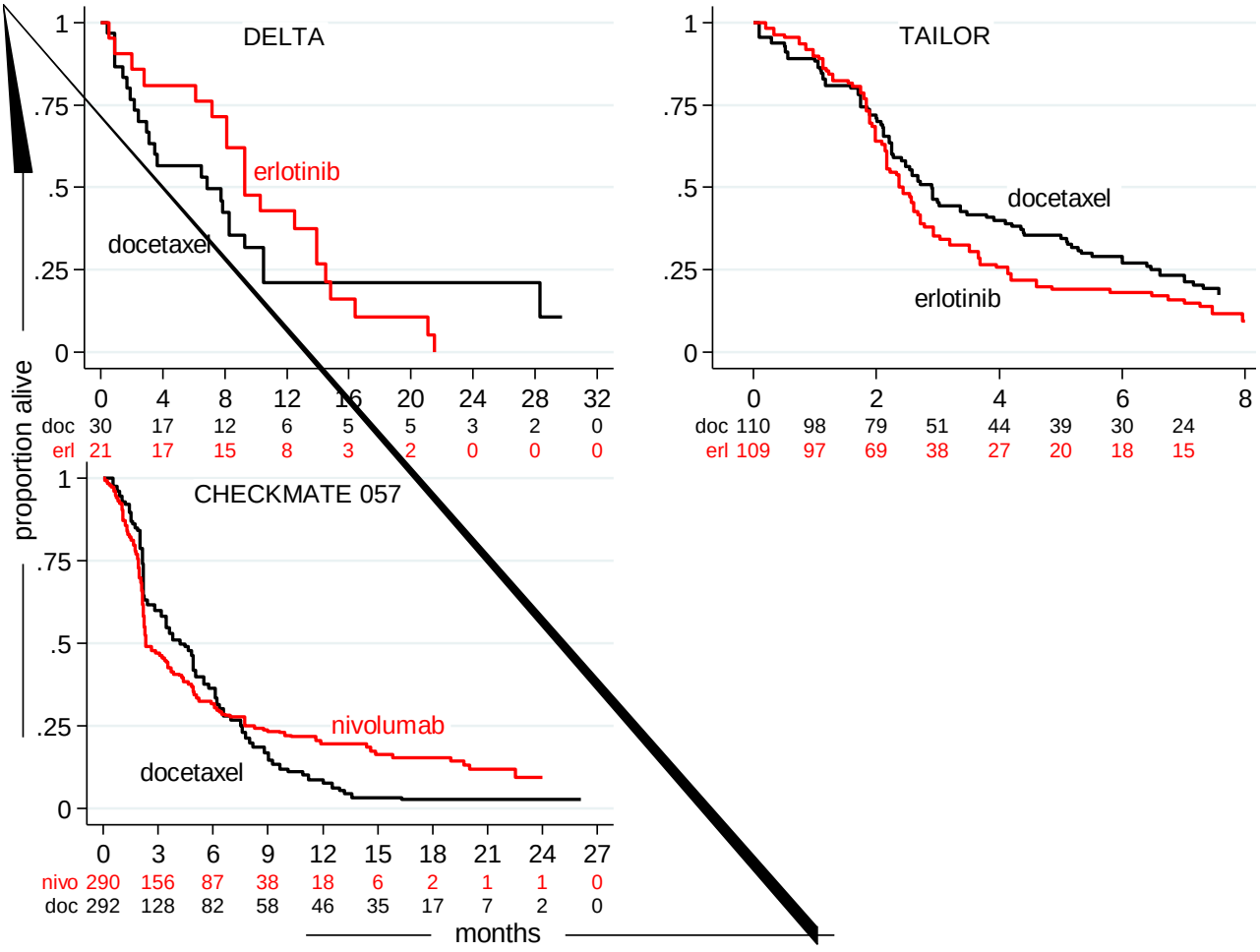
Appendix 5: Comparison of OS in docetaxel arms of relevant trials



Appendix 6: Comparison of OS according to trial arm in REVEL and LUME 1 adenocarcinoma populations.



Appendix 7: Progression free survival in additional trials.



Kaplan Meier plots of progression free survival. nb: the populations shown for DELTA and TAILOR trials were EGFR positive and EGFR wild type respectively.

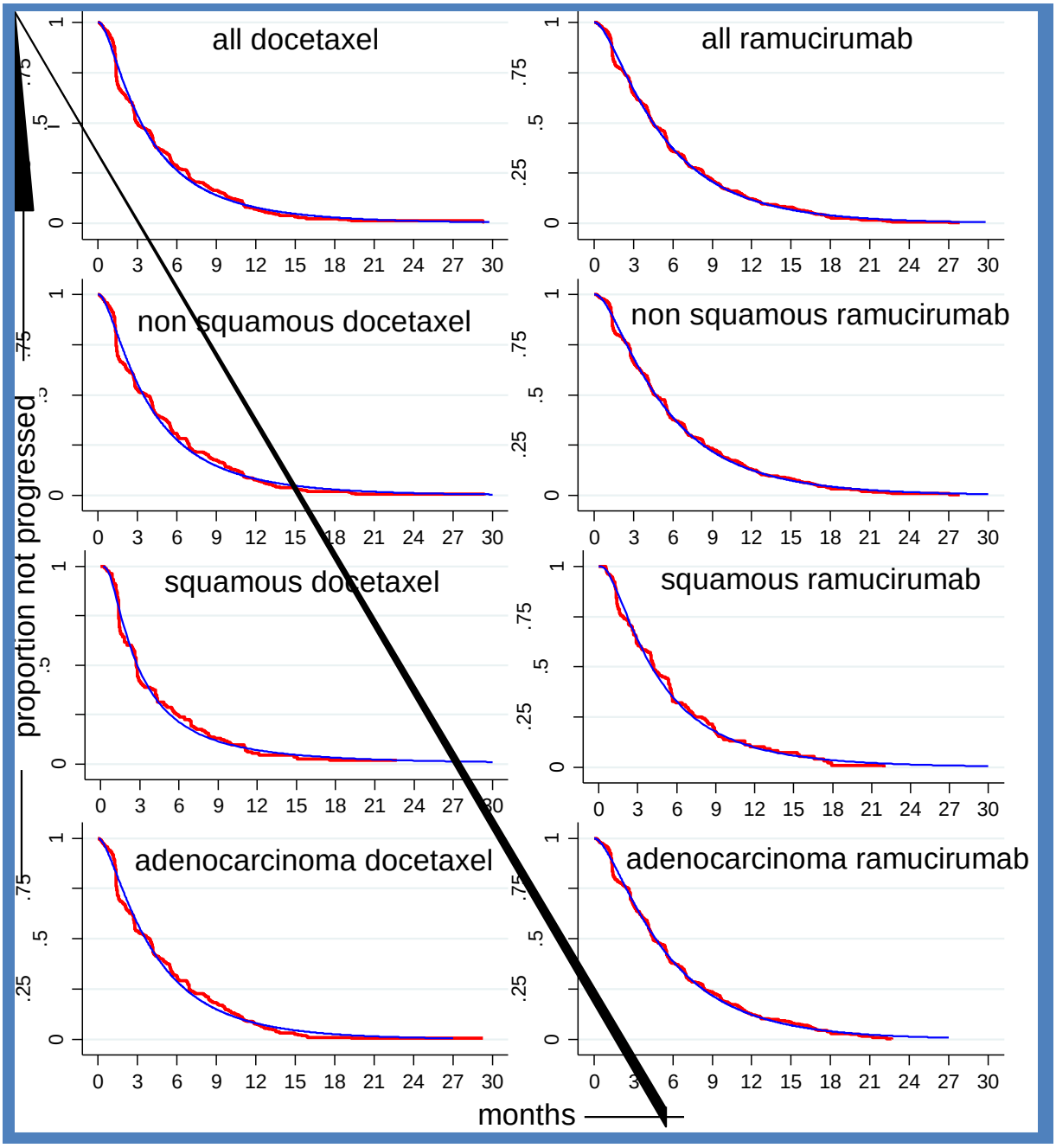
PFLMG over observed period estimated from AUC of the Kaplan-Meier plots

STUDY	**Population**	**Intervention PFLMG**	**Control PFLMG**	**Intervention Gain**	**Observation Period Φ**
CHECKMATE 057	Non squamous	Nivolumab **6.62**	Doce **5.32**	1.30	24
REVEL	Non squamous	Ramu **6.22**	Doce **4.94**	1.29	27.8
REVEL	All	Ramu **6.00**	Doce **4.85**	1.15	27.8
DELTA	EGFR +ve	Erlotinib **2.33**	Doce **1.90**	0.43	33.7
TAILOR	EGFR wild type	Erlotinib **0.59**	Doce **0.77**	-0.181	19.5
Φ months;					

Estimated PFLYMG over a 15 year time horizon estimated using separate unadjusted gamma models for each arm¥

STUDY	**Population**	**Intervention PFLMG**	**Control PFLMG**	**Intervention Gain**
CHECKMATE 057	Non squamous	Nivolumab **10.18**	Doce **5.85**	**4.333**
REVEL	Non squamous	Ramu **6.69**	Doce **5.42**	**1.270**
REVEL	All	Ramu **6.46**	Doce **5.31**	**1.146**
DELTA§	EGFR +ve	Erlotinib **10.63**	Doce **17.84**	**-10.21**
TAILOR	EGFR wild type	Erlotinib **3.93**	Doce **4.77**	**-0.84**
Estimates do not include discounting or half cycle adjustment. . § n.b. the extended survival tail in the docetaxel plot results in an anomalous model.				

Appendix 8: Unadjusted gamma models of PFS for patient groups in REVEL



National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID838]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 4 March 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9, the ERG report (dated 24th February 2016) states that MA has not yet been granted for the NSCLC indication and colorectal indication	Marketing Authorisation was granted in January 2016 for the additional indications. The text may be amended to simply state that "Cyramza is indicated for adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy, in addition to other indications in gastric and colorectal cancer"	Factual accuracy	Accepted. Text revised.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, top line, the HR has been incorrectly quoted with the two decimals reversed: 1.10 instead of 1.01	Correct to 1.01	To avoid giving the impression of differential efficacy; it seems likely this is just a typo and therefore the economic model should be unaffected.	Accepted. Typo amended.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, penultimate paragraph, "and so dominates nintedanib + docetaxel" is incorrect	Suggest this may be simply reworded to "and so nintedanib + docetaxel dominates"	Factual accuracy	Accepted. Also applies to the same text in section 6 on page 150 of the ERG report. Revised to …"and so dominates ramucirumab + docetaxel"

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22, Section 3.2 the ERG report (dated 24th February 2016) states that MA has not yet been granted for the NSCLC indication and colorectal indication Immediately following the report states "According to the summary of product characteristics of ramucirumab in gastric cancer"	Marketing Authorisation was granted in January 2016 for the additional indications. The text may be amended to simply state that "Cyramza is indicated for adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy, in addition to other indications in gastric and colorectal cancer" Remove the words "in gastric cancer" from the reference to the SmPC that immediately follows as this wording remains in the current multi-indication SmPC	Factual accuracy	Accepted. Text revised to reflect the granting of marketing authorisation

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23, last paragraph, the ERG report states "The ERG notes that erlotinib was also subject to ongoing NICE review but this wasn't excluded from the list of comparators in the decision problem. In addition, ramucirumab is currently not available within the NHS but its clinical effectiveness is being reviewed. Consequently, the ERG	Change this section to state: "Furthermore, NICE has not recommended nivolumab for squamous cell NSCLC in their draft guidance (http://www.nice.org.uk/guidance/GID-TAG506/documents/appraisal-consultation-document). This calls into question whether nivolumab will ever become routinely used in the UK. The ERG notes that erlotinib was, at the time of submission, still approved in the second line position under TA162 (2008) and thus available in the NHS. In addition, whilst ramucirumab is as yet unavailable in the NHS it is the intervention of interest in this appraisal and is therefore inherently included. Consequently, the ERG considers that the	To reflect the NICE methods guide, the specified intervention in this appraisal and the actual approval status of erlotinib and nivolumab at the point of submission	ERG accepts that text referring to erlotinib being subject to NICE review, and ramucirumab not being currently available is misleading and therefore these two sentences have been removed. However, it is ERG opinion not a factual inaccuracy, that nivolumab should have been

considers that the exclusion of nivolumab is not justified and that nivolumab should be included” This is factually unjustified in a number of points corrected in the next column	exclusion of nivolumab is justified and that nivolumab should not be included” It is further noted that NICE appraisals do not include within their scope therapies not yet in use – this is in accordance with the NICE methods guide (para 6.2.2 and 6.2.3). A recent example would include the appraisals TA303, TA312 and TA320 which all overlapped in time and considered three new drugs for the same indication: none of these drugs were compared to any of the others in their respective appraisals. If the above is accepted, we also suggest the following amendments are made: Remove this text on Page 14 “however, does not believe that the exclusion of nivolumab is justified, not least because there was RCT evidence identified by the CS that could have allowed this comparison to be made” Remove this text on Page 21: “The ERG considers that nivolumab should be considered (see Section 3.3).” Remove this text on Page 21: “With the exclusion of nivolumab from the submission it is not possible to apply much confidence to these budget impact projections.” Remove this text on Page 30: “The ERG considers that nivolumab is a relevant comparator and two RCTs of nivolumab were identified in the company update searches for the NMA but were not included, although nivolumab was listed in the CS as a tier 1 intervention.		included. No other changes made.

	One of these RCTs of nivolumab is in the licensed population of squamous NSCLC and therefore relevant to the scope." Remove this text Page 31: "is relevant to the NICE scope for this appraisal" Remove this text Page 32: "is an eligible comparator" Remove this text Page 36: "is relevant to the NICE scope" Remove this text Page 45: "but is relevant to the NICE scope."		

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 of the ERG report states that there "were discrepancies between the flow-chart on page 81, the text on page 79 and Table 29 on page 80" – this is not the case	Change "There are discrepancies in the CS between" to: "The CS explains the differences between" Change "The flow-chart shows that 7 additional tier 1 studies were included (the text states 10)" to: "The flow-chart shows that 7 primary reports of tier 1 studies were included, while the text notes that in total 10 studies were identified in the updated SLR (3 of which had had their primary reports identified in the original SLR)" Change "The CS says these were unique	Factual accuracy and avoiding the impression that there were inconsistencies in the reporting of the updated SLR	This is a helpful clarification, the ERG found the CS text and flow-chart around the updated SLR difficult to follow, in particular the use of the term 'unique'. There were other discrepancies noted but not reported in the ERG report, however, text amended to: 'There are differences in the CS between the flow-chart on page 81, the text on page 79 and Table 29 on page 80 with respect to the numbers of studies identified. The flow-chart shows that 7 additional tier 1 studies were included,

	studies but 5 had already been identified" to: "The CS noted these were unique studies within the updated SLR searches and that 5 had already been identified" Change "There were 5 unique studies" to: "There were 5 new unique studies"		while the text notes that in total 10 studies were identified (3 of which had had their primary reports identified in the original SLR)'. 'The CS describes these as unique studies but 5 had already been identified'

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30, last paragraph, "The company reiterated their position that nivolumab is not part of established clinical practice and does not comply with the definition of a comparator as laid out in the NICE Guide to Methods of Technology Appraisal" is incomplete	Amend to add on to the end of that statement: "They furthermore noted that the ACD for nivolumab had recently been published and recommended rejection of nivolumab by NICE"	Factual accuracy in terms of completeness	Accepted Text revised on p31 to state: that "furthermore the recently published NICE ACD suggested nivolumab would not be recommended".

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31, top paragraph, "Although the ERG acknowledge that the company do not consider nivolumab a suitable comparator for the decision problem, the NMA included other comparators in tier	Remove the quoted text entirely	Factual accuracy	This is helpful clarification, however, is not a factual inaccuracy. The justification for the choice of studies included in Tier 1 was not reported in the CS. No action.

1 that were not directly relevant to the decision problem but were presumed to have been included to reduce uncertainty. Therefore, the studies identified at the update search, including those for nivolumab, should have been included in the NMA." is an incorrect presumption – the SLR and NMA were undertaken to inform appraisals in many countries, which have a variety of different relevant comparators			

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 the ERG report states "In addition, a secondary outcome specified in the clinical trial record (https://clinicaltrials.gov/ct2/show/NCT01168973)22 and relevant to the decision problem, maximum improvement on LCSS, was not reported in the publication or CS. Therefore there is a high risk of selective reporting bias in the trial." Given that the "missing" outcome has (a) been published in the literature and (b) been included in the ERG report on Page 53, it is not accurate to claim there is a high risk of selective reporting bias	Change this text to: "In addition, a secondary outcome specified in the clinical trial record (https://clinicaltrials.gov/ct2/show/NCT01168973)22 and relevant to the decision problem, maximum improvement on LCSS, was not reported in the publication or CS. However the publication stated clearly that QoL outcomes would be in a subsequent paper which the ERG review on page 53. Therefore there does not appear to be any selective reporting bias in the trial." Remove on Page 10: "and selective reporting bias"	Factual accuracy and internal consistency of the ERG report	Accepted, was not updated when the ERG identified the publication of this outcome. Text amended (page 36 and p10).

	Remove on Page 36: “with a risk of selective reporting bias”		

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48, top paragraph “The ERG considers this assumption was violated by a number of studies especially relevant for the decision problem (e.g. for nintedanib,18 erlotinib,19 and nivolumab20). Consequently the output HR estimates may be less robust than desirable.24” Firstly, erlotinib and nivolumab are not relevant to the decision problem as noted above Secondly, the violation of PH in the nintedanib trial is for the squamous population which is not relevant to this appraisal – the non-squamous population did not violate PH as was noted in the submission and again in the clarification response	Change the text to: “The ERG notes that this assumption was only violated by a number of studies that were not relevant for the decision problem (e.g. for nintedanib only the squamous subgroup not the relevant non-squamous subgroup, erlotinib is no longer relevant following TA374, and nivolumab is not a relevant comparator). Consequently the output HR estimates may be less robust than desirable only for comparisons that are not central to the decision problem.24”	Factual accuracy in relation to scope and in relation to which nintedanib trial subgroups met and which violated the PH assumption	Many studies included in the CS NMA are irrelevant to the decision question. The ERG consider that nivolumab is a valid comparator and that the HR from the CHECKMATE 057 trial should be included in the NMA. In addition, there are inconsistencies in the reporting of which studies violate the PH assumption. However, text amended to state: “The ERG considers this assumption was violated by a number of studies ~~especially relevant for the decision problem (e.g. for nintedanib,18 erlotinib,19 and nivolumab20).~~ Consequently the output HR estimates may be less robust than desirable.24”

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49, Bottom paragraph, the ERG report states “comparing estimates of LYG for non-squamous patients in the REVEL trial with that modelled by the manufacturer of nintedanib”: this is not a clear description of what was presented because the estimates were not for “patients in the REVEL trial” (RAM+DOC vs PBO+DOC) but for the effect of NIN+DOC vs PBO+DOC in the economic model	Change “comparing estimates of LYG for non-squamous patients in the REVEL trial with that modelled by the manufacturer of nintedanib” to: “comparing estimates of LYG from the economic model for patients treated with nintedanib in the modelled non-squamous population with that modelled by the manufacturer of nintedanib” This makes clear that the submission table compares equivalent outcomes from different modelling approaches and finds a similar result from each This may allow the ERG to consider removing the text “The ERG are unclear how this supports the company’s approach to modelling overall survival because” that follows	As presently worded it could appear that the CS compared survival in RAM+DOC vs PBO+DOC in the submission model to a comparison of NIN+DOC vs PBO+DOC in another submission which would indeed be of unclear relevance. Changing this text will make it clear that the Table compares one outcome modelled by three different economic model approaches which is an appropriate pragmatic approach to cross-model validation.	Accepted Text amended on p49-50 to state: On CS pages 182-183 (Table 93) the company considers the validity of their loglogistic extrapolation by pointing to the close similarity of estimates of LYG from their economic model for patients treated with nintedanib in the modelled non-squamous population with that modelled by the manufacturer of nintedanib (Boerhinger) for the Reck et al (2014)(18) nintedanib trial that was recently assessed by NICE in a completed STA appraisal. The Boerhringer approach for nintedanib was very substantially different; it did not apply proportional hazards loglogistic modelling but employed direct Kaplan-Meier estimates observed in the trial up to a pre-determined point and then applied to each arm “per cycle” mortality risks based on an unadjusted log-normal model fit to an extract of data from LUCADA (UK National

			Lung Cancer Audit) encompassing various unspecified treatments.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53, last sentence "Quality of life in the areas of fatigue, activity level, and global QoL had the highest scores at baseline, most scores had worsened by the 30-day follow-up" requires additional text to be factually complete	Append the following text in bold to the sentence: "… follow-up **in both treatment arms**." Adding the text above avoids giving the impression that QoL only worsened in the treatment group	Factual completeness and avoidance of any impression that QoL worsened only in the treatment arm	Accepted Text revised.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57, top paragraph, "However, as stated above, there was only a significant benefit seen for PFS for EGFR wild-type or unknown" This statement is misleading as it implies that there was evidence that the effect was not seen in EGFR mutant. In fact the n numbers for this are 15 and 18 in each arm and therefore the CIs are very wide as expected but the point estimate is consistent	Remove this statement: "However, as stated above, there was only a significant benefit seen for PFS for EGFR wild-type or unknown "	Remove the false implication that subgroup analyses showed no effect in EGFR mutant	Accepted Text revised.

(indeed it is more favourable)			

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57, end of middle paragraph, the HR has been incorrectly quoted with the two decimals reversed: 1.10 instead of 1.01 The value is correct in the table below	Correct to 1.01	To avoid giving the impression of differential efficacy; it seems likely this is just a typo and therefore the economic model should be unaffected.	Accepted. Typo amended.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 “Table x to x” and “228.2%”	Minor typos – the ERG may wish to tidy up	Clarity	Accepted. Typos amended.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64, Table 21 the footnotes do not match the symbols in the table and it is unclear what is intended	ERG to clarify the intended meaning and placement of the footnotes	To allow interpretation of the table	Accepted. Footnotes changed to: Φ months. * NICE only recommend nintedanib for NSCLC adenocarcinoma. §§analysis of a very small

			subgroup at risk of imbalance.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67, Table 23 contains a serious error in footnote § Firstly, the footnote relates to non-squamous but is placed against squamous Secondly, the footnote quotes data for NIN+DOC but states that it is for RAM+DOC	ERG Report states "§ Data from CS Table 93 for the REVEL non-squamous population indicates 1.666 and 1.390 LYG for Ramu and Doce arms respectively providing an intervention gain of 0.276 LY" This is incorrect – the comparison in Table 93 is for **NIN**+DOC to DOC as it is an attempt to cross validate the current model with that in TA347. The ERG need to re-visit this table and clarify what was intended here both in where to place the footnote and what it was intended to convey	To correct a serious error	Accepted Table amended

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70, Table 26, the columns for multivariate have been transposed with the PBO and RAM values in the wrong column	Correct this transposition	Clarity and correctness	Accepted Table amended

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106, Table 56, the costs given here have not been inflated as they are in CS. The CS states that these should total £429.16	Correct total to £429.16 and each cost in the second column above to the inflated cost	To reflect the actual figure used in the model; the annualised figure quoted in the text was correct	Accepted. Text after Table 56 added: "The above costs are inflated to £429.16".

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113, Table 61, missing AiC highlighting on two rows: PPS QoL and PFS QoL in the Low V and High V columns	Please mark these values AiC	To maintain confidentiality	Accepted. Changed to AIC

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123, last paragraph "The economic model assumes that the parameterised curves are based upon one month being equal to 1/12th of a year. It is possible that within the trial data one month related to 4 weeks or 1/13th of a year. If this was the case it would tend to extend the modelled curves slightly, by around 1/13th or 7% as illustrated in Figure 25	Please amend to "The economic model assumes that the parameterised curves are based upon one month being equal to 1/12th of a year. This is the same assumption as was used in the REVEL trial." Within REVEL, our way of handling time unit is using months as the basic unit (e.g. survival data), and 1 month = 30.4375 days = 1 year of 365.25 days divided by 12	Factual accuracy	The ERG welcomes the clarification but there is no factual error in terms of the ERG report when it was written. This aspect was uncertain hence the ERG highlighting it in its report. No revision required.

for the log logistic overall survival curves" implies uncertainty in what was modelled	1 week = 7 days = 7/30.4375 weeks = 0.23 months It is the same assumption as used in the economic model.		

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130 "The ERG finds this surprising and cannot readily account for it." In this statement the ERG do not reflect on the implications of the differences in the "N Pat" column apparent between the rows it compares in their immediately preceding Table 71. This statement is therefore factually incomplete as it does not acknowledge that the comparisons drawn are between subgroups of substantially different sizes (N=587 vs N=493 and N=580 vs N=489)	Change this to the following text: "The ERG found this surprising, however they do note the N Pat values in ERG report Table 71, which are greater for PFS than for baseline. Change from baseline can only be calculated in the further subset of patients who complete at baseline and at least one further PFS occasion and this subset is ~100 patients smaller in each arm than the patient pool for PFS in each arm which may explain the difference observed." In addition, change: "The ERG remains confused by the p-values for the mean PFS quality of life and the mean changes from baseline, given the mean baseline values" to: "The ERG remained uncertain of the p-values for the mean PFS quality of life and the mean changes from baseline, given the mean baseline values but noted that substantial differences in subgroup size in the comparisons may result in quite different patients being included in each subgroup"	Completeness, internal consistency in the ERG report and avoidance of unnecessary doubt	The clarification of the company is welcome. But it still does not seem to explain the p-value for PFS changes from baseline given the standard errors of the estimates and what would seem to be the implied upper and lower confidence limits for the estimated changes from baseline. No revision required.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130 “The ERG is also confused by the large number of EQ-5D responses that enter the PFS calculations, but the very much smaller number of EQ-5D responses for the two PFS health states of response and stable disease. Unfortunately the ERG did not ask about this at clarification.” Table 7 of the ERG report shows that a proportion of patients were not allocated into one of the definitive CR/PR/Stable categories. The ERG therefore have reported the answer to this point elsewhere in their report.	Append the following text “However, as noted in Table 7 of this report, not all patients were assessed into the formal definitions of CR, PR and Stable, and it may therefore be expected that there will be differences in numbers between overall PFS and formal subcategories of PFS”	Completeness, internal consistency in the ERG report and avoidance of unnecessary doubt	Accepted. Text changed to: The ERG was also confused by the large number of EQ-5D responses that enter the PFS calculations, but the very much smaller number of EQ-5D responses for the two PFS health states of response and stable disease. The ERG did not ask about this at clarification but the at error check company has clarified that it is due to many patients not being assessed into the formal definitions of CR, PR and Stable.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130 “In the light of the above the ERG has conducted a sensitivity analysis which applies the mean changes from baseline for PFS to the pooled mean baseline value of 0.701 to yield PFS quality of life estimates of	Please replace this text with “The model allowed a scenario where instead of applying utilities irrespective of treatment and treatment-specific disutilities for AEs, as in the base case, the estimated PFS utilities in each arm of the REVEL trial were applied.”	Use of actual data for by-arm PFS utilities rather than incorrect substitutes	No factual error though the ERG welcomes the further clarification by the company. The differences at baseline argue against the company proposal. No revision required.

0.643 for ramucirumab + docetaxel and 0.681 for docetaxel." This is an inappropriate approach to analysing different utilities for each arm as it mixes mean values from different subgroups of patients to generate utility figures for PFS by treatment arm when in fact the actual values for these groups are available in the model (and presented in the ERG report)	Please then replace the results of the ERG scenario SA10 with results that use the actual observed by-arm PFS utilities. The ERG will find this option as the first setting on the "Utility Weights Inputs" sheet in the model. 528 patients completed EQ5D at baseline but would be incorrect to assume that patients who failed to complete the baseline EQ5D did not complete a later EQ5D. This is evident from the N Pat values in ERG report Table 71 which are greater for PFS than for baseline. Change from baseline can only be calculated in the further subset of patients who complete at baseline and at least one further PFS occasion. In contrast a much larger sample of patients inform the by-arm PFS utility values and these may be used in the model to provide a more robust attempt at this scenario than that presented by the ERG		

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 134, 2nd Paragraph "The 94.6% dose intensity is not used to account for dose delays. This is separately accounted for by the 92.9% drug administration percentage as calculated from 6.10 administrations over 19.7	Replace the sentence "In the opinion of the ERG this is incorrect and it should not be applied" with: "While not the approach the ERG would naturally take to this issue, it is acknowledged that a different approach is not incorrect"	Removing an incorrect criticism and acknowledging different approaches are not in fact invalid	No factual error. No revision required.

weeks. The dose intensity percentage is used to increase the patient weight that can be treated with a given number of vials and an assumed dose of 10mg/kg, or equivalently to assume that the mean dose per administration is 9.46mg/kg. In the opinion of the ERG this is incorrect and it should not be applied." Is incorrect in its final statement	In our approach to the calculation of drug costs, the ERG is correct that we do not use the relative dosing intensity from REVEL to account for dose delays, but to estimate the mean dose delivered in each administration. This is intended to reflect the assumption that the mean dose delivered in clinical practice may differ from the recommended dose. We then use the mean treatment duration and the mean number of administrations to estimate the proportion of infusions actually provided in REVEL to independently account for dose delays and discontinuations. We therefore do not think our approach of using the relative dose intensity from REVEL is incorrect, and we think it reflects a different approach based on the assumption that the mean dose delivered in each infusion may differ in clinical practice from the recommended dose. The duration of 19.7 has taken account of the dose delays and they both are very similar average values.		

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

ERG Erratum pages post company factual accuracy check

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The CS decision problem matches the population, interventions and outcomes described in the final NICE scope, as seen in Box 1. The CS decision problem differs from the NICE scope on the comparators, with nivolumab and crizotinib being excluded from the decision problem.

Ramucirumab is indicated for adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy, in addition to other indications in gastric and colorectal cancer. A positive opinion recommending changes to the marketing authorisation of ramucirumab was adopted by the Committee for Medicinal Products for Human Use in December 2015 to include adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy.

Box 1: NICE final scope

	Final scope issued by NICE
Population	People with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed after platinum based chemotherapy.
Intervention	Ramucirumab in combination with docetaxel
Comparator (s)	Docetaxel Erlotinib (subject to ongoing NICE review) Nintedanib in combination with docetaxel (adenocarcinoma tumour histology) Nivolumab (squamous tumour histology), subject to ongoing NICE appraisal Crizotinib for people with anaplastic-lymphoma-kinase (ALK)-positive NSCLC
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life

1.2 Summary of submitted clinical effectiveness evidence

The CS undertook a systematic review to search for evidence of relevance to the decision problem, including searches for studies on the intervention and separate searches for comparator studies for a network meta-analysis.

- difference in OS (HR 1.01 (95% CI 0.82, 1.25). The comparison with erlotinib showed greater OS with ramucirumab + docetaxel.
- Similar results were observed for PFS and ORR.
- A post-hoc subgroup analysis comparing ramucirumab + docetaxel with nintedanib + docetaxel in the adenocarcinoma population, in which nintedanib is indicated, were similar for OS and PFS.

1.3 Summary of the ERG's critique of submitted clinical evidence

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial that compared ramucirumab with one of the scoped comparators, docetaxel. The outcomes and analytical approach to the phase 3 trial were appropriate. The population in the trial appear to be relevant to those treated in the NHS and the ERG do not have any reason to consider the results of the trial to be significantly biased.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of a scoped comparator, nivolumab, from the decision problem. Nivolumab in the squamous NSCLC population is currently being considered by NICE in an ongoing appraisal. For this reason the CS consider that nivolumab is not a relevant comparator as it is not currently used in NHS practice. The ERG has considered the clinical effectiveness evidence for this potential comparator.
- The evaluation of the NMA is restricted, in part owing to the limited details provided as regards some aspects of the analysis and results.
- The ERG agrees with the rationale presented in the CS for using hierarchical models for the NMA. Comprehensive heterogeneity and inconsistency analyses revealed complex treatment-by-covariate interactions and limited trial evidence which could result in uncertainty in the analysis which was accommodated through exchangeability.
- The assumption of similarity in the NMA is not stated or justified in the CS. The ERG note any known differences between the studies of relevance to the scope but have not been able to assess similarity between the wider studies included in the NMA.
- Assumptions of the survival data compared in the NMA are questioned by the ERG, in particular the assumption of proportional hazards and the potential for adjusted HRs to result in double counting of variables.

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to nintedanib + docetaxel typically suggests small QALY gains or losses which render the cost effectiveness estimate unstable. The base case net cost estimate of £12,899 shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS worsens it to £13,563
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £11,660
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £24,374
- Assuming a febrile neutropenia cost of £7,352 worsens it to £13,372

Not tapering the OS hazard ratio and applying the company hazard ratio for ramucirumab + docetaxel both cause the model to estimate that nintedanib + docetaxel provides small patient gains and so dominates ramucirumab + docetaxel.

The scenario analysis of applying the ERG linear trends curves to the adenocarcinoma subgroup results in a cost effectiveness estimate for the adenocarcinoma subgroup that is approximately £14k per QALY worse than the corresponding estimate for the non-squamous subgroup. Within this the ERG retained the drug use estimates for the non-squamous subgroup.

This indicates that patients are likely to receive more ramucirumab infusions compared to docetaxel which will also necessitate more hospital stays compared to patients treated with docetaxel alone.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population in the decision problem, and subsequent clinical evidence, matches the population described in the final scope. The population of relevance is people with locally advanced or metastatic NSCLC who have progressed after platinum based chemotherapy.

3.2 Intervention

The intervention in the decision problem is ramucirumab in combination with docetaxel and this matches the final scope. The company provides a description of the technology and the mechanism of action of ramucirumab (CS page 22) which the ERG clinical advisor has confirmed is accurate. Ramucirumab is an intravenously administered medication already authorised for use in patients with gastric cancer. In December 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending changes to the marketing authorisation of ramucirumab[8] and since January 2016 ramucirumab is indicated for adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy, in addition to other indications in gastric and colorectal cancer. According to the summary of product characteristics, ramucirumab is a human receptor-targeted antibody that specifically binds Vascular Endothelial Growth Factor (VEGF) Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells.

The indication of ramucirumab in NSCLC, which is the target of NICE scope, has already been approved by the U.S. Food and Drug Administration (FDA) (gained on 12th December 2014).[9] The conclusions of the FDA was that ramucirumab given in combination with docetaxel meets the criteria for approval and has a favourable risk-benefit profile for the treatment of patients with metastatic NSCLC who have

progressed on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.

The FDA has emphasized some areas of uncertainties on the risk/benefit analysis of ramucirumab. First, the safety and efficacy of ramucirumab have not been adequately evaluated in patients with EGFR mutation or ALK rearrangement-positive NSCLC. Second, the benefit of adding ramucirumab to docetaxel in older patients is unclear.

Ramucirumab will be assessed by the Scottish Medicines Consortium in 2016.

Table 7 in the CS (page 24-5) summarises administration and costs of ramucirumab, and information provided in this table regarding the treatment administration concur with those in the REVEL trial. The cost of a course of treatment was calculated based on data on drug wastage and patient weight in the REVEL trial. The calculated cost is consistent with data provided on patients' weight and men/women proportions stated on CS page 149. In Table 7, the dose adjustments section specifies that the mean relative dose intensity of ramucirumab was 94.6% in the REVEL trial (mean dose of 9.5mg/kg, Table 59, page 149). Ramucirumab is given in combination with docetaxel (intended dose 75mg/m^2). For docetaxel the dose intensity varied in the REVEL trial, in those treated with ramucirumab and docetaxel this was a mean dose of 68.3mg/m^2 and in those treated with placebo and docetaxel this was a mean dose of 70.2mg/m^2.

3.3 Comparators

The comparators described in the decision problem are docetaxel, erlotinib in EGFR-negative patients only, nintedanib in combination with docetaxel for adenocarcinomas only. This differs substantially compared to the NICE final scope as follows:

The company has excluded nivolumab and crizotinib from the list of comparators. The reason for excluding nivolumab is because a STA is being undertaken by NICE on nivolumab (on the licensed population of squamous NSCLC) and the CS states it is therefore not currently available for patients within the NHS. The ERG

4.1.3.1 Identified studies for the NMA

The CS includes a systematic review to allow a network-meta analysis of studies including comparator evidence, to fulfil the decision problem. As described above, a broad range of interventions were eligible, however, the studies were divided into three tiers, with tier one studies (and four tier 2 studies) being included in the CS as having interventions that were most relevant to the decision problem. These were docetaxel, erlotinib, gemcitabine, nintedanib + docetaxel, nivolumab, pemetrexed, ramucirumab + docetaxel, vinorelbine (and gefitinib from tier 2). From the searches the CS identified 45 tier 1 studies that met the inclusion criteria. Three of these were not reported in English language publications and were deemed irrelevant to the decision problem, 24 other studies (therefore 27 in total) were excluded from the final NMA. Four studies from tier 2 were also included, the intervention was gefitinib and these were reported to be included to inform the network. Update searches were undertaken in September 2015.

There are differences in the CS between the flow-chart on page 81, the text on page 79 and Table 29 on page 80 with respect to the numbers of studies identified. The flow-chart shows that 7 additional tier 1 studies were included, while the text notes that in total 10 studies were identified (3 of which had had their primary reports identified in the original SLR). The CS describes these as unique studies but 5 had already been identified. The study was undertaken in a Japanese population and the dose of docetaxel was 60mg/m^2 which the CS states is therefore not relevant to the UK setting (see Section 0). The other four studies were of pemetrexed + erolotinib, nivolumab (2 studies) and pemetrexed or docetaxel. It is unclear to the ERG why the pemetrexed + erlotinib trial was excluded as this had a comparator of pemetrexed and would appear to meet the network for tier 1, and the two nivolumab studies were of potential relevance to the NICE scope. The CS states (p79) that the excluded studies were not relevant to informing the relative efficacy of the comparators in the decision problem, however, tier 1 of the NMA did not only include studies of relevance to the decision problem and therefore this study should have been included in the NMA for completeness. The company confirmed at clarification that no studies identified from the update searches were included. It is also unclear whether the studies reported only in abstract form at the initial searches were updated. The ERG considers that nivolumab is a relevant comparator and two RCTs of nivolumab were identified in the company update searches for the NMA but were not included, although nivolumab was listed in the CS as a tier 1 intervention. One of these RCTs of nivolumab is in the licensed population of squamous NSCLC and therefore relevant to the scope.

The ERG requested the company to reconsider adding nivolumab into the NMA as tier 1 studies. The company reiterated their position that nivolumab is not part of established clinical practice and does not

4.1.5 Relevant studies not included in the submission

A phase 2 study of ramucirumab and docetaxel compared with docetaxel alone and undertaken in Japan was excluded by the company because the dose of docetaxel was lower than the standard dose used in the UK (60mg versus 75mg). The ERG asked in a clarification request (A24) that this study be included in a sensitivity analysis in the NMA. The company stated that connecting the study to the network would likely be difficult owing to the lack of studies connecting docetaxel 60mg with the rest of the network. The ERG considers that this study could have been included as a sensitivity analysis in the ramucirumab and docetaxel versus docetaxel arm, regardless of the different dose of docetaxel used. Hosomi et al[21] conducted a phase 2 RCT (sponsored by Eli Lilly) in Japan comparing ramucirumab and docetaxel with placebo and docetaxel, using the lower dose of docetaxel (60mg/m^2) as recommended in Japan. The study is currently reported in an abstract and poster presentation only. Results from this study can be seen in **Error! Reference source not found.**.

As discussed above, the ERG considers that one RCT of nivolumab is relevant to the NICE scope and has been summarised in the relevant sections of the ERG report.

4.1.6 Description and critique of the approach to validity assessment

The CS provided quality assessment for the included REVEL study[16] (CS Table 20) and for 45 studies identified for the NMA (CS Appendix 7), using criteria recommended by NICE. The ERG has checked the company's QA for the REVEL trial and the comparator trial of relevance to the decision problem versus docetaxel: Reck et al 2014[18] (nintedanib + docetaxel vs docetaxel) see **Error! Reference source not found.**. For the erlotinib versus docetaxel trial, Garassino et al 2013[19] see **Error! Reference source not found.**). In addition, the ERG has provided quality assessment of the trial of nivolumab in the squamous population (Brahmer et al 2015[20]).

The ERG QA mostly agrees with the company assessment of study quality for REVEL, which has a low risk of selection bias or bias due to lack of blinding (performance bias or detection bias). However the ERG notes that there were some imbalances in reasons for treatment discontinuations between groups, which are suggestive of attrition bias. A secondary outcome specified in the clinical trial record (https://clinicaltrials.gov/ct2/show/NCT01168973)[22] and relevant to the decision problem, maximum improvement on LCSS, was not reported in the publication or CS but was reported subsequently. Therefore there does not appear to be any selective reporting bias in the trial.

felt the assumption was not met. No further details are provided. The ERG considers this assumption was violated by a number of studies especially relevant for the decision problem (e.g. for nintedanib,[18] erlotinib,[19] and nivolumab[20]). Consequently the output HR estimates may be less robust than desirable.[24]

B) Although the NMA was designed for binary outcomes[25] and HRs may be regarded as ORs of risk,[26] the extraction of only HRs from the published survival analyses does not use most of the survival information in the constituent studies, specifically information embodied in the shape of the survival curves and their disposition along the time axis. When only HRs are used to estimate LYG (area under the survival curve (AUC)) they can fail to provide useful information since identical HRs for pairs of survival curves with proportional hazards deliver different LYG depending on their shape and dispersion on the time axis (illustrative examples are provided in **Error! Reference source not found.**).

C) The ERG is concerned that the use of adjusted HRs as output from the NMA might result in double counting of variables (e.g. tumour histology) when used in conjunction with an adjusted baseline loglogistic model for the placebo + docetaxel arm from REVEL.[16] The ERG requested values for the HR inputs to the NMA and whether these were adjusted or unadjusted (the submission appendix provides log HR inputs to 2 decimal places) in clarification request A16. The requested values were not supplied, however, the company stated that all input HRs were unadjusted.

D) To model OS for comparator treatments the company has applied NMA HRs (generated under the assumption of proportional hazards; see above) to a loglogistic model for the docetaxel arm of REVEL that was developed under assumed proportional hazards between REVEL trial arms (treatment as a covariate); both "adjusted" and "unadjusted" models were generated with and without patient level variables respectively. Unfortunately loglogistic models used in this way are not consistent with the assumption of proportional hazards because the resulting hazard ratio is not invariant through time (see examples in Section **Error! Reference source not found.**). Royston and Lambert (2011)[27] explain that unlike parametric models with monotonic hazard functions (e.g. Weibull, exponential), log logistic models allow for a turning point in the underlying hazard function, but that it is not possible to use them in a proportional hazards model. The ERG believes that if the choice of parametric model is to be loglogistic then this should be fit separately to each trial arm (i.e. no assumption of proportional hazards).

E) Although the log logistic models of OS developed in the CS may fit reasonably well to the observed data from the REVEL trial, their extrapolation in modelling survival beyond the observed data from about 3 years to the time horizon of 15 years (see Section **Error! Reference source not found.**) may not be appropriate. Firstly, the models were

developed under a proportional hazards assumption inappropriate for log logistic models. Secondly, beyond the observed data, these models predict continuously decreasing hazard for death for the diminishing population of survivors (Figure 1). As noted elsewhere (STA of nivolumab for NSCLC) such decreasing hazard implies that a few months intervention with docetaxel or ramucirumab confers a lifelong reduction in risk from all causes of death for which there is no obvious biological explanation. In the ongoing STA of nivolumab for squamous NSCLC the ERG remark that the company's extrapolated loglogistic model eventually results in a lower probability of death for nivolumab treated NSCLC patients with progressed disease than for similarly aged members of the general population.

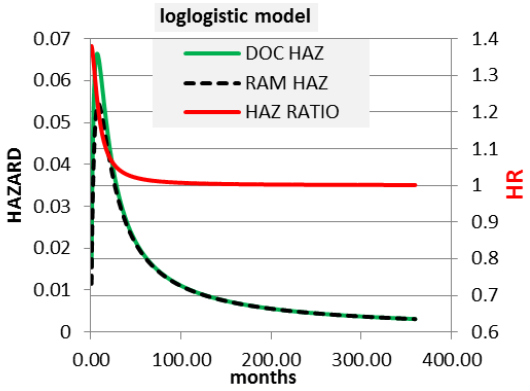


Figure 1 Log logistic hazard plots for all patients in REVEL; note decreasing hazard in both arms from ~8 months onwards

When data is incomplete (i.e. patients not followed up until all are dead) a likely consequence of using loglogistic models for extrapolation is that the estimated proportion of mean survival due to extrapolation may represent an appreciable proportion of the estimated total mean survival. Data for PFS is more complete than for OS and when combined with a decreasing hazard loglogistic model for OS may result in the apparent benefit of treatment accruing well after progression and cessation of treatment. For example the ERG for the nintedanib STA remarked that the company's loglogistic model results in only 15% of mean survival being attributable to the pre-progression phase.

On CS pages 182-183 (Table 93) the company considers the validity of their loglogistic extrapolation by pointing to the close similarity of estimates of LYG from their economic model for patients treated with nintedanib in the modelled non-squamous population with that modelled by the manufacturer of nintedanib (Boerhinger) for the Reck et al (2014)[18] nintedanib trial that was recently assessed by NICE in a completed STA appraisal. The Boerhringer approach for nintedanib was very substantially different; it did not apply proportional hazards loglogistic modelling but employed direct Kaplan-Meier estimates observed in the trial up to a pre-determined point and then applied to each arm "per cycle" mortality risks

Partial response (PR)	141 (22.5)	83 (13.3)
Stable disease (SD)	258 (41.1)	244 (39.0)
Progressive disease (PD)	128 (20.4)	206 (33.0)
Unknown/Not done	98 (15.6)	90 (14.4)
Objective response (CR+PR) rate (%) (95% CI)	22.9 (19.7, 26.4)	13.6 (11.0, 16.5)
p-value (based on the Cochran-Mantel-Haenszel test adjusting for the stratification variables)	<0.001	

CI = confidence interval; PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.

4.2.4 Health-related quality of life (HRQoL)

The CS presents data from the REVEL trial on the Lung Cancer Symptom Score (LCSS) and the EQ-5D. For the LCSS the CS presents the time to deterioration on each of the 6 symptom questions (appetite loss, fatigue, cough, dyspnoea, haemoptysis, pain) together with the Average Symptom Burden Score (ASBI); the 3 global items (symptom distress, difficulties with daily activities, quality of life) together with the total score (all nine items). Each item is assessed with a 100-mm visual analogue scale with higher ratings equating to poorer quality of life. The definition of time to deterioration was predefined as the time from randomisation to the first 15mm increase. No reference was provided for this definition in the CS; the ERG's clinical advisor agrees this is a reasonable definition for this measure. Compliance rates for completion of the LCSS questionnaire was reported to be 78% at baseline in both treatment groups, at 30-day follow-up (post treatment discontinuation) this was reported to be 61% in the ramucirumab and docetaxel group and 62.2% in the docetaxel group. The data for the time to deterioration was presented in a figure (CS Figure 8, p64), where it was seen that none of the 11 items were significantly different between groups (all confidence intervals for the reported HRs crossed 1.0).

A recent publication of the quality of life results from the REVEL trial has been identified by the ERG.[11] In this publication the mean scores on the LCSS at baseline and at 30-days follow-up (post treatment discontinuation) were presented by treatment group and have been reproduced in **Error! Reference source not found.**. As reported in the Perol 2016[11] paper the symptom burden was similar between the treatment arms across the LCSS throughout treatment (no p-values were reported). Quality of life in the areas of fatigue, activity level, and global QoL had the highest scores at baseline, most scores had worsened by the 30-day follow-up in both treatment arms.

testing for EGFR mutation status was undertaken in only 437 patients (35.1%), thereby limiting the analysis of the pre-specified subgroup analysis of EGFR mutation positive, wild-type or unknown. The CS states that a consistent treatment effect was observed in the ramucirumab and docetaxel arm compared to the docetaxel, across those with EGFR-mutated, wild type, or unknown mutation status. The CS also states that it is unlikely that imbalance in the EGFR mutation status between groups has an impact on survival, or that imbalance in those treated with EGFR TKI's post discontinuation impacts on the survival seen.

4.2.6 NMA results

The results of the NMA for OS for ramucirumab and docetaxel versus the comparators in the CS decision problem are summarised in **Table 1**. Ramucirumab and docetaxel showed a significantly better OS than docetaxel alone (HR 0.86 (95% CI 0.75, 0.98)) in line with the results of the REVEL trial. The comparison with erlotinib is in the EGFR negative subpopulation and is not considered to be an appropriate comparator but is presented in **Error! Reference source not found.** for completeness. The comparison of ramucirumab and docetaxel with combination nintedanib and docetaxel in the non-squamous subpopulation shows no significant difference in OS (HR 1.01 (95% CI 0.82, 1.25)).

The CS undertook a separate subgroup NMA for the comparison of ramucirumab and docetaxel with nintedanib and docetaxel (**Error! Reference source not found.**). This was for the adenocarcinoma subpopulation because nintedanib and docetaxel is indicated in this subgroup only. The HRs seen were similar to those seen for the comparison with the ramucirumab and docetaxel in Table 1. The company confirmed in clarification C1 that these analyses were post hoc comparisons.

Table 1: Overall survival NMA HR results, fixed effect model

Intervention	**Comparator**	
	Docetaxel (all populations)	Nintedanib and docetaxel (non-squamous)
Ramucirumab and docetaxel (all populations)	0.86 (95% CI 0.75, 0.98)	1.01 (95% CI 0.82, 1.25)
Nintedanib and docetaxel (non-squamous)	0.85 (95% CI 0.71, 1.00)	

CS Table states Ramu + doc is for all populations, the ERG believes the population differs in relation to the comparison of relevance.

increased lacrimination (13.4% vs 4.5%), and thrombocytopenia (13.4% vs 5.2%) (Table 18 to 20). Anaemia was more common in the placebo + docetaxel group (ramucirumab + docetaxel 20.9% vs 228.2% placebo + docetaxel) (Table 2).

A similar proportion of participants in each group was hospitalised (ramucirumab + docetaxel 41.9% vs placebo + docetaxel 42.6%) and the duration of stay was also similar (ramucirumab + docetaxel median 9.0 days (range 1 to 128) vs placebo + docetaxel median 8.0 days (range 1 to 56); hospitalisation per patient: ramucirumab + docetaxel mean 14.5 days (SD 16.5) vs placebo + docetaxel mean 11.3 days (SD 9.9)).

Table 2: Haematological adverse events

Haematological adverse events, n (%)	**RAM+DOC N = 627**				**PBO+DOC N = 618**			
	Any grade		**Grade ≥3**		**Any grade**		**Grade ≥3**	
Neutropenia[a]	**345**	**(55.0)**	**306**	**(48.8)**	**284**	**(46.0)**	**246**	**(39.8)**
Leukopenia [a]	134	(21.4)	86	(13.7)	117	(18.9)	77	(12.5)
Anaemia [a]	131	(20.9)	18	(2.9)	174	(28.2)	35	(5.7)
Febrile neutropenia	**100**	**(15.9)**	**100**	**(15.9)**	**62**	**(10.0)**	**62**	**(10.0)**
Thrombocytopenia [a]	**84**	**(13.4)**	18	(2.9)	**32**	**(5.2)**	4	(0.6)

PBO + DOC: placebo + docetaxel; RAM + DOC: Ramucirumab + docetaxel.
Garon 2014[16]. Bold font indicates adverse events occurring ≥5% in ramucirumab group. [a] Consolidated term.

Table 3: Adverse events of special interest

Adverse event, n (%)	**RAM+DOC N = 627 n (%)**		**PBO+DOC N = 618 n (%)**	
	Any Grade	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Bleeding or haemorrhage	**181 (28.9)**	15 (2.4)	**94 (15.2)**	14 (2.3)
Epistaxis	**116 (18.5)**	2 (0.3)	**40 (6.5)**	1 (0.2)
Gastrointestinal haemorrhage	17 (2.7)	4 (0.6)	10 (1.6)	2 (0.3)
Pulmonary haemorrhage	49 (7.8)	8 (1.3)	46 (7.4)	8 (1.3)
Haemoptysis	36 (5.7)	4 (0.6)	32 (5.2)	4 (0.7)
Hypertension[a]	**68 (10.8)**	35 (5.6)	**30 (4.9)**	13 (2.1)
Infusion-related reaction	23 (3.7)	5 (0.8)	28 (4.5)	4 (0.7)
Proteinuria	21 (3.3)	1 (0.2)	5 (0.8)	0
Venous thromboembolic events	16 (2.6)	11 (1.8)	36 (5.8)	18 (2.9)

advantage of introducing study level variables offered by the NMA, the resulting models may bear a poor relationship to the observed survival seen in the relevant trials. The extent of such incongruity is difficult to judge from the CS because of the lack of information provided about observed survival in RCTs other than REVEL; the only information provided was log HR NMA inputs (see above) and hazard ratio outputs from the NMA. Therefore the ERG has attempted to provide more detailed survival information for these important trials.

In view of the concerns outlined above, the ERG has estimated LYG and progression-free life months gained (PFLMG) using, as far as possible, the observed data from the relevant trials (thereby retaining the properties of shape and temporal dispersion of the survival curves observed in the trial). Differences in the observed survival in the control arms of the trials were also examined (**Error! Reference source not found.**). The RCT for ramucirumab, nintedanib and nivolumab interventions were REVEL, Reck et al (2014)[18], and Brahmer et al 2015[20]. These studies and their published median OS, median PFS and HRs are summarised in Table 4.

Table 4: Survival estimates from key studies of relevance to the NICE scope

Study	Intervention comparator	Median Φ	Difference in medians	Population	HR	Comment
Brahmer 2015 CHECKMATE 017	nivolumab docetaxel	9.2 6.0	3.2	Squamous	0.59	Monotherapy one RCT
Garon 2014 REVEL	Ram+doc docetaxel	10.5 9.1	1.4	All	0.86	Dual therapy One RCT
	Ram+doc docetaxel	8.2 9.5	1.3	Squamous	0.88	Dual therapy One RCT
	Ram+doc docetaxel	11.1 9.7	1.4	Non squamous	0.83	Dual therapy One RCT
Paz-Arez 2015 (abs)	Ram+doc docetaxel	11.2 9.8	1.4	Adenocarcinoma	0.83	Dual therapy One RCT
Kasahara 2015 (abs)§§	Ram+doc docetaxel	NR	NR	ERGF +ve	NR	Dual therapy One RCT
Reck 2014 LUME1-Lung	Nin+doc docetaxel	12.6 10.3	2.3	Adenocarcinoma	0.83	Dual therapy One RCT
	Nin+doc docetaxel	10.1 9.1	1.0	All *	0.94	Dual therapy One RCT

Φ months. * NICE only recommend nintedanib for NSCLC adenocarcinoma. §§analysis of a very small subgroup at risk of imbalance.

ramucirumab (relative to docetaxel) may be less than that observed in the trials for the comparator treatments.

Table 5: Estimated LYG over a 15 year time horizon estimated using separate unadjusted loglogistic models for each arm¥

STUDY	Population	Intervention LYG	Control LYG	Intervention Gain
REVEL	Non squamous	RAM **1.805**	DOC **1.589**	**0.216**
Brahmer 2015 CHECKMATE 017	Squamous	Nivolumab **2.14**	DOC **1.36**	**0.780**
REVEL	Squamous	RAM **1.371**	DOC **1.205**	**0.166**
Reck 2014 LUME 1 lung	Adenocarcinoma	Nintedanib **1.891**	DOC **1.436**	**0.455**
REVEL	Adenocarcinoma	RAM **1.947**	DOC **1.649**	**0.298**
REVEL*	All	RAM **1.67**	DOC **1.48**	**0.186**

¥ estimates do not include discounting or tapering of the drug effect beyond the observed data. * Data from CS Table 45 using multivariate adjusted model intervention provides LYG estimates of 1.574 and 1.319 for Ramu and Doce arms respectively with an intervention gain of 0.255 LY.
DOC: Docetaxel; LYG: Life years gained; RAM: ramucirumab

Based on the estimates in **Error! Reference source not found.** and Table 5 the proportion of mean LYG that accrues from log logistic model extrapolations is between 31% and 36% for the REVEL trial populations, more than 50% for the squamous Brahmer et al 2015[20] population, and 33% and 23% respectively for the adenocarcinoma nintedanib and docetaxel populations in Reck et al (2014)[18].

Error! Reference source not found. summarises the PFS KM plots for nintedanib, ramucirumab, and nivolumab in patients subgroups categorised by tumour histology (other potentially relevant KM plots are provided in **Error! Reference source not found.**). To be consistent with the manufacturer's approach gamma models of progression fee survival were fit separately for each trial arm and PFLMG were estimated.

treatments varies through time. The covariates included in the multivariate models did not encompass consideration of post progression treatments.

Table 6 shows the data from CS Table 45 in which estimates of the modelled LYG are presented according to various parametric models (either unadjusted or adjusted for patient covariates). The ERG has inserted extra columns showing the gain from ramucirumab + docetaxel relative to placebo + docetaxel for each model. The adjusted multivariate loglogistic models generate the greatest gain for ramucirumab + docetaxel. These models are the only ones to meet the three months survival gain suggested by NICE as an end of life criterion. On the basis that the adjusted loglogistic models provided the best fit to the observed data they were selected by the company for input to the economic analysis.

Table 6: LYG according to adjusted and unadjusted parametric models

	RAM+DOC	**PBO+DOC**		**RAM+DOC**	**PBO+DOC**	
Distribution	**Mean OS (years) (Unadjusted)**	**Mean OS (years) (Unadjusted)**	**RAM+DOC MINUS PBO+DOC**	**Mean OS (years) (Multivariate)**	**Mean OS (years) (Multivariate)**	**RAM+DOC MINUS PBO+DOC**
Exponential	1.278	1.116	0.162	1.289	1.080	0.209
Weibull	1.216	1.068	0.148	1.198	1.012	0.186
Lognormal	1.615	1.396	0.219	1.527	1.285	0.242
Log-logistic	1.659	1.437	0.222	1.574	1.319	0.255
Generalized gamma	1.345	1.166	0.179	1.279	1.073	0.206
It is unclear if these estimates involve implementation of tapering treatment effect to zero after 6 months as is used in the economic model; in practice the difference between tapered and non-tapered estimates are extremely small DOC: Docetaxel; PBO: placebo; RAM: ramucirumab						

Figure 27 of the CS, p129) shows the fit for each of the multivariate adjusted parametric models superimposed on the observed KM plot for each arm of REVEL (all patients). The loglogistic model (CS Figure 27, reproduced as **Error! Reference source not found.**) provides a good fit for the ramucirumab + docetaxel arm but the fit is poorer for the placebo + docetaxel arm (**Error! Reference source not found.**). From about 10 months onward the placebo + docetaxel loglog fit underestimates the observed survival seen in the KM plot. This underestimate of survival for placebo + docetaxel arm relative to ramucirumab + docetaxel would be continued in extrapolation; with these models about 44% of the gain from ramucirumab over PBO + docetaxel is accrued beyond the observed data (estimated with no discounting or "tapering" of drug effect). Since this placebo + docetaxel arm fit is used in the economic model for calculating OS for any comparators (using

Vin+C						£340.12
Erlotinib	21	150mg	Tablets 1	Tablets 21	Unit cost £54.38	Cost £1,142.07
Cost per 3wk cycle						£473.78
*10mg/ml						

Note that the above includes erlotinib. As a consequence, the erlotinib PAS inclusive cost for the above is: £340.12*(25/30) + £1,142.07 *(5/30) * (1- PAS_Erlotinib). This means that the cost effectiveness estimate for ramucirumab + docetaxel compared with docetaxel is very slightly affected by the erlotinib PAS. The effect is negligible.

The annual £7,464 cost for BSC (Table 7) is drawn from the nintedanib submission.

Table 7: PPS BSC costs

	Cost	Per 3wk cycle	% patients
Palliative visit	£74.00	3	100%
Blood transfusion	£140.36	1	50%
Radiotherapy	£126.17	1	50%
Oxygen	£14.24	1	50%
Bone scan	£232.08	1	20%
X-Ray	£29.60	0.28	100%
Cost per 3wk cycle			£417.09

The above costs are inflated to £429.16

SAE costs

Unit costs per SAE are drawn from the nintedanib STA and inflated by 2.9% as drawn from Consumer Prices Index data to arrive at costs in 2014 prices. As for the SAE quality of life decrements, these unit costs are modified by the estimated SAE event rates to arrive at treatment specific SAE costs (Table 8). These costs are applied once within the model during the first cycle.

Table 8: SAE costs by treatment

Toxicity	Cost	RAM+D	DOC	ERL	NIN+D
Neutropenia	£356	48.8%	39.8%	0.0%	12.1%
Febrile neutropenia	£2,070	15.9%	10.0%	0.0%	7.0%
Fatigue	£381	14.0%	10.5%	0.6%	5.7%
Nausea/vomiting	£1,975	1.3%	1.9%	0.0%	0.0%

For the comparison of ramucirumab + docetaxel with docetaxel in the non-squamous population the revised ERG base case results in net costs of £27,268 and a net gain of 0.167 QALYs and so a cost effectiveness estimate of £163k. The comparison with nintedanib + docetaxel has net costs of £12,899 and net gains of 0.008 QALYs and a cost effectiveness estimate of £1.6mn. Probabilistic modelling suggests that there is no probability of ramucirumab being cost effective for willingness to pay values up to £100k per QALY.

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to docetaxel shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS which worsens it to £188k per QALY
- Applying the ERG linear trends OS curves improves it to £114k per QALY.
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £156k per QALY
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £232k per QALY.
- Revising the REVEL PFS QoL values to be treatment specific as might be implied by appendix 11 of the company submission worsens it to £199k per QALY

In the non-squamous subgroup, the cost effectiveness estimate for ramucirumab + docetaxel compared to nintedanib + docetaxel typically suggests small QALY gains or losses which render the cost effectiveness estimate unstable. The base case net cost estimate of £12,899 shows some sensitivity to:

- Applying the Weibull rather than the log logistic for OS worsens it to £13,563
- Reinstating the company drug utilisation percentage for ramucirumab improves it to £11,660
- Assuming the number of ramucirumab administrations is determined by the parameterised PFS curve worsens it to £24,374
- Assuming a febrile neutropenia cost of £7,352 worsens it to £13,372

Not tapering the OS hazard ratio and applying the company hazard ratio for ramucirumab + docetaxel both cause the model to estimate that nintedanib + docetaxel provides small patient gains and so dominates ramucirumab + docetaxel.