NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Necitumumab for untreated advanced or metastatic, squamous non-small-cell lung cancer [ID835]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Necitumumab for untreated advanced or metastatic, squamous non-small-cell lung cancer [ID835]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Necitumumab for untreated advanced, metastatic, squamous 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

- The company presents clinical and cost-effectiveness evidence based on 4 populations within the pivotal trial: intention-to-treat (ITT), Western European, EGFR-expressing (whole trial), and EGFR-expressing Western European. Which population is most appropriate to inform the decision?
- The company presents comparisons with a number of platinum-based chemotherapy regimens, but some comparators specified in the scope were excluded because of a lack of evidence or limited use in clinical practice. Are the comparators presented in the company submission appropriate and sufficient for decision-making?

Clinical effectiveness evidence

- The company presents evidence from the SQUIRE trial, which included people with stage IV tumours and ECOG performance statuses of 0 to 2. Are the results from this trial generalisable to people with advanced, metastatic, squamous NSCLC in England?
- The median survival benefit associated with necitumumab in SQUIRE was 1.6–1.7 months in the ITT and EGFR-expression (whole trial) populations, rising to [redacted] in the Western European and EGFR-expressing Western European populations. Are the benefits associated with necitumumab clinically significant?
- The company presents indirect comparisons between necitumumab and platinum-based chemotherapy regimens using a network meta-analysis, although noted limitation in this analysis. What conclusions can be drawn from this analysis?

Cost effectiveness evidence

- Are the assumptions in the company's economic model appropriate and clinically plausible?
  - What is the most appropriate approach for extrapolating overall survival and progression-free survival?
  - Are the utility scores and utility decrements in the model appropriate?
  - Should the costs associated with testing for EGFR expression be included in the modelling?
- What is the most plausible ICER for necitumumab?

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 necitumumab within its marketing authorisation for untreated advanced, metastatic, squamous non-small-cell lung cancer.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company
Pop.	People with untreated advanced, metastatic, squamous non-small-cell lung cancer	People with locally advanced/metastatic (stage IV) squamous cell non-small-cell lung cancer who have not received prior chemotherapy for this condition	The marketing authorisation was granted for people with EGFR-expressing tumours; results for this population were presented in the response to clarification
Int.	Necitumumab in combination with gemcitabine plus cisplatin		–
Com.	A platinum drug (carboplatin or cisplatin) in combination with: • docetaxel • gemcitabine • paclitaxel • vinorelbine	4–6 cycles of doublet chemotherapy, using either cisplatin or carboplatin in combination with taxanes (paclitaxel, docetaxel), gemcitabine, vinorelbine	Current standard of care in the NHS is gemcitabine + carboplatin or cisplatin Vinorelbine + platinum (the second most common combination) was not included due to lack of evidence
Out.	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life		–

2 The technology and the treatment pathway

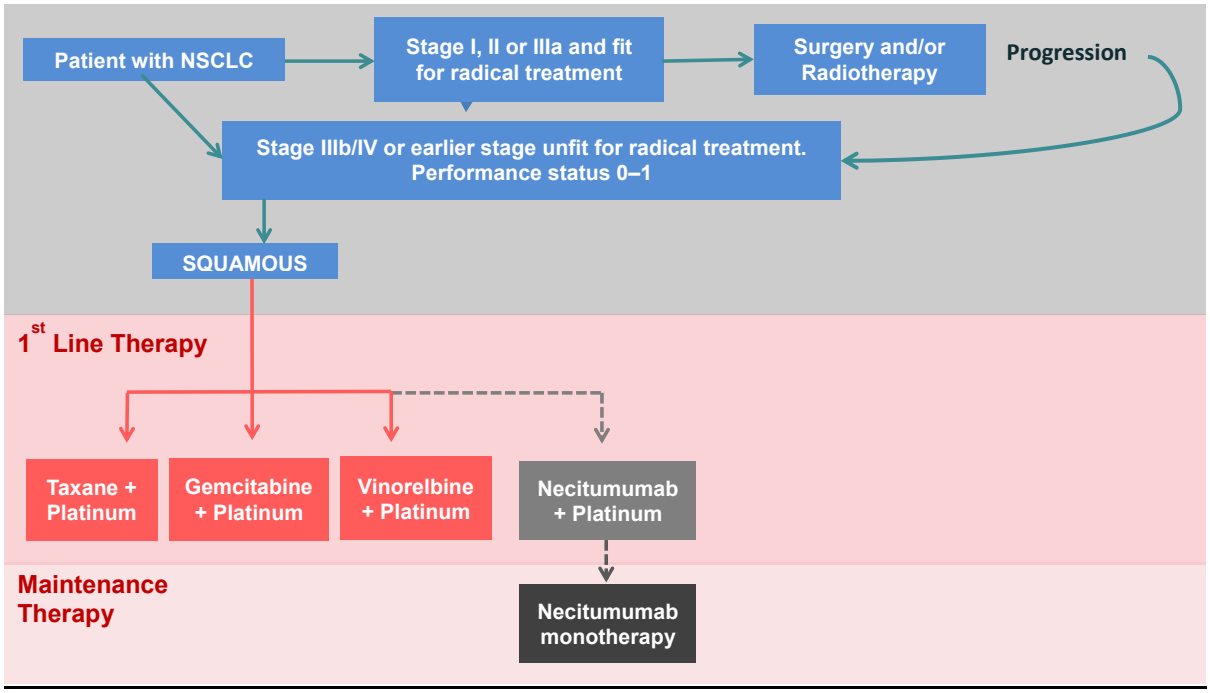
2.1 Necitumumab (Portrazza, Eli Lilly) is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR). It has a marketing authorisation in the UK, in combination with gemcitabine and cisplatin, for treating locally advanced or metastatic EGFR-expressing squamous non-small-cell lung cancer (NSCLC), in adults who have not received prior chemotherapy for this condition. It is administered by intravenous infusion (800 mg on days 1 and 8 of each 3-week cycle); treatment continues in combination with gemcitabine and cisplatin for up to 6 cycles (induction),

followed by necitumumab alone (maintenance) until disease progression or unacceptable toxicity.

2.2 Squamous NSCLC is a type of NSCLC arising from the flat, surface-covering cells in the airways, and comprises about 33% of NSCLC cases. The treatment pathway for squamous NSCLC is summarised in Figure 1. NICE clinical guideline 121 recommends that people with stage III or IV squamous NSCLC and good performance status (Eastern Cooperative Oncology Group [ECOG] status 0–1) should be offered chemotherapy with platinum (cisplatin or carboplatin) in combination with a third-generation drug (gemcitabine, vinorelbine, paclitaxel or docetaxel). The company stated that platinum in combination with gemcitabine is the most commonly used first-line treatment for squamous NSCLC ([redacted] of cases) followed by platinum in combination with vinorelbine ([redacted]); carboplatin is the most commonly used platinum drug ([redacted] of cases). The company stated that people whose disease progresses are treated with docetaxel or erlotinib as second-line therapy; NICE technology appraisal 374 does not recommend erlotinib for treating previously treated NSCLC in people with EGFR mutation-negative tumours.

2.3 EGFR is a receptor involved in signalling pathways that contribute to the growth of cancer cells. Most squamous NSCLC tumours (82–95%) express EGFR; that is, EGFR is detectable on the surface of the tumour cells. EGFR expression is distinct from EGFR mutations – mutations in EGFR are an established target for cancer treatments such as erlotinib and gefitinib, but are rare in squamous tumours. Necitumumab is thought to block the EGFR pathway independently of EGFR mutations, and as a result is indicated for treating squamous NSCLC tumours that express EGFR. The ERG stated that tests for EGFR expression are currently not routinely used in clinical practice. It was unclear how this test may be funded and what effect this may have on service provision.

Figure 1 Treatment pathway for non-small-cell lung cancer



Source: Company submission, figure 1

Table 2 Technology

	Necitumumab	**Platinum doublet chemotherapy: cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel or docetaxel**
Marketing authorisation	In combination with gemcitabine and cisplatin, for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small-cell lung cancer, in adults who have not received prior chemotherapy for this condition	Cisplatin, gemcitabine, vinorelbine, paclitaxel and docetaxel: for treating advanced or metastatic (stage 3 or 4) non-small-cell lung cancer* Carboplatin has a marketing authorisation for treating small-cell lung cancer (not indicated for non-small-cell lung cancer)
Administration method	Intravenous: 800 mg on days 1 and 8 of each 3-week cycle In combination with gemcitabine + cisplatin for up to 6 cycles (induction), followed by monotherapy (maintenance) until disease progression	Cisplatin: 50–120 mg/m^2 every 3 to 4 weeks Carboplatin: 400 mg/m^2 every 4 weeks Gemcitabine: 1250 mg/m^2 on days 1 and 8 of each 3-week cycle Vinorelbine: 25–30 mg/m^2 on days 1 and 8 of each 3-week cycle Paclitaxel: 175 mg/m^2 every 3 weeks

			Docetaxel: 75 mg/m^2 every 3 weeks All are administered intravenously
Acquisition cost	*List price:* £1,450 per 800-mg vial (£2,900 per cycle)	*PAS:* £[redacted] per 800-mg vial (£[redacted] per cycle; [redacted]% discount)	*Average NHS price*[¶] Cisplatin: £15.60 per 100-mg vial Carboplatin: £3.51 per 50-mg vial Gemcitabine: £5.11 per 200-mg vial Vinorelbine: £29–329.50 per 10-mg vial Paclitaxel: £3.78 per 30-mg vial Docetaxel: £7.45 per 20-mg vial
Estimated cost per course	Induction[†]: £13,816 Maintenance[‡]: £17,400	Induction[†]: £[redacted] Maintenance[‡]: £[redacted]	Cisplatin[†]: £122.68 Carboplatin[†]: £163.60 Gemcitabine[†]: £352.82 Vinorelbine[§]: £1,334 Paclitaxel[†]: £140.20 Docetaxel[†]: £260.20
[*]For details of the marketing authorisations, please consult the individual summaries of product characteristics. [†]Assuming costs per cycle of £76.70 for gemcitabine, £26.67 for cisplatin, £35.56 for carboplatin, £56.56 for docetaxel and £30.49 for paclitaxel, and a mean duration of 4.6 cycles; company submission, table 6 and company economic model. [‡]Assuming a mean duration of 6 cycles; company submission, table 6. [¶]Source: eMIT data, taken from company submission table 66, except vinorelbine (list price: BNF, accessed April 2016). [§]Assuming a dosage of 25 mg/m^2, the lowest list price of £29 per 10-mg vial, and a mean duration of 4.6 cycles.			

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

3 Comments from consultees

3.1 Clinical and patient experts highlighted the important unmet need for people with advanced squamous NSCLC. They noted that the prognosis for people with this condition is poor, and there have been few advances in treatment in the last 10–25 years. The experts emphasised the value of new treatments for squamous NSCLC.

3.2 The clinical experts stated that gemcitabine in combination with platinum is the standard of care for people with untreated metastatic squamous NSCLC. One expert considered that gemcitabine is more commonly combined with carboplatin than cisplatin, and noted that cisplatin is often unsuitable for people with impaired renal function. This expert considered

that the effect of necitumumab in combination with carboplatin (rather than cisplatin) is unknown.

3.3 The clinical experts described the significant improvements in survival associated with necitumumab in the SQUIRE trial (see section 4.1). They noted that this trial was relevant to clinical practice in the UK. One expert considered that analysis of the results by geographic region was valuable for understanding the applicability of the findings to the UK population. He highlighted that in an analysis of EU5 countries (UK, France, Italy, Spain and Germany), the median overall survival benefits was 3.8 months, and emphasised this benefit was highly important to patients (note that this analysis is similar to the company's Western European population described in section 4.2, but was based on fewer countries and gave a larger median overall survival benefit). Conversely, the other expert considered that the survival benefits were modest and of questionable clinical significance. This expert also noted that, although necitumumab was not associated with markedly worse toxicity than chemotherapy alone, it also did not improve quality of life. Clinical and patient experts emphasised the importance of quality of life for people with squamous NSCLC.

3.4 The clinical experts noted that necitumumab treatment continues as maintenance therapy after the initial induction phase. They stated that, although this would be associated with costs, the impact on service delivery would be minimal as maintenance therapy is well established as part of the treatment of non-squamous NSCLC.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 1 relevant randomised controlled trial: SQUIRE. This was an international, open-label, phase III study in adults with advanced (stage IV) squamous NSCLC who had not

had previous chemotherapy for their lung cancer. Patients were randomised to receive necitumumab in combination with gemcitabine and cisplatin (necitumumab + GCis; n=545) or gemcitabine and cisplatin alone (GCis; n=548). Treatments were administered in 3-week cycles, consistent with their marketing authorisations. In both groups, induction treatment (GCis with or without necitumumab) continued for up to 6 cycles; after this, patients in the necitumumab + GCis group continued to have necitumumab alone (maintenance therapy; median 4 cycles) until disease progression or unacceptable toxicity. Full details of the SQUIRE trial can be found in sections 4.3–4.8 of the company submission.

4.2 The company presented the results from SQUIRE in 4 populations: the intention-to-treat population (ITT; n=1093), patients treated in Western Europe (n=348), and patients with EGFR-expressing tumours in the whole-trial and Western European populations (n=935 and n=300 respectively; referred to in this document as 'EGFR-expressing (whole trial)' and 'EGFR-expressing Western European'; see response to clarification, appendix 1). The EGFR-expressing populations were presented to match the marketing authorisation for necitumumab. Neither the Western European nor EGFR-expressing populations were pre-specified. Patient characteristics for the ITT and EGFR-expressing (whole trial) populations are summarised in Table 3; patient characteristics were well balanced between treatment groups in these populations. Some differences between treatment groups were seen in the Western European populations, notably in the age groups and ECOG performance status; see section 4.7 of the company submission and appendix 1 of the response to clarification for more details. The company highlighted that the SQUIRE trial included people with an ECOG performance status of 0–2; currently available chemotherapies are recommended for people with an ECOG status of 0 or 1.

Table 3 Patient characteristics in the SQUIRE trial: intention-to-treat and EGFR-expressing (whole trial) populations

	Intention-to-treat population		EGFR-expressing (whole trial) population	
	Necitumumab + GCis (n=545)	GCis (n=548)	Necitumumab + GCis (n=462)	GCis (n=473)
Age: median (range), years	62 (32–84)	62 (32–86)	[redacted]	[redacted]
Sex: % male	83%	84%	[redacted]	[redacted]
ECOG status:				
% 0	30%	33%	[redacted]	[redacted]
% 1	61	58%	[redacted]	[redacted]
% 2	9	9%	[redacted]	[redacted]
Race: % white	84%	83%	[redacted]	[redacted]
Smoking status: % smokers	92%	90%	[redacted]	[redacted]

ECOG, Eastern Cooperative Oncology Group; GCis, gemcitabine + cisplatin

Source: developed from company submission table 13 and response to clarification, appendix 1 table 1.

ERG comments

4.3 The ERG considered that SQUIRE was a well-conducted trial, providing a comparison with the current gold-standard treatment in a population that is representative of people seen in clinical practice in England. It highlighted that this trial was large, had a long duration of follow-up, and was not affected by treatment cross-over or other serious sources of bias. The ERG noted that this trial only included people with stage IV NSCLC, and not people with stage III disease, and queried whether the effect of necitumumab might differ in people with less-advanced disease. It also expressed concerns about differences in reporting of some outcomes and subgroups between the company submission, trial publications and clinical study report, suggesting that there was a risk of selective outcome reporting bias. It noted that progression-free survival and tumour response outcomes were not independently reviewed, and so there was a risk of

detection bias in these outcomes. Overall, the ERG considered that SQUIRE was of good quality.

Clinical trial results

4.4 In the EGFR-expressing (whole trial) population, necitumumab + GCis was associated with statistically significant improvements in overall survival and progression free survival (Table 4 and Figure 2). The company stated that the overall survival gain associated with necitumumab of 1.7 months was moderate but clinically significant; it noted that the difference between treatment arms in median progression-free survival (0.23 months) was distorted by the stepped shape of the curve, resulting from radiographic assessment of progression occurring every 6 weeks. Similar results were seen in the ITT population: in this group, necitumumab was associated with gains in median overall and progression-free survival of 1.6 months and 0.2 months respectively. Necitumumab was also associated with improvements in objective response and disease control rates, although these were not statistically significant in the EGFR-expressing (whole trial) population (p=[redacted] and p=[redacted] respectively).

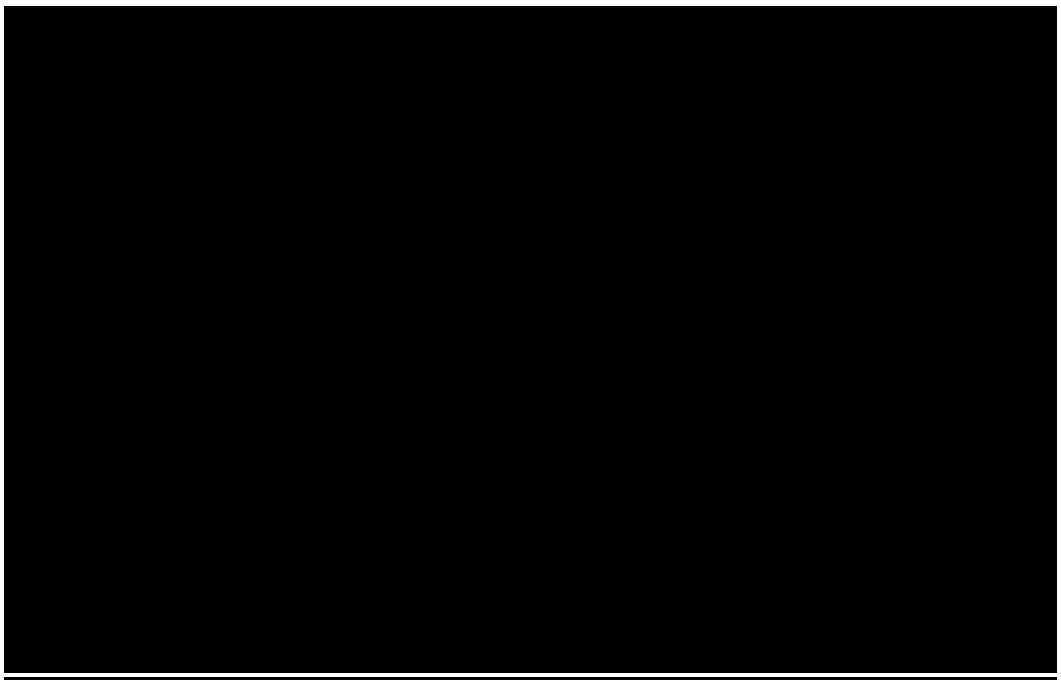
Table 4 Clinical effectiveness outcomes in the SQUIRE trial: EGFR-expressing (whole trial) population

	Necitumumab + GCis (n=462)	**GCis (n=473)**
Overall survival		
Median (95% CI), months	11.73 ([redacted])	9.99 ([redacted])
Hazard ratio (95% CI)	0.79 (0.69 to 0.92) p=0.002	
Progression-free survival		
Median (95% CI), months	5.72 ([redacted])	5.49 ([redacted])
Hazard ratio (95% CI)	0.84 (0.72 to 0.97) p=0.018	

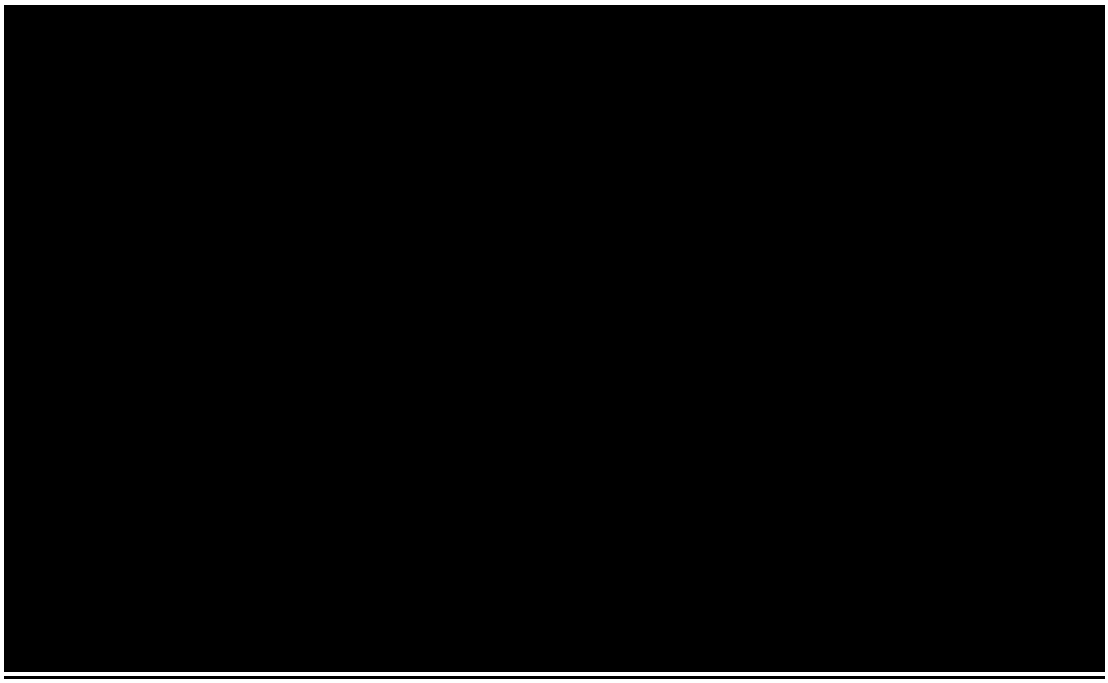
Response rates	
Objective response rate: % (95% CI)	[redacted]
Disease control rate: % (95% CI)	[redacted]
95% CI, 95% confidence interval; GCis, gemcitabine + cisplatin Source: company response to clarification, appendix 1, tables 2, 4 and 8.	

Figure 2 Overall survival and progression-free survival in the SQUIRE trial: EGFR-expressing (whole trial) population

A, overall survival



B, progression-free survival



Source: company response to clarification, appendix 1, figures 1 and 3.

4.5 The effect of necitumumab on quality of life was assessed using the EuroQol EQ-5D questionnaire, the lung cancer symptom scale (LCSS) and changes over time in ECOG status. No apparent differences between necitumumab + GCis and GCis in the deterioration of symptoms, normal activities, quality of life or performance were observed (formal statistical comparisons were not presented); for further details, see section 4.9 of the company submission.

4.6 The company presented results for overall survival and progression-free survival in post-hoc Western European populations. In the Western European and EGFR-expressing Western European populations, necitumumab was associated with a larger improvement in overall survival than was seen in the ITT and EGFR-expressing (whole trial) populations, although the improvement in progression-free survival [redacted] (Table 5). The company presented pre-specified subgroup analyses based on geographical region in its response to clarification (appendix 6); however, evidence for a statistically significant interaction was not presented. The company stated that patients in Hungary and

Poland had better overall survival with GCis than necitumumab + GCis (contrary to other regions), and that a comprehensive analysis of prognostic factors found no substantial imbalances. The company therefore concluded that the difference in effect between the Western European population and the ITT population was caused by an unobserved treatment effect modifier, such as smoking behaviour or social and cultural practices. It noted that there is evidence that the burden of NSCLC (both the incidence and mortality) vary between countries in Europe, and is higher in Eastern Europe. The company considered that the Western European population was the most generalisable population to England.

4.7 The company also presented pre-specified subgroup analyses based on patient and disease characteristics (including age, race, gender, smoking, ECOG status and EGFR expression). These analyses showed a consistent benefit associated with necitumumab. The overall survival benefit with necitumumab was higher in patients with higher EGFR expression (H-score greater than 200), although no statistically significant subgroup interaction effect was observed. In addition, the European Public Assessment Report (EPAR) for necitumumab presents a comparison of the overall survival benefit with necitumumab based on whether the tumour expresses any EGFR (H-score greater than 0): although necitumumab was beneficial in people with EGFR-expressing tumours, no significant difference between necitumumab + GCis and gemcitabine + cisplatin was seen in people without EGFR expression (p-value for subgroup interaction 0.018). For further details of the subgroup analyses, see section 4.8 of the company submission and table 43 of the EPAR.

Table 5 Summary of clinical effectiveness outcomes in the SQUIRE trial by population – Intention-to-treat (n=1093), EGFR-expressing (whole trial) (n=935), Western European (n=348) and EGFR-expressing Western European (n=300) populations

	Necitumumab + GCis	GCis	Difference
Overall survival			
Median (95% CI), months ITT EGFR-expressing (whole trial) Western Europe EGFR-expressing Western Europe	11.5 (10.4–12.6) 11.73 [redacted]	9.9 (8.9–11.1) 9.99 [redacted]	1.6 months [redacted]
HR (95% CI) ITT EGFR-expressing (whole trial) Western Europe EGFR-expressing Western Europe	0.84 (0.74–0.96); p=0.01 0.79 (0.69–0.92); p=0.002 [redacted]		
Progression-free survival			
Median (95% CI), months ITT EGFR-expressing (whole trial) Western Europe EGFR-expressing Western Europe	5.7 (5.6–6.0) 5.72 [redacted]	5.5 (4.8–5.6) 5.49 [redacted]	0.2 months [redacted]
HR (95% CI) ITT EGFR-expressing (whole trial) Western Europe EGFR-expressing Western Europe	0.85 (0.74–0.98); p=0.02 0.84 (0.72–0.97); p=0.018 [redacted]		
95% CI, 95% confidence interval; GCis, gemcitabine + cisplatin; HR, hazard ratio; ITT, intention-to-treat Source: ERG report table 17			

ERG comments

4.8 The ERG stated that it was unclear how clinically meaningful the overall survival benefit associated with necitumumab was. The ERG noted that its clinical adviser considered that these benefits were clinically meaningful.

4.9 The ERG noted that the company considered the Western European population to be the most generalisable population to the population in England, but considered that this population had important limitations. This group was not pre-specified, so had a high risk of bias. Moreover, the ERG considered that the company did not provide adequate justification for using the Western European population:

- There was no clear rationale for why the countries selected were particularly appropriate (and why countries such as Australia, USA and Canada were excluded)
- There was insufficient clinical justification for why the effectiveness of necitumumab may differ between regions
- There was no statistically significant interaction between the Western European population and the remaining patients in the SQUIRE trial.

The ERG considered that the company's explanation focusing on environmental and social factors (see section 4.6) was unconvincing, because such factors would affect both the necitumumab + GCis and the gemcitabine + cisplatin arm. The ERG noted that the small differences between treatment arms in ECOG status in the Western European population may have marginally favoured the necitumumab + GCis arm. The ERG noted that its clinical adviser considered that evidence from all geographical regions would be representative of patients in England. Taking this into account, and noting that the marketing authorisation for necitumumab is specifically for people with EGFR-expressing tumours, the ERG considered that the EGFR-expressing (whole trial) population was the most relevant population for this appraisal.

Indirect comparisons

4.10 The company presented indirect comparisons between necitumumab + GCis and 14 alternative first-line chemotherapy regimens. The analyses were performed in a Bayesian framework using a fixed-effects model, based on data from SQUIRE (ITT population) and 9 other randomised

controlled trials. The primary analysis was based on hazard ratio data; a secondary analysis using median overall survival and progression-free survival was also presented, to allow additional studies and additional comparators (notably vinorelbine + cisplatin) to be included. Full details are provided section 4.10 of the company submission.

4.11 The results of the indirect comparisons suggested that necitumumab was associated with improved overall survival and progression-free survival compared with all regimens included in the analysis (Table 6). However, the 95% credible intervals were wide and many of them crossed 1. Similar results were seen in the secondary analysis; in this analysis, necitumumab + GCis was associated with a higher median overall survival than vinorelbine + cisplatin, although the 95% credible interval crossed 1.

Table 6 Results of the indirect comparisons – analysis of hazard ratio data

Intervention: Necitumumab + GCis	**Comparator:**				
	Paclitaxel + carboplatin	Gemcitabine + cisplatin	Paclitaxel + cisplatin	Docetaxel + cisplatin	Gemcitabine + carboplatin
Overall survival					
Median hazard ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival					
Median hazard ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

95% CrI, 95% credible interval; GCis, gemcitabine + cisplatin.

The company also presented results for nab-paclitaxel + carboplatin, gemcitabine alone, gemcitabine + docetaxel + vinorelbine, gemcitabine + paclitaxel, and erlotinib (progression-free survival only); because these comparators are not in the decision problem, results are not shown here.

Source: company submission tables 25 and 28

4.12 The company highlighted limitations in the network meta-analysis. In particular, it emphasised the wide credible intervals and lack of statistical significance, limitations in the amount and quality of evidence available for

squamous NSCLC populations, and the large number of links in the networks. The company therefore stated that the results should be interpreted with caution.

ERG comments

4.13 The ERG agreed that the company's network meta-analysis had a number of limitations. In addition to those noted by the company, the ERG highlighted 4 key issues.

- The company's systematic review was 1 year out of date, and several studies were excluded inappropriately. The ERG considered that not all relevant trials were included in the analysis.
- The evidence informing the analysis was limited. Of the evidence that was available, much was drawn from subgroups of trials and was therefore likely to be underpowered.
- It was unclear whether the included studies were sufficiently similar, in particular with regard to the length of follow-up and patient characteristics.
- The fixed-effects model, with no adjustment for covariates, may not be appropriate.

Although the ERG noted that there were some statistically significant differences between necitumumab + GCis and some comparators in the analysis, it considered that the results were highly uncertain.

Adverse effects of treatment

4.14 The company presented adverse event data from the 1079 patients in the SQUIRE trial who received at least 1 dose of treatment. The company noted that, because of the maintenance treatment phase, the duration of treatment and observation was longer in the necitumumab + GCis arm; it stated that this may have contributed to a higher incidence of adverse events (AEs) in this arm, and therefore presented results for the induction phase separately.

4.15 The majority of patients in both treatment arms (98–99%) experienced AEs. The most common AEs with severity grade 3 or more included neutropenia, anaemia and thrombocytopenia. Necitumumab + GCis was associated with an increased incidence of grade 3–5 treatment-related hypomagnesaemia, rash, pulmonary embolism and vomiting, compared with GCis. During the induction phase, necitumumab + GCis was associated with an increased risk of serious and severe AEs compared with GCis, whereas deaths from AEs were more common with GCis in this phase. [redacted] Overall, 83 people died from an AE during the study (40 [7.4%] in the necitumumab + GCis arm, 43 [7.9%] in the GCis arm). The company highlighted that the AE findings in the Western European population were similar to the ITT population.

4.16 The company identified a group of AEs of special interest, based on previous experiences with anti-EGFR antibodies and necitumumab. Of these, thromboembolism, skin reactions, hypomagnesaemia and eye disorders were all more common with necitumumab + GCis than GCis; the incidence of fatigue, interstitial lung disease and haematological toxicities was similar between arms.

Table 7 Summary of adverse events in the SQUIRE trial

	Necitumumab + GCis (N = 538)		GCis (N = 541)
	Induction	Maintenance	
AEs			
Patients with 1 or more AE	99.1%	77.5%	97.8%
Toxicity grade ≥3	67.7%	28.7%	61.6%
Leading to treatment delay/modification	60%		58%
Leading to discontinuation	31%		25%
SAEs and deaths			
Treatment-emergent SAEs	42.6%	17.1%	37.5%
Deaths related to AEs (excluding disease	5.9%	3.6%	6.8%

progression)		
Treatment-related AEs, grade ≥3, more common with necitumumab		
Hypomagnesaemia	9%	1%
Rash	4%	<1%
Pulmonary embolism	3.5%	2%
Vomiting	2.8%	<1%

AE, adverse event; GCis, gemcitabine + cisplatin; SAE, serious adverse event;
Source: company submission section 4.12 and table 39.

ERG comments

4.17 The ERG commented that the AEs seen in the EGFR-expressing (whole trial) population (company response to clarification, appendix 1) generally reflected those in the ITT population. It noted that rates of hypomagnesaemia were higher in the EGFR-expressing (whole trial) population than the ITT population, whereas rash was less common in the EGFR-expressing (whole trial) population.

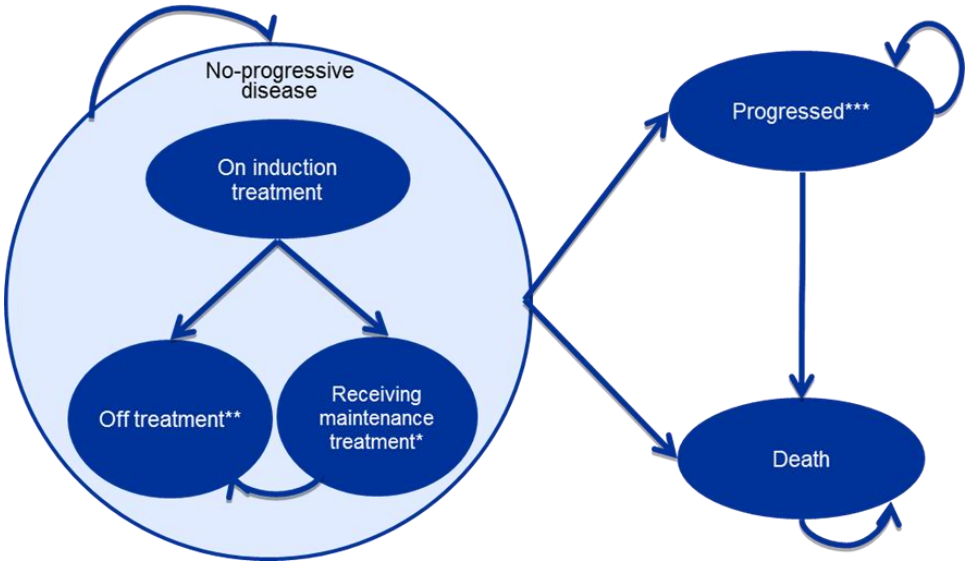
5 Cost-effectiveness evidence

Model structure

5.1 The company presented a state-transition model with 3 health states: pre-progression, post-progression and death. The pre-progression state was divided into 3 treatment states reflecting induction therapy, maintenance therapy and completion or discontinuation of treatment. Patients entered the model in the pre-progression, on induction state, from which they could move through the treatment states or, if their disease progressed, to the post-progression health state. The model structure is summarised in Figure 3.

5.2 The company's model used a cycle length of 1 week and had a lifetime time horizon. 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



Source: company submission figure 36

ERG comments

5.3 The ERG considered that the company's model was appropriately structured, appropriate for the decision problem and well implemented.

Model details

5.4 The model population comprised adults with advanced, metastatic, squamous NSCLC who had not had previous chemotherapy for their lung cancer. The company presented its base-case analysis based on the EGFR-expressing Western European population (response to clarification). Analyses were also presented based on the other populations from SQUIRE (ITT, Western European, and EGFR-expressing (whole trial); see section 4.2). The results from the Western European analysis can be found in section 5.7 of the company submission and are not summarised here (for brevity and consistency with the marketing authorisation).The company stated that it considered that the EGFR-expressing Western European and Western European populations were most generalisable to the NHS in England.

5.5 The company presented a direct comparison of necitumumab + GCis with gemcitabine + cisplatin, based on data from the SQUIRE trial, and an indirect comparison of necitumumab + GCis with gemcitabine + carboplatin, paclitaxel + carboplatin and docetaxel + cisplatin using evidence from the company's network meta-analysis. The company stated that vinorelbine + cisplatin, vinorelbine + carboplatin and docetaxel + carboplatin were not included in the analysis because of insufficient evidence, whereas paclitaxel + cisplatin was excluded because it is rarely used in clinical practice.

5.6 The proportion of people in each health state in each cycle was based on overall survival, progression-free survival and time to treatment discontinuation data, using a partitioned-survival (or 'area under the curve') approach. Overall survival and progression-free survival were based initially on survival data from SQUIRE (up to 36 months), followed by extrapolation over the model's time horizon. The company identified extrapolation models based on the form of each potential function, whether the proportional hazards assumption was met, goodness of fit and clinical plausibility:

- For the direct comparison of necitumumab + GCis with gemcitabine + cisplatin, the company used log-logistic functions, separately fitted to each treatment arm, to extrapolate both overall survival and progression-free survival.
- For the indirect comparisons, the company used a Weibull function fitted to the necitumumab + GCis arm of SQUIRE. This was adjusted for each comparator using the hazard ratios for overall survival and progression-free survival taken from the company's network meta-analysis. The company stated this method was based on the proportional hazards assumption (although this assumption was not met), and so a Weibull function was more appropriate than log-logistic for this analysis. It should be noted that, because of this use of different

extrapolation functions, the results for necitumumab + GCis differ between the direct and indirect comparisons.

Full details are available in section 5.3 of the company submission.

5.7 Health-related quality of life was incorporated into the model by applying utility scores to each health state (Table 8). The utility scores for the pre-progression states were derived from EQ-5D utility index data collected in SQUIRE, valued using the UK value set. The utility score in the post-progression state was based on data from Khan et al. (2015). Quality of life was also affected by adverse events, by applying utility decrements for each event with a severity grade of 3 or 4 and an incidence of at least 2.5% in SQUIRE and grade 3 or 4 febrile neutropenia; the utility decrements were taken from published sources (Nafees et al. [2008], Doyle et al. [2008] and Locadia et al. [2004]) and ranged from 0.0325 (hypomagnesaemia) to 0.32 (pulmonary embolism).

Table 8 Health state utility values in the company model

	Utility value
Pre-progression	
Induction therapy	[redacted]
Maintenance therapy	[redacted]
No treatment	[redacted]
Post-progression	0.55

5.8 The model included costs associated with drug acquisition and administration, disease monitoring and supportive care, adverse events and end-of-life care. Drugs were assumed to be given in regimens consistent with their marketing authorisations or, where different, the key clinical trials. The duration of therapy was based on time to discontinuation data from SQUIRE adjusted to reflect treatment delays in this trial. Costs for second-line chemotherapy with either docetaxel or erlotinib were included in the post-progression health state. Resource use associated with disease monitoring and adverse events were based on a

retrospective chart review of people with squamous NSCLC and a study by Brown et al. (2013). Costs were derived from NHS reference costs, PSSRU the BNF, the Commercial Medicines Unit's Electronic Market Information Tool (eMIT) and, for the necitumumab acquisition cost, the patient access scheme.

ERG comments

5.9 The ERG considered that the company's approach was generally appropriate, and it agreed with most of the company's assumptions. It commented that the model parameters were appropriate, clinically plausible and based on the best available evidence. The ERG considered that the company's approach to estimating resource use and costs, including a retrospective chart review, was well conducted and very thorough. Although it queried the relevance of second-line treatment with erlotinib and commented that more recent eMIT data are available, overall the ERG considered that the costs included were appropriate and comprehensive.

5.10 The ERG highlighted 2 key uncertainties in the company's modelling: the population and the extrapolation of overall survival and progression-free survival. These uncertainties strongly influenced the results of the economic model.

- The ERG re-iterated its concerns about the appropriateness and robustness of using evidence from the EGFR-expressing Western European population of SQUIRE (see section 4.9). It considered that it would be more appropriate to use the overall survival and progression-free survival data from the EGFR-expressing (whole trial) population in the economic model – that is, not to use the post-hoc population based on geographical region. The ERG also highlighted the utility scores for the pre-progression states were based on the Western European population; it noted that the corresponding utility scores from the ITT population were lower ([redacted] for the induction,

maintenance and off treatment states respectively), which would reduce the benefits associated with necitumumab.

- The ERG highlighted that, by extrapolating overall survival and progression-free survival only after the end of the trial data, the company's model had been strongly influenced by the later stages of the survival data. At this point, few patients remained in the analysis so the data were uncertain and had wide confidence intervals. The ERG commented that this approach tended to favour necitumumab. In addition, the ERG considered that the company's log-logistic extrapolation function exaggerated the number of people who would survive in the longer term, and was therefore not clinically plausible for people with advanced squamous NSCLC.

5.11 In addition, the ERG noted 3 further limitations in the company's model.

- Although the exclusion of vinorelbine + cisplatin, vinorelbine + carboplatin and docetaxel + carboplatin from the analysis was justified, it was not necessary to omit paclitaxel + cisplatin. The ERG acknowledged that this combination is rarely used in practice, but stated that it could have been included in the analysis (consistent with the scope) for completeness.
- The ERG noted that the utility decrements used to reflect adverse events in the model were based on data that did not match the NICE reference case (that is, they were not based on EQ-5D and time trade-off). Moreover, it may not have been necessary to include these decrements, because people in the SQUIRE trial would have taken adverse events into account when completing the EQ-5D. The utility decrements associated with adverse events were not important drivers of the economic model results.
- The ERG highlighted that costs associated with testing for EGFR expression were not included in the economic model. It understood that this test would be required to meet the marketing authorisation for necitumumab, but is not currently routinely performed in clinical

practice. It considered that this would increase the costs associated with necitumumab, although the cost of the test was unknown.

Company's base-case results and sensitivity analysis

5.12 In the company's base case (EGFR-expressing Western European population), necitumumab + GCis was associated with additional costs of £19,516 and 0.338 additional quality-adjusted life years (QALYs), compared with gemcitabine + cisplatin, giving an incremental cost-effectiveness ratio (ICER) of £57,725 per QALY gained. In the indirect comparison with gemcitabine + carboplatin, paclitaxel + carboplatin and docetaxel + cisplatin, necitumumab + GCis was associated with ICERs ranging from £59,031 to £116,344 per QALY gained.

5.13 The company presented a scenario analysis based on the EGFR-expressing (whole trial) population. In this population, the ICER for necitumumab + GCis compared with gemcitabine + cisplatin was considerably higher than the EGFR-expressing Western European population, rising to £110,248 per QALY gained (corrected by the ERG; see ERG report pages 14 and 133).

Table 9 Results of the company's base case analysis: EGFR-expressing Western European population

	Total costs	Total LYG	Total QALYs	Necitumumab + GCis vs comparator:		
				Incr costs	Incr QALYs	ICER (£/QALY)
Direct comparison						
Necitumumab + GCis	[redacted]	[redacted]	[redacted]			
GCis	[redacted]	[redacted]	[redacted]	£19,516	0.338	£57,725
Indirect comparison						
Necitumumab + GCis	[redacted]	[redacted]	[redacted]			
GCarbo	[redacted]	[redacted]	[redacted]	£20,316	0.344	£59,031
DCis	[redacted]	[redacted]	[redacted]	£19,948	0.312	£63,982
PCarbo	[redacted]	[redacted]	[redacted]	£20,036	0.172	£116,344

DCis, docetaxel + cisplatin; GCarbo, gemcitabine + carboplatin; GCis, gemcitabine + cisplatin; ICER, incremental cost-effectiveness ratio; incr, incremental; LYG, life year gained; PCarbo, paclitaxel + carboplatin; QALY, quality-adjusted life year

Source: adapted from company response to clarification, appendix 1, tables 22 and 23

5.14 The company presented both deterministic and probabilistic sensitivity analyses, in the EGFR-expressing Western European population. The deterministic sensitivity analysis showed that the model results were most sensitive to overall survival, treatment discontinuation for necitumumab, drug acquisition costs for necitumumab and progression-free survival. The company conducted a probabilistic sensitivity analysis, but did not present probabilistic ICERs; the cost-effectiveness acceptability curves suggested that the probability that necitumumab + GCis was cost effective was negligible if the maximum acceptable ICER were £20,000, £30,000 or £50,000 per QALY gained (see company submission, appendix 1 figure 21 and ERG report figure 11).

ERG comments

5.15 The ERG highlighted that the company presented its results as pairwise comparisons, rather than a fully incremental comparison as specified in the NICE reference case. In an incremental analysis of the company's base case (EGFR-expressing Western European population), docetaxel + cisplatin and gemcitabine + cisplatin were dominated, and the ICER for necitumumab + GCis was £116,344 per QALY gained, compared with the next best non-dominated comparator (paclitaxel + carboplatin). At the same time, the ERG noted that the differences in costs and effectiveness between the comparators was small; this was consistent with advice the ERG received from its clinical adviser, which stated that all of the platinum combination regimens are equally effective. The relevance of the differentiation between the individual comparators is therefore unclear.

Company scenarios

5.16 In addition to its scenario analysis relating to the EGFR-expressing (whole trial) population (see section 5.13), the company presented a series of

scenario analyses to explore uncertainties and assumptions in the economic model. These included alternative sources of utility scores, a different treatment discontinuation assumption, alternative overall survival extrapolation functions, a 5-year time horizon (to censor the 'tail' of the log-logistic survival function) and a different definition of disease progression. The results are summarised in Table 10. Notably, the use of alternative survival extrapolations or a 5-year time horizon substantially increased the ICER for necitumumab + GCis compared with gemcitabine + cisplatin.

Table 10 Results of the company's scenario analyses: EGFR-expressing Western European population, necitumumab + GCis compared with gemcitabine + cisplatin

Scenario		**ICER (£/QALY)**
Base-case		**£ 57,725**
1)	Utilities from Chouaid et al. and adverse event decrements from Nafees et al.	£ 57,788
2)	Utility post-progression from Chouaid et al.	£ 55,751
3)	Time to treatment discontinuation assumed same as GCis for all comparators	£ 64,713
4)	ITT patient population[1]	£ 151,152 *[ERG corrected: £110,248]*
5)	Overall survival extrapolation: Weibull[1]	£ 87,543 *[ERG corrected: £79,412]*
6)	Overall survival extrapolation: log-logistic for necitumumab + GCis and Weibull for GCis[1]	£ 53,433 *[ERG corrected: £49,802]*
7)	Overall survival extrapolation: exponential[1]	£ 78,868 *[ERG corrected: £73,194]*
8)	5-year time horizon[1]	£ 83,205 *[ERG corrected: £76,744]*
9)	Symptomatic deterioration considered progression[1]	£ 64,251 *[ERG corrected: £57,354]*

[1]The ERG highlighted that in the company submission, scenarios 4–9 also included the assumption that time to discontinuation was the same as GCis for all comparators (that is, the amended assumption in scenario 3, rather than the base-case assumption). The ERG presented corrected figures using the base-case assumption, shown here in italics.

GCis, gemcitabine + cisplatin; ICER, incremental cost-effectiveness ratio; ITT, intention-to-

treat; QALY, quality-adjusted life year
Source: company response to clarification, appendix 1, table 38 and ERG report table 45

ERG exploratory analyses

5.17 The ERG identified and corrected a small number of errors and inconsistencies in the company's economic model. It stated that none of these substantially affected the model results.

5.18 The ERG presented an exploratory analysis based on its preferred assumptions. This analysis used outcomes from the EGFR-expressing (whole trial) population and extrapolated overall survival and progression-free survival using Weibull functions, from the last timepoint at which at least 20 patients remained in the analysis. The ERG stated that this approach reduced the dependence on the later stages of the curves when few patients remained; it considered that the Weibull function was more clinically plausible than a log-logistic function and fitted similarly well to the data. This analysis was presented as probabilistic results, and included paclitaxel + cisplatin as a comparator for completeness. In this analysis, necitumumab + GCis was associated with an ICER of £169,612 per QALY gained, compared with the next best, non-dominated comparator, gemcitabine + cisplatin (Table 11).

Table 11 Results of the ERG's preferred analysis: EGFR-expressing (whole trial) population, probabilistic results

	Total costs	Total QALYs	Incr costs	Incr QALYs	ICER (£ per QALY)	Comparison
PCis	[redacted]	[redacted]			-	
DCis	[redacted]	[redacted]	-	-	Extendedly dominated	
PCarbo	[redacted]	[redacted]	£1,001	0.135	£7,429	vs PCis
GCarbo	[redacted]	[redacted]	-	-	Dominated	
GCis	[redacted]	[redacted]	£1,579	0.013	£124,663	vs PCarbo
Necitumumab + GCis	[redacted]	[redacted]	£19,993	0.118	£169,612	vs GCis
DCis, docetaxel + cisplatin; GCarbo, gemcitabine + carboplatin; GCis, gemcitabine +						

cisplatin; ICER, incremental cost-effectiveness ratio; incr, incremental; PCarbo, paclitaxel + carboplatin; PCis, paclitaxel + cisplatin; QALY, quality-adjusted life year
Source: ERG report, table 50

5.19 The ERG presented 16 exploratory scenario analyses, to further examine the sensitivity of the model to key assumptions (Table 12). It noted that all of its analyses illustrated the sensitivity of the model to changes in overall survival, progression-free survival and time to treatment discontinuation estimates. In addition, the ICERs in all analyses were above £100,000 per QALY gained, except the ERG's most optimistic scenario. In that scenario (based on a log-logistic extrapolation function for necitumumab + GCis and a Weibull function for gemcitabine + cisplatin), the ICER decreased to £84,188 per QALY gained; however, the ERG considered that this scenario did not provide realistic estimates of overall survival for the modelled population. Further details can be found in section 4.4.2 of the ERG report.

Table 12 Results of the ERG's exploratory scenario analyses

	Necitumumab + GCis versus GCis			**Necitumumab + GCis versus next best comparator**			
	Incremental		ICER	Incremental		ICER	*Comp-arator*
	Cost	QALYs		Cost	QALYs		
Company analyses							
Base case, direct analysis	**£19,516**	**0.3381**	**£57,725**				
Base case, direct and indirect analysis	£18,918	0.234	£80,912	£20,036	0.172	£116,344	*PCarbo*
Base case with EGFR-expressing (whole trial) population: deterministic	£20,584	0.134	£153,947	£22,148	0.142	£155,654	*PCarbo*
Base case with EGFR-expressing (whole trial) population: probabilistic	£20,591	0.134	£154,024	£21,999	0.116	£189,679	*PCarbo*
ERG analyses							
ERG's preferred analysis	**£19,993**	**0.118**	**£169,612**	**£19,993**	**0.118**	**£169,612**	*GCis*

5-year time horizon	£19,976	0.117	£170,755	£19,976	0.117	£170,755	*GCis*
KM for OS and PFS to final endpoint	£20,474	0.134	£153,085	£22,018	0.142	£154,569	*PCarbo*
KM + Weibull OS and PFS (joint)	£20,037	0.123	£163,154	£21,596	0.132	£163,340	*PCarbo*
KM + log-logistic OS and PFS (separate)	£20,571	0.149	£138,018	£20,571	0.149	£138,018	*GCis*
KM + log-logistic OS and PFS (joint)	£20,608	0.156	£132,263	£20,608	0.156	£132,263	*GCis*
Weibull OS & PFS (separate), no KM	£19,903	0.119	£167,233	£19,903	0.119	£167,233	*GCis*
Log-logistic OS & PFS (separate), no KM	£20,514	0.142	£144,432	£20,514	0.142	£144,432	*GCis*
Log-logistic Necitumumab + GCis and Weibull GCis	£21,152	0.251	£84,188	£22,368	0.205	£109,214	*PCarbo*
GCis OS at lower 95% limit	£20,427	0.185	£110,177	£21,572	0.131	£165,250	*PCarbo*
GCis OS at upper 95% limit	£19,516	0.043	£457,474	£19,516	0.043	£457,474	*GCis*
Necitumumab + GCis OS at lower 95% limit	£19,337	0.039	£493,999	£19,337	0.039	£493,999	*GCis*
Necitumumab + GCis OS at upper 95% limit	£20,666	0.200	£103,574	£21,816	0.145	£150,426	*PCarbo*
Necitumumab + GCis PFS at lower 95% limit	£19,805	0.110	£180,194	£19,805	0.110	£180,194	*GCis*
Necitumumab + GCis PFS at upper 95% limit	£20,106	0.126	£159,862	£21,690	0.132	£163,922	*PCarbo*
Necitumumab + GCis TTD at lower 95% limit	£17,591	0.116	£151,908	£17,591	0.116	£151,908	*GCis*
Necitumumab + GCis TTD at upper 95% limit	£21,943	0.120	£183,597	£21,943	0.120	£183,597	*GCis*

GCis, gemcitabine + cisplatin; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PCarbo, paclitaxel + carboplatin; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

Source: ERG report, table 51

Innovation

5.20 The company highlighted that there have been limited improvements in the survival of people with squamous NSCLC over the last 2 decades, and no new first-line chemotherapies have been licensed in this time. It emphasised that this condition is often difficult to treat, because people are frequently older, have several co-morbidities and are diagnosed at an advanced stage of disease. The company stated that necitumumab is the first drug to provide a consistent, significant survival benefit in the first-line setting.

6 End-of-life considerations

6.1 The company considered that necitumumab fulfils the criteria to be considered as an end-of-life treatment.

Table 13 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Expected survival for people with squamous NSCLC receiving current standard of care is 6.5–9.4 months[1] The ERG agreed that median survival in this population is typically less than 1 year Median survival in the gemcitabine + cisplatin arm of the SQUIRE trial:[2] - EGFR-expressing Western European population: [redacted] - EGFR-expressing (whole trial) population: 9.99 months Mean overall survival with gemcitabine + cisplatin predicted by the economic model:[3] - EGFR-expressing Western European population (company base case): [redacted] - EGFR-expressing (whole trial) population (ERG's preferred analysis): [redacted]
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	Median overall survival benefit associated with necitumumab + GCis (compared with GCis) in SQUIRE:[4] - EGFR-expressing Western European population: [redacted]

	- EGFR-expressing (whole trial) population: 1.7 months Overall survival benefit associated predicted by the economic model:[5] - EGFR-expressing Western European population (company base case): mean 6.5 months, median 2.99 months - EGFR-expressing (whole trial) population (ERG's preferred analysis): mean 2.25 months, median 1.61 months
The treatment is licensed or otherwise indicated for small patient populations	Company estimated that 2,575 people have locally advanced or metastatic squamous NSCLC *(32,364 people with lung cancer, of whom 84% have NSCLC, 33% have squamous tumours, 48% have stage IIIB or IV disease and 60% receive 1st-line treatment[1,6])* The ERG highlighted that the population with EGFR-expressing tumours is likely to be smaller
[1]Company submission, page 134; [2]Company response to clarification, appendix 1, tables 2 and 3; [3]Company response to clarification, appendix 1, table 22 and ERG report, table 49; [4]Company submission, section 4.7 and company response to clarification, appendix 1, section 1; [5]Company response to clarification, appendix 1, tables 22 and 24 and ERG report, table 49; [6]Company submission, page 233	

7 Equality issues

7.1 The company stated that it did not anticipate any equality issues associated with this appraisal. No equality issues were identified during the scoping process.

8 Authors

Ian Watson

Technical Lead

Nwamaka Umeweni

Technical Adviser

with input from the Lead Team (Paula Ghaneh, Simon Dixon and Malcolm Oswald).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003886/WC500202696.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Necitumumab as a first-line treatment of locally advanced or metastatic squamous non-small-cell lung cancer [ID: 835]

Prepared by Eli Lilly and Company

Company evidence submission

January 20 2016

File name	Version	Contains confidential information	Date
Necitumumab_squamous_NSCLC ID835_MainSubmission_18012016	**Final**	**Yes**	**18/01/2016**

Please note academic in confidence (AIC) information are underlined and highlighted in yellow

Commercial in confidence (CIC) information are underlined and highlighted in turquoise

Contents

Tables and figures

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List of abbreviations

AE	Adverse event
AESI	Adverse Events of Special Interest
AIC	Akaike Information Criteria
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
ANC	Absolute neutrophil cell count
ASCO	American Society of Clinical Oncology
ASR	Age-standardised rates
AST	Aspartate transaminase
ATE	Arterial thromboembolic event
BATMAN	BAysian Tool for Meta-Analysis of Networks
BIC	Bayesian information criteria
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CG	Clinical guideline
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CT	Computed tomography
Ctx =	Chemotherapy
DCis	Docetaxel plus cisplatin
DCR	Disease control rate
DIC	Deviance Information Criterion
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
eCRFs	Electronic case report forms
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMIT	Electronic market information tool
EOL	End-Of-Life
EQ-5D	Euro-Qol-5D
ERG	Evidence review group
EU	European Union
FDA	Food and Drug Administration
GCarbo	Gemcitabine plus carboplatin
GCis	Gemcitabine plus cisplatin

GCis	Gemcitabine plus cisplatin
GP	General practitioner
HR	Hazard ratio
HRQOL	Health related quality of life
HSR	Hypersensitivity reactions
HUI	Health Utilities Indexes
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
LYG	Life year gain
Mai	Maintenance
MCMC	Markov Chain Monte Carlo
MedDRATM =	Medical Dictionary for Regulatory Activities
N	Necitumumab
NA	Not Applicable
NCPE	National Centre for Pharmacoeconomics
NE	Not evaluable
NHS	National Health Services
NHS EED	NHS Economic evaluation database
NHS/PSS	NHS personal social services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PASLU	Patient access schemes liaison unit |
PCarbo	Paclitaxel plus carboplatin
PCis	Paclitaxel plus cisplatin
PD	Progressive disease
PFS	Progression free survival
PH	Proportional hazards
PK	Pharmacokinetics
PP	Per protocol

PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life years
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAEs	Serious adverse events
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
SD	Standard deviation
SF-36	Short Form 36 Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
SQUIRE	SQUamous NSCLC treatment with the Inhibitor of EGF Receptor
STA	Single technology assessment
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TK	Tyrosine kinase
TSD	Technical support document
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTO	Time to trade-off
ULN	Upper limit of normal
VAS	Visual analogue scale
VCarbo	Vinorelbine plus carboplatin
VCis	Vinorelbine plus cisplatin
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolic event
WE	Western Europe
WHO	World Health Organization
WTP	Willingness to pay

1. Executive summary

Squamous non-small-cell lung cancer is a distinct disease with difficult to treat patients. There are currently no targeted first-line biologic treatments available for use in England for patients with locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC). No new chemotherapies have been approved in first-line squamous NSCLC by the EMA in the last two decades. This is due to the lack of relevant oncogenic drivers to inform the treatment discussion, exacerbated by the fact that patients are older and, with over 90% also being smokers, they frequently experience several comorbidities. The median survival for patients with squamous NSCLC receiving current therapy is between 6.5 and 9.4 months (1).

Patients with lung cancer suffer more distressing symptoms than other types of cancer patients (2) and frequently experience multiple symptoms such as pain, fatigue, anxiety, depression, breathlessness and cough (3). Increased symptom distress not only has an impact 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 (3).Thus therapies are evaluated not only on their effect on overall survival (OS) but also impact on quality of life (QoL).

Necitumumab is a new treatment that will be available as a first-line treatment option in patients suffering from locally advanced or metastatic squamous non-small-cell lung cancer who have not received prior chemotherapy for this condition. This treatment will offer a clinically meaningful OS and PFS advantage over existing therapy with manageable toxicity and no detrimental effect to QoL. Necitumumab qualifies as an end of life (EOL) treatment and can provide health-related benefits to patients suffering from locally advanced or metastatic squamous NSCLC.

1.1 Statement of decision problem

This submission presents the clinical and economic data for necitumumab in combination with gemcitabine and cisplatin (GCis + N) in people with locally advanced or metastatic squamous non-small cell lung cancer who have not received prior chemotherapy for this indication. Necitumumab in combination with gemcitabine and cisplatin has been compared to standard of care in England which is a combination of a single third generation drug

(docetaxel, gemcitabine, paclitaxel) plus a platinum drug (either cisplatin or carboplatin). The decision problem for this submission is specified in 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 untreated advanced, metastatic, squamous non-small-cell lung cancer	Patients with locally advanced/metastatic (stage IV) squamous cell non-small cell lung cancer who have not received prior chemotherapy for this condition	The submission includes patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment. This population is consistent with the SQUIRE trial and NICE scope; however, it is not consistent with the indication provided in the summary of product characteristics for necitumumab. Additional analysis will be provided to NICE at a later stage to reflect this population.
Intervention	Necitumumab in combination with gemcitabine plus cisplatin	Necitumumab 800 mg (flat dose IV) on days 1 and 8 of each 21-day cycle, in combination with gemcitabine 1250 mg/m^2 (IV) on days 1 and 8 and of each 21-day cycle and cisplatin 75mg/m^2 IV on days 1 of each 21-day cycle, up to 6 cycles. Necitumumab 800mg monotherapy (flat dose IV) on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.	N/A
Comparator (s)	A platinum drug (carboplatin or cisplatin) in combination with: • docetaxel • gemcitabine • paclitaxel • vinorelbine	Four to six cycles of doublet chemotherapy, using either cisplatin or caboplatin in combination with taxanes (paclitaxel, docetaxel), gemcitabine, vinorelbine. Current standard of care in the NHS is gemcitabine+carboplatin/cisplatin.	Vinorelbine in combination with a platinum drug has not been included in the analysis due to lack of studies that would allow direct or indirect comparison against GCis + N. The market share data showed that Vinorelbine in combination with platinum drug (17%) is the second most commonly used first-line treatment in the UK.

Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	• Health related quality of life • Overall survival • Progression free survival • Response rates • Adverse effects of treatment	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. 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.	A cost-utility analysis of treatments, expressed in incremental cost per quality-adjusted life year. The time horizon of the model is a lifetime. Costs will be considered from the NHS and Personal Social Services perspective.	N/A
Subgroups to be considered	None	No identified subgroups	
Special considerations including issues related to equity or equality	None	Currently available treatments are recommended for patients with an ECOG PS 0-1. Necitumumab has been found to be clinically effective in patients with an ECOG PS 0-2.	

N/A: Not Applicable; ECOG: Eastern Cooperative Oncology Group; PS: Performance status

1.2 Description of the technology being appraised

Table 2 Technology being appraised

UK approved name and brand name	Approved name: Necitumumab Brand name: Portrazza®
Marketing authorisation/CE mark status	Necitumumab received a positive opinion from the EMA on 17th December 2015. Necitumumab will receive marketing authorisation for first-line treatment of squamous-cell NSCLC in early March 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Necitumumab in combination with gemcitabine and cisplatin (GCis + N) is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition. Following induction therapy, necitumumab monotherapy is continued until disease progression or unacceptable toxicity.
Method of administration and dosage	Necitumumab 800 mg (flat dose IV) on days 1 and 8 of each 21-day cycle.

1.3 Summary of the clinical effectiveness analysis

SQUIRE trial

Necitumumab has been studied in a large, phase III, multinational (n=26) multicenter (n=184) two arm open-label trial, called SQUIRE, which included patients with advanced stage IV squamous NSCLC who have not received prior chemotherapy for this condition. In total 1093 patients were randomised in the trial: 545 patients to GCis + N arm and 548 patients to GCis arm. Median duration of follow-up was 25.2 months (95% CI 23.7 to 27.1) in the GCis + N arm and 24.8 months (95% CI 22.8 and 28.3) in the GCis arm. The clinical effectiveness analysis has been explored for two population groups – the intention-to-treat (ITT) populations (includes all randomised patients receiving the study drugs) and the Western European subpopulation (patients from Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, Belgium)

Primary and secondary outcomes

Overall survival (OS) for the ITT population was statistically significantly improved among patients in the GCis + N Arm compared with those in the GCis Arm (HR = 0.84 [0.74, 0.96]; p = .01). The median OS was 11.5 months in the GCis + N Arm and 9.9 months in the GCis Arm. Survival rates at 1 and 2 years also favored the necitumumab arm. The 1-year survival rates were 47.7% and 42.8% in the GCis + N and GCis Arms, respectively; the corresponding figures for 2-year survival were 19.9% and 16.5%.

Progression-free survival (PFS) for the ITT population was statistically significantly improved among patients in the GCis + N Arm compared with those in the GCis Arm (HR = 0.85 [0.74, 0.98]; p = .02). The median PFS was 5.7 months in the GCis + N Arm and 5.5 months in the GCis Arm.

Time to Treatment Failure (TTF) was statistically significantly improved in the GCis + N Arm compared to patients in the GCis Arm (HR = 0.844 [0.747, 0.953]; p=0.0061). The median TTF was 4.3 months in the GCis + N Arm and 3.6 months in the GCis Arm.

OS for the Western Europe subpopulation was statistically significantly improved among patients in the GCis + N Arm compared with those in the GCis Arm [redacted]. The median OS was [redacted] months in the GCis + N Arm and [redacted] months in the GCis Arm. Survival rates at 1 and 2 years also favored the necitumumab arm. The 1-year

survival rates were [redacted] and [redacted] in the GCis + N and GCis Arms, respectively; the corresponding figures for 2-year survival were [redacted] and [redacted].

PFS for the Western Europe subpopulation was not statistically significant among patients in the GCis + N Arm compared with those in the GCis Arm [redacted]. The median PFS was [redacted] months in the GCis + N Arm and [redacted] months in the GCis Arm.

TTF for the Western Europe subpopulation was not statistically significant among patients in the GCis + N Arm compared to patients in the GCis Arm [redacted]. The median TTF was [redacted] months in the GCis +N Arm and [redacted] months in the GCis Arm.

Subgroup analyses were undertaken for analyses of OS and PFS with respect to prognostic factors (age, sex, race, smoking status and PS) and according to EGFR expression levels (high: H-score ≥200; low: H-score <200).The treatment effect was consistent across all pre-specified subgroups. According to EGFR protein expression, patients with high EGFR expression (H-score ≥200) had more favourable OS than those with low EGFR level (H-score <200). There was no difference between high (H-score ≥200) and low (H-score <200) EGFR expression when assessing PFS.

Patient reported outcomes

The Lung Cancer Symptom Scale (LCSS) is a nine-item questionnaire including six major lung cancer symptoms and three global measures of how the disease affects overall symptoms, normal activities, and quality of life. In the SQUIRE trial, LCSS was assessed by patients prior to the start of each cycle and every 6 weeks thereafter until the patient progressed. Post-hoc analysis of the LCSS found that the addition of necitumumab to gemcitabine and cisplatin substantially improved the poor prognosis associated with higher severity of baseline LCSS items. The addition of necitumumab to gemcitabine and cisplatin substantially improved OS, PFS, and key LCSS outcomes among patients with higher severity of baseline LCSS items.

Adverse events

Due to the design of the study, patients in the GCis + N arm received a maximum of 6 cycles of their treatment regimen and those whose disease did not progress received necitumumab as monotherapy until disease progression. In contrast, patients in the control arm only received treatment with GCis for a maximum of 6 cycles. Therefore, the safety period was slightly longer in the GCis + N arm. Almost 99% of patients in both arm experienced an

adverse event (AE). The proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) of grade ≥3 was slightly higher in the GCis + N arm than in the GCis arm (72% vs. 62%). Most common grade ≥3 AEs in both arms were neutropenia, anaemia and thrombocytopenia.

More patients in the GCis + N arm experienced treatment specific grade ≥3 AEs, these events were hypomagnesaemia (9% vs. 1%), rash (4% vs. <1%), pulmonary embolism (3.5% vs. 2%) and vomiting (2.8% vs. <1%). Patients in the GCis + N arm more frequently experienced arterial and venous thromboembolic events of any grade (arterial: 5.4% vs. 3.9%; venous: 9.1% vs. 5.4%). The number of Grade ≥3 thromboembolic events was also more common in the GCis + N arm (arterial: 5% vs. <1%; venous: 3.9% vs. 2%). However, there was no difference between treatment arms with respect to fatal venous (<1% in both arms) or fatal arterial thromboembolism (<1% in both arms). The safety data obtained in the SQUIRE was consistent with the safety profile expected for an anti-EGFR monoclonal antibody, with skin reactions and hypomagnesaemia being the most commonly reported events in the necitumumab arm.

Network meta-analysis

A network meta-analysis (NMA) was undertaken to compare the survival (OS, PFS) of GCis + N against with those of published RCTs reporting on patients with squamous NSCLC in the first-line setting. Not all studies identified by the systematic literature review reported OS or PFS HRs therefore, secondary analysis were conducted using median survival data. The comparisons relevant to the UK health care setting are those of PCarbo/PCis, GCarbo/GCis, DCis and VCarbo/VCis. Although few studies on Vinorelbine were identified by the systematic literature review, an indirect comparison of GCis + N with Vinorelbine in combination with a platinum agent was not feasible for the primary analysis as these studies could not be connected within the network required to conduct the NMA. The NMA results suggest the comparative value of necitumumab plus gemcitabine and cisplatin in the squamous NSCLC population against other available treatment regimens, although data are limited.

End of life criteria (EOL)

Necitumumab fulfils all the three EOL criteria specified in NICE's 'Supplementary Advice for Appraising life-extending, end of life treatments'. Therefore the supplementary advice should be applied to this appraisal:

- **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**: Median OS for patients receiving current standard of care ranges from 6.5 to 9.4 months

- **There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment:** The modelled mean OS benefit for the Western Europe subpopulation was 5.76 months for GCis + N (19.82 months) when compared to GCis (14.06 months).

- **The treatment is licensed or otherwise indicated for small patient populations:** We anticipate that a small number of patient population (n=2,575) in England would be eligible for first-line treatment with necitumumab (please see Table 3)

Table 3 Eligible patient population in England

Population	Value	Source
Incident cases of lung cancer	32,364	Cases submitted to the National Lung Cancer Audit; LUCADA 2014 (4)
NSCLC (All lung cases excluding small cell and mesothelioma)	84%	LUCADA 2014 (4)
Stage IIIB/IV	48%	Cancer Research UK (5)
Receive 1st line chemotherapy	59.80%	LUCADA 2014 (4)
Squamous proportion	33%	Brown et al. 2013 (6)
Total eligible patient population	**2,575**	

1.4 Summary of the cost-effectiveness analysis

Patient Population

Subgroup analysis based on geographic region found that that the clinical efficacy of necitumumab within the SQUIRE trial does vary across regions. Therefore, a post-hoc analysis was completed for patients in Western Europe (including Austria, Belgium, Germany, France, Greece, Italy, Portugal, Spain and UK). Statistical analysis of the SQUIRE trial found that patients in Hungary and Poland performed better on the GCis arm than the GCis + N. However, patients in Western Europe performed better on the GCis+ N arm than the GCis arm, which is consistent with the findings in the ITT patient population. A comprehensive statistical analysis of this data has been completed on general prognostic factors to determine the cause of this difference. However, the analysis concluded that there were no substantial imbalances in demographics, patient characteristics, exposure to treatment or other prognostic factors between the regions.

Due to the clinical efficacy of necitumumab varying across regions despite no statistically significant difference in demographics or treatment received within the SQUIRE trial, it is believed that this difference in clinical efficacy is a result of unobserved treatment effect modifiers that have been detected within the SQUIRE trial. Potential unobserved treatment effect modifiers include the associated disease burden of squamous NSCLC and environmental causes of cancer including social and cultural practices such as heavy smoking across Europe. Therefore, the economic evidence presented in this submission is based on the Western Europe subpopulation of the SQUIRE trial as it is considered the most generalisable to patients in England and therefore decision making in England.

Model overview

A Markov cohort state transition model was developed to assess the cost-effectiveness of necitumumab in combination with gemcitabine and cisplatin against other available relevant comparators in England. The model tracks patients through three mutually exclusive health states and three treatment states. These health states include:

- Pre-progression
    - On induction treatment
    - Receiving maintenance treatment (discontinued or completed induction therapy and on maintenance treatment)
    - Off treatment (discontinued or completed induction therapy or maintenance therapy and off active treatment)
- Post-progression
- Death

A weekly cycle has been chosen since the administration schedules of gemcitabine, cisplatin and carboplatin are different. Patients start in the pre-progression health state and on first-line induction treatment. Within each weekly cycle, patients can stay in that state, complete induction treatment and receive maintenance treatment ("Pre-progression, receiving maintenance treatment") or discontinue/complete induction treatment or maintenance treatment prior to progression ("Pre-progression, off treatment") or progress or die. In accordance with the NICE reference case an NHS and personal social services (PSS) perspective was used and an annual discount rate of 3.5% and half-cycle correction were applied to costs and benefits. A lifetime time horizon was employed to capture all the costs and benefits relevant for patients receiving the intervention and comparators.

Intervention and comparators

The economic model compares GCis + N to other chemotherapy agents currently used in NHS clinical practice in England for the first-line treatment of locally advanced or metastatic squamous NSCLC. These treatment options include a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either cisplatin or carboplatin) and have been included in the NICE scope for necitumumab. The economic model compares GCis + N to GCis, GCarbo, PCarbo and DCis. The primary comparison in this evaluation is GCis + N compared to GCis, as studied in the SQUIRE trial. The additional comparisons presented are based on indirect comparison data from the NMA. All treatment options were implemented in the model consistent with their marketing authorisation with the exception of GCarbo which is used frequently in the NHS but is not licensed in Europe for advanced NSCLC. This appraisal does not include vinorelbine plus cisplatin as an indirect comparator as a result of an indirect comparison not being possible due to lack of data specific to squamous NSCLC patients treated with vinorelbine plus cisplatin.

Inputs in the model

The OS, PFS and time to treatment discontinuation (TTD) estimates for GCis + N and GCis were calculated by using the Kaplan-Meier (KM) estimates from the SQUIRE trial and long term projections were done by fitting the best-fitting clinically plausible parametric survival curve after the observed period. For OS and PFS, a separately fitting log-logistic parametric survival function was used to extrapolate long term outcomes. For indirect comparators, the OS and PFS curves were estimated by applying the hazard ratios (HRs) from the NMA for indirect comparators versus GCis + N. A separately fitted Weibull parametric survival function was used to estimate OS and PFS curves.

Pooled utilities for the pre-progression states (including on induction, on maintenance and off treatment) were derived from the SQUIRE trial using the EQ-5D-3L. As the utility values for the pre-progression health states were assumed to be equivalent across treatment arms, disutility's for AEs were included to adjust for differences in utility values due to AEs experienced with treatment. Utilities for the post-progression states were obtained from the literature.

Results

Base-case de novo analysis

The perspective of the costs included is the NHS/PSS perspective, and thus reflects the NICE reference case. The measurement of health effects is in terms of quality adjusted life years (QALYs) gained. The time horizon is lifetime and the results are reported as an incremental cost-effectiveness ratio (ICER).

The modelled mean OS benefit of GCis + N compared to GCis is 5.76 months in the Western Europe subpopulation. The corresponding mean discounted QALY is [redacted] per patient. The overall incremental cost per patient is higher in the GCis + N arm (an additional [redacted]) than the GCis arm primarily due to drug acquisition and administration cost. The higher total average cost per patient as well as greater efficacy benefits results in an estimated ICER is £64,713 per QALY when comparing GCis + N to GCis. These findings are consistent across the indirect comparators with an ICER of £60,133/QALY when comparing GCis + N to GCarbo, an ICER of £65,135/QALY when comparing GCis + N to DCis and an ICER of £119,912 when comparing GCis + N to PCarbo.

Table 4 Base-case results of GCis+N vs GCis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCis + N	[redacted]	[redacted]	[redacted]				
GCis	[redacted]	[redacted]	[redacted]	£18,770	0.480	0.290	£64,713

Table 5 Base-case results of GCis+N vs Indirect Comparators

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
GCis + N	[redacted]	[redacted]	[redacted]				
GCarbo	[redacted]	[redacted]	[redacted]	£19,704	0.504	0.328	£60,133
DCis	[redacted]	[redacted]	[redacted]	£19,335	0.464	0.297	£65,135
PCarbo	[redacted]	[redacted]	[redacted]	£19,480	0.227	0.162	£119,912

Sensitivity analyses were conducted and the results indicated that the main drivers of the cost-effectiveness analyses were OS and PFS estimates for both treatments, the time to treatment discontinuation of GCis + N arm and the acquisition cost of necitumumab. Probabilistic sensitivity analysis incorporating the uncertainty in the model parameters indicates a slightly higher estimated ICER when comparing GCis + N to Cis of £65,050 per

QALY gained. Examination of the CEAC demonstrates that at a £50,000/QALY threshold, the probability of GCis + N being cost-effective compared to GCis is 24%.

2. The technology

2.1 Description of the technology

Brand Name	Portrazza®
Approved Name	Necitumumab
Therapeutic class	EGFR monoclonal antibody

Mechanism of action

Necitumumab is a recombinant human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 class, which targets the epidermal growth factor receptor- 1 (EGFR). Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. *In vitro* studies further demonstrate that Necitumumab inhibits EGFR-dependent tumour cell proliferation, and can exert cytotoxic effect in tumour cells through antibody-dependent cell cytotoxicity.

The EGFR is a member of the human EGFR family of receptor tyrosine kinases (TKs). EGFR activation leads to stimulation of TK-dependent signal transduction pathways that can contribute to neoplastic transformation and tumour growth. It has furthermore been associated with chemoresistance and radioresistance. Inhibition of the EGFR pathway in cells can result in disruption of cell cycle progression and mitosis, decrease angiogenesis, and block the inhibitory effect on apoptosis.

Many common human tumours express EGFR, including colorectal, head and neck, pancreatic, breast, and lung. EGFR tumours are those with detectable EGFR on the surface of any tumour cell. EGFR expression is different than EGFR mutation. In the latter the gene sequence gets altered whereas in the former EGFR protein increases. The mechanism causing over expression of EFGR is not known however, it is thought that gene amplification might be responsible (7). Immunohistochemical staining methods (IHC) are commonly used for the detection of membrane-bound EGFR. The overexpression of EGFR is higher in the advanced non-small cell lung cancer (8). The vast majority of patients with squamous NSCLC show EGFR expression in the tumour tissue with a (min-max) range of 82%-95.2% (9-15). The lower limit of 82% (12) refers to the proportions of patients with intermediate to high expressing of EGFR and therefore represents an underestimate, as the proportion of patients with weak EGFR expression is not included in this estimate.

Pharmacologic inhibition of EGFR signaling through competitive inhibition of ligand binding has been shown to play a role in the treatment of several cancers, leading to successful registration of 2 anti-EGFR mAbs in a number of indications.

Necitumumab has been developed in combination with cisplatin for the treatment of patients who have not received prior chemotherapy for locally advanced or metastatic squamous non-small cell lung cancer (NSCLC), a patient population with high unmet medical need. Necitumumab blocks the eGFR pathway in ways independent of those associated with EGFR TKs and independent of EGFR mutation status.

2.2 Marketing authorisation/CE marking and health technology assessment

Approved indication

On 17th December 2015, the European Medicines Agency (EMA) adopted a positive opinion (16), recommending the granting of a marketing authorisation for Necitumumab for the following indication:

"Portrazza® is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition."

It is expected that Necitumumab will receive the marketing authorisation in early March 2016 (67 days after the positive opinion). Necitumumab is expected to be commercially available in England in April 2016.

Regulatory approval outside the UK

Food and Drug Administration (FDA)

Lilly made an application to the FDA in 2014 with a proposed indication of necitumumab to be used in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC. Necitumumab was reviewed by the FDA in July 2015, and has now been approved for the above indication in November 2015 (17).

Other health technology assessment in the UK

Necitumumab is anticipated to be appraised by the Scottish Medicines Consortium (SMC) and National Centre for Pharmacoeconomics (NCPE) Ireland in 2016.

2.3 Administration and costs of the technology

Necitumumab in combination with gemcitabine and cisplatin (GCis + N) should be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy (in an outpatient setting). GCis + N is administered up to 6 cycles of treatment followed by Necitumumab as a single agent in patients whose disease has not progressed, until disease progression or unacceptable toxicity. The recommended dose of Necitumumab is 800 mg (flat dose) administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle.

Table 6 Costs of the technology being appraised

		Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate)	SPC (Appendix 1)
Acquisition cost (excluding VAT) *	800mg=£1,450 (List price) [redacted]	
Method of administration	Necitumumab: intravenous infusion over 60 minutes	SPC (Appendix 1)
Doses	Necitumumab: 800 mg (flat dose) Gemcitabine: 1250 mg/m^2 Cisplatin: 75 mg/m^2	SPC (Appendix 1)
Dosing frequency	Days 1 and 8 of each 3-week cycle	SPC (Appendix 1)
Average length of a course of treatment	21 days	SPC (Appendix 1)
Average cost of a course of treatment	Cost of necitumumab per cycle is estimated to be [redacted]. Necitumumab is given in combination with gemcitabine and cisplatin, with an estimated cost per cycle of £76.70 and £26.67 respectively (assuming wastage and based on the average BSA for NSCLC patients in England).	
Anticipated average interval between courses of treatments	Treatment as per dosing frequency until disease progression or unacceptable toxicity	
Anticipated number of repeat courses of treatments	In the Phase 3 trial, SQUIRE, the mean length of GCis + N induction therapy was 4.6 cycles and the mean length of necitumumab maintenance therapy was 6 cycles.	
Dose adjustments	No	
Anticipated care setting	Outpatient	

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.
SPC = summary of product characteristics; PASLU = Patient access schemes liaison unit; BSA = Body surface area; NSCLC = non-small cell lung cancer; GCis + N = Necitumumab plus gemcitabine plus cisplatin

2.4 Changes in service provision and management

Currently in England, after completion of 4 to 6 cycles of first-line treatment with a platinum doublet, patients with squamous NSCLC undergo a chemotherapy free observation period until disease progression. During this time, patients may receive best supportive care (BSC) and are clinically assessed every one to three months and radiologically every three to six weeks but, that varies regionally. With the introduction of necitumumab, patients will be treated with necitumumab in combination with gemcitabine plus cisplatin (GCis + N) for a maximum of 6 cycles of treatment followed by necitumumab as a single agent in patients whose disease has not progressed until disease progression or unacceptable toxicity.

Patients whose disease progresses while on necitumumab therapy will receive docetaxel or erlotinib as a second-line therapy.

We anticipate necitumumab to be administered in combination with gemcitabine and cisplatin (GCis + N) in an outpatient setting. It is to be administered on the same days as gemcitabine, thus not requiring additional visits to the chemotherapy unit. GCis + N will be given for a maximum of 6 cycles during the induction phase. Therefore, there will be some additional cost associated with up to two additional cycles. The maintenance phase will be associated with additional cost such as drug acquisition cost, administration cost, disease monitoring and cost for treatment related adverse events.

2.5 Innovation

Necitumumab will offer an innovative first-line treatment option for patients with advanced or metastatic squamous NSCLC. Patients with squamous NSCLC have a distinct disease and are difficult to treat due to comorbidities and late diagnosis, and there has been very little improvement in survival in squamous patients over the last two decades (18). This is due to the lack of relevant oncogenic drivers to inform the treatment discussion as well as having an older patient population with over 90% being smokers with several comorbidities (19-21)(22). No new chemotherapies have been approved in first-line squamous NSCLC by the EMA in two decades and there are currently no targeted first-line biologic treatments available. SQUIRE is the first and only prospective study in patients with advanced squamous NSCLC to demonstrate benefit in OS in the first-line setting. This achievement in OS was obtained in a patient population with metastatic disease, with high disease burden and PS 0-2 patients. Improvement in OS was consistently observed in favour of the necitumumab arm across the majority of pre-specified subgroups.

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

Lung cancer

Lung cancer is the second most common cancer diagnosed in the UK, accounting for 13% of all new cases in the UK (23). In 2012 32,364 people in the UK were diagnosed with lung cancer (LUCADA) (4). It is the second most common cancer in both sexes (14% of the male total) and females (12% of the female total) (23). Lung cancer is also the most common cause of death, with 22% of cancer deaths being attributed to lung cancer (24) in the UK in 2012.

Smoking is the main cause of lung cancer and is linked to about 86% of lung cancer cases in the UK (25). Other known risk factors for lung cancer include exposure to asbestos, arsenic, radon and non-tobacco related polycyclic aromatic hydrocarbons (26).

Histologically, lung cancer can be broadly categorised into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell lung cancer (NSCLC) accounts for approximately 84% of all lung cancers (LUCADA)(4); The three main histological subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell carcinoma accounting for 33%, 30-40% and 10-15% of all lung cancers respectively with the latter two collectively termed non squamous lung cancer (6)(27).

Squamous NSCLC predominantly affects men with history of heavy smoking. In squamous NSCLC, the tumour is most likely to be located centrally thereby resulting in haemorrhage from blood vessel invasion and bronchial obstruction.

One other notable feature of squamous NSCLC is relatively high EGFR protein expression in around 95% of tumours however; EGFR mutations are rare in squamous NSCLC. Patients with squamous NSCLC have a distinct disease and are older, smokers and often associated with diseases such as chronic obstructive pulmonary disease, heart diseases (19-21)(22)(28).

Prognosis and burden of the disease

Although survival for most cancer types is improving due to faster diagnosis and advances in treatment, five- and ten-year survival for lung cancer has not shown much improvement in the last 40 years in the UK(5). Like most cancers, the prognosis of NSCLC depends considerably on the stage in which the cancer is diagnosed. The majority of patients with

lung cancer are diagnosed with locally advanced or metastatic disease which is associated with poor survival outcomes.

Advanced and metastatic squamous NSCLC is an aggressive cancer that grows quickly with a median doubling time significantly shorter than adenocarcinoma. Thus, squamous NSCLC is associated with a worse prognosis than non-squamous NSCLC, irrespective of treatment.

Lung cancer has a significant impact on society, costing the UK economy an estimated £2.4 billion per year (29). 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 (29). According to Cancer Research UK (CRUK), each lung cancer patient is thought to cost the UK healthcare system £9,071 annually (30).

Variation in the incidence and mortality of patients with lung cancer across Europe

There is published evidence that suggest that the disease burden of lung cancer vary across the regions in Europe. Ferlay et al. 2013 (31) found that the age-standardised rates (ASR) for lung cancer incidence and mortality vary across Europe with Eastern Europe (Hungary, Poland and Serbia) having the highest ASR for incidence and Hungary and Poland having the highest ASR for mortality. Additionally, the ASR for incidence and mortality are lowest in Finland and Sweden. The age standardised incidence rate of lung cancer per 100,000 in men was higher in the Central and Eastern European countries (Hungary 109, Macedonia 102, Serbia 99 and Poland 90) whereas, the incidence was lowest in some Northern European Countries (Finland 45, Sweden 29). In contrast in women the incidence was higher in Northern Europe (Denmark 55, The Netherlands 44) and lower in the Eastern European countries (Ukraine and Belarus 9, The Russian Federation 10). When both sexes were combined, the incidence rate of lung cancer was found to be highest in Hungary (109 in male, 47 in female) and Poland (89 in male, 31 in female) whereas, the lowest was in Cyprus (38 in male, 11 in female). The variations of mortality rates were similar to that of the incidence rates. The ASR for incidence and mortality is consistent within Western European countries suggesting similar disease burden across Western Europe (3). Please see Table 7 for the estimated ASR incidence and mortality rates.

Table 7 Incidence and mortality estimates across different European countries (table created using data reported in Ferlay et al 2013)

	Estimated age- standardised rates (ASR) (European Standards) of cancer incidence			Estimated age- standardised rates (ASR) (European Standards) of cancer mortality		
	Male	**Female**	**Average**	**Male**	**Female**	**Average**
Northern/Southern/Western Europe						
UK	53.3	38.5	45.9	46.7	32.4	39.55
Italy	58.8	19.2	39	52.2	15.6	33.9
Spain	76.8	15.7	46.25	60.0	11.3	35.65
France	74.5	27.9	51.2	58.7	18.4	38.55
Germany	57.3	25.4	41.35	47.0	21.1	34.05
Finland	45.4	17.9	31.65	39.6	14.2	26.9
Sweden	28.8	27.5	28.15	26.4	24.1	25.25
Denmark	62.5	54.9	58.7	53.9	42.3	48.1
The Netherlands	66.1	44.5	55.3	59.6	35.6	47.6
Cyprus	38.1	10.7	43.5	36.8	8.6	22.7
Eastern Europe						
Hungary	109.3	46.5	77.9	96.4	37.7	67.05
Serbia	99.2	32.9	66.05	27.3	4.0	15.65
Poland	89.3	31.1	60.2	82.9	25.3	54.1
Ukraine	66.9	8.7	37.8	56.5	6.6	31.55
Belarus	77.3	14.8	46.05	72.3	5.4	38.85

Additionally, Vrdoljak et al. 2011 compared incidence and mortality due to different cancers in eight selected Southern, Central and Eastern European countries (Croatia, Czech Republic, Hungary, Poland, Romania, Slovakia, Serbia and Montenegro). The age standardised incidence rate of lung cancer per 100,000 in both sexes was found to be higher in Hungary (male 94.6; female 24.9). The age standardised incidence rate in other countries were as follows: Central Serbia (male 64.2, female 18.4), Croatia (male 63.7, female 13.6), Poland (male 60.2, female 14.5), Czech Republic (male 58.2, female 15.5), Slovakia (male 55.8, female 10.4) and Romania (male 50.0, female 8.5).Similarly, Hungary had the highest age standardised mortality rate per 100,000 in both sexes (male 72.5; female 22.3). The next country to have the highest mortality rate was Poland (male 64.6, female 14.3). The authors believed that this variation in incidence and mortality across European countries was

due to a combination of factors including risk factors, host susceptibility, cancer detection rates, reporting, classification, treatment and follow-up. The authors also highlighted differences in quality of care observed between European countries, especially between old and new EU member states. They explained that the mortality trends for all cancer sites were better in the former 15 EU countries compared to the Central and the Eastern European countries which entered the EU in 2004 and 2007 including Hungary, Czech Republic, Poland, Slovakia and Romania. These new entry countries particularly had the highest rates not only for lung cancer but, also for other tobacco related diseases since the consumption of tobacco was particularly high in Eastern Europe (32).

UK Lung Cancer Clinical guidelines/guidance

The National Institute for Health and Care Excellence (NICE) have published clinical guidelines (CG121) (33) that provide recommendations for good practice in the diagnosis and treatment of lung cancer in England. Although the NICE CG121 provides recommendations in the diagnosis and treatment of lung cancer, these recommendations are not specific to those diagnosed with squamous NSCLC.

The other relevant NICE guidance is TA162 which provides recommendations on erlotinib as a second-line therapy in NSCLC.

Table 8 Relevant NICE documents

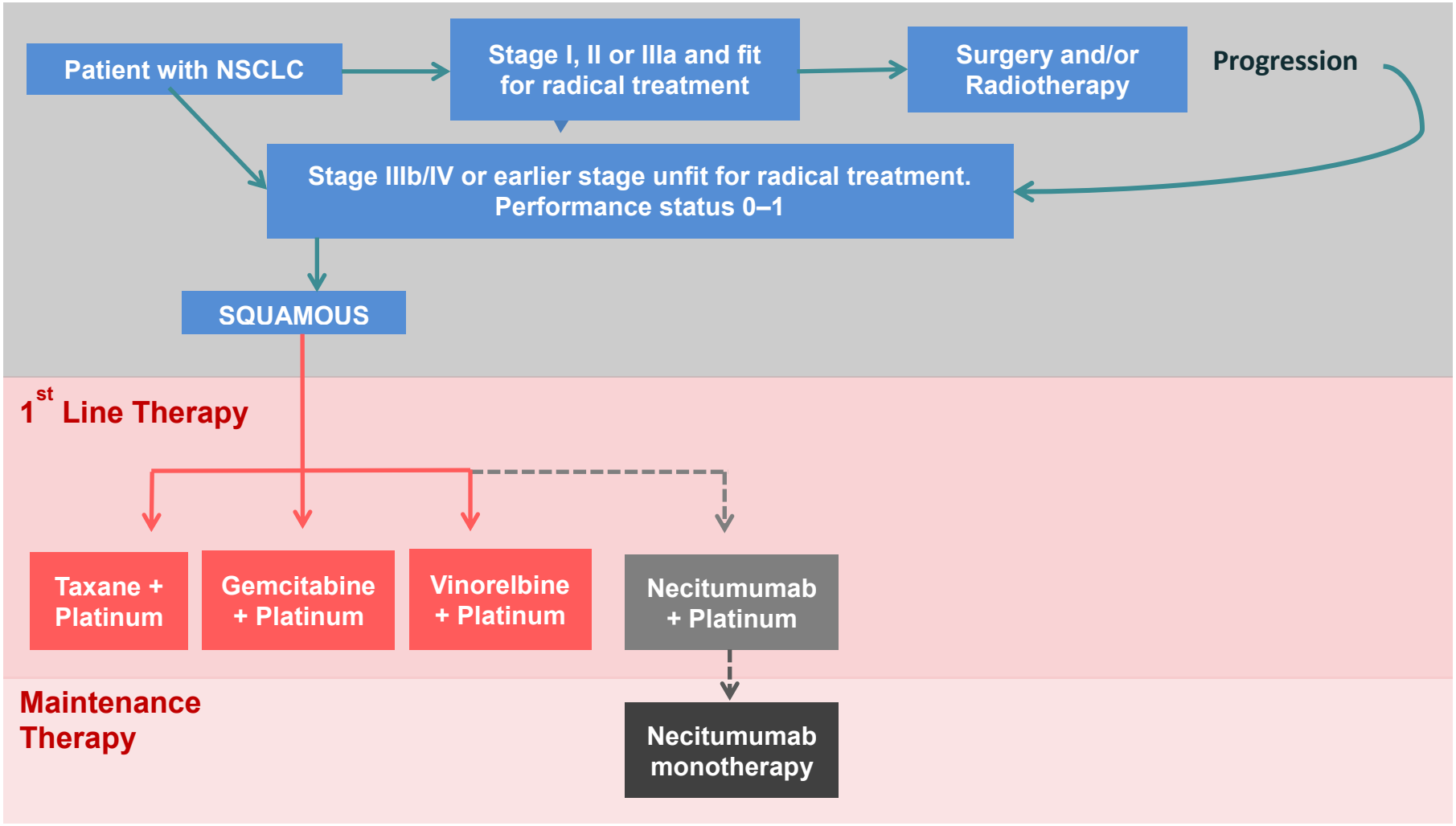
NICE Clinical Guideline/Guidance	Patient group	Recommended treatment
First-line		
CG121 (33) The diagnosis and treatment of lung cancer	All patients with NSCLC of good performance status (WHO 0 or 1 or Karnofsky score of 80 to 100)	Platinum doublet docetaxel, gemcitabine, vinorelbine or paclitaxel. Or single agent if unable to tolerate platinum therapy
Second-line		
CG121 (33) 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

Current treatment pathway

The aims of treatment for NSCLC are to extend survival, improve quality of life and control disease symptoms. In England, the current first-line treatment for patients with advanced (stage III or IV), good performance status (WHO 0, 1 or a Karnofsky score of 80-100), metastatic, squamous NSCLC is to offer cytotoxic therapy with cisplatin or carboplatin-based doublets. Patients can also be offered a combination therapy of a platinum drug (either cisplatin or carboplatin) plus a single third-generation drug such as paclitaxel, gemcitabine, docetaxel or vinorelbine (Figure 1). Patients who do not tolerate a platinum combination therapy can be offered single-agent chemotherapy with a third-generation drug.

In England, patients receive this treatment as part of induction therapy for up to 4 to 6 cycles. Following induction treatment, patients whose disease does not progress or who experiences intolerable toxicities, will remain in a chemotherapy free state until disease progresses. Those whose disease progresses will either receive docetaxel or erlotinib as a second-line therapy.

Figure 1 **Current clinical practice in England for patients diagnosed with NSCLC**



Market share data:

The market share data show that gemcitabine in combination with a platinum drug ([redacted] Q4 2014 to Q3 2015) is the most commonly used first-line treatment in advanced stage IV squamous NSCLC in the UK (35). The market share data show that carboplatin is the most commonly used platinum drug ([redacted] vs. [redacted]cisplatin). NICE CG 121 recommends using either cisplatin or carboplatin as a platinum drug however, this recommendation is not specific to squamous NSCLC patients. Vinorelbine in combination with platinum drug ([redacted]) is the second most commonly used first-line treatment in the UK. Other combinations chemotherapy found to be used, though in very small proportions, included paclitaxel plus carboplatin and docetaxel plus cisplatin. Some preparations including vinorelbine, carboplatin and docetaxel were used as monotherapy however, the proportion of patients using these therapies were very small.

Equality

Necitumumab will be available as the first-line treatment option in patients suffering from squamous NSCLC who have not received prior chemotherapy for this condition. We do not anticipate any inequality issues with this treatment.

4. Clinical effectiveness

Key messages

- SQUIRE, a phase III, multinational (n=26) multicenter (n=184) two arm open-label trial provided evidence of GCis + N against GCis in patients with advanced stage IV squamous NSCLC naïve to chemotherapy treatment. In total 1093 patients were randomised in the trial: 545 patients to GCis + N arm and 548 patients to GCis arm.

- In the ITT population, median OS in patients receiving GCis + N was 11.5 months (95% CI 10.4 to 12.6 months) and 9.9 months (95% CI 8.9 to 11.1 months) in patients receiving GCis only. Median PFS was 5.7 months (95% CI 5.6 to 6.0 months) in the GCis + N arm whereas 5.5 months (95% CI 4.8 to 5.6 months) in the GCis only arm.

- In the Western European subpopulation, median OS in patients receiving GCis + N was [redacted] months and [redacted] months in patients receiving GCis only, thereby causing a statistically significant better median OS of [redacted] months in the former group. The Median PFS ([redacted] months) was not statistically significantly better in the GCis + N arm.

- An indirect comparison was undertaken to compare GCis + N against other relevant comparators as a first-line treatment in patients diagnosed with squamous NSCLC. 13 articles identified representing 11 unique RCTs. The comparison of GCis + N was made against PCarbo, GCarbo and DCis. It was concluded that GCis + N was associated with a lower HR than all comparators for both OS and PFS.

- The proportion of patients experiencing at least one TEAE of grade ≥3 was slightly more in the GCis + N arm than in the GCis arm in both the ITT and Western Europe patient subpopulation, with the most common TEAE being neutropenia, anaemia and thrombocytopenia.

- Necitumumab is an important advancement in the treatment of patients with metastatic squamous NSCLC, where limited progress has been made over the last two decades when compared to non-squamous NSCLC. Necitumumab fulfills the criteria to be assessed as an end of life treatment by NICE.

4.1 Identification and selection of relevant studies

A systematic review was undertaken in August 2015 to identify all the relevant randomised controlled trials (RCTs) investigating the efficacy and safety of Necitumumab as first-line treatments in squamous NSCLC populations. The literature search was conducted in Medline, Medline In process, Embase and the Cochrane Library. Details of the search strategy are reported in Appendix 2. In addition, conference abstracts from annual meetings (American Society of Clinical Oncology or ASCO) were searched electronically. Full reference list of all the included studies were also checked thoroughly to find any relevant studies.

The details of inclusion and exclusion criteria used to select the relevant studies are given in Table 9.

Table 9 Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with locally advanced or metastatic squamous NSCLC naïve to treatment	Non squamous NSCLC; previously treated squamous NSCLC
Intervention	Necitumumab in combination with gemcitabine plus cisplatin given as first-line treatment	Necitumumab in combination with gemcitabine plus cisplatin given as second line treatment
Comparators	Combination of a single drug plus platin drug (carboplatin or cisplatin): docetaxel gemcitabine, paclitaxel, vinorelbine	
Outcomes	OS; PFS; response rates; health related quality of life and safety	
Study design	Randomised controlled trials (phase III or phase IV)	Non-randomised trials; phase I/II trial; case series, case reports; editorials, observational studies
Language restrictions	English language	Non English

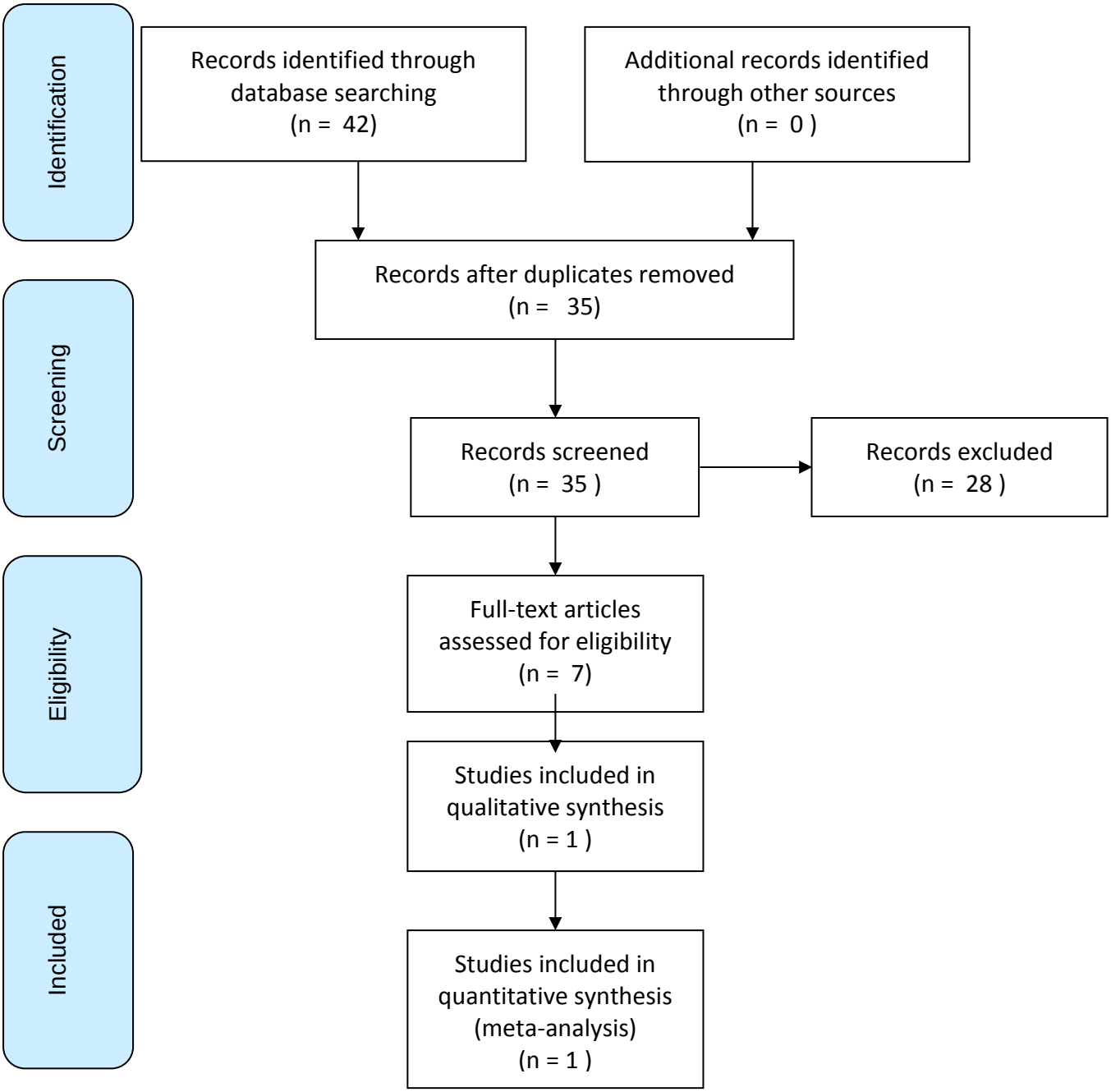
4.2 List of relevant randomised controlled trials

Only one RCT met the inclusion criteria. SQUamous NSCLC treatment with the Inhibitor of EGF Receptor (SQUIRE) trial is the largest phase III multinational, multi-centre, randomised, two-arm, open-label trial in the first-line treatment for metastatic squamous NSCLC. The study compared an experimental 3-drug combination of necitumumab plus gemcitabine and cisplatin (GCis + N) to the control treatment of gemcitabine and cisplatin (GCis) as first-line therapy in 1093 patients with Stage IV squamous NSCLC (per the American Joint

Committee on Cancer [AJCC] Staging Manual, Seventh Edition [AJCC7]) for a maximum of 6 cycles. Following up to 6 cycles of necitumumab and gemcitabine plus cisplatin, patients without disease progression continued to receive necitumumab monotherapy until there was radiographic documentation of progressed disease.

Results presented in the submission are available in the primary publication and other supplement materials unless stated otherwise.

Figure 2 PRISMA diagram



4.3 Summary of methodology of the relevant randomised controlled trials

Trial Design

SQUIRE was a multinational, randomised, two-arm, open-label, phase III study that randomised 1093 patients with squamous NSCLC. Patients enrolled in the SQUIRE trial were randomised on a 1:1 basis to GCis + N arm or the GCis alone arm by investigative sites accessing a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The randomisation was stratified by ECOG PS 0-1 vs 2 and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

The IVRS/IWRS assigned a unique identification number for each patient and randomised the patient to one of the treatment arms according to a stratified, permuted block randomisation plan (block size of four). The patient identification number was to be recorded on all electronic case report forms (eCRFs) and correspondence regarding the patient, and used in lieu of the patient's name to protect the patient's identity when reporting adverse events (AEs) and/or other trial-related data. Upon completion of randomisation, the first dose of study therapy was to be administered within 7 days of randomisation.

SQUIRE was conducted as an open-label study due to the expected occurrence of acne form rash (common with EGFR inhibitors) in the GCis + N arm relative to the GCis arm, which would have unblinded most patients and investigators to the treatment assignment. However, the clinical data provided to Eli Lilly and Company during the study were blinded with respect to treatment assignment. Eli Lilly and Company had unblinded access to serious adverse events (SAEs) data only and had no unblinded access to aggregate data from the clinical database. The safety data was assessed regularly by an independent monitoring committee, which included three medical oncologists, a drug safety expert and a biostatistician, all of them with no financial or other interest in the study.

Eligibility Criteria for participants

Eligible participants were all adults aged 18 years or over with histologically or cytologically confirmed, Stage IV squamous NSCLC (per AJCC7) at the time of study entry, previously untreated for metastatic disease, with ECOG PS 0-2 and adequate hepatic, renal, and hematologic function. Eligible patients were required to have archived tumour tissue available (minimum of 4 slides, paraffin-embedded) for biomarker analysis. Exclusion criteria

were patients with non-squamous NSCLC (adenocarcinoma/large cell or other), prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF) or VEGF receptor and major surgery or any investigational therapy in the 4 weeks prior to randomisation. The full list of inclusion and exclusion criteria is given in Appendix 3.

Study Sites

A total of 1281 patients were screened from 191 sites in 26 countries (Australia, Austria, Belgium, Brasil, Canada, Croatia, France, Germany, Greece, Hungary, Italy, Korea, Philippines, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, United Kingdom and United States of America). Out of 1281 screened patients, a total of 1093 patients were randomised from a total of 184 investigative sites in 26 countries.

The number of sites that screened patients, the number of patients screened, and number of patients randomised (total and to each treatment arm) are summarised by country in Table 10.

Table 10 Participants – Settings and Locations

Country	Number of Sites	Number of Patients Screened	Number of Patients Randomised, n(%)		
			GCis + N Arm (N=545)	GCis Arm (N=548)	Total (N=1093)
[redacted]					

Abbreviations: GCis = gemcitabine and cisplatin; GCis + N = gemcitabine and cisplatin plus necitumumab. Source: SQUIRE CSR, Table JFCC.14.1 and Table JFCC.14.2 (Pages 161-196)

At each investigative site a trained clinical trial personnel administered the treatments to the patients. A record of investigational product disposition was maintained at each study site. Compliance was monitored by the review of drug accountability records and drug administration data was recorded in each patient's medical records.

Premedications

Pretreatment hydration with 1 to 2 liters of fluid infused (I.V.) for 8 to 12 hours prior to a cisplatin dose was recommended; especially in outpatient settings, oral hydration may also have been acceptable based on local standards. Adequate hydration and urinary output were to be maintained for at least 24 hours following cisplatin administration. Administration and monitoring were performed according to local standards.

Antiemetic premedication was administered according to local standards. Additional antiemetic premedication may have been employed at the discretion of the investigator.

There was no routine premedication for necitumumab mandated by the study protocol**.** However, pre-emptive treatment with skin moisturisers, topical steroids, doxycycline, or sunscreen was permitted as clinically appropriate to patients receiving necitumumab in Cycle 2 and beyond. Pre-emptive treatment for skin toxicity was allowed only after the first cycle.

Prior and concomitant therapy

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients on this trial. Supportive care measures could include but were not limited to antidiarrhoeal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors.

All treatments taken during the study were recorded on the eCRF; any use of excluded medication was a violation of the protocol and was documented.

Interventions

Patients in the intervention arm received a 3-drug combination of necitumumab plus gemcitabine and cisplatin (GCis + N) following necessary premedication. The 3-drug combination included:

- Necitumumab: 800 mg (flat dose, intravenous [I.V.]) on Days 1 and 8 of each 3-week cycle
- Gemcitabine: 1250 mg/m^2 (I.V.) on Days 1 and 8 of each 3-week cycle (maximum of 6 cycles)
- Cisplatin: 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

Gemcitabine was administered following the completion of the necitumumab infusion. Cisplatin was administered at least 30 minutes after the completion of the infusion of gemcitabine.

Patients in the GCis + N arm received necitumumab in combination with gemcitabine and cisplatin chemotherapy for a maximum of 6 cycles, or until there was radiographic documentation of progressive disease (PD), toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Patients without disease progression continued to receive necitumumab alone until there was radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

Patients in the control arm received a doublet combination of gemcitabine and cisplatin (GCis) following necessary premedication. The doublet combination included:

- Gemcitabine: 1250 mg/m^2 (I.V.) on Days 1 and 8 of each 3-week cycle (maximum of 6 cycles)
- Cisplatin: 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

Cisplatin was administered at least 30 minutes after the completion of the infusion of gemcitabine.

All patients received the same initial dose of each study therapy (as defined above). Modifications to the doses of necitumumab (GCis + N Arm only), gemcitabine, and cisplatin were permitted; the dose of any agent could be reduced a maximum of two times.

Patients in the GCis arm continued to receive gemcitabine and cisplatin chemotherapy for a maximum of 6 cycles, or until there was radiographic documentation of progressed disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Patients in the GCis arm with a tumour response of stable disease (SD) or better after completion of chemotherapy were observed, with no additional systemic anticancer therapy permitted, until documentation of progressed disease.

Primary Outcome

The primary objective of SQUIRE was to evaluate the OS in patients with Stage IV squamous NSCLC treated with GCis + N versus GCis in the first-line metastatic setting.

In this study, OS was defined as the time from the date of randomisation to the date of death from any cause. Patients who did not die at the end of the extended follow-up period, or who were lost to follow-up during the study, were censored at the last date they were known to be alive.

Secondary outcome

The secondary objectives were to evaluate the PFS, objective response rate (ORR), TTF, the safety profile, PK and immunogenicity of necitumumab as well patient reported health outcomes.

PFS was defined as the time from randomisation until the first radiographic documentation of objective progression as defined by RECIST Version 1.0, or death from any cause. Patients who died without a reported prior progression were considered to have progressed on the day of their death. Patients who did not progress or were lost to follow-up were censored at the day of their last radiographic tumour assessment. If no baseline or post-baseline radiologic assessment was available, the patient was censored at the date of randomisation. If death or PD occurred after two or more consecutive missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy prior to the occurrence of PD resulted in censoring at the date of last radiographic assessment prior to initiation of new therapy.

Objective response rate (ORR) was defined as the proportion of patients achieving a best overall response of confirmed partial or complete response (PR + CR), according to RECIST (Version 1.0) from the start of the treatment until disease progression or recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Time to treatment failure (TTF) was defined as the time from randomisation to the first observation of progressive disease, death due to any cause, early discontinuation of treatment (all reasons from eCRF - except “completed treatment” for the GCis arm), or initiation of new anticancer therapies. Patients who did not experience the event were censored at the day of their last adequate radiographic tumour assessment or date of last

treatment, whichever came last. Patients who did not receive treatment were censored at the date of randomisation.

The safety profile of necitumumab in combination with gemcitabine and cisplatin chemotherapy was determined by reported adverse events, physical examinations, and laboratory tests in the GCis + N arm only. Treatment-emergent adverse events (TEAEs) were defined as events that met either of the following criteria:

- Onset date occurred any time during or after the administration of the first dose of study treatment or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment); or
- The event occurred prior to the date of first dose and worsened while on therapy or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment).
- For the purposes of this study, an SAE was defined as any untoward medical occurrence that at any dose:
    - resulted in death;
    - was life-threatening;
    - required inpatient hospitalisation or caused prolongation of existing hospitalisation;
    - resulted in persistent or significant disability/incapacity;
    - was a congenital anomaly/birth defect;
    - required intervention to prevent permanent impairment/damage; and/or
    - was an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [for example, medical, surgical] to prevent one of the other serious outcomes listed in the definition above)

The PK of necitumumab were determined by obtaining blood samples for serum PK analysis (one tube at 7.5 mL/tube) at specified timepoints during the study from patients enrolled in

the GCis + N Arm only. Samples were to be drawn at baseline (prior to the first [Cycle 1] infusion of necitumumab), and prior to the first necitumumab infusion (Day 1) in Cycles 2 through 6. PK parameters to be reported included, but were not limited to, trough (Cmin) concentrations of necitumumab.

To determine the immunogenicity of necitumumab serum samples for analysis of antibodies against necitumumab (immunogenicity) were to be obtained from blood drawn for PK analysis as described above. Specifically, immunogenicity was to be assessed using serum drawn prior to the necitumumab infusion on Day 1 of Cycles 1, 3, and 5 (GCis + N Arm only). An additional sample was to be collected at the 30-day safety follow-up visit. Immunogenicity samples were also to be obtained in the setting of a hypersensitivity or infusion-related reaction, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Patient reported health outcomes were measured using the Patient Lung Cancer Symptom Scale (LCSS) and the EuroQol 5-dimension 3-level tool (EQ-5D-3L). The LCSS is a self-reported disease- and site-specific instrument consisting of nine items including six major lung cancer symptoms and three global measures of symptom distress, activity, and QoL (Hollen et al. 1994).The EQ-5D-3L is a nonspecific and standardised instrument for use as a measure of self-reported health status designed to be used in conjunction with other patient-reported measures.

Both the LCSS and EQ-5D-3L were measured prior to treatment (within 14 days of randomisation), prior to the first infusion of Cycles 1-6, and every 6 weeks (± 3 days) thereafter (i.e., concurrent with radiological evaluation after discontinuation of chemotherapy) until PD. Both instruments were to be administered together and in sequence order (the Patient LCSS first, directly followed by the EQ-5D instrument). The instruments were to be completed at the beginning of the visit, before any extensive contact and consultation with the clinician/study investigator. The Patient LCSS and the EQ-5D-3L were to be completed by all patients when there was a validated language/cultural translation in a language/culture in which the patient was fluent.

Subgroup analysis

Pre-specified subgroup analysis for both the primary and secondary endpoints included: age (<70 versus ≥70 years; and <65 versus ≥65 years), gender (female versus male), race (White versus non-white), smoking status (never smoker [non-smoker and light ex-smoker

combined] versus smoker), performance status (0 versus 1 versus 2 and 0-1 versus 2), regions and/or countries with enrolment of more than 40 patients (North America, Europe and Australia versus South America, South Africa, India versus Eastern Asia), patients that displayed a rash within the first-cycle and patients with an EGFR protein expression with an H-score of 200. Post-hoc subgroup analysis was also completed for patients in Western Europe.

Table 11 Comparative summary of trial methodology

Trial number (acronym)	**SQUIRE**
Location	• 184 investigative sites in 26 countries • Australia, Austria, Belgium, Brasil, Canada, Croatia, France, Germany, Greece, Hungary, Italy, Korea, Philippines, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, United Kingdom and United States of America
Trial design	• Two-arm, randomised Phase III multinational, multicentre, open-label study • randomised on a 1:1 basis • Stratified by ECOG PS (0-1 vs 2) and geographic regions (North America, Europe, and Australia vs. South American, South Africa and India vs. Eastern Asia).
Eligibility criteria for participants	• Histologically or cytologically confirmed squamous NSCLC, with measurable or nonmeasurable disease at the time of study entry (per Response Evaluation Criteria in Solid Tumours, Version 1.0). • Stage IV disease (per the AJCC Staging Manual, Seventh Edition) at the time of study entry. • Age ≥ 18 years. • ECOG PS score of 0-2. • Adequate hepatic, renal, and hematologic function, specifically: o Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x the ULN in the presence of liver metastases or ≤ 2.5 x the ULN in the absence of liver metastases. o Serum creatinine ≤ 1.2 x the ULN or calculated creatinine clearance > 50 mL/minute. o White blood cell count ≥ 3000/µL, absolute neutrophil cell count (ANC) ≥ 1500/µL, haemoglobin ≥ 9.5 g/dL, and platelets ≥ 100,000/µL. o Archived tumour tissue available for biomarker analysis.
Settings and locations where the data were collected	• At all investigative sites trained clinical trial personnel administered study therapy to the patients; therefore, treatment compliance was ensured. A record of investigational product disposition was maintained at each study site. Compliance was monitored by the review of drug accountability records and drug administration data recorded in each patient's medical records and eCRFs.
Trial drugs (the interventions for each group with sufficient details to allow	Gemcitabine+Cisplatin+Necitumumab (GCis+N) (N=545) • Necitumumab 800mg (flat dose IV) on days 1 and 8 of each 3-week cycle • Gemcitabine 1250 mg/m^2 (IV) on days 1 and 8 and of each 3 week cycle

replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	(maximum of 6 cycles) • Cisplatin 75mg/m^2 IV on days 1 of each 3 week cycle (maximum 6 cycles). • Following 6 cycles patients without disease progression continue to receive necitumumab monotherapy until there is radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Gemcitabine+Cisplatin (GCis) (N=548) • Gemcitabine 1250 mg/m^2 (IV) on days 1 and 8 and of each 3 week cycle (maximum of 6 cycles) • Cisplatin 75mg/m^2 IV on days 1 of each 3 week cycle (maximum 6 cycles).
Primary outcomes (including scoring methods and timings of assessments)	• OS is the primary outcome • OS is defined as the time from the date of randomisation to the date of death from any cause. Patients who did not die at the end of the extended follow-up period, or who were lost to follow-up during the study, were censored at the last date they were known to be alive.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	• PFS, time to treatment failure and overall response rate are secondary outcomes. • PFS is defined as the time from randomisation until the first radiographic documentation of objective progression as defined by RECIST 1.0, or death from any cause. Patients who did not progress or were lost to follow-up were censored at the day of their last radiographic tumour assessment. If no baseline or post-baseline radiologic assessment was available, the patient was censored at the date of randomisation. If death or PD occurred after two or more consecutive missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visit. The use of a new anticancer therapy prior to the occurrence of PD resulted in censoring at the date of last radiographic assessment prior to initiation of new therapy. • TTF is defined as the time from randomisation to the first observation of progressive disease, death due to any cause, early discontinuation of treatment, or initiation of new anticancer therapy. Patients who did not experience the event were censored at the day of their last adequate radiographic tumour assessment of date of last treatment, whichever came last. Patients who did not receive treatment were censored at the date of randomisation. • ORR is define as the proportion of patients achieving best overall response of confirmed partial or complete response (PR+CR) according to RECIST (version 1.0) from the start of the treatment until disease progression/recurrence. DCR is equal to the proportion of patients achieving a best overall response of CP, PR or stable disease (PR+CR+SD) according to RECIST 1.0. • Patient reported outcomes: LCSS, EQ-5D
Subgroups	• Pre-specified subgroups include: age, gender, race, smoking status, performance status, regions and/or countries with enrolment of more than 40 patients, patients that displayed a rash within the first-cycle and EGFR protein expression with an h-score at 200. • Post-hoc subgroups include: Western Europe

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

Primary Outcome

The primary outcome, OS, was estimated using the Kaplan-Meier (KM) method. The OS in both treatment arms were compared using the log-rank test. The overall significance level was set at 0.05. The HR and its 95% confidence limit were to be estimated from a stratified proportional hazard model (Cox model) with stratification factors.

The 95% CI for the median survival time was calculated according to Brookmeyer and Crowley. The primary analysis was performed using the stratification variables as captured by the IVRS/IWRS. A sensitivity analysis was performed using the stratification variables. The primary analysis was performed on the ITT population; however, additional analysis was completed for per protocol (PP) population and for each subgroup.

The HR for treatment effect was estimated using an unstratified multivariate Cox proportional hazard model, constructed by selecting variables among all the potential variables using stepwise selection method with entry p-value 0.05 and exit p-value 0.1. The treatment factor was excluded from the model throughout the covariate selection process and only added into the final model. The HR for treatment effect and the corresponding 95% confidence interval (CI) was estimated from the final model.

Secondary Clinical Outcomes

PFS was compared using a stratified log-rank test. An additional analysis with an unstratified log-rank test was also performed. The estimation of survival curves for the two treatment groups was generated using the KM methodology. A stratified Cox regression analysis was performed to generate the HR. Unstratified HRs were presented. The estimation of PFS curves for the two treatment groups was generated using the KM methodology. The median PFS time, as well as the 3-month and 6-month PFS rates together with the 2-sided 95% CIs, was presented for each treatment group based on the KM product-limit estimates. PFS was analysed for the ITT population. Additionally, PFS was analysed for the PP population. PFS analysis was also to be performed using the stratification variables as reported on the eCRF. Subgroup analyses were also to be conducted as done for OS. Sensitivity analyses using alternative censoring rules as described in the statistical analysis plan (SAP) were also to be performed for the ITT

population. The censoring rules for the main PFS analysis and sensitivity analyses are specified in the SAP.

The number of patients achieving a response (CR or PR) was divided by the total of patients randomised to yield the proportion responding. Frequencies for best overall response (BOR) were to be presented by treatment group, as well as disease control (confirmed best overall response of CR, PR, or SD) rates observed in each treatment group together with 95% CI using the Wilson formula (36)(37).The ORR and DCR in each treatment group were to be compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables as captured by IVRS/IWRS. In addition, the stratified odds-ratio (Group B over Group A) and the estimated difference (A minus B) in ORR were presented along with the corresponding 95% CI (38).

Follow-up period

Follow-up time was defined from the date of randomisation and using the inverse of the censoring rules for OS, that is, considering all censoring times for OS as event times (times when the patient is known to be still alive and under follow-up) and censoring patients at the date of death.

Follow-up time was compared across treatment groups using the same methodology as for PFS time (using the unstratified log-rank test, and KM product-limit estimates). Follow-up time was analysed using the ITT population.

Sample Size and power calculation

To detect a statistically significant difference in OS between treatment arms with an overall significance level of 5% and a HR of 0.80, a sample size of 1080 patients was required. This sample size was based upon the assumption of a 27-month accrual period, a follow-up of 19 months after the last patient was enrolled, and 1:1 randomisation to treatment and control arms, respectively. A dropout rate of 5% was also considered. Final analysis was to be performed when at least 844 deaths were observed.

Data management/Patient withdrawals

Data from all treatment centres were to be pooled for analysis; due to the generally very small sample size within each centre, evaluation of results by study centre was not planned and has not been performed.

All analyses and descriptive summaries are based on the observed data. Routine data listing or tabulation review during the study conduct was performed to identify missing data, anomalies, outliers, etc. Missing data was not imputed.

4.5 Participant flow in the relevant randomised controlled trials

A total of 1093 eligible patients were randomly assigned in the trial either in the GCis + N arm (n=545) or GCis arm (n=548). Seven patients in each group did not receive study treatment hence were not included in the safety population (1079 patients - 538 in the GCis + N arm and 541 in the GCis arm).

As of the data cutoff (17 June 2013), nine patients (1.7%) in the GCis + N Arm and no patients in the GCis Arm were still receiving treatment; seven patients in the GCis + N Arm (1.3%) and nine patients in the GCis Arm (1.6%) were off treatment but still on study (i.e., undergoing radiographic follow-up of disease progression and/or safety follow-up). At that time, 76.7% of patients in the GCis + N arm and 80.7% of patients in the GCis arm had died, with a censoring rate of 23.3% and 19.3% respectively.

Five patients in each arm (0.9%) had major protocol violations:

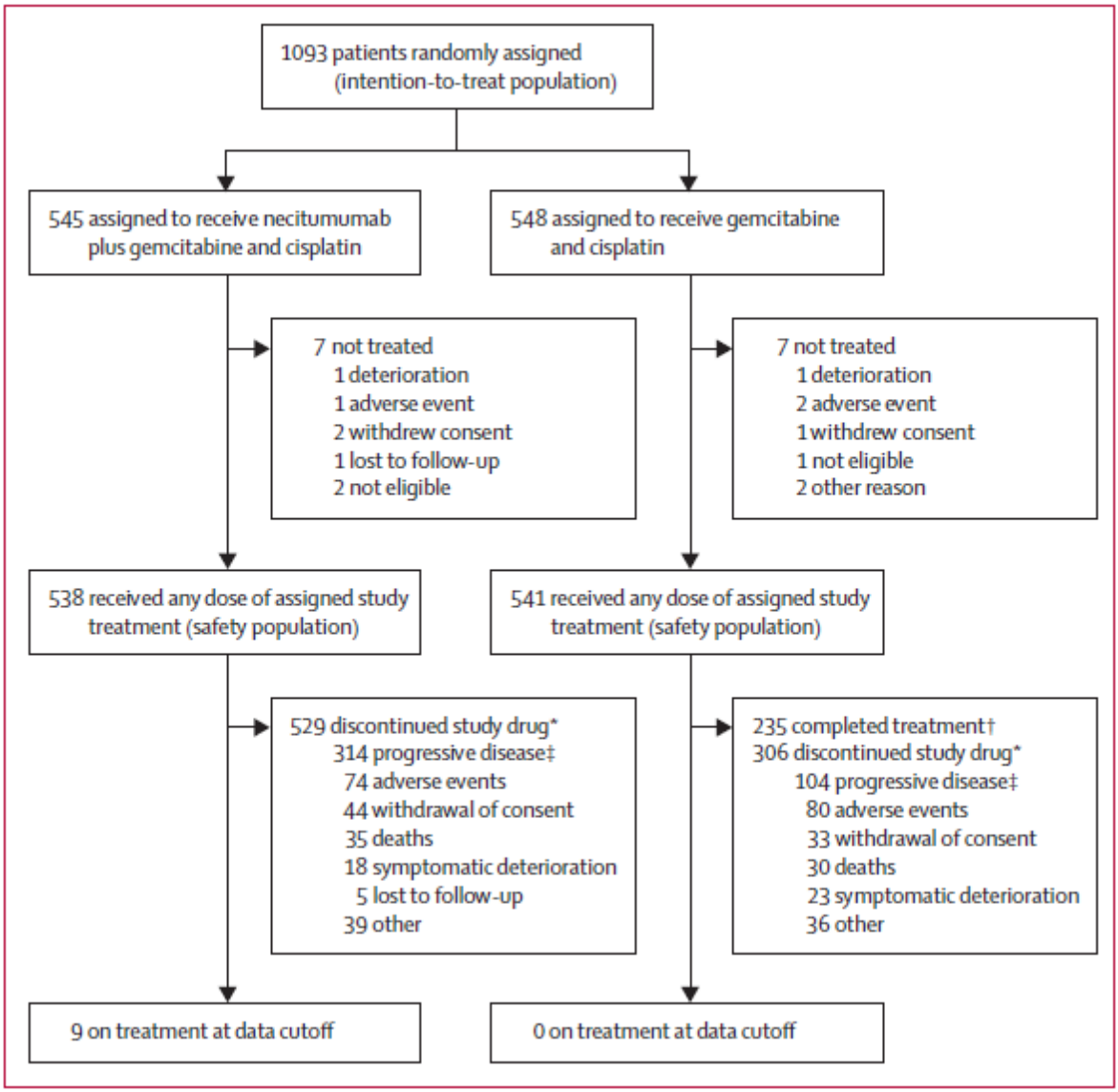
- Two patients in the GCis + N Arm and three patients in the GCis Arm who did not have confirmed squamous NSCLC at study entry;
- Two patients in each arm who did not have Stage IV disease at study entry;
- One patient (GCis Arm) with ECOG PS > 2;
- One patient (GCis + N Arm) with prohibited concurrent therapy.

These protocol violations were not likely to have affected the analyses or conclusions presented in this report. Patients with major protocol violations were excluded from the PP population. A total of 535 patients were included in the PP population in the GCis + N Arm versus 537 in the GCis Arm.

Approximately 43% of patients in the control (GCis) arm completed the study treatment i.e. all planned cycles of chemotherapy. The proportion of patients discontinuing study drug was

97% and 56% in the GCis+ N arm and GCis arm respectively. Details of patient flow in the trial are given in Figure 3.

Figure 3 Participant flow in the trial



*Primary reasons are listed; †Patients who completed all planned cycles of chemotherapy; ‡Radiologically documented

4.6 Quality assessment of the relevant randomised controlled trials

A quality assessment of the SQUIRE trial is given in Table 12.

Table 12 Quality assessment of SQUIRE

NICE quality assessment of the relevant randomised controlled trials	SQUIRE
Was randomisation carried out appropriately?	Patients were randomised on a 1:1 basis to the GCis + N arm or the GCis Arm. Randomisation was stratified by ECOG PS (0-1 vs 2) and geographic regions (North America, Europe, and Australia vs. South American, South Africa and India vs. Eastern Asia). Centres enrolled patients into the study by accessing a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The IVRS/IWRS assigned a unique identification number for each patient and randomised the patient to one of the two treatment arms according to a stratified, permuted block randomisation plan. The patient identificant number was to be recorded on all eCRFs and correspondence regarding the patient, and used in lieu of the patients name to protect the patients identify when reporting AEs and/or other trial-related data.
Was the concealment of treatment allocation adequate?	Centres enrolled patients into the study by accessing a call-in IVRS or IWRS. The IVRS/IWRS assigned a unique identification number for each patient and randomised the patient to one of the two treatment arms according to a stratified, permuted block randomisation plan. The patient identificant number was to be recorded on all eCRFs and correspondence regarding the patient, and used in lieu of the patients name to protect the patients identify when reporting AEs and/or other trial-related data.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, the patient population was similar in terms of prognostics factors in both treatment arms. For both arms the median was 62 years, 83% of patients were male, 83% of patients were white, 59% reported an ECOG PS1, and 90% were smokers.
Were the care providers, participants and outcome assessors blind to treatment allocation?	The care providers and participants were not blinded to treatment allocation. The outcome assessors at Eli Lilly were blinded to treatment assignment, with the exclusion of SAE data. The study was conducted open-label, because the expected occurrence of acne form rash (common with EGFR inhibitors) in the GCis + N Arm relative to the GCis Arm. The clinical data provided to Eli Lilly during the study were blinded with respect to treatment assignment. Eli Lilly had unblinded access to SAE data only and had no unblinded access to aggregate data from the clinical database, in order to preserve the integrity of the trial.

Were there any unexpected imbalances in drop-outs between groups?	There was no relevant difference between arms in terms of patients discontinuing due to radiographically documented PD, death, symptomatic deterioration, or withdrawal of consent. The number of patients with radiographically documented disease progression was similar between the treatment arms (68.1% in GCis + N Arm vs. 63.5% in GCis Arm).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all measured outcomes, both statistically significant and non-statistically significant, have been reported in this submission.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Primary analyses include all randomised patients following the ITT principle, regardless of compliance with the treatment regimen and protocol. All analyses and descriptive summaries were to be based on the observed data. Routine data listing or tabulation review during the study conduct was to be performed to identify missing data, anomalies, outliers, etc. Unless otherwise specified, missing data were not imputed. Imputation rules were documented in the SAP.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Baseline patient demographic and clinical characteristics

The baseline characteristics of the treatment groups were balanced (Table 13); including percentages of patients with ECOG PS of 2 at baseline (9.0% and 8.6% in the GCis + N Arm and the GCis Arm, respectively) and Asian patients (7.9% vs. 7.7%). In general, baseline patient characteristics were representative of an advanced squamous NSCLC patient population. The ITT population included 908 male and 185 female patients (83.1% and 16.9%, respectively), at a median age of 62 years (range, 32 to 86 years).

The baseline characteristics of the treatment groups in the Western European (includes patients from Austria, Belgium, Germany, France, Greece, Italy, Portugal, Spain and UK) population appeared generally similar. However, there were some differences between treatment groups at baseline. The proportion of patients in the age group ≥18 to <65 years was slightly lower in the GCis + N arm than in the GCis arm (54% vs 62%) whereas the proportion of patients aged ≥70 years was higher in the GCis + N arm than in the GCis arm (23% vs. 14%). The percentage of patients with ECOG 1 was higher in the GCis + N arm than in the GCis arm (57% vs, 49%). In contrast, GCis arm had comparatively greater percentage of patients with ECOG 2 than in the GCis + N arm (7% vs. 2%).

Table 13 Patient Demographic Characteristics at Baseline as Reported on the Case Report Form (ITT Population and Western Europe)

	ITT			Western Europe		
Characteristic	**GCis+N N = 545 n (%)**	**GCis N = 548 n (%)**	**Total N = 1093 n (%)**	**GCis+N N = 172 n (%)**	**GCis N = 176 n (%)**	**Total N = 348 n (%)**
Age (years)						
Median	62.0	62.0	62.0	[redacted]	[redacted]	[redacted]
Range	32 – 84	32 - 86	32 - 86	[redacted]	[redacted]	[redacted]
Age Group, n (%)						
≥18 - <65 years	332 (60.9)	340 (62.0)	672 (61.5)	[redacted]	[redacted]	[redacted]
≥65 years - < 70 years	105 (19.3)	111 (20.3)	216 (19.7)	[redacted]	[redacted]	[redacted]
≥70 years	108 (19.8)	97 (17.7)	205 (18.8)	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	450 (82.6)	458 (83.6)	908 (83.1)	[redacted]	[redacted]	[redacted]
Female	95 (17.4)	90 (16.4)	185 (16.9)	[redacted]	[redacted]	[redacted]
ECOG PS at baseline, n (%)						
0	164 (30.1)	180 (32.8)	344 (31.5)	[redacted]	[redacted]	[redacted]
1	332 (60.9)	320 (58.4)	652 (59.7)	[redacted]	[redacted]	[redacted]
2	49 (9.0)	47 (8.6)[a]	96 (8.8)[a]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	457 (83.9)	456 (83.2)	913 (83.5)	[redacted]	[redacted]	[redacted]
Asian	43 (7.9)	42 (7.7)	85 (7.8)			
Black or African American	5 (0.9)	6 (1.1)	11 (1.0)			
All Others[b]	40 (7.3)	44 (8.0)	84 (7.7)			
Smoking History						
Ex-Light Smoker	18 (3.3)	26 (4.7)	44 (4.0)	[redacted]	[redacted]	[redacted]
Non-Smoker	26 (4.8)	27 (4.9)	53 (4.8)	[redacted]	[redacted]	[redacted]
Smoker	500 (91.7)	495 (90.3)	995 (91.0)	[redacted]	[redacted]	[redacted]
Missing	1 (0.2)	0	1 (0.1)	[redacted]	[redacted]	[redacted]

Geographic Region						
North America, Europe, Australia	472 (86.6)	475 (86.7)	947 (86.6)	[redacted]	[redacted]	[redacted]
South America, South Africa, India	30 (5.5)	32 (5.8)	62 (5.7)	[redacted]	[redacted]	[redacted]
Eastern Asia	43 (7.9)	41 (7.5)	84 (7.7)	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; GCis = gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category.

a One patient with ECOG PS = 3 at baseline was randomised to the GCis Arm; this patient did not receive treatment.

b Including eCRF categories “American Indian or Alaska Native,” “Native Hawaiian or Other Pacific Islander,” “Multiple Race,” and “Other.”

Primary endpoint: Overall Survival

The primary endpoint of SQUIRE was OS. Any data entered into the database after the cut-off date was excluded from the analyses described in these sections. Primary and secondary endpoints were analysed using the ITT population.

The median follow-up time was 25.2 months (95% CI 23.7 to 27.1) in the GCis + N arm and 24.8 months (95% CI 22.8 and 28.3) in the GCis arm. Loss to follow-up was low in the study (GCis + N: 16 [2.9%], GCis: 15 [2.7%]) and 43 patients withdrew consent for follow-up for the primary OS analysis (GCis + N: 23 [4.2%], GCis: 20 [3.6%]).

Patients that received necitumumab had a statistically significant improvement in OS compared to patients in the GCis Arm (HR = 0.842; 95% CI=0.736, 0.962; p = .0120), with an estimated reduction in the risk of death of 16% in GCis + N arm. The median OS for patients in the GCis + N arm was 1.6 months longer compared with GCis (11.5 months vs. 9.9 months) (Table 14).

Table 14 Overall Survival (ITT Population)

	ITT	
	GCis+N N =545	**GCis N = 548**
Number of deaths, n (%)	418 (77)	442 (81)
Number censored, n (%)	127 (23)	106 (19)
Log-rank p-value (two-sided) Stratified*	.01	
Hazard ratio[b] (95% CI[b]) Stratified*	0.84 (0.74, 0.96)	
Median OS[a] – months (95% CI[a])	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Survival rate[a] % (95% CI)[a]		
6-month	78.9 (75.2, 82.1)	72.3 (68.3, 75.9)
1-year	48 (43, 52)	43 (39, 47)
18-month	28.9 (25.0, 32.9)	24.3 (20.7, 28.1)
2-year	20 (16, 24)	17 (13, 20)

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GCis = gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; OS = overall survival.

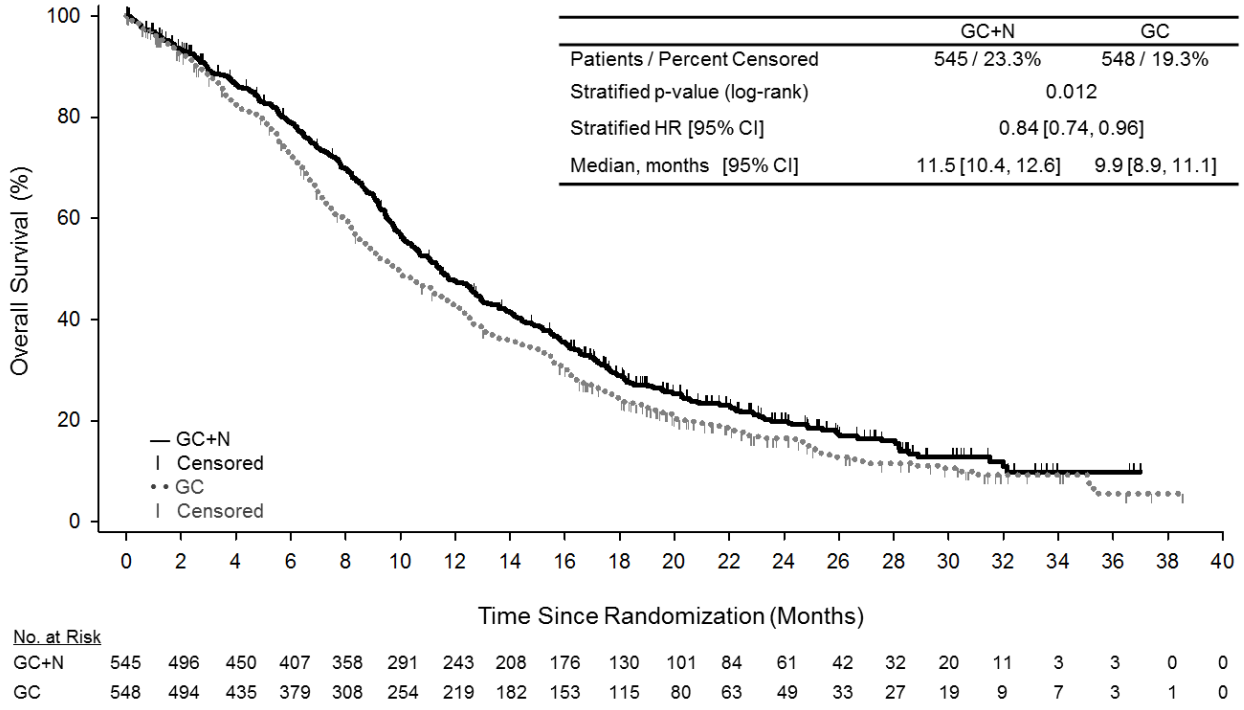
* Stratified by the randomisation strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a Estimated by the KM method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

The KM curve shows an early separation of the curves in favour of the GCis + N Arm that is maintained over the duration of the study (Figure 4). This is reflected in one year survival rates of 48% for the GCis + N arm compared with 43% in the GCis Arm. The corresponding figures for 2-year survival were 20% and 17% respectively.

Figure 4 Kaplan-Meier curve for overall survival (ITT Population).]



No. at Risk

GC+N	545	496	450	407	358	291	243	208	176	130	101	84	61	42	32	20	11	3	3	0	0
GC	548	494	435	379	308	254	219	182	153	115	80	63	49	33	27	19	9	7	3	1	0

Abbreviations: CI = confidence interval; cis = cisplatin; GCis = gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; gem = gemcitabine; HR = hazard ratio; ITT = intent-to-treat; neci = necitumumab; No. = number.

Source: Thatcher et al 2015

In the Western European population, the median OS was statistically significantly greater in the GCis + N arm than in the GCis arm ([redacted]). The KM curve shows an early separation of the curves in favour of the GCis + N Arm that is maintained over the duration of the study (Figure 5).

Figure 5 Kaplan-Meier curve for overall survival (Western European Population)

An incremental improvement in OS of 1.6 months to [redacted] months is a moderate improvement in survival. However, the squamous-NSCLC population consist of older patients with a history of chronic smoking and added comorbidities, including hypertension, COPD, and previous heart attacks. 55% of patients in SQUIRE had ≥2 metastatic sites. Thus, an increase in OS of 1.6 months to [redacted] months in this patient population (including those with performance status 2) may be considered clinically significant.

Additionally, OS in SQUIRE measured death from any cause. However, more patients died in the GCis arm due to disease progression than in the GCis + N arm (67.8% vs 63%). Also, more patients died in the GCis arm due to AEs than in the GCis + N arm (7% vs 6.5%).

Progression-Free Survival Results

Patients in the necitumumab arm had a statistically significant improvement in PFS compared to patients in the GCis Arm (HR = 0.85; 95% CI 0.74, 0.98; p = .02), with an estimated reduction in the risk of progression or death of 15% in GCis+ N arm (Table 15). The median PFS for patients in the GCis + N arm was 0.2 months longer compared with the GCis arm (5.7 months versus 5.5 months).

Table 15 Progression-Free Survival (ITT Population)

	ITT	
	GCis+N N =545	**GCis N = 548**
Number of events, n (%)	431 (79)	417 (76)
Number censored, n (%)	114 (21)	131 (24)
Log-rank p-value (two-sided) Stratified*	.02	
Hazard ratio[b] (95% CI[b]) Stratified*	0.85 (0.74, 0.98)	
Median PFS – months (95% CI[a])	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
PFS rate[a] % (95% CI)[a] 3-month 6-month	79 (76, 83) 45 (40, 49)	73 (68, 76) 37 (33, 42)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; PFS = progression-free survival.

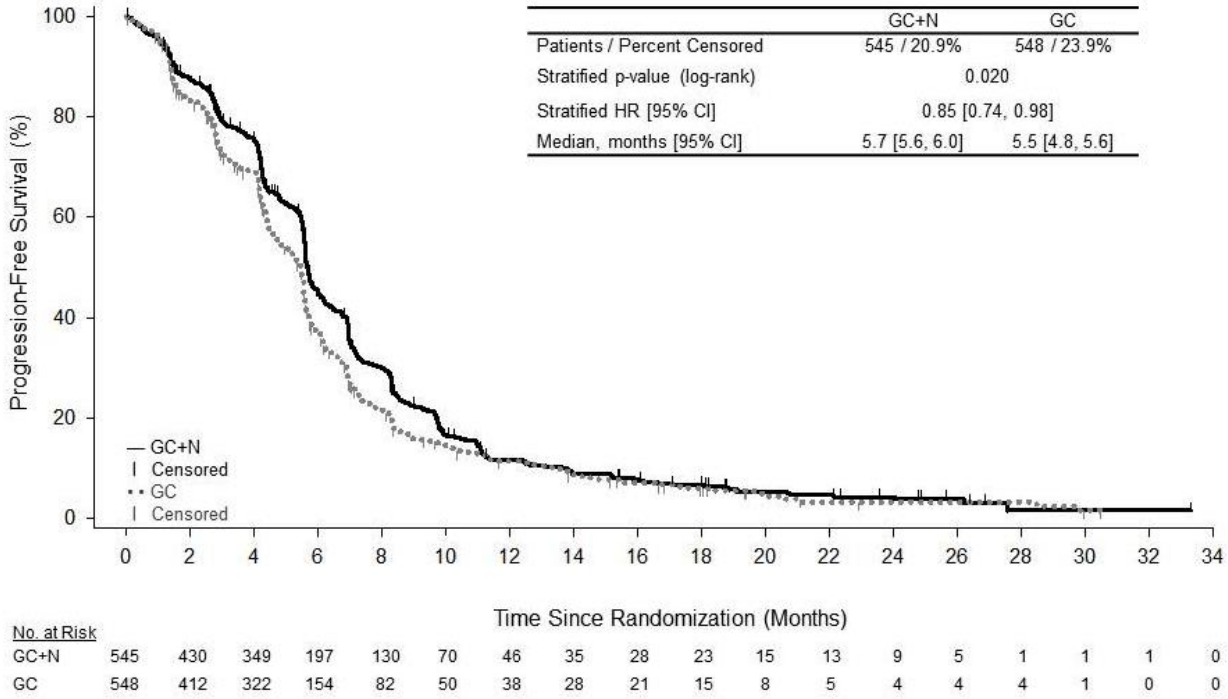
* Stratified by the randomisation strata (ECOG performance status [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a Estimated by the KM method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

The KM curves show an early separation of the curves that continue to be separated, coming closer together at regular intervals corresponding to imaging time points (every 6 weeks per protocol), resulting in a step like pattern (Figure 6).

Figure 6 Kaplan-Meier curve for progression-free survival (ITT Population).



Abbreviations: cis = cisplatin; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; gem = gemcitabine; ITT = intent-to-treat; neci = necitumumab; No. = number.

The 3-month PFS rates were 79% for the GCis + N arm compared with 73% in the GCis Arm. The 6 month PFS rates were 45% for the GCis + N arm compared with 37% in the GCis arm.

The KM curve show an early separation favouring the experimental treatment arm, but show touch points at each of these regular 6-week intervals where radiologic assessments occurred. The difference in median PFS between arms appears to be a distorted estimate due to the pattern of the timing of radiologic assessments. The difference between treatment arms is better represented by the PFS HR of 0.85, which indicates the total amount of separation of the PFS curves. Therefore, the results for PFS are very consistent with the results for OS (HR = 0.84).

In the Western European population, the median PFS in patients receiving GCis + N was [redacted] months and [redacted] months in the GCis arm (difference [redacted] months PFS in the GCis + N arm; [redacted]). The KM curve showed an early separation suggesting favourable results in the GCis + N arm (Figure 7).

Figure 7 Kaplan-Meier curve for progression-free survival (Western European Population).

Objective Response Rate (ORR)

Patients in the GCis + N arm did not have a statistically significant improvement in ORR compared to patients in the GCis Arm (31% versus 29%) (p= 0.40) (Table 16). In contrast, disease control was statistically significantly more common in the GCis + N arm than in the GCis arm (p=0.043)

Table 16 Overall Response (ITT Population)

	GCis+N N = 545	GCis N = 548	p-Value[a]
Best Overall Response n (%)			
CR	0	3 (<1)	
PR	170 (31)	155 (28)	
SD	276 (51)	264 (48)	
PD	41 (8)	55 (10)	
NE	4 (<1)	12 (2)	
NA	54 (10)	59 (11)	
Objective response rate[b] n (%) (95% CI)[c]	170 (31) (27, 35)	158 (29) (25, 33)	0.40
Disease control rate[d] n (%) (95% CI)[c]	446 (82) (78, 85)	422 (77) (73, 80)	.043

Abbreviations: CI = confidence interval; CR = complete response; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; NA = no assessment; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

a Derived from two-sided Cochran-Mantel-Haenszel test adjusting for the randomisation strata: Eastern Cooperative Oncology Group performance status (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

b Response rate = CR + PR.

c Estimated using the Wilson formula.

d Disease control rate = CR + PR+ SD.

Table 17 Objective response (CR + PR) (Western European population)

	GCis + N (n=172)	GCis (n=176)
Objective response, n(%)	[redacted]	[redacted]
95% CI (%)*	[redacted]	[redacted]
95% CI difference of response rates*	[redacted]	
Odds Ratio# (95% CI)	[redacted]	

* Estimated using the Wilson formula.
# Odds ratio is expressed as treatment/control.

In the Western European population, the objective response rate was not statistically significantly more common in the GCis + N arm than in the GCis arm.

Time to Treatment Failure (TTF)

Patients in the necitumumab arm had a statistically significant improvement in TTF compared to patients in the GCis arm (HR=0.84; 95% CI 0.75, 0.95; p=0.006). The median time to treatment failure for patients in the GCis + N arm was 0.7 months longer compared with the GCis arm (4.3 months vs. 3.6 months). Patients in the GCis + N arm had a 16% reduction in the risk of treatment failure compared to patients in the GCis Arm.

Table 18 Time to Treatment Failure (ITT Population)

	GCis+N N =545	GCis N = 548
Number of events, n (%)	529 (97.1)	528 (96.4)
Disease progression	312 (57.2)	280 (51.1)
Death	1 (0.2)	30 (5.5)
Early discontinuation of study treatment for any reason other than 'completed treatment' (for GCis Arm)	214 (39.3)	202 (36.9)
Initiation of new anti-cancer therapy	2 (0.4)	16 (2.9)
Number censored, n (%)	16 (2.9)	20 (3.6)
Alive without treatment failure	9 (1.7)	13 (2.4)
No treatment received	7 (1.3)	7 (1.3)
Stratified log-rank p-Value (2-sided)	.0061	
Stratified HR[b] (95%CI)	0.844 (0.747, 0.953)	
Median TTF[a], months	4.3	3.6
(95% CI)[a]	(4.2, 4.8)	(3.3, 4.1)

Abbreviations: CI = confidence interval; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; TTF = time to treatment failure.

a Estimated by the KM method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

Note: Stratified log-rank test, as well as the hazard ratio from a stratified proportional hazard model, is stratified by the randomisation strata: ECOG performance status (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

Table 19 Time to treatment failure (Western European population)

	GCis + N (n=172)	GCis (n=176)
Number of events, N (%)	[redacted]	[redacted]
Median*, months (95% CI*)	[redacted]	[redacted]
HR# (95% CI)	[redacted]	
Log-rank p-value@	[redacted]	
Inter-action p-value$	[redacted]	

* Estimated by the Kaplan-Meier method.
# Hazard ratio is expressed as treatment/control and estimated from unstratified Cox model (without the treatment-by-subgroup interaction).
@ Unstratified and unadjusted log-rank two-sided p-value.
$ Wald test of treatment-by-subgroup interaction from unstratified Cox model (with treatment-by-subgroup interaction)

In the Western European population, the TTF improved in the GCis + N arm by [redacted] months. There was [redacted] reduction in the risk of treatment failure in the GCis + N arm than in the GCis arm.

Figure 8 Time to treatment failure (Western European population)

4.8 Subgroup analysis

Subgroup analyses were performed for OS, PFS by assigned treatment arm. Each analysis was completed using similar methodology as for the primary analysis. Tests within each subgroup and tests for subgroup-by-treatment interaction terms was completed using an unstratified test and unstratified Cox proportional hazards model. A Forest plot of the estimated HRs with 95% CIs is included in (Figure 9).

Planned subgroup analyses included a series of analyses based on geographic region, as follows:

- Korea and Taiwan combined vs. all others

- Eastern Asia (Korea, Taiwan, Singapore, Philippines, and Thailand) vs. all others
- Eastern Europe (including Russia, Poland, Hungary, Romania, Croatia, Serbia, and Slovakia) vs. Eastern Asia vs. all others
- Eastern Europe vs. all others
- Each non-Eastern country with >40 patients randomized vs. Eastern Asia vs. all others
- Each country with >40 patients randomized vs. all others

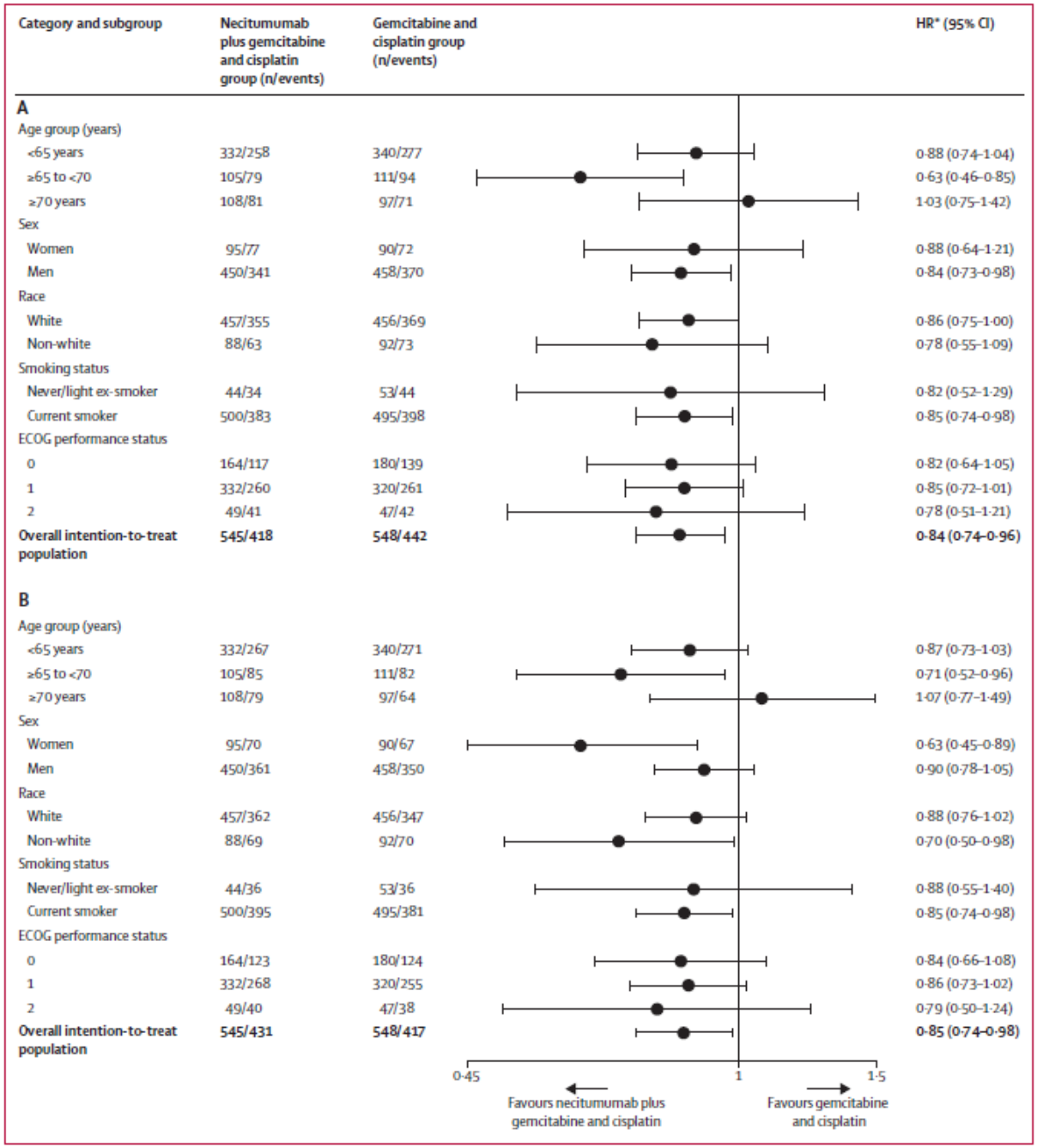
Other planned subgroup analyses were based on general prognostic factors (based on CRF data), including:

- age (<70 vs. ≥70 years; and <65 vs. ≥65 years);
- gender (female vs. male);
- race (White vs. non-White);
- ECOG PS (0 vs. 1 vs. 2 and 0-1 vs. 2); and
- smoking history (never smoker [non-smoker and light ex-smoker combined] vs. smoker).

Post-hoc analysis was also completed for patients in Western Europe.

The pre-specified subgroup analysis found a consistently statistically significant advantages in terms of OS and PFS in the ITT population in favour of GCis + N arm, demonstrating internal consistency of the data. The post-hoc subgroup analysis found that the clinical efficacy of necitumumab within the SQUIRE trial does vary across regions. Statistical analysis of the SQUIRE trial found that patients in Hungary and Poland performed better on the GCis arm than the GCis + N arm with a HR of [redacted] and [redacted] respectively. However, patients in Western Europe performed better on the GCis + N arm than the GCis arm with a HR of [redacted]. A comprehensive analysis of this data has been completed on general prognostic factors to determine the cause of this difference including: disposition, demographics, pre-treatment disease characteristics, medical history, con meds, OS, PFS, ORR, post study therapy, exposure, dose modifications/delays, TEAEs, AEs of special interest, summary of arterial thromboembolic events (ATE)/ venous thromboembolic events (VTE) (including fatal), ECOG PS by time point, hospitalisation and LCSS. However, the analysis concluded that there were no substantial imbalances in demographics, patient characteristics, exposure to treatment or other prognostic factors between the regions.

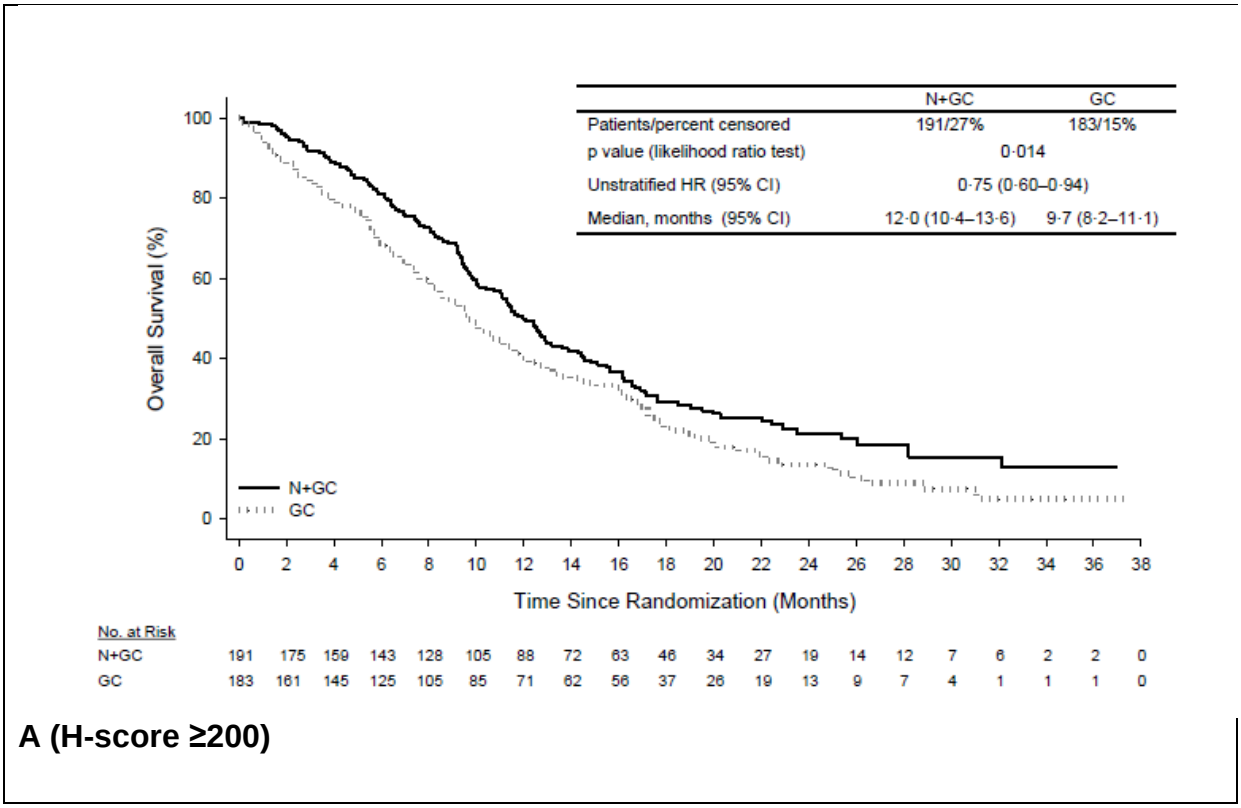
Figure 9 Subgroup analyses (in ITT population)



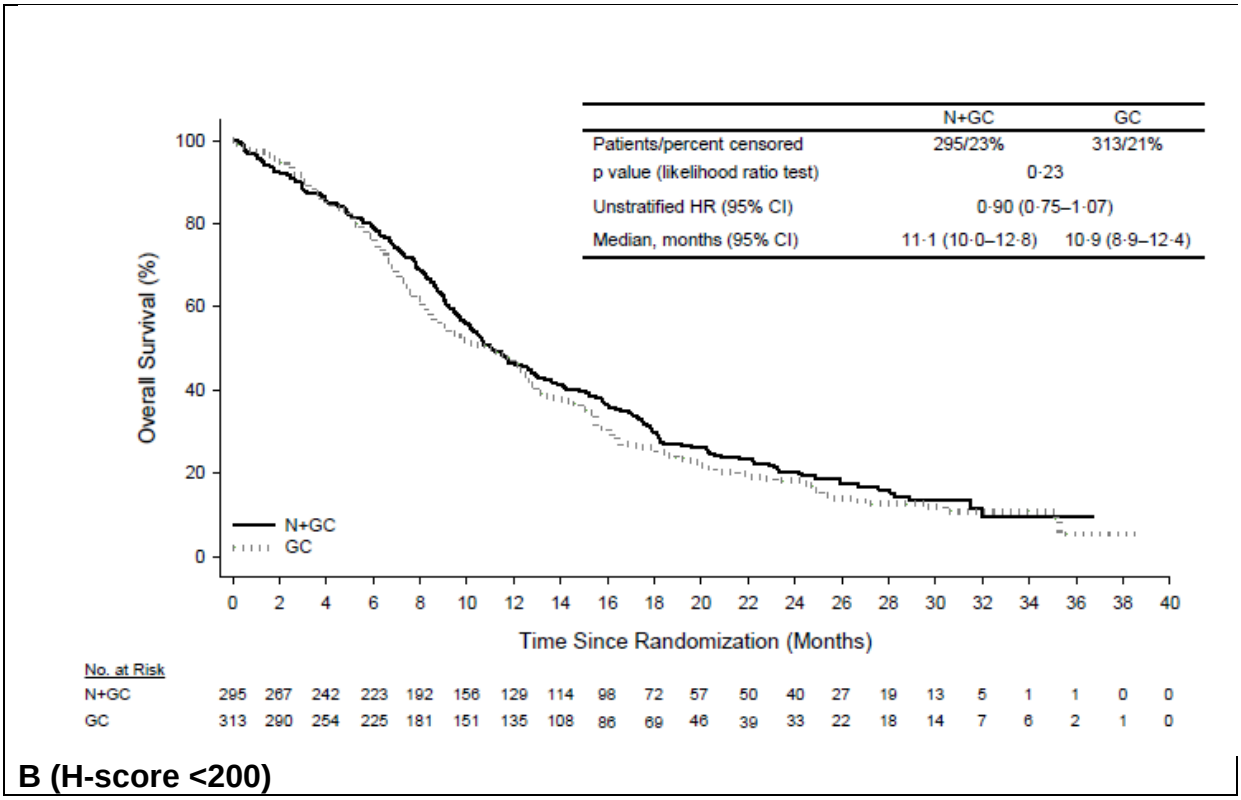
A) Overall survival B) Progression free survival in subgroups defined by baseline characteristics. HR = Hazard ratio, ECOG = Eastern Cooperative Oncology Group. * Stratified HR for ITT population; unstratified HR for HR groups
Source: Thatcher et al 2015

According to EGFR H-score levels, patients with high expression-score (≥200) had more favourable OS than those with low H-score (<200). There was a 25% reduction in the risk of death in the high expression-score level patients (HR 0.75 95% CI 0.60 to 0.94) whereas only 10% reduction in the risk of death in the low expression-score level patients (HR 0.90 95% CI 0.75 to 1.07). There was no difference between high and low expression-score level patients when assessing PFS.

Figure 10 Overall survival (A, B) according to EGFR expression group and treatment groups

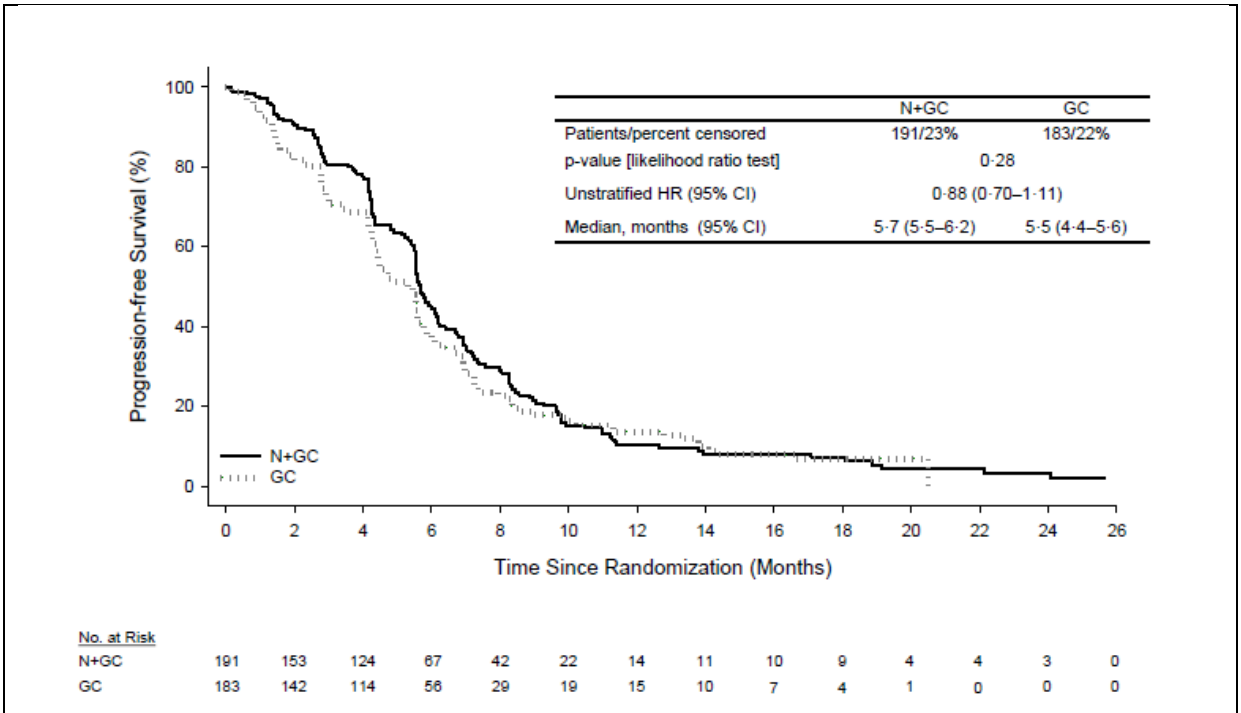


A (H-score ≥200)

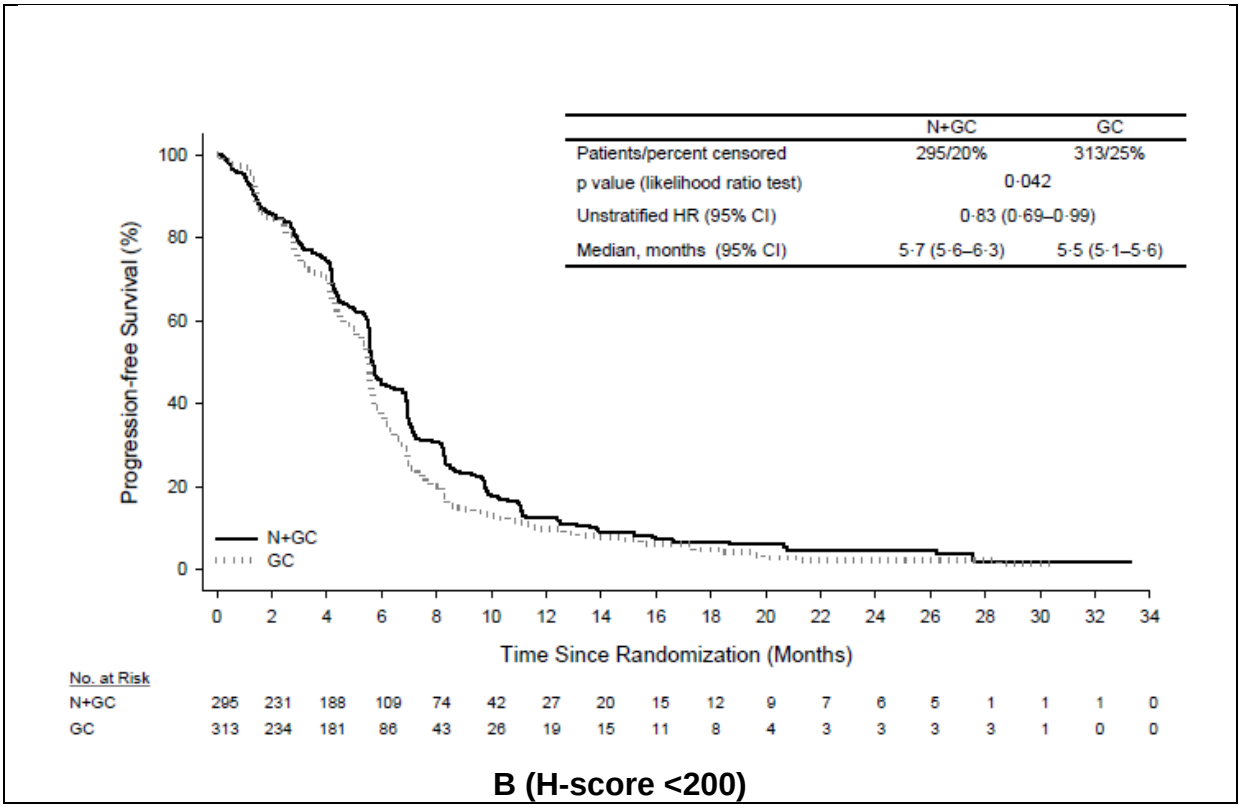


B (H-score <200)

Figure 11 PFS (A, B) according to EGFR expression group and treatment groups



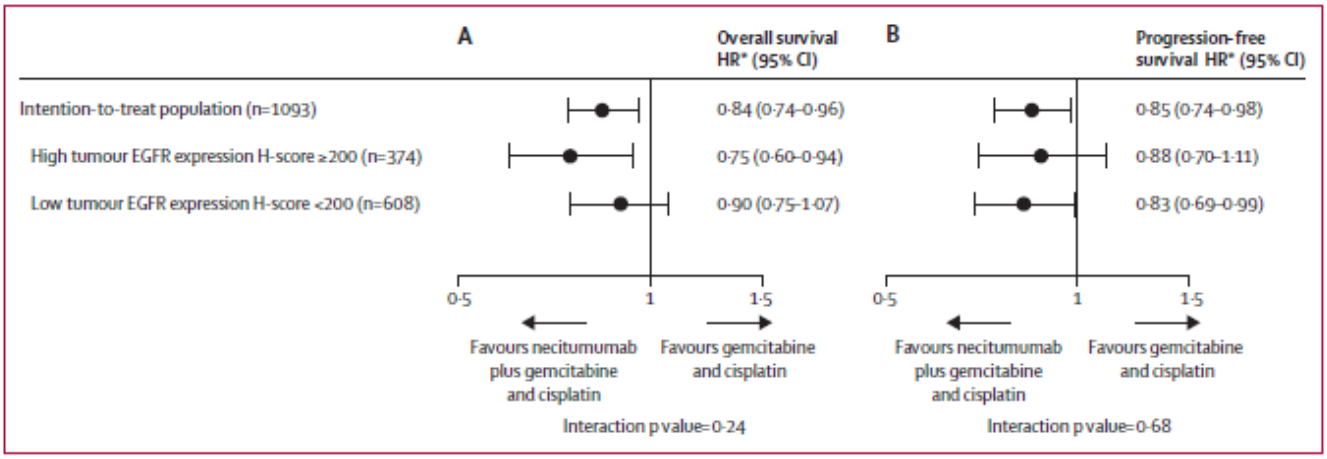
A (H-score ≥200)



B (H-score <200)

The interaction test for both OS and PFS showed no significant difference in HRs between the two groups according to EGFR expression (Figure 12) thereby suggesting that H-score threshold of 200 is not predictive of a differential effect.

Figure 12 Forest plots of OS (A) and PFS (B) in high (H-score ≥200) and low (H-score <200) tumour EGFR expression groups



HR = Hazard ratio. * Stratified HR for ITT population; unstratified HR for H-scores ≥200 and <200
Source: Thatcher et al 2015

4.9 Quality of life (QoL)

Lung Cancer Symptom Scale (Patient Scale)

Of the 545 patients in the GCis + N Arm, 481 (88.3%) had a baseline and at least one completed post baseline LCSS assessment. In the GCis Arm, 482 (88%) of the 548 patients had a baseline and at least one completed post baseline LCSS assessment.

Table 20 shows the baseline LCSS. The results suggest SQUIRE patients tended to report, at baseline, moderate-to-high symptoms, interference with normal activities, and impact on QoL typical of patients with first-line squamous NSCLC (Socinski et al. 2015).

Table 20 Summary of Baseline LCSS Items in SQUIRE (ITT Population)

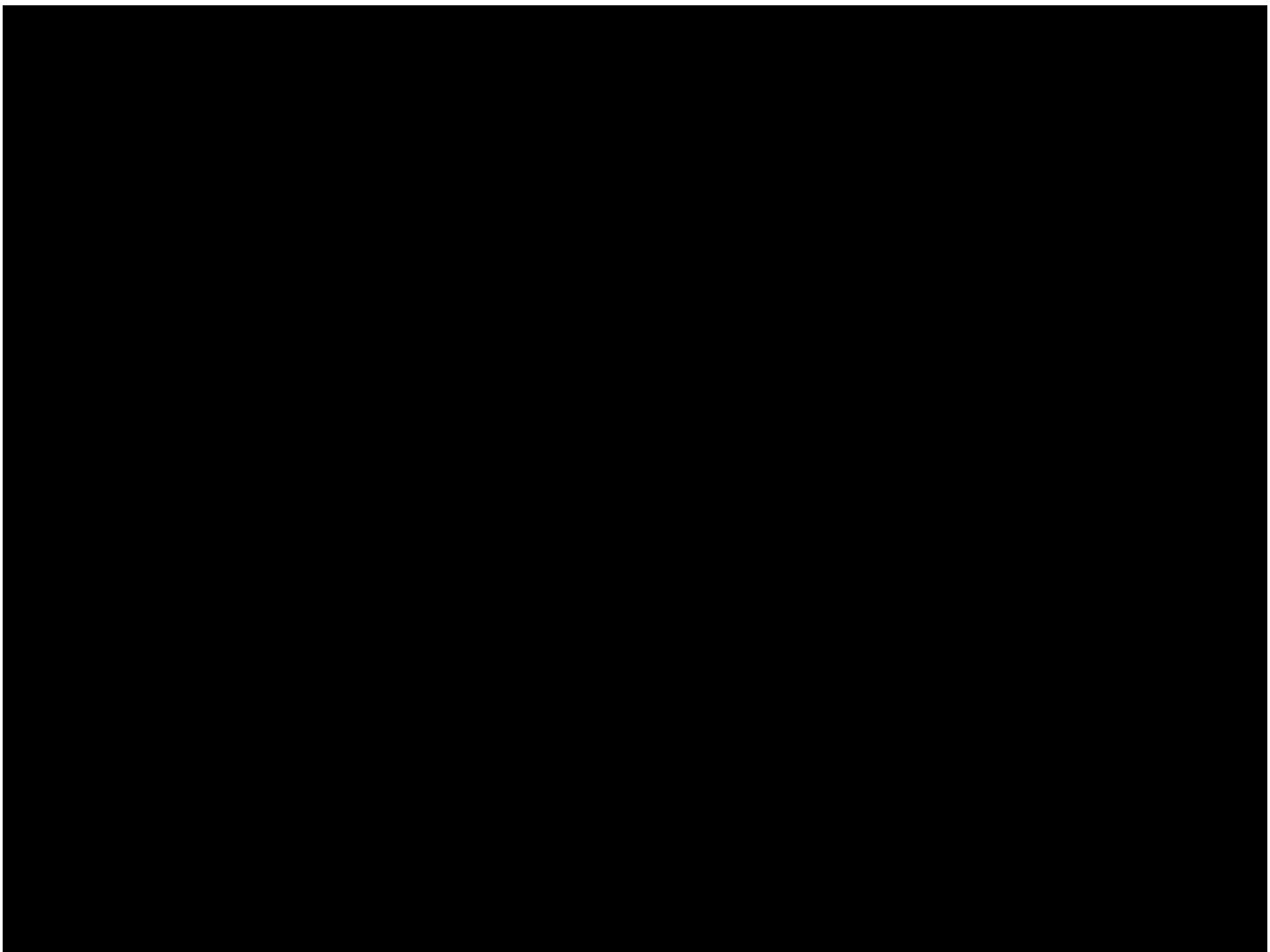
	GCis + N (N = 545)			GCis (N = 548)		
LCSS Items	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**n**	**Mean (SD)**	**Median (Q1-Q3)**
Loss of Appetite	514	30.7 (26.63)	25.0 (7.0-49.0)	521	28.1 (25.71)	22.0 (5.0-47.0)
Fatigue	517	37.0 (26.99)	35.0 (12.0-54.0)	518	35.9 (25.67)	36.0 (11.0-53.0)
Cough	518	31.9 (27.60)	25.0 (7.0-51.0)	520	31.2 (26.24)	26.5 (7.0-51.0)
Dyspnoea	520	31.6 (27.89)	24.5 (6.0-51.0)	517	30.7 (27.62)	23.0 (5.0-53.0)
Haemoptysis	518	6.8 (15.83)	0.0 (0.0-5.0)	519	6.9 (16.85)	0.0 (0.0-4.0)
Pain	518	23.0 (27.48)	9.0 (1.0-39.0)	521	22.4 (25.25)	11.0 (2.0-39.0)
Overall Symptoms	518	30.8 (27.50)	24.0 (6.0-50.0)	516	30.0 (26.58)	24.0 (6.0-48.5)
Normal Activities	519	34.9 (28.79)	30.0 (9.0-55.0)	521	37.1 (28.28)	35.0 (10.0-58.0)
Quality of Life	517	39.3 (26.21)	40.0 (17.0-54.0)	521	39.4 (25.35)	41.0 (18.0-55.0)

Abbreviations: GCis = gemcitabine and cisplatin; GCis + N = gemcitabine and cisplatin plus necitumumab; LCSS=Lung Cancer Symptom Scale,.

Figure 14 shows the Forest plot of HRs and the 95% CIs for time to deterioration (TTD), over the entire assessment period, for each of the 12 LCSS variables. None of the 95% CIs excluded a HR of 1.0, which suggest that adding necitumumab to gemcitabine-cisplatin did not impact, overall, on the deterioration of symptoms, normal activities and QoL, as measured by the LCSS.

Figure 13 LCSS responses by visit

a. Symptoms*



b. Global Items*

[redacted]

c. Total Score*

*response compared to baseline

[redacted]

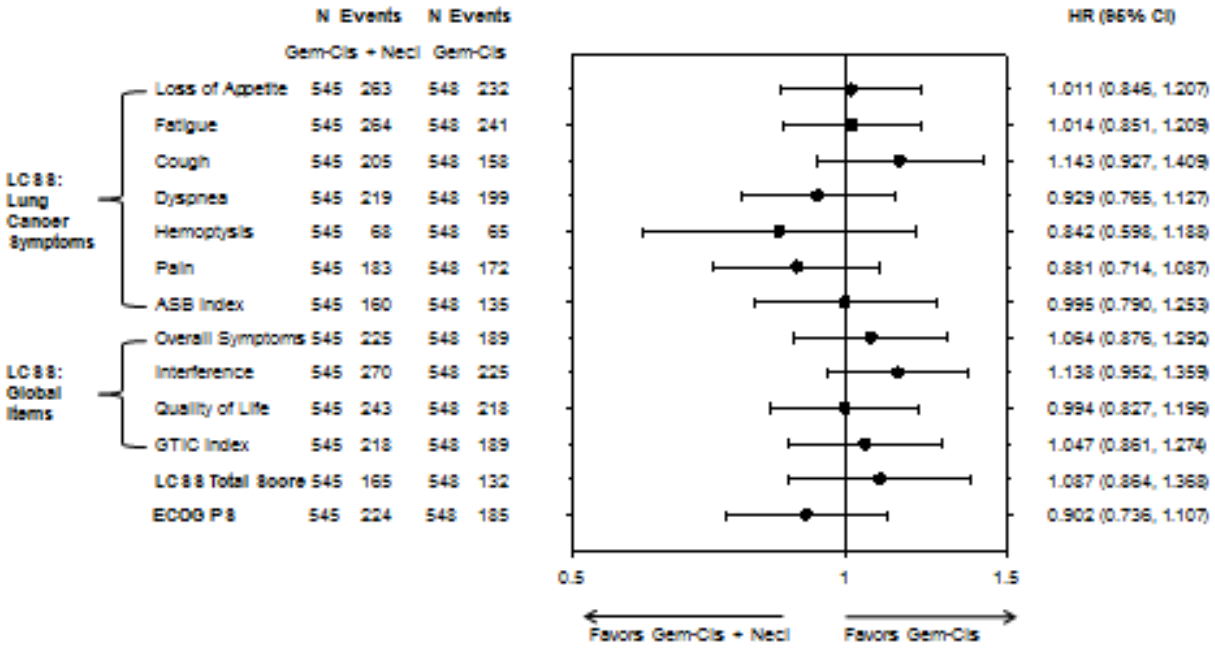
*response compared to baseline

LCSS, Lung Cancer Symptom Scale; N+GC, Necitumumab + Gemcitabine-Cisplatin; GC, Gemcitabine-Cisplatin

ECOG PS

ECOG PS also represents an element of QoL as well as the patient reported outcomes data collected in the trial. The analyses of ECOG PS by time point and time to deterioration, suggested adding necitumumab to gemcitabine-cisplatin did not impact, overall, on the deterioration of ECOG PS as none of the 95% CIs for time to deterioration ECOG PS excluded an HR of 1.0 (Figure 14). The results suggested that adding necitumumab to G+ C did not impact the LCSS scores.

Figure 14 Forest plot of hazard ratio and the 95% CI for time to deterioration of LCSS and ECOG PS scores - SQUIRE (ITT population).



Abbreviations: ASB = average symptom burden; CI = confidence interval; GCis = gemcitabine-cisplatin; GCis+N = gemcitabine-cisplatin+ necitumumab; GTIC = global three-item composite; HR = hazard ratio; LCSS = Lung Cancer Symptom Scale; N = number of patients
Source: Reck et al 2014.

A post-hoc analyses was also completed on the LCSS to evaluate whether more severe baseline LCSS scores are prognostic for worse OS and/or predictive of a stronger relative OS benefit with the addition of necitumumab to gemcitabine and cisplatin. The analysis defined the most severe baseline value (MSS) for each patient as the worst (maximum) score among the nine individual LCSS items in any single LCSS assessment. MSS and other LCSS items were analysed as continuous variables among all patients providing baseline LCSS data, evaluated as prognostic and predictive factors for OS and PFS using Cox and KM methods. This analysis concluded that higher severity of LCSS items are prognostic for shorter OS in the control arm. On the GCis arm, there was a statistically

significant increase in the risk of death associated with any 15-point higher baseline MSS. However, on the GCis + N arm, there was only a 3% increase in the risk of death associated with any 15-point higher baseline MSS. Therefore, the addition of necitumumab to gemcitabine and cisplatin appears to reduce the poor prognosis associated with higher severity of patient reported baseline LCSS items.

EQ-5D

Of the 545 patients in the GCis + N Arm, 484 (88.8%) had a baseline and at least one completed post-baseline EQ-5D assessment. In the GCis Arm, 489 (89.2%) of the 548 patients had a baseline and at least one completed post-baseline EQ-5D assessment.

For each assessment (baseline, Cycles 2-6 and end of therapy), most patients in the GCis + N Arm and the GCis Arm experienced no or some problems in each of the five dimensions. Less than 6.5% of patients in either arm experienced extreme problems on any of the five dimensions. EQ-5D index and VAS scores (baseline, Cycles 2-6, best and worse scores) were similar between arms.

Figure 15 Percentage of patient responses (no problems, some problems, extreme problems) for each EQ-5D dimension over time.

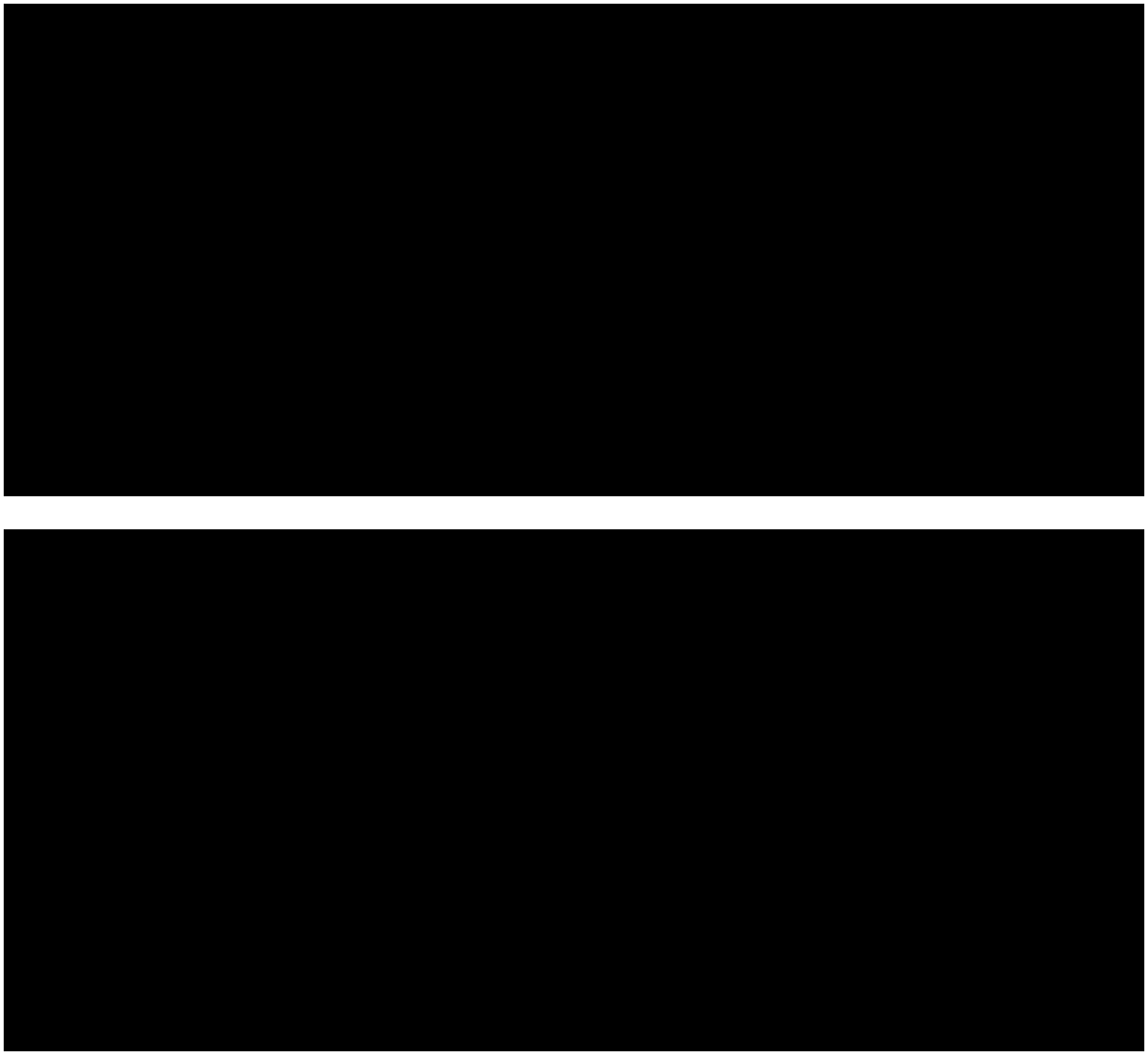


Figure 16 Percentage of patient responses (no problems, some problems, extreme problems) for each EQ-5D dimension over time (continued).

Figure 17 Percentage of patient responses (no problems, some problems, extreme problems) for each EQ-5D dimension over time (concluded).

Figure 18 Mean EQ-5D VAS (±SD) by time point.

Figure 19 Mean EQ-5D VAS Index (±SD) by time point.

Figure 20 Mean EQ-5D visual analog scale (VAS) (± SD) by visit

SD, Standard Deviation; Neci+Gem-Cis, Necitumumab + Gemcitabine-Cisplatin; Gem-Cis , Gemcitabine-Cisplatin

Figure 21 Percentage of patients experiencing no problems, some problems, and severe problems for each of the EQ-5D dimensions (mobility, pain and discomfort, anxiety and depression, self-care, and usual activities) by visit

N+GC, Necitumumab + Gemcitabine-Cisplatin; GC, Gemcitabine-Cisplatin

4.9 Meta-analysis

No head-to-head clinical trials were found that provided evidence of the efficacy and safety of GCis + N against other comparators identified in the NICE scope. Therefore, no meta-analysis was undertaken.

4.10 Indirect and mixed treatment comparisons

A systematic literature review was conducted with a primary aim of identifying all the RCTs of chemotherapy treatment for the first-line treatment of patients diagnosed with squamous NSCLC. The trials did not have to solely include NSCLC patients with squamous histology, but one of the required outcome variables (OS, PFS, toxicity or QoL) had to be reported

separately for patients with advanced or metastatic (Stage IV) NSCLC of squamous histology. Other specific aims included performing indirect and direct comparisons of GC + N to all identified comparators for OS, PFS, toxicity, and QoL. The analyses were performed on an ITT basis for survival outcomes. Analyses were planned with and without adjusting for covariate information, and using both fixed-effect and random-effect models. The manuscript is under preparation for publication (39).

Search strategy

Three databases were searched for relevant publications – Medline, Embase and PubMed. The search employed to identify studies for inclusion in the systematic literature review comprised of automated searches of electronic databases and manual searches of bibliographies of previously conducted systematic reviews and meta-analyses. Clinical trials.gov was also searched for additional trials either recently completed or not yet published.

The comprehensive search strategy included a combination of disease/diagnosis terms (e.g. non-small cell lung cancer), study design terms (e.g. randomised controlled trials), and year and language terms. The complete search strategies employed in each of the reference databases are provided in the Appendix 4. The search strategy was initially executed on August 3, 2013 and refreshed on January 27, 2015. Studies published prior to 1995 were excluded as NSCLC histology was not consistently differentiated prior to 2000. Publications were limited to the English language. Publications that were case reports, reviews, editorials and other studies that were not randomised trials were excluded. The eligibility criteria applied to selected appropriate studies are detailed in Table 21.

Table 21 Criteria used in the trial selection process

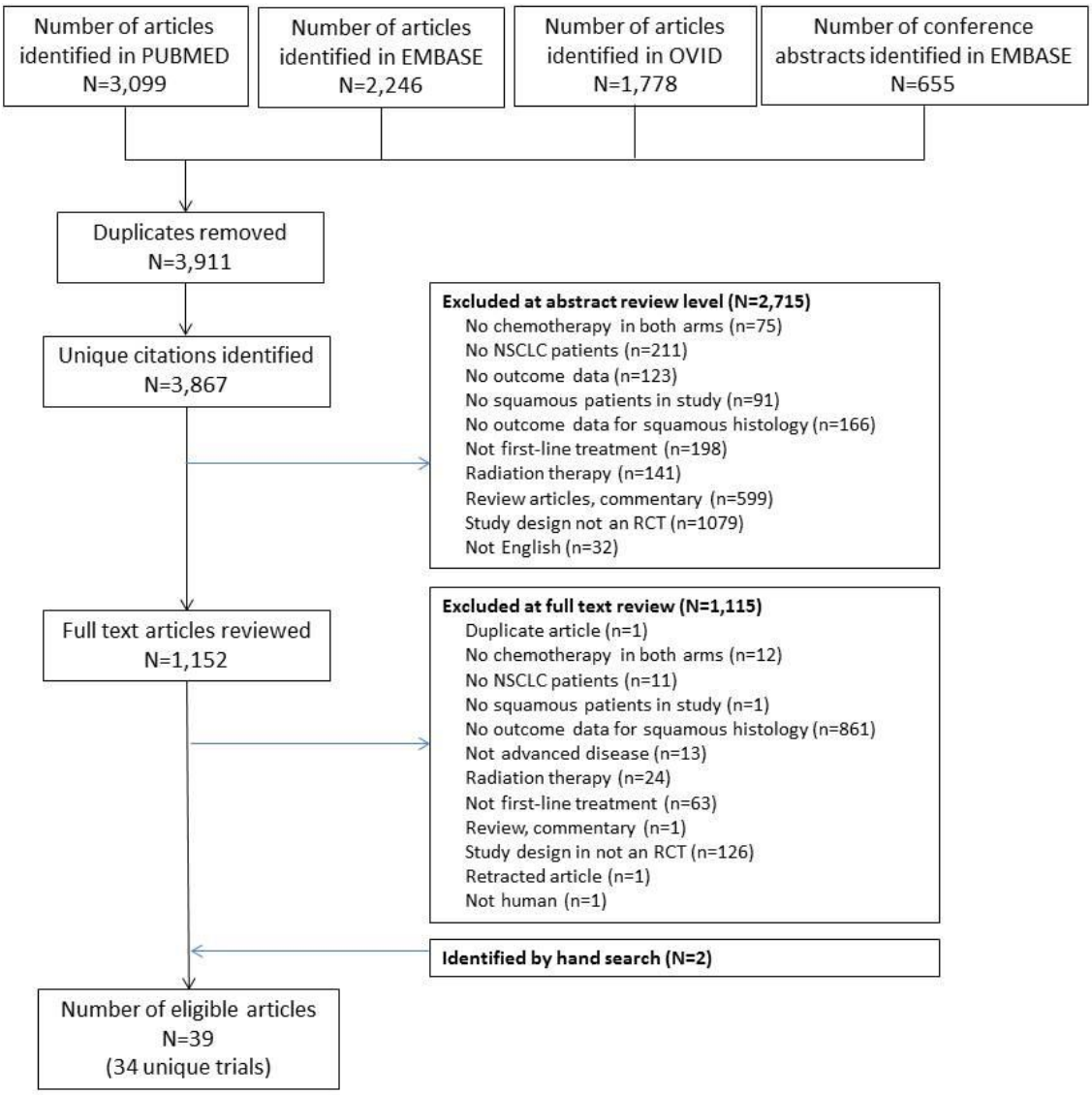
Inclusion criteria	Exclusion criteria
Population: Male or female patients with histologically- or cytologically-confirmed squamous NSCLC included in the study. Study participants must have not received chemotherapy treatment prior to first-line chemotherapy for NSCLC at the time of randomisation in the study **Intervention:** The study assesses a chemotherapy treatment in each study arm. No limits are placed on the type of chemotherapy used. **Comparators:** The study assesses a chemotherapy treatment in each study arm. No limits are placed on the type of chemotherapy used. **Outcomes**: At least one of the required outcome variables (OS, PFS, toxicity or QoL) must be reported separately for patients with advanced or metastatic (Stage IV) NSCLC of squamous histology **Trial design:** RCTs **Language:** English	**Interventions:** Not first-line treatment, with first-line defined as patients with no prior exposure to chemotherapy. Radiation therapy in the absence of concurrent chemotherapy in any treatment group **Study design:** Review articles, news, editorials, and commentaries. While systematic reviews and meta-analyses are ineligible, the references were culled to ensure that no relevant studies have been inadvertently excluded **Year:** Publication date prior to 1995

Study selection

On applying the search strategy to the sources outlined above, a total of 3,867 unique citations were identified as potentially eligible for inclusion in our review. On further review of the titles or abstracts and, if necessary full text review, only 39 articles (representing 34 unique RCTs) met the inclusion criteria presented above. As detailed in Appendix 5, trials were excluded from the final analysis if they did not have any similar comparators to enable connection to the network through a common comparator (n=5), if they investigated experimental agents not approved for use or recommended for use (n=10), or if the agent use is limited to non-squamous cell NSCLC (e.g. pemetrexed- or bevacizumab-containing regimens, n=6) or not used in NSCLC (n=1). One additional study was excluded because it compared two dosing schedules of the same regimen and did not contribute information to the network (n=1). The remaining 13 articles, representing 11 unique RCTs were included in the Bayesian network meta-analysis (NMA) and are summarised in Table 22. Data were limited to outcomes from patients with squamous cell carcinoma within these trials for the meta-analysis. All outcome data associated with the non-squamous subgroup were excluded from the analyses for consistency with the population enrolled to the SQUIRE trial.

Despite identifying 13 eligible publications (Table 22), not every study reported HR data. As a result, a pre-planned secondary analysis was conducted using median survival data (Figure 24).

Figure 22 PRISMA Diagram of Search Results



Statistical analyses

For the primary analyses, the summaries of treatment effects for both OS and PFS are presented as HRs. For the secondary analyses of median data, the results are median time to death for the OS analysis and the median time to progression for the PFS analysis, as well as the ratio of the median time to event ratio. Note, a ratio of median time to event of <1 indicates the median time to event is shorter in the control, a ratio of >1 indicates the median time to event is shorter in the experimental treatment, and a ratio of 1 indicates no difference between the experimental and comparator treatments.

The summary data are presented as median and mean outcomes for all OS and PFS analyses. Means are presented for purposes of the economic modelling.

To conduct the primary analyses the HR and 95% CIs were extracted from the text of the article, calculated from data in the text, or extracted from the KM plot following digitisation of the curve data using XY Scan and in accordance with the methods of Guyot and colleagues (40). This method derives from the published KM survival curves a close approximation to the original individual patient time-to-event data from which they were generated. Specifically, the method provides numerical solutions to the inverted KM equations, using where available information on number of events and numbers at risk.

Study analyses were performed using the BAysian Tool for Meta-Analysis of Networks (BATMAN). The BATMAN tool uses JAGS for Bayesian computation. JAGS model and WinBUGS model are largely equivalent and interchangeable. This tool was developed by Small Implementation Group (SIG) of Bayesian Computation Expert (BCoE) group, including Eli Lilly and Inventiv Health Clinical statisticians, to address the frequent requests for high-quality NMA using a Bayesian approach. The BATMAN tool allows for two types of distribution for the outcome: binomial distribution for binary outcome; normal distribution for continuous outcome (e.g., log hazard, log odds). For relative treatment effects model, two types of models can be fitted: 1) “fixed” – the relative treatment effect is assumed to be constant across studies; (2) “random” – the relative treatment effect is assumed to follow a normal distribution with a common mean and standard deviation that describes the between study heterogeneity. Additionally, there is a meta-regression option within the tool; this option allows for no adjustment, adjusting baseline risk, and adjusting covariates. The models included in this tool are based on those presented in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Documents. The IT validation of this tool has been conducted per Lilly Standard Operating Procedures.

The statistical validation was done by using the same models found in a series of NICE submission documents and comparing the results produced by BATMAN. In addition, the primary NMA results presented in the submission have been independently replicated using OpenBUGs. The validation reports are available for review upon request.

For all studies providing KM curves, the curves were digitized using XY Scan and the proportional hazard (PH) assumption was tested using the extracted data using the cox.zph package in R. The cox.zph function performs the test of the PH assumption for the treatment variable, by correlating the scaled Schoenfeld residuals with the default transformation of time [the KM estimate of the survival function]. If the PH assumption is true, the correlation should be 0 and it is appropriate for individual studies to use the Cox model for time to survival analyses.

The log transformation of the median time to progression or death was used to measure OS and PFS, respectively. Where the standard error (se) for the HR was not available, it was estimated from the se for median time to event assuming an exponential distribution of survival time and log (HR) = - log(median time ratio) or from the number of subjects with events as specified below:

If median time and confidence limit were provided in the manuscript, steps 1 and 2 were conducted to estimate the se for the HR:

- 'medianTime': median time to event (death for OS outcomes or disease progression for PFS outcomes, respectively), which is converted into log(median time)
- The standard error was estimated ('se')for log(median time) as (log(upper confidence limit) – log(lower confidence limit))/2/quantile(confidence level) if a treatment arm had a non-missing value for all three variables.

However, if median time is provided but no confidence limit, step 3 is also conducted:

- The number of subjects (n) with events was used to estimate the standard error for log(median time) as 1/sqrt(n) for a treatment arm.

Both the primary and secondary analyses for OS and PFS were conducted as an unadjusted analysis. An attempt was made to adjust the analysis using data on the total study population where squamous population data were not available. However, inclusion of the covariates resulted in the adjusted models failing to converge due to the small number of studies. The covariates were, however, very consistent between studies, with the exception

of performance status for the Morabito et al. 2013 (CAPPA2 study) and Lilenbaum et al. studies. Therefore, the unadjusted analyses were used for all analyses reported here.

The parameters of the models were estimated using a Markov Chain Monte Carlo (MCMC) method as implemented in the BATMAN software. All analyses using two chains, were run for 10,000 iterations that were discarded as 'burn-in', and the model was run for a further 2,000 iterations for the sampling from the posterior. Convergence of the chains was evaluated by inspection of the trace plots.

Heterogeneity/inconsistency

Heterogeneity was explored by visual inspection of the forest plots. The consistency assumption was planned to be explored by examining network diagrams to identify any closed "loops" where inconsistencies can occur. Density plots of the posterior samples from models based on direct, indirect and mixed evidence were compared. In addition, the heterogeneity parameters (variance and standard deviation) and model fit (residual deviance and Deviance Information Criterion (DIC), a Bayesian criterion for model comparison) between the random and fixed effects models were explored.

Had both fixed and random effects models been used, the DIC could have been compared to assess model fit. However, due to the limited number of studies (e.g. most comparators were supported by only one study) and small patient numbers, the random effects heterogeneity variance became inestimable and the random effects models did not converge in all instances. Therefore, all analyses were conducted using a fixed effects model. The DIC information is thus provided for informational purposes only and was not used to select the best model fit.

Sensitivity analyses

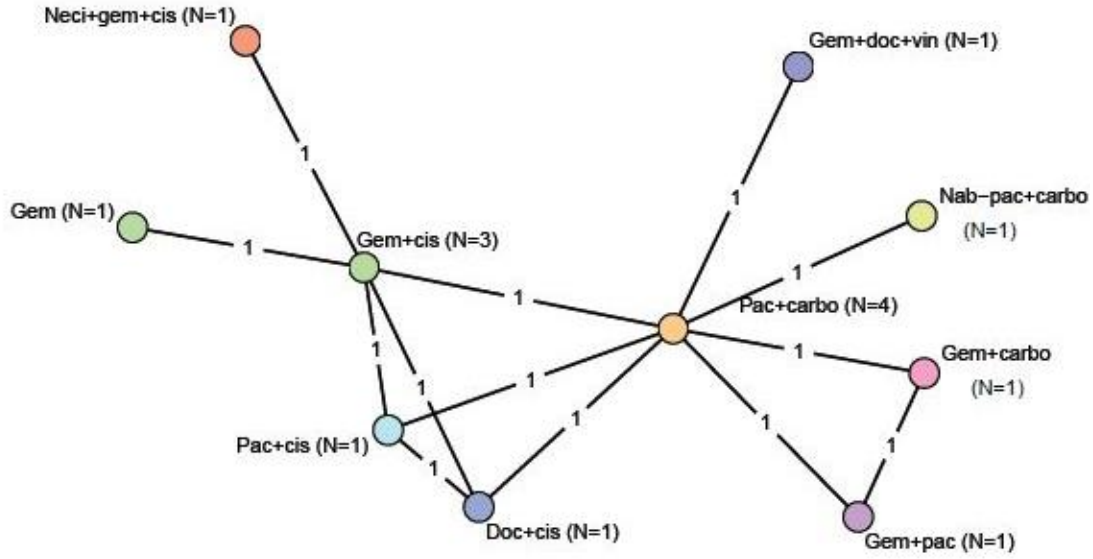
Preplanned sensitivity analyses were designed to test the robustness of findings under different assumptions including: conducting the meta-analysis using a frequentist approach using the methods of Rücker and Krahn;(41,42) comparing the HR versus median time for survival outcomes; limiting included studies by geographical site of study enrollment; limiting included studies to those with metastatic (stage IV) disease; limiting to direct comparisons only; excluding phase II trials; limiting the analysis to studies with a mean age over the age of 70; limiting the analysis to high-quality and low quality studies (PEDro scale value ≥ 6 and < 6, respectively);and by removing studies considered to be biased according to the Cochrane Risk of Bias Tool.

For studies with median time data, the log transformation of the median time was used as a continuous outcome. Missing values were not imputed in any analysis.

Evidence network for meta-analysis

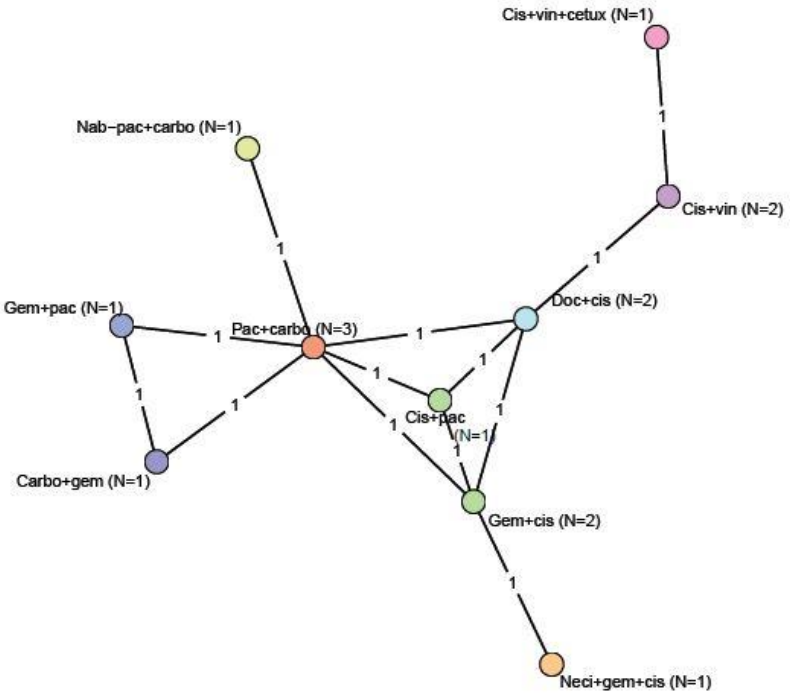
A network diagram from the systematic literature review demonstrates the studies that are connected via a common comparator. The network diagram for all studies that link to GC + N via a comparator is provided from Figure 23 to Figure 26. The scope of the original systematic review was wide hence all the comparators, including those that are not relevant for this submission, were included. Results of non-relevant comparators will not be discussed since this is outside the remit of the submission.

Figure 23 Network diagram for the analysis of OS HR data



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine. Included studies (N=6): Study numbers 1027, 806, 1266, 1263, 603, 1115

Figure 24 Network diagram for the analysis of OS median data



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine. Included studies (N=6): Study 1027, 806, 1266, 1115, 1089, 859

Figure 25 Network diagram for the analysis of PFS HR data

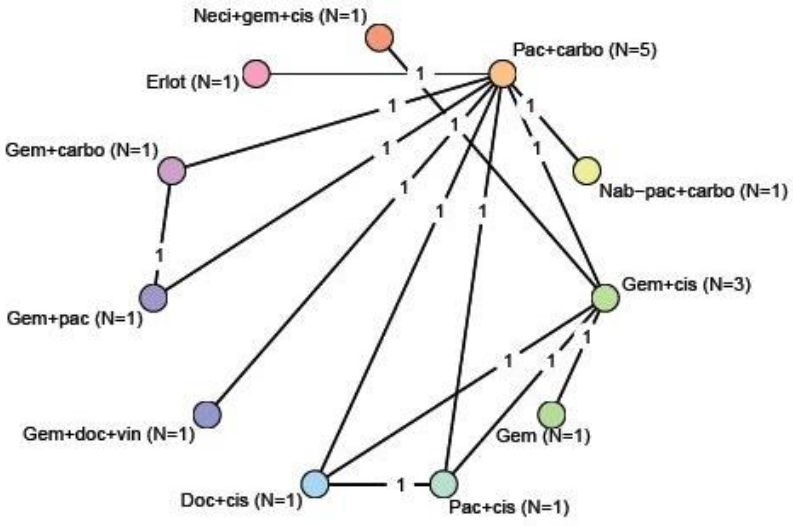
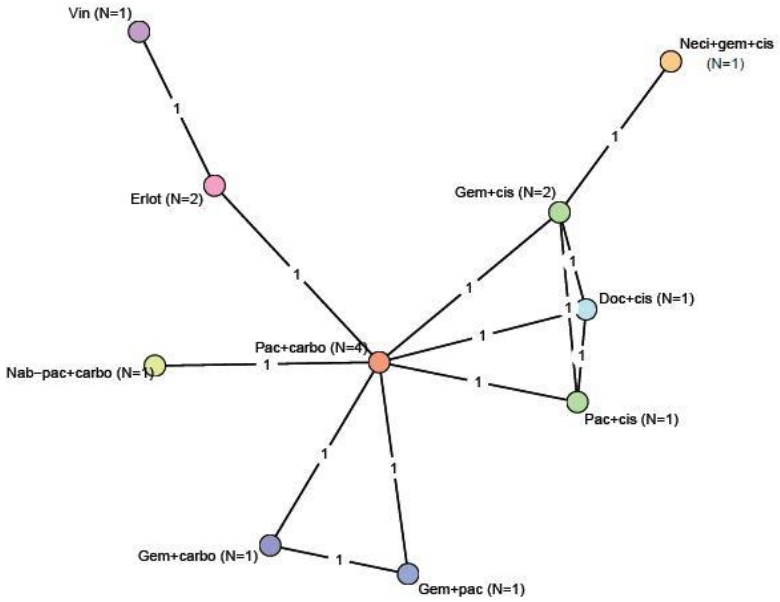


Figure 26 Network diagram for the analysis of PFS median data



KEY: Gem=gemcitabine; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine. Included studies (N=6): Study 806, 1266, 1115, 1027, 171, 655)

Table 22 Summary of the trials used to carry out the indirect or mixed treatment comparison (n=13, representing 11 studies)

Study Number	Citation	Phase	Comparators	Number of squamous patients (% of study arm)	Progression free survival (PFS) overall survival (OS)	Stratific-ation by histology
171	Chen, et al. 2012	II	erlotinib 150 mg/day	19 (33.3%)	Median PFS: 4.07 months	Yes
			vinorelbine 60-80 mg/m^2	13 (23.2%)	Median PFS: 1.47 months	
1266	Hoang, et al. 2013	III	paclitaxel 135 mg/m^2 + cisplatin 75 mg/m^2	60 (20.9%)	Median OS: 6.9 months Median PFS: 2.6 months	No
			gemcitabine 1000 mg/m^2 + cisplatin 75 mg/m^2	50 (17.8%)	Median OS: 9.4 months Median PFS: 4.3 months	
			docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2	56 (19.6%)	Median OS: 8.1 months Median PFS: 3.1 months	
			paclitaxel 225 mg/m^2 + carboplatin AUC 6	58 (20.3%)	Median OS: 9.3 months Median PFS: 3.7 months	
603	Kubota, et al. 2008	III	docetaxel 60 mg/m^2 + gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2	46 (23%)	OS HR: 0.94 (0.56–1.57; p=0.802) PFS HR: 1.04 (0.65–1.68; p=0.861)	No
			paclitaxel 225 mg/m^2 + carboplatin AUC 6	30 (15%)		
655	Lilenbaum, et al. 2008	II	erlotinib 150 mg/day	11 (21.2%)	Median PFS: 2.1 months, PFS HR: 3.45 (1.11 to 10.72; p=0.024)	No
			paclitaxel 200 mg/m^2 + carboplatin AUC 6	8 (15.7%)	Median PFS: 5.1 months	
1263	Morabito et al. 2013 (CAPPA-2)	III	gemcitabine 1200 mg/m^2	9 (32%)	OS HR: 0.32 (0.10-0.98) PFS HR: 0.28 (0.09-0.86)	No
			gemcitabine 1000 mg/m^2 + cisplatin 60 mg/m^2	10 (36%)		

858, 859, 338	Pirker 2009,Pirker 2012, Gatzemeier 2011 (FLEX)	III	cisplatin 80 mg/m^2 + vinorelbine 25 mg/m^2	187 (33%)	OS HR: 0.80 (0.64–1.00)	No
			cisplatin 80 mg/m^2 + vinorelbine 25 mg/m^2 + cetuximab 250 mg/m^2 (starting dose 400 mg/m^2)	190 (34%)		
1027	Socinski, et al. 2012	III	nab-paclitaxel 100 mg/m^2 + carboplatin AUC 6	229 (44%)	Median OS: 10.7 months, OS HR: 0.89 (0.719-1.101) Median PFS: 5.6 months, PFS HR: 0.865	Yes
			paclitaxel 200 mg/m^2 + carboplatin AUC 6	221 (42%)	Median OS: 9.5 months Median PFS: 5.7 months	
1089	Tan, et al. 2009 (GLOB-3)	III	docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2	64 (33.5%)	Median OS: 9.82 months	No
			vinorelbine (IV 30 mg/m^2; oral 80mg) + cisplatin 80 mg/m^2	65 (34.2%)	Median OS: 8.87 months	
806	Thatcher, et al. 2014 (SQUIRE)		gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2	548 (100%)	Median OS: 9.9 months Median PFS: 5.5 months	N/A
			necitumumab 800 mg/m^2 + gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2	545 (100%)	Median OS: 11.5 months, OS HR: 0.84 (0.74-0.96, p=0.01) Median PFS: 5.7 months, PFS HR: 0.85 (0.74-0.98. p=0.02)	
1115	Treat, et al. 2010	III	gemcitabine 1000 mg/m^2 + carboplatin AUC 5.5	67 (17.7%)	Median PFS: 4.3 months Median OS: 6.6 months	No
			gemcitabine 1000 mg/m^2 + paclitaxel 200 mg/m^2	74 (19.6%)	Median PFS: 5.0 months Median OS: 10.2 months	
			paclitaxel 225 mg/m^2 + carboplatin AUC 6	61 (16.1%)	Median PFS: 5.7 months Median OS: 10.3 months	

1336	Yoshioka, et al. 2013 (LETS Study)	III	paclitaxel 200 mg/m^2 + carboplatin AUC 6	59 (20.9%)	Median OS: 10.6 months Median PFS: 4.37 months	Yes
			S-1 40 mg/day, days 1-14 + carboplatin AUC 5	55 (19.5%)	Median OS: 14.0 months, OS HR: 0.713 (0.476–1.068) Median PFS: 4.87, PFS HR: 0.938 (0.642–1.371)	

Study number=internally assigned publication-specific identification number used for data management purposes

Table 23 Regimens and data included in the network meta-analyses[a]

Regimen	OS analyses	PFS analyses
Erlotinib (150 mg/day)	No	HR and Median
Vinorelbine (60-80 mg/m^2)	No	Median
Gemcitabine (1200 mg/m^2)	HR	HR
Carboplatin (AUC 5-6) + Gemcitabine (1000-1200 mg/m^2)	HR and Median	HR and Median
Cisplatin (60-75 mg/m^2) + Gemcitabine (1000 mg/m^2)	HR and Median	HR and Median
Carboplatin (AUC 6) + Paclitaxel (200-225 mg/m^2)	HR and Median	HR and Median
Paclitaxel (200 mg/m^2) + Gemcitabine (1000mg/m^2)	HR and Median	HR and Median
Cisplatin (75, 80 mg/m^2) + Paclitaxel (135-175 mg/m^2)	HR and Median	Median
Cisplatin (75-100mg/m^2) + Docetaxel (75-100mg/m^2)	HR and Median	HR and Median
Cisplatin (80 mg/m^2) + Vinorelbine (25-60 mg/m^2, oral)	Median	No
Cisplatin (80 mg/m^2) + Vinorelbine (25mg/m^2) + Cetuximab (400 mg/m^2)	Median	No
Docetaxel (60mg/m^2) + Gemcitabine (1000mg/m^2) + Vinorelbine (35 mg/m^2)	HR	HR
Carboplatin (AUC 5) + S-1 (80 mg/m^2)	HR and Median	HR and Median
Carboplatin (AUC 6) + nab-Paclitaxel (100mg/m^2)	HR and Median	HR
Necitumumab (800 mg/2) + gemcitabine (1250 mg/m^2) + cisplatin (75 mg/m^2)	HR and Median	HR and Median

[a] this table reflects the network(s) to which the comparators are able to be connected, not necessarily all data reported in the publication

Results

As highlighted above, the only direct evidence related to necitumumab is based on the SQUIRE trial. All other evidence for outcomes in comparison with GC + N is based on indirect comparisons. Therefore, all other comparisons are based in the results of the indirect comparisons in the NMA.

No studies connected to GC + N for either a toxicity or QoL network due to lack of reported data, and were thus not evaluated. The regimens included in the OS and PFS analyses

using HR or median survival data are provided in Table 1. The results of the regimens considered relevant (which are Pcarbo, GCis, DCis, GCarbo, Pcis) to the health care settings in England are presented below. Importantly, for comparative analyses versus vinorelbine, this could only be compared in the median analyses.

Proportional Hazards (PH)

The PH assumption was tested in a limited number of studies that provided sufficient data to ensure there would be no violations in the conduct of the planned analyses. The results are presented in Table 24 below, showing no evidence of violation of this assumption, with a marginal result for Pcarbo versus GCarbo in the Treat et al., 2010 study. This analysis was limited to the three studies in the OS or PFS networks that provided a KM curve for digitization (Table 24), so conclusions cannot be drawn across all studies in the network. Studies reporting numeric data but no curve could not be evaluated due to limited data.

The results of indirect comparisons are presented below for survival outcomes, OS and PFS, first using the HR data and, secondly, using the median time to death data.

Table 24 Results of proportional hazards (PH) assumption assessment

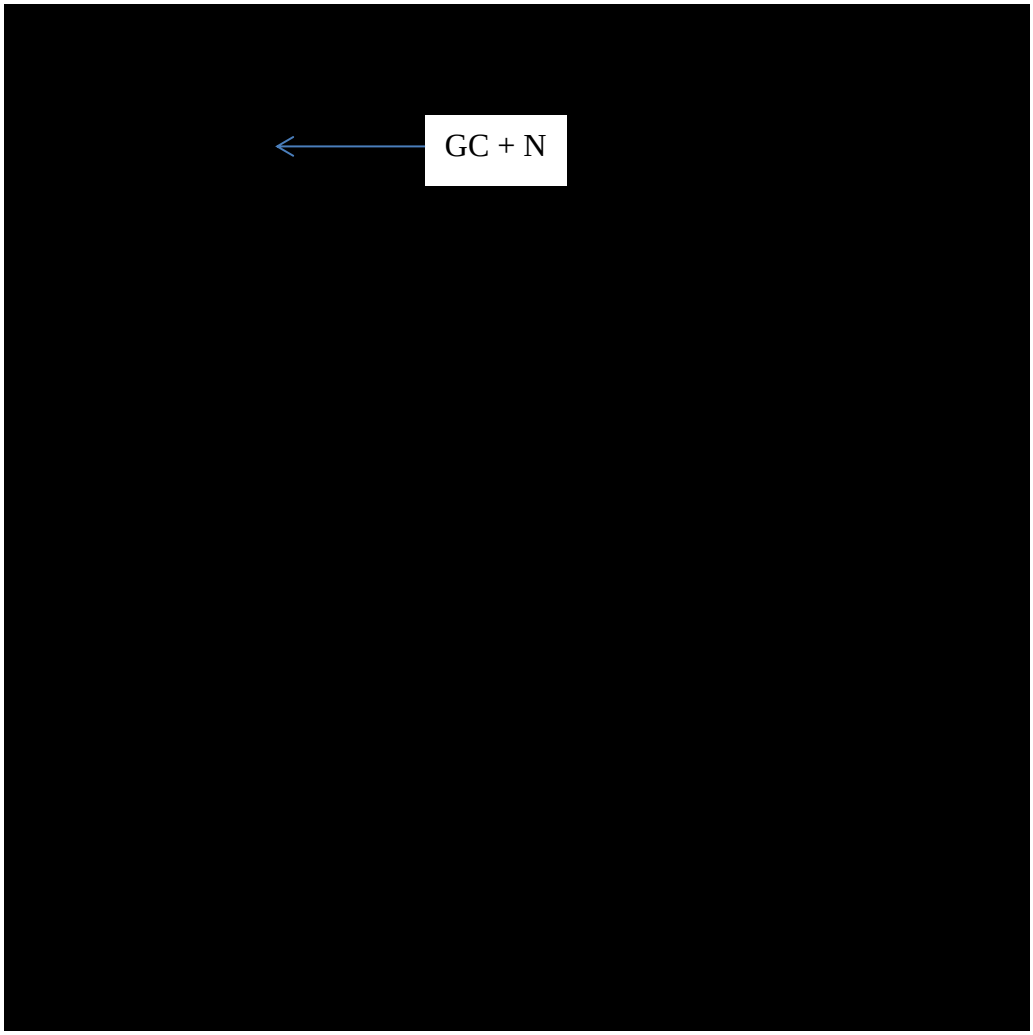
Study number	Included trial	Comparators	Reconstructed HR and 95% CI	P-value for PH
1115	Treat et al 2010	Carboplatin + paclitaxel vs. gemcitabine + paclitaxel	1.232 (0.857-1.775)	0.056
1115	Treat et al 2010	Carboplatin + paclitaxel vs. gemcitabine + paclitaxel	1.106 (0.762-1.603)	0.289
1027	Socinski et al 2012	Carboplatin + paclitaxel vs. carboplatin + nab-paclitaxel	0.908 (0.732-1.126)	0.949

Overall survival – analysis of HR data

Only six studies contributed to this analysis, thus, not all comparators relevant to the decision problem could be included in the analysis. GC + N was associated with a lower HR than all the comparators included in the analysis. The OS HR analysis demonstrated a very wide credible interval in one study as demonstrated by the width of the curve in Figure 27 (Morabito et al 2013, CAPPA-2, Study number 1263(43) comparing GC + N; this study was removed in sensitivity analyses in Appendix 6 to understand the impact of this study on the OS findings. The exclusion of the CAPPA-2 study (Study 1263, Morabito et al 2013) gave consistent results with smaller intervals.

The pairwise comparisons (HRs with 95% credible intervals) are presented in Table 25 and Table 26. Comparators not relevant to decision problem, which were included in the original analysis, are presented for completeness.

Figure 27 Posterior distribution of OS HRs of comparators versus GC + N



KEY: Gem (G)=gemcitabine; Neci (N)=necitumumab; Cis ©=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 25 Pairwise comparisons (median OS HR and credible intervals); Fixed relative treatment effect model with independent baseline treatment effect

Intervention	Pac+carbo	Nab-pac +carbo	Gem+cis	Gem	Pac+cis	Doc+cis	Gem+doc+vin	Gem + pac	Gem + Carbo
Pac+carbo									
Nab-pac+ carbo									
Gem+cis									
Gem									
Pac+cis									
Doc+cis									
Gem + doc + vin									
Gem + pac									
Gem+carbo									
Neci+gem+cis									

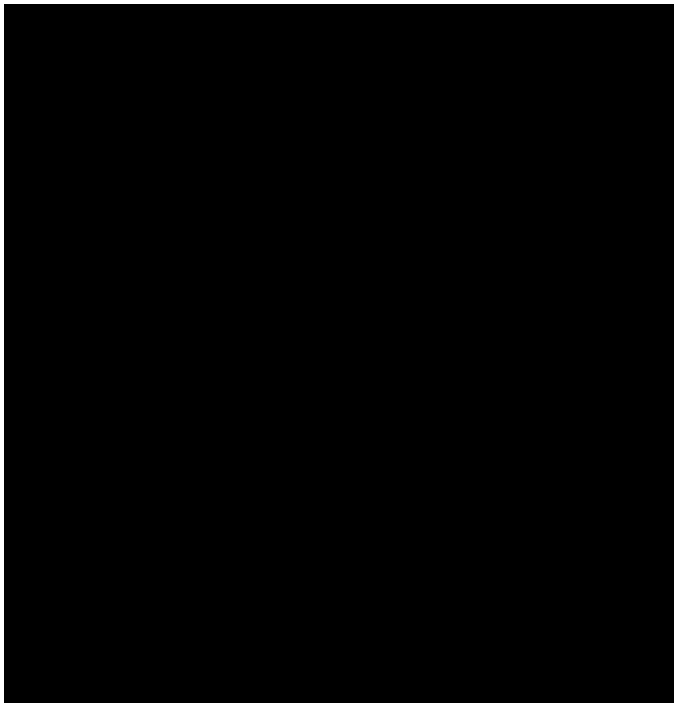
KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac = Nab-paclitaxel; Vin=Vinorelbine

Table 26 Pairwise comparisons (mean OS HR with estimated 95% credible intervals*); Fixed relative treatment effect model with independent baseline treatment effect

Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Gem	Pac+cis	Doc+cis	Gem+doc+vin	Gem+pac	Gem + Carbo
Pac+carbo									
Nab-pac + carbo									
Gem+cis									
Gem									
Pac+cis									
Doc+cis									
Gem + doc + vin									
Gem + pac									
Gem+carbo									
Neci+gem+cis									

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=nab-paclitaxel; Vin=vinorelbine
*95% credible intervals (CrI) are obtained from the median analyses. The use of these CrI data are reasonable given they are taken from the same distribution

Figure 28 Forest plot of OS HRs for the comparator treatments relative to GC + N (top: posterior median and credible intervals; bottom: posterior mean and credible intervals)



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 27 Rank relative to necitumumab plus gemcitabine and cisplatin; Fixed relative treatment effect model with independent baseline treatment effect, OS analysis using HR data

Intervention	Rank	OS Mean HR difference (95% CrI)	P(being best)
Neci+gem+cis	[redacted]	[redacted]	[redacted]
Nab-pac+carbo	[redacted]	[redacted]	[redacted]
Gem+doc+vin	[redacted]	[redacted]	[redacted]
Gem+cis	[redacted]	[redacted]	[redacted]
Pac+carbo	[redacted]	[redacted]	[redacted]
Gem+pac	[redacted]	[redacted]	[redacted]
Doc+cis	[redacted]	[redacted]	[redacted]
Gem+carbo	[redacted]	[redacted]	[redacted]
Pac+cis	[redacted]	[redacted]	[redacted]
Gem	[redacted]	[redacted]	[redacted]

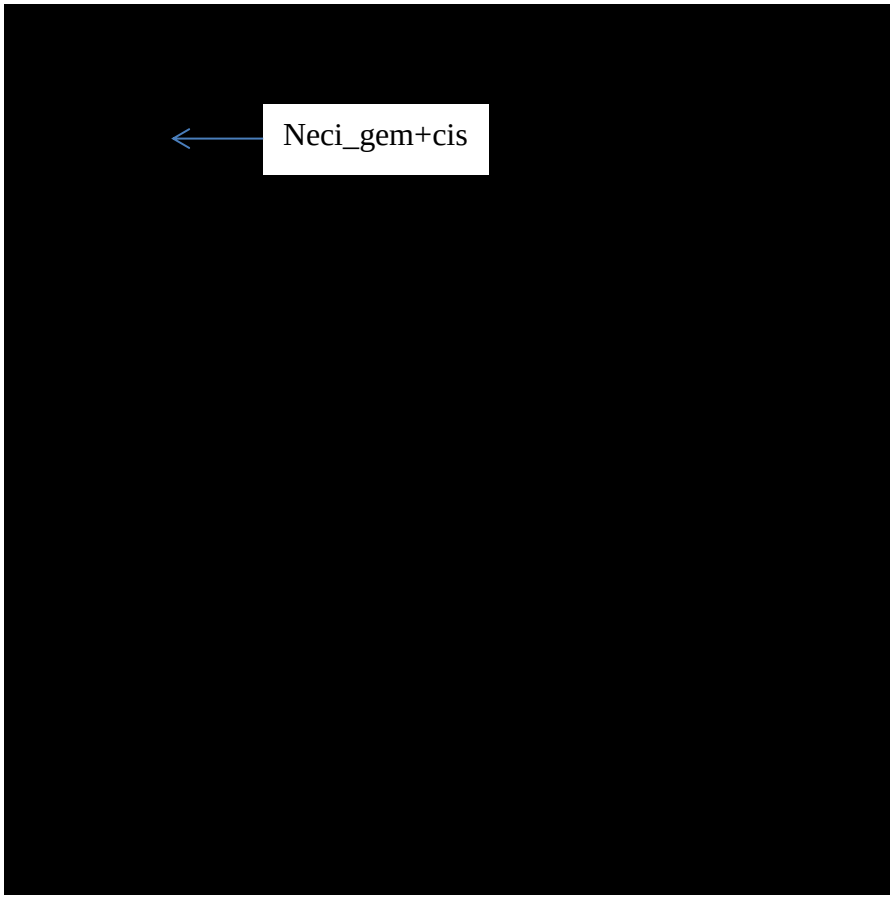
Effect is relative to Neci+gem+cis. A lower effect is considered better, and ranked a lower number.

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Progression-free survival – analysis of HR data

The network diagram for PFS using HR data is presented in Figure 25. Six studies provided evidence to this analysis, thus, not all comparators relevant to the decision problem could be included in the analysis. GC + N was associated with a lower HR than all comparators. The pairwise comparisons (HR with 95% credible intervals) are presented in Table 1 and Table 29.

Figure 29 Posterior distribution of PFS HRs of comparators versus necitumumab plus gemcitabine and cisplatin



KEY: Gem=gemcitabine; Cetux=cetuximab; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 28 Pairwise comparisons (median PFS HR with 95% credible intervals); fixed relative treatment effect model with independent baseline treatment effect

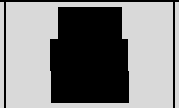
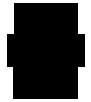
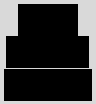
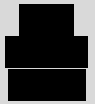
Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Gem	Pac+cis	Doc+cis	Gem + doc + vin	Gem + pac	Gem + Carbo	Erlot
Pac+carbo										
Nab-pac + carbo										
Gem+cis										
Gem										
Pac+cis										
Doc+cis										
Gem + doc + vin										
Gem + pac										
Gem+carbo										

Erlot	[redacted]									
Neci + gem + cis	[redacted]									

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=nab-paclitaxel; Vin=vinorelbine; Erlot=erlotinib

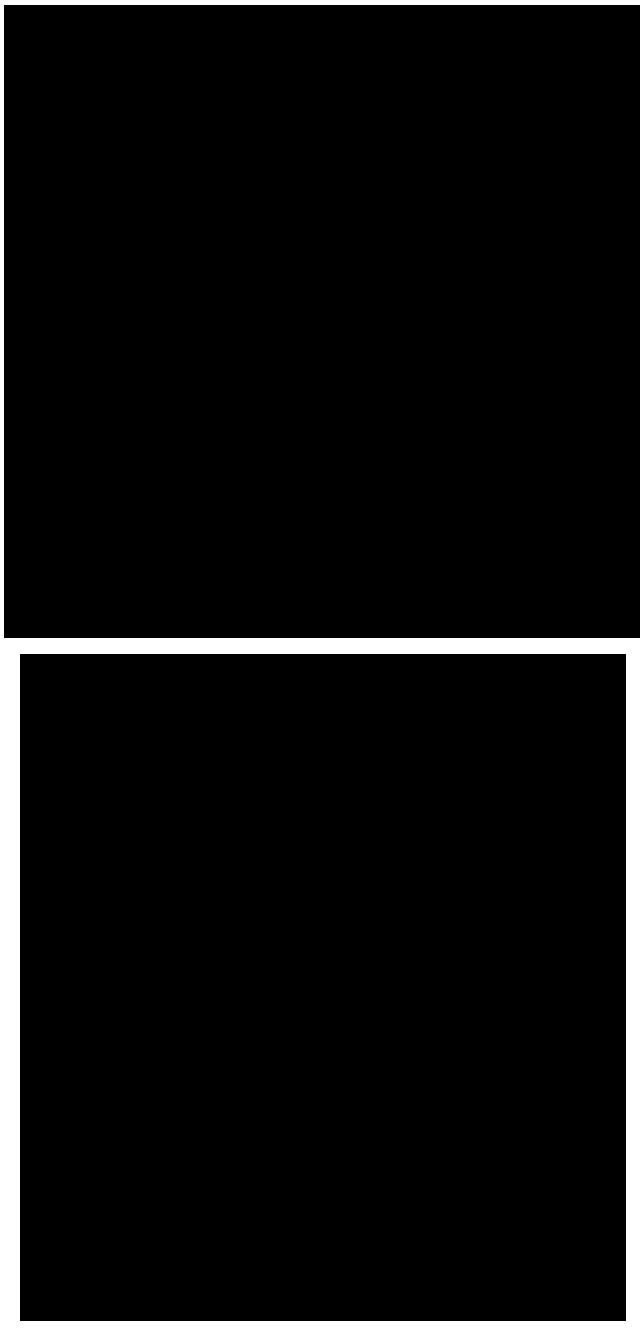
Table 29 Pairwise comparisons (mean PFS HR with 95% credible interval*); fixed relative treatment effect model with independent baseline treatment effect

Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Gem	Pac+cis	Doc+cis	Gem + doc + vin	Gem + pac	Gem + Carbo	Erlot
Pac+carbo	[redacted]									
Nab-pac + carbo	[redacted]									
Gem+cis	[redacted]									
Gem	[redacted]									
Pac+cis	[redacted]									
Doc+cis	[redacted]									
Gem + doc + vin	[redacted]									

Gem + pac										
Gem+carbo										
Erlot										
Neci + gem + cis										

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=nab-paclitaxel; Vin=vinorelbine; Erlot=erlotinib *95% credible intervals (CrI) are obtained from the median analyses. The use of these CrI data are reasonable given they are taken from the same distribution

Figure 30 Forest plot of PFS HRs for the comparator treatments relative to necitumumab plus gemcitabine and cisplatin (top: posterior median and credible intervals; bottom: posterior mean and credible intervals)



KEY: Gem=gemcitabine; Cetux=cetuximab; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 30 Rank relative to necitumumab plus gemcitabine and cisplatin; Fixed relative treatment effect model with independent baseline treatment effect, PFS analysis using HR data

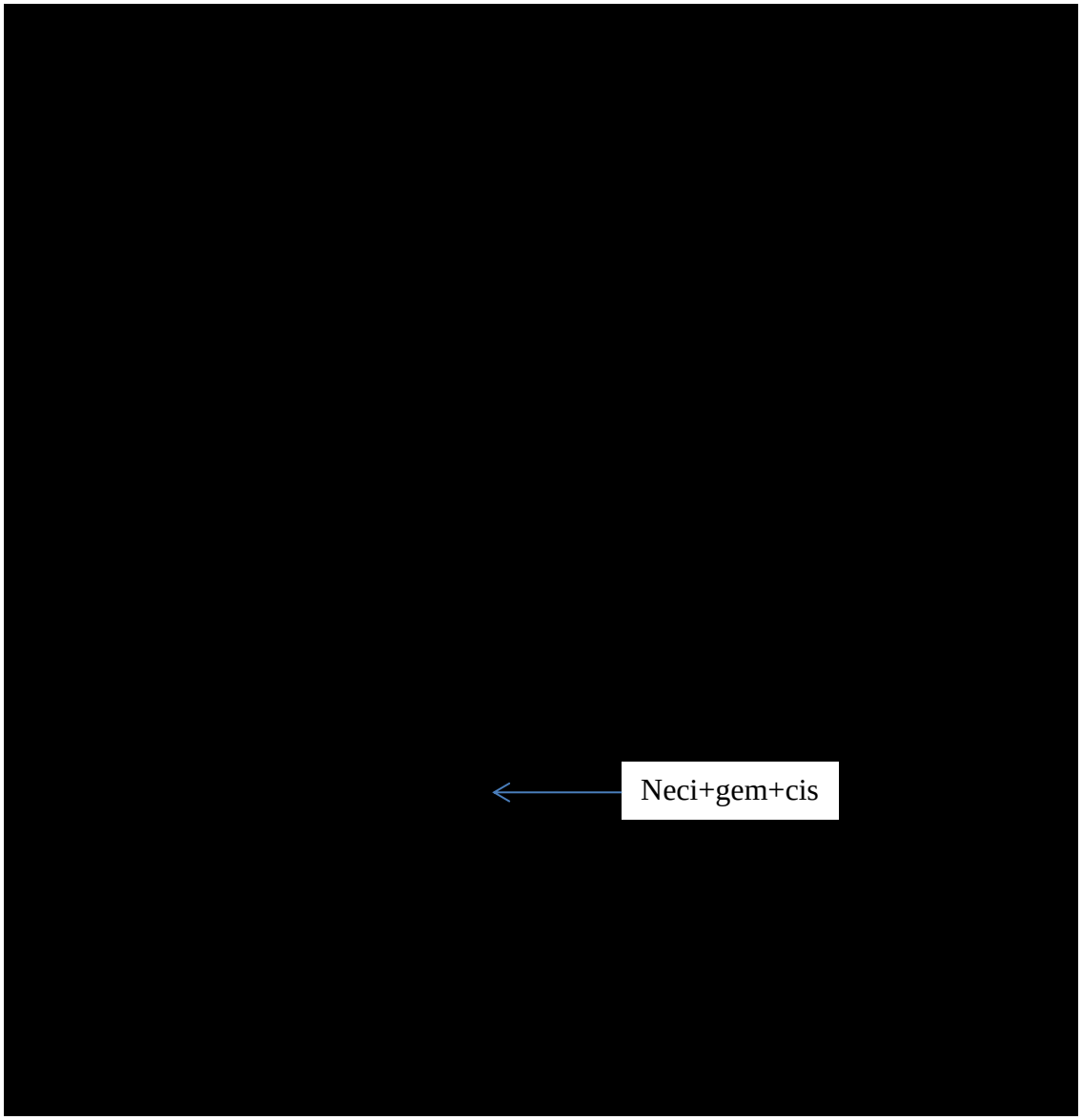
Intervention	Rank	Mean PFS HR difference (95% CrI)	P(being best)
Neci+gem+cis			
Nab-pac+carbo			
Gem+cis			
Pac+carbo			
Gem+doc+vin			
Doc+cis			
Gem+pac			
Pac+cis			
Gem+carbo			
Gem			
Erlot			

KEY: CrI: credible interval; Gem=gemcitabine; Cetux=cetuximab; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Overall survival – secondary analysis of median data

A number of studies did not report HRs and did not report KM curves. As a result, median data were used for survival estimates to expand the network (Figure 24). Six studies provided evidence for this analysis. Vinorelbine in combination with cisplatin (VCis) and paclitaxel plus carboplatin (PCarbo) were included. GC + N (single study) could not be used as the primary comparator as the model failed to converge with a single study reference comparator. Hence the comparator with the largest number of contributing trials (PCarbo) was used for the median analyses. However, data are provided versus the necitumumab regimen whenever possible. GC + N was associated with a longer time until death than all comparators in the unadjusted OS median analysis. The pairwise comparisons presented as posterior mean differences with 95% credible intervals are presented in Table 31 and Table 32.

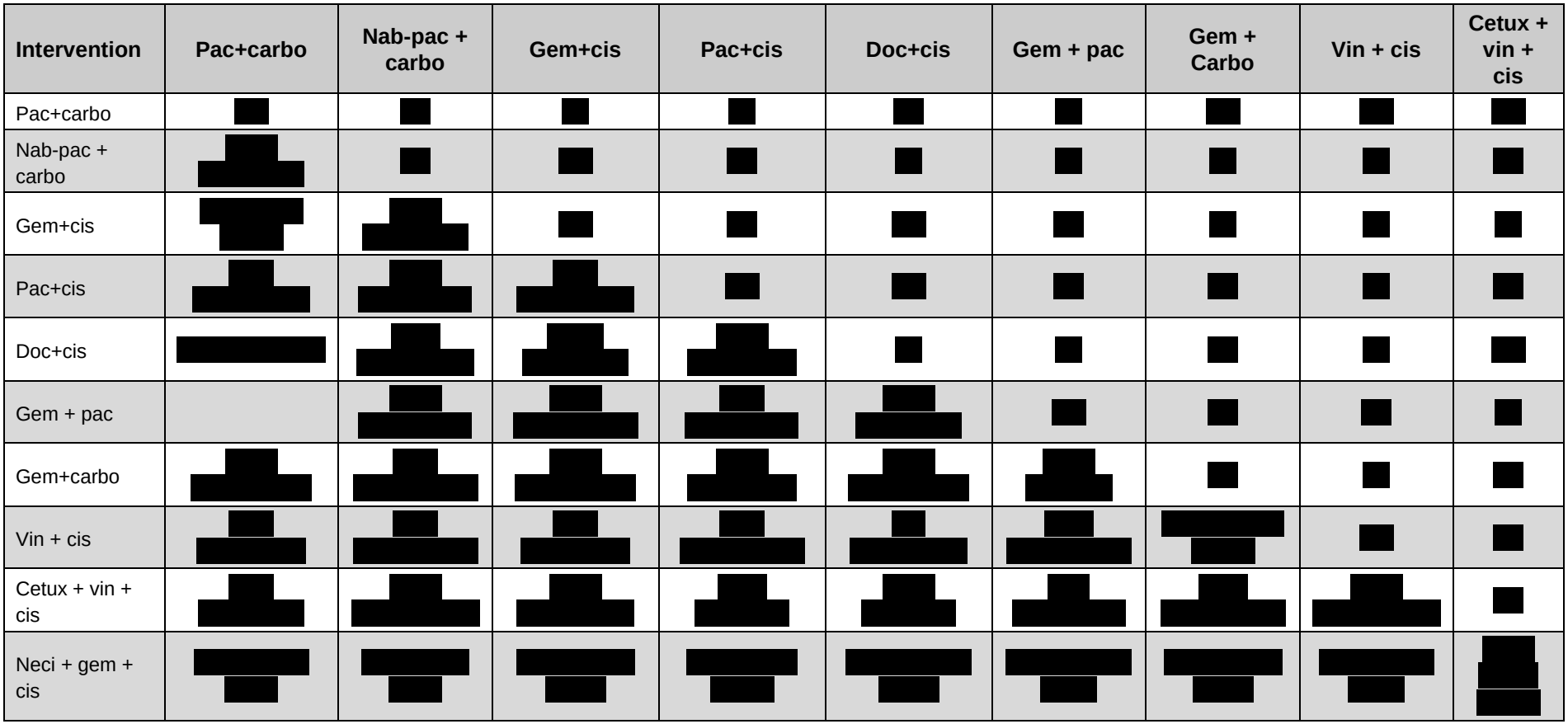
Figure 31 Posterior distribution of median OS of comparators and necitumumab plus gemcitabine and cisplatin



KEY: Gem=gemcitabine; Cetux=cetuximab; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 31 Relative treatment effect of median OS pairwise comparisons expressed as posterior median median time ratio (with 95% credible intervals)

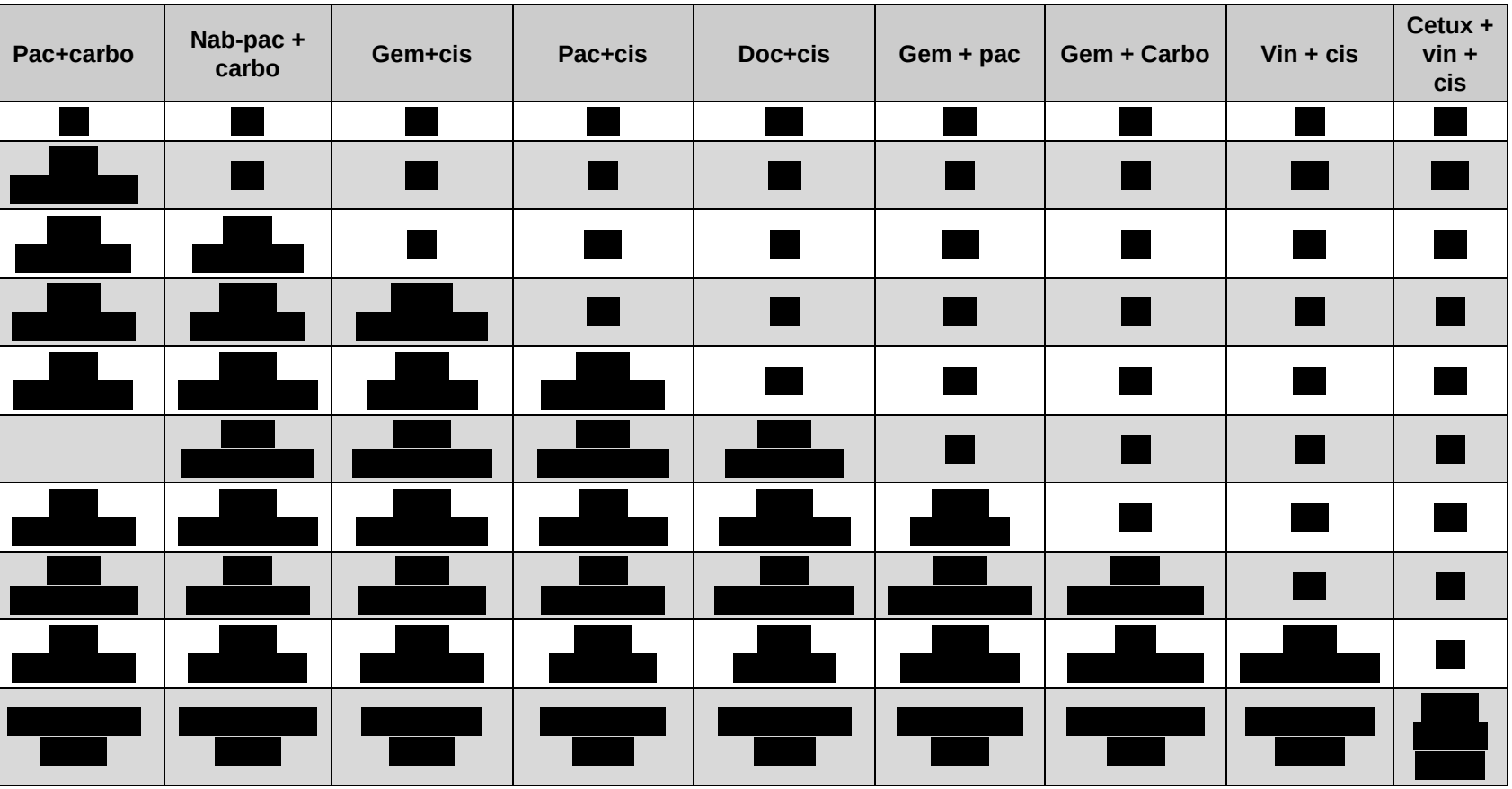
Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Pac+cis	Doc+cis	Gem + pac	Gem + Carbo	Vin + cis	Cetux + vin + cis
Pac+carbo									
Nab-pac + carbo									
Gem+cis									
Pac+cis									
Doc+cis									
Gem + pac									
Gem+carbo									
Vin + cis									
Cetux + vin + cis									
Neci + gem + cis									



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Vin=Vinorelbine; Nab-pac=nab-paclitaxel; Cetux=cetuximab

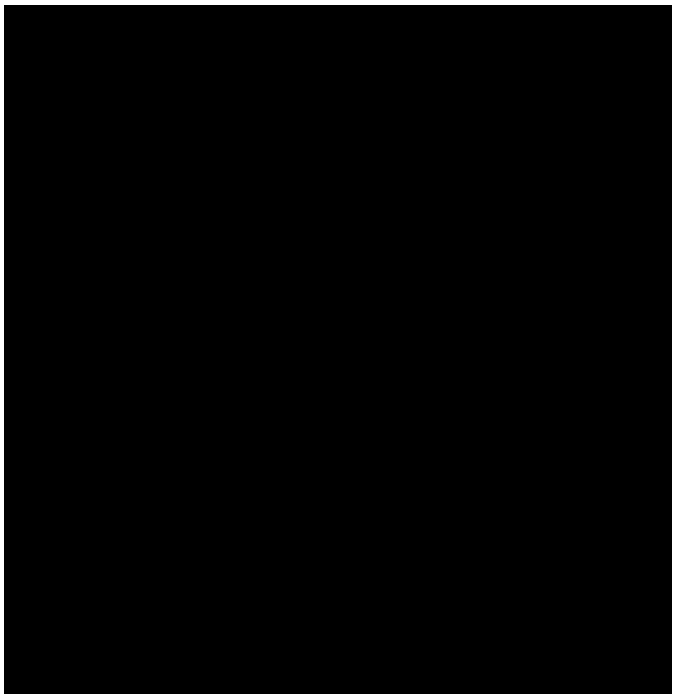
Table 32 Relative treatment effect of median OS pairwise comparisons expressed as posterior mean median time ratio (with 95% credible intervals)

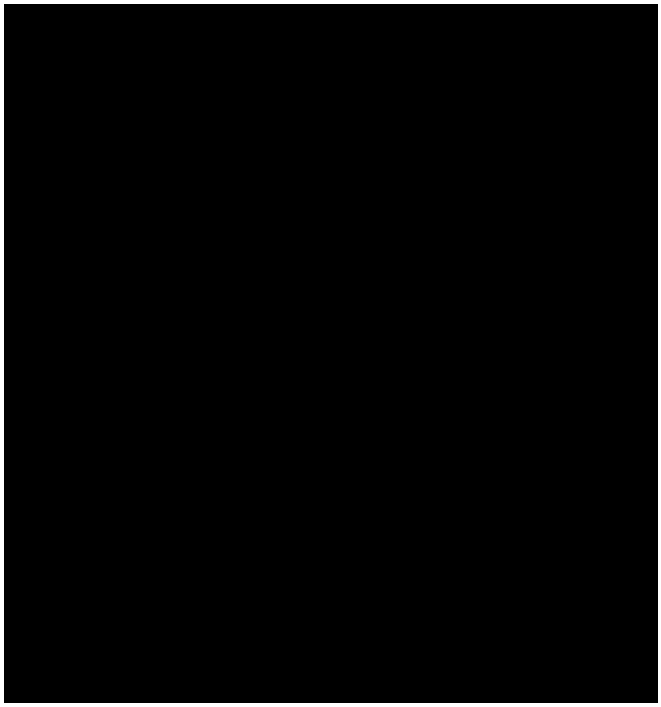
Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Pac+cis	Doc+cis	Gem + pac	Gem + Carbo	Vin + cis	Cetux + vin + cis
Pac+carbo									
Nab-pac + carbo									
Gem+cis									
Pac+cis									
Doc+cis									
Gem + pac									
Gem+carbo									
Vin + cis									
Cetux + vin + cis									
Neci + gem + cis									



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Vin=Vinorelbine; Nab-pac=nab-paclitaxel; Cetux=cetuximab

Figure 32 Forest plot of ratio of median OS (median time to death) for comparator treatments relative to necitumumab plus gemcitabine and cisplatin (top: posterior median and credible intervals; bottom: posterior mean and credible intervals)





KEY: Gem=gemcitabine; Cetux=cetuximab; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 33 Rank relative to carboplatin plus paclitaxel; Fixed relative treatment effect model with independent baseline treatment effect, OS analysis using median data

Intervention	Rank	Median OS (months)(95% CrI)	P(being best)
Neci+gem+cis	[redacted]	[redacted]	[redacted]
Nab-pac+carbo	[redacted]	[redacted]	[redacted]
Pac+carbo	[redacted]	[redacted]	[redacted]
Gem+pac	[redacted]	[redacted]	[redacted]
Gem+cis	[redacted]	[redacted]	[redacted]
Cetux+vin+cis	[redacted]	[redacted]	[redacted]
Doc+cis	[redacted]	[redacted]	[redacted]
Vin+cis	[redacted]	[redacted]	[redacted]
Pac+cis	[redacted]	[redacted]	[redacted]
Gem+carbo	[redacted]	[redacted]	[redacted]

Effect is relative to Pac+carbo. A lower effect is considered better, and ranked a lower number

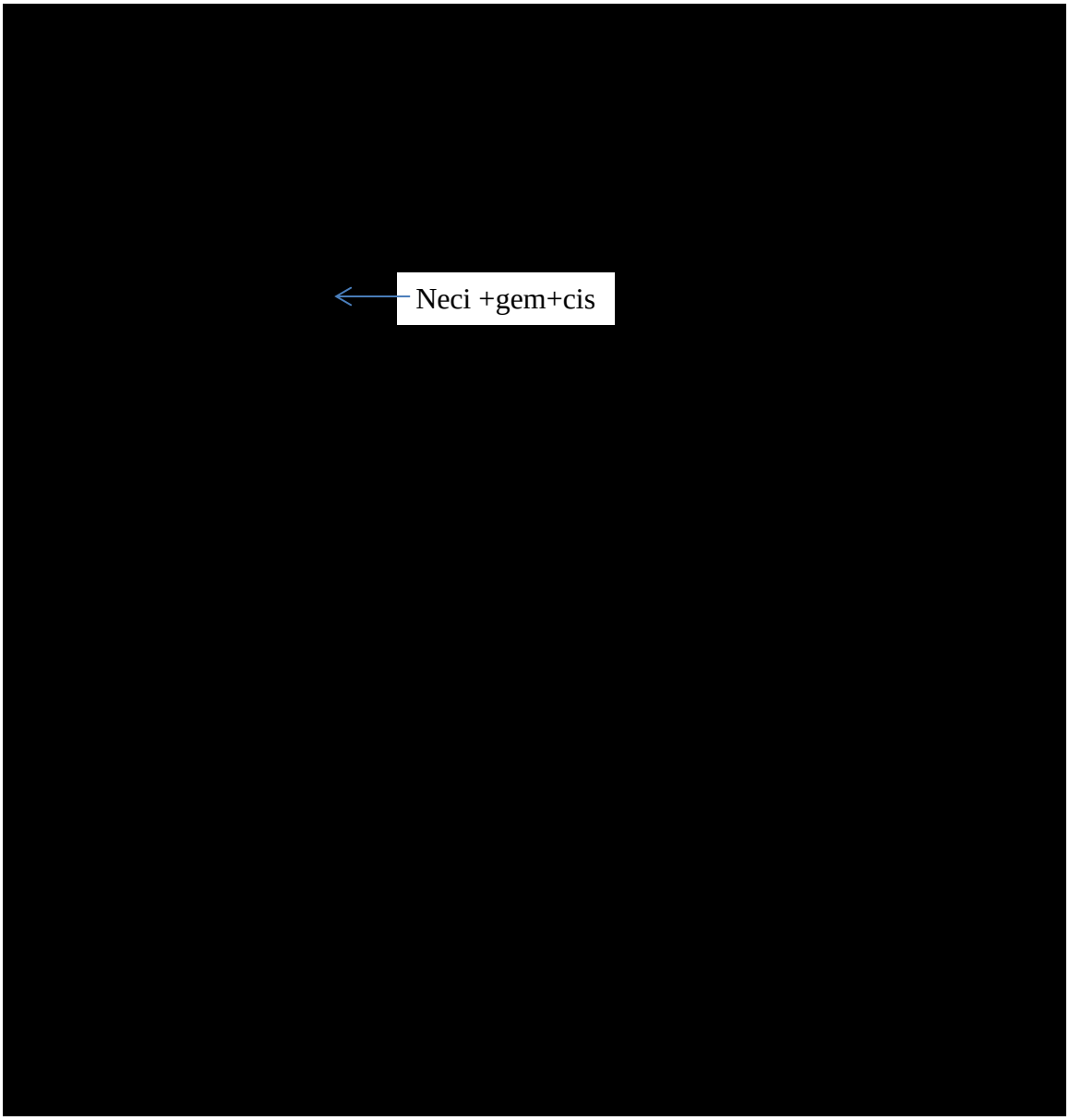
KEY: Gem=gemcitabine; Cetux=cetuximab; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Progression-free survival – secondary analysis of median data

A number of studies did not report HRs and did not report KM curves. Only six studies were included in the analysis. Due to lack of comparative studies, VCis could not be included in the analysis. Also GC + N (single study) could not be used as the primary comparator as the model failed to converge with a single study reference comparator. Hence the comparator with the largest number of contributing trials (PCarbo) was used.

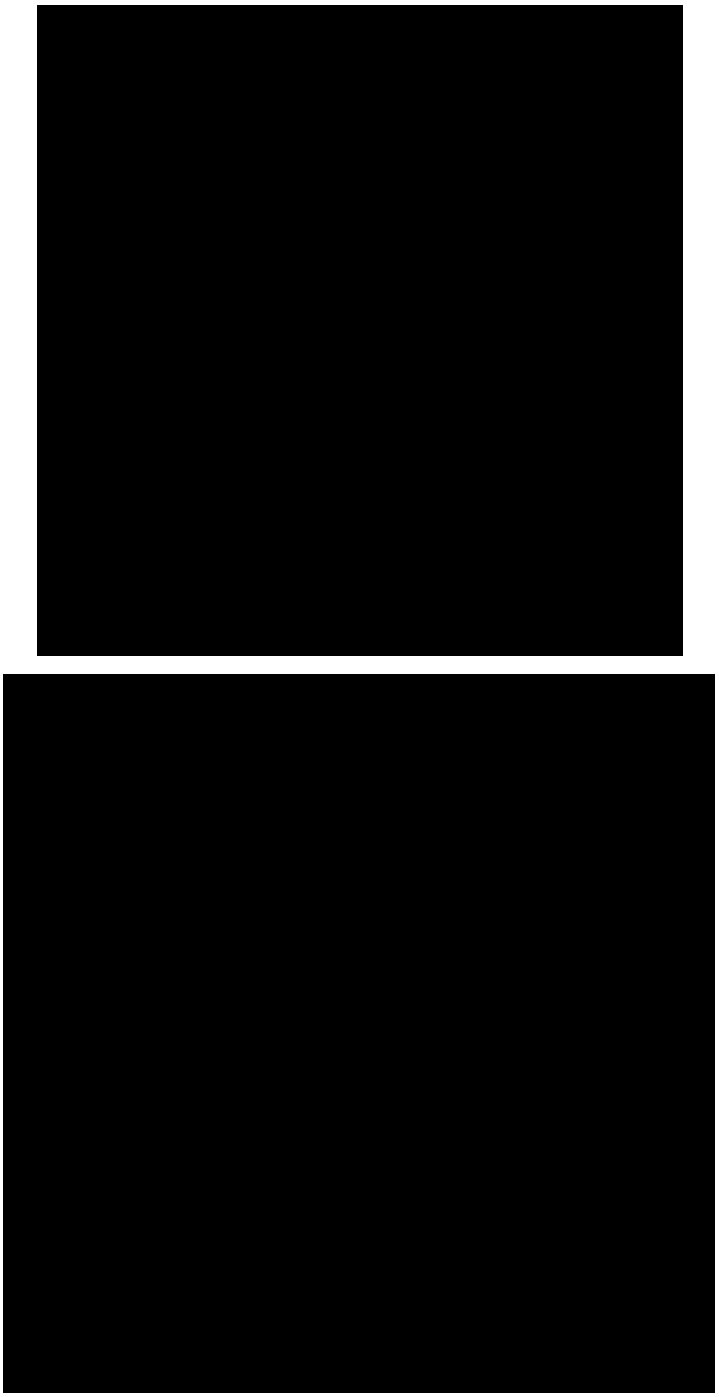
The network diagram for PFS using median data is presented in Figure 26. GC + N was associated with a longer time to progression than all comparators in the unadjusted PFS analysis. The pairwise comparisons presented as posterior mean differences with 95% credible intervals are presented in Figure 33.

Figure 33 Posterior distribution of median PFS of comparators and necitumumab plus gemcitabine and cisplatin



KEY: Gem=gemcitabine; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Figure 34 Forest plot of ratio of median PFS for the comparator treatments relative to necitumumab in combination with gemcitabine and cisplatin (top: posterior median and credible intervals; bottom: posterior mean and credible intervals)



KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Table 34 Relative treatment effect of pairwise comparisons expressed as posterior median median PFS ratio (with 95% credible intervals)

Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Pac+cis	Doc+cis	Gem + pac	Gem + Carbo	Vin	Erlot
Pac+carbo									
Nab-pac + carbo									
Gem+cis									
Pac+cis									
Doc+cis									
Gem + pac									
Gem+carbo									
Vin									
Erlot									
Neci + gem + cis									

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Vin=Vinorelbine; Nab-pac=nab-paclitaxel; Erlot=erlotinib

Table 35 Relative treatment effect of pairwise comparisons expressed as posterior mean median PFS ratio (with 95% credible intervals)

Intervention	Pac+carbo	Nab-pac + carbo	Gem+cis	Pac+cis	Doc+cis	Gem + pac	Gem + Carbo	Vin	Erlot
Pac+carbo									
Nab-pac + carbo									
Gem+cis									
Pac+cis									
Doc+cis									
Gem + pac									
Gem+carbo									
Vin									
Erlot									
Neci + gem + cis									

KEY: Gem=gemcitabine; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Pac=paclitaxel; Carbo=carboplatin; Vin=Vinorelbine; Nab-pac=nab-paclitaxel; Erlot=erlotinib

Table 36 Rank relative to paclitaxel plus carboplatin; Fixed relative treatment effect model with independent baseline treatment effect, PFS analysis using median data

Intervention	Rank	Median PFS (months) (95% CrI)	P(being best)
Neci+gem+cis	[redacted]	[redacted]	[redacted]
Gem+cis	[redacted]	[redacted]	[redacted]
Pac+carbo	[redacted]	[redacted]	[redacted]
Nab-pac+carbo	[redacted]	[redacted]	[redacted]
Gem+pac	[redacted]	[redacted]	[redacted]
Doc+cis	[redacted]	[redacted]	[redacted]
Gem+carbo	[redacted]	[redacted]	[redacted]
Pac+cis	[redacted]	[redacted]	[redacted]
Erlot	[redacted]	[redacted]	[redacted]
Vin	[redacted]	[redacted]	[redacted]

Median time is derived from adding the relative treatment effect to the posterior distribution of response in the baseline treatment of Pac+carbo. A higher median time is considered better, and ranked a lower number.

KEY: Gem=gemcitabine; Erlot=erlotinib; Neci=necitumumab; Cis=cisplatin; Doc=docetaxel; Erlot=Erlotinib; Pac=paclitaxel; Carbo=carboplatin; Nab-pac=Nab-paclitaxel; Vin=Vinorelbine

Sensitivity analyses

Only two of the pre-planned sensitivity analyses could be conducted due to the fragmentation of the network that occurred once studies were removed. The median analyses demonstrated consistent results. All other sensitivity analyses (limiting by age and geographic site, limiting to stage IV disease, direct comparisons only, excluding phase 2 trials, and limiting by study quality and bias) could not be conducted due to fragmentation of the network. The majority of comparators were populated with only one study, and the removal of studies restricted the comparators that could be analysed.

However, there was one study that contributed heterogeneity to the OS analysis that was not central to the network connections. Study 1263 (Morabito et al, CAPPA-2 study; N=19, gemcitabine vs GCis) was removed from the OS HR analysis in a post hoc sensitivity analysis, as this study was identified as contributing to the wide credible intervals seen in both survival analyses, The removal of this trial does not affect the results versus the necitumumab region, as the CAPPA-2 study was not located centrally in the network. Similarly, two studies contributed heterogeneity to the PFS analysis that were also not central to the network connections. Study 1263 (Morabito et al, CAPPA-2 study; N=19, gemcitabine vs GCis) and Study 655 (Lilenbaum et al, 2008; N=19 erlotinib vs PCarbo) were

identified as contributing to the wide credible intervals seen in the PFS analyses. Similar to the analyses for OS, the removal of these studies do not affect the comparisons with the necitumumab regimen as these studies are not central to the network.

Heterogeneity and consistency assessment

Heterogeneity was identified by the wide credible intervals for Morabito et al., 2013 (33) in the OS HR analysis and from Morabito et al., 2013 (33) and Lilenbaum et al., 2008 (36) in the PFS HR analysis; these studies were removed in sensitivity analyses. The removal of these studies did not alter the results with regard to GCis + N, as they were not central to the study network. The consistency assumption could not be explored due to the lack of closed loops that included GCis + N.

Heterogeneity parameters (variance and standard deviation) and model fit (residual deviance and DIC a Bayesian criterion for model comparison) are presented in detail in Appendix 7.

Conclusions and Limitations

The results of this analysis suggest that GCis + N may be the best option in terms of OS and PFS versus comparators included in the analysis. However, this is based on a small number of studies and no direct clinical trials or real-world observational trials have conducted to compare these regimens with GCis + N. This conclusion is solely based on the high probability of being best or occupying a high ranking and due to the point estimates for the relative effects against all comparators and must be interpreted with this limitation.

This meta-analysis was limited to randomised trials reporting squamous-specific survival data that were connected by an evidence network to the necitumumab regimen. Many studies were limited to the squamous subset of data and as such there may be less statistical rigour when limited to a relatively small subpopulation of the larger study. Further, not all trials stratified based on histology. While many trials reported similar number of patients with squamous tumours by treatment arm, there is no guarantee that these cases were equally balanced in the randomisation process. The data related to cetuximab may have little relevance post-2015. At the time of the analysis, cetuximab was included in National Comprehensive Cancer Network (NCCN) treatment guidelines in the U.S.; however, in 2015 the use of cetuximab was removed from guidelines because of toxicity and limited efficacy (44). Therefore, this comparator may have little value to decision makers at this present time, and particularly outside of the US. Although the two studies contributing

data on erlotinib met the inclusion/exclusion criteria for the NMA, the results relating to erlotinib should be viewed with caution. Both of the studies were phase II studies with small sample sizes (n≤30) (45,46). In addition, in practice, a very small number of squamous NSCLC patients are EGFR mutation positive and thus eligible for EGFR TKI treatment. Lastly, there may be other regimens of interest that were not able to be compared in this analysis due to the limited number of studies.

Survival data were analysed using HR data. The calculation of a pooled HR is usually based on the PH assumption. This assumption implies that two treatment groups are considered in the model, even though the individual treatment hazards may vary over time, the hazard of the event for one group at any time point is proportional to the hazard in the other group. Not all studies reported data on HRs, and some were estimated from digitization and analysis of the survival curves. Thus an additional pre-planned analysis was performed including all studies that reported median data. The median analysis allowed an indirect comparison with additional comparators, such as VCis, which was not possible with HR data alone and demonstrated consistent findings for both OS and PFS. However, not all studies reported median data, so not all comparators could be repeated for both analyses.

As already mentioned, there were a number of limitations due to the small number of studies that could be included in the meta-analysis. Additionally, most of the studies included patients with non-squamous histology, and only data from the subset of squamous patients were used (in most cases, this was less than 30% of the overall study population). This led to wide credible intervals and difficulty in clearly distinguishing one comparator from another in terms of either HR or median survival estimates. The wide credible intervals reflect the uncertainty in the data and results should be interpreted with caution. Additionally, for many comparators, only one study contributed to the evidence. The evidence networks were analysed via a single pair-wise meta-analysis and a series of indirect comparisons. It is important to be aware that indirect comparison estimates will increase in uncertainty with each additional link in the evidence network, and there are up to four links for some of the comparisons versus GCis + N. Pre-planned analyses of toxicity and QoL data were not possible due to limited data. Additionally, most of the sensitivity analyses that were planned were also not possible due to fragmentation of the network (e.g. data for most comparators were based on only one trial).

Despite these limitations, the findings suggest the comparative value of necitumumab plus gemcitabine and cisplatin in the squamous NSCLC population against other available

treatment regimens and may be considered an effective treatment option for the care of newly diagnosed patients with squamous NSCLC.

4.11 Non-randomised and non-controlled evidence

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

4.12 Adverse reactions (AEs)

Treatment exposure

Out of 1093 randomised patients, 1079 received at least one dose of study therapy, which included 538 patients in the GCis + N arm and 541 patients in the GCis arm and these patients constitute safety population of the trial(9). Due to the study design, patients in the GCis arm were permitted to undergo study treatment for a maximum of 6 cycles (chemotherapy phase), while patients in the GCis + N arm could receive a maximum of 6 cycles of chemotherapy in combination with necitumumab and continue to receive single-agent necitumumab until disease progresses (maintenance or continuation phase). As a result, the treatment period and safety observation period were longer in the GCis + N arm, which may lead to an increased number of AEs in the GCis + N arm. In order to better represent the difference in observation periods, safety data is presented as overall and for chemotherapy and maintenance phase only (cycles 1 to maximum of 6) to allow for appropriate comparisons between arms.

In the GCis + N arm, the median number of cycles was 6.0 and the median number of infusions was 12.0 (Table 37). Almost 60% of patients completed six cycles of necitumumab. 275 patients (51%) in the GCis + N Arm went on to receive a median of 4 (2 to 8) maintenance cycles of necitumumab (for a median duration 12.10 weeks (6.0 to 23.9)) after the end of chemotherapy. The median number of cycles of gemcitabine and cisplatin was similar in the two treatment groups (6 vs. 5). Slightly more patients in the GCis + N arm completed 6 cycles of the two drugs than in the GCis arm (gemcitabine 55% vs. 48%; cisplatin 53% vs. 46%).

Table 37 Treatment exposure

	GCis + N arm	GCis arm
Necitumumab (overall)		
Number of patients	538	-
Median duration of therapy (weeks), median (IQR)	20 (11 to 31.9)	-
Median number of cycles (IQR)	6 (3 to 10)	-
Patients completing 6 cycles, n (%)	316 (59%)	-
Necitumumab (maintenance phase only)		
Number of patients	275	-
Median duration of therapy (weeks), median (IQR)	12.1 (6 to 23.9)	-
Median number of cycles (IQR)	4 (2 to 8)	-
Gemcitabine		
Number of patients	538	541
Median duration of therapy (weeks), median (IQR)	17.9 (10.7 to 19.0)	17 (9 to 18.6)
Median number of cycles (IQR)	6 (3 to 6)	5 (3 to 6)
Patients completing 6 cycles, n (%)	294 (55%)	259 (48%)
Cisplatin		
Number of patients	538	541
Median duration of therapy (weeks), median (IQR)	18 (11 to 19)	16.9 (9.1 to 18.9)
Median number of cycles (IQR)	6 (3 to 6)	5 (3 to 6)
Patients completing 6 cycles, n (%)	286 (53%)	249 (46%)

Treatment-Related Events

Treatment-emergent adverse events (TEAEs) were defined as events that met either of the following criteria:

> Onset date occurred any time during or after the administration of the first dose of study treatment or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment); or
>
> The event occurred prior to the date of first dose and worsened while on therapy or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment).

Majority of the patients (99% in the GCis + N arm and 98% in the GCis arm) experienced AEs in the study. A total of 388 patients in the GCis + N Arm (72%) and 333 patients in the

GCis Arm (62%) experienced at least 1 TEAE of Grade ≥ 3 that was considered at least possibly related to one or more study drug(s). The most common grade ≥3 AEs in both treatment arms were neutropenia (23% in GCis + N arm vs. 27% in GCis arm), anaemia (11% in both) and thrombocytopenia (10% in both). Related Grade ≥3 TEAEs occurring at a higher rate in the GCis + N Arm vs. the GCis Arm were hypomagnesaemia (47/538 (9%)vs. 6/541 (1%), rash (20/538 (4%) vs. 1/541 (<1%)), pulmonary embolism (19/538 (3.5%) vs. 10/541 (2%)), and vomiting (15/541(2.8%) vs. 5/541 (<1%)). The only related Grade 4 event that was significantly more common in the GCis + N Arm than in the GCis Arm was hypomagnesaemia (13/538 (2.4% vs. 0). The addition of necitumumab was not associated with a relevant increase of typical chemotherapy-induced toxicities, in particular with respect to hematologic toxicities, including Grade 3 and 4 events.

Table 38 Treatment-emergent adverse events of grade 3 to 5, occurring in one or more patients in either treatment group, by preferred Term

Preferred Term	GCis+N N = 538 n (%)			GCis N = 541 n (%)		
	Gr.3	Gr.4	Gr.5	Gr.3	Gr.4	Gr.5
Patients with any AE	248 (46)	74 (14)	66 (12)	201 (37)	75 (14)	57 (11)
Neutropenia	94 (17)	34 (6)	0	103 (19)	43 (8)	0
Thrombocytopenia	36 (7)	17 (3)	0	33 (6)	21 (4)	0
Anaemia	54 (10)	2 (<1)	0	56 (10)	3 (<1)	0
Hypomagnesaemia	34 (6)	13 (2)	0	6 (1)	0	0
Leukopenia	20 (4)	2 (<1)	0	31 (6)	5 (<1)	0
Rash	20 (4)	0	0	1(<1)	0	0
Asthenia	22 (4)	1 (<1)	0	19 (4)	1 (<1)	0
Pulmonary Embolism	12 (2)	6 (1)	1 (<1)	2 (<1)	8 (1)	0
Nausea	15 (3)	0	0	14 (3)	0	0
Vomiting	14 (3)	1 (<1)	0	5 (<1)	0	0
Fatigue	17 (3)	0	0	17 (3)	1 (<1)	0

Abbreviations: AE = adverse event; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; N = number of treated patients; n = number of patients in category

The proportion of patients whose treatment got delayed or one of the study drugs had to be modified due to AEs was similar in the two groups (60% in GCis + N vs. 58% in GCis). The most common AEs causing delay or modification of treatment were blood and lymphatic system disorders (neutropenia, thrombocytopenia, anaemia and leukopenia, which accounted for 40% in the GCis + N arm and 42% in the GCis arm. Slightly more patients in the GCis + N arm than in the GCis arm (31% vs. 25%) discontinued at least one of the drugs

due to AEs. The most common AEs causing discontinuation were neutropenia and thrombocytopenia.

Treatment related adverse events in different treatment phase

When comparing the chemotherapy phases, the number of patients with a TEAE was similar between treatment arms but the incidences of serious and severe (Grade ≥3) events were higher among patients in the GCis + N Arm. Of note, the difference between arms in terms of fatal events was largely attributable to fatal cases of disease progression; when such events were excluded, the absolute difference was reduced to ~1%. This small difference persisted when considering only those events (excluding fatal cases of disease progression) considered related to any study therapy (GCis + N Arm: 14 [2.6%] vs. GCis Arm 10 [1.8%]). Notably, events with an outcome of death (including fatal cases of disease progression) occurred in more patients in the GCis Arm than in the chemotherapy phase of the GCis + N Arm.

Table 39 Overview of Treatment-Emergent Adverse Events in SQUIRE (safety population)

Adverse Event	Gem-Cis+Neci Ctx Phase N = 538 %	Gem-Cis N = 541 %	Gem-Cis+Neci Mai Phase N = 275 %
Patients with ≥1 TEAE	99.1	97.8	77.5
Patients with ≥1 TEAE Grade ≥3	67.7	61.6	28.7
Patients with ≥1 treatment-emergent SAE	42.6	37.5	17.1
Patients with any TEAE with outcome death[a]	9.3	10.5	5.8
Patients with any TEAE with outcome death (excluding fatal cases of disease progression)	5.9	6.8	3.6

Abbreviations: Mai = maintenance; Ctx = chemotherapy; Gem-Cis = gemcitabine and cisplatin; Gem-Cis+Neci = gemcitabine and cisplatin plus necitumumab; N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Includes fatal cases of disease progression.

Adverse Events of Special Interest (AESI) / Consolidated Adverse Events

In order to assess potentially significant safety issues in SQUIRE, selected composite event categories were considered and analysed as AESI. Adverse events of special interest categories included events related to hematologic toxicity, skin and eye toxicity, fatigue, hypersensitivity reactions, hypomagnesaemia, interstitial lung disease, and

thromboembolism; these events were identified based on safety data known for other monoclonal anti-EGFR antibodies and/or clinical experience with necitumumab, as described in the sections below.

Thromboembolic Events

Thromboembolic events were identified as AESIs based on the safety signal identified in the INSPIRE trial (I4X-IE-JFCB; IMCL CP11-0805, necitumumab plus pemetrexed and cisplatin vs. pemetrexed and cisplatin alone in the first-line treatment of Stage IV nonsquamous NSCLC) and data suggesting that such events may be a class effect (47). Table 40 shows the frequencies of venous and arterial thromboembolic events observed in SQUIRE, including all preferred terms reported for two or more patients in the GCis + N Arm.

Table 40 Adverse Events of Special Interest – Thromboembolic Events

AESI[a]	GCis+N N = 538 n (%)				GCis N = 541 n (%)			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Venous Thromboembolic Events (VTEs)	49 (9.1)	19 (4) (5.0)	7 (1)	1 (<1)	29 (5.4)	5 (<1)	8 (1)	1 (<1)
Arterial Thromboembolic Events (ATEs)	29 (5.4)	21 (3.9)	23 (4.3)	16 (3.0)	21 (3.9)	8 (1)	2 (<1)	1 (<1)

Abbreviations: AE = adverse event; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; MedDRA™ = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category

a MedDRA™ preferred term based on progression event recorded as an AE by the investigator.

Adverse events that were pooled under the composite term “venous thromboembolic events” (VTEs) were reported in 49 patients (9.1%) in the GCis + N Arm, and 29 patients (5.4%) in the GCis Arm. The corresponding rates of Grade ≥3 events were 5.0%.

Arterial thromboembolic events (ATEs) occurred more often in the necitumumab arm (GCis + N) than in the GCis Arm (5.4% [3.9% Grade ≥3] vs. 3.9% [2.0% Grade ≥3]).

Notably, there were no relevant differences between treatment arms with respect to fatal venous thromboembolism (<1% in both arms) or fatal arterial thromboembolism (<1% in both arms).

Thromboembolic events according to different treatment phase

Table 41 Adverse Events of Special Interest – Thromboembolic Events in SQUIRE (Safety Population) Reported for 2 or More Patients in the GCis + N Arm

AESI	Ctx Phase				Mai Phase	
	GCis + N N = 538 n (%)		GCis N = 541 n (%)		GCis + N N = 275 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Arterial Thromboembolic Events	23 (4.3)	16 (3.0)	21 (3.9)	11 (2.0)	[redacted]	[redacted]
Ischaemic Stroke	4 (0.7)	4 (0.7)	0	0	[redacted]	[redacted]
Cerebral Ischaemia	2 (0.4)	1 (0.2)	0	0	[redacted]	[redacted]
Acute Myocardial Infarction	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Aortic Thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	0	[redacted]	[redacted]
Cerebral Infarction	0	0	0	0	[redacted]	[redacted]
Myocardial Infarction	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)	[redacted]	[redacted]
Peripheral Arterial Occlusive Disease	2 (0.4)	1 (0.2)	1 (0.2)	0	[redacted]	[redacted]
Peripheral Artery Thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Transient Ischaemic Attack	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)	[redacted]	[redacted]
Venous Thromboembolic Events	44 (8.2)	23 (4.3)	29 (5.4)	14 (2.6)	[redacted]	[redacted]
Pulmonary Embolism	24 (4.5)	17 (3.2)	13 (2.4)	10 (1.8)	[redacted]	[redacted]
Deep Vein Thrombosis	8 (1.5)	4 (0.7)	5 (0.9)	0	[redacted]	[redacted]
Thrombosis	4 (0.7)	1 (0.2)	3 (0.6)	0	[redacted]	[redacted]
Mesenteric Vein Thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Pulmonary Artery Thrombosis	2 (0.4)	0	2 (0.4)	1 (0.2)	[redacted]	[redacted]
Pulmonary Venous Thrombosis	1 (0.2)	0	0	0	[redacted]	[redacted]
Venous Thrombosis Limb	1 (0.2)	0	0	0	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; AE = adverse event; Mai = maintenance; Ctx = chemotherapy; GCis = gemcitabine and cisplatin; GCis + N = gemcitabine and cisplatin plus necitumumab; MedDRATM = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category.

When considering the chemotherapy phase only, ATEs occurred more often in the necitumumab arm (GCis + N) than in the GCis Arm (4.3% [3.0% Grade ≥3] versus 3.9% [2.0% Grade ≥3]), The observed imbalance was mainly due to events affecting the cerebrovascular system. Preferred Terms (PTs) of ischemic stroke (n = 4 in the GCis + N Arm versus n = 0 in the GCis Arm), cerebral ischemia (n = 2 in the GCis + N Arm versus n = 0 in the GCis Arm), and aortic thrombosis (n = 2 in the GCis + N Arm vs. n = 0 in the GCis Arm) were the individual events contributing most to the imbalance.

Adverse events that were pooled under the composite term “venous thromboembolic events” were reported in 44 patients (8.2%) in the chemotherapy phase of the GCis + N Arm, and 29 patients (5.4%) in the GCis Arm. The corresponding rates of Grade ≥3 events were 4.3% and 2.6%. The most common PTs in this category were pulmonary embolism (4.5% in the GCis + N Arm versus 2.4% in the GCis Arm) and deep vein thrombosis (1.5% vs. 0.9%).

Other AESI and Events from Consolidated Term Analysis

Events related to skin and eye toxicity, fatigue, hypersensitivity reactions, hypomagnesaemia, interstitial lung disease and hematologic toxicity were assessed as AESI or using consolidated term analysis based on safety data known for other monoclonal anti-EGFR antibodies. Frequencies reported for these categories of events are displayed in Table 42.

Events pooled under the category of skin reactions (including the category of rash, a subset of skin reactions) and hypomagnesaemia were reported with higher incidence in the GCis + N Arm as compared to the GCis Arm Grade ≥3 (8% vs. <% for skin reactions [7% vs. <1% for rash]; 9% vs. 1% for hypomagnesaemia).

Eye disorders were also more common in the GCis + N Arm than in the GCis Arm (7% vs. 2%); there were, however, only two patients (<1%) with events of Grade ≥3 (both in the GCis + N Arm).

Incidences of fatigue-related events and of events pooled under the category of Interstitial Lung Disease, including incidences of events of Grade ≥3, were similar in both arms. Events related to hematologic toxicity, pooled under the composite terms of neutropenia, febrile neutropenia, anaemia, and thrombocytopenia, were similar between arms, with a trend toward more common in the GCis Arm than in the GCis + N Arm; this also included events of Grade ≥3.

Table 42 Adverse events (of grade 3 to 5) of interest possibly related to study drug, events occurring in one or more patients in either treatment group, by preferred Term

Preferred Term	GCis+N N = 538 n (%)				GCis N = 541 n (%)			
	Grade 1-2	Gr.3	Gr.4	Gr.5	Grade 1-2	Gr.3	Gr.4	Gr.5
Neutropenia	104 (19)	97 (18)	34 (6)	0	99 (18)	106 (20)	43 (8)	0
Febrile neutropenia	2 (<1)	3 (<1)	1 (<1)	0	1 (<1)	6 (1)	1 (<1)	0
Anaemia	168 (31)	55 (10)	2 (<1)	0	189 (35)	56 (10)	3 (<1)	0
Thrombocytopenia	62 (12)	38 (7)	17 (3)	0	88 (16)	35 (6)	23 (4)	0
Diarrhoea	75 (14)	9 (2)	0	0	53 (10)	6 (1)	2 (<1)	0
Fatigue	190 (35)	38 (7)	1 (<1)	0	192 (35)	36 (7)	2 (<1)	0
Hypomagnesaemia	118 (22)	37 (7)	13 (2)	0	79 (15)	6 (1)	0	0
Skin reactions	380 (71)	44 (8)	0	0	61 (11)	3 (<1)	0	0
Rash	372 (69)	38 (7)	0	0	53 (10)	2 (<1)	0	0
Hypersensitivity / infusion-related reaction	6 (1)	2 (<1)	0	0	11 (2)	0	0	0
Conjunctivitis	38 (7)	2 (<1)	0	0	12 (2)	0	0	0
Interstitial lung disease (pneumonitis)	3 (<1)	1 (<1)	0	1 (<1)	1 (<1)	3 (<1)	0	0

Other Adverse Events of Special Interest according to different treatment phase

Table 43 Other Adverse Events of Special Interest - SQUIRE (Safety Population)

AESI Category[a]	Ctx Phase				Mai Phase	
	GCis + N N = 538 %		GCis N = 541 %		GCis + N N = 275 %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	43.7	24.3	45.8	27.5	[redacted]	[redacted]
Febrile Neutropenia	0.7	0.6	1.5	1.3	[redacted]	[redacted]
Anaemia	40.1	10.4	45.8	10.9	[redacted]	[redacted]
Thrombocytopenia	21.6	10.2	27.0	10.7	[redacted]	[redacted]
Fatigue	40.7	6.9	42.5	7.0	[redacted]	[redacted]
Hypomagnesaemia	30.1	8.9	15.7	1.1	[redacted]	[redacted]
Rash[b]	75.3	5.6	10.2	0.4	[redacted]	[redacted]
Hypersensitivity/IRR	1.5	0.4	2.0	0	[redacted]	[redacted]
Eye Disorders	5.6	0	2.2	0	[redacted]	[redacted]
Interstitial Lung Disease	0.7	0.2	0.7	0.6	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; Mai = maintenance; Ctx = chemotherapy; Gem-Cis = gemcitabine and cisplatin; Gem-Cis+Neci = gemcitabine and cisplatin plus necitumumab; IRR = infusion-related reaction; N = number of treated patients.

[a] AESI include preferred terms and related disorders identified by Lilly.

[b] The category of "Rash" is a subset of the category "Skin Reactions."

As shown in Table 43, when comparing similar observation periods, events pooled under the categories of rash and hypomagnesaemia were reported with higher incidence in the GCis + N Arm as compared to the GCis Arm (75.3% versus 10.2% for rash; 30.1% versus 15.7% for hypomagnesaemia). This included events of Grade ≥3 (5.6% versus 0.4% for rash; 8.9% versus 1.1% for hypomagnesaemia).

Eye disorders were also more common in the GCis + N Arm than in the GCis Arm (5.6% versus 2.2%); there were no Grade ≥3 events reported during the chemotherapy phase in either arm (2 patients [0.7%] reported Grade 3 conjunctivitis during the maintenance phase in the GCis + N Arm).

Events categorised as hypersensitivity reactions (HSR) were infrequent overall and occurred more often in the GCis Arm (2.0%) than in the GCis + N Arm (1.5%); only 2 patients (0.4%) were reported with a HSR of Grade ≥3 (both in the GCis + N Arm).

Incidences of fatigue-related events and of events pooled under the category of Interstitial Lung Disease, including incidences of events of Grade ≥3, were similar in both arms.

Events related to hematologic toxicity, pooled under the composite terms of neutropenia, febrile neutropenia, anaemia, and thrombocytopenia, were similar between arms, with a trend toward higher incidence in the GCis Arm than in the GCis + N Arm; this also included events of Grade ≥3.

Adverse events in Western European population

The AEs findings in the Western European population were similar to that seen in the ITT population. The proportion of patients developing TEAEs in the Western European population was similar across the two treatment groups (any grade – [redacted] GCis+ N [redacted] in GCis; grade ≥3 – [redacted]). There was no difference between the two treatment groups in terms of number of patients developing any grade or grade ≥3 events like anaemia, neutropenia, fatigue and thrombocytopenia. However, significantly more patients in the GCis + N arm developed hypomagnesaemia (any grade – [redacted]) and rash (any grade – [redacted] and grade ≥3 – [redacted]). The ATEs and VTEs were similar in the two groups.

Table 44 Selected consolidated treatment emergent adverse events (Safety population)

	GCis + N (n=170)		GCis (n=175)		p-value	
	Any Grade	**Grade >=3**	**Any Grade**	**Grade >=3**	**Any Grade**	**Grade >=3**
Patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arterial thromboembolic events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous thromboembolic events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Patient is only counted once for each category.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Missing grades are included in Any Grade.Treatment emergent adverse events were coded using MedDRA dictionary version 16.0.(1) Two-sided p-value for comparing TEAEs using Fisher's exact test.

Deaths

Deaths are summarised by primary cause of death as assigned by the investigator in Table 45**.** For the assignment of the primary cause of death, progression of disease is considered separate from AEs. Overall, most patients in both arms died primarily due to disease progression, with a higher rate in the GCis Arm compared to the GCis + N Arm (339 patients [63.0%] in the GCis + N Arm versus 367 patients [67.8%] in the GCis Arm).

Among the patients who died while on treatment or within 30 days of the last dose of study therapy, the most common primary cause of death in both arms was assigned as an AE. A total of 35 patients (6.5%) in the GCis + N Arm and 38 patients (7.0%) in the GCis Arm died with an AE as the primary cause of death. An additional five patients in the GCis + N Arm and five patients in the GCis Arm died with an AE as the primary cause of death more than 30 days after the last dose of study therapy.

Table 45 Summary of Deaths with Primary Cause of Death as Assigned by the Investigator - SQUIRE (Safety Population)

	GCis + N N = 538 n (%)	**GCis N = 541 n (%)**
All Deaths (%)	414 (77.0)	437 (81)
Due to Disease Progression[a]	339 (63.0)	367 (67.8)
Due to an Adverse Event[a]	40 (7.4)	43 (7.9)
Due to Other Causes[a,b]	35 (6.5)	27 (5.0)
Deaths on Treatment or Within 30 Days of Last Dose (%)	60 (11.2)	57 (10.5)
Due to Disease Progression[a]	18 (3.3)	18 (3.3)
Due to an Adverse Event[a]	35 (6.5)	38 (7.0)
Due to Other Causes[a,c]	7 (1.3)	1 (0.2)

Abbreviations: Gem-Cis = gemcitabine and cisplatin; Gem-Cis+Neci = gemcitabine and cisplatin plus necitumumab; N = number of treated patients; n = number of patients in category.

[a] Primary cause of death as classified by investigator.

[b] Includes patients where the cause of death was not specified (e.g., the patient died at home with only a verbal report of death from family), as well as deaths from other events (e.g., pneumonia, stroke, etc.) that were not reported as adverse events because they were not related to study therapy and occurred more than 30 days following the last dose.

[c] Consists of patients where the cause of death was unknown (e.g., the patient died at home with only a verbal report of death from family).

4.13 Interpretation of clinical effectiveness and safety evidence

SQUIRE trial

SQUIRE was a multi-national, multicenter, open label, randomised phase III trial comparing GCis + N to GCis as a first-line therapy in patients with Stage IV squamous- NSCLC. SQUIRE was a well-controlled, multicenter, confirmatory phase III trial (N=1093) with clear, prospectively determined clinical and statistical analytic criteria. The trial was open-label, consistent with the design of other trials with other anti-EGFR mAbs, with the sponsor blinded to aggregate data. The randomisation to treatment arm was stratified by PS 0-1 versus 2 and geographic regions as potential prognostic factors for OS. Patients with PS 2 were included to reflect a more real-world population.

The selected chemotherapy of gemcitabine and cisplatin is an efficacious standard first-line treatment for squamous NSCLC and was administered at the recommended dose and schedule in both treatment arms. The demographics and disease characteristics were well balanced between treatment arms and generally reflective of a Western patient population with advanced squamous NSCLC and similar standards of care. The study population consisted of patients with heavy metastatic disease burden, including approximately 55% of patients with metastases to >2 organ systems and 9% of patients with an ECOG PS of 2, and patients with a medium to high symptomatic burden as indicated by the LCSS baseline scores. In this global, multicenter study, 86.6% of patients were from Europe, Australia, and North America (3.8% in US and Canada), with the remainder from Eastern Asia (7.7%), South America, South Africa, and India (5.7%).

The primary endpoint was OS; major secondary endpoints were PFS, ORR, safety, and PK. OS was selected as a primary endpoint because it can be measured accurately and represents a direct benefit to the patient. The statistical methods were adequate and included prespecified sensitivity analyses and multiple subgroup analyses for OS. The methods of tumour and PFS assessment were adequate, with radiographic disease assessments applying the same methods and time intervals (every 6 weeks following the first dose) until radiographically documented PD according to RECIST in both arms.

Survival outcomes

Survival was evaluated in the SQUIRE trial using OS and PFS. In the trial, two population groups were compared (ITT and WE). The OS was found to be statistically significantly improved among patients in the GCis + N arm compared with those in the GCis arm in both

population group i.e. ITT (p=0.01) and WE (p=0.008). The HR of 0.84 showed a risk reduction of death by 16% for patients who had received necitumumab in the ITT population. In the ITT population, the survival rates were 47.7% versus 42.8% and 19.9% versus 16.5% for 1 and 2 years, respectively. These findings are of particular note, because the presented study included patients with a performance status 2, which is usually associated with shorter median OS and PFS in comparison to patients with an ECOG PS 0/1 (48-50). In addition, the patient population consists of older patients with a history of chronic smoking and with reported comorbidities. 55% of the patients in SQUIRE had more than 2 metastatic sites.

The secondary outcomes of PFS was also met, with statistically significant advantages (p = 0.02) for necitumumab. The risk reduction for disease progression or death was 15% in favor of the experimental arm. The point estimate for median PFS was 5.7 months vs. 5.5 months. To date, SQUIRE is the only phase III study that has demonstrated a statistically significant survival benefit for a biologic in combination with gemcitabine and cisplatin, specifically in the population of patients with metastatic squamous NSCLC, for whom first-line platinum-based chemotherapy doublets have been the standard of care.

The NMA results also suggest the comparative value of necitumumab plus gemcitabine and cisplatin in the squamous NSCLC population against other available treatment regimens, although data are limited.

Adverse events

In general, the safety data obtained in SQUIRE were consistent with the safety profile expected for an anti-EGFR mAb, with skin reactions and hypomagnesaemia being the most reported events occurring at higher rates in the necitumumab arm. There were no major differences in AE rates across subgroups; in particular, there was no evidence for an increased safety risk due to necitumumab for ECOG PS 2 patients.

The addition of necitumumab does not appear to be associated with a clinically relevant increase of typical toxicities observed with gemcitabine and cisplatin, such as hematologic toxicities, including Grade 3 and 4 events. Findings regarding eye-related disorders were consistent with the expected safety profile for an anti-EGFR mAb, with most events in this category being Grade <3 and manageable. Consistent with data published for other anti-EGFR mAbs (47,51), both ATEs and VTEs were observed more often in patients receiving necitumumab in combination with chemotherapy compared with chemotherapy alone. However, there were no relevant differences between treatment arms with respect to fatal

venous thromboembolism or fatal arterial thromboembolism. Overall, the difference between arms in all AEs with an outcome of death was five patients (42 [GCis + N] vs. 37 [GCis]), a difference consistent with statistical variation. Notably, when considering equivalent evaluation periods (GCis + N Arm chemotherapy phase only), the number of AEs with outcome of death was higher in the GCis Arm (32 vs. 37), a difference also consistent with statistical variation.

Necitumumab is an important advance in the treatment options for patients with metastatic squamous NSCLC, where limited progress has been made over the last two decades when compared to non-squamous NSCLC. There are no relevant oncogenic drivers in squamous NSCLC to help inform treatment decisions for this patient population. The patient population consist of older patients, with 38% being over the age of 65, greater than 90% having at least one comorbidity, and approximately 90% being smokers. In addition, 9% of patients in both arms had an ECOG PS2, which do tend to have a poorer prognosis in clinical practice.

End of life criteria

Necitumumab fulfils all the criteria specified in NICE's 'Supplementary Advice for Appraising life-extending, end of life treatments' (criteria 1 to 3) (Table 46).

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

The current expected survival reported in the literature for this patient population is between 6.5 and 9.4 months depending on therapy received which is below the 24 month criterion.

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 modelled mean OS benefit for the Western Europe subpopulation was 5.76 months for GCis + N (19.82 months) when compared to GCis (14.06 months).

Criterion 3. The treatment is licensed or otherwise indicated for small patient populations

The patient population eligible for necitumumab is expected to be less than 7,000 patients with approximately 2,575 patients in England having locally advanced or metastatic squamous NSCLC.

Table 46 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Without treatment, the survival of patient population is between 6.5 and 9.4 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The incremental modelled mean OS for the Western Europe subpopulation was 5.76 months.
The treatment is licensed or otherwise indicated for small patient populations	A small patient population in England would be eligible for first-line treatment with Necitumumab (approximately 2,575 patients)

4.14 Ongoing studies

Study: EGFR Inhibitor AZD9291 and Necitumumab in Treating Patients With EGFR-Positive Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor

Study ID: NCT02496663/ 4T-MC-JVD*L*

Objective: To study the side effects and best dose of necitumumab when given together with epidermal growth factor receptor (EGFR) inhibitor AZD9291 (osimertinib) in treating patients with EGFR-positive non-small cell lung cancer that is stage IV or has come back (recurrent) and who have progressed on a previous EGFR tyrosine kinase inhibitor.

Study design: Phase I trial

Current status: This study is not yet open for participant recruitment

Study start date: April 2016

Estimated study completion date: August 2016

Last updated: December 2016

Link: https://clinicaltrials.gov/ct2/show/NCT02496663

Study: A Study of Necitumumab and Chemotherapy in Participants With Stage IV Squamous Non-Small Cell Lung Cancer

Study ID: NCT01769391

Objective: To evaluate if necitumumab added to standard chemotherapy of paclitaxel and carboplatin is more effective to treat cancer than the standard chemotherapy of paclitaxel and carboplatin alone.

Study design: Phase II trial

Current status: This study is ongoing, but not recruiting participants.

Study start date: January 2013

Estimated study completion date: December 2015

Last updated: May 8, 2015

Link: https://clinicaltrials.gov/ct2/show/NCT01769391

Study: A Study of Nab-Paclitaxel and Carboplatin Plus Necitumumab (LY3012211) in Participants With Stage IV Squamous NSCLC

Study ID: NCT02392507

Objective: To determine if nab-paclitaxel and carboplatin chemotherapy plus necitumumab is effective and safe in participants with stage IV squamous non-small cell lung cancer.

Study design: Phase II trial

Current status: This study is currently recruiting participants.

Study start date: October 2015

Estimated study completion date: August 2017

Last updated: December 4, 2015

Link: https://clinicaltrials.gov/ct2/show/NCT02392507

Study: A Study of LY3023414 and Necitumumab in Squamous Lung Cancer

Study ID: NCT0244333**7**

Objective: To evaluate the safety and activity of the study drug known as LY3023414 in combination with necitumumab in participants with metastatic squamous non-small cell lung cancer (NSCLC).

Study design: Phase II trial

Current status: This study is currently recruiting participants

Study start date: July 2015

Estimated study completion date: December 2017

Last updated: November 19, 2015

Link: https://clinicaltrials.gov/ct2/show/NCT02443337

Study: A Study of Necitumumab and Abemaciclib in Participants With Non-Small Cell Lung Cancer (NSCLC)

Study ID: NCT02411591/ I4X-MC-JFCU

Objective: To evaluate the safety and efficacy of two new medicines (necitumumab and abemaciclib), administered in combination in participants affected by a defined type of advanced lung cancer (stage IV non-small-cell lung cancer).

Study design: Phase I trial

Current status: This study is currently recruiting participants

Study start date: June 2015

Estimated study completion date: March 2017

Last updated: December 21, 2015

Link: https://clinicaltrials.gov/ct2/show/NCT02411591

Study: A Study of the Combination of Necitumumab (LY3012211) and Pembrolizumab (MK3475) in Participants With NSCLC

Study ID: NCT02451930/ I4X-MC-JFCQ

Objective: To evaluate the safety and efficacy of the combination of necitumumab with pembrolizumab in participants with stage IV NSCLC.

Study design: Phase I trial

Current status: This study is currently recruiting participants.

Study start date: September 2015

Estimated study completion date: March 2019

Last updated: December 21, 2015

Link: https://clinicaltrials.gov/ct2/show/NCT02451930?term=necitumumab&rank=14

5. Cost effectiveness

Key messages

- Due to the clinical efficacy of necitumumab varying across regions despite no statistically significant difference in demographics or treatment received within the SQUIRE trial, it is believed that this difference in clinical efficacy is a result likely due to unobserved treatment effect modifiers that have been detected within the SQUIRE trial. Potential unobserved treatment effect modifiers include the associated disease burden of squamous NSCLC and environmental causes of cancer including social and cultural practices such as heavy smoking across Europe.
- The economic evidence presented in this submission is based on the Western Europe subpopulation of the SQUIRE trial as it is considered the most generalizable to patients in England and therefore decision making in England.
- The cost- effectiveness of GCis + N was compared to GCis using the SQUIRE trial data. GCarbo, DCis and PCarbo were also compared using indirect comparative data.
- The OS and PFS curves for GCis + N and GCis were generated using the observed KM product-limit estimates from the SQUIRE trial, with a separately fitted log-logistic survival curve after the last observation for long-term projections. For all indirect comparators, the HRs derived from the NMA were used to generate the OS and PFS curves.
- GCis + N is associated with a higher total average per patient lifetime cost compared to GCis as well as greater efficacy benefits, resulting in an incremental cost effectiveness ratio (ICER) of £64,713 per QALY when comparing GCis + N to GCis.
- Necitumumab fulfils the end of life criteria in terms of a small patient population (approximately n=2,575), with a current expected median survival of 6.5 months to 9.4 months. The modelled mean OS benefit suggests a trend towards increased OS of at least three months, with results ranging from an incremental gain of 3.97 months to 5.76 months depending on the extrapolation method used.

5.1 Published cost-effectiveness studies

Identification of studies

A comprehensive systematic literature review was conducted using Embase, Medline (including MEDLINE-R In-Process), EconLit and NHS EED to identify studies assessing the cost-effectiveness of GCis + N compared to GCis in the first-line treatment of squamous NSCLC. The search was designed to identify economic evaluations of pharmacological treatments for patients with locally advanced or metastatic squamous NSCLC first-line treatment in clinical practice. Due to the limited literature on squamous NSCLC, a wider scope was applied to the search strategy to include all NSCLC populations to identify more publications. However, to identify full economic evaluations relevant to the appraisal of necitumumab, an additional inclusion criterion was added to include studies if the patient population consisted of less than 80% of the population having adenocarcinoma or non-squamous histology. The complete search strategy is provided in the Appendix 9. The searches were performed on 13 May 2014 and sought to capture all full economic evaluations published since 2004.

Title and abstracts of every record identified was assessed for relevance according to the pre-defined inclusion and exclusion criteria (see Table 47). If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria. The review was conducted by one reviewer and was validated by a second reviewer. Any discrepancies were resolved by a third reviewer.

Table 47 Economic Evaluation Search Inclusion/Exclusion Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated squamous NSCLC patients	Small cell lung cancer patients, non-squamous NSCLC patients, Non-lung cancer patients (mesothelioma), previously treated patients
Intervention	GCis + N	
Comparator	GCis	
Outcome	Cost per QALY gained, Cost per LY gained	
Study Design	Economic Evaluations (cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-minimisation analyses)	RCTs, observational data, Budget Impact Assessments

In total, 976 records were identified via the four databases. Of these, 674 studies were excluded upon initial screening of title and abstract (see the PRISMA diagram below for the rationale for these exclusions) and 44 were deemed potentially relevant. These results were retrieved and assessed more comprehensively against the initial inclusion/exclusion criteria with additional exclusion criteria applied to exclude studies that consisted primarily of non-squamous NSCLC patients. The systematic literature review identified 10 economic evaluations pertaining to the first-line treatment of squamous NSCLC. Studies were primarily excluded due to not being an economic evaluation, not regarding NSCLC and not regarding a first-line treatment.

Description of identified studies

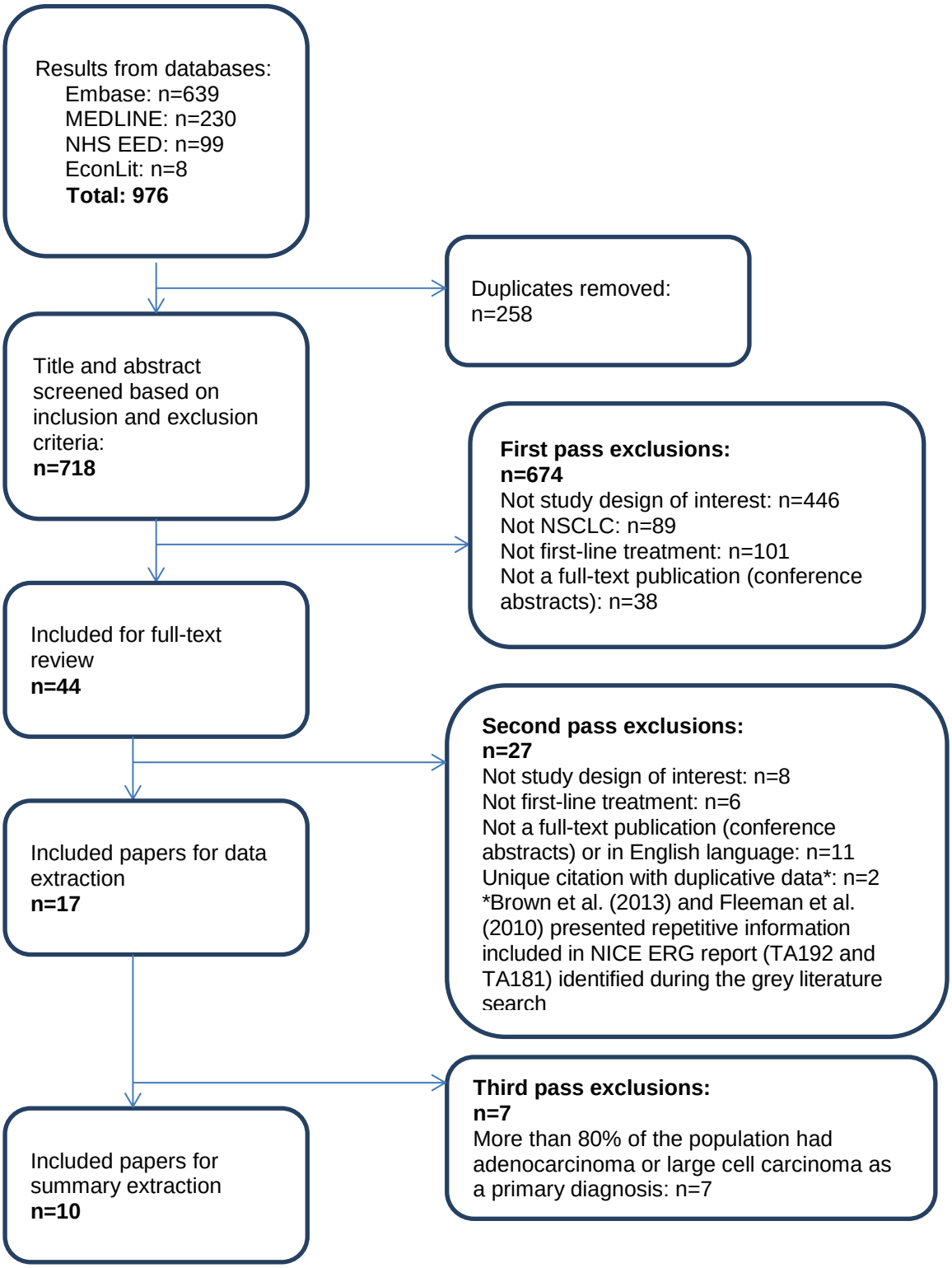
Of the 10 economic evaluations pertaining to the first-line treatment of NSCLC, no relevant studies pertaining to the cost-effectiveness of necitumumab for the first-line treatment of squamous NSCLC were identified in the systematic review.

Three articles described a state transition model (22-24) and seven articles reported results of economic evaluations alongside clinical trials (25-31). Two article assessed outcomes in the United Kingdom (23, 30) and three studies compared gemcitabine plus cisplatin (22, 28, 30). The average patient populations in these evaluations were mostly over 60 years of age and had advanced NSCLC. None of the studies included an exclusively squamous population. Therefore, a de novo economic evaluation has been conducted for this appraisal.

The 10 articles that were identified in the systematic literature review have been quality assessed according to the Drummond checklist (32). The quality assessment is located in Appendix 10.

Since the completion of the systematic literature review in 2014, a US specific publication regarding the range of drug costs for necitumumab that would make GCis + N a cost-effective treatment option for locally advanced or metastatic squamous NSCLC patients in the US was published. Goldstein et al. 2015(52) highlighted that the cost-effectiveness of necitumumab relies on the OS and QALY estimates as well as the price of necitumumab and the WTP threshold of the payer (52). Given that the publication is US specific with Medicare reimbursement rates used for resource use and AEs, the generalisability of the results to England is uncertain. Additionally, the analysis only compared GCis + N to GCis. Therefore, the model presented within this evaluation is considered the most relevant for the decision problem.

Figure 35 PRISMA Flow-chart of economic evaluation search



5.2 De novo analysis

Patient Population

The economic evaluation includes patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment. This population is consistent with the SQUIRE trial and NICE scope; however, it is not consistent with the indication provided in the summary of product characteristics for necitumumab: 'Portrazza in combination with gemcitabine and cisplatin chemotherapy is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition.' Additional analysis will be provided to NICE at a later stage to reflect this population.

Subgroup analysis based on geographic region found that that the clinical efficacy of necitumumab within the SQUIRE trial does vary across regions (see section 4.8). Therefore, a post-hoc analysis was completed for patients in Western Europe (including Austria, Belgium, Germany, France, Greece, Italy, Portugal, Spain and UK).

Statistical analysis of the SQUIRE trial found that patients in Hungary and Poland performed better on the GCis arm than the GCis + N arm with a HR of [redacted] and [redacted] respectively. However, patients in Western Europe performed better on the GCis + N arm than the GCis arm with a HR of [redacted]. This finding of improved clinical efficacy of patients in the GCis + N arm compared to the GCis arm in Western Europe patients is consistent with the findings in the ITT patient population, with a HR 0.85.

A comprehensive analysis of this data has been completed on general prognostic factors to determine the cause of this difference including: disposition, demographics, pre-treatment disease characteristics, medical history, con meds, OS, PFS, ORR, post study therapy, exposure, dose modifications/delays, TEAEs, AEs of special interest, summary of ATE/VTE (including fatal), ECOG PS by time point, hospitalisation and LCSS. However, the analysis concluded that there were no substantial imbalances in demographics, patient characteristics, exposure to treatment or other prognostic factors between the regions.

Due to the clinical efficacy of necitumumab varying across regions despite no statistically significant difference in demographics or treatment received within the SQUIRE trial, it is thought that this difference in clinical efficacy is likely due to unobserved treatment effect modifiers that have been detected within the SQUIRE trial. Potential unobserved treatment effect modifiers include heavier smoking exposure, the associated disease burden of

squamous NSCLC and environmental causes of cancer including social and cultural practices such as heavy smoking across Europe.

It has been well established in the literature that the different countries and regions of Europe show marked differences in lung cancer incidence and mortality rates (see section 3). According to a report completed by Coleman et al. 2008(53), the observed variations in incidence and mortality rates reflect the varying prevalence and distribution of risk factors within and between European countries, as well as disparities in the effective delivery of cancer control measures. A substantial proportion of the lung cancer burden across Europe may be attributed to environmental causes of cancer including social and cultural practices such as heavy smoking. Therefore, the variations in cancer incidence partially reflect underlying differences in the distribution of the determinants or risk within each country and the local effectiveness of primary prevention measures (particularly tobacco control). These rates may also reflect the availability and quality of cancer treatment and management nationally (53).

While it is conventional to use data from the ITT population, the SQUIRE trial has reported a difference in the clinical efficacy of necitumumab across regions. Statistical analysis has concluded that this is not due to a difference in baseline characteristics or treatment received during the SQUIRE trial, but is likely due to potential unobserved treatment effect modifiers such as disease burden and environmental causes of cancer including social and cultural practices such as heavy smoking. The literature suggests that this is likely to have resulted in higher incidence and mortality rates for lung cancer patients in Eastern Europe than in Western Europe. The unobserved treatment effect modifiers in the SQUIRE trial may have contributed to an overall varying impact on health outcomes geographically for necitumumab. Therefore, it is considered appropriate to employ data which has been generated from a patient population reflective of the disease burden of NSCLC patients in England. As a result, the economic evidence presented in this submission is based on the Western Europe subpopulation of the SQUIRE trial as it is considered the most generalisable to patients in England and therefore decision making in England. The ITT patient population will be explored as a scenario analysis.

Model structure

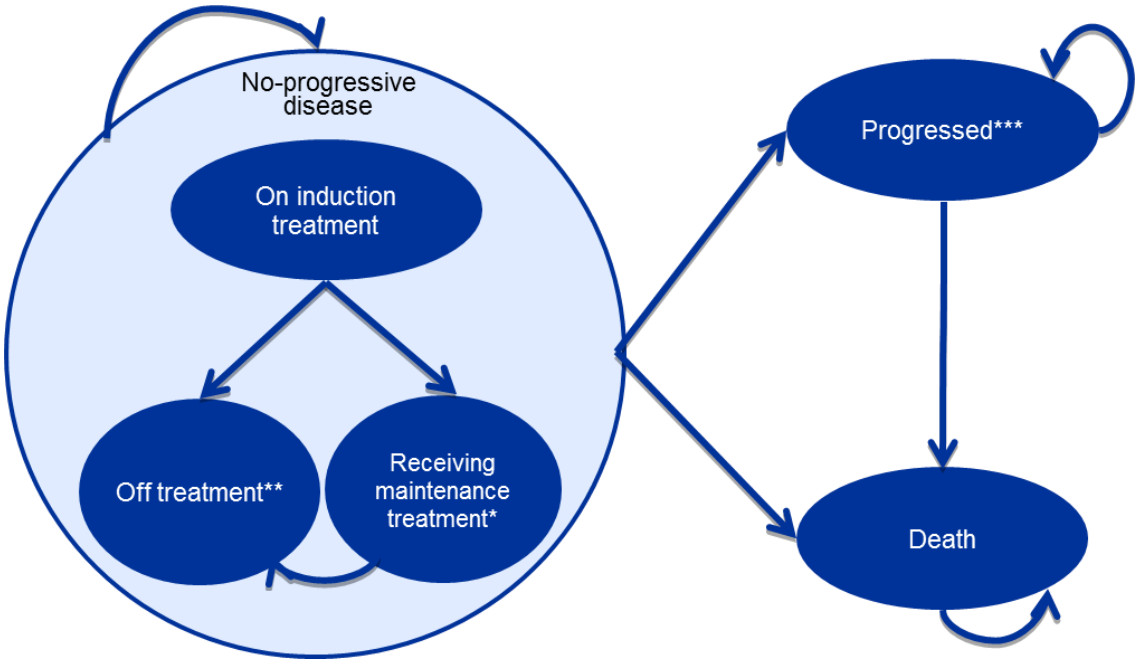
A Markov cohort state transition model with weekly cycles was developed for this analysis. Weekly cycles are considered appropriate for this model to account for the different administration schedules of gemcitabine, cisplatin and carboplatin. The model tracks

patients through three mutually exclusive health states and three treatment states. These health states include:

- Pre-progression
    - On induction treatment
    - Receiving maintenance treatment (discontinued or completed induction therapy and on maintenance treatment)
    - Off Treatment (discontinued or completed induction therapy or maintenance therapy and off active treatment)
- Post-progression
- Death

Patients start in the pre-progression health state and on first-line induction treatment. Within each weekly cycle, patients can stay in that state, complete induction treatment and receive maintenance treatment ("Pre-progression, receiving maintenance treatment") or discontinue/complete induction treatment or maintenance treatment prior to progression ("Pre-progression, off treatment") or progress or die. Figure 36 demonstrates the model structure.

Figure 36 Model Design



* Patients who completed up to six cycles of first-line treatment and are receiving maintenance treatment.
** Patients who discontinued induction treatment or maintenance treatment due to AEs, or physician or patient preference.

*** At least a 20% increase in the sum of the longest diameter of target lesions or unequivocal increase in the size of non-target lesions or the appearance of one or more new lesions.[23]

In order to account for the progressive nature of locally advanced or metastatic squamous NSCLC, a Markov cohort transition model was implemented. The state transition approach represents an appropriate way of modelling terminal disease when patients pass through a series of clearly defined and mutually exclusive health states based on the treatment received and progression. In addition, state transition models have the ability to reflect time-dependent parameters such as OS and PFS through the use of survival curves using a partition approach. By calculating the area under the survival curve in each cycle, the distribution of the patient cohort between the different health states defined by these curves can be estimated. This approach has been used extensively in previous NICE STAs for NSCLC and is in line with the NICE pathway for treatment of NSCLC.

Health States

The three main health states and three treatment states are designed to capture the following:

- **Pre-progression**
    - **On induction treatment:** This state represents patients who have been diagnosed with locally advanced or metastatic squamous NSCLC that are receiving first-line induction therapy and have not progressed. Patients remain in this health state while receiving induction treatment.
    - **Receiving maintenance treatment:** This health state represents patients that have not progressed and have completed induction therapy and are receiving maintenance therapy. Maintenance therapy is only available for patients that have received GCis + N induction therapy. Patients remain in this health state until treatment discontinuation, progression or death.
    - **Off Treatment:** This health state represents patients that have not progressed and discontinued or completed therapy. Patients can remain in this health state until progression or death.
- **Post Progression:** This health state represents patients that have progressed. This health state does include patients that receive second-line therapy following progression after first-line therapy as well as patients that receive BSC following progression. Patients can remain in this health state until death.

- **Death:** This health state is the absorbing state. Death captures all-cause mortality. Patients can move to this state from any point of the model.

Patients move between health states at the end of each weekly cycle. All patients enter the model in the pre-progression health state. Patients remain in the progression free health state until they experience disease progression or die. Once patients enter the post-progression disease state, they remain there until death.

Table 48 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	NICE Reference Case
Cycle Length	1 week	The cycle length was chosen to capture three-week treatment cycles in addition to the monitoring schedule. The weekly cycle is also sensitive to changes in OS and PFS.
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference Case
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case
Half-cycle correction	Yes	NICE Reference Case
Perspective (NHS/PSS)	Yes	NICE Reference Case
PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

The economic model compares GCis + N to other chemotherapy agents currently used in NHS clinical practice in England for the first-line treatment of locally advanced or metastatic squamous NSCLC. These treatment options include a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either cisplatin or carboplatin) and have been included in the NICE scope for necitumumab. The economic model compares GCis + N to GCis, GCarbo, PCarbo and DCis. The primary comparison in this evaluation is GCis + N compared to GCis, as studied in the SQUIRE trial. The additional comparisons presented are based on indirect comparison data from the NMA. All treatment options were implemented in the model consistent with their marketing authorization with the exceptions of GCarbo and PCarbo. GCarbo is used frequently in the NHS but is not licensed in Europe for advanced NSCLC. Additionally, the dose and schedule used for PCarbo varies between the summary of product characteristics and its respective pivotal clinical trials (54)(1,46,55). For consistency with the obtained OS and PFS, the dose and schedule from the pivotal trials was used. This appraisal does not include VCis

as an indirect comparator because an indirect comparison was not possible due to lack of data specific to squamous NSCLC patients treated with vinorelbine plus cisplatin.

Continuation Rule

In the SQUIRE trial, patients received induction therapy with GCis + N or GCis for a maximum of 6 cycles, consistent with the European marketing authorisation for necitumumab (located in Appendix I) and the current European Society for Medical Oncology (ESMO) treatment guidelines (56). Patients in the GCis + N arm continue to receive necitumumab monotherapy until disease progression. Patients in the GCis arm receive BSC and disease monitoring until disease progression. The continuation of necitumumab monotherapy is specified in the SPC.

Currently in England, after completion of 4 to 6 cycles of first-line treatment with a platinum doublet, patients with squamous NSCLC undergo a chemotherapy free observation period until disease progression. With the introduction of necitumumab, patients will be treated a maximum of 6 cycles of treatment followed by necitumumab as a single agent in patients whose disease has not progressed until disease progression or unacceptable toxicity. In the SQUIRE trial 85% of patients that continued to receive necitumumab as monotherapy did receive 6 cycles of induction therapy.

Necitumumab maintenance therapy can be continued until disease progression with no maximum number of cycles defined. Within the SQUIRE trial, progression was defined by RECIST 1.0, which requires at least a 20% increase in the sum of the longest diameter of target lesions, an unequivocal increase in the size of non-target lesions, or the appearance of one or more new lesions.

Radiographic progression is a plausible endpoint that is easily defined and measured. Within SQUIRE, radiographic progression was measured every 6 weeks. Clinical expert opinion suggests that this may be more frequent than occurs in clinical practice in England. Clinical experts have stated that they typically perform a chest X-ray every 3 weeks and if there is a sign of potential progression, they will check for radiographic progression. If this is not the case, they may choose to scan for progression every 9 to 12 weeks. However, this varies significantly by location. Therefore an assumption of checking for radiographic progression every 6 weeks is reasonable for this evaluation.

Radiographic progression is considered a more clinically appropriate measure of progression than symptomatic progression as a result of patients potentially progressing

before symptoms of progression are reported. The additional cost associated with the continuation of treatment has been implemented into the model. This includes drug acquisition treatment, administration cost, disease monitoring and TEAEs.

5.3 Clinical parameters and variables

Clinical data in the model

Clinical outcomes to inform the GCis + N and GCis arms were obtained from the SQUIRE trial. Survival for GCis + N and GCis was calculated by using the KM product-limit estimates of the observed OS, PFS and TTD curves over the trial duration (approximately 36 months). Due to the survival data from the SQUIRE trial being incomplete, it is necessary to extrapolate OS, PFS, and other time-to-event outcomes using parametric models based on the survival patterns observed in the clinical trial (57). At the time of final database lock on 13 June 2013, 76.7% of patients in the GCis + N arm and 80.7% of patients in the GCis arm had died, with a censoring rate of 23.3% and 19.3% respectively. Parametric survival analysis was therefore used to extrapolate survival data beyond the trial period in order to obtain an estimate of the total mean survival, cost and health effects throughout the lifetime of a patient. Thus, for long-term projections of OS and PFS a parametric survival curve was applied after 36 months of observed data. For indirect comparators, the OS and PFS estimates were calculated by applying HRs for the comparators versus GCis + N estimated from the NMA to the survival curve estimated for the GCis + N patients.

In all analyses, weeks were used as the time unit corresponding to the model cycle length. Predictors were not included in the parametric curves as it was assumed that the trial population was representative of clinical practice. Additionally, since the economic model is a cohort model, covariate adjustment could not be incorporated as individual-level simulation is required.

In order to determine the most appropriate parametric survival curve, an exploratory analysis was conducted based on the NICE DSU technical support document 14 with the goodness-of-fit being assessed using parametric plots, observed and predicted plots, long-term projections and statistical tests (Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC)) for each treatment arm (58). Where the exploratory analysis shows that the optimal fit for each treatment arm is based on the same distribution and the shapes of these fits are similar, modelling the two arms including treatment as a predictor was considered. The parametric diagnostic plots are detailed in Appendix 11 and Appendix 12, highlighting

the performance of each candidate distribution against the observed data. The Gompertz distribution did not converge and therefore has been excluded from the analysis.

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 OS and PFS.

1. Assess the functional form of the underlying hazard, including if the 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 49.

Table 49 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
	Kernel-smoothed hazard function	Assess the behaviour of the hazard function 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

Overall Survival efficacy data from SQUIRE

Overall survival estimates have been calculated using the OS KM curves over the trial duration and long-term projections of OS using a parametric survival curve for approximately 15% in the GCis + N arm and 6% in the GCis arm of patients whom have not died at the end of the trial.

The plot of smoothed hazard function of OS from the SQUIRE trial in in Figure 38 demonstrate that the curves from GCis + N and GCis have a non-parallel shape, indicating that the proportional hazards assumption is violated. Therefore the OS parametric survival models have been fitted separately for GCis + N and GCis. In addition, the hazard curves are non-monotonic, suggesting that the use of monotonic distributions such as Weibull and exponential are inappropriate. Among the remaining distributions, the log-logistic seems to provide the best fit for the GCis + N Arm and the Weibull seems to provide the best fit for GCis (on the basis of AIC and BIC) followed very closely by the generalized gamma and log-logistic distribution. However, to assume different extrapolation methods for the two arms is not clinically credible. A further examination of the goodness of fit of the alternative distributions was made using Cox-Snell residuals. Visual inspection of these plots confirmed that the Log-Logistic model was the best fitting model for the GCis + N OS data from the SQUIRE trial.

Despite being the best-fitting distribution, the log-logistic distribution did not fit well with the early portion of the observed OS curve. Therefore, the KM product-limit estimates were used to predict OS with a separately fitted log-logistic distribution applied for long-term projections. This decision was based on consideration of the AIC and BIC statistics, the presence of non-proportional and non-monotonic hazards, and visual inspection of the Cox-Snell residuals.

The estimated median OS for the GCis + N and GCis arm using separately fitted log-logistic distribution was 11.73 and 8.74 respectively, as compared to the observed median OS of [redacted] months and [redacted] respectively. The estimated median OS for GCis is consistent with the OS reported in the literature by Hoang et al. 2013 (1) for squamous NSCLC patients of 9.4 months (5.7-15.6 months) (1).

The estimated mean OS for the GCis + N and GCis arm using separately fitting log-logistic distribution was 19.82 vs 14.06 months respectively. Figure 37 displays the OS KM curve graphically and Figure 44 displays the Log-Logistic extrapolation to model OS graphically. Findings of a higher mean versus median gain in life expectancy are common in oncology modelling. This can be attributed to a proportion of patients remaining alive after the study

follow-up and experiencing a longer life expectancy. As the median estimates do not account for these patients, the potential full benefit is not captured (59).

For the GCis + N arm, the OS benefit is experienced in the progression free and on induction treatment (19%), progression free and on maintenance treatment (13%), progression free and off treatment (15%) and in the post-progression health state (54%). For the GCis, the OS benefit is experienced in the progression free and on induction treatment (24%), progression free and off treatment (31%) and in the post-progression health state (45%). Within the model, approximately 7% of GCis + N patients are still alive at year 5 and 3% of GCis patients. These estimates are consistent with the published estimates of 5.9% of patients still alive at year 5 with NSCLC (5).

Figure 37 Kaplan-Meier curve for overall survival

Figure 38 Smoothed Hazard Function

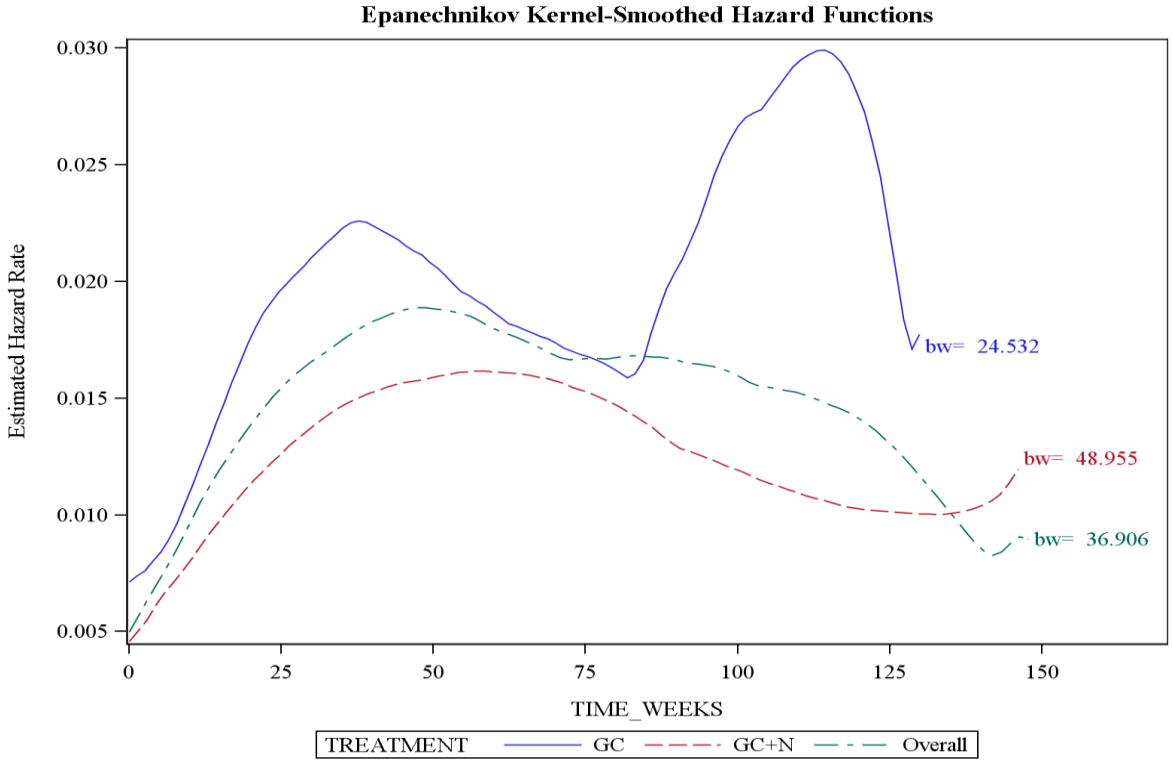
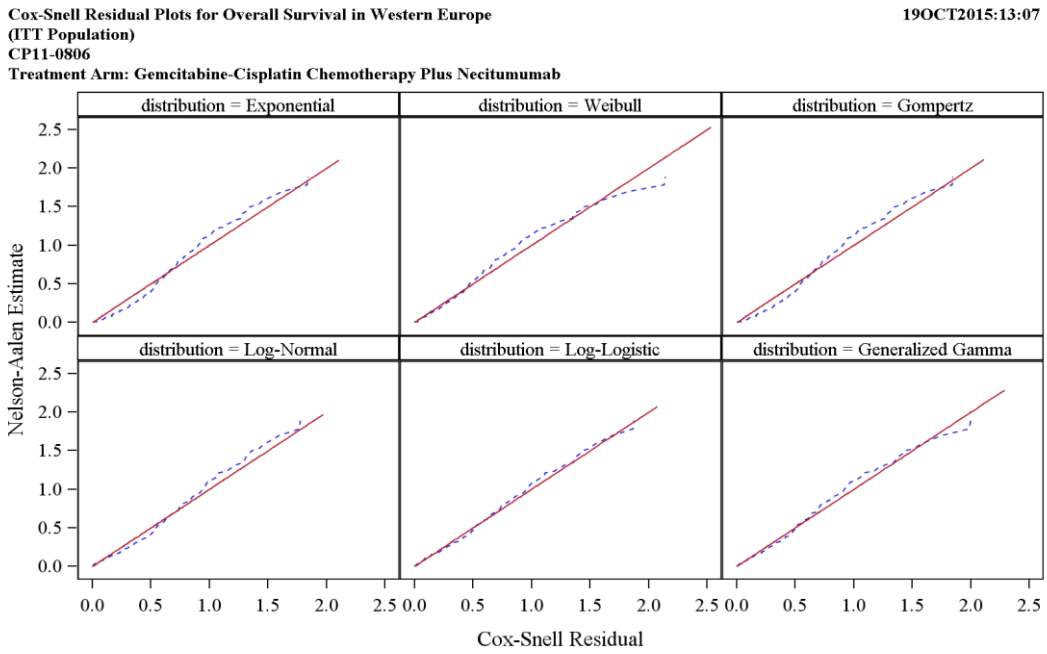


Figure 39 Cox Snell Residuals for overall survival (GCis+N)



Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and GC.
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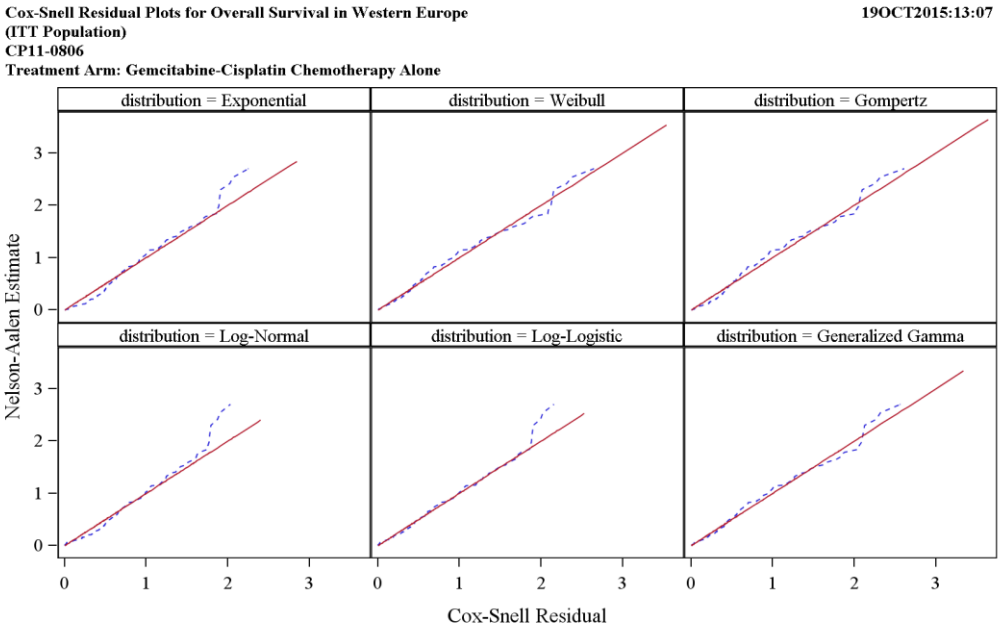
Figure 40 Cox Snell Residuals for overall survival (GCis)



Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and GC.
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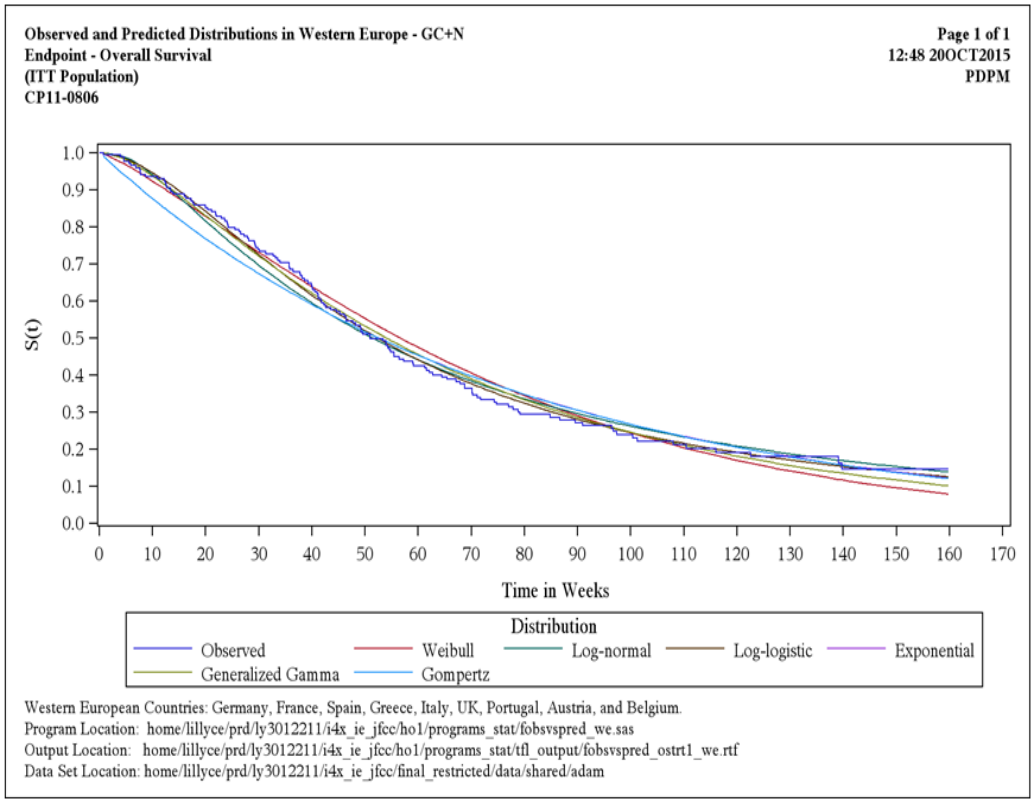
Figure 41 Observed and Predicted Distributions OS (GCis+N)



Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Figure 42 Observed and Predicted Distributions OS (GCis)

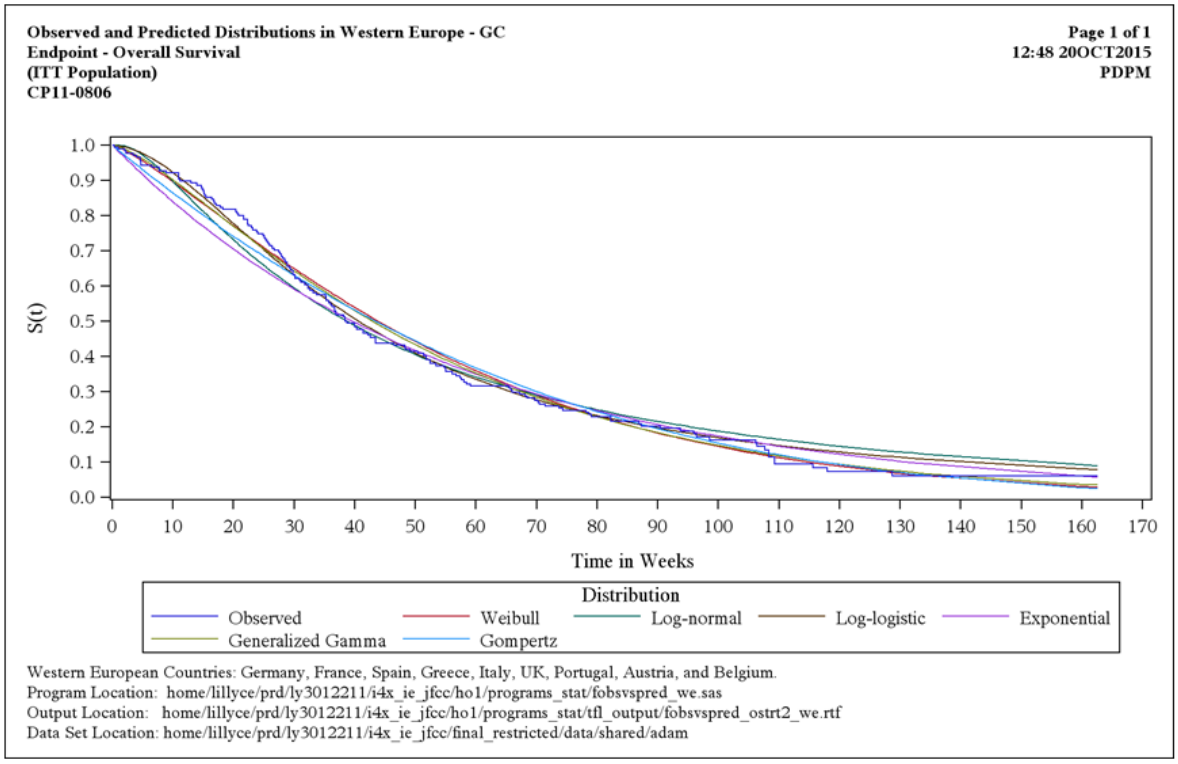


Figure 43 Parametric Diagnostic Plots for Overall Survival - Log-logistic Distribution

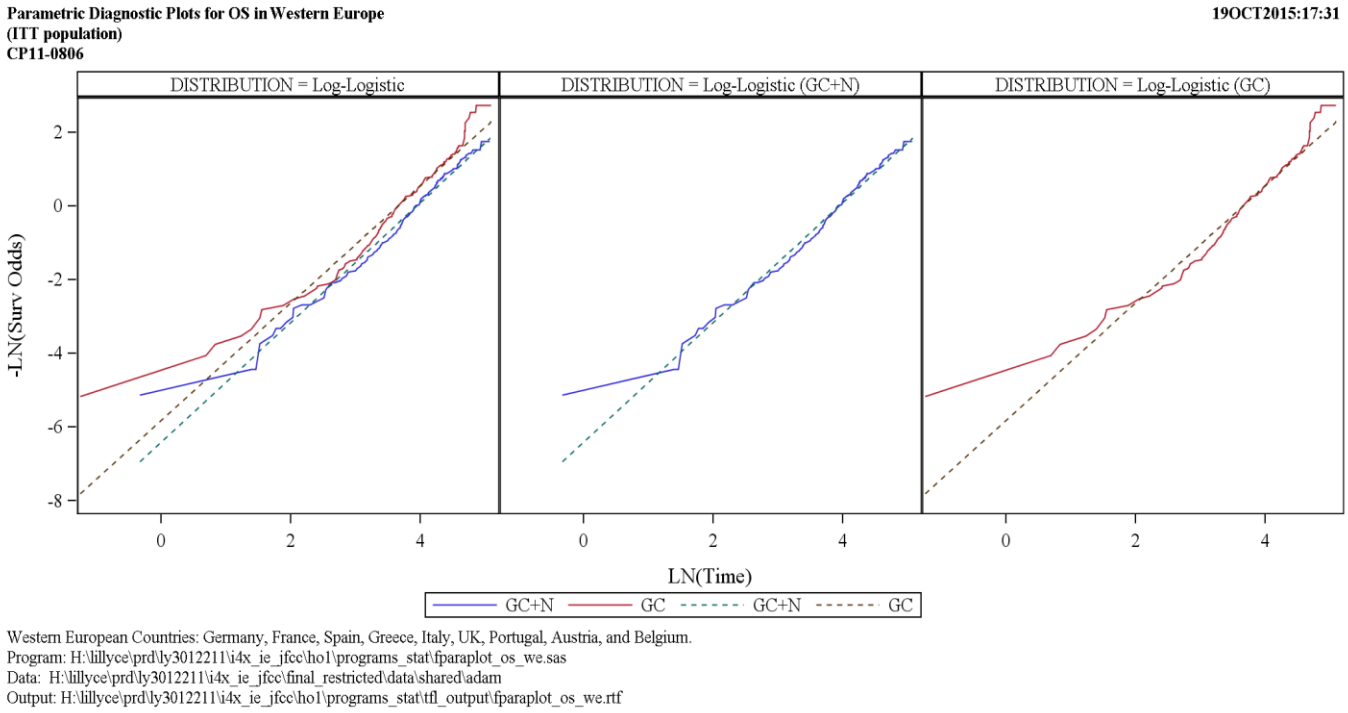


Figure 44 Separately Fitted Log-Logistic extrapolation of OS

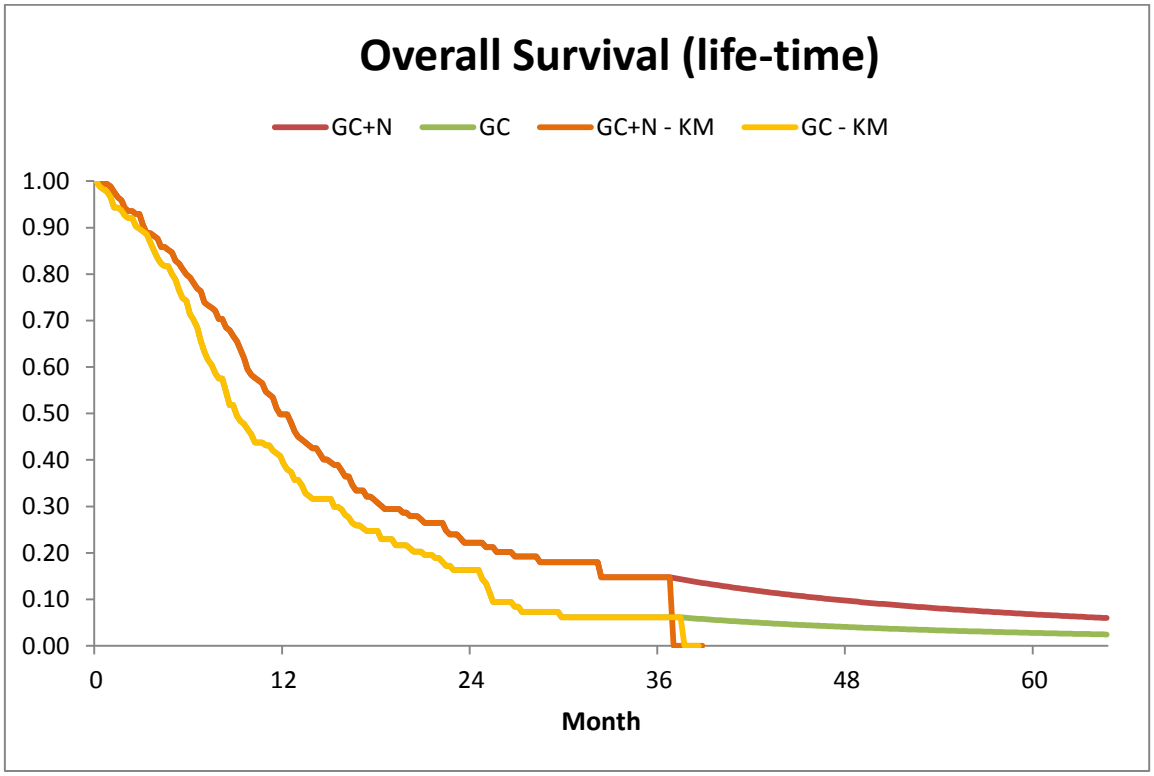


Table 50 Parameter Estimates AIC and BIC – Overall Survival

	AIC	BIC
GCis+N		
Weibull	458.332	464.627
Log-normal	460.011	466.306
Log-logistic	452.292	458.587
Exponential	465.017	468.165
Generalized Gamma	456.52	465.963
GCis		
Weibull	485.283	491.624
Log-normal	504.357	510.698
Log-logistic	487.468	493.809
Exponential	493.37	496.541
Generalized Gamma	486.508	496.019

Progression free survival efficacy data from SQUIRE

The PFS analysis was based on the primary definition of PFS (time from randomisation until first radiographic documentation of objective progression, or death from any cause). PFS estimates have been calculated using the PFS KM product-limit estimates over the trial

duration and long-term projections of PFS using a parametric survival curve for approximately 4% of patients whom have not progressed at the end of the trial.

The smoothed hazard function of PFS from the SQUIRE trial in Figure 46 demonstrates that the curves for GCis + N and GCis cross, which implies non-proportional hazards is present. Therefore the PFS parametric survival models have been fitted separately for GCis + N and GCis. The hazard function also revealed a non-monotonic pattern with increasing hazards initially, which then peaked and started declining to accelerate again. This implies monotonic parametric models, like exponential, Weibull and Gompertz, are inadequate and log-normal or log-logistic models would more accurately capture this type of pattern. Among the distributions, the log-logistic seems to provide the best fit across both arms (on the basis of AIC and BIC).

Despite being the best-fitting distribution, the log-logistic distribution did not fit well with the early portion of the observed survival. Therefore, the KM product-limit estimates were used for predictions of the observed PFS from the SQUIRE trial with a separately fitted log-logistic distribution applied for long-term projections. This decision was based on consideration of the AIC and BIC statistics, the presence of non-proportional and non-monotonic hazards, and visual inspection of the Cox-Snell residuals.

The estimated median PFS for the GCis + N and GCis arm using a separately fitted Log-Logistic distribution was 5.52 and 4.37 respectively, as compared to the observed median PFS of [redacted] months and [redacted], respectively. The estimated median PFS for GCis is consistent with the PFS reported in the literature by Hoang et al. 2013 (1) for squamous NSCLC of 4.3 months (3.3-6.6 months) (1).

The estimated mean PFS for the GCis + N and GCis arm using a separately fitted Log-Logistic distribution was 7.88 months and 6.85 months respectively. Figure 45 displays the PFS KM curve graphically and Figure 50 displays the Log-Logistic extrapolation to model PFS graphically.

Figure 45 Kaplan Meier Curve for Progression Free Survival

Figure 46 Smoothed Hazard Function

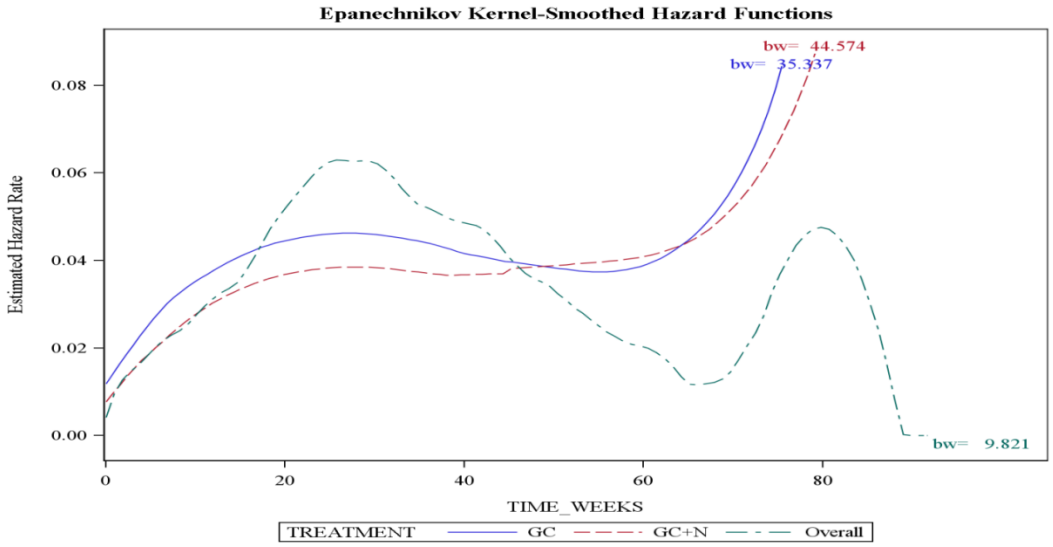


Figure 47 Observed and Predicted Distributions PFS (GCis+N)

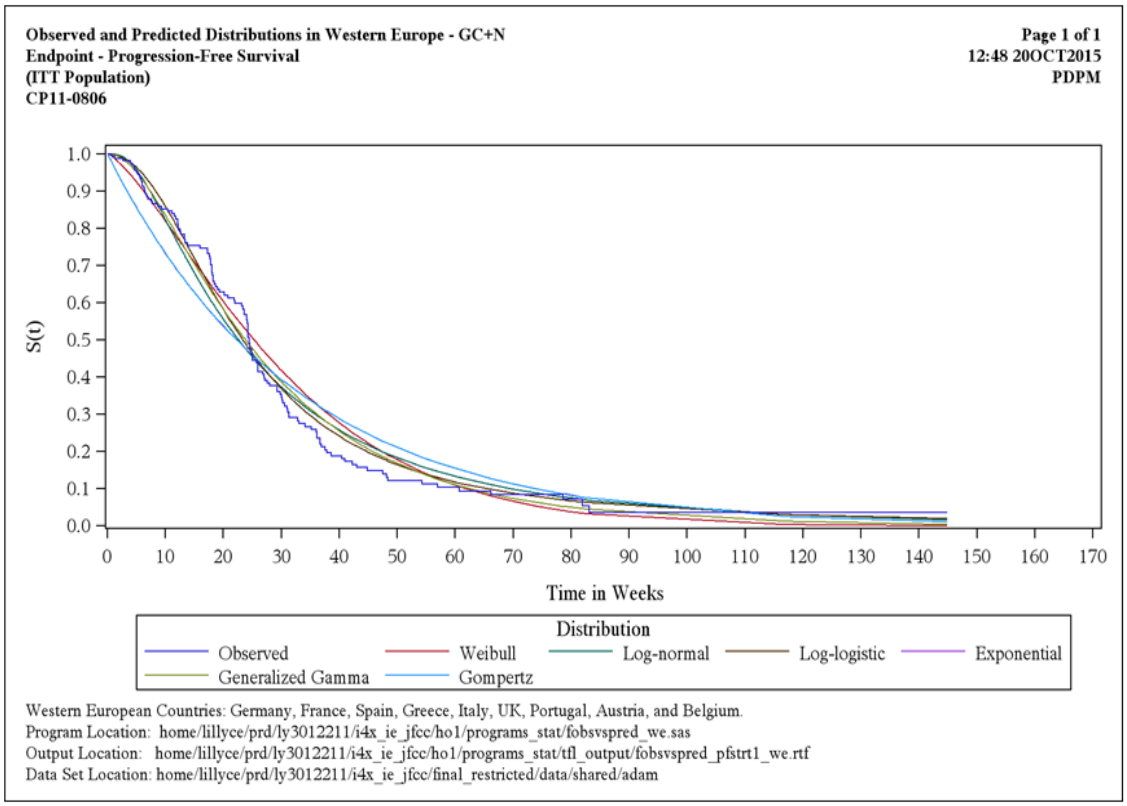


Figure 48 Observed and Predicted Distributions PFS (GCis)

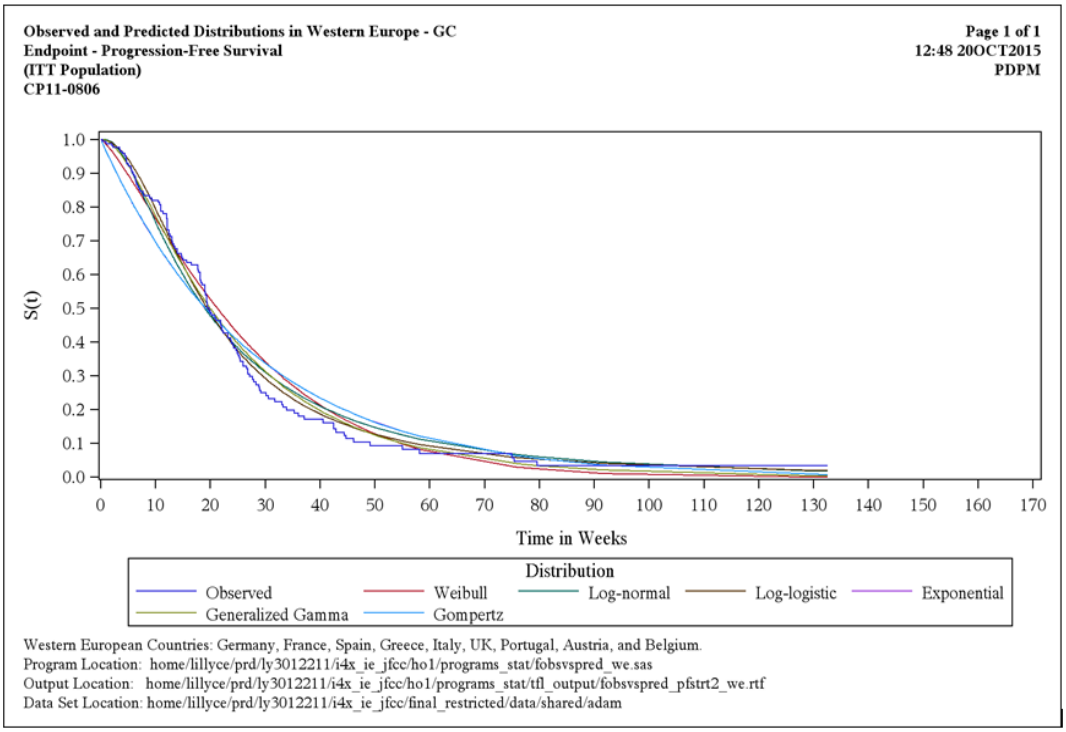
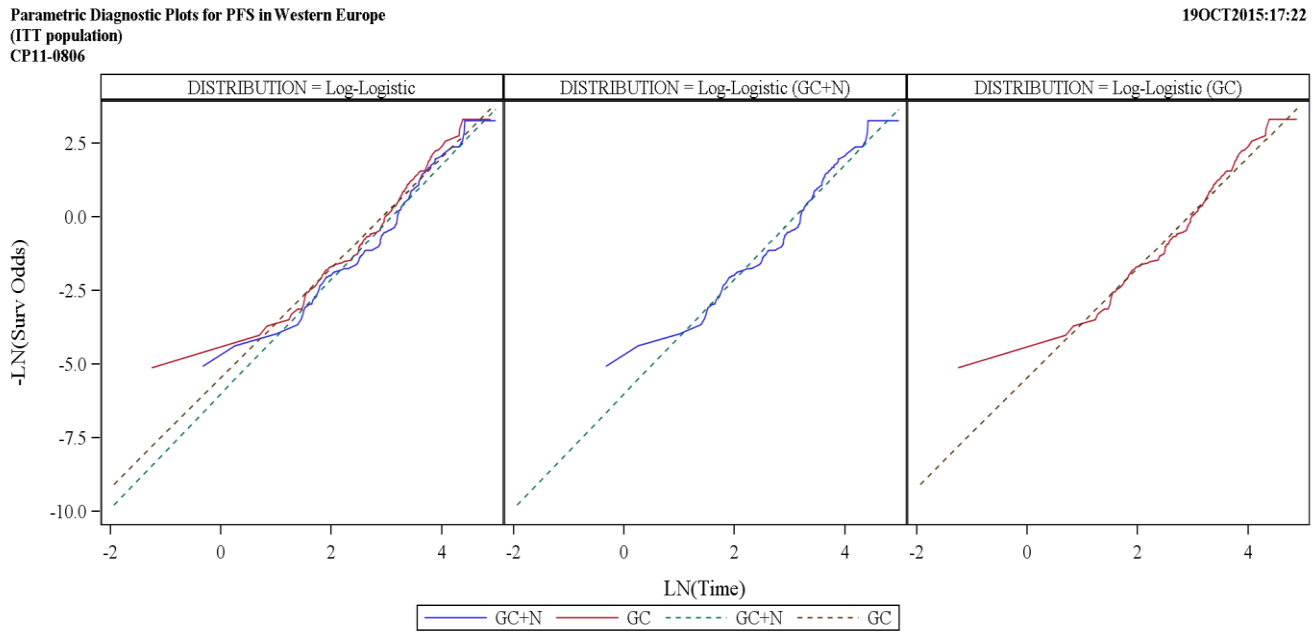


Figure 49 Parametric Diagnostic Plots for Overall Survival - Log-logistic Distribution



Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Figure 50 Separately Fitted Log-Logistic extrapolation of PFS

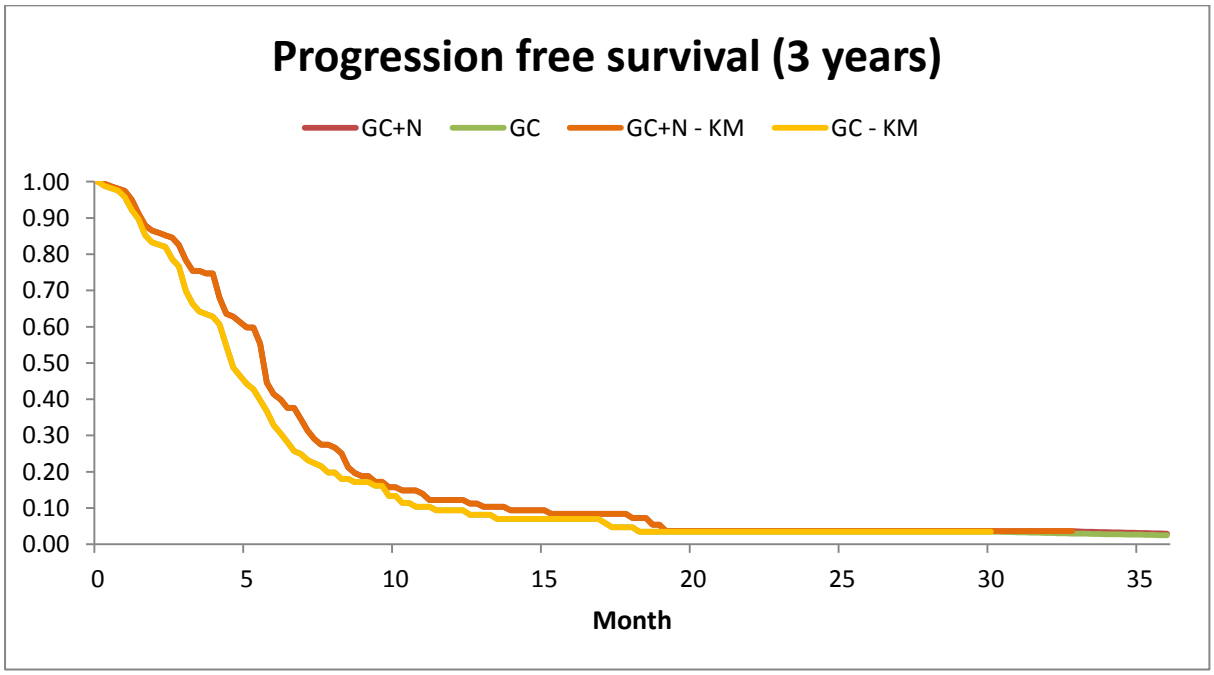


Table 51 Parameter Estimates AIC and BIC – Progression Free Survival

	AIC	BIC
GCis+N		
Weibull	372.143	378.438
Log-normal	368.886	375.181
Log-logistic	358.047	364.342
Exponential	387.61	390.757
Generalized Gamma	365.193	374.635
GCis		
Weibull	399.58	405.921
Log-normal	396.506	402.847
Log-logistic	383.065	389.406
Exponential	409.852	413.022
Generalized Gamma	391.325	400.836

Table 52 Estimated Mean OS and PFS for each parametric survival distribution

Analysis	GCis+N (Mean)	GCis (Mean)	Incremental Difference
PFS			
Weibull	7.20	6.19	1.01
Log-normal	7.56	6.54	1.02
Log-logistic	7.88	6.85	1.03
Exponential	7.33	6.29	1.04
Generalized Gamma	7.32	6.30	1.02
OS			
Weibull	16.61	12.64	3.97
Log-normal	19.12	13.73	5.39
Log-logistic	19.82	14.06	5.76
Exponential	17.41	12.9	4.51
Generalized Gamma	17.39	12.73	4.66

Time to Treatment Discontinuation (TTD) from SQUIRE

For TTD a KM analysis was conducted on the SQUIRE safety population for each drug in the treatment regimen. The safety population included all patients who received at least one dose of the assigned therapy. Patients may discontinue a specific agent and continue to receive the other agents within a treatment regimen. For example, patients in the GCis + N arm could discontinue gemcitabine and continue to receive cisplatin and necitumumab. Moreover, patients may discontinue the treatment of different agents within a regimen at different times, for example due to the occurrence of TEAEs occurring at different times.

Therefore, a clinician may decide that a patient should discontinue receiving one agent while continuing to receive the other agents within the regimen as planned.

Parametric analysis was not conducted as the curves were close to zero by the end of the trial. 99.63% of patients had discontinued GCis and 98.91% of patients discontinued GCis + N by the end of the trial. Patients received up to six cycles of induction therapy, thus there was sharp decline around 18 weeks. However, due to delays in administration, some patients stayed on treatment for longer than 18 weeks as the maximum 6 cycles of treatment was distributed over a longer time period. For patients that continued necitumumab monotherapy, there was not a sharp decline after six cycles. The KM curves for each treatment have been provided in Appendix 13.

None of the studies included in the NMA reported on treatment discontinuation specific to the squamous population. Therefore, the HR of treatment continuation for indirect comparators was assumed to be equivalent to the HR of PFS. PFS was considered the most suitable proxy for continuation of therapy as only progression-free patients can remain on treatment. This assumption has been validated with clinical experts as clinically plausible.

Treatment Duration Adjustment

In the SQUIRE trial, patients experienced delays in administration and treatment holidays, resuming therapy when possible. The delays in treatment may be as a result of patients experiencing AEs or due to patients requesting delays in treatment for personal reasons. As a result of these delays within the trial, a proportion of patients remained in the induction therapy state beyond 18 weeks (i.e. six cycles from the trial start). Without adjusting for these delays in administration, the cost of treatment is overestimated as it is assumed that patients receive treatment in every cycle until they discontinue treatment. Without adjusting for treatment duration, the days of administration estimated by the model is 15.5 days for GCis + N and 8.96 days for GCis. This is an overestimation of the data observed in SQUIRE which found GCis + N was administered 13.6 days and GCis was administered 7.4 days.

In order to adjust for this discrepancy in the model and the observed data, the drug and administration cost were multiplied by a treatment duration adjustment of 0.88 (13.6/15.5) for the GCis + N arm and 0.83 for the GCis arm (7.4/8.96). Treatment intensity for the indirect comparator treatments was assumed to be equivalent to the GCis arm, 0.83.

Efficacy data from Indirect Comparison

To estimate the cost-effectiveness of GCis + N against other relevant comparators not included in the SQUIRE trial, an indirect comparison was performed using a NMA. The HRs for OS and PFS for these comparators versus GCis + N were estimated using the fixed effects model and are detailed in section 4.10.

The HRs from the NMA were applied to the GCis + N OS and PFS survival curve to generate survival estimates for all available comparators (GCis, GCarbo, PCis, PCarbo and DCis) that have been included in the NICE scope for necitumumab with the exception of vinorelbine plus platinum. This appraisal does not include VCis as an indirect comparator because an indirect comparison was not possible due to lack of data specific to squamous NSCLC patients treated with VCis. The HRs from the NMA for all included indirect comparisons was based on studies that consisted of at least 30% of squamous NSCLC patients. Therefore, they are not entirely reflective of the patient population in this evaluation.

As stated in the NICE DSU technical support document 14, a PH assumption is required for indirect comparators if the HR from an indirect comparison is used for the entire modelled period. Therefore, it is most appropriate to use a PH model such as the exponential, Gompertz or Weibull distribution when a HR has been used for the entire modelled period. Log-logistic and log-normal are both accelerated failure time models, thus the PH assumption does not hold (57). As a result, A Weibull model was used to model OS and PFS curves for all indirect comparisons including GCis + N due to it being the best fitting proportional hazard distribution even when it did not provide the best fit due to a constant HR being used for the entire modelled period. Therefore, the results for GCis + N vary between the direct and indirect comparisons due to different distributions used to model OS and PFS curves.

None of the studies included in the NMA reported on treatment discontinuation specific to the squamous population. Therefore, the HR of treatment continuation for indirect comparators was assumed to be equivalent to the HR of PFS. PFS was considered the most suitable proxy for continuation of therapy as only progression-free patients can remain on treatment. This assumption has been explored in the sensitivity analysis.

Incidence and Duration of adverse events

The incidence and duration of AEs for direct comparators were taken from the SQUIRE trial. Treatment emergent grade 3 and 4 AEs, occurring in at least 2.5% of the total patient

population in the SQUIRE trial were included in the economic model. In addition, grade 3 and 4 febrile neutropenia is considered to have important cost and utility consequences, and was therefore also included as well.

To convert the risk of AEs measured over duration of treatment to weekly probabilities, the average duration of induction period on the GCis + N and GCis arms as well as maintenance period for the GCis + N arm was used. This corresponded to 13.60 weeks, 12.80 weeks, and 21.70 weeks respectively.

None of the studies included in the NMA reported AEs specific to the squamous population. In absence of comparative data on AEs, the relative risk of AEs for indirect comparators versus GCis + N was assumed to be equivalent to the relative risk of GCis versus GCis + N. This assumption has been validated with clinical experts.

How transition probabilities were calculated

State transition models allow the use of a partition approach. In the partition approach, transitions between health states are not characterised by transition probabilities from one health state to another. Rather, the distribution of the patient cohort between the different health states was estimated by calculating the area under the respective survival curve in each cycle.

PFS, OS and TTD curves for GCis + N and GCis were derived from the SQUIRE trial. For the indirect comparators, the OS and PFS curves were estimated by applying the HRs from the NMA for indirect comparators versus GC+N. The hazard was then converted to a per cycle risk, which was subtracted from 1 applied to the survival in the previous cycle. This is only possible for PH models, therefore a PH model was assumed for the indirect comparators event if it did not provide the best fit. Once the PFS, OS and TTD curves were estimated for all comparators, the distribution of the patient cohort between the different health states was calculated using the same methodology.

The PFS curve defined the pre-progression disease state, while the post-progression disease state was defined by all surviving patients (OS) less those who remain progression free (PFS); thus, the calculation to determine the patients in the progression state was OS-PFS. The death state was defined as 1-OS. An illustration of how patients transitioned through the health states is in Figure 51.

Figure 51 Illustration of health states derived from OS and PFS curves

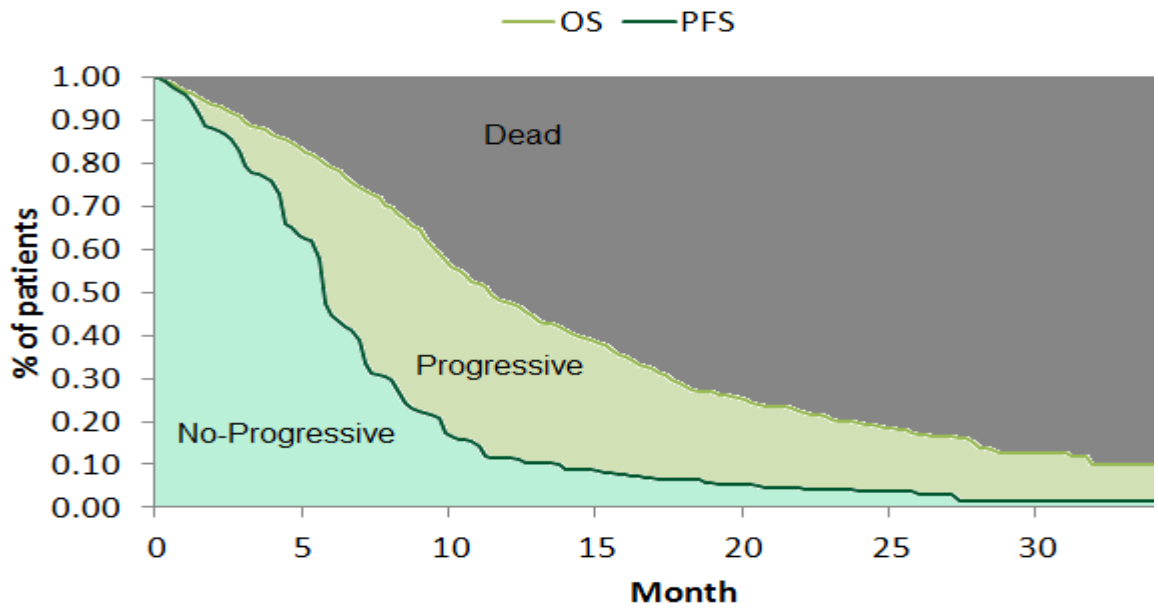


Table 53 summarises how the transitions within the pre-progression health states were calculated. An illustration of how patients transitioned through the treatment states within the pre-progression health state is in Figure 52.

Figure 52 Illustration of treatments stated within the pre-progression health state

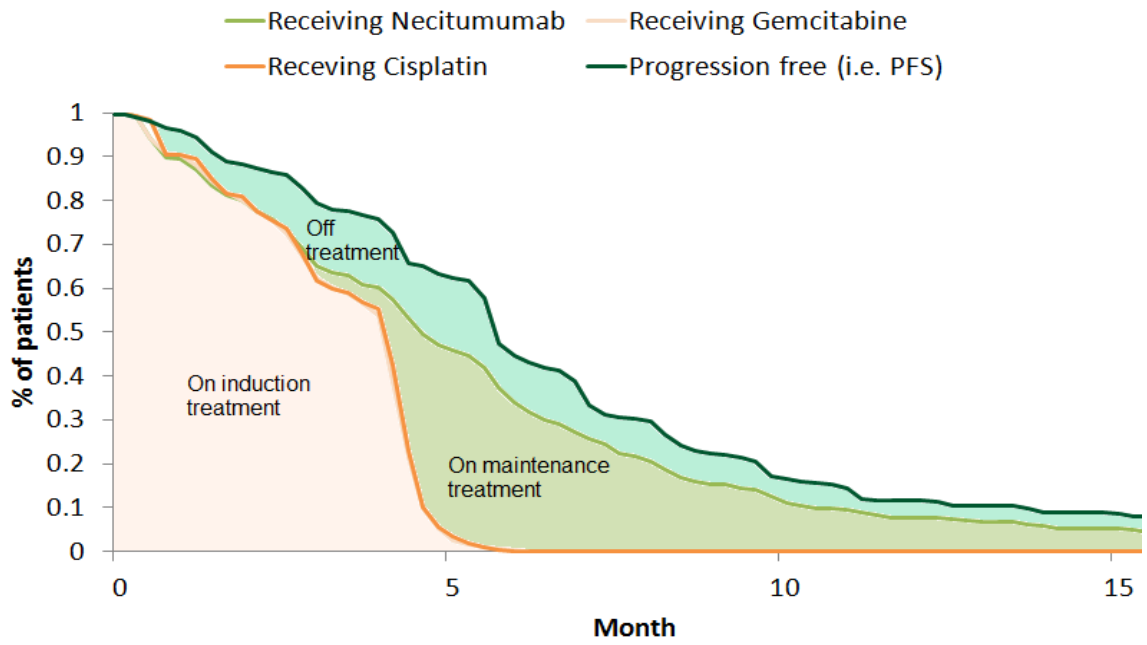


Table 53 Methodology used to determine transitions between health states

Health State	Methodology
PFS-on induction treatment	Derived from the survival curves for TTD for each treatment arm and treatment compound. Defined as the maximum of the proportion of patients receiving gemcitabine or cisplatin and less or equal to the proportion of patients who were progression-free.
PFS-off treatment	Patients that remain progression-free and are not receiving maintenance or induction treatment. This is calculated by subtracting the proportion of patients on treatment from the proportion of patients in the progression-free disease state.
PFS-on maintenance treatment	The proportion of patients on maintenance treatment was estimated as the proportion of patients on treatment minus those on induction treatment.
PD	All patients surviving (OS) minus those who remain progression-free. (OS-PFS)
Death	(1-OS)

Impact on transition probabilities over time

The KM curves and smoothed hazard curves showed that PFS, OS and discontinuation varied over time. This time dependency was taken into account with the partition approach and the use of time dependent parametric and non-parametric survival curves for PFS, OS, and treatment discontinuation.

Adverse event probabilities were not modelled with respect to time. While AEs are likely to be experienced at different stage of treatment, incorporating time variant probabilities was dismissed as almost all patients had discontinued treatment by the end of the trial and as a result, all potential TEAEs were observed.

Clinical Experts

External clinical and economic advisors in the UK were consulted to assess the validity of the clinical assumptions included in the analysis as well as the method of extrapolating OS and PFS from the SQUIRE trial, the validity of the utility values collected during the trial and to validate the resource use associated with locally advanced or metastatic squamous NSCLC in England. An advisory board was attended by four NHS consultant oncologists, three UK academic health economists and two UK academic statisticians. All of the recommendations from the experts have been addressed in this analysis. The discussion guide used during the advisory board has been provided in Appendix 17.

5.4 Measurement and valuation of health effects

HRQoL data from clinical trials

The SQUIRE trial collected HRQOL data using the LCSS and EQ-5D-3L until patients progressed. Only the EQ-5D is relevant for the economic model as it can be used to estimate utility values associated with the health states. EQ-5D assessments in the SQUIRE trial were performed once at baseline, once during each 3-weekly cycle of study chemotherapy and once every 6 weeks until disease progression. The EQ-5D was scored according its scoring manual. Each dimension of the health state profiles (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) included the proportion of patients reporting “no health problems”, “moderate health problems” and “extreme health problems”. A health utility index score for UK patients was calculated using the standard algorithm provided in the manual (60).

The EQ-5D is a standardised and validated generic instrument and the preference elicitation is based on a time trade off algorithm, which corresponds to the NICE reference case.

To estimate utility values, the pre-progression EQ-5D indices based on UK weights was averaged over all assessments and for each treatment phase (i.e., induction treatment, maintenance treatment, and off treatment). This resulted in a pooled mean (SE) utility for the progression free health state on induction treatment of [redacted], a mean (SE) utility for the progression free health state and on maintenance treatment of [redacted] and a pooled mean (SE) utility for the progression free health state and off treatment [redacted]. As the utility values for the health states were assumed to be equivalent across treatment arms, disutility’s for AEs were included to adjust for differences in utility values due to AEs experienced with treatment. See Table 57 for the disutility’s applied.

The EQ-5D utility values for patients on maintenance treatment were slightly higher than in the induction period. This could be due to patients on maintenance therapy no longer receiving cytotoxic agents such as gemcitabine and cisplatin or due to patients experiencing stable disease and tumour shrinkage. The utility values for patients off treatment were lower than patients on maintenance therapy. This could be due to patients experiencing a natural worsening of the disease over time while not receiving active therapy and before progressing.

Mapping

Mapping was not used as pre-progression utilities were available from the SQUIRE trial and no additional HRQOL information was collected post-progression in the SQUIRE trial.

Health-related quality-of-life studies

A systematic literature review was performed to identify utility values for advanced and metastatic NSCLC and to validate the utility values that have been used in the economic model.

The following databases were systematically searched:

- PubMed
- EMBASE (including MEDLINE)
- Cochrane Library
- National Health Service (NHS) Economic Evaluation Database (EED)
- Cost Effectiveness Analysis Registry from the Centre for the Evaluation of Value and Risk in Health
- EconLit

PubMed, EMBASE and the Cochrane library were accessed via the OVID platform. Aside from finding articles in the above databases, Health Technology Assessment, a journal of the National Institute of Health Research (NIHR) was also searched. ASCO and ISPOR conference abstracts as well as NICE ERG reports and ClinicalTrials.gov were manually searched.

The search included all articles published since 2000. The search strategy is included in Appendix 14. Titles and abstracts were screened in accordance with pre-defined inclusion/exclusion criteria in Table 54.

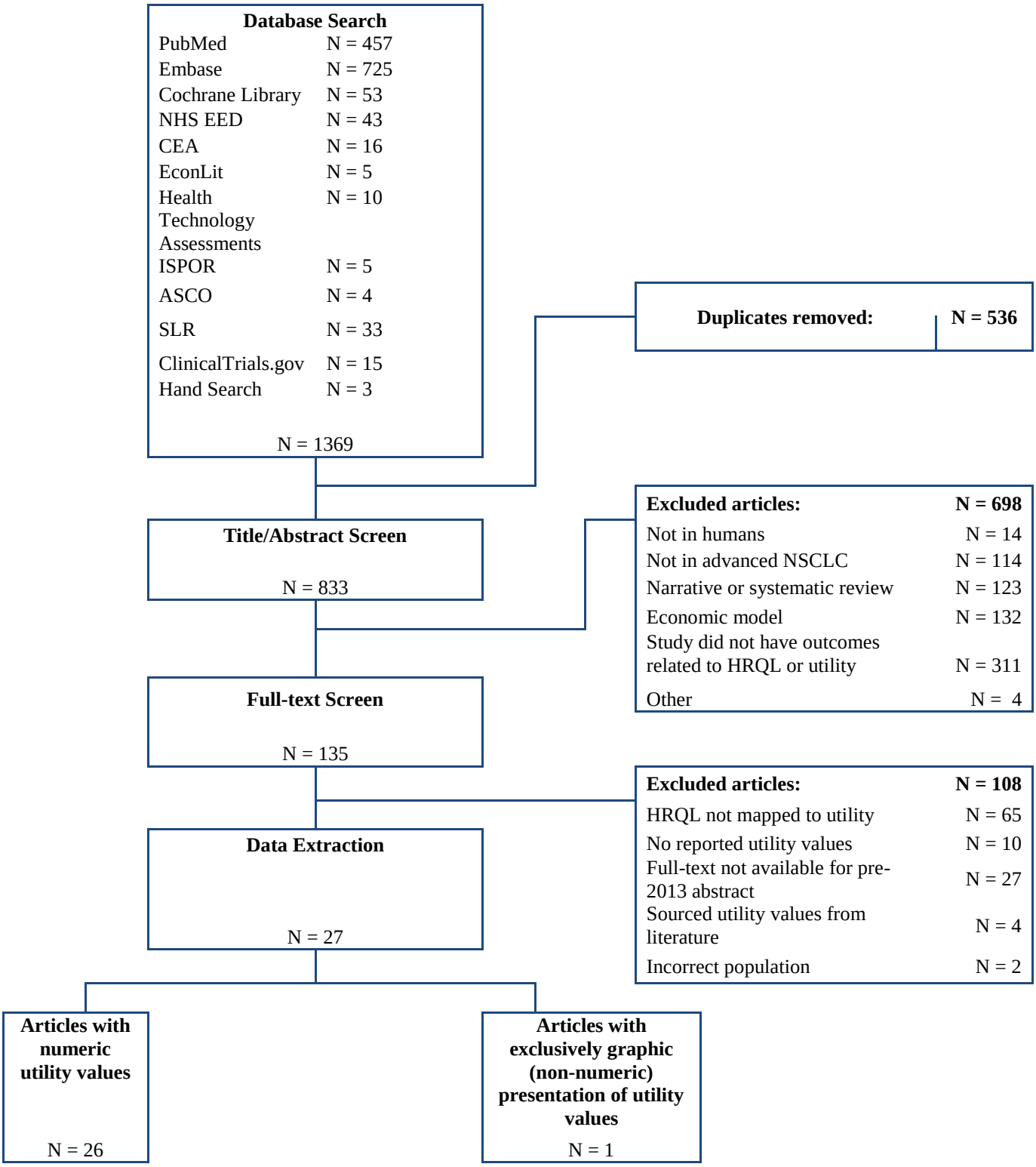
Table 54 Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion criteria
Population	Adult patients with metastatic or advanced NSCLC	Small-cell lung cancer; not advanced or metastatic; stage I, II, III only
Intervention	Not restricted	
Comparator	Not restricted	
Outcomes	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)
Language	English	Non-English
Date	2000 onwards [b]	Prior to 2000 [b]

Notes: 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] 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.[4] 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 year 2013 were excluded.

For those deemed potentially relevant the full publication was retrieved and reassessed using the same eligibility criteria. Studies that did not meet the full inclusion criteria were excluded and their reason for exclusion was documented. The systematic literature review identified 1370 publications. 537 publications were excluded due to being duplicates. A total of 698 references were excluded based on title and abstract. 135 publications were considered to be potentially relevant and underwent full text screening, of which 27 were extracted.

Figure 53 PRISMA Diagram of included and excluded HRQOL publications



Description of identified studies

27 HRQOL publications pertaining to the treatment of NSCLC were identified. Studies were primarily excluded due to HRQOL measurements not being mapped to utility values, not reporting utilities, and economic models or other articles including utility values from the literature. Three articles pertaining to the first-line treatment of squamous NSCLC patients were identified (61) (62) (63). The other articles identified were not considered relevant to necitumumab as they did not provide utilities for squamous NSCLC patients. The utility values from the identified studies have been summarised below.

Table 55 Summary of utility values from literature

Study	**Chouaid et al.2013** (61)	**Iyler et al. 2013** (62)	**Khan et al. 2015**(63)	
Study design	Survey	Observational	Randomised controlled trial	
Histology	Squamous & non-squamous	Squamous & non-squamous	Squamous & non-squamous	
Instrument	EQ-5D	EQ-5D	EQ-5D	
Respondent	Patient	Patient	Patient	
Treatment type	Varies	Varies	Erlotinib	Placebo
All patients		0.63		
Pre-progression	0.71		0.65	0.64
Post-progression	0.67		0.55	0.58

Notes:
AQoL: Assessment of Quality of Life questionnaire; EQ-5D: Euro-Qol 5 Domains; FACT-L: Functional Assessment of Cancer Therapy - Lung.
[a]For Galetta (2012), non-baseline utility values were calculated from the utility differences reported in the literature.

Quality Assessment

The three articles that were identified as relevant to necitumumab have been quality assessed according the NICE TSD for assessment of health state specific utility studies (64). Key criteria used for this quality assessment included sample size, recruitment and response rate. A summary of the quality assessment is in Table 56 below. The quality of assessment of the remaining articles that are not relevant to necitumumab is located in Appendix 16.

Table 56 Relevant Studies for Necitumumab Submission

Study	Population	Recruitment	Sample Size and Response Rate	Description of Health States	Methods of Elicitation, Valuation, and Mapping
Chouaid et al. 2013 (61)	Patients were >18 years with an ECOG status 0-2 and had been receiving care for at least 2 cycles; 17.1% of patients are squamous cell patients.	Patients were enrolled prospectively at a total at 25 hospitals in Australia, Belgium, Canada, France, Italy, Turkey, The Netherlands, Sweden and the UK.	319 enrolled and 56 were excluded	Utility values were reported by treatment line and disease progression	EQ-5D, UK utility weighted algorithm
Iyer et al. 2013 (62)	Receiving first or second line drug treatment for lung cancer in non-clinical trial settings; 29.3% of patients of patients are squamous patients.	Patients were recruited across France and Germany from the ADELPHI NSCLC Disease Specific Programme	1213 eligible and 837 completed the survey	Utility values reported at baseline, by treatment line (first or second) and by country	EQ-5D Utility index, weighted method NR
Khan et al. 2015 (63)	Pathologically confirmed, newly diagnosed stage IIIB/IV NSCLC patients who were chemotherapy naïve and no symptomatic brain metastases and deemed unsuitable for chemotherapy due to ECOG status >=2 and/or multiple comorbidities, including renal impairment	Patients were recruited in the UK for a randomised controlled trial (the TOPICAL Phase III)	670 enrolled and 648 were evaluable	Utility values reported by disease status and treatment (erlotinib vs. placebo) with subgroup analyses by AE (rash)	EQ-5D, UK utility weighted algorithm using TTO

Notes: NR: not reported; BSC: best supportive care; UK: United Kingdom; EQ-5D: Euro-Qol 5 domains; TTO: Time trade-off; ECOG: Eastern Cooperative Oncology Group

Utility values comparison

None of the articles identified in the systematic literature review presented pre-progression utility values by treatment state. Therefore, the pre-progression utility values in the literature capture both the on treatment and off treatment pre-progression utility values from the SQUIRE trial.

The pre-progression utility values from Chouaid et al. 2013 (61) are within the 95% confidence interval of the reported utility values in the SQUIRE trial for patients in the pre-

progression health state while receiving treatment (61). The pre-progression utility values from Khan et al. 2015 (63)are within the 95% confidence interval of the reported utility values in the SQUIRE trial for patients in the pre-progression health state while off treatment (63). All pre-progression utility values obtained from the literature are within the 95% confidence interval of the reported utility values in the SQUIRE trial. Therefore, the utility values within SQUIRE accurately reflect locally advanced or metastatic squamous NSCLC patients. The use of utility values from the literature has been explored in the sensitivity analysis.

The post-progression utility value from Chouaid et al. 2013 (61) is 0.67 (61). The post-progression utility value from Khan et al. 2015 (63)is 0.55 for patients that received erlotinib and 0.58 for patients that received placebo (63). While both Chouaid et al. 2013 (61)and Khan et al. 2015 (63) present pre-progression utility values that are within the 95% confidence interval of the pre-progression utility values from the SQUIRE trial, the use of the post-progression utility values from Khan et al. 2015 (63) is considered more appropriate for this decision problem as it reflects a UK population. The Chouaid et al. 2013 (61) publication consisted of patients in Australia, Belgium, Canada, France, Italy, Turkey, The Netherlands, Sweden and UK.

Adverse reactions

Treatment emergent grade 3 and 4 AEs occurring in at least 2.5% of the total patient population of the SQUIRE trial and grade 3 and 4 febrile neutropenia were included in the economic analysis. It was assumed that AEs that occurred in less than 2.5% of the total patient population would not have a large enough impact on the cost or utilities of either treatment to result in an incremental difference between treatment arms. Utility decrements due to AEs are included in the base case analysis as the effects of AEs on utilities account for potential HRQOL difference s in treatment arms.

Description of identified studies

Of the 27 HRQOL publications pertaining to the treatment of NSCLC, four articles pertaining to the disutility associated with adverse events for NSCLC patients were identified (65) (66) (67) (63). The disutility values from the identified studies have been summarised in Table 57 and a description of each study has been provided in Table 58.

Table 57 Disutility of Adverse Events

Title		Doyle et al. 2008 (65)	Nafees et al. 2008 (66)	Lewis et al. 2010 (67)	Khan et al. 2015 (63)	
Treatment Line		NR	Second-line	Second-line or higher	First-line	
Utility Instrument Used		Interview	Interview	EQ-5D	EQ-5D	
Utility Elicitation Technique		Standard gamble	Standard gamble	VAS	Time trade-off	
Respondent Type		General public	General public	General public	Patient	
Disease State	Adverse Event				Erlotinib	Placebo
Stable	Cough	-0.046				
Stable	Dyspnea	-0.05				
Stable	Pain	-0.069				
Stable	Cough, dyspnea and pain	-0.165				
Stable	Rash		-0.032	-0.051	-0.0075	-0.0245
Stable	Diarrhea		-0.047	-0.131		
Stable	Nausea/vomiting		-0.048	-0.131		
Stable	Neutropenia		-0.09	-0.131		
Stable	Febrile neutropenia		-0.09	-0.261		
Stable	Hair loss		-0.045			
Stable	Fatigue		-0.073	0.0		
Stable	Neuropathy			-0.141		
Stable	Stomatitis			-0.131		
Stable	Anorexia			**0.0**		
Stable	Infection			0.0		
Responding	Rash		-0.033			
Responding	Diarrhea		-0.047			
Responding	Nausea/vomiting		-0.049			
Responding	Neutropenia		-0.09			
Responding	Febrile neutropenia		-0.091			
Responding	Hair loss		-0.045			
Responding	Fatigue		-0.074			
Post-progression	Rash				0.0031	-0.0004

Notes: To aid in comparison across studies, AG calculated all utility decrements associated with adverse events from the utility values provided in the articles.
[a]Disutility of adverse event separated by drug type.

Table 58 Relevant Studies for Necitumumab Submission

Study	Country	Treatment Line	Stage	Squamous/Non-squamous	Study Design
Doyle et al. 2008 (65)	UK	NR	NR	NR	Questionnaire/ Interview
Nafees et al. 2008 (66)	UK	Second-line	Metastatic	NR	Questionnaire/ Interview
Lewis et al. 2010 (67)	UK	Second-line or higher	IIIb/IV	NR	Questionnaire/ Interview
Khan et al. 2015 (63)	UK	First-line	IIIb/IV	Both	Randomised controlled trial

Notes: NR: not reported;

HRQOL data used in the cost-effectiveness analysis

Patients with lung cancer suffer more distressing symptoms than other types of cancer patient (2) and frequently have comorbidities and multiple symptoms such as pain, fatigue, anxiety and depression and breathlessness and cough (3). Increased symptom distress not only has an impact on QoL 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 QoL for patients and their carers; finances, emotional well-being, relationships with friends and family and employment are all adversely affected (3).Thus therapies are evaluated not only on their effect on OS but also PFS and impact on QoL. The impact on HRQOL of adding necitumumab to gemcitabine and cisplatin for patients with locally advanced or metastatic squamous NSCLC has been measured by calculating utility values using the EQ-5D-3L and values published in the literature.

Table 59 presents the utility values that have been used in the cost-effectiveness analysis. Pre-progression pooled utilities were obtained from the SQUIRE trial. Please refer to section 5.4.1 for the methodology of how they were calculated. Post-progression utilities were obtained from the literature as the SQUIRE trial only conducted EQ-5D assessments until disease progression. For the post-progression health state, the value of 0.55 from Khan et al. 2015 (63) was utilised. Within the post-progression health state, patients are assumed to have the same utility independent of treatment lines.

The Khan et al. 2015 (63) value for post-progression health state following first-line treatment with erlotinib was chosen due to it being reflective of a patient progressing following treatment until progression, similar to necitumumab. In addition, the values were obtained from the EQ-5D and were valued using UK weights. Therefore, they have been considered the most appropriate values from the literature for the post-progression health

state for this analysis. However, The use of these values provide a conservative estimate due to the patients in the Khan et al. 2015 (63) study being stage IIIb/IV NSCLC patients that are unfit for chemotherapy with an ECOG PS of >2.

The utility values are assumed to be constant over time in each health state. The assumption of constant utility values is valid due to the weighted average utility being calculated for each treatment phase (on induction treatment, on maintenance treatment and off treatment). Therefore, any fluctuations in HRQOL over time have been captured in the respective health states.

The literature identified in the review presented utility values for all patients irrespective of health, pre-progression, post-progression and AEs. These health effects have been accounted for in the analysis with the exception of all patients irrespective of health state. These utility values have not been included in the analysis as it would not be reflective of any health states in the cost-effectiveness model.

Clinical experts have confirmed the applicability of the utility values in this evaluation and the separation of the pre-progression health state into several treatment states.

Table 59 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Utility Value: standard error	95% confidence interval	Reference in submission (section and page number)	Justification
Pre-progression and on induction treatment	[redacted]	[redacted]	[redacted]	5.4 Pg. 166	Trial based pooled utilities were used where available to reflect the HRQOL of the specific patient population
Pre-progression and on maintenance treatment	[redacted]	[redacted]	[redacted]	5.4 Pg.166	Trial based utilities were used where available to reflect the HRQOL of the specific patient population
Pre-progression and off treatment	[redacted]	[redacted]	[redacted]	5.4 Pg. 166	Trial based pooled utilities were used where available to reflect the HRQOL of the specific patient population
Post-progression	0.55	0.016	(0.52, 0.58)	5.4 Pg. 166 and Pg. 174	In the absence of trial based utilities, Khan et al.2015 values for PD have been used due to the utility values being reflective of patients progressing following first-line treatment using the EQ-5D with UK weights. (63)

Table 60 Summary of utility decrements for cost-effectiveness analysis

	Disutility	SE	Source	Duration	Source
Neutropenia	-0.0897	0.0154	Nafees et al. 2008(66)	7 days	NICE TA162 (34)
Anaemia *	-0.0735	0.0185	Nafees et al. 2008(66)	7 days	NICE TA162 (34)
Thrombocytopenia **	-0.0897	0.0154	Nafees et al. 2008(66)	7 days	Assumption
Hypomagnesaemia***	-0.0325	0.0117	Nafees et al. 2008(66)	12.3 days	Assumption
Pulmonary embolism****	-0.3200	0.1189	Locadia et al. 2004 (68)	30.4 days	Locadia et al. 2004(68)
Asthenia	-0.0735	0.0185	Nafees et al. 2008(66)	7 days	Assumption
Leukopenia	-0.0897	0.0154	Nafees et al. 2008(66)	7 days	Assumption
Skin rash	-0.0325	0.0117	Nafees et al. 2008(66)	12.3 days	NICE TA310 (69)
Fatigue	-0.0735	0.0185	Nafees et al. 2008(66)	32. days	NICE TA310 (69)
Nausea*	-0.0480	0.0162	Nafees et al. 2008(66)	3 days	NICE TA181 (70)
Vomiting*	-0.0480	0.0162	Nafees et al. 2008(66)	3 days	NICE TA181 (70)
Febrile neutropenia	-0.0900	0.0163	Nafees et al. 2008(66)	7 days	NICE TA162 (34)
Pneumonia	-0.0735	0.0185	Nafees et al. 2008(66)	7 days	NICE TA310 (69)
Hypokalaemia	-0.0735	0.0185	Nafees et al. 2008(66)	7 days	NICE TA310 (69)
Hypernatremia	-0.0735	0.0185	Nafees et al. 2008(66)	7 days	NICE TA310 (69)
Dyspnoea	0.050		Doyle 2008 (65)	7 days	Doyle 2008 (65)

Notes: * assumed same as fatigue; ** assumed same as neutropenia; *** Assumed equal to febrile neutropenia based on UK clinical expert opinion

5.5 Cost and healthcare resource use identification, measurement and valuation

Parameters included in cost-effectiveness analysis

In line with recent NICE technology appraisals of NSCLC treatments, the range of cost inputs considered in the economic model include:

- Drug acquisition cost
- Drug administration cost
- Disease monitoring and supportive care
- Treatment for adverse events
- End-of-life care

Resource use for disease monitoring and supportive was obtained from a retrospective medical chart review and validated by expert opinion. Resource use for treatment of AEs and end-of-life care was obtained from Brown et al. 2013 (6). Unit costs were derived from the NHS Reference Cost, PSSRU, EMIT, and BNF. NHS reference costs were used for outpatient administration of chemotherapy, medical oncology outpatient appointments, palliative care specialists, biochemistry tests, CT scans, Chest X-rays, radiation therapy, RBC transfusions, hospitalisations and Accident and Emergency outpatient visits. PSSRU was used for GP visits, clinical nurse specialists, GP home visits and community nurse visits. EMIT was used for all pharmacological treatments with the exception of erlotinib and dietary supplements, which were obtained from BNF. Clinical experts have confirmed the resource use assumptions in this evaluation.

Resource identification, measurement and valuation studies

A systematic literature review for resource use data in the UK was conducted. The search strategy built upon the search strategies conducted as part of the erlotinib STA submission in June 2011 (TA258) (71) and updated as part of the crizotinib STA submission in June 2012 (TA296) (72) related to advanced or metastatic lung cancer.

Medline, Medline In Process and EMBASE were searched using the OVID platform. An expanded strategy was adopted for the NHS EED and NICE technology appraisals. For the update of the resource use systematic literature review, the date limits were restricted to 2012 onwards to account for the time elapsed since the searches performed for erlotinib and crizotinib.

Titles and abstracts were screened in accordance with pre-defined inclusion/exclusion criteria included in Table 61.

Table 61 Resource use SLR inclusion and exclusion criteria

Population	**Adult patients with metastatic or advanced lung cancer**
Interventions	Any
Comparators	Any
Outcomes	Resource use from a UK NHS perspective
Study Design	Any
Exclusion Criteria	• Not in metastatic/advanced lung cancer • Not UK specific • Not regarding resource use • Publications prior to 2012

For those deemed potentially relevant the full publication was retrieved and reassessed using the same eligibility criteria. Studies that did not meet the full inclusion criteria were excluded and their reason for exclusion was documented. The updated search (i.e. 2012-September 2015) for advanced or metastatic lung cancer identified 102 publications. Following the removal of duplications, 100 publications were screened for eligibility. 13 publications were considered to be potentially relevant and underwent full text screening, of which 9 were extracted. This includes four full text publications: Brown et al. 2013 (6), Greenhalgh et al.2015 (73), Walleser et al. 2012 (74), and Westwood et al. 2014 (75). Five NICE STAs were also identified: TA258 (71), TA296 (72), TA309 (76), TA310 (69), TA347 (77).

The original review for NICE TA258 identified 93 individual records across the five databases searched. Twelve publications were identified for full text screening of which seven were found to be relevant. This includes two full publications: Lewis et al. 2010 (67) and Maslove et al. 2005 (78). Five NICE STAs were also identified; TA162 (34), TA190 (79), TA181 (70), TA192 (80) with NICE TA227 (81) not being identified in the initial search but added later.

The updated review for NICE TA296 was time restricted to identify articles published between 2011 and 2012. The updated search identified 114 individual records across the five databases searched. 18 publications were identified for full text screening of which three full publications were found to be relevant: Califano et al. 2011(82), Chamberlin et al. 2011(83) and Dickson et al. 2011(84).

A total of 19 records (seven identified in the original review for NICE TA258, three identified in the updated review for NICE TA296 and nine in the review conducted for this appraisal) were extracted. These include 10 NICE STAs: TA162 (34), TA181 (70), TA190 (79), TA192 (80), TA227 (81), TA258 (71), TA296 (72), TA309 (76), TA310 (69) and TA347 (77). 9 publications were also identified: Maslove et al. 2005 (78), Lewis et al. 2010 (67), Califano et al. 2011 (82), Chamberlin et al. 2011 (83), Dickson et al. 2011 (84), Walleser et al. (74)(74), Brown et al. 2013 (6), Westwood et al. 2014 (75) and Greenhalgh et al. 2015 (73). 0, Table 63 and Table 64 summarise the objectives and valuations methods used to derive cost estimates for economic analyses in the identified studies.

While all of the studies were conducted in the UK and are thus applicable to clinical practice in England, none of the studies presented squamous specific data. Due to squamous NSCLC patients typically suffering from several comorbidities and being diagnosed at a later stage in the disease than non-squamous NSCLC patients, it is assumed that the resource use for these different patient populations vary. Therefore, the relevance to the decision problem for necitumumab is limited.

Figure 54 PRISMA Flow-chart of economic evaluation search

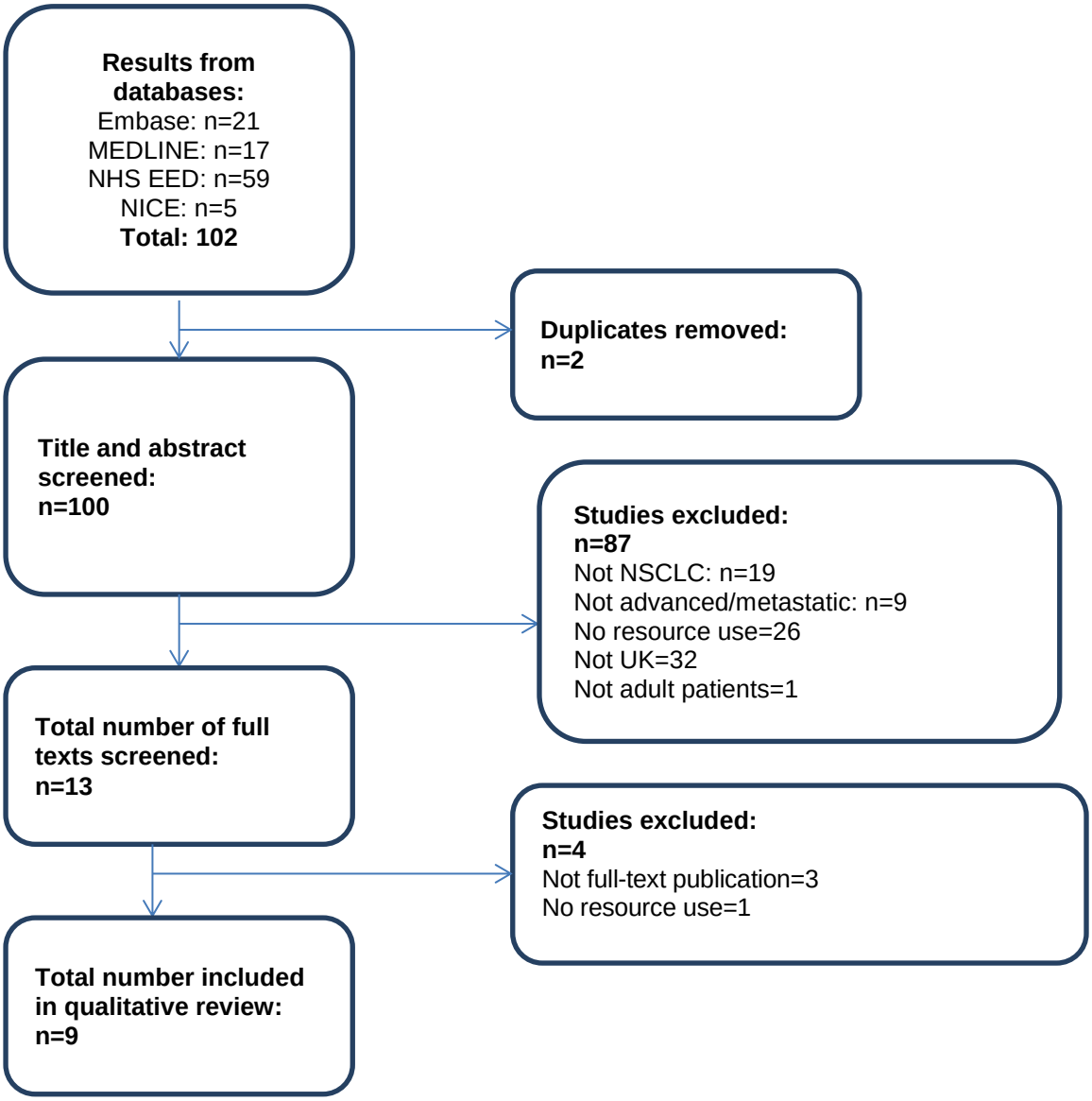


Table 62 Studies identified in NICE TA258

Study	Country	Date	Objective	Cost valuation used	Cost for use in economic analysis	Technology Cost
TA227(81)	UK	2010	To assess the cost-utility of erlotinib for the first-line maintenance treatment of NSCLC in three patient populations from UK NHS perspective	**Pharmacy costs:** - BNF (2009) **Administration costs:** - NHS Reference cost (2009) - NCAT (2009)(resource use); CPORT 2009 **Health state costs:** - Physicians opinion as in TA162 (resource use) - Costs in TA162 inflated to PSSRU (2009) - BNF (2009) **Adverse events:** - Costs in TA162 inflated to PSSRU (2009) - Eli Lilly (2009)	- Pharmacy costs: - Administration costs: - Health state costs: - Adverse events:	Costs reported: - Erlotinib 150 mg
TA192(80)	UK	2010	To assess the cost-utility of gefitinib compared with doublet chemotherapy in the first-line treatment of patients with NSCLC with EGFR-TKI from UK NHS perspective	**Pharmacy Cost:** - NHS Reference cost (2008) **Administration costs:** - NHS Reference cost (2008) - BNF (2009) **Health state costs:** - Clegg (2002) inflated to 2007/2008 - Erlotinib ERG report (2006) inflated to	- Administration costs - Administration costs - Health state costs - Adverse events	NR*

				2007-08 **Adverse events:** - Erlotinib ERG report (2006) - Erlotinib ERG addendum (2007) - STA Pemetrexed (2009) Patient monitoring costs: - NHS Reference cost (2008)		
TA190 (79)	UK	2010	To assess the cost-utility of pemetrexed as the maintenance treatment of NSCLC from UK NHS perspective	**Pharmacy costs:** - MIMS (2009) **Administration costs:** - NHS Reference costs (2009) **Health state costs:** - NICE/University of Sheffield (2004) estimates inflated based on data in PSSRU (2008) **Adverse events:** - Survey of clinical experts - Duran et al. 2008 - Hanna et al. 2004	- Pharmacy costs - Administration costs - Health state costs - Adverse events	Costs reported: - Docetaxel 20 mg - Docetaxel 80 mg - Erlotinib 150 mg

TA181 (70)	UK	2009	To assess the cost-utility of pemetrexed in combination with cisplatin for the first-line treatment of NSCLC from UK NHS perspective	**Pharmacy costs:** - BNF (2008) **Administration costs:** - NHS Reference cost (2008) **Health state costs:** - NICE (2005b) inflated to 2007 costs **Adverse events:** - Duran et al. 2008 - Paul et al. 2006 inflated to 2006/07 using PSSRU (2008)	- Pharmacy costs - Administration costs - Health state costs - Adverse events	Costs reported: - Docetaxel 20 mg - Docetaxel 80 mg
TA162 (34)	UK	2008	To assess the cost-utility of erlotinib in relative to docetaxel as the treatment for relapsed NSCLC from UK NHS perspective	**Pharmacy costs:** - BNF (2006) **Administration costs:** - Physicians opinion **Health state costs:** - Physicians opinion (resource use) - PSSRU - BNF (2006) - NHS Reference cost 2004 **Adverse events:** - Physicians opinion (resource use) - PSSRU (2004) - BNF (2006) - NHS Reference cost (2004)	- Pharmacy costs - Administration costs - Health state costs - Adverse events	Costs reported: - Docetaxel 20 mg - Docetaxel 80 mg - Erlotinib 150 mg

Maslove et al. 2005 (78)	UK	2005	A costing study that aimed to evaluate the cost of chemotherapy on the UK NHS. This costing study was based on the retrospective collection of resource use data from hospital records	Pharmacy costs: - BNF (2000 Administration costs: - English Trust Financial Returns (1999/2000) Hospitalisation (medical & oncology): - English Trust Financial Returns (1999/2000) Outpatient costs: - English Trust Financial Returns (1999/2000) Hospice inpatient care: - English Trust Financial Returns (1999/2000) Primary care, GP/Nurse: - PSSRU (2000)	- Administration costs - Hospitalisation (medical & oncology) - Outpatient costs - Hospice inpatient care - Primary care, GP/Nurse	NR

Table 63 Studies identified in NICE TA296

Study	Country	Date	Objective	Cost valuation used	Cost for use in economic analysis	Technology Cost
Califano et al. 2011 (82)	UK	2011	To identify which dose can be safely given to PS2 chemo-naïve patients with stage III (unsuitable for radical treatment) and stage IV NSCLC and to obtain preliminary efficacy data	Resource use estimates: - As observed in DOC PS2 trial	Resource use: - Hospitalisation - Antibiotics - Transfusions	NR
Chamberlin et al. 2011 (83)	UK	2011	To assess the quality of EGFR mutation testing, and to obtain data regarding those patients who had tested positive in order to improve local policy through a retrospective audit	Diagnostic costs: EGFR mutation test - As observed in 9 NHS trusts	-Diagnostic costs	NR

Table 64 Studies identified in the updated review (2012-2015)

Study	Country	Date	Objective	Cost valuation used	Cost for use in economic analysis	Technology Cost
Greenhalgh et al. (73)	UK	2015	To appraise the clinical effectiveness and cost-effectiveness of erlotinib [Tarceva®, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca) compared with each other, docetaxel or best supportive Care (BSC) for the treatment of NSCLC after disease progression following prior chemotherapy. The effectiveness of treatment with gefitinib was considered only for patients with epidermal growth factor mutation-positive (EGFR M+) disease.	Pharmacy Cost: BNF (2013); Administration cost: PSSRU (2011), Health state cost: Physicians opinion used in TA162. Cost in TA162 inflated using NHS Reference Cost 2011/2012, PSSRU 2011, BNF 2012, emit. Adverse events: Cost from TA162 inflated using reference cost 2011/2012, PSSRU 2011, BNF2012, emit.	Pharmacy Cost, drug cost, health state cost, adverse events	Docetaxel and Gefitinib
Walleser 2012 (74)	UK	2012	To assess the cost-effectiveness of first-line maintenance erlotinib specifically in EGFR wild-type metastatic NSCLC.	Pharmacy Cost: (BNF 58) Adverse events: Cost determined by expert interviews	Drug cost, adverse events	erlotinib, docetaxel

Westwood 2014 (75)	UK	2014	To compare the performance and cost-effectiveness of EGFR-TK mutation tests used to identify previously untreated adults with locally advanced or metastatic NSCLC, who may benefit from first-line treatment with TKIs.	Pharmacy Cost: (TA192, Brown 2010-ERG report); administration cost: Reference Cost 2012, transportation cost: PSSRU adverse events: PSSRU BSC: PSSRU	Drug Cost, Administration Cost, Transportation Cost, Adverse Events, BSC	Pemetrexed and Cisplatin
TA 258 (71)	UK	2012	To assess the cost-utility of Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC	Pharmacy Cost: NICE TA227 Administration Cost: Pharmacist time dispensing medication (PSSRU 2010) Health State Cost: Resource obtained from TA227, TA181, and TA190. This includes palliative care cost from 2004 report by University of Sheffield, CT assessment every 3 months. Adverse Event Cost: TA192	Pharmacy Cost, Administration Cost, Health State Cost, Adverse Events	Erlotinib, Gefitinib

TA296 (72)	UK	2013	To assess the cost-utility of Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.	Pharmacy costs: - BNF Administration costs: - NHS Reference cost 2010-2011 Health state costs: - Physician Opinion used in TA162 and TA258 (resource use) -PSSRU (2011) NHS Reference Cost 2010-2011 Lewis et al. 2010 Adverse events: BNF	Drug Cost, Administration Cost, Health State Cost, adverse events	Crizotinib, Docetaxel, Pemetrexed
TA309 (76)	UK	2014	To assess the cost-utility of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous NSCLC.	Pharmacy Cost: BNF (2012) Administration Cost: -NHS Reference Cost 2011-2012 Health State Cost: -Adapted from TA190 Adverse Events: Costs inflated from TA190	Drug Cost, Administration Cost, Health State Cost, Adverse events	Pemetrexed, Docetaxel, Erlotinib
TA310 (69)	UK	2014	To assess the cost-utility of afatinib in treating epidermal growth factor receptor mutation-positive (EGFR M+) locally advanced or metastatic non-small-cell lung cancer	Pharmacy costs: - BNF (2011) Administration costs: - NHS Reference cost (2013) Health state costs: - LUX-LUNG 3 (resource use) -PSSRU (2011) Lewis et al. 2010 Adverse events: Redacted	Drug Cost, Administration Cost, Health State Cost, Adverse Events	Gefitinib, Erlotinib, Afatanib

TA347 (77)	UK	2015	To assess the cost-utility of nintedanib for previously treated locally advanced, metastatic, or locally recurrent non−small−cell lung cancer	Pharmacy costs: - BNF (2013) Administration costs: - NHS Reference cost (2013) Health state costs: - expert opinion with questionnaire (resource use) -NHS Reference Costs (2012-2013) -PSSRU (2012) Adverse events: -expert opinion (resource use) -NHS Reference Cost (2012-2013) -PSSRU (2012)	Drug Cost, Administration Cost, Health State Cost, Adverse Events	Nintedanib, Docetaxel, Erlotinib, Carboplatin, Vinorelbine

Retrospective Medical Chart Review

Of the 19 studies pertaining to the UK resource use for adult patients with locally advanced or metastatic lung cancer, no studies presented specific resource use for first-line treatment of squamous NSCLC. Therefore, a retrospective medical chart review was conducted to assess treatment patterns among patients receiving first-line treatment with a platinum based doublet regimen for metastatic squamous NSCLC in the UK.

The retrospective medical chart review provides estimates for disease monitoring and supportive care. These estimates were validated by expert clinical opinion. The resource use associated with treatment for AEs and end-of-life care was obtained from the literature due to not being collected as part of the chart review.

The systematic literature review identified Brown et al. 2013 (6) as a UK relevant source for cost and resource use associated with NSCLC. However, the Brown et al. 2013 (6) article does not present squamous NSCLC resource use. Due to squamous NSCLC patients typically suffering from several comorbidities and being diagnosed at a later stage in the disease than non-squamous NSCLC patients, it is assumed that the resource use for these different patient populations vary.

Therefore, the retrospective medical chart review has been supplemented by the resource use and cost in Brown et al. 2013 (6) for data not collected as part of the retrospective medical chart review.

The methods of the retrospective medical chart review are in Table 65.

Table 65 Retrospective medical chart review methodology

objective	To assess treatment patterns among patients with a diagnosis of metastatic squamous NSCLC and who are receiving first-line treatment with a platinum-based doublet regimen in the UK.
Study design	This study was carried out using a retrospective, non-interventional observational review of medical records for patients with a confirmed diagnosis of metastatic squamous NSCLC (i.e., Stage IIIB with pleural effusions according to the 6th edition of the AJCC guidelines or Stage IV according to the 6th or 7th edition of the AJCC guidelines; or initially diagnosed with a more limited stage and progressed to metastatic disease). In this study, physicians served as the direct data abstractors, allowing for efficient and accurate interpretation of their own notes and records. Participating physicians selected patients who met the screening criteria and abstracted the requested data elements which existed in the patient's chart at the time of abstraction. Physicians then entered the abstracted data into a web-based DCF, which was compiled into a patient-level analytic file. As patient chart data may contain highly sensitive and private personal health information, only anonymous data were collected for use in this study. The patient's physician was the only entity who had access to potentially sensitive patient data.
Sample size	Due to the retrospective, descriptive nature of this study, the study size was not based on formal statistical considerations. A sample of 54 physicians in the UK participated in the study with 203 patients in the UK.
Physician Selection	Physicians recruited to perform the patient-level medical record abstractions must have been located in the UK, with A case load of at least 6 patients with metastatic squamous NSCLC treated in the past 12 month. They must have also been in practice for 5 to 30 years after completion of formal training or board certification and a medical specialty of medical oncology, clinical oncology, haematology-oncology, pulmonology, or internal medicine specialized in pulmonology.
Patient Selection	The patients must have a confirmed diagnosis of metastatic squamous NSCLC, Aged at least 18 years on the date of diagnosis of metastatic squamous NSCLC, initiated systemic treatment after diagnosis of metastatic disease with a platinum-based doublet regimen (i.e., cisplatin or carboplatin in combination with another agent) and stopped first-line systemic treatment and stopped maintenance therapy (if any maintenance therapy was received after first-line treatment). Maintenance therapy was defined as either the continuation of one first-line therapy agent or a switch to another single agent before any disease progression occurred.
Outcomes Measured	Overall treatment patterns, systematic therapy and supportive care

Cost identification

The sources of unit costs were based on previous NICE STAs on NSCLC and have been considered appropriate for the costing of treatment provided in the NHS.The unit cost for all resource items were obtained from the most recent publication of NHS Reference Cost

(2013/2014) (85), EMIT (December 2014) (86), BNF 68 (2015) (87) and PSSRU (2014) (88). These sources of unit costs reflect how treatment for NSCLC is currently valued in the NHS and have been used extensively in previous NICE submission for NSCLC. Unit cost from previous years was inflated to present values. Clinical experts have validated the resource use estimates for disease monitoring, supportive care, treatment of adverse events and end-of-life care.

Intervention and comparator's cost and resource use

The cost associated with each treatment consists of drug acquisition costs and outpatient administration of the treatment.

The acquisition cost of each treatment is presented in Table 66 and Table 67. The acquisition costs for treatments were obtained from EMIT (86) and BNF (87). Patients are assumed to receive treatment as a day case outpatient appointment based on previous literature and clinical expert opinion (6). The first administration is associated with NHS Reference Code SB14Z for delivery of complex chemotherapy at first attendance. Subsequent infusions are associated with NHS Reference Code SB15Z for delivery of subsequent elements of a chemotherapy cycle. Costs associated with treatment and administration is applied until a patient discontinues first-line treatment.

Once discontinuing first-line treatment, patients are either off treatment or receiving second-line therapy after confirmed progression. The subsequent treatments do incur additional acquisition and administration cost. The cost is applied as one-off cost at the time of progression. The use and duration of subsequent therapies by first-line treatment was derived from the SQUIRE trial. The use and duration of subsequent treatments for indirect comparators were assumed to be equivalent to those observed in the GCis arm.

Within the SQUIRE trial, approximately half of patients on both treatment arms received second-line therapy after confirmed progression (47.3% in the GCis + N arm and 44.7% in the GCis Arm). The therapy received was reasonably balanced between the treatment arms, with the exceptions of docetaxel (30.6% in the GCis + N arm vs. 23.2% in the GCis arm) and erlotinib (10.5% in the GCis + N Arm vs. 13.7% in the GCis Arm). Hence, approximately 65% of patients in the GCis + N arm and 52% in the GCis arm receive docetaxel as a second-line therapy. Approximately 22% of patients in the GCis + N arm and 31% in the GCis arm receive erlotinib as a second line therapy. Within the SQUIRE trial, patients also received gemcitabine and vinorelbine monotherapy, which is not clinical practice in England.

Therefore, it has been assumed in the model that patients that receive subsequent treatment following progression on first-line therapy either receive docetaxel or erlotinib. Based on market research, approximately 70% of squamous NSCLC patients receive docetaxel and 30% receive erlotinib second-line (35).

While the second-line therapies in the model vary from the therapies used in SQUIRE, it was considered inappropriate to use treatments in the model that are not used in clinical practice in England. It has been assumed that choice of 2nd line therapy has no impact on the clinical efficacy outcomes of GCis + N vs GCis (see Table 1). It has also been assumed that no patients receive third-line therapies for squamous NSCLC in the NHS. Therefore, the model assumes that patients receive BSC following the discontinuation of active second-line therapy.

Cycle length and number of administrations for each subsequent therapy was obtained from the appropriate SPCs for each comparator.

Table 66 Technology Cost

Regimen	Technology	Recommended Dose	Cycle Length	Unit Cost	Source
GCis+N	Necitumumab	800 mg on Days 1 and 8	3 weeks	800mg vial=£1,450 [redacted]	
	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	EMIT December 2014(86)
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	EMIT December 2014 (86)
GCis	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	EMIT December 2014(86)
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	EMIT December 2014(86)
GCarbo	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	EMIT December 2014(86)
	Carboplatin	400 mg/m^2 on day 1	3 weeks	450mg/45ml=£19.07; 150mg/15ml=£7.71; 50mg/5ml=£3.51	EMIT December 2014(86)
PCarbo	Paclitaxel	175 mg/m^2	3 weeks	150mg/25ml=£12.71; 30mg/5ml=£3.78	EMIT December 2014(86)
	Carboplatin	400 mg/m^2 on day 1	3 weeks	450mg/45ml=£19.07; 150mg/15ml=£7.71; 50mg/5ml=£3.51	EMIT December 2014(86)
DCis	Docetaxel	75 mg/m^2	3 weeks	80mg/ml=£25.73; 20mg/1ml=£7.45; 140mg/7ml=£54.60	EMIT December 2014(86)
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	EMIT December 2014(86)

Table 67 Second-line technology cost

Regimen	Technology	Recommended Dose	Cycle Length	Unit Cost	Source
D	Docetaxel monotherapy	75 mg/m^2	3 weeks	80mg/ml=£25.73; 20mg/1ml=£7.45; 140mg/7ml=£54.60	EMIT December 2014(86)
E	Erlotinib monotherapy	150 mg	3 weeks	25mg=£378; 100mg=£1,324; 150mg=£1,632 *All strengths are provided as 30 tablets	BNF 68 March 2015(87)

Note: The Unit cost of erlotinib does not reflect the PAS submitted by the manufacturer.

Table 68 Cost of Chemotherapy Administration

Description	Unit Cost	Reference
Deliver Complex Chemotherapy, at First Attendance	£401	NHS Reference Cost 2013-2014. Chemotherapy administration. Day Case. Currency Code SB14Z.(85)
Deliver subsequent elements of a chemotherapy cycle	£328	NHS Reference Cost 2013-2014. Chemotherapy administration. Day Case. Currency Code SB15Z. (85)

Health-state unit cost and resource use

In addition to acquisition and administration cost, supportive and palliative care is provided to all patients. The resource use required for patients does vary if they are receiving treatment or receiving supportive care. Therefore, the resource and costs have been presented for each patient are receiving active therapy or receiving supportive care.

The retrospective medical chart review determined that patients receiving active therapy require the following resource use: medical oncologist outpatient visits, GP visits, clinical nurse specialists, biochemistry tests, full blood count tests, CT scans, Chest X-rays, RBC transfusions, opiate analgesics, antiemetic's, A&E visits and oral dietary supplements. This resource use was determined to be appropriate for all patients receiving active treatment, even if they had previously progressed.

For patients that have progressed and are only receiving BSC, the retrospective medical chart review determined that patients receive the following resource use: medical oncologist outpatient appointments, GP home visits, district nurse visits, clinical nurse specialist home visits, chest x-rays opiate analgesics, antibiotics and A&E visits.

For patients that are within the last two weeks of life and receiving palliative care, it has been assumed based on Brown et al. that 55.8% of patients receive palliative care in hospital,

16.9% will receive palliative care in hospice and 27.3% will receive palliative care at home with the aid of a Macmillan nurse, community nurse and GP home visits (6).

The acquisition cost of all resource use is presented in Table 69 and Table 70. The cost for the resource use was obtained from NHS Reference Cost and PSSRU.

Table 69 Resource use and costs for patients receiving active therapy in the economic model

Patients receiving active therapy	Resource Required	Frequency	Unit Cost	Reference
	Outpatient Visit with medical oncologist	100%; Once every 3 weeks	£147	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
	GP Visit	100%; Once monthly	£35	Resource use: Brown (2013), Appendix 1 NICE CG81 Cost: PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Surgery consultation lasting 11.7 minutes.
	Clinical Nurse Specialist	100%; Once every 3 weeks	£22	Resource use: Clinical Expert Opinion Cost: PSSRU 2014. 10.7 Nurse advanced (includes lead specialist, clinical nurse specialist, and senior specialist). £22 per surgery consultation (excluding qualification cost).
	Complete Blood Count	100%; Once per week	£3	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Haematology. Currency Code DAPS05.
	Biochemistry (Renal and Liver Function)	100%; Once per week	£2	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Clinical Biochemistry. Currency Code DAPS04.
	CT-Scan(Chest)	100%; once every 6 weeks	£110	Resource use:

				Retrospective Medical Chart Review Cost: NHS Reference Cost 2013/2014. Weighted average of computerised tomography scan with outpatient service description. Currency Code (RA08A, RA09A, RA10Z-RA14Z, RA50Z).
	Chest X-ray	100%; once every 3 weeks	£30	Resource use: Retrospective Medical Chart Review Unit Cost: NHS Reference Cost 2013/2014. Directly Accessed Diagnostic Services. Direct Access Plain Film (Currency Code DAPF).
	Opiate analgesics (30mg of codeine 4 times daily)	30%; daily	£0.11 per day	Resource use: Retrospective Medical Chart Review Unit Cost: EMIT December 2014. Codeine 30mg tablets/Pack size 100=£2.86
	Antiemetic's (16mg ondansetron daily)	100%; 3 day of every cycle	£0.36 per day	Resource use: Clinical Expert Opinion Cost: EMIT December 2014. Ondansetron 8mg tablets / Pack size 10=£1.82
	Red blood cell transfusion	21%; two units every 3 months	£195 per transfusion	Resource use: Retrospective Medical Chart Review Cost: NHS Reference Cost 2013/2014. Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over. Procedures in Outpatients (Currency Code SA13A)
	Accident & Emergency visit	11%; once every 12 weeks	£88	Resource use: Retrospective Medical Chart Review Cost: Non-Consultant led Outpatient Attendances. Non-admitted Face to Face Attendance, First. Currency Code (WF01B). Accident & Emergency.
	Antibiotics	25%; 7 days in	£1.71	Resource use:

		every cycle	per day	Retrospective Medical Chart Review Cost: 500 mg of levofloxacin once daily for 7 days. Levofloxacin 500mg/pack size 10=£17.19
	Oral dietary supplement (200 ml Ensure daily)	11%; daily while on	£2.02 per day	Resource use: Retrospective Medical Chart Review Cost: Ensure Plus. Liquid. Bottle, 200ml=£2.02

Table 70 Resource use and costs for patients receiving supportive care in the economic model

Patients receiving supportive care	Resource Required	Frequency	Unit Cost	Reference
	Outpatient Visit with medical oncologist	100%; Once every 3 weeks	£147	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
	District Nurse	100%; Twice monthly	£19	Resource Use: Brown (2013) Cost: PSSRU 2014. 10.1 Community nurse (includes district nursing sister, district nurse.) £57 per hour of patient related work. Excluding qualifications costs. (Assuming each visit has a 20 minute duration according to Brown et al. 2013)
	GP home Visit	100%; Twice monthly	£35.00	Resource use: Brown (2013), Appendix 1 NICE CG81 Cost: PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Surgery consultation lasting 11.7 minutes.

	Clinical Nurse Specialist- home visit	17%; Once every 4 months	£22.00	Resource use: Brown (2013), Appendix 1 NICE CG81 Cost: PSSRU 2014. 10.7 Nurse advanced (includes lead specialist, clinical nurse specialist, and senior specialist). £22 per surgery consultation (excluding qualification cost).
	Chest X-ray	100%; once every 3 weeks	£30	Resource use: Clinical Expert Opinion Unit Cost: NHS Reference Cost 2013/2014. Directly Accessed Diagnostic Services. Direct Access Plain Film (Currency Code DAPF).
	Opiate analgesics (30mg of codeine 4 times daily)	30%; daily	£0.11 per day	Resource use: Retrospective Medical Chart Review Unit Cost: EMIT December 2014. Codeine 30mg tablets/Pack size 100=£2.86
	Accident & Emergency visit	11%; once annually	£88	Resource use: Retrospective Medical Chart Review Cost: Non-Consultant led Outpatient Attendances. Non-admitted Face to Face Attendance, First. Currency Code (WF01B). Accident & Emergency.
	Antibiotics	25%; 7 days in every cycle	£1.71 per day	Resource use: Retrospective Medical Chart Review Cost: 500 mg of levofloxacin once daily for 7 days. Levofloxacin 500mg/pack size 10=£17.19
	Oral dietary supplement (200 ml Ensure daily)	11%; daily	£2.02 per day	Resource use: Retrospective Medical Chart Review Cost: Ensure Plus. Liquid. Bottle, 200ml=£2.02

Table 71 End-of-life care

Description	Resource Use	Unit Cost	Source
Palliative Care-Hospital	55.8%	£4,153	Resource use: Brown (2013) Cost: NHS Reference Cost 2013/2014: Non-elective inpatient (long stay). Respiratory Neoplasms with CC Score 11+. Currency Code DZ17E.
Palliative Care- Hospice	16.9%	£5,191	Resource use: Brown (2013) Cost: Brown (2013) assumed hospice was a 25% increase in hospital inpatient cost. NHS Reference Cost 2013/2014: Non-elective inpatient (long stay). Respiratory Neoplasms with CC Score 11+. Currency Code DZ17E.
Palliative Care- Home	27.3%	Community Nurse Visit: £266 GP Home visit: £70 Macmillan Nurse: £1901	Resource use: Brown (2013) Cost: Community Nurse Visit- PSSRU 2014. 10.1 Community nurse (includes district nursing sister, district nurse.) £57 per hour of patient related work. Excluding qualifications costs. (Assuming each visit has a 20 minute duration and occurs for 14 days during terminal care according to Brown et al. 2013) GP Home Visit- PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Home visit lasting 11.4 minutes. (Assuming occurs weekly- twice in 14 days) Macmillan Nurse-PSSRU 2014. Brown (2013) assumed a Macmillan nurse was 66.7% of the cost of a community nurse (£57 per hour). Also assumed would be required for 50 hours for terminal care.

Adverse reaction unit costs and resource use

The resource use associated with the treatment of grade 3 and 4 TEAEs were obtained from Brown et al.(6) and the NICE DSU document on febrile neutropenia (89). The costs were obtained from NHS Reference Costs.

In addition to treatment cost and disease management cost, patients did experience grade 3 and 4 TEAEs. Only TEAEs grade 3 and 4 occurring in ≥2.5% of patients in either arm have been included in the analysis as they are the AEs that are expected to have an impact on the cost-effectiveness analysis. Adverse events for GCis + N are presented separately for induction therapy and maintenance therapy to allow for appropriate comparison to the GCis Arm.

The resource use required for the AEs was obtained from Brown et al. 2013 (6) and validated with expert opinion.

Brown et al. (2013) determined that most AEs did require at least one hospitalisation (neutropenia, anaemia, hypomagnesaemia, pulmonary embolism, fatigue, and nausea). In addition, it was assumed that thrombocytopenia requires RBC transfusions, a skin rash requires an outpatient appointment, and febrile neutropenia requires a range of interventions that have been documented in the NICE DSU document on the risks and cost of febrile neutropenia in patients with NSCLC treated with docetaxel (89).

The acquisition cost of all resource use is presented in Table 72. The cost for the resource use was obtained from NHS Reference Cost (85), EMIT (86) and the NICE DSU document on the cost of febrile neutropenia (89).

All resource use items and costs incorporated into the model have been described in the sections above.

Table 72 Calculation of resource use and cost of adverse events

Description	Unit Cost	Reference
Neutropenia	£349.34	NHS Reference Cost 2013/2014. Weighted average of mean costs for HRG code WA02W (disorders of immunity without HIV/AIDS with complicating condition) across non-elective long- and short-stay episodes and day-case admissions.
Anaemia	£755.53	NHS Reference Cost 2013/2014. Weighted average of Iron Deficiency Anaemia with CC Score 0-14+ (Currency Code SA04G, H, J, K, L) non-elective inpatient long stay, non-elective inpatient short stay and day case.
Thrombocytopenia	£195	NHS Reference Cost 2013/2014. Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over. Procedures in Outpatients (Currency Code SA13A)
Hypomagnesaemia	£590.00	EMIT December 2014. Magnesium sulphate 10% solution for infusion 20mmol IV over a 6 hour period for a maximum of 5 days. (£9.68/day, totalling £48.42). NHS Reference Cost 2013/2014. Assumed the infusion given as a non-elective inpatient short stay as a Neoplasm Related Admission with CC Score 0-3+ (Currency Code WA17A-WA17D) (£541.80 (£319.70, £612.30)
Pulmonary embolism	£654.84	NHS Reference Cost 2013/2014: Weighted average of Deep Vein Thrombosis with CC Score 0-12+ (Currency Code YQ51A-YQ51E) inpatient long stay, short stay and day case.
Skin rash	£147.39	NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
Fatigue	£3008.41	NHS Reference Cost 2013/2014. Weighted average of the non-elective long-stay. Neoplasm Related Admission with CC Score 0 to 3+). Currency code WA17A-WA17D.
Nausea	£1494.00	NHS Reference Cost 2013/2014. Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over as a non-elective short-stay episode. Currency Code FZ13C. Each hospitalisation cost £747 (£459, £833) with two hospital admissions typically required during chemotherapy.
Febrile Neutropenia	£4,402.87	The NICE Decision Support Unit report (2007) on the cost of febrile neutropenia as an inpatient estimated the cost to be £2572.44 (89). The cost from 2007 has been inflated to 2015 using the CPI from the ONS to £3144.19 Brown (2013) assume 1.4 episodes per patient during the four cycles (12 weeks) of chemotherapy.

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

Base-case de novo analysis

The cost-effectiveness analysis presented represents the NICE reference cost in terms of being completed from an NHS/PSS perspective, measurement of health effects in QALYs, lifetime time horizon and the reporting of results as an incremental cost-effectiveness ratio (ICER).

Variables included in the cost-effectiveness analysis

A list of all variables included in the cost-effectiveness analysis including the values used, distribution and range have been included in Table 73. A list of all assumptions in the economic model and justification for each assumption has been included in Table 1.

Table 73 Summary of variables applied in the economic model

	Variable	Mean	Lower 95% CI	Higher 95% CI	Distribution
Model Settings	Costs Discount Rate	0.035			
	Health Discount Rate	0.035			
Patient Characteristics	BSA	1.85 m^2			
	Weight (kg)	73.98			
Overall survival (HR)	Gemcitabine + Carboplatin	1.71	0.88	2.99	Lognormal
	Paclitaxel + Carboplatin	1.24	0.75	1.90	Lognormal
	Docetaxel + Cisplatin	1.62	0.99	2.53	Lognormal
Progression free survival (HR)	Gemcitabine + Carboplatin	1.99	1.00	3.52	Lognormal
	Paclitaxel + Carboplatin	1.47	0.87	2.36	Lognormal
	Docetaxel + Cisplatin	1.60	0.96	2.47	Lognormal
Discontinuation of induction treatment (HR)	Gemcitabine + Carboplatin	1.99	1.00	3.52	Lognormal
	Paclitaxel + Carboplatin	1.47	0.87	2.36	Lognormal
	Docetaxel + Cisplatin	1.60	0.96	2.47	Lognormal
Proportion of AE events grade 3/4 GCis+N	Neutropenia	0.27	0.21	0.34	Beta
	Anaemia	0.10	0.06	0.15	Beta
	Thrombocytopenia	0.14	0.09	0.19	Beta
	Hypomagnesaemia	0.04	0.02	0.08	Beta
	Pulmonary Embolism	0.06	0.03	0.10	Beta
	Asthenia	0.06	0.03	0.10	Beta
	Leukopenia	0.07	0.04	0.11	Beta
	Rash	0.07	0.04	0.11	Beta
	Fatigue	0.05	0.02	0.09	Beta
	Nausea	0.04	0.01	0.07	Beta
	Vomiting	0.02	0.01	0.05	Beta
	Hypokalaemia	0.03	0.01	0.06	Beta
	Hyponatraemia	0.02	0.01	0.05	Beta
	Febrile neutropenia	0.01	0.00	0.03	Beta

	Dyspnoea	0.03	0.01	0.06	Beta
	Pneumonia	0.02	0.00	0.04	Beta
Proportion of AE events grade 3/4 GCis	Neutropenia	0.31	0.24	0.38	Beta
	Anaemia	0.12	0.08	0.17	Beta
	Thrombocytopenia	0.11	0.07	0.16	Beta
	Hypomagnesaemia	0.02	0.00	0.04	Beta
	Pulmonary Embolism	0.05	0.02	0.08	Beta
	Asthenia	0.04	0.02	0.07	Beta
	Leukopenia	0.08	0.04	0.12	Beta
	Rash	0.01	0.00	0.02	Beta
	Fatigue	0.06	0.03	0.10	Beta
	Nausea	0.04	0.02	0.07	Beta
	Vomiting	0.02	0.01	0.05	Beta
	Hypokalaemia	0.02	0.00	0.04	Beta
	Hyponatraemia	0.03	0.01	0.07	Beta
	Febrile neutropenia	0.02	0.01	0.05	Beta
	Dyspnoea	0.09	0.05	0.14	Beta
	Pneumonia	0.05	0.02	0.09	Beta
Proportion of AE events grade 3/4 Necitumumab Maintenance	Neutropenia	0.01	0.00	0.05	Beta
	Anaemia	0.01	0.00	0.05	Beta
	Thrombocytopenia	-	0.00	0.01	Beta
	Hypomagnesaemia	0.01	0.00	0.05	Beta
	Pulmonary Embolism	0.01	0.00	0.03	Beta
	Asthenia	0.01	0.00	0.05	Beta
	Leukopenia	-	0.00	0.01	Beta
	Rash	0.02	0.00	0.06	Beta
	Fatigue	-	0.00	0.01	Beta
	Nausea	-	0.00	0.01	Beta
	Vomiting	-	0.00	0.01	Beta
	Hypokalaemia	-	0.00	0.01	Beta
	Hyponatraemia	0.01	0.00	0.05	Beta
	Febrile neutropenia	0.01	0.00	0.05	Beta
	Dyspnoea	0.01	0.00	0.05	Beta
	Pneumonia	-	0.00	0.01	Beta
Proportion of AE events grade 3/4	Neutropenia	1.14	0.82	1.59	Lognormal

Indirect Comparators					
	Anaemia	1.20	0.66	2.19	Lognormal
	Thrombocytopenia	0.81	0.46	1.43	Lognormal
	Hypomagnesaemia	0.42	0.11	1.59	Lognormal
	Pulmonary Embolism	0.78	0.32	1.92	Lognormal
	Asthenia	0.68	0.26	1.74	Lognormal
	Leukopenia	1.13	0.54	2.36	Lognormal
	Rash	0.09	0.01	0.62	Lognormal
	Fatigue	1.19	0.51	2.79	Lognormal
	Nausea	1.14	0.39	3.34	Lognormal
	Vomiting	0.96	0.25	3.74	Lognormal
	Hypokalaemia	0.59	0.14	2.43	Lognormal
	Hyponatraemia	1.26	0.38	4.18	Lognormal
	Febrile neutropenia	1.92	0.36	10.20	Lognormal
	Dyspnoea	3.14	1.17	8.43	Lognormal
	Pneumonia	2.83	0.79	10.20	Lognormal
Per cycle risk of adverse events induction	Gemcitabine+ Cisplatin + Necitumumab	7.80%	5.46%	10.14%	
	Gemcitabine+ Cisplatin	8.66%	6.06%	11.26%	
	Gemcitabine + Carboplatin	8.14%	5.70%	10.59%	
	Paclitaxel + Carboplatin	8.14%	5.70%	10.59%	
	Docetaxel + Cisplatin	8.14%	5.70%	10.59%	
Utilities	Pre-progression and on induction treatment	0.72	0.70	0.74	Beta
	Pre-progression and off treatment	0.70	0.65	0.75	Beta
	Pre-progression and receiving maintenance treatment	0.77	0.72	0.82	Beta
	Relapsed progressive disease	0.55	0.52	0.58	Beta
Utility decrement for AEs grade 3/4	Neutropenia	0.09	0.05	0.13	Beta
	Anaemia	0.07	0.04	0.12	Beta
	Thrombocytopenia	0.09	0.05	0.13	Beta
	Hypomagnesaemia	0.09	0.06	0.12	Beta

	Pulmonary Embolism	0.32	0.12	0.57	Beta
	Asthenia	0.07	0.04	0.12	Beta
	Leukopenia	0.09	0.05	0.13	Beta
	Rash	0.03	0.02	0.05	Beta
	Fatigue	0.07	0.04	0.12	Beta
	Nausea	0.05	0.02	0.09	Beta
	Vomiting	0.05	0.02	0.09	Beta
	Hypokalaemia	-	0.00	0.00	Beta
	Hyponatraemia	-	0.00	0.00	Beta
	Febrile neutropenia	0.09	0.06	0.12	Beta
	Dyspnoea	0.05	0.02	0.10	Beta
	Pneumonia	0.07	0.04	0.12	Beta
Utility decrement duration for AEs grade 3/4 (days)	Neutropenia	7.00			
	Anaemia	7.00			
	Thrombocytopenia	7.00			
	Hypomagnesaemia	12.30			
	Pulmonary Embolism	30.44			
	Asthenia	7.00			
	Leukopenia	7.00			
	Rash	12.30			
	Fatigue	32.00			
	Nausea	2.50			
	Vomiting	2.50			
	Hypokalaemia	7.00			
	Hyponatraemia	7.00			
	Febrile neutropenia	7.00			
	Dyspnoea	7.00			
	Pneumonia	7.00			
Treatment intensity factor	Gemcitabine+ Cisplatin + Necitumumab	0.88	0.81	0.94	Beta
	Gemcitabine+ Cisplatin	0.83	0.80	0.86	Beta
	Gemcitabine + Carboplatin	0.83	0.80	0.86	Beta
	Docetaxel + Cisplatin	0.83	0.80	0.86	Beta
	Paclitaxel +	0.83	0.80	0.86	Beta

	Carboplatin				
Post study - Proportion of patients on palliative care	Gemcitabine+ Cisplatin + Necitumumab	0.14	0.00	0.32	Beta
	Gemcitabine+ Cisplatin	0.08	0.03	0.13	Beta
	Gemcitabine + Carboplatin	0.08	0.03	0.13	Beta
	Docetaxel + Cisplatin	0.08	0.03	0.13	Beta
	Paclitaxel + Carboplatin	0.08	0.03	0.13	Beta
Cost of resource use	Cost of resource use whilst on treatment	£77.23	£38.71	£128.83	Gamma
	Cost of resource use post treatment - off treatment	£68.48	£34.33	£114.23	Gamma
	Cost of resource use post treatment - on maintenance	£73.59	£36.89	£122.76	Gamma
	Chemotherapy administration	£5,065.28	£2,538.92	£8,449.43	Gamma
	End-of-life	£72.36	£36.27	£120.71	Gamma
	Cost of post-progression, active treatment	£53.53	£26.83	£89.29	Gamma
	Cost of post-progression, on BSC	£77.23	£38.71	£128.83	Gamma
Treatment of adverse events cost	Neutropenia	£349.34	£175.10	£582.74	Gamma
	Anaemia	£755.53	£378.70	£1,260.31	Gamma
	Thrombocytopenia	£193.15	£96.81	£322.19	Gamma
	Hypomagnesemia	£590.00	£295.73	£984.18	Gamma
	Pulmonary Embolism	£654.84	£328.23	£1,092.34	Gamma
	Asthenia	£3,008.41	£1,507.94	£5,018.35	Gamma
	Leukopenia	£193.15	£96.81	£322.19	Gamma
	Skin rash	£147.39	£73.88	£245.86	Gamma
	Fatigue	£3,008.41	£1,507.94	£5,018.35	Gamma
	Nausea	£747.00	£374.43	£1,246.08	Gamma
	Vomiting	£747.00	£374.43	£1,246.08	Gamma
	Febrile neutropenia	£4,402.87	£2,206.90	£7,344.46	Gamma
	Dyspnoea	£541.80	£271.57	£903.78	Gamma

	Pneumonia	£3,008.41	£1,507.94	£5,018.35	Gamma
Drug cost per administration	Necitumumab	[redacted]	[redacted]	[redacted]	
	Carboplatin	£34.78	£24.35	£45.21	
	Cisplatin	£26.67	£18.67	£34.67	
	Docetaxel	£54.73	£38.31	£71.15	
	Erlotinib	£57.12	£39.98	£74.26	
	Gemcitabine	£38.35	£26.85	£49.86	
	Paclitaxel	£31.22	£21.85	£40.59	
	Chemotherapy administration first attendance	£401.00	£201.00	£668.91	Gamma
	Chemotherapy administration subsequent attendance	£328.00	£164.41	£547.14	Gamma

Table 74 Methodological and Structural Assumptions

Assumption	Assumption Description	Justification
Patient Population	The Western European subpopulation of the SQUIRE trial is representative of the UK NSCLC patient population.	The SQUIRE trial has reported a difference in the clinical efficacy of necitumumab across regions. Statistical analysis has determined that this is not due to a difference in baseline characteristics or treatment received during the SQUIRE trial, but is likely due to of potential unobserved treatment effect modifiers including difference in the disease burden associated with NSCLC and environmental causes of cancer including social and cultural practices such as heavy smoking. The literature suggests that this is likely to have resulted in higher incidence and mortality rates for lung cancer patients in Eastern Europe than in Western Europe. The unobserved treatment effect modifiers in the SQUIRE trial may have contributed to an overall varying impact on health outcomes geographically for necitumumab. Therefore, it is considered appropriate to employ data which has been generated from a patient population reflective of the disease burden of NSCLC patients in England. As a result, the economic evidence presented in this submission is reflective of the Western Europe subpopulation of the SQUIRE trial as it is considered the most appropriate for decision making regarding the NHS. The Western European subpopulation of patients consists of patients from Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain and UK.
Maximum of 6 cycles of induction treatment	It is assumed that patients receive induction treatment for a maximum of 6 cycles.	The SQUIRE clinical trial data allowed patients to continue induction treatment for a maximum of 6 cycles before initiating necitumumab maintenance treatment. While this varies from UK clinical practice in which patients typically only receive 4 cycles, it has been assumed that this discrepancy has no impact on the outcomes associated with treatment.
BSA	The average body surface area was considered to be 1.85 m^2. This was used to calculate the cost for all comparators.	The BSA from the trial was slightly lower than the average UK patient found in Sacco et al. (2010) for NSCLC patients (90). Therefore, it was determined to use the BSA of the average UK NSCLC patient rather than the average BSA from the trial.

Second-line therapies	It is assumed that the second-line therapies reported in the SQUIRE trial have the same efficacy and utility as those assumed to be routinely used in UK clinical practice.	A number of the treatments used in the SQUIRE trial are not representative of the UK clinical practice. However, the rates of use are similar on both arms therefore OS should not differ by arm due to second-line therapy.
Choice of second-line therapy	Second-line therapies in the model are docetaxel and erlotinib	Brown (2013) assumed that docetaxel and erlotinib are used equally in the second-line setting for NSCLC patients. Positive NICE appraisals for each of these treatments support their choice as second-line therapy in the UK.
Duration of subsequent treatment	The duration of subsequent treatment is the median duration of each therapy received in SQUIRE	To determine the number of infusions of each subsequent treatment received, the median duration was used in combination with the cycle length and number of administrations per cycle. Median duration was preferred over the mean, as many patients had not completed subsequent treatment which would result in an underestimated duration if the mean was used. Data was not available to inform use and duration of subsequent treatments for the indirect comparators. Therefore the use and duration of subsequent treatments for indirect comparators was assumed to be equivalent to those observed in the GCis arm. This assumption was tested in scenario analysis.
End-of-life Care	All patients are assumed to receive 2 weeks of End-Of-Life care	EOL care is assumed to occur for 2 weeks and is can be provided at home by Macmillan Nurse, in Hospice or a Hospital according to Brown (2013)
Utility following progression	The utility value for patients that have progressed following first-line treatment is based on Khan et al.	Post-progression health state utilities were obtained from the literature as the SQUIRE trial only conducted EQ-5D assessments until disease progression. For the post-progression health state, the values by Khan et al. 2015 were used because they are values obtained during RCT for patients that have had an active treatment until progression and valued based on UK weights applied to the EQ-5D-3L.
NMA AE	The rate of adverse events for indirect comparators is set equal to adverse events observed in the GCis arm.	In the base-case analysis the relative safety profile of indirect comparators versus GCis+N was assumed to be equivalent to the relative safety profile of GCis versus GCis+N. This was because the systematic literature review did not identify AE data specific to the squamous population for these comparators. To examine the impact of this assumption two extreme scenarios were tested, where the risk of adverse events for all indirect comparators was set to 0 or to double that associated with the GCis+N arm.

5.7 Base-case results

Results of the Cost-Effectiveness Analysis

Table 75 presents the total cost, life-years gained (LYG) and QALYs over a patient's lifetime by treatment as well as the incremental difference between GCis + N and GCis with a separately fitted log-logistic parametric survival function to extrapolate OS and PFS. As shown in Table 75 , GCis + N has a higher total average per patient lifetime cost compared to GCis as well as greater efficacy benefits. The higher total average lifetime cost and greater efficacy benefits results in an ICER of £64,713/QALY when comparing GCis + N to GCis.

0 present the total cost, LYG and QALYs and incremental difference between GCis + N and GCarbo, DCis and PCarbo. The indirect comparators were estimated by applying the HRs from the NMA for the indirect comparators versus GC+N with a separately fitted Weibull parametric survival function to estimate the OS and PFS curves. Therefore, the results for GCis + N vary for the direct and indirect comparisons. As shown in 0, GCis + N has a higher total average per patient lifetime cost compared to all the indirect comparators as well as greater efficacy benefits. The higher total average lifetime cost and greater efficacy benefits results in an ICER of £60,133/QALY when comparing GCis + N to GCarbo, an ICER of £65,135/QALY when comparing GCis + N to DCis and an ICER of £119,912 when comparing GCis + N to PCarbo.

As Table 77 demonstrates, all estimated values are within the 95% confidence interval for the reported trial estimates.

Base-case incremental cost effectiveness analysis results

Table 75 Base-case results of GCis+N vs GCis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCis+N	[redacted]	[redacted]	[redacted]				
GCis	[redacted]	[redacted]	[redacted]	£18,770	0.480	0.290	£64,713

Table 76 Base-case results of GCis+N vs Indirect Comparators

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
GCis+N	[redacted]	[redacted]	[redacted]				
GCarbo	[redacted]	[redacted]	[redacted]	£19,704	0.504	0.328	£60,133
DCis	[redacted]	[redacted]	[redacted]	£19,335	0.464	0.297	£65,135
PCarbo	[redacted]	[redacted]	[redacted]	£19,480	0.227	0.162	£119,912

Table 77 Model results compared with clinical data

Outcome	GCis+ N		GCis	
	SQUIRE result (median)	Model result (median)	SQUIRE result (median)	Model result (median)
Progression free survival (months)	5.6 (5.4, 6.0)	5.52	4.5 (4.2, 5.3)	4.37
Overall survival (months)	11.7 (10.3, 13.6)	11.73	8.9 (7.8, 11.1)	8.74

Disaggregated results of the base case incremental cost effectiveness analysis

Table 78 Summary of QALY gain by health state (GCis+N vs GCis)

Health state	QALY GCis+N	QALY GCis	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.011	3.71%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.132	45.52%
Pre-progression and off treatment	[redacted]	[redacted]	-0.070	-24.07%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.217	74.96%
Total	[redacted]	[redacted]	0.290	100%

Table 79 Summary of QALY gain by health state (GCis+N vs GCarbo)

Health state	QALY GCis+N	QALY GCarbo	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.048	14.71%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.132	40.29%
Pre-progression and off treatment	[redacted]	[redacted]	0.009	2.77%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.140	42.59%
Total	[redacted]	[redacted]	0.328	100%

Table 80 Summary of QALY gain by health state (GCis+N vs DCis)

Health state	QALY GCis+N	QALY DCis	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.033	11.02%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.132	44.48%
Pre-progression and off treatment	[redacted]	[redacted]	-0.016	-5.45%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.149	50.25%
Total	[redacted]	[redacted]	0.297	100%

Table 81 Summary of QALY gain by health state (GCis+N vs PCarbo)

Health state	QALY GCis+N	QALY PCarbo	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.027	16.59%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.132	81.28%
Pre-progression and off treatment	[redacted]	[redacted]	-0.029	-17.65%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.033	20.27%
Total	[redacted]	[redacted]	0.162	100%

Table 82 Summary of costs by health state (GCis+N vs. GCis)

Health state	Cost intervention (GCis+N)	Cost comparator (GCis)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£9,404	50.10%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,200	43.69%
Pre-progression and off treatment	[redacted]	[redacted]	-£358	-1.91%
Post-progression	[redacted]	[redacted]	£1,524	8.12%
Total	[redacted]	[redacted]	£18,770	100%

Table 83 Summary of costs by health state (GCis+N vs. GCarbo)

Health state	Cost intervention (GCis+N)	Cost comparator (GCarbo)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£10,410	52.83%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,200	41.62%
Pre-progression and off treatment	[redacted]	[redacted]	£46	0.24%
Post-progression	[redacted]	[redacted]	£1,048	5.32%
Total	[redacted]	[redacted]	£19,704	100%

Table 84 Summary of costs by health state (GCis+N vs. DCis)

Health state	Cost intervention (GCis+N)	Cost comparator (DCis)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£10,099	52.23%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,200	42.41%
Pre-progression and off treatment	[redacted]	[redacted]	-£83	-0.43%
Post-progression	[redacted]	[redacted]	£1,119	5.79%
Total	[redacted]	[redacted]	£19,335	100%

Table 85 Summary of costs by health state (GCis+N vs. PCarbo)

Health state	Cost intervention (GCis+N)	Cost comparator (PCarbo)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£11,081	56.88%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,200	42.10%
Pre-progression and off treatment	[redacted]	[redacted]	-£147	-0.75%
Post-progression	[redacted]	[redacted]	£345	1.77%
Total	[redacted]	[redacted]	£19,480	100%

Table 86 Summary of predicted resource use by category of cost (GCis+N vs GCis)

Item	Cost intervention (GCis+N)	Cost comparator (GCis)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£14,981	80%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,015	11%
Subsequent treatment cost	[redacted]	[redacted]	£237	1%
Subsequent treatment administration cost	[redacted]	[redacted]	-£27	0%
Disease monitoring and supportive care	[redacted]	[redacted]	£360	2%
Adverse Events	[redacted]	[redacted]	-£110	-1%
Palliative Care	[redacted]	[redacted]	£1,314	7%
Total	[redacted]	[redacted]	£18,770	100%

Table 87 Summary of predicted resource use by category of cost (GCis+N vs GCarbo)

Item	Cost intervention (GCis+N)	Cost comparator (GCarbo)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,035	76%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,509	13%
Subsequent treatment cost	[redacted]	[redacted]	£254	1%
Subsequent treatment administration cost	[redacted]	[redacted]	-£12	0%
Disease monitoring and supportive care	[redacted]	[redacted]	£973	5%
Adverse Events	[redacted]	[redacted]	£139	1%
Palliative Care	[redacted]	[redacted]	£805	4%
Total	[redacted]	[redacted]	£19,704	100%

Table 88 Summary of predicted resource use by category of cost (GCis+N vs DCis)

Item	Cost intervention (GCis+N)	Cost comparator (DCis)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,094	78%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,306	12%
Subsequent treatment cost	[redacted]	[redacted]	£254	1%
Subsequent treatment administration cost	[redacted]	[redacted]	-£11	0%
Disease monitoring and supportive care	[redacted]	[redacted]	£758	4%
Adverse Events	[redacted]	[redacted]	£59	0%
Palliative Care	[redacted]	[redacted]	£877	5%
Total	[redacted]	[redacted]	£19,335	100%

Table 89 Summary of predicted resource use by category of cost (GCis+N vs PCarbo)

Item	Cost intervention (GCis+N)	Cost comparator (PCarbo)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,138	78%
Induction and maintenance administration cost	[redacted]	[redacted]	£3,306	17%
Subsequent treatment cost	[redacted]	[redacted]	£237	1%
Subsequent treatment administration cost	[redacted]	[redacted]	-£28	0%
Disease monitoring and supportive care	[redacted]	[redacted]	£661	3%
Adverse Events	[redacted]	[redacted]	£29	0%
Palliative Care	[redacted]	[redacted]	£137	1%
Total	[redacted]	[redacted]	£19,480	100%

5.8 Sensitivity analyses

Various sensitivity analyses were completed to explore the main areas of uncertainty within the model, including parameter uncertainty in the deterministic and probabilistic sensitivity analyses and structural uncertainty in the scenario analysis.

Probabilistic sensitivity analysis

To account for variability in outcomes due to parameter uncertainty, probabilistic sensitivity analyses (PSA) were performed. The PSAs were run for 2,000 simulations with the parameters estimates repeatedly sampled from the determined probability distributions. A log-normal distribution was used for HRs and RRs, a gamma distribution was applied to costs and duration, and a beta distribution was applied to the risk of AEs and utilities. The number of simulations was chosen by running the probabilistic analysis over 10,000 simulations and examining where the CEAC converged to a constant value.

Figure 55 presents the scatterplot of 2,000 simulations of the incremental cost-effectiveness analysis of GCis + N compared with GCis at a £50,000/QALY threshold. It can clearly be seen that GCis + N provides an incremental gain in costs and QALY gain. Results of GCis + N vs all indirect comparators and presented in Figure 56, Figure 57 and Figure 58. The

associated cost-effectiveness acceptability curves for all comparators are presented below in Figure 59.

Figure 55 Probabilistic Sensitivity Analysis scatter plot (GCis+N vs GCis)

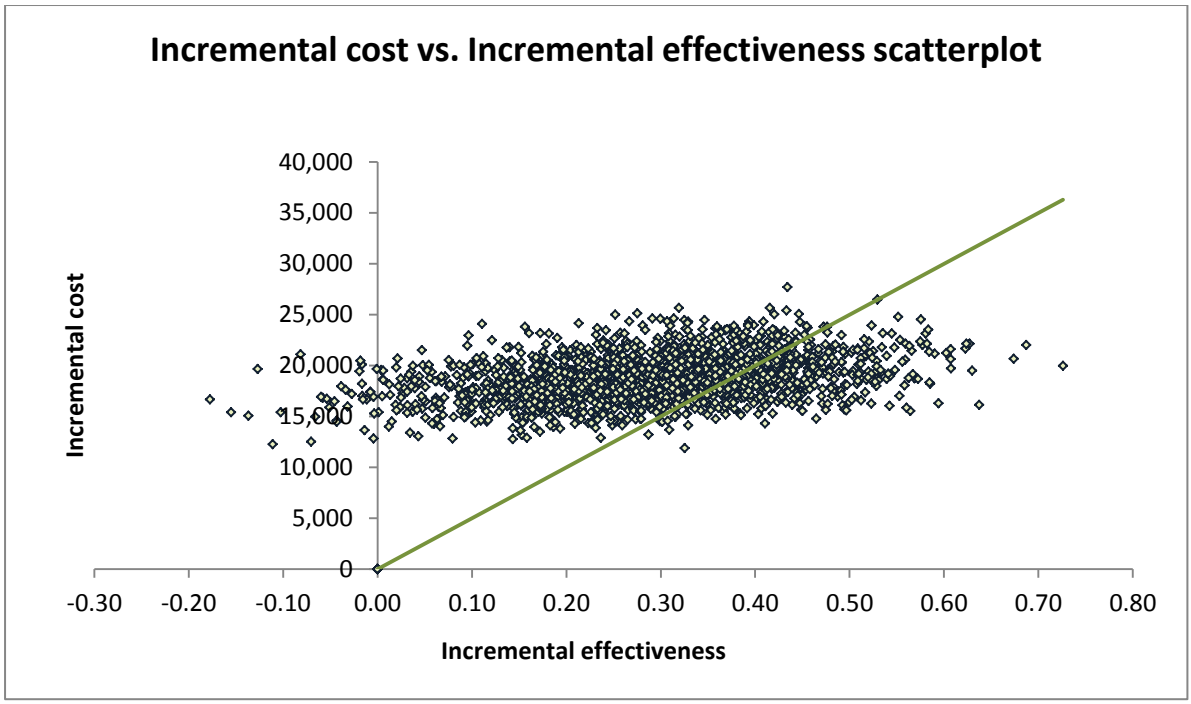


Figure 56 Probabilistic Sensitivity Analysis scatter plot (GCis+N vs GCarbo)

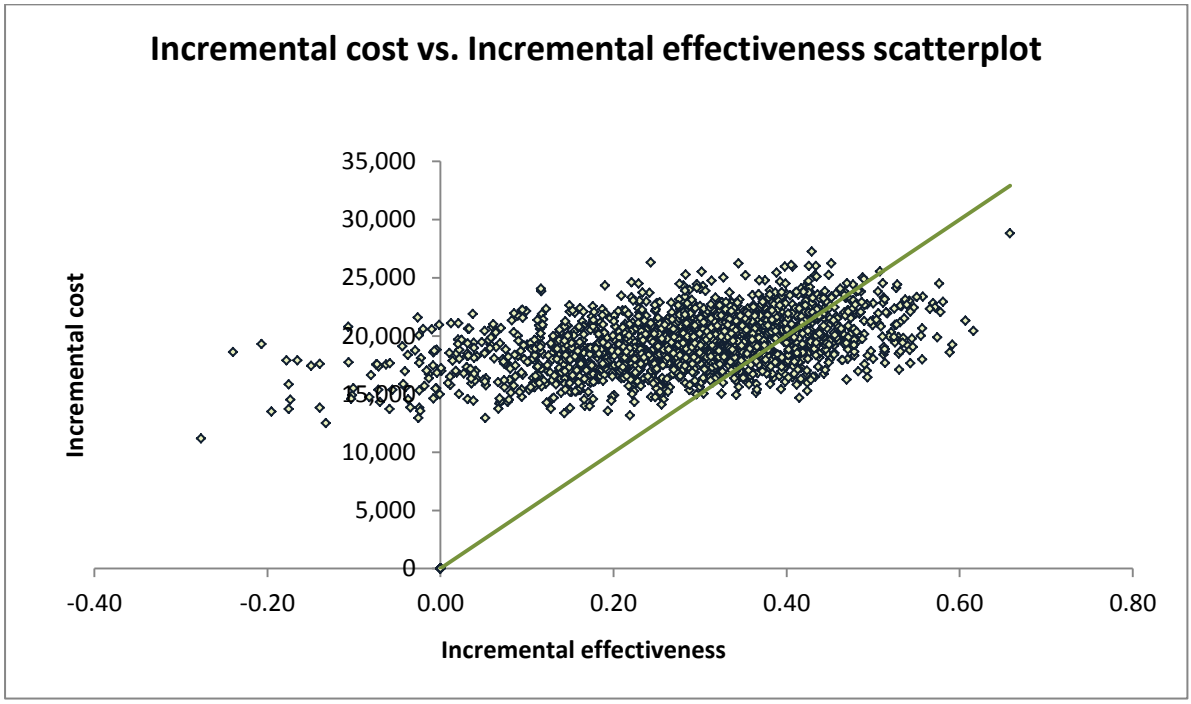


Figure 57 Probabilistic Sensitivity Analysis scatter plot (GCis+N vs DCis)

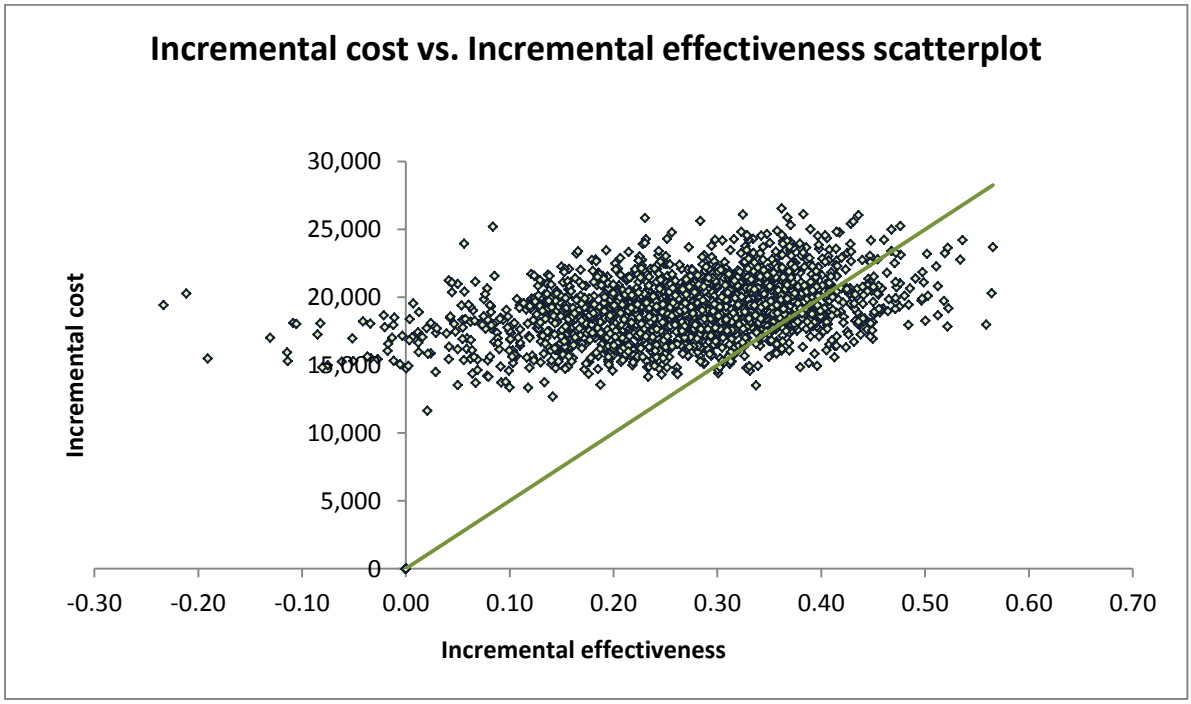


Figure 58 Probabilistic Sensitivity Analysis scatter plot (GCis+N vs PCarbo)

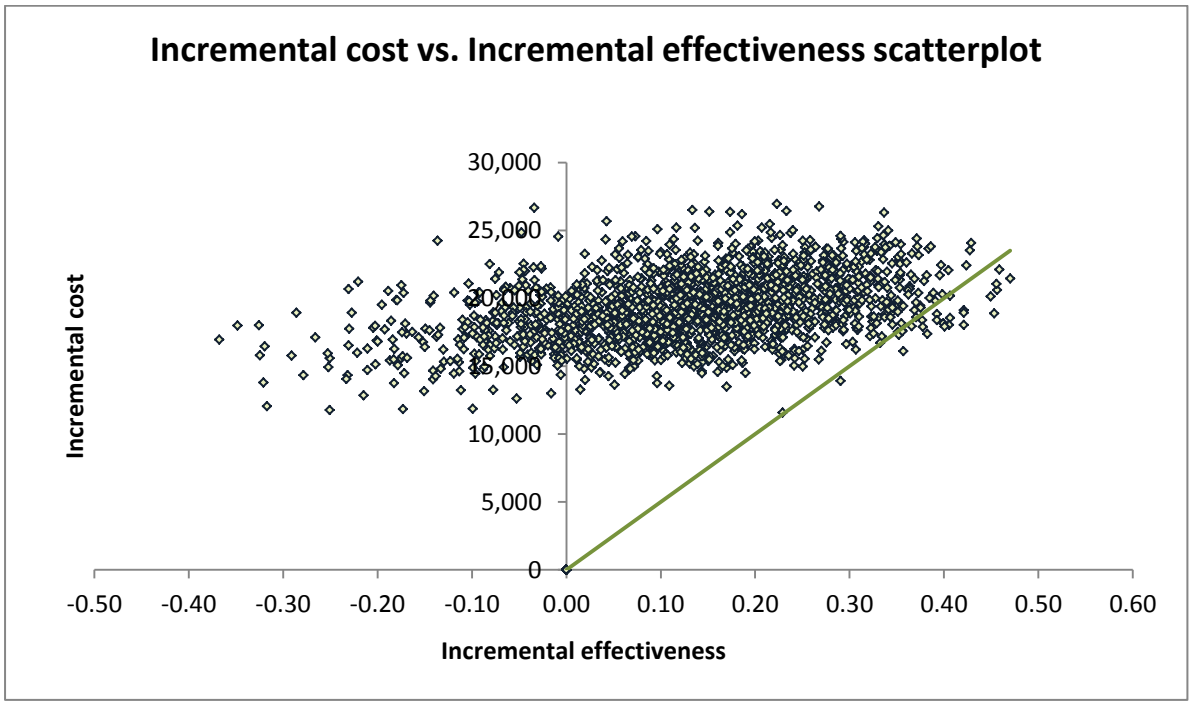
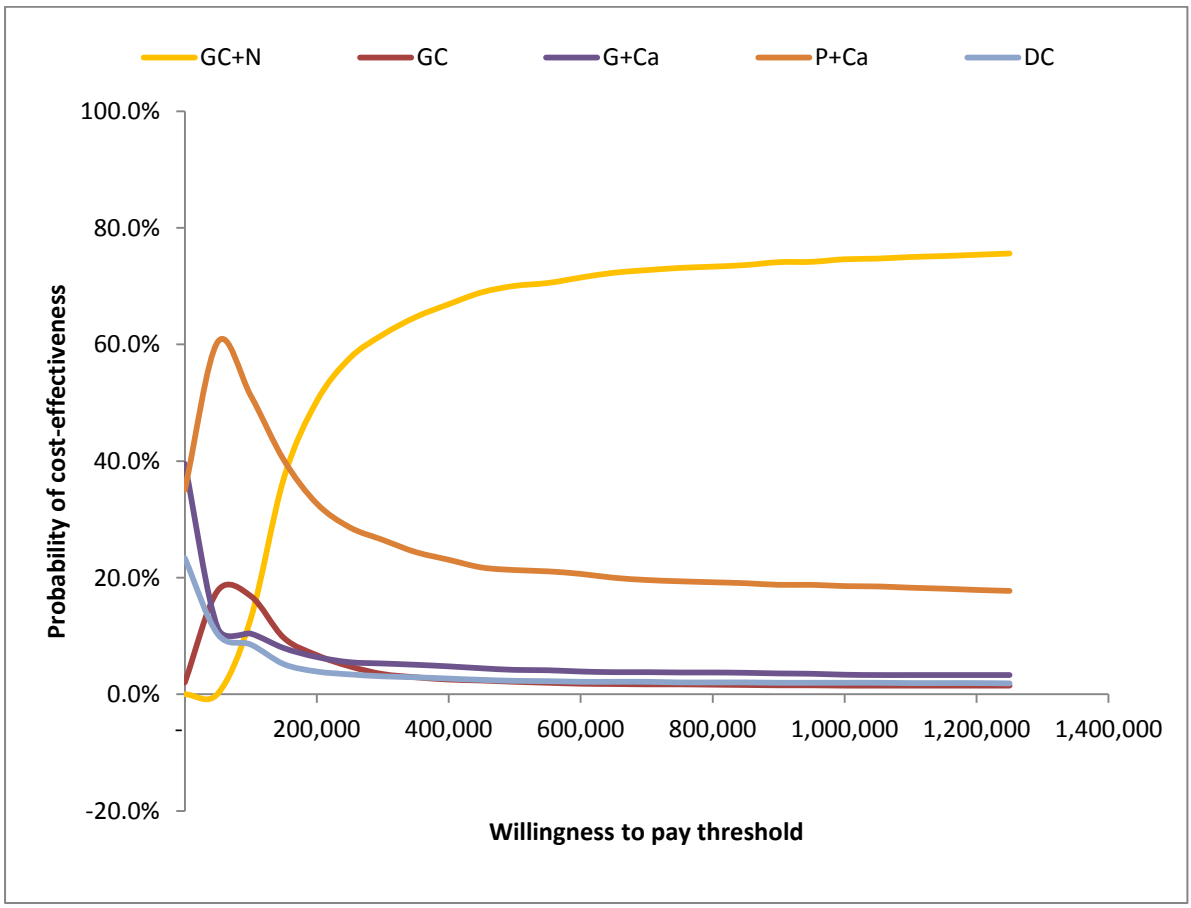


Figure 59 Cost-Effectiveness Acceptability Curve



Deterministic sensitivity analysis

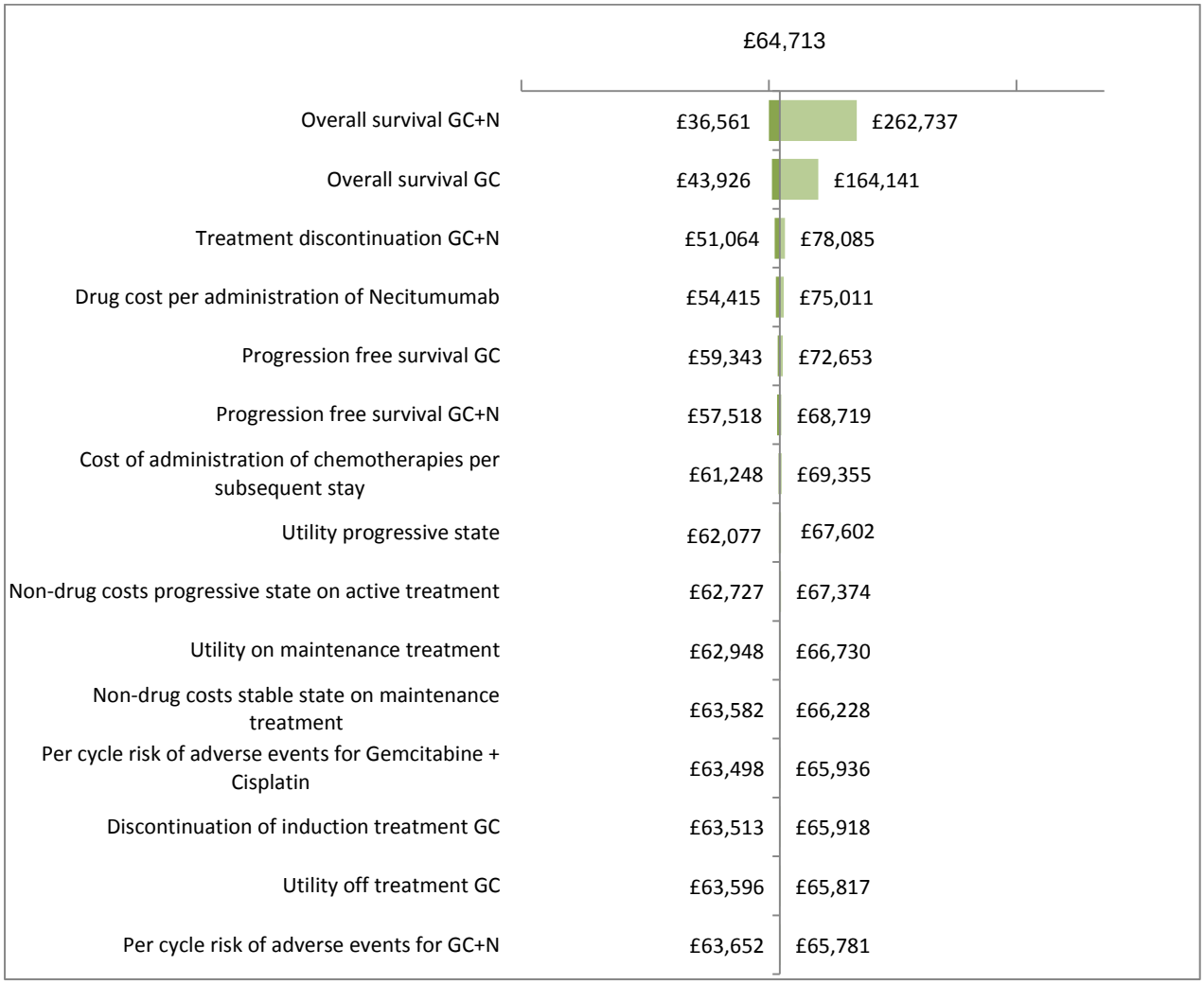
A deterministic sensitivity analysis assessed the impact of key variables on the model outcomes. HRs for OS and utility values were varied between the upper and lower limits of the 95% confidence interval. For other parameters, values were varied plus or minus 20% from the base-case value. Results of the deterministic sensitivity analysis are displayed in a tornado diagram. The following values were presented in the tornado diagram:

Table 90 Variables and Ranges explored through deterministic sensitivity analysis

Description	Lower Range	Upper Range	Base
Incremental costs			
Treatment discontinuation GC+N	£14,542	£23,069	£18,770
Drug cost per administration of Necitumumab	£15,783	£21,757	£18,770
Overall survival GC+N	£17,361	£20,438	£18,770
Cost of administration of chemotherapies per subsequent stay	£17,765	£20,117	£18,770
Overall survival GC	£17,588	£19,827	£18,770
Non-drug costs progressive state on active treatment	£18,194	£19,542	£18,770
Progression free survival GC+N	£17,930	£18,745	£18,770
Non-drug costs stable state on maintenance treatment	£18,442	£19,210	£18,770
Discontinuation of induction treatment GC	£18,405	£19,138	£18,770
Per cycle risk of adverse events for Gemcitabine + Cisplatin	£18,475	£19,065	£18,770
Cost per AE Gemcitabine + Cisplatin	£18,475	£19,065	£18,770
Per cycle risk of adverse events for GC+N	£18,525	£19,016	£18,770
Cost per AE GC+N	£18,525	£19,016	£18,770
Non-drug costs stable state off treatment	£18,531	£18,949	£18,770
Non-drug costs progressive state on palliative care	£18,647	£18,935	£18,770
Incremental QALYs			
Overall survival GC+N	0.066	0.559	0.290
Overall survival GC	0.107	0.451	0.290
Progression free survival GC+N	0.261	0.326	0.290
Progression free survival GC	0.259	0.316	0.290
Utility progressive state	0.278	0.302	0.290
Utility on maintenance treatment	0.281	0.298	0.290
Treatment discontinuation GC+N	0.285	0.295	0.290
Utility off treatment GC	0.285	0.295	0.290
Per cycle risk of adverse events for GC+N	0.289	0.291	0.290
Utility decrement associated with AEs in induction period GC+N	0.289	0.291	0.290
Per cycle risk of adverse events for Gemcitabine + Cisplatin	0.289	0.291	0.290
Utility decrement associated with AEs in induction period Gemcitabine + Cisplatin	0.289	0.291	0.290
Utility on induction treatment	0.290	0.290	0.290
Discontinuation of induction treatment GC	0.290	0.290	0.290
Drug cost per administration of Necitumumab	0.290	0.290	0.290

ICER			
Overall survival GC+N	£36,560.88	£262,736.67	£64,713.20
Overall survival GC	£43,926.04	£164,140.73	£64,713.20
Treatment discontinuation GC+N	£51,063.69	£78,085.35	£64,713.20
Drug cost per administration of Necitumumab	£54,415.21	£75,011.20	£64,713.20
Progression free survival GC	£59,342.62	£72,653.08	£64,713.20
Progression free survival GC+N	£57,518.36	£68,719.20	£64,713.20
Cost of administration of chemotherapies per subsequent stay	£61,248.23	£69,354.68	£64,713.20
Utility progressive state	£62,077.20	£67,602.47	£64,713.20
Non-drug costs progressive state on active treatment	£62,726.83	£67,374.03	£64,713.20
Utility on maintenance treatment	£62,948.25	£66,730.02	£64,713.20
Non-drug costs stable state on maintenance treatment	£63,582.15	£66,228.29	£64,713.20
Per cycle risk of adverse events for Gemcitabine + Cisplatin	£63,498.42	£65,935.60	£64,713.20
Discontinuation of induction treatment GC	£63,513.44	£65,917.77	£64,713.20
Utility off treatment GC	£63,595.93	£65,817.47	£64,713.20
Per cycle risk of adverse events for GC+N	£63,652.41	£65,781.17	£64,713.20
Overall survival GC+N	£36,560.88	£262,736.67	£64,713.20

Figure 60 Tornado Diagram for ICER



Scenario analysis

The structural uncertainty was explored by assessing the change in results using alternative functional forms, assumptions or sources for key input parameters. A detailed summary of each scenario has been explained below:

Population: In the base case, the clinical trial data from the SQUIRE trial were representative of the Western Europe subpopulation. Use of the ITT population, including patients all from all sites in SQUIRE, was investigated in the scenario analysis.

Functional forms for OS and PFS: In the base-case analysis, the KM estimates were used for both OS and PFS, followed by the log-logistic distribution after last observation. As the data were not fully observed, there was some uncertainty associated with the long-term projections and determining which distributions provided the most appropriate fit to the data.

Due to this uncertainty, separate Weibull distributions (the second best-fitting distribution for GC+N and best fitting for GC) were examined in place of the log-logistic for extrapolation beyond the last OS observation. In addition, a log-logistic for GC+N and Weibull for GC were investigated. These represent the best fitting distribution to each arm although it may not be plausible to assume a different distribution for each arm. Finally, although the exponential distribution was a poorer fit for OS, this distribution was also examined in place of the log-logistic for extrapolation beyond the last OS observation, due to their prominence in economic models and use in previous HTAs.

Definition of PFS: In addition to testing alternative parametric functions, alternative definitions of PFS were assessed in sensitivity analyses. In the base case, PFS was defined as radiographic documentation of progression or death according to the primary definition in the SQUIRE trial; however, progression could be defined in several ways. Therefore, an additional definition was examined with PFS being defined as radiographic documentation of progression and or death or symptomatic deterioration for progression.

Time-horizon: A potential criticism of the use of the log-logistic distribution for OS is its long tail for survival. In order to investigate the impact of the long tail a scenario considering a 5 year time horizon, thus censoring the tail, was investigated.

Source of utilities: As mentioned in section 5.4, pre-progression pooled utilities were estimated from the SQUIRE trial, and post-progression utilities were taken from Khan et al. (63). Additional sources were identified that also reported relevant utility values. These studies used different valuation methods and included different health states, resulting in varying estimates for both the pre-progression and post-progression health states. The use of utilities from Chouaid et al. (61) and AE utility decrements from Nafees et al. (66) was investigated in one scenario analysis. Due to the uncertainty associated with the post-progression health state utility from Khan et al. (63), post-progression utility values from Chouaid et al. (61) were examined in another scenario.

The scenario analysis and impact on the ICER can be found in Table 91.

Table 91 Scenario Analysis Results (GCis+N vs. GCis)

Scenario	Description	ICER
Base-case	Base Case results	£64,713
1)	Utilities from Chouaid et al. (61) and AE decrements from Nafees et al. (66)	£57,788
2)	Utility post-progression from Chouaid et al (61)	£55,751
3)	Time to treatment discontinuation assumed same as GC for all comparators	£64,713
4)	Using ITT as patient population	£188,831
5)	Using separate Weibull for OS	£87,543
6)	Using Log-logistic for OS in GC+N and Weibull in GC arm	£53,433
7)	Using separate Exponential distributions for OS	£78,868
8)	5 year time horizon	£83,205
9)	Symptomatic deterioration considered progression	£64,251

Summary of sensitivity analyses results

The overall conclusion of the sensitivity and scenario analyses is that the model is robust to changes in key parameters and assumptions. For the GCis + N vs GCis comparison, the sensitivity analysis indicate that the key cost drive for cost effectiveness results are OS and PFS estimates for both treatments, the time to treatment discontinuation of GCis + N and the acquisition cost of necitumumab. The variation in utility values and BSC costs has little impact on the ICER. Therefore, the assumptions on the long term incremental survival benefit associated with necitumumab as well as the acquisition cost of necitumumab have the greatest impact on the cost-effectiveness results.

Probabilistic sensitivity analysis incorporating the uncertainty in the model parameters indicates a slightly higher estimated ICER when comparing GCis + N to Cis of £65,050 per QALY gained. Examination of the CEAC demonstrates that at a £50,000/QALY threshold, the probability of GCis + N being cost effective compared to GCis is 24%.

5.9 Subgroup analysis

Due to the clinical efficacy of necitumumab varying across regions despite no statistically significant difference in demographics or treatment received within the SQUIRE trial, it is believed that this difference in clinical efficacy is likely due to unobserved treatment effect modifiers that have been detected within the SQUIRE trial. Potential unobserved treatment effect modifiers include the associated disease burden of squamous NSCLC and environmental causes of cancer including social and cultural practices across Europe such as heavy smoking. This is likely to have resulted in higher incidence and mortality rates in

Eastern Europe than in Western Europe, as reported in the literature. The economic analysis has been completed using the subpopulation data from Western Europe; however, the Western Europe subpopulation data is not a subgroup due to it lacking a statistically significant interaction between Western Europe and the remaining patients in the SQUIRE trial and not being predictive of clinical efficacy.

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 Modelling Good Research Practices describes model validity simply, as “how well the model reproduces reality” (91). 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 to validate that the model structure and modelling assumptions reflect the clinical pathway of patients with locally advanced or metastatic squamous NSCLC in England.

To ensure internal validity, the structure and programming of the completed Microsoft Excel model was validated by two modelling experts not involved in developing the model, but within the organisation that was consulted to develop the model. They also performed a variety of stress tests to ensure that the model behaved as expected. Both extreme values and equal values across treatment arms were input and results were compared against

results expected. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy the discrepancy.

To address cross validity and/or external validity, the modelled median OS and PFS was compared with that observed in the SQUIRE trial (Table 92) and the health-state utility estimates generated from the SQUIRE trial were compared to literature-based estimates (see Section 5.4).

Predictive validity refers to comparing the model results with prospectively observed events. At this time, predictive validity in terms of GCis + N cannot be assessed.

Statistical fittings for OS and PFS were also validated by comparing the observed median OS and PFS for patients with locally advanced or metastatic squamous NSCLC in the literature to values derived from the model. Table 92 demonstrated that the modeled medians for all comparators are within the 95% confidence intervals of previously reported estimates for this patient population. Therefore, the values reported in the SQUIRE trial for the Western Europe patient subpopulation is consistent with published estimates.

Table 92 Model results compared with estimates from literature

Outcome	Clinical Trial Result	Model Result
GCis		
OS (median)	9.4 months (1)	10.35 months
PFS (median)	4.3 months (1)	4.60 months
PCarbo		
OS (median)	9.3 months (1)	10.35 months
PFS (median)	3.7 months (1)	4.6 months
DCis		
OS (median)	8.1 months (1)	8.97 months
PFS (median)	3.1 months (1)	4.14 months

5.11 Interpretation and conclusions of economic evidence

There is currently no published literature of the cost-effectiveness of necitumumab first-line therapy for locally advanced or metastatic squamous NSCLC in England. Therefore, it is not possible to validate or compare these results with previous evaluations.

The economic evaluation includes patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment. This population is consistent with the SQUIRE trial and NICE scope; however, it is not consistent with the indication provided in the summary of

product characteristics for necitumumab in Europe. Additional analysis will be provided to NICE at a later stage to reflect this population.

The modelled mean OS benefit of using GCis + N rather than GCis is 5.76 months. The corresponding mean discounted QALY is 0.29 per patient. The overall incremental cost per patient is higher in the GCis + N arm (an additional £18,770) than in the GCis arm due to drug acquisition and administration cost. The higher total average cost per patient as well as greater efficacy benefits results in an estimated ICER is £64,713 per QALY when comparing GCis + N to GCis. The results of the model were extensively tested in deterministic, probabilistic and scenario analysis. The results of the sensitivity analyses determined that the results are most affected by the uncertainty in the extrapolation methods used to estimate the OS and PFS survival curve.

The model inputs are generalisable to England, with clinical inputs primarily comprising a phase III, randomised, double blind clinical trial (SQUIRE) comparing GCis + N to GCis. External clinical advisors consulted considered it generalisable to patients with locally advanced or metastatic squamous NSCLC in the NHS.

The main strengths of this evaluation are the following:

High quality study: The clinical evidence is this economic evaluation has been based on SQUIRE, the first and only prospective study in patients with locally advanced or metastatic squamous NSCLC to demonstrate benefit in OS in the first-line setting.

Standard of care comparator: The use of comparative efficacy estimates for GCis + N vs GCis based on HRs from the active-comparator RCT

Utility Values: Pre-progression utility values were measured directly from patients in SQUIRE, which allowed squamous specific NSCLC utility values to be implemented in the model

Modelling assumptions: Approximately 85% of patients in the GCis + N arm and 94% of patients in the GCis arm of patients died during trial. Therefore, the uncertainty regarding the extrapolated estimates is minimal.

The main weaknesses of this evaluation are:

Indirect Comparators: the HRs from the NMA are based on studies that consisted of at least 30% of squamous NSCLC patients. Therefore, they are not entirely reflective of the

patient population in this evaluation. Other limitations were: inclusion of phase II studies, small studies, only one study providing evidence for most comparators in the network, and digitisation of KM curves to estimate HRs.

Utility values: Post-progression utility values were not collected from patients in SQUIRE. Therefore, the post-progression utility values are from a UK specific publication on erlotinib.

Necitumumab is an innovative first-line treatment option for patients with locally advanced or metastatic squamous NSCLC that offers a benefit in OS and PFS. Patients with squamous NSCLC have a distinct disease and are difficult to treat due to comorbidities and late diagnosis, and there has been very little improvement in survival in squamous patients over the last few decades. No new chemotherapies have been approved in first-line squamous NSCLC by the EMA in two decades and there are currently no targeted first-line biologic treatments available.

Necitumumab meets the criteria to be assessed as an end-of-life treatment:

- The patient population eligible for necitumumab is expected to be less than 9,000 patients with approximately 2,575 patients in England having locally advanced or metastatic squamous NSCLC (see section 6).
- The modelled mean OS benefit for the Western Europe subpopulation demonstrates a mean incremental survival benefit of 5.76 months for GCis + N (19.82 months) when compared to GCis (14.06 months).
- The current expected median survival reported in the literature for this patient population is between 6.5 and 9.4 months depending on therapy received (1) which is below the 24 month criterion.

6. Assessment of factors relevant to the NHS and other parties

Currently in England, after completion of 4 to 6 cycles of first-line treatment with a platinum doublet, patients with squamous NSCLC undergo a chemotherapy free observation period until disease progression. During this time, patients may receive BSC and are clinically assessed every one to three months and radiologically every three to six weeks but, that varies regionally. With the introduction of necitumumab, patients will be treated with necitumumab in combination with gemcitabine plus cisplatin (GCis + N) for up a maximum of 6 cycles of treatment followed by necitumumab as a single agent in patients whose disease has not progressed until disease progression or unacceptable toxicity.

In 2012 there were 32,364 new cases of lung cancer in England (4). Approximately 84% of lung cancer is NSCLC (4) and 33% is of squamous histology (6,92). Approximately 48% of patients are diagnosed with stage IV disease (5) and 59.8% receive 1st line therapy (4). This results in an estimated eligible patient population for GCis + N of 2,575 patients in England. With an estimated PFS of 7 months for GCis + N, it has been assumed that no patients will be receiving necitumumab for longer than one year. It has also been assumed that the incidence of new lung cancers will continue to be stable from 2016-2020.

Table 93 Eligible patient Population

Population	Value	Source
Incident cases of lung cancer	32,364	Cases submitted to the National Lung Cancer Audit; LUCADA 2014 (4)
NSCLC (All lung cases excluding small cell and mesothelioma)	84%	LUCADA 2014 (4)
Stage IIIB/IV	48%	Cancer Research UK (5)
Receive 1st line chemotherapy	59.80%	LUCADA 2014 (4)
Squamous proportion	33%	Brown et al. (6)
Total eligible patient population	**2,575**	

Market share

The current market shares are based on market research (Lilly data on file) and internal forecasts (Table 94). In a situation without necitumumab, the current market shares are assumed not to change over the next 5 years (Table 94). This assumption was made because on uncertainty regarding the approval and availability of new first-line lung cancer treatments for locally advanced or metastatic squamous NSCLC. The predicted market share of necitumumab in year 1 and year 2 is 15%, and 20% year 3-5. Necitumumab market share is expected to come proportionally from gemcitabine plus cisplatin and gemcitabine plus carboplatin based on their relative market share.

Table 94 Current market share in 1st Line therapy for locally advanced or metastatic squamous NSCLC

	2016	2017	2018	2019	2020
GCis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCarbo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCarbo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 95 Future market share with necitumumab

	2016	2017	2018	2019	2020
GCis+N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCarbo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCarbo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs

Treatment acquisition cost is one of the main driver of cost differences between therapies in the cost-effectiveness model. The treatment duration was assumed to be 4.6 cycles of GCis + N induction therapy followed by 6.4 cycles of necitumumab maintenance therapy until disease progression. The treatment duration of all other therapies were assumed to be 4 cycles based on clinical expert opinion. Administration costs have also been included as these differ between the comparators. No other costs were considered to be relevant. The annual drug acquisition costs are presented in Table 96 and were derived from the unit costs previously presented in in Section 5.5.

Table 96 Annual drug acquisition costs used in the budget impact model (per patient)

	GCis+N	GCis	GCarbo	PCarbo	DCis
Drug acquisition- induction therapy	[redacted]	£388	£334	£231	£275
Drug acquisition- maintenance therapy	[redacted]	£0	£0	£0	£0
Administration- induction therapy	[redacted]	£2,438	£1,944	£1,147	£2,147
Administration- maintenance therapy	[redacted]	£0	£0	£0	£0
Subtotal	[redacted]	£2,826	£2,278	£1,378	£2,423

Budget impact results

The introduction of necitumumab in England is expected to result in a net budget impact of £7,679,598 in each of the first two years after introduction and £10,226,845 in years 3–5 after introduction (Table 97).

Table 97 Budget impact results

	2016	2017	2018	2019	2020	Total
Total without Necitumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total with Necitumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Discussion

The budget impact model does not include costs associated with disease state and assumes that patients remain on GCis + N induction therapy for 6 cycles and receive necitumumab maintenance therapy for 6 cycles, which is more than was reported in SQUIRE. Therefore the reported budget impact is most likely an overestimate.

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 for necitumumab is forecast-based only. The assumption that the market share of GCis + N will replace a proportion of the market share of GCis and GCarbo may also be conservative.

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Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Necitumumab for untreated metastatic squamous non-small-cell lung cancer [ID835]

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 20 January 2016 from Eli 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 **2 March 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 Ian Watson, Technical Lead (Ian.Watson@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

Additional analysis

A1. **Priority question**: The submission states (on pages 15, 142 and 231) that additional analyses will be provided to reflect the population in the summary of product characteristics (SPC). Please provide these analyses, including full details of the methods and population in the analysis.

Systematic reviews

A2. The PRISMA flowchart for the main systematic review (figure 2 on page 41 of the submission) shows that 34 studies were excluded at the screening and full-text assessment stages of the systematic review; please provide a list of the excluded studies and list the reasons why the 6 studies excluded at the full-text assessment stage were excluded.

A3. Please provide details of the processes followed for study selection, data extraction and risk of bias assessment when carrying out the systematic reviews. In particular, please state how many reviewers carried out each task and, if more than one reviewer was involved, whether the reviewers carried out these tasks independently.

A4. The PRISMA flowchart for the systematic review for the network meta-analysis (figure 22) indicates that 39 studies were eligible for the NMA; however, only 13 studies were included.

a. Appendix 5 states that some studies were excluded because of use of experimental/unapproved agents, but this is not stated as an exclusion criterion in the study eligibility criteria (table 21). Please confirm the exclusion criteria that were applied.
b. There are 7 studies that included comparators relevant to the scope and so whose exclusion from the NMA does not seem to be justified (Heymach et al. 2008, Langer et al. 2014, Lara et al. 2011, Paz-Ares et al. 2013, Scagliotti et al. 2010, Von Pawel et al. 2014, and Spigel et al. 2013). Please explain why these studies have been excluded?

A5. **Priority question**: Please confirm if the NMA included studies of people with stage IV squamous non-small-cell lung cancer (NSCLC) only, or if studies of people with stage IIIA and/or IIIB disease were also included.

SQUIRE trial patient population

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A6. **Priority question**: Please provide additional details of the subgroup analyses by geographical region, including the post-hoc 'Western European' subgroup.

a. Please clarify the rationale for the choice of countries included in the Western European subgroup. Please explain why the subgroup did not also include other countries that may have similar populations to those from Western Europe (e.g. Australia, Canada).
b. Please provide the additional 'Race' baseline characteristics for the Western European subgroup that are not included in table 13 ('Asian', 'Black or African American' and 'Other' for each arm and the whole subgroup).
c. On pages 68 and 69, a number of planned subgroup analyses by geographical region are listed. Please provide results from these analyses, in a Forest plot format, including the hazard ratios and 95% confidence intervals.

A7. **Priority question**: Please clarify the number and proportion of patients in each arm of the SQUIRE trial:

- with high tumour EGFR expression (H-score ≥ 200)
- with low tumour EGFR expression (H-score <200)
- without EGFR expressing NSCLC
- with a missing result for EGFR H-score

Please provide this information for both the intention-to-treat (ITT) population and the Western Europe subgroup. For people with low EGFR expression, what was the lowest H-score?

SQUIRE trial methodology

A8. **Priority question**: Please confirm what previous treatments were permitted before entry into the SQUIRE trial. In particular, could patients have had previous treatment for less advanced disease? What proportion of the population in the SQUIRE trial in each arm received prior treatment?

A9. During the SQUIRE trial, who assessed progressive disease or toxicity to define whether maintenance therapy was given? Were they blinded to treatment allocation?

A10. Was an independent review of the assessment of progression free survival (PFS), objective response rate (ORR) and time to treatment failure (TTF) used in the SQUIRE trial?

Health-related quality of life results in SQUIRE trial

A11. Table 20: Please provide the mean and median LCSS total score at baseline in each arm.

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A12. Figure 14 presents time to deterioration of LCSS and ECOG performance status from the ITT population; however, there were a number of patients who did not have a baseline and post baseline assessment. Please clarify how the ITT population was generated for these outcomes, and provide a forest plot based on patients with a baseline and post-baseline assessment.

A13. Was comparison of EQ-5D index scores between the study arms pre-specified in the SQUIRE statistical analysis plan? If so, please describe the methods of analysis and present the results.

Adverse events in the SQUIRE trial

A14. Table 39 provides the rate of serious adverse events (SAEs) reported. Please provide details of what SAEs were reported in each study group and the number and proportion of participants who experienced each SAE.

A15. Of those discontinuing the SQUIRE study due to adverse events, how many in each arm discontinued due to SAEs?

A16. In the SQUIRE trial, did any treatment emergent adverse events lead to delays in the delivery of subsequent cycles of the treatments?

Network meta-analysis

Studies and data

A17. **Priority question**: Please confirm that ITT data from the SQUIRE trial is used in the NMA (that is, data for the whole SQUIRE trial population rather than the Western Europe subgroup). If not, please update the NMA for the ITT population.

A18. **Priority question**: There are discrepancies between tables 22 and 23, as follows. Please clarify these discrepancies and, if necessary, provide corrected versions of the tables.

a. For some comparators (specifically carboplatin + gemcitabine, paclitaxel + gemcitabine, cisplatin + paclitaxel and cisplatin + docetaxel; Treat et al., Hoang et al. and Tan et al.), table 22 suggests that only the median was available but table 23 states that hazard ratios (HRs) were also available. Please confirm what data were available for these comparators and provide the HRs that were used from each study.
b. Table 23 states the dose of gemcitabine when used in combination with cisplatin is 1000 mg/m^2, but the gemcitabine + cisplatin arm of the SQUIRE study used a gemcitabine dose of 1250 mg/m^2. Please confirm whether this arm of the SQUIRE study was included in the NMA.
c. Table 22 states that HR data are available for cisplatin + vinorelbine and cisplatin + vinorelbine + cetuximab, from the study by Pirker/Gatzemeier et

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al.; however, table 23 states that only median OS data are available. Which table is correct?

d. Table 22 states that only HR data are available for carboplatin + nab-paclitaxel; however, table 23 states that Socinski et al. provided both median and HR. Which table is correct?

A19. The study by Yoshioka et al. listed in table 22 does not appear in any of the network diagrams (figures 23 to 26). Please confirm if this study was included in the NMA. Please also clarify what drug "S-1" is.

A20. Please provide additional details of the trials that were included in the NMA, including: sample size, number with squamous NSCLC, key baseline characteristics (e.g. age, sex, ECOG, stage, race, region [proportion from Western Europe]) and length of follow-up, by trial arm.

A21. **Priority question**: Please provide a tabulated quality assessment of the studies included in the NMA that are relevant to the decision problem, using the NICE-recommended criteria (and giving definitive judgements for each criterion, e.g. 'yes', 'no', 'unclear'). Please also provide a brief summary of the overall quality of the evidence base.

Methods of analysis

A22. **Priority question**: Please provide OpenBUGS code for the analysis of mean overall survival (OS) and progression-free survival (PFS) used in the NMA.

A23. The submission states (page 89) that fixed-effects models were selected because the random-effects model did not converge in all instances. For random-effects analyses that did converge, were the outcomes compared with the outcomes from the fixed-effects models? Please provide the results of these comparisons.

A24. Please provide additional information on how the meta-analysis models were implemented, including assumptions made about the model and the priors used in the base-case and sensitivity analyses (e.g. priors for distributions for scale parameters, treatment effects, and initial values).

A25. The submission states (page 89) that convergence was assessed through trace plots. Were any other diagnostics considered (e.g. autocorrelation)? If so please provide the findings.

A26. Please confirm whether tests of the proportional hazards assumption were conducted using data from the SQUIRE study. If so, please provide the results. If these were not conducted, please explain why not.

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A27. **Priority question**: The submission states (pages 162 and 231) that "HRs from the NMA are based on clinical studies that consisted of at least 30% squamous NSCLC". However, in some studies in table 22 less than 30% of the population has squamous NSCLC. Please confirm whether only data from squamous patients were used in the NMA. If so, please clarify the meaning of the statements on pages 162 and 231.

Results and conclusions

A28. Figures 28, 30, 32 and 34 are not referred to in the text.

a. Please comment on the findings in these figures.
b. The HRs in the figures do not appear to match the results reported in the corresponding tables (tables 25–26, 28–29, 31–32 and 34–35). Please provide an explanation for these differences.
c. The upper and lower panels of these figures appear identical. Are they correct? If not, please provide corrected figures.

Section B: Clarification on cost-effectiveness data

B1. Were the extrapolations of survival validated against observational data, for any of the comparators?

B2. **Priority question**: Tables 25 and 28 in Appendix 11 provide Kaplan–Meier outputs for overall- and progression-free survival in the Western European population. Please provide equivalent tables for the ITT population.

B3. **Priority question**: Paclitaxel in combination with cisplatin is listed as an available comparator on page 162, but is not included in the base case. Please explain why this comparator was not included.

B4. **Priority question**: Please provide the mean and standard deviation for the EQ-5D-3L index score data at baseline and at each follow-up point for each study group in the SQUIRE trial, for the ITT population, using the table below. Please include a full description of the amount of missing data.

Visit	GCis + N (N=)				GCis (N=)			
	Time	n	mean	SD	Time	n	mean	SD
Baseline								
1								
2								
3								
…								
17								

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Section C: Textual clarifications and additional points

C1. Table 1 states that the population in the decision problem "is not consistent with the indication provided in the summary of product characteristics for necitumumab". Please clarify how the decision problem and the SPC differ.

C2. Please provide full-text references for the following studies: Socinski et al. 2015 (cited on page 74) Socinski et al. 2012, Kubota et al. 2008, Pirker 2009, Pirker 2012, Gatzemeier 2011 and Tan et al. 2009 (cited in table 22). Please also provide the supplementary appendix for the following reference: Goldstein et al. Necitumumab in Metastatic Squamous Cell Lung Cancer: Establishing a Value-Based Cost. JAMA Oncol 2015.

C3. Please clarify whether figure 19 shows the EQ-5D-3L index score or VAS measurement.

C4. Please confirm whether figures 17-21 are for the ITT population, or the Western European subgroup.

C5. Table 24 (page 97) refers to the same comparators for the Treat et al. (2010) study twice (top and middle rows). Please confirm if this is correct, and if not provide a corrected table.

1st March 2016

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation, NICE
Level 1A, City Tower
Manchester
M1 4BT

Eli Lilly and Company Limited

Lilly House
Priestley Road
Basingstoke
Hants

RE: Lilly response to STA clarification questions: Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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 necitumumab.

Please contact me if you have any further queries, either by email or telephone (01256 775022).

Kind regards

[redacted]

Section A: Clarification on effectiveness data

Additional analysis

A1. **Priority question**: The submission states (on pages 15, 142 and 231) that additional analyses will be provided to reflect the population in the summary of product characteristics (SPC). Please provide these analyses, including full details of the methods and population in the analysis.

Please see Appendix 1 for results pertaining to patients with EGFR expressing tumours only, reflecting the population in the summary of product characteristics (SPC). The clinical section includes data for both the total and Western Europe subpopulations of patients with EGFR expressing tumours. The economic section only includes data for the Western Europe subpopulation of patients with EGFR expressing tumours. The data for EGFR expressing tumours were analysed using the same statistical methods as that of the ITT population. Please see section 4.4 of the main submission for Necitumumab for full details of the methods used for the analysis provided in the clinical section. Please see sections 5.3, 5.4, 5.5 and 5.6 of the main submission for Necitumumab for full details of the methods used for the analysis provided in the cost-effectiveness section.

Systematic reviews

A2. The PRISMA flowchart for the main systematic review (figure 2 on page 41 of the submission) shows that 34 studies were excluded at the screening and full-text assessment stages of the systematic review; please provide a list of the excluded studies and list the reasons why the 6 studies excluded at the full-text assessment stage were excluded.

Please see Appendix 2 for the list of all excluded studies and the justifications for exclusion. Additionally, there has been a typographical error in the flow diagram. The six studies excluded at the full-text assessment were not abstracts. Please see Appendix 2 for additional details.

A3. Please provide details of the processes followed for study selection, data extraction and risk of bias assessment when carrying out the systematic reviews. In particular, please state how many reviewers carried out each task and, if more than one reviewer was involved, whether the reviewers carried out these tasks independently.

Please see Appendix 3 for details of the systematic reviews undertaken for this appraisal.

A4. The PRISMA flowchart for the systematic review for the network meta-analysis (figure 22) indicates that 39 studies were eligible for the NMA; however, only 13 studies were included.

We would like to clarify that 11 studies were included for the NMA and not 13. In the main submission, we have mentioned that 13 papers pertaining to 11 studies were included for the NMA.

a. Appendix 5 states that some studies were excluded because of use of experimental/unapproved agents, but this is not stated as an exclusion criterion in the study eligibility criteria (table 21). Please confirm the exclusion criteria that were applied.

We confirm that we did not have this as an exclusion criterion for the systematic review, however for the NMA we excluded studies investigating agents without market authorisation in any country for the first-line treatment of patients with advanced or metastatic sqNSCLC, but not necessarily limited by histology (we did not have this as an exclusion criterion for the NMA). However, studies investigating agents without market authorisation but recommended by clinical treatment guidelines and/or used off-label for the first-line treatment of advanced or metastatic sqNSCLC were included to ensure the comparators were relevant for decision making.

Please see Appendix 4 to find exclusion and inclusion criteria of the NMA.

b. There are 7 studies that included comparators relevant to the scope and so whose exclusion from the NMA does not seem to be justified (Heymach et al. 2008, Langer et al. 2014, Lara et al. 2011, Paz-Ares et al. 2013, Scagliotti et al. 2010, Von Pawel et al. 2014, and Spigel et al. 2013). Please explain why these studies have been excluded?

Studies were excluded from the final analysis if they did not have any similar comparators to enable connection to the network through a common comparator (n=5), if they investigated experimental agents not approved for use (n=10), or if the agent use is limited to non-squamous cell NSCLC (e.g. pemetrexed- or bevacizumab-containing regimens, n=6) or not used in NSCLC (n=1).

Heymach et al 2008, Langer et al 2004, Lara et al 2011, Paz-Ares et al 2013, Scagliotti et al 2010, Von Pawel et al 2014 and Spigel et al 2013 investigated agents without market authorisation for the first-line treatment of patients with advanced or metastatic sqNSCLC, but not necessarily limited by histology.

A5. **Priority question**: Please confirm if the NMA included studies of people with stage IV squamous non-small-cell lung cancer (NSCLC) only, or if studies of people with stage IIIA and/or IIIB disease were also included.

We confirm that only patients with advanced or metastatic squamous NSCLC (IIIB/IV) were included in the NMA.

SQUIRE trial patient population

A6. **Priority question**: Please provide additional details of the subgroup analyses by geographical region, including the post-hoc 'Western European' subgroup.

a. Please clarify the rationale for the choice of countries included in the Western European subgroup. Please explain why the subgroup did not also include other countries that may have similar populations to those from Western Europe (e.g. Australia, Canada).

Randomisation was stratified by ECOG PS (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia). Pre-specified subgroup analyses did include a series of analyses based on geographic region, as follows:

- ***Korea and Taiwan combined vs. all others***
- ***Eastern Asia (Korea, Taiwan, Singapore, Philippines, and Thailand) vs. all others***
- ***Eastern Europe (including Russia, Poland, Hungary, Romania, Croatia, Serbia, and Slovakia) vs. Eastern Asia vs. all others***
- ***Eastern Europe vs. all others***
- ***Each non-Eastern country with >40 patients randomized vs. Eastern Asia vs. all others***
- ***Each country with >40 patients randomized vs. all others***

All countries in Europe that were not included in the pre-specified Eastern Europe subgroup were included in the post-hoc Western Europe subpopulation. Australia and Canada were not included as they are not part of Europe. Additionally, it is believed that the Western Europe subpopulation is more generalisable to clinical practice in England than the populations across Australia, Canada and Europe combined.

b. Please provide the additional 'Race' baseline characteristics for the Western European subgroup that are not included in table 13 ('Asian', 'Black or African American' and 'Other' for each arm and the whole subgroup).

Please see Appendix 5

c. On pages 68 and 69, a number of planned subgroup analyses by geographical region are listed. Please provide results from these analyses, in a Forest plot format, including the hazard ratios and 95% confidence intervals.

Please see Appendix 6

A7. **Priority question**: Please clarify the number and proportion of patients in each arm of the SQUIRE trial:

- with high tumour
- EGFR expression (H-score ≥ 200)
- with low tumour EGFR expression (H-score <200)

- without EGFR expressing NSCLC
- with a missing result for EGFR H-score

Please provide this information for both the intention-to-treat (ITT) population and the Western Europe subgroup. For people with low EGFR expression, what was the lowest H-score?

Archived tissue was collected from 1060 of 1093 patients (97% of ITT population). Tumour EGFR protein expression data based on IHC were available for 982 of 1093 (90%) patients out of whom 935 (95%), had tumour samples expressing EGFR protein (EGFR>0). The lowest H-score was 0 (on the scale 0 to 300).

In SQUIRE, exploratory analyses to evaluate the relationships between biomarkers and clinical outcomes were performed based on a mandatory tissue collection rate of 97%. For the preplanned exploratory analysis for EGFR protein expression based on an H-score cutoff of 200 (refer to Section 11.5.3 of the SQUIRE CSR)

Inconsistent results across major outcome parameters (OS and PFS) were demonstrated. A more favourable treatment HR for OS in patients bearing tumours with high EGFR expression as compared with low expression was observed, however, an opposite trend was seen for PFS. Interaction test results for both OS and PFS were statistically non-significant, indicating that an H-score threshold of 200 was not of value to predict a differential necitumumab effect in squamous NSCLC.

Additionally an H-score cutoff of 0 was assessed; the large majority of patients (95.2% of evaluable patients; n = 935) had tumour samples expressing EGFR protein benefit from the addition of necitumumab to gemcitabine and cisplatin therapy; small subpopulation of patients without detectable EGFR (H-score=0; 4.8% of evaluable patients; N=47) may not benefit from the addition of necitumumab to gemcitabine and cisplatin therapy

EGFR Expression >0		***EGFR Expression =0***	
GCis +N (N=462)	***GCis (N=473)***	***GCis+N (N=24)***	***GCis (N=23)***

SQUIRE trial methodology

A8. **Priority question**: Please confirm what previous treatments were permitted before entry into the SQUIRE trial. In particular, could patients have had previous treatment for less advanced disease? What proportion of the population in the SQUIRE trial in each arm received prior treatment?

The SQUIRE exclusion criteria included the following:

- ***Prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor.***

- ***Previous chemotherapy for advanced NSCLC (patients who have received adjuvant chemotherapy were eligible if the last administration of the prior adjuvant regimen occurred at least 1 year prior to randomization).***

Prior anti-cancer therapy is summarised in Table JFCC.14.14 on page 212 and Table JFCC.14.15 on page 213 of the CSR which was provided along with the submission.

A9. During the SQUIRE trial, who assessed progressive disease or toxicity to define whether maintenance therapy was given? Were they blinded to treatment allocation?

The assessment for progressive disease or toxicity to define whether maintenance therapy was given was completed by investigators. The investigators were not blinded to treatment allocation as this study was conducted open-label, because of the expected occurrence of acneform rash (common with EGFR inhibitors) in the GCis+N Arm relative to the GCis Arm. The rash would have unblinded most patients and investigators to treatment assignment.

A10. Was an independent review of the assessment of progression free survival (PFS), objective response rate (ORR) and time to treatment failure (TTF) used in the SQUIRE trial?

No, an independent review of the assessment of PFS, ORR and TTF used in the SQUIRE was not conducted as the primary endpoint of the study was OS.

<u>Health-related quality of life results in SQUIRE trial</u>

A11. Table 20: Please provide the mean and median LCSS total score at baseline in each arm.

Please see Table JFCC.11.16 on page 110 of the CSR which was provided along with the submission.

A12. Figure 14 presents time to deterioration of LCSS and ECOG performance status from the ITT population; however, there were a number of patients who did not have a baseline and post baseline assessment. Please clarify how the ITT population was generated for these outcomes, and provide a forest plot based on patients with a baseline and post-baseline assessment.

The LCSS analysis was done on the ITT population. For each of the 12 LCSS variables, all patients with a baseline value and at least 1 post-baseline value of the variable were to be included in the following analyses. Patients without baseline and/or post-baseline assessments were censored at the randomisation date. Please see page 62 of the CSR for additional details.

A13. Was comparison of EQ-5D index scores between the study arms pre-specified in the SQUIRE statistical analysis plan? If so, please describe the methods of analysis and present the results.

No formal statistical test of difference between arms was planned in the SAP. The pre-specified analysis was descriptive and to present the frequency and percentage of patient's responses (no problem, some problem, and extreme problem) for each of the 5 dimensions by treatment arm and at each assessment time. Responses were also to be presented graphically using stacked bar charts overtime. Also, to be presented were summary statistics, including change from baseline, for index score (using UK weights) and the VAS for each assessment visit in the chemotherapy phase (up to cycle 6) by treatment arm. Graphical presentation was to be box plots overtime. (Please see Figure JFCC.14.17 and Figure JFCC.14.18 on page 634 of the CSR)

Best and worst change from-baseline mean scores for index score (using UK weights) and VAS were to be analysed with descriptive statistics presented at each assessment visit for the chemotherapy phase (up to cycle 6) by treatment arm with a graphic figure depicting the mean best and worst change from baseline. .

Please see Appendix 7 for the EQ-5D results.

Adverse events in the SQUIRE trial

A14. Table 39 provides the rate of serious adverse events (SAEs) reported. Please provide details of what SAEs were reported in each study group and the number and proportion of participants who experienced each SAE.

Please see pages 144 to 146 of the CSR.

A15. Of those discontinuing the SQUIRE study due to adverse events, how many in each arm discontinued due to SAEs?

Please see section 12.3.3.1 on page 146 of the CSR

A16. In the SQUIRE trial, did any treatment emergent adverse events lead to delays in the delivery of subsequent cycles of the treatments?

Please see section 12.3.3.2 on page 149 of the CSR.

Network meta-analysis

Studies and data

A17. **Priority question**: Please confirm that ITT data from the SQUIRE trial is used in the NMA (that is, data for the whole SQUIRE trial population rather than the Western Europe subgroup). If not, please update the NMA for the ITT population.

We confirm that ITT data from the SQUIRE trial was used in the NMA.

A18. **Priority question**: There are discrepancies between tables 22 and 23, as follows. Please clarify these discrepancies and, if necessary, provide corrected versions of the tables.

a. For some comparators (specifically carboplatin + gemcitabine, paclitaxel + gemcitabine, cisplatin + paclitaxel and cisplatin + docetaxel; Treat et al., Hoang et al. and Tan et al.), table 22 suggests that only the median was available but table 23 states that hazard ratios (HRs) were also available. Please confirm what data were available for these comparators and provide the HRs that were used from each study.

Please see Appendix 8 for more information on which outcomes were available from each study

b. Table 23 states the dose of gemcitabine when used in combination with cisplatin is 1000 mg/m^2, but the gemcitabine + cisplatin arm of the SQUIRE study used a gemcitabine dose of 1250 mg/m^2. Please confirm whether this arm of the SQUIRE study was included in the NMA.

The dose of gemcitabine used in the SQUIRE trial is 1250 mg/m^2 and this arm and dosage was used in the NMA.

c. Table 22 states that HR data are available for cisplatin + vinorelbine and cisplatin + vinorelbine + cetuximab, from the study by Pirker/Gatzemeier et al.; however, table 23 states that only median OS data are available. Which table is correct?

Pirker study is connected via Tan, et al. 2009 (GLOB-3) which has no HR data so for the HR based analysis Pirker study is not connected. Please also see Appendix 8.

d. Table 22 states that only HR data are available for carboplatin + nab-paclitaxel; however, table 23 states that Socinski et al. provided both median and HR. Which table is correct?

Please see Appendix 8.

A19. The study by Yoshioka et al. listed in table 22 does not appear in any of the network diagrams (figures 23 to 26). Please confirm if this study was included in the NMA. Please also clarify what drug “S-1” is.

We can confirm that results provided in the main submission do not include S-1 as it is not relevant to countries outside of Japan.

S-1 is a combination of three drugs: tegafur, a fourth generation pro-drug of 5-fluorouracil (5-FU); gimeracil; and oteracil. It was approved to treat NSCLC in Japan in 2004 for use alone or in combination with platinum compounds. Outside of Japan, it is not approved to treat patients with NSCLC and is not seen as a treatment option in western countries despite being standard of care in Japan.

A20. Please provide additional details of the trials that were included in the NMA, including: sample size, number with squamous NSCLC, key baseline characteristics (e.g. age, sex, ECOG, stage, race, region [proportion from Western Europe]) and length of follow-up, by trial arm.

Please see Appendix 9.

A21. **Priority question**: Please provide a tabulated quality assessment of the studies included in the NMA that are relevant to the decision problem, using the NICE-recommended criteria (and giving definitive judgements for each criterion, e.g. 'yes', 'no', 'unclear'). Please also provide a brief summary of the overall quality of the evidence base.

Please see Appendix 10.

Methods of analysis

A22. **Priority question**: Please provide OpenBUGS code for the analysis of mean overall survival (OS) and progression-free survival (PFS) used in the NMA.

Please see Appendix 11.

A23. The submission states (page 89) that fixed-effects models were selected because the random-effects model did not converge in all instances. For random-effects analyses that did converge, were the outcomes compared with the outcomes from the fixed-effects models? Please provide the results of these comparisons.

Due to the limited number of studies (e.g. most comparators were supported by only one study) and small patient numbers, the random effects heterogeneity variance became difficult to estimate and the random effects models did not converge. Therefore, all analyses were conducted using a fixed effects model.

A24. Please provide additional information on how the meta-analysis models were implemented, including assumptions made about the model and the priors used in the base-case and sensitivity analyses (e.g. priors for distributions for scale parameters, treatment effects, and initial values).

We assumed the relative treatment effect is fixed i.e. it is constant across studies. For both the base (using HR outcome) and sensitivity analyses (using median outcome), we assumed the following

i. diffuse priors on the parameters

ii. 2 chains with initial values listed in the openbugs codes

1000 burn-in iterations, 2000 posterior samples (1000 for each chain)

A25. The submission states (page 89) that convergence was assessed through trace plots. Were any other diagnostics considered (e.g. autocorrelation)? If so please provide the findings.

The autocorrelation plots suggest that convergence was reached for the models considered.

A26. Please confirm whether tests of the proportional hazards assumption were conducted using data from the SQUIRE study. If so, please provide the results. If these were not conducted, please explain why not.

The Kernel-smoothed hazard function has been used to assess the behaviour of the hazard function and the plausibility of the proportional hazards assumption. The plot of smoothed hazard function of OS from the SQUIRE trial in Figure 6 which demonstrate that the curves from GCis + N and GCis have a non-parallel shape, indicating that the proportional hazards assumption is violated for the Western Europe subpopulation.

A27. **Priority question**: The submission states (pages 162 and 231) that "HRs from the NMA are based on clinical studies that consisted of at least 30% squamous NSCLC". However, in some studies in table 22 less than 30% of the population has squamous NSCLC. Please confirm whether only data from squamous patients were used in the NMA. If so, please clarify the meaning of the statements on pages 162 and 231.

The statement given in the dossier was incorrect. Most studies included in the NMA consisted of a patient population with at least 30% of patients having squamous NSCLC. This is a descriptive statement of the findings and was not an exclusion criteria applied to the NMA.

Results and conclusions

A28. Figures 28, 30, 32 and 34 are not referred to in the text.

a. Please comment on the findings in these figures.

These figures presents forest plot of HRs of the comparators versus necitumumab plus gemcitabine and cisplatin (GCis + N). A HR lower than 1 is associated with a lower risk of death and a HR above 1 is a greater risk of death versus necitumumab plus gemcitabine and cisplatin. Data were consistent for median and mean effects. Figure 28 presents OS HR for the comparators against GCis + N and shows that GCis + N was associated with a lower HR than all comparators. Figure 30 presents PFS HRs for the comparators against GCis + N. The results show that GCis + N was associated with a lower HR than all comparators. Figure 32 and 33 presents forest plot of ratio of median OS and PFS and show that GCis + N was associated with a longer time to progression than all comparators.

b. The HRs in the figures do not appear to match the results reported in the corresponding tables (tables 25–26, 28–29, 31–32 and 34–35). Please provide an explanation for these differences.

In the tables HR results comparing GCis + N against all the comparators have been exponentiated. If you exponentiate HR of a particular comparison from any figure then it will give you the value given in the table for that particular comparison.

c. The upper and lower panels of these figures appear identical. Are they correct? If not, please provide corrected figures.

Upper figure refers to median and lower figure to mean. They are identical within hundredths of a decimal point in most cases, so the figures look identical.

Section B: Clarification on cost-effectiveness data

B1. Were the extrapolations of survival validated against observational data, for any of the comparators?

Within the model, approximately 7% of GCis + N patients are still alive at year 5 and 3% of GCis patients. These estimates are consistent with the published estimates of 5.9% of patients still alive at year 5 with NSCLC.[1] No observational data on the survival of advanced or metastatic squamous NSCLC for any of the comparators was identified.

B2. **Priority question**: Tables 25 and 28 in Appendix 11 provide Kaplan–Meier outputs for overall- and progression-free survival in the Western European population. Please provide equivalent tables for the ITT population.

Please see Appendix 12

B3. **Priority question**: Paclitaxel in combination with cisplatin is listed as an available comparator on page 162, but is not included in the base case. Please explain why this comparator was not included.

***Paclitaxel in combination with cisplatin was included in the NMA; however, it was not included in the cost-effectiveness analysis as it is not typically used in clinical* practice in England.**

Market share data (Table 94 of the original submission) suggests that approximately [redacted] of all first-line squamous NSCLC patients receive Paclitaxel plus carboplatin. [redacted] of patients receive other combinations. The market share data showed that Vinorelbine in combination with platinum drug ([redacted]) is the second most commonly used first- line treatment in the UK. Therefore, it can be assumed that less than [redacted] of

[1] **Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Zero**

patients receive Paclitaxel plus cisplatin in England. Therefore, it was determined that it is not typically used in clinical practice in England.

B4. **Priority question**: Please provide the mean and standard deviation for the EQ-5D-3L index score data at baseline and at each follow-up point for each study group in the SQUIRE trial, for the ITT population, using the table below. Please include a full description of the amount of missing data.

Please see Appendix 13

Section C: Textual clarifications and additional points

C1. Table 1 states that the population in the decision problem "is not consistent with the indication provided in the summary of product characteristics for necitumumab". Please clarify how the decision problem and the SPC differ.

The decision problem and the submission is for necitumumab in combination with gemcitabine and cisplatin (GCis + N) in people with locally advanced or metastatic squamous non-small cell lung cancer who have not received prior chemotherapy for this indication. The SPC states that necitumumab is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition. Therefore, the decision problem and submission has not been limited to patients with EGFR expressing squamous NSCLC patients.

Following CHMP decision, the timelines for NICE submission did not allow adequate time to update the document and run cost-effectiveness analysis pertaining to patients with EGFR expressing tumours.

C2. Please provide full-text references for the following studies: Socinski et al. 2015 (cited on page 74) Socinski et al. 2012, Kubota et al. 2008, Pirker 2009, Pirker 2012, Gatzemeier 2011 and Tan et al. 2009 (cited in table 22). Please also provide the supplementary appendix for the following reference: Goldstein et al. Necitumumab in Metastatic Squamous Cell Lung Cancer: Establishing a Value-Based Cost. JAMA Oncol 2015.

These full references have now been provided.

C3. Please clarify whether figure 19 shows the EQ-5D-3L index score or VAS measurement.

Figure 19 is EQ-5D-3L index scores, Figure 20 is the EQ-5D-3L VAS scores

C4. Please confirm whether figures 17-21 are for the ITT population, or the Western European subgroup.

Figure 17-21 is for the ITT population.

C5. Table 24 (page 97) refers to the same comparators for the Treat et al. (2010) study twice (top and middle rows). Please confirm if this is correct, and if not provide a corrected table.

Please see corrected table in Appendix 14

Appendices

Appendix 1. Response to question A1

Full analyses have been provided below that reflect the population in the summary of product characteristics (SPC) for Necitumumab, EGFR expressing tumour patients (H-score >0). The clinical section includes data for both the total EGFR expressing tumour population and the Western Europe EGFR expressing tumour subpopulation. The economic section only includes data for the Western Europe EGFR expressing tumour subpopulation, consistent with the main NICE submission for Necitumumab. The data for the EGFR expressing tumour population were analysed using the same statistical methods as those outlined in the main submission.

1. CLINICAL EFFECTIVENESS SECTION

Please see section 4.4 of the main submission for Necitumumab for full details of the methods used for the analysis provided below.

Table 1 Patient Demographic Characteristics at Baseline for patients with EGFR expressing tumour (Total and Western European sub population). This table replaces table 13 in the main submission.

	Total population			Western European sub population		
Characteristic	**GCis+N N = 462 n (%)**	**GCis N = 473 n (%)**	**Total N = 935 n (%)**	**GCis+N N = 145 n (%)**	**GCis N = 155 n (%)**	**Total N =300 n (%)**
Age (years)						
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Group, n (%)						
≥18 - <65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years - < 70 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥70 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS at baseline, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking History, n (%)						
Ex-Light Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]			
Geographic Region						
North America, Europe, Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
South America, South Africa, India	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eastern Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; GCis = gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category.

a One patient with ECOG PS = 3 at baseline was randomised to the GCis Arm; this patient did not receive treatment.

b Including eCRF categories “American Indian or Alaska Native,” “Native Hawaiian or Other Pacific Islander,” “Multiple Race,” and “Other.”

Primary endpoint: Overall Survival

Table 2 Overall survival in patients with EGFR expressing tumour (total population). This table replaces table 14 in the main submission.

	Total (EFGR expressing)	
	GCis+N N =462	**GCis N = 473**
Number (%) of events	[redacted]	[redacted]
Number (%) of subjects censored	[redacted]	[redacted]
Median (months)*	11.73	9.99
95% CI	[redacted]	[redacted]
Hazard ratio (95% CI)#	0.79 (0.69 to 0.92)	
Log-rank p-value @	0.002	

*Estimated by Kaplan-Meier method

Hazard ratio is expressed as treatment/control and estimated from stratified Cox model

@ Stratified log-rank two-sided p-value

Figure 1 Kaplan-Meier curve for Overall survival patients with EGFR expressing tumour (total population). This figure replaces figure 4 in the main submission.

Table 3 Overall survival in patients with EGFR expressing tumour (Western European subpopulation). This table replaces information provide in section 4.7 (page 61) in the main submission.

	Western European subpopulation	
	GCis+N N =145	**GCis N = 155**
Number of events, n (%)	[redacted]	[redacted]
Median (months)*	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio# (95% CI)	[redacted]	
Log-rank p-value @	[redacted]	

WE includes Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, Belgium

*Estimated by Kaplan-Meier method

Hazard ratio is expressed as treatment/control and estimated from unstratified Cox model

@ Unstratified and unadjusted log-rank two-sided p-value

Figure 2 Kaplan-Meier curve for overall survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 5 in the main submission.

Arm A: GCis + N; Arm B: GCis

Progression-Free Survival Results

Table 4 Progression free survival in patients with EGFR expressing tumours (total population). This table replaces table 15 in the main submission.

	Total (EFGR expressing)	
	GCis+N N =462	**GCis N = 473**
Number (%) of subjects with events	[redacted]	[redacted]
Number (%) of subjects censored	[redacted]	[redacted]
Median (months)*	5.72	5.49
95% CI	[redacted]	[redacted]
Hazard ratio (95% CI)#	0.84 (0.72 to 0.97)	
Log-rank p-value @	0.018	

*Estimated by Kaplan-Meier method

Hazard ratio is expressed as treatment/control and estimated from stratified Cox model

@ Stratified log-rank two-sided p-value

Figure 3 Kaplan-Meier curve for the progression free survival in patients with EGFR expressing tumours (total population). This figure replaces figure 6 in the main submission.

Table 5 Progression free survival in patients with EGFR expressing tumours (Western European subpopulation). This table replaces information provide in section 4.7 (page 64) in the main submission.

	Western European subpopulation	
	GCis+N N =145	**GCis N = 155**
Number of events, n (%)	[redacted]	[redacted]
Median (months)*	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio# (95% CI)	[redacted]	
Log-rank p-value @	[redacted]	

WE includes Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, Belgium

*Estimated by Kaplan-Meier method

Hazard ratio is expressed as treatment/control and estimated from unstratified Cox model

@ Unstratified and unadjusted log-rank two-sided p-value

Figure 4 Kaplan-Meier curve for progression-free survival in patients with EGFR expressing tumours (Western European subpopulation). This figure replaces figure 7 in the main submission.

Arm A: GCis + N; Arm B: GCis

Time to Treatment Failure (TTF)

Table 6 Time to Treatment Failure in patients with EGFR expressing tumours (total population). This table replaces table 18 in the main submission.

	GCis+N N =462	GCis N = 473
Number of events, n (%)	[redacted]	[redacted]
Stratified log-rank p-Value (2-sided)	[redacted]	
Stratified HR[b] (95%CI)	[redacted]	
Median TTF[a], months	[redacted]	[redacted]
(95% CI)[a]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; TTF = time to treatment failure.

a Estimated by the KM method.

b Hazard ratio is expressed as treatment/control and estimated from stratified Cox model.

Time to treatment failure (Western European population)

Table 7 Time to Treatment Failure in the Western European subpopulation. This table replaces table 19 in the main submission.

	GCis+N N =145	GCis N = 155
Number of events	[redacted]	[redacted]
Stratified log-rank p-Value (2-sided)	[redacted]	
Stratified HR[b] (95%CI)	[redacted]	
Median TTF[a], months	[redacted]	[redacted]
(95% CI)[a]	[redacted]	[redacted]
HR[b]	[redacted]	
95% CI	[redacted]	
Log-rank p-value[c]	[redacted]	

Abbreviations: CI = confidence interval; GCis =gemcitabine and cisplatin; GCis+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of randomised patients; n = number of patients in category; TTF = time to treatment failure.

a Estimated by the KM method.

b Hazard ratio is expressed as treatment/control and estimated from unstratified Cox model.

c Unstratified and unadjusted log-rank two-sided p-value

Objective response

Table 8 Objective response in patients with EGFR expressing tumours (total population). This table replaces table 16 in the main submission.

	GCis + N (N=462	GCis (N=473)	Difference	OR	p-value
Complete response (CR)					
Partial Response (PR)					
Stable Disease (SD)					
Progressive Disease (PD)					
Unable to evaluate					
Not applicable					
Objective Response (CR + RR)					
95% CI for Response rate					
Disease control (CR + PR + DR)					
95% CI for response rate					

N = number of patients in analysis population; CI = confidence interval; OR =odds ratio.

Table 9 Objective response for the Western European subpopulation. This table replaces table 17 in the main submission.

	GCis + N (N=145)	GCis (N=155)
Objective response (CR + PR), n		
%, (95% CI)		
95% of difference of response rate*		
OR# (95% CI)		

*Estimated using the Wilson formula
#Odds ratio is expressed as treatment/control

Adverse events

Table 10 Treatment-emergent adverse events of any grade or grade ≥3 in patients with EGFR expressing tumours (Safety population). This table replaces table 38 in the main submission.

Preferred Term	GCis+N N = 456 n (%)		GCis N = 468 n (%)	
	Any grade	Gr. ≥3	Any grade	Gr. ≥3
Patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; N = number of treated patients; n = number of patients in category

Table 11 Treatment-emergent adverse events of any grade or grade ≥3 in patients with EGFR expressing tumours (Western European, Safety Population). This table provides additional information to table 38 in the main submission.

Preferred Term	GCis+N N = 144 n (%)		GCis N = 154 n (%)	
	Any grade	Gr. ≥3	Any grade	Gr. ≥3
Patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term	GCis+N N = 144 n (%)		GCis N = 154 n (%)	
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; N = number of treated patients; n = number of patients in category

Table 12 Adverse Events of Special Interest in patients with EGFR expressing tumours – Thromboembolic Events (Total, Safety population). This table provides additional information table 40 in the main submission.

AESI	GCis+N N = 456 n (%)		GCis N = 468 n (%)	
	Any Grade	Grade 3	Any Grade	Grade 3
Venous Thromboembolic Events (VTEs)	[redacted]	[redacted]	[redacted]	[redacted]
Arterial Thromboembolic Events (ATEs)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category

Table 13 Adverse Events of Special Interest in patients with EGFR expressing tumours – Thromboembolic Events (Western European, Safety Population). This table replaces table 40 in the main submission.

AESI	GCis+N N = 144 n (%)		GCis N = 154 n (%)	
	Any Grade	Grade 3	Any Grade	Grade 3
Venous Thromboembolic Events (VTEs)	[redacted]	[redacted]	[redacted]	[redacted]
Arterial Thromboembolic Events (ATEs)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; GCis = gemcitabine and cisplatin; GCis+N = necitumumab plus gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category

Thromboembolic events according to different treatment phase

Table 14 Adverse Events of Special Interest in patients with EGFR expressing tumours – Thromboembolic Events in SQUIRE (Safety Population) Reported for 2 or More Patients in the GCis + N Arm. This table replaces table 41 in the main submission.

AESI	Ctx Phase				Mai Phase	
	GCis + N N = 456 n (%)		GCis N = 468 n (%)		GCis + N N = 242 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Arterial Thromboembolic Events	[redacted]					
Ischaemic Stroke	[redacted]					
Cerebral Ischaemia	[redacted]					
Cerebral infarction	[redacted]					
Acute Myocardial Infarction	[redacted]					
Aortic Thrombosis	[redacted]					
Myocardial Infarction	[redacted]					
Peripheral Arterial Occlusive Disease	[redacted]					
Peripheral Artery Thrombosis	[redacted]					
Transient Ischaemic Attack	[redacted]					
Cerebrovascular accident	[redacted]					
Peripheral Embolism	[redacted]					
Angina pectoris	[redacted]					
Coronary artery disease	[redacted]					
Peripheral artery stenosis	[redacted]					
Peripheral ischaemia	[redacted]					
Renal infarct	[redacted]					
Splenic infarction	[redacted]					
Acute coronary syndrome	[redacted]					
Coronary artery stenosis	[redacted]					
Embolism	[redacted]					
Femoral artery occlusion	[redacted]					
Vascular graft occlusion	[redacted]					
Venous thromboembolic events (VTE)	[redacted]					
Pulmonary embolism	[redacted]					
Deep Vein thrombosis	[redacted]					
Thrombosis	[redacted]					
Mesenteric Vein Thrombosis	[redacted]					
Pulmonary Artery Thrombosis	[redacted]					

AESI	Ctx Phase				Mai Phase	
	GCis + N N = 456 n (%)		GCis N = 468 n (%)		GCis + N N = 242 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Axillary Vein Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis in device	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vena cava thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous Thrombosis Limb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subclavian vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Superior vena cava syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis superficial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary venous thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; AE = adverse event; Mai = maintenance; Ctx = chemotherapy; GCis = gemcitabine and cisplatin; GCis + N = gemcitabine and cisplatin plus necitumumab; MedDRATM = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category

Table 15 Adverse Events of Special Interest in patients with EGFR expressing tumours – Thromboembolic Events in SQUIRE (Western European, Safety Population) Reported for 2 or More Patients in the GCis + N Arm. This table provides additional information for table 41 in the main submission.

AESI	Ctx Phase				Mai Phase	
	GCis + N N = 144 n (%)		GCis N = 154 n (%)		GCis + N N = 70 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Arterial Thromboembolic Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute Myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aortic Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral Arterial Occlusive Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral Artery Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transient Ischaemic Attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral Embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal infarct	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous thromboembolic events (VTE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deep Vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mesenteric Vein Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary Artery Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axillary Vein Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous Thrombosis Limb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subclavian vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombophlebitis superficial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; AE = adverse event; Mai = maintenance; Ctx = chemotherapy; GCis = gemcitabine and cisplatin; GCis + N = gemcitabine and cisplatin plus necitumumab; MedDRATM = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category

Other Adverse Events of Special Interest according to different treatment phase

Table 16 Other Adverse Events of Special Interest in patients with EGFR expressing tumours - SQUIRE (Safety Population). This table replaces table 43 in the main submission.

AESI Category[a]	Ctx Phase				Mai Phase	
	GCis + N N = 456 %		GCis N = 468 %		GCis + N N = 242 %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	[redacted]					
Anaemia	[redacted]					
Thrombocytopenia	[redacted]					
Fatigue	[redacted]					
Hypomagnesaemia	[redacted]					
Rash	[redacted]					
Hypersensitivity/IRR	[redacted]					
Eye Disorders	[redacted]					
Interstitial Lung Disease	[redacted]					

Abbreviations: AESI = adverse events of special interest; Mai = maintenance; Ctx = chemotherapy; Gem-Cis = gemcitabine and cisplatin; Gem-Cis+Neci = gemcitabine and cisplatin plus necitumumab; IRR = infusion-related reaction; N = number of treated patients.

[a] AESI include preferred terms and related disorders identified by Lilly.

Table 17 Other Adverse Events of Special Interest in patients with EGFR expressing tumours - SQUIRE (Western European, Safety Population). This table provides additional information for table 43 in the main submission.

AESI Category[a]	Ctx Phase				Mai Phase	
	GCis + N N = 144 %		GCis N = 154 %		GCis + N N = 70 %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/IRR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interstitial Lung Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; Mai = maintenance; Ctx = chemotherapy; Gem-Cis = gemcitabine and cisplatin; Gem-Cis+Neci = gemcitabine and cisplatin plus necitumumab; IRR = infusion-related reaction; N = number of treated patients.

[a] AESI include preferred terms and related disorders identified by Lilly.

2. COST-EFFECTIVENESS RESULTS

Please see sections 5.3, 5.4, 5.5 and 5.6 of the main submission for Necitumumab for full details of the methods used for the analysis provided below.

Figure 5 Kaplan-Meier curve for overall survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 37 in the main submission.

Arm A: GCis + N; Arm B: GCis

Figure 6 **Smoothed Hazard Function for overall survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 38 in the main submission.**

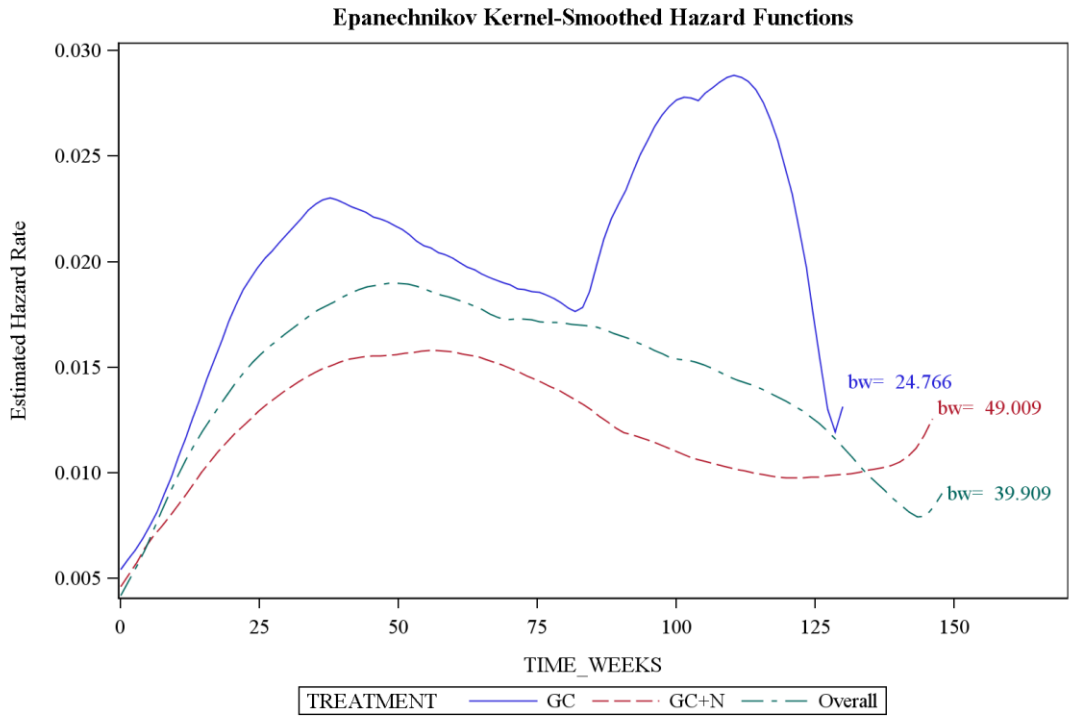
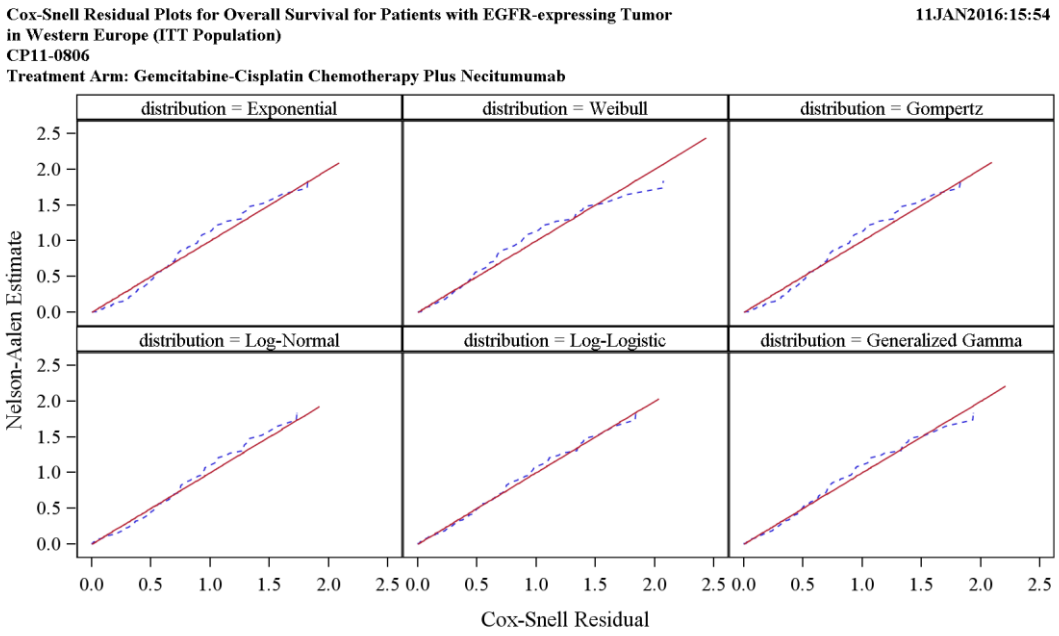


Figure 7 **Cox Snell Residuals for overall survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis+N). This figure replaces figure 39 in the main submission.**



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and/or GC.
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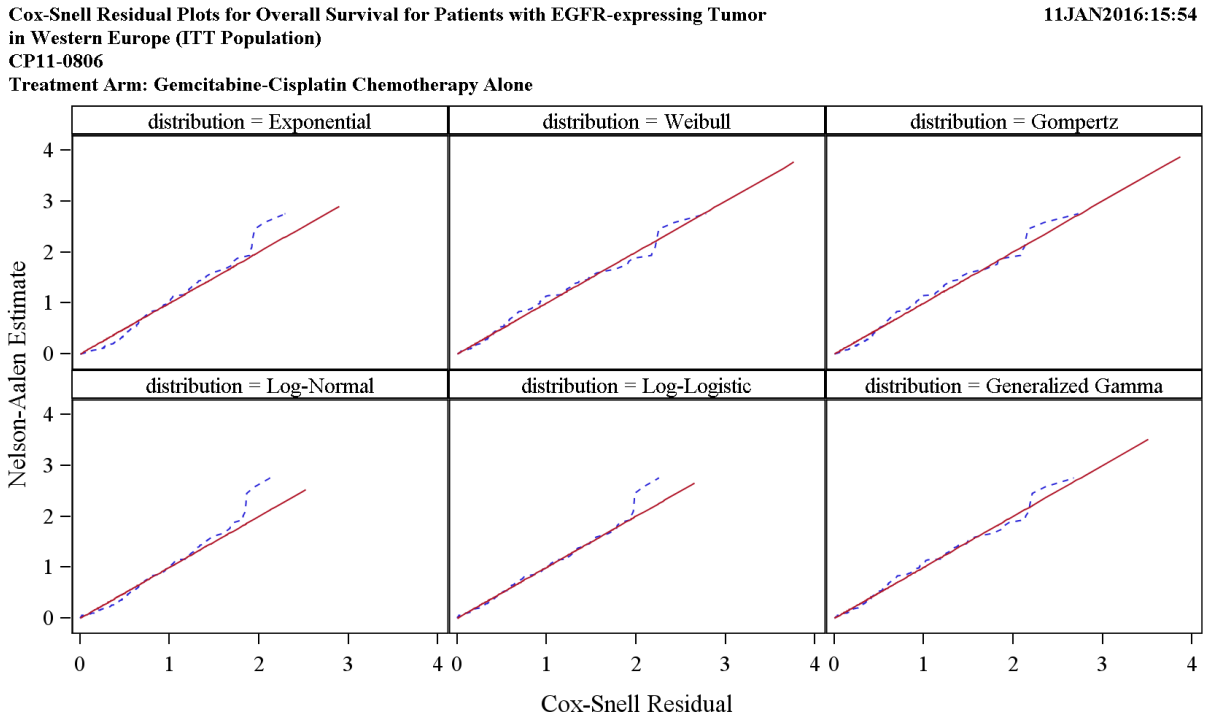
Figure 8 **Cox Snell Residuals for overall survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis). This figure replaces figure 40 in the main submission.**



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and/or GC.
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Figure 9 **Observed and Predicted Distributions overall survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis+N). This figure replaces figure 41 in the main submission.**

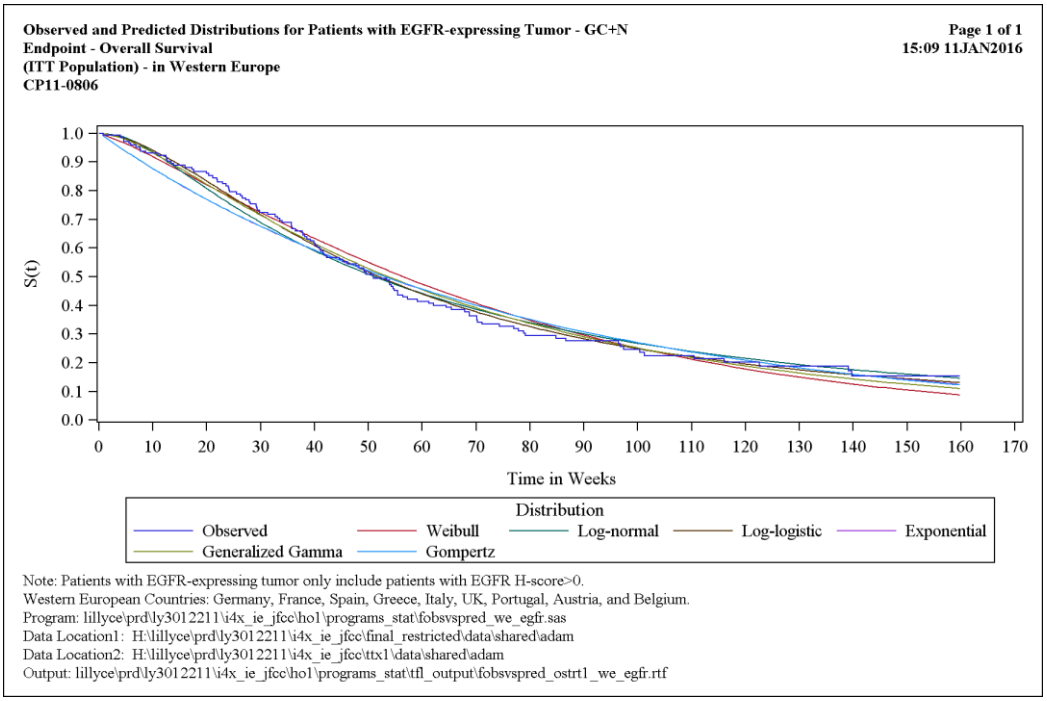


Figure 10 **Observed and Predicted Distributions Overall Survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis). This figure replaces figure 42 in the main submission.**

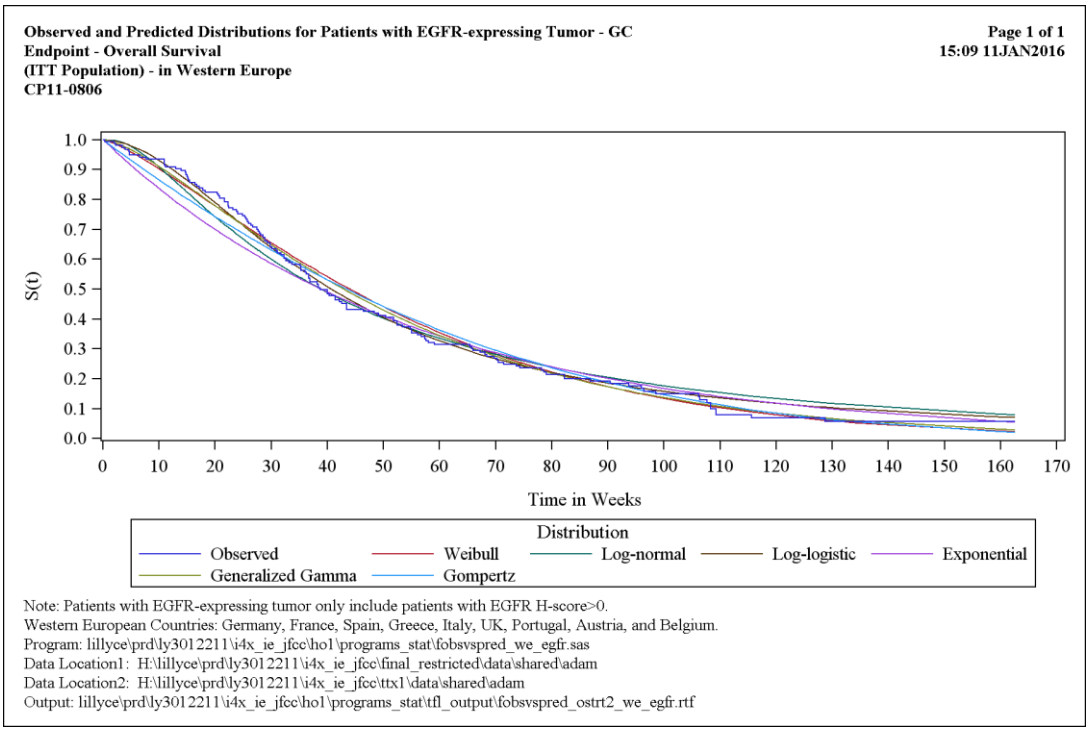
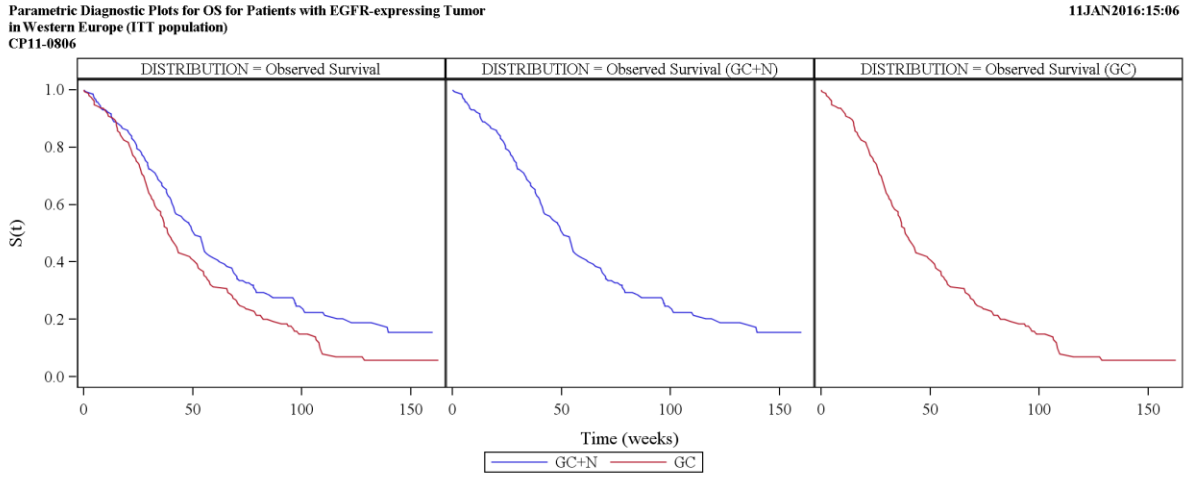


Figure 11 Parametric Diagnostic Plots for Overall Survival in patients with EGFR expressing tumour (Western European subpopulation). These figures replace figure 43 in the main submission.



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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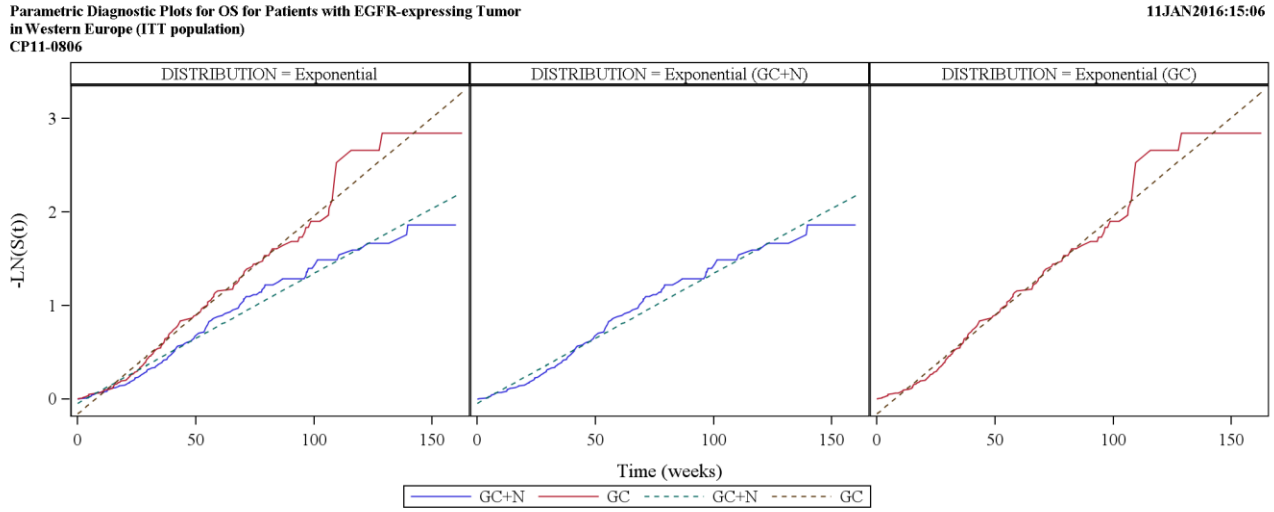

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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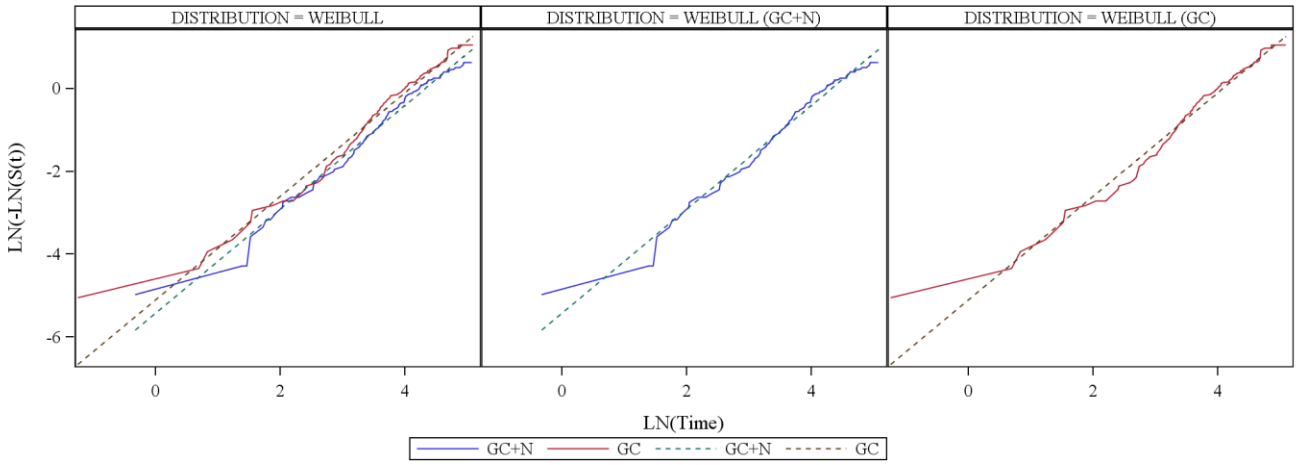
Data Location2: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ttx1\data\shared\adam
Output: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\tfl_output\fparaplot_os_we_egfr.rtf

Parametric Diagnostic Plots for OS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

11JAN2016:15:06



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Data Location2: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ttx1\data\shared\adam
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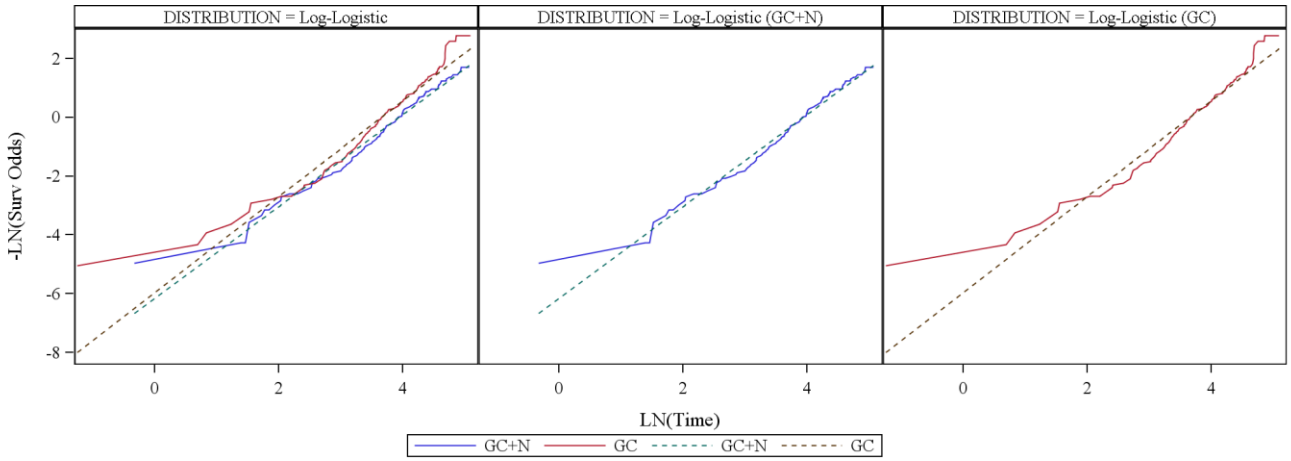
Parametric Diagnostic Plots for OS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

11JAN2016:15:06



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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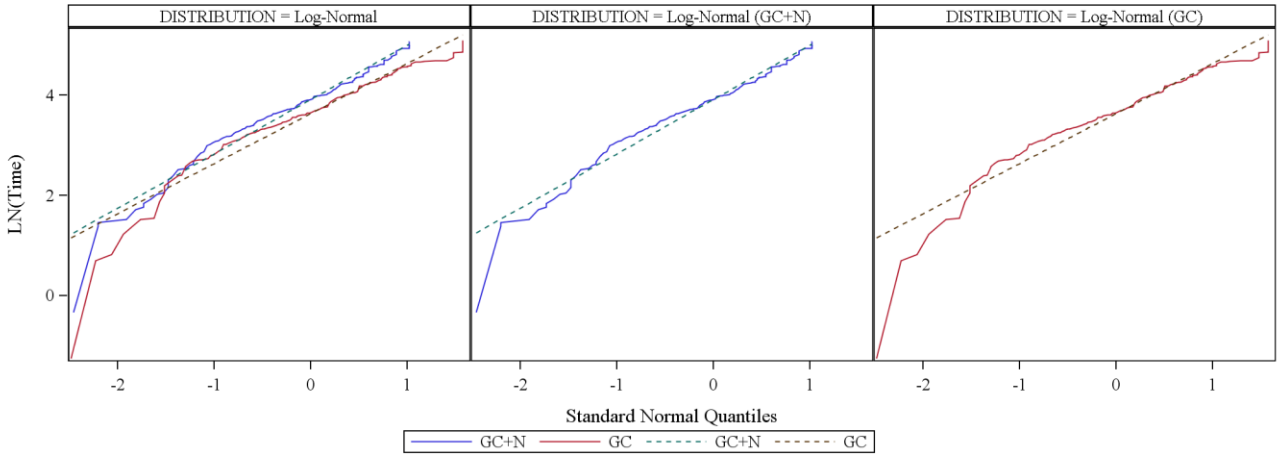
Parametric Diagnostic Plots for OS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

11JAN2016:15:06



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Parametric Diagnostic Plots for OS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

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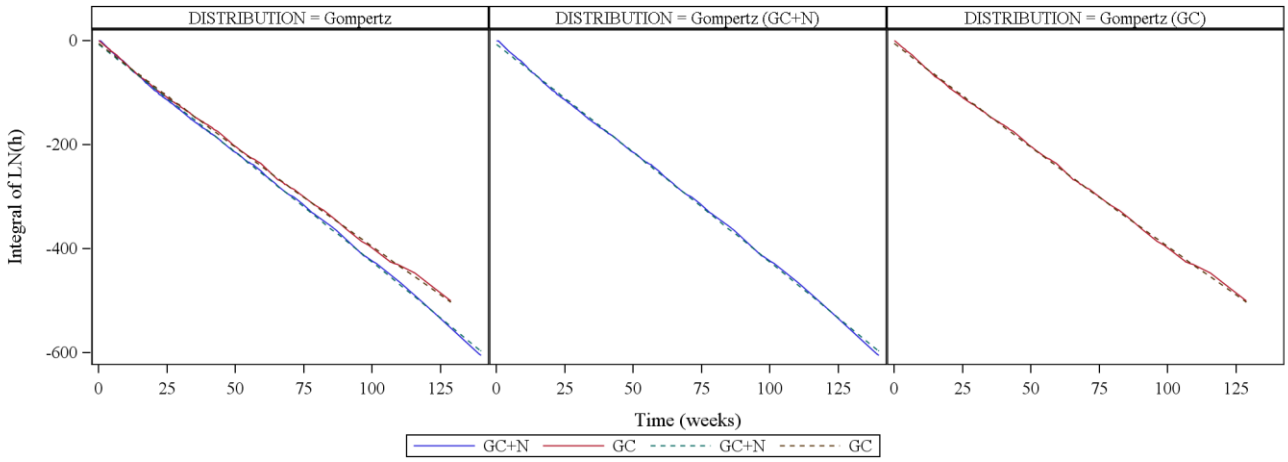

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Figure 12 **Separately Fitted Log-Logistic extrapolation of overall survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 44 in the main submission.**

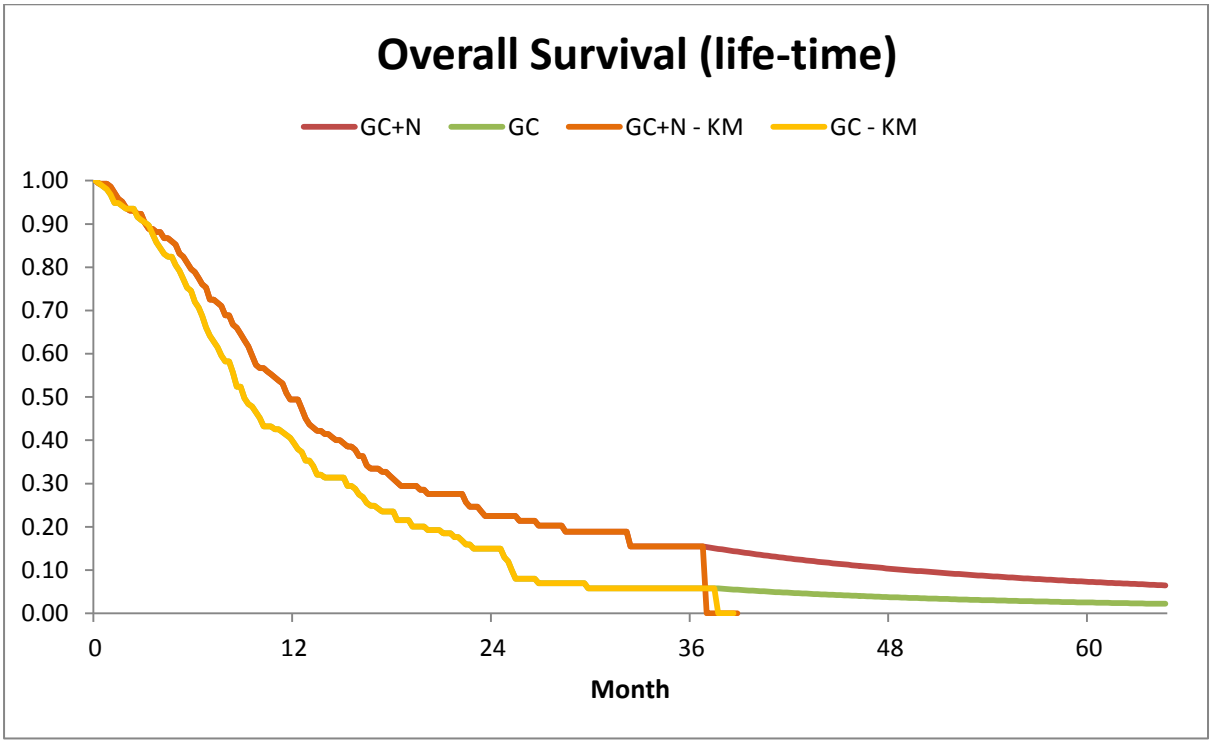


Table 18 **Parameter Estimates AIC and BIC – Overall Survival in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 50 in the main submission.**

	AIC	BIC
GCis+N		
Weibull	391.893	397.847
Log-normal	392.795	398.748
Log-logistic	385.977	391.931
Exponential	395.275	398.252
Generalized Gamma	390.397	399.327
GCis		
Weibull	416.062	422.149
Log-normal	433.06	439.147
Log-logistic	416.941	423.028
Exponential	426.513	429.556
Generalized Gamma	417.003	426.134

Figure 13 Kaplan Meier Curve for Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 45 in the main submission.

Arm A: GCis + N; Arm B: GCis

Figure 14 Smoothed Hazard Function for Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 46 in the main submission.

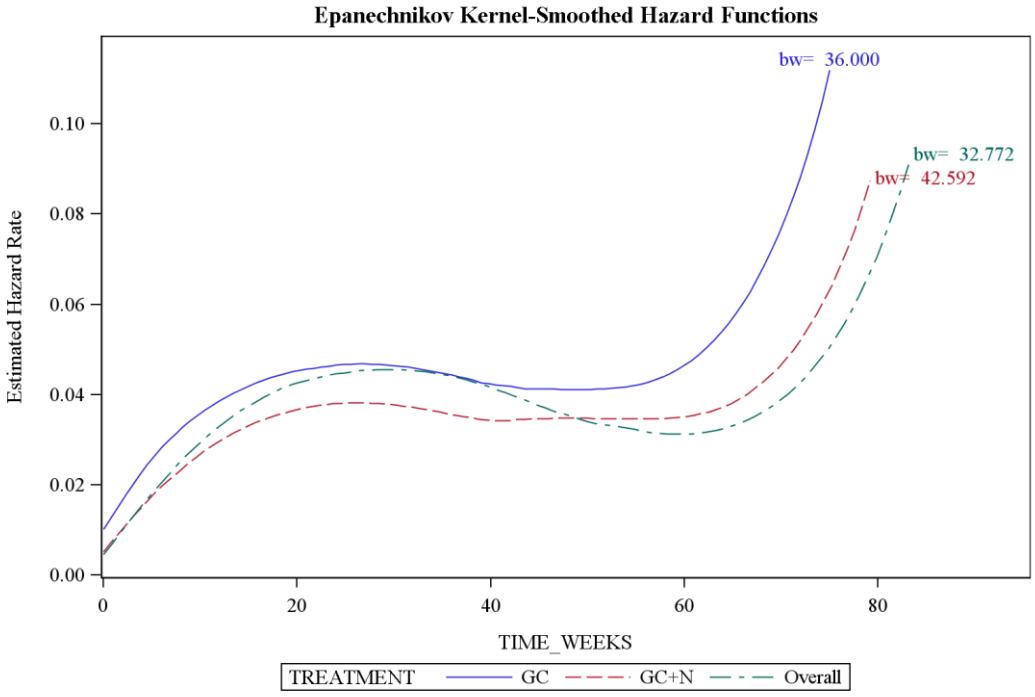
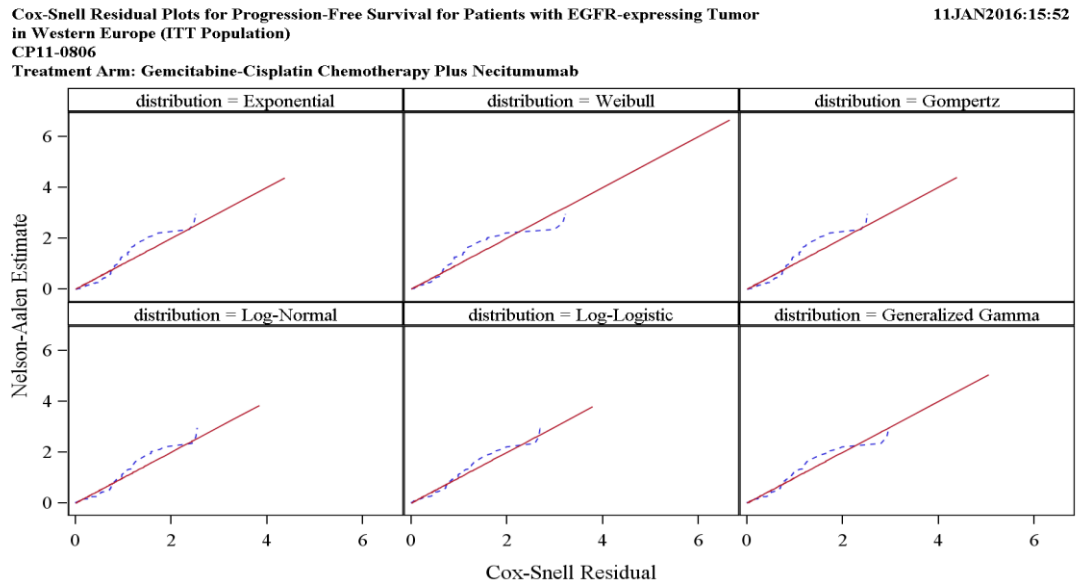


Figure 15 Cox Snell Residuals for progression free survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis+N)



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and/or GC.
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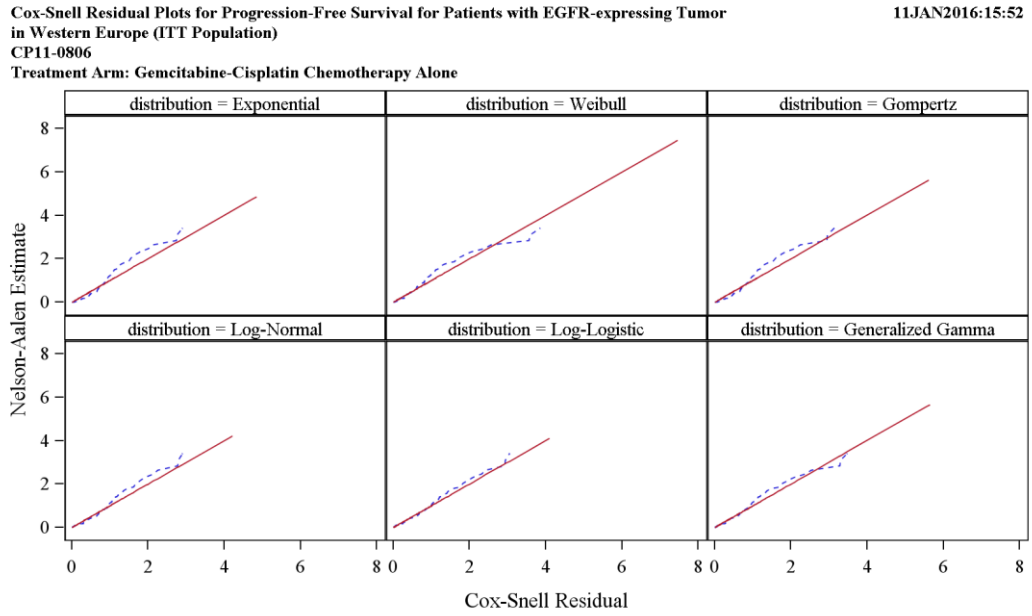
Figure 16 Cox Snell Residuals for progression free survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis)



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Note: Cox-Snell Residual Values under the Gompertz distribution could not be computed for GC+N and/or GC.
Program: lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\fcoxsnell_pfs_we_egfr.sas
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Figure 17 **Observed and Predicted Distributions for Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis+N). This figure replaces figure 47 in the main submission.**

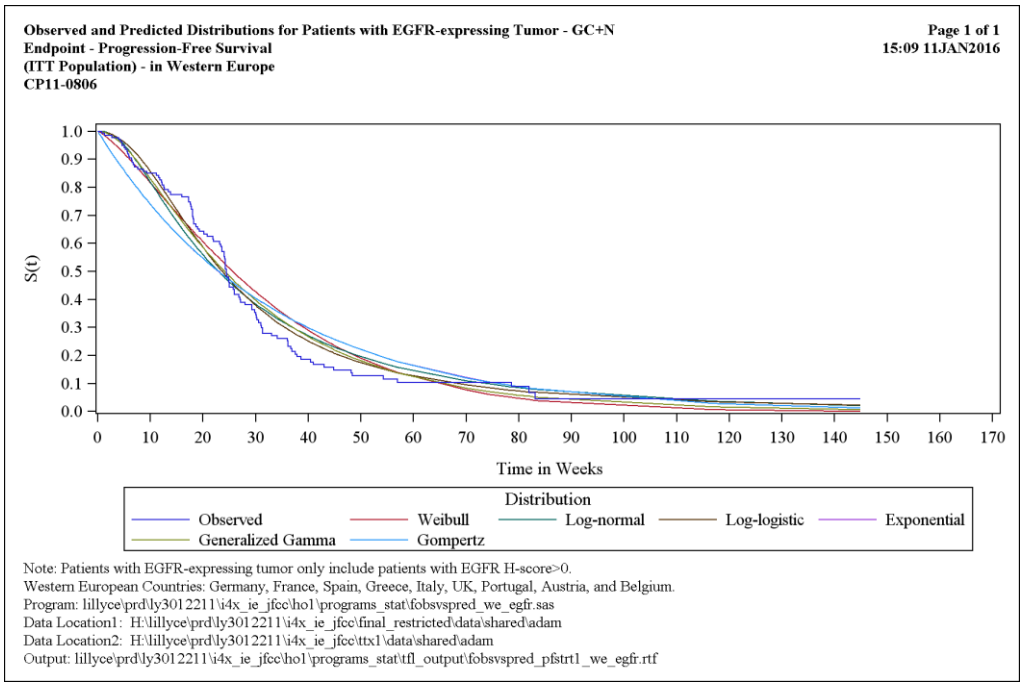


Figure 18 **Observed and Predicted Distributions for Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation) (GCis). This figure replaces figure 48 in the main submission.**

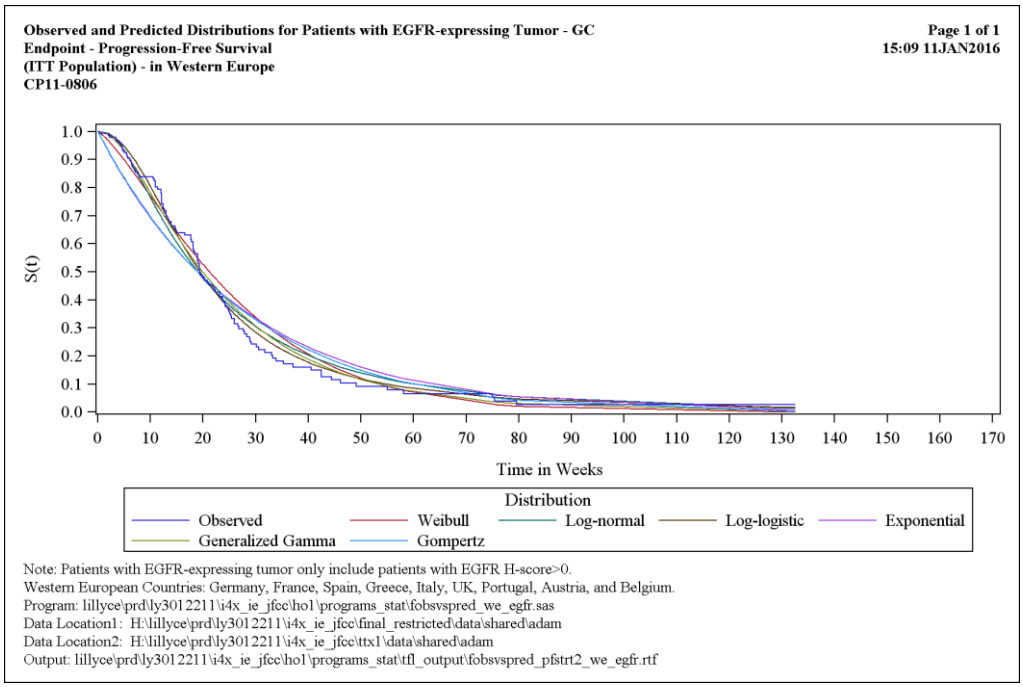
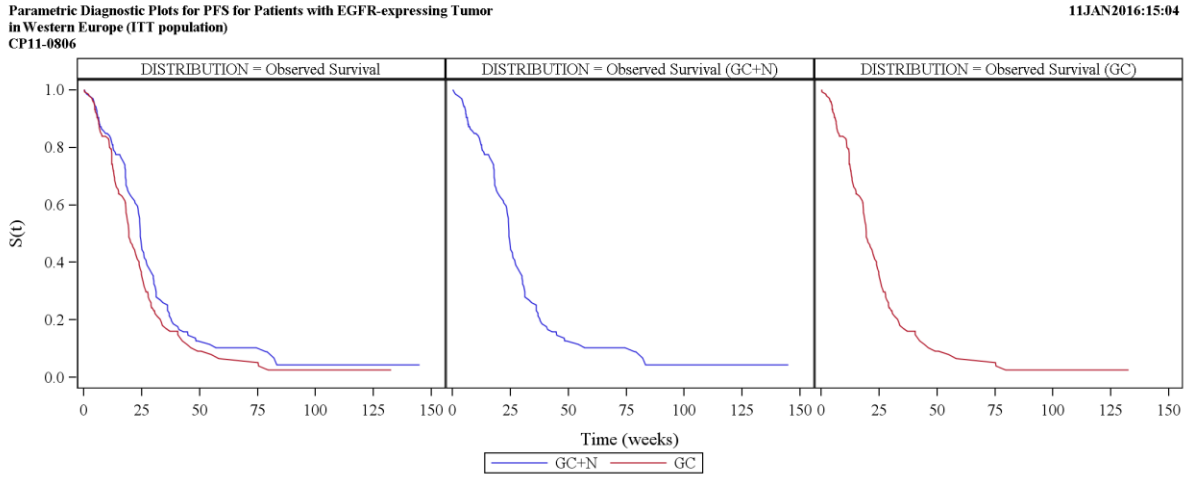


Figure 19 Parametric Diagnostic Plots for Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 49 in the main submission.



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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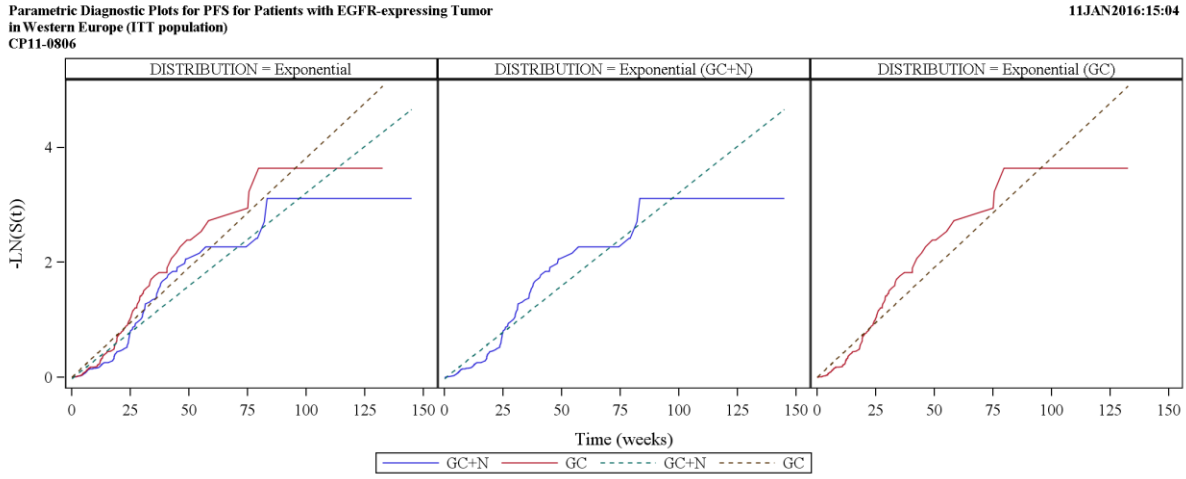

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Parametric Diagnostic Plots for PFS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

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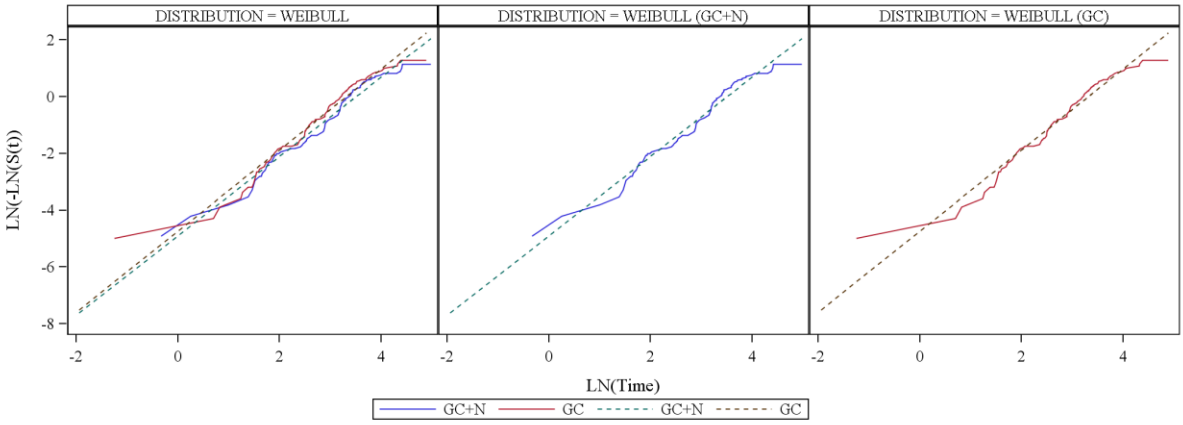

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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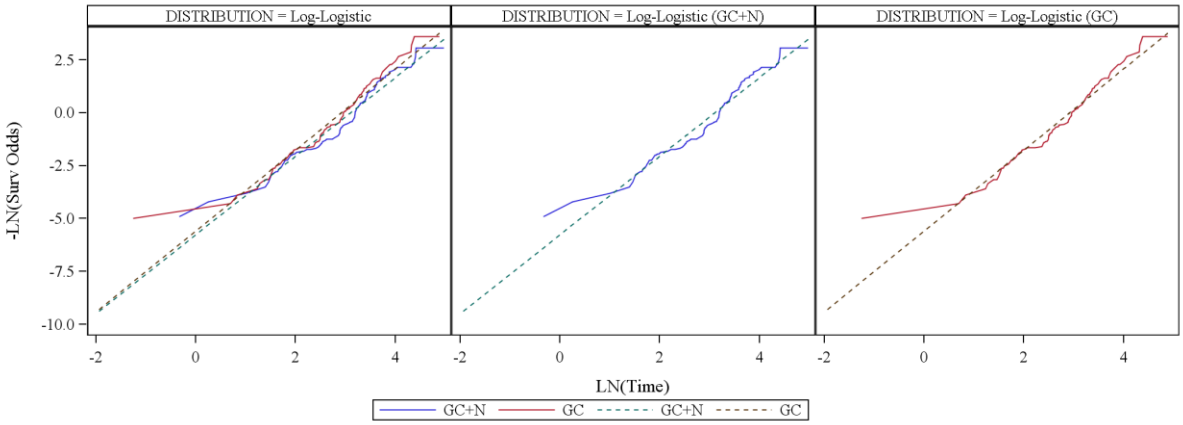
Parametric Diagnostic Plots for PFS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

11JAN2016:15:04



Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Parametric Diagnostic Plots for PFS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

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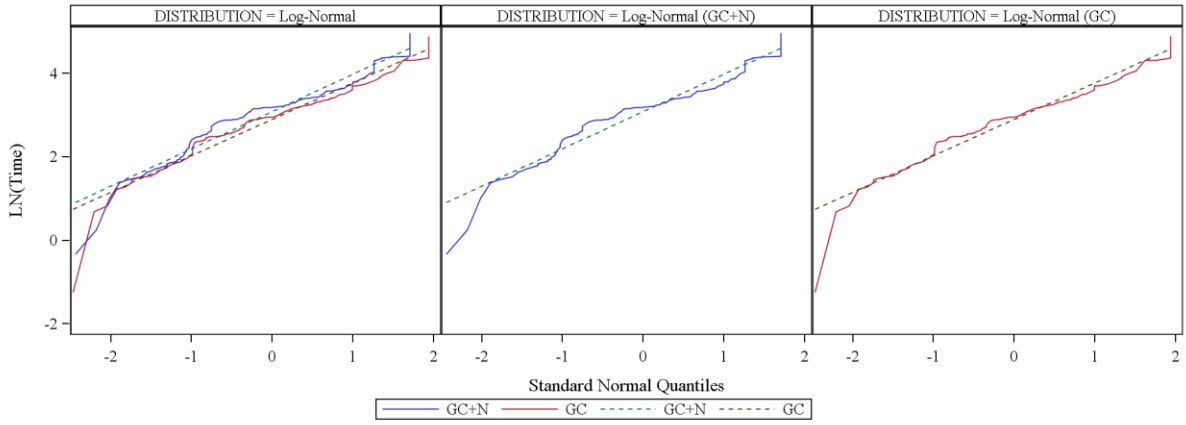

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Parametric Diagnostic Plots for PFS for Patients with EGFR-expressing Tumor in Western Europe (ITT population)
CP11-0806

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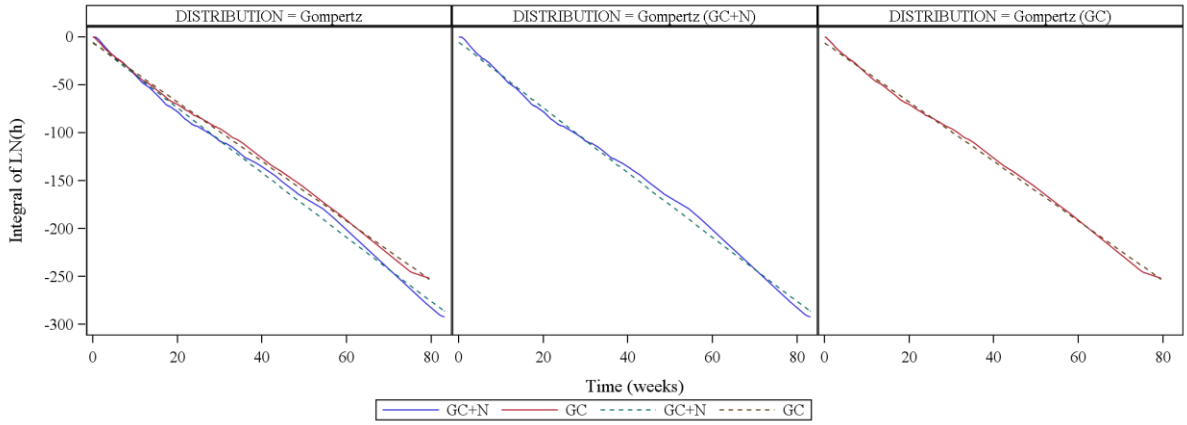

Note: Patients with EGFR-expressing tumor only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
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Figure 20 **Separately Fitted Log-Logistic extrapolation of Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 50 in the main submission.**

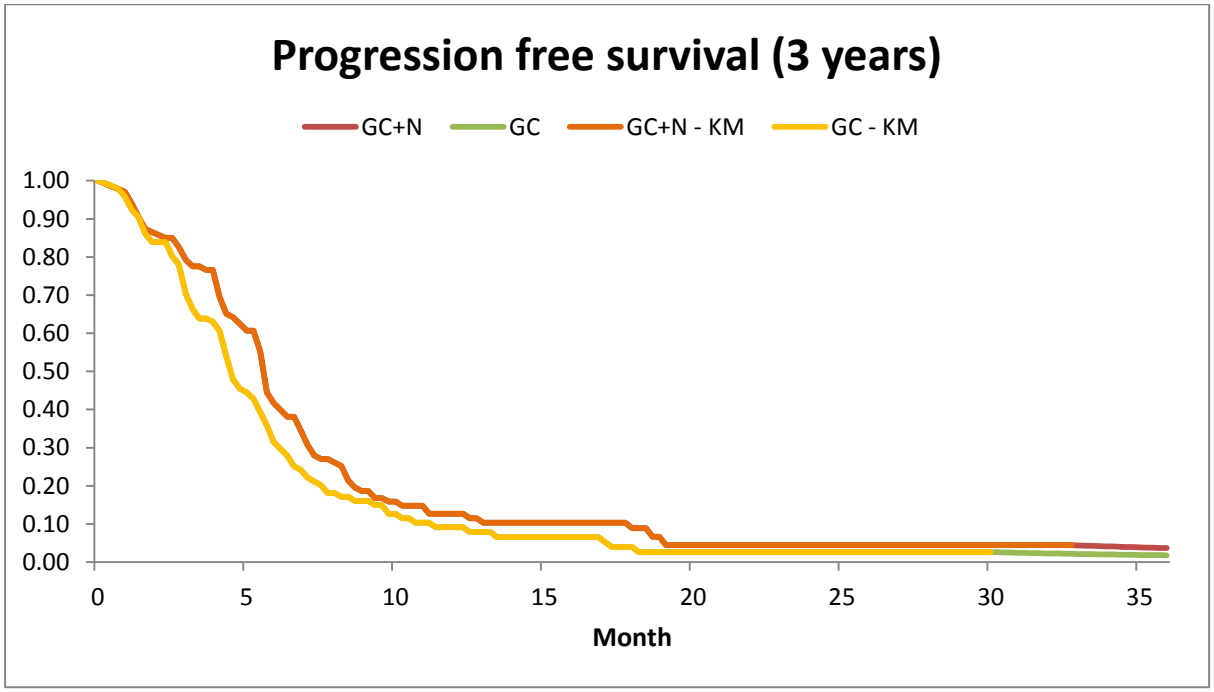


Table 19 **Parameter Estimates AIC and BIC – Progression Free Survival in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 51 in the main submission.**

	AIC	BIC
GCis+N		
Weibull	322.782	328.736
Log-normal	320.118	326.071
Log-logistic	309.465	315.418
Exponential	332.877	335.853
Generalized Gamma	317.181	326.111
GCis		
Weibull	345.399	351.486
Log-normal	341.457	347.544
Log-logistic	328.638	334.725
Exponential	356.621	359.665
Generalized Gamma	337.000	346.130

Table 20 Estimated Mean OS and PFS for each parametric survival distribution in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 52 in the main submission.

Analysis	GCis+N (Mean)	GCis (Mean)	Incremental Difference
PFS			
Weibull	7.46	6.00	1.69
Log-normal	7.93	6.24	1.85
Log-logistic	8.31	6.46	1.54
Exponential	7.62	6.08	1.53
Generalized Gamma	7.61	6.08	
OS			4.37
Weibull	16.82	12.45	6.19
Log-normal	19.58	13.39	6.53
Log-logistic	20.25	13.72	4.84
Exponential	17.57	12.73	5.17
Generalized Gamma	17.72	12.55	1.69

Table 21 Summary of utility values for cost-effectiveness analysis in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 59 in the main submission.

State	Utility value: mean	Utility Value: standard error	95% confidence interval
Pre-progression and on induction treatment	[redacted]	[redacted]	[redacted]
Pre-progression and on maintenance treatment	[redacted]	[redacted]	[redacted]
Pre-progression and off treatment	[redacted]	[redacted]	[redacted]
Post-progression	0.55	0.016	(0.52, 0.58)

Table 22 Base-case results of GCis+N vs GCis in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 75 in the main submission.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCis+N	[redacted]	[redacted]	[redacted]				
GCis	[redacted]	[redacted]	[redacted]	£19,516	0.544	0.338	£57,725

Table 23 **Base-case results of GCis+N vs Indirect Comparators in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 76 in the main submission.**

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
GCis+N	[redacted]	[redacted]	[redacted]				
GCarbo	[redacted]	[redacted]	[redacted]	£20,316	0.523	0.344	£59,031
DCis	[redacted]	[redacted]	[redacted]	£19,948	0.482	0.312	£63,982
PCarbo	[redacted]	[redacted]	[redacted]	£20,036	0.236	0.172	£116,344

Table 24 **Model results compared with clinical data in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 77 in the main submission.**

Outcome	GCis+ N		GCis	
	SQUIRE result (median)	Model result (median)	SQUIRE result (median)	Model result (median)
Progression free survival (months)	5.6 (5.4, 6.2)	5.52	4.5 (4.2, 5.3)	4.37
Overall survival (months)	11.7 (9.6, 13.6)	11.73	8.9 (8.1, 11.1)	8.74

Table 25 **Summary of QALY gain by health state (GCis+N vs GCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 78 in the main submission.**

Health state	QALY GCis+N	QALY GCis	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.010	2.94%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.141	41.83%
Pre-progression and off treatment	[redacted]	[redacted]	-0.027	-8.09%
Disutility due to adverse events	[redacted]	[redacted]	-0.007	0.00%
Post-progression	[redacted]	[redacted]	0.215	63.64%
Total	[redacted]	[redacted]	0.338	100%

Table 26 Summary of QALY gain by health state (GCis+N vs GCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 79 in the main submission.

Health state	QALY GCis+N	QALY GCarbo	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.048	13.92%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.141	41.09%
Pre-progression and off treatment	[redacted]	[redacted]	0.016	4.54%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.141	40.97%
Total	[redacted]	[redacted]	0.344	100%

Table 27 Summary of QALY gain by health state (GCis+N vs DCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 80 in the main submission.

Health state	QALY GCis+N	QALY DCis	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.032	10.40%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.141	45.35%
Pre-progression and off treatment	[redacted]	[redacted]	-0.012	-3.83%
Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.151	48.58%
Total	[redacted]	[redacted]	0.312	100%

Table 28 Summary of QALY gain by health state (GCis+N vs PCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 81 in the main submission.

Health state	QALY GCis+N	QALY PCarbo	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	0.027	15.48%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	0.141	82.11%
Pre-progression and off treatment	[redacted]	[redacted]	-0.026	-14.96%

Disutility due to adverse events	[redacted]	[redacted]	-0.006	0.00%
Post-progression	[redacted]	[redacted]	0.031	18.22%
Total	[redacted]	[redacted]	0.172	100%

Table 29 Summary of costs by health state (GCis+N vs. GCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 82 in the main submission.

Health state	Cost intervention (GCis+N)	Cost comparator (GCis)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£9,512	48.74%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,565	43.89%
Pre-progression and off treatment	[redacted]	[redacted]	-£138	-0.71%
Post-progression	[redacted]	[redacted]	£1,576	8.07%
Total	[redacted]	[redacted]	£19,516	100%

Table 30 Summary of costs by health state (GCis+N vs. GCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 83 in the main submission.

Health state	Cost intervention (GCis+N)	Cost comparator (GCarbo)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£10,518	51.77%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,565	42.16%
Pre-progression and off treatment	[redacted]	[redacted]	£79	0.39%
Post-progression	[redacted]	[redacted]	£1,154	5.68%
Total	[redacted]	[redacted]	£20,316	100%

Table 31 Summary of costs by health state (GCis+N vs. DCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 84 in the main submission.

Health state	Cost intervention (GCis+N)	Cost comparator (DCis)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£10,207	51.17%

Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,565	42.94%
Pre-progression and off treatment	[redacted]	[redacted]	-£60	-0.30%
Post-progression	[redacted]	[redacted]	£1,236	6.20%
Total	[redacted]	[redacted]	£19,948	100%

Table 32 Summary of costs by health state (GCis+N vs. PCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 85 in the main submission.

Health state	Cost intervention (GCis+N)	Cost comparator (PCarbo)	Increment	% absolute increment
Pre-progression and on induction treatment	[redacted]	[redacted]	£11,157	55.69%
Pre-progression and on maintenance treatment	[redacted]	[redacted]	£8,565	42.75%
Pre-progression and off treatment	[redacted]	[redacted]	-£130	-0.65%
Post-progression	[redacted]	[redacted]	£443	2.21%
Total	[redacted]	[redacted]	£20,036	100%

Table 33 Summary of predicted resource use by category of cost (GCis+N vs GCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 86 in the main submission.

Item	Cost intervention (GCis+N)	Cost comparator (GCis)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,245	78%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,168	11%
Subsequent treatment cost	[redacted]	[redacted]	£166	1%
Subsequent treatment administration cost	[redacted]	[redacted]	£129	1%
Disease monitoring and supportive care	[redacted]	[redacted]	£604	3%
Adverse Events	[redacted]	[redacted]	-£78	0%
Palliative Care	[redacted]	[redacted]	£1,281	7%
Total	[redacted]	[redacted]	£19,516	100%

Table 34 Summary of predicted resource use by category of cost (GCis+N vs GCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 87 in the main submission.

Item	Cost intervention (GCis+N)	Cost comparator (GCarbo)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,298	75%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,653	13%
Subsequent treatment cost	[redacted]	[redacted]	£191	1%
Subsequent treatment administration cost	[redacted]	[redacted]	£150	1%
Disease monitoring and supportive care	[redacted]	[redacted]	£1,034	5%
Adverse Events	[redacted]	[redacted]	£178	1%
Palliative Care	[redacted]	[redacted]	£813	4%
Total	[redacted]	[redacted]	£20,316	100%

Table 35 Summary of predicted resource use by category of cost (GCis+N vs DCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 88 in the main submission.

Item	Cost intervention (GCis+N)	Cost comparator (DCis)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,354	77%
Induction and maintenance administration cost	[redacted]	[redacted]	£2,456	12%
Subsequent treatment cost	[redacted]	[redacted]	£194	1%
Subsequent treatment administration cost	[redacted]	[redacted]	£153	1%
Disease monitoring and supportive care	[redacted]	[redacted]	£808	4%
Adverse Events	[redacted]	[redacted]	£94	0%
Palliative Care	[redacted]	[redacted]	£890	4%
Total	[redacted]	[redacted]	£19,948	100%

Table 36 Summary of predicted resource use by category of cost (GCis+N vs PCarbo) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 89 in the main submission.

Item	Cost intervention (GCis+N)	Cost comparator (PCarbo)	Increment	% absolute increment
Induction and maintenance treatment cost	[redacted]	[redacted]	£15,403	77%
Induction and maintenance administration cost	[redacted]	[redacted]	£3,421	17%
Subsequent treatment cost	[redacted]	[redacted]	£178	1%
Subsequent treatment administration cost	[redacted]	[redacted]	£139	1%
Disease monitoring and supportive care	[redacted]	[redacted]	£706	4%
Adverse Events	[redacted]	[redacted]	£63	0%
Palliative Care	[redacted]	[redacted]	£125	1%
Total	[redacted]	[redacted]	£20,036	100%

Figure 21 **Cost-Effectiveness Acceptability Curve in patients with EGFR expressing tumour (Western European subpopulation). This table replaces figure 59 in the main submission.**

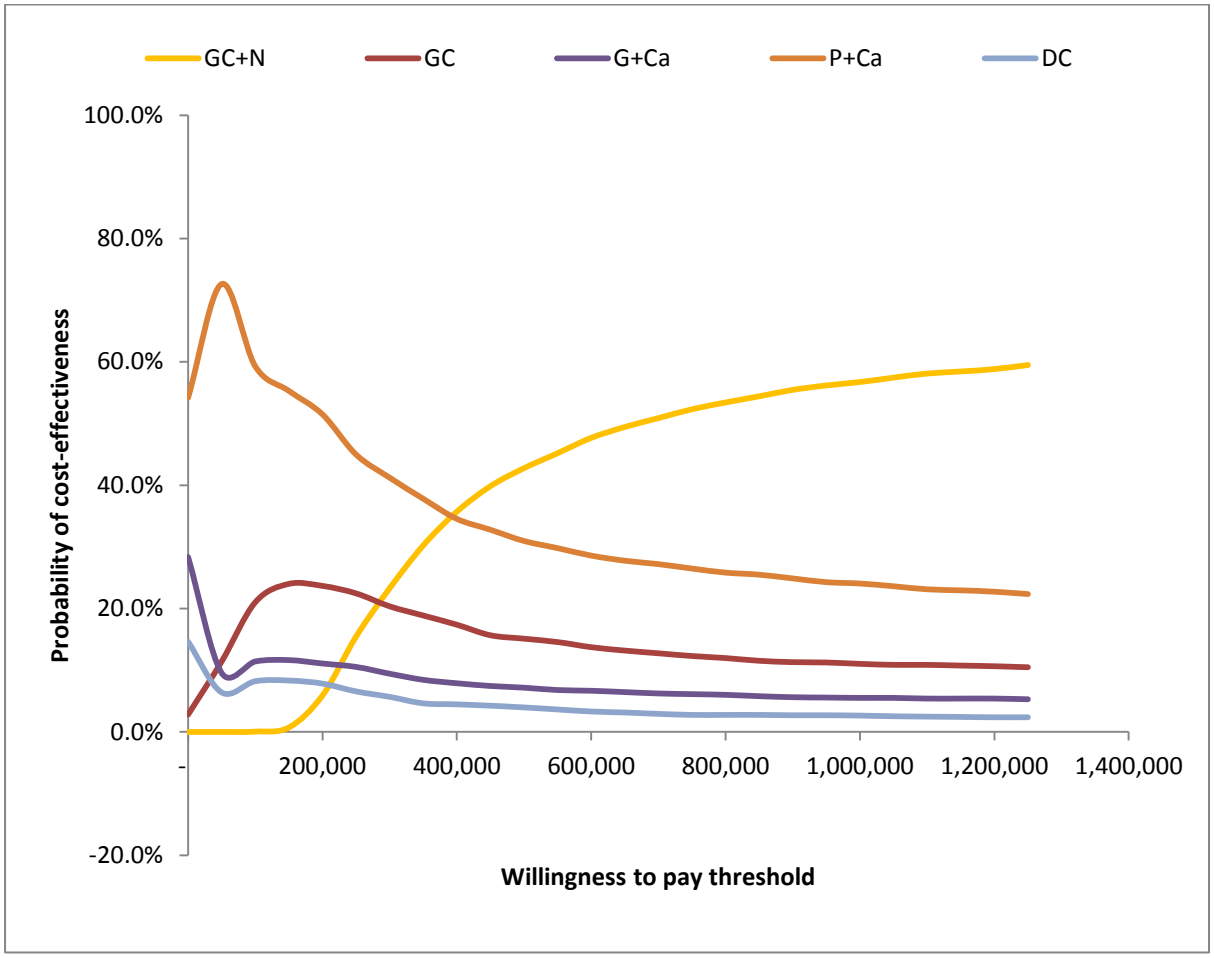


Table 37 Variables and Ranges explored through deterministic sensitivity analysis in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 90 in the main submission.

Description	Lower Range	Upper Range	Base
Incremental costs			
Treatment discontinuation GC+N	£ 17,944.64	£ 21,400.02	£ 19,515.59
Drug cost per administration of Necitumumab	£ 18,348.05	£ 20,551.78	£ 19,515.59
Overall survival GC+N	£ 18,546.31	£ 19,484.79	£ 19,515.59
Cost of administration of chemotherapies per subsequent stay	£ 19,497.17	£ 19,554.71	£ 19,515.59
Overall survival GC	£ 14,806.29	£ 24,382.57	£ 19,515.59
Non-drug costs progressive state on active treatment	£ 19,135.29	£ 19,897.02	£ 19,515.59
Progression free survival GC+N	£ 19,253.14	£ 19,778.03	£ 19,515.59
Non-drug costs stable state on maintenance treatment	£ 19,210.71	£ 19,820.46	£ 19,515.59
Discontinuation of induction treatment GC	£ 19,515.59	£ 19,515.59	£ 19,515.59
Per cycle risk of adverse events for Gemcitabine + Cisplatin	£ 19,515.59	£ 19,515.59	£ 19,515.59
Cost per AE Gemcitabine + Cisplatin	£ 19,515.59	£ 19,515.59	£ 19,515.59
Per cycle risk of adverse events for GC+N	£ 19,515.59	£ 19,515.59	£ 19,515.59
Cost per AE GC+N	£ 19,515.59	£ 19,515.59	£ 19,515.59
Non-drug costs stable state off treatment	£ 19,515.59	£ 19,515.59	£ 19,515.59
Non-drug costs progressive state on palliative care	£ 16,478.50	£ 22,552.68	£ 19,515.59
Incremental QALYs			
Overall survival GC+N	0.0888	0.6427	0.3381
Overall survival GC	0.1583	0.4956	0.3381
Progression free survival GC+N	0.3011	0.3848	0.3381
Progression free survival GC	0.3058	0.3625	0.3381
Utility progressive state	0.3320	0.3444	0.3381
Utility on maintenance treatment	0.3380	0.3381	0.3381
Treatment discontinuation GC+N	0.3370	0.3391	0.3381
Utility off treatment GC	0.3372	0.3389	0.3381
Per cycle risk of adverse events for GC+N	0.3377	0.3384	0.3381
Utility decrement associated with AEs in induction period GC+N	0.3295	0.3460	0.3381
Per cycle risk of adverse events for Gemcitabine + Cisplatin	0.3361	0.3401	0.3381
Utility decrement associated with AEs in induction period Gemcitabine + Cisplatin	0.3258	0.3503	0.3381
Utility on induction treatment	0.3370	0.3391	0.3381
Discontinuation of induction treatment GC	0.3372	0.3389	0.3381
Drug cost per administration of Necitumumab	0.3381	0.3381	0.3381

ICER			
Overall survival GC+N	£ 33,298.25	£ 202,036.31	£ 57,724.54
Overall survival GC	£ 41,467.23	£ 115,907.32	£ 57,724.54
Treatment discontinuation GC+N	£ 50,640.10	£ 61,589.81	£ 57,724.54
Drug cost per administration of Necitumumab	£ 53,786.74	£ 63,948.96	£ 57,724.54
Progression free survival GC	£ 44,601.27	£ 70,788.03	£ 57,724.54
Progression free survival GC+N	£ 56,594.42	£ 58,858.24	£ 57,724.54
Cost of administration of chemotherapies per subsequent stay	£ 56,770.15	£ 58,684.94	£ 57,724.54
Utility progressive state	£ 56,679.94	£ 58,774.42	£ 57,724.54
Non-drug costs progressive state on active treatment	£ 57,667.91	£ 57,782.78	£ 57,724.54
Utility on maintenance treatment	£ 56,396.96	£ 59,236.59	£ 57,724.54
Non-drug costs stable state on maintenance treatment	£ 57,378.32	£ 58,057.24	£ 57,724.54
Per cycle risk of adverse events for Gemcitabine + Cisplatin	£ 55,716.02	£ 59,897.84	£ 57,724.54
Discontinuation of induction treatment GC	£ 57,544.01	£ 57,906.21	£ 57,724.54
Utility off treatment GC	£ 57,579.46	£ 57,870.36	£ 57,724.54
Per cycle risk of adverse events for GC+N	£ 48,741.22	£ 66,707.86	£ 57,724.54
Overall survival GC+N	£ 57,710.70	£ 57,738.39	£ 57,724.54

Figure 22 Tornado Diagram for ICER in patients with EGFR expressing tumour (Western European subpopulation). This figure replaces figure 60 in the main submission.

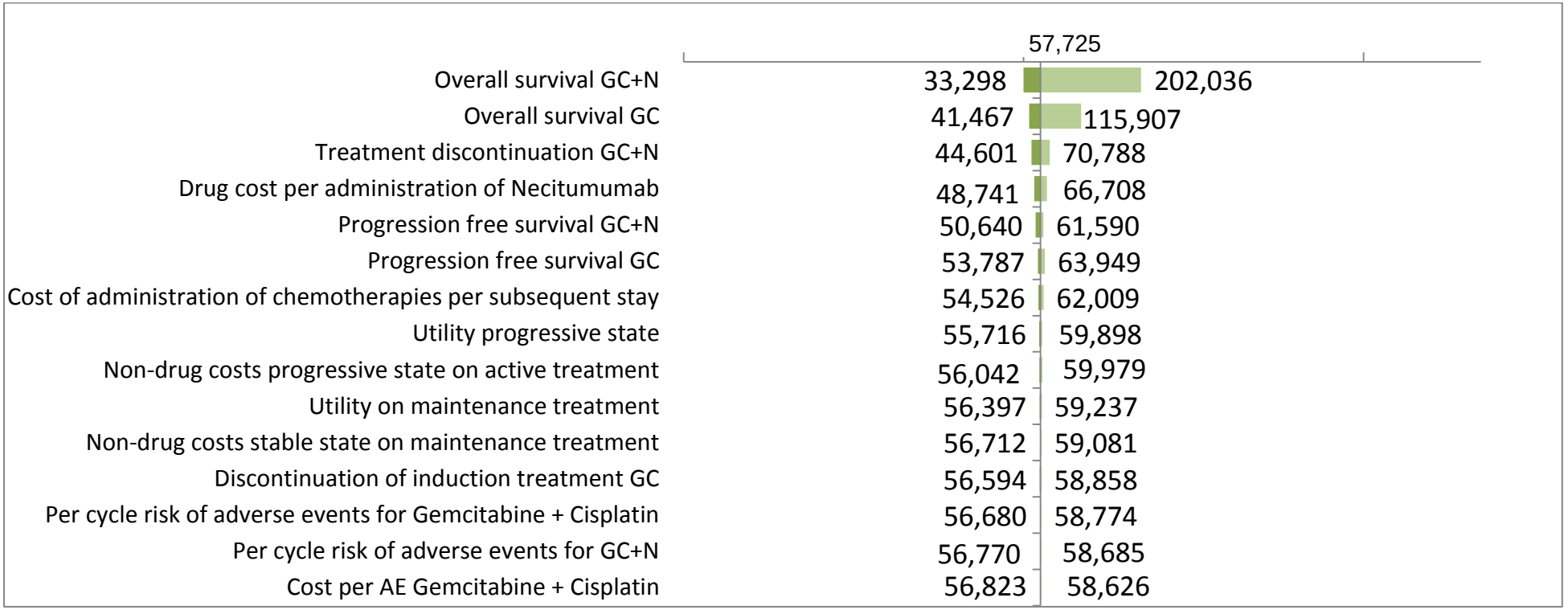


Table 38 Scenario Analysis Results (GCis+N vs. GCis) in patients with EGFR expressing tumour (Western European subpopulation). This table replaces table 91 in the main submission.

Scenario	Description	ICER
Base-case	Base Case results	£ 57,725
1)	Utilities from Chouaid et al. (61) and AE decrements from Nafees et al. (66)	£ 57,788
2)	Utility post-progression from Chouaid et al (61)	£ 55,751
3)	Time to treatment discontinuation assumed same as GC for all comparators	£ 64,713
4)	Using ITT as patient population	£ 151,152
5)	Using separate Weibull for OS	£ 87,543
6)	Using Log-logistic for OS in GC+N and Weibull in GC arm	£ 53,433
7)	Using separate Exponential distributions for OS	£ 78,868
8)	5 year time horizon	£ 83,205
9)	Symptomatic deterioration considered progression	£ 64,251

Appendix 2. Response to question A2

Table 39 Table of excluded studies with reasons

	Authors	Title	Journal	Reason for exclusion
1	Pirker R.	Epidermal growth factor receptor-directed monoclonal antibodies in nonsmall cell lung cancer: an update. [Review]	Current Opinion in Oncology. 27(2):87-93, 2015 Mar. [Journal Article. Review]	Not relevant
2	Paz-Ares L; Mezger J; Ciuleanu TE; Fischer JR; von Pawel J; Provencio M; Kazarnowicz A; Losonczy G; de Castro G Jr; Szczesna A; Crino L; Reck M; Ramlau R; Ulsperger E; Schumann C; Miziara JE; Lessa AE; Dediu M; Balint B; Depenbrock H; Soldatenkova V; Kurek R; Hirsch FR; Thatcher N; Socinski MA; INSPIRE investigators.	Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study.	Lancet Oncology. 16(3):328-37, 2015 Mar.	Non-squamous
3	DeLozier AM; Brown J; Natanegara F; Zhao L; Cui ZL; Able SL; Bowman L; Treat J; Hess LM.	Study protocol: systematic review and meta-analysis of randomized controlled trials in first-line treatment of squamous non-small cell lung cancer. [Review]	Systems Review. 3:102, 2014.	Study protocol
4	Pirker R.	EGFR-directed monoclonal antibodies in non-small cell lung cancer. [Review]	Targeted Oncology. 8(1):47-53, 2013 Mar.	Not relevant
5	Pirker R; Filipits M.	Monoclonal antibodies against EGFR in non-small cell lung cancer. [Review]	Critical Reviews in Oncology-Hematology. 80(1):1-9, 2011 Oct. [Journal Article. Review]	Not relevant
6	Yee D.	Receptor kinase inhibitors target NSCLC: two antibodies and a small-molecule MET inhibitor.	Biodrugs. 25(4):271-3, 2011 Aug 1.	Not relevant
7	Di Maio M.	Is there still room for large registrative	Expert Opinion on	Not relevant

	Authors	Title	Journal	Reason for exclusion
		trials in unselected cancer patients? The case of anti-epidermal growth factor receptor antibodies in advanced non-small-cell lung cancer.	Biological Therapy. 11(9):1131-3, 2011 Sep.	
8	Dienstmann R; Felip E.	Necitumumab in the treatment of advanced non-small cell lung cancer: translation from preclinical to clinical development. [Review]	Expert Opinion on Biological Therapy. 11(9):1223-31, 2011 Sep.	Expert opinion (excluded at full-text level)
9	Gridelli C.	New molecular targets - The next generation of drugs.	Annals of Oncology. Conference: 35th ESMO Congress Milan Italy. Conference Start: 20101008 Conference End: 20101012. Conference Publication: (var.pagings). 21 (pp viii25), 2010. Date of Publication: October 2010.	Not relevant
10	Greillier L; Tomasini P; Barlesi F.	Necitumumab for non-small cell lung cancer.	Expert Opinion on Biological Therapy. 15(8):1231-9, 2015.	Expert opinion (Excluded at full-text level)
11	Stinchcombe TE.	Recent advances in the treatment of non-small cell and small cell lung cancer. [Review]	F1000Prime Reports. 6:117, 2014.	Not relevant
12	Takeda M. Nakagawa K.	Role of EGFR monoclonal antibodies in the management of non-small cell lung cancer.	Current Cancer Drug Targets. 15 (9) (pp 792-802), 2015. Date of Publication: 01 Nov 2015.	Not relevant
13	Goldstein D.A. Chen Q. Ayer T. Howard D.H. Lipscomb J. Ramalingam S.S. Khuri F.R. Flowers C.	Necitumumab in metastatic squamous non-small cell lung cancer (mSqNSCLC): Establishing a value-based cost.	Journal of Clinical Oncology. Conference: 2015 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20150529 Conference End: 20150602. Conference Publication: (var.pagings). 33 (15 SUPPL. 1) (no pagination), 2015.	Not relevant
14		REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B)	Clinical Advances in Hematology and Oncology. 12 (10	Non relevant comparator

	Authors	Title	Journal	Reason for exclusion
		versus doc and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy.	Supplement 18) (pp 10-12), 2014. Date of Publication: 01 Oct 2014.	
15	Reichert J.M.	Antibodies to watch in 2015.	mAbs. 7 (1) (pp 1-8), 2015. Date of Publication: 01 Jan 2015.	Not relevant
16	Paz-Ares L. Mezger J. Ciuleanu T. Fischer J.R. Von Pawel J. Provencio M. Kazarnowicz A. Losonczy G. Castro Jr. G. Szczesna A. Crino L. Reck M. Ramlau R. Ulsperger E. Schumann C. Miziara J.E. Lessa A. Depenbrock H. Soldatenkova V. Balint B. Hirsch F.R. Socinski M.A.	Randomized phase-3 trial (inspire) of necitumumab plus cisplatin-pemetrexed versus cisplatin-pemetrexed alone as first-line therapy in stage iv non-squamous NSCLC.	Journal of Thoracic Oncology. Conference: 15th World Conference on Lung Cancer Sydney, NSW Australia. Conference Start: 20131027 Conference End: 20131030. Conference Publication: (var.pagings). 8 (pp S139-S140), 2013. Date of Publication: November 2013.	Non squamous
17	Pirker R.	Metastatic lung cancer.	Onkologie. Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2013 Wien Austria. Conference Start: 20131018 Conference End: 20131022. Conference Publication: (var.pagings). 36 (pp 1), 2013. Date of Publication: October 2013.	Not relevant
18	Boyd B. Bozzo J. Castaner J.	Lapatanib: Oncolytic dual EGFR and erbB-2 inhibitor.	Drugs of the Future. 30 (12) (pp 1225-1239), 2005. Date of Publication: December 2005.	Not relevant

	Authors	Title	Journal	Reason for exclusion
19	Tonra J.R. Li H. Deevi D.S. Bao C. Samakoglu S.	Necitumumab (IMC-11F8), a recombinant human anti EGFR antibody, increases the antitumor effects of cisplatin/paclitaxel in human NSCLC xenograft models.	Cancer Research. Conference: 102nd Annual Meeting of the American Association for Cancer Research, AACR 2011 Orlando, FL United States. Conference Start: 20110402 Conference End: 20110406. Conference Publication: (var.pagings). 71 (8 SUPPL. 1) (no pagination), 2011. Date of Publication: 15 Apr 2011.	Not relevant
20	Deevi D. Samakoglu S. Li H. Claros N. Wang S. Bassi R. Prewett M. Tonra J.	Mechanisms underlying the therapeutic benefit of Necitumumab (imc-11f8) in combination with cisplatin/gemcitabine in NSCLC xenograft models.	European Journal of Cancer, Supplement. Conference: 22nd EORTC - NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics Berlin Germany. Conference Start: 20101116 Conference End: 20101119. Conference Publication: (var.pagings). 8 (7) (pp 35), 2010. Date of Publication: November 2010.	Not relevant
21	Besse,B.;Felip,E.;Barlesi,F.;Mazieres,J.;Zalcman,G.;Von	Results of a randomized phase 2 trial of gemcitabine/ cisplatin/iniparib (GCI) vs gemcitabine/cisplatin (GC) in patients with stage IV NSCLC.	Journal of Thoracic Oncology.Conference: 14th World Conference on Lung Cancer Amsterdam Netherlands.Conference Start: 20110703 Conference End:2011; 6 SUPPL. 2; S469	Not relevant
22	Pirker,R.	Novel drugs against non-small-cell lung cancer	Curr.Opin.Oncol.2014; March 26:2; 145-151	Not relevant (Excluded at full-text level)
23	Kuenen B, Witteveen PO; Ruijter R, Giaccone G, Dontabhaktuni A, Fox F, Katz T, Youssoufian H, Zhu J, Rowinsky EK and	A Phase I Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG1Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies	Clin Cancer Res March 15, 201016; 1915Published Online First March 2, 2010; doi: 10.1158/1078-0432.CCR-09-2425	Not relevant

	Authors	Title	Journal	Reason for exclusion
	Voest EE			
24	D. Patel, B. Saxena, Q. Zhou, W. Walton, R. Srikakulum, R. Manteiga, J. Haurum, J. R. Tonra and X. Kang	Differential induction of antibody-dependent cellular cytotoxicity (ADCC) against human EGFR-expressing NSCLC cell lines by necitumumab, cetuximab, and panitumumab.	Journal of Clinical Oncology, 2011 ASCO Annual Meeting Abstracts Part 1.Vol 29, No 15_suppl (May 20 Supplement), 2011: e21075	Not relevant
25	Sacco PC, Maione P, Rossi A, Sgambato A, Casaluce F, Palazzolo G, Gridelli C	Necitumumab for the treatment of stage IV metastatic squamous non-small-cell lung cancer	Expert Review of Respiratory Medicine Volume 9, Issue 3, 2015 pages 245-254	Not relevant (Excluded at full-text level)
26	Filipits M	New developments in the treatment of squamous cell lung cancer	Current Opinion in Oncology: March 2014 - Volume 26 - Issue 2 - p 152–158 doi: 10.1097/CCO.0000000000000049	Not relevant (Excluded at full-text level)
27	Zhou F; Zhou C.	Necitumumab for patients with non-squamous NSCLC: uninspiring results.	Lancet Oncology. 16(3):246-7, 2015 Mar.	Expert opinion (Excluded at full-text level)
28	Cohen B	Current challenges and clinical investigations of epidermal growth factor receptor (EGFR)- and ErbB family-targeted agents in the treatment of head and neck squamous cell carcinoma (HNSCC). [Review]	Cancer Treatment Reviews. 40(4):567-77, 2014 May.	Not relevant
29	Samakoglu S; Deevi DS; Li H; Wang S; Murphy M; Bao C; Bassi R; Prewett M; Tonra JR.	Preclinical rationale for combining an EGFR antibody with cisplatin/gemcitabine for the treatment of NSCLC.	Cancer Genomics & Proteomics. 9(2):77-92, 2012 Mar-Apr.	Not relevant
30	Nokihara H. Yamamoto N. Tamura Y. Tanabe Y. Honda K. Asahina H. Enatu S. Kurek R. Yamada Y. Tamura T.	A phase 1 study of necitumumab (anti-EGFR monoclonal antibody) in Japanese patients with advanced solid tumors.	Annals of Oncology. Conference: 12th Annual Meeting of the Japanese Society of Medical Oncology Fukuoka Japan. Conference Start: 20140717 Conference End: 20140719. Conference Publication: (var.pagings). 25 (pp v70), 2014. Date of Publication: October 2014.	Not relevant

	Authors	Title	Journal	Reason for exclusion
31	Pirker R.	Systemic therapy of NSCLC stage IV - Chemotherapy and combinations.	Oncology Research and Treatment. Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie 2014 Hamburg Germany. Conference Start: 20141010 Conference End: 20141014. Conference Publication: (var.pagings). 37 (pp 196), 2014. Date of Publication: October 2014.	Not relevant
32	Saxena B. Sundaram S.T. Walton W. Patel I. Kuo P. Khan S. Matathia A. Purohit A. Crowley R. Zhou Q.	Differentiation between the EGFR antibodies necitumumab, cetuximab, and panitumumab: In vitro biological and binding activities.	Journal of Clinical Oncology. Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607. Conference Publication: (var.pagings). 29 (15 SUPPL. 1) (no pagination), 2011. Date of Publication: 20 May 2011.	Not relevant
33	Yu D. Wuertz J. Taqui A. Li Z. Fox F.E. Qian J. Liu T. Li M. Hsieh M. Zhou Q.	Differentiation between the EGFR antibodies necitumumab (Neci), cetuximab (Cetux), and panitumumab (Pan): Glycosylation and IgE reactivity.	Journal of Clinical Oncology. Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607. Conference Publication: (var.pagings). 29 (15 SUPPL. 1) (no pagination), 2011. Date of Publication: 20 May 2011.	Not relevant
34	Topper M.B. Tonra J.R. Pytowski B. Eastman S.W.	Differentiation between the EGFR antibodies necitumumab, cetuximab, and panitumumab: Antibody internalization and EGFR degradation.	Journal of Clinical Oncology. Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference	Not relevant

	Authors	Title	Journal	Reason for exclusion
			Start: 20110603 Conference End: 20110607. Conference Publication: (var.pagings). 29 (15 SUPPL. 1) (no pagination), 2011. Date of Publication: 20 May 2011.	

Appendix 3. Response to question A3

Details of the processes of systematic reviews for this appraisal

[redacted]

[redacted]

[redacted]

Appendix 4. Response to question A4a

Table 40 Criteria used in the trial selection process for the NMA

Inclusion criteria	Exclusion criteria
[redacted]	[redacted]

Appendix 5. Response to question A6b

Table 41 Baseline characteristics (Race)

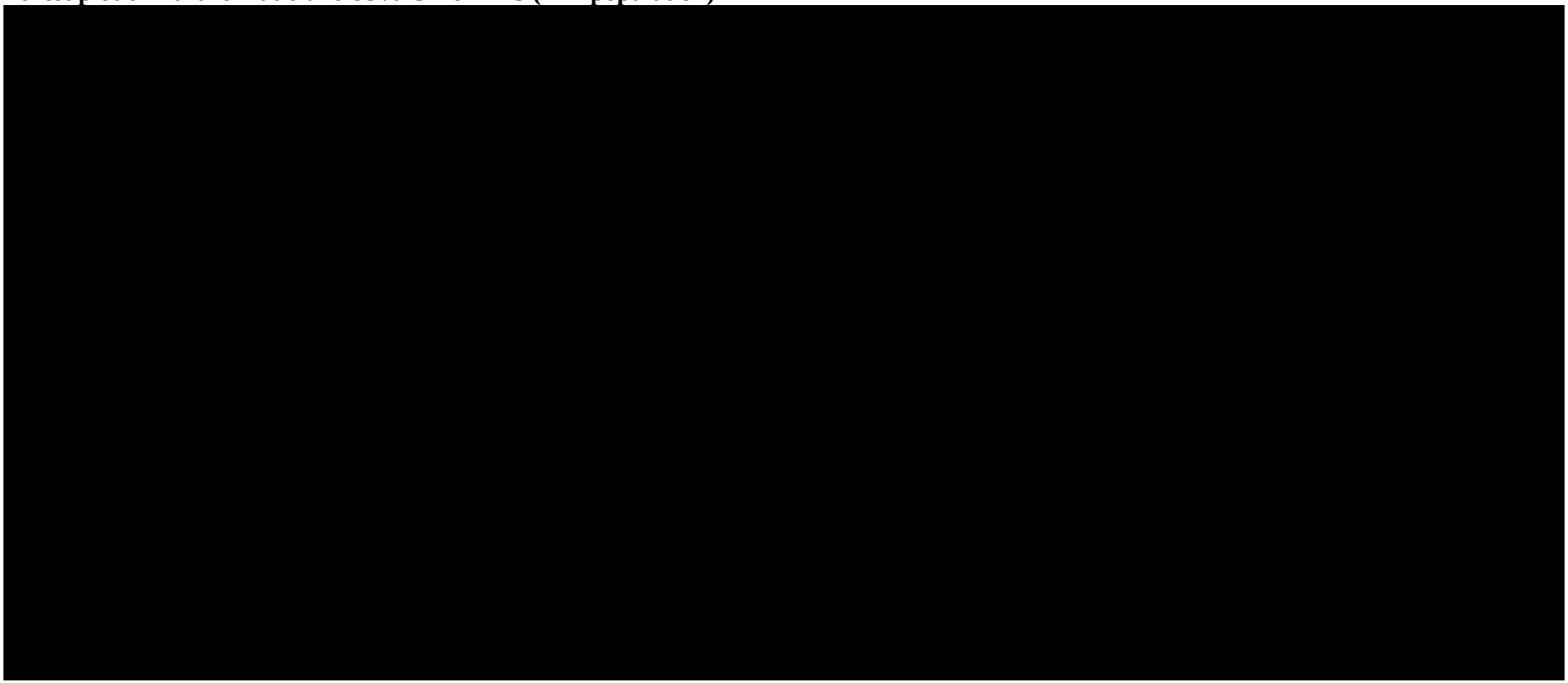
	Western Europe		
Characteristic	**GCis+N N = 145 n (%)**	**GCis N = 155 n (%)**	**Total N = 300 n (%)**
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
All Others	[redacted]	[redacted]	[redacted]

Appendix 6. Response to question A6c

Forest plot of Hazard Ratio and 95% CI for OS (ITT population)

Note: Hazard Ratio is expressed as treatment/control.
Note: Plus Necitumumab**=Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab; Alone**=Gemcitabine-Cisplatin Chemotherapy Alone.
Note: (1) Includes Austria, Belgium, Croatia, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Slovakia,Spain, UK.
(2) Includes France, Germany, Spain, Italy, and UK. (3) Includes Germany, France, Spain, Greece, Italy, UK, Portugal, Austria,Belgium.

Forest plot of Hazard Ratio and 95% CI for PFS (ITT population)



Note: Hazard Ratio is expressed as treatment/control.
Note: Plus Necitumumab**=Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab; Alone**=Gemcitabine-Cisplatin Chemotherapy Alone.
Note: (1) Includes Austria, Belgium, Croatia, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Slovakia,Spain, UK.
(2) Includes France, Germany, Spain, Italy, and UK. (3) Includes Germany, France, Spain, Greece, Italy, UK, Portugal, Austria,Belgium.

Appendix 7. Response to question A13

Table 42 EQ-5D Visual Analogue Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Baseline				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Q1-Q3	[redacted]		[redacted]	
Min-Max	[redacted]		[redacted]	
Cycle 2				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* The visual analogue score is scored from 0 (worst imaginable health state) through 100 (best imaginable health state).

Table 43 EQ-5D Visual Analogue Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Cycle 3				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* The visual analogue score is scored from 0 (worst imaginable health state) through 100 (best imaginable health state).

Table 44 EQ-5D Visual Analogue Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Cycle 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Best Score for Chemotherapy Phase				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score for Chemotherapy Phase				
n	[redacted]	[redacted]	[redacted]	[redacted]

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* The visual analogue score is scored from 0 (worst imaginable health state) through 100 (best imaginable health state).

Table 45 EQ-5D Visual Analogue Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Best Score During Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score During Necitumumab Maintenance Period and Post-Treatment Period for Chemo only Arm				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* The visual analogue score is scored from 0 (worst imaginable health state) through 100 (best imaginable health state).

Table 46 EQ-5D Visual Analogue Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Best Score Overall				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score Overall				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* The visual analogue score is scored from 0 (worst imaginable health state) through 100 (best imaginable health state).

Table 47 EQ-5D Index Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Baseline				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Q1-Q3	[redacted]		[redacted]	
Min-Max	[redacted]		[redacted]	
Cycle 2				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Table 48 EQ-5D Index Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Cycle 3				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Table 49 EQ-5D Index Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Cycle 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Best Score for Chemotherapy Phase				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score for Chemotherapy Phase				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Table 50 EQ-5D Index Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	**Change from Baseline**	**Observed Value ***	**Change from Baseline**
Best Score During Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score During Necitumumab Maintenance Period and Post-Treatment Period for Chemo only Arm				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Table 51 EQ-5D Index Score by Time Point (ITT Population)

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab N=545		Gemcitabine-Cisplatin Chemotherapy Alone N=548	
	Observed Value *	Change from Baseline	Observed Value *	Change from Baseline
Best Score Overall				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]
Worst Score Overall				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]	[redacted]

* Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Table 52 ANCOVA Analysis of Best Change from Baseline for EQ-5D Index and Visual Analogue Score (ITT Population)

Phase	Item	Therapy/Effect	N	LS Mean	SE	p-value*a	p-value*b
Chemotherapy Phase	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Phase	Item	Therapy/Effect	N	LS Mean	SE	p-value*a	p-value*b
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	

*a - p-value for each treatment arm is for testing mean of within group change equal 0; for treatment comparison is based on ANCOVA LS means.
*b - Mann-Whitney-Wilcoxon test p-value

Table 53 ANCOVA Analysis of Best Change from Baseline for EQ-5D Index and Visual Analogue Score (ITT Population)

Phase	Item	Therapy/Effect	N	LS Mean	SE	p-value*a	p-value*b
Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm	Visual Analogue Score	Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*a - p-value for each treatment arm is for testing mean of within group change equal 0; for treatment comparison is based on ANCOVA LS means.
*b - Mann-Whitney-Wilcoxon test p-value

Table 54 ANCOVA Analysis of Worst Change from Baseline for EQ-5D Index and Visual Analogue Score(ITT Population)

Phase	Item	Therapy/Effect	N	LS Mean	SE	p-value*a	p-value*b
Chemotherapy Phase	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	

*a - p-value for each treatment arm is for testing mean of within group change equal 0; for treatment comparison is based on ANCOVA LS means.
*b - Mann-Whitney-Wilcoxon test p-value

Table 55 ANCOVA Analysis of Worst Change from Baseline for EQ-5D Index and Visual Analogue Score (ITT Population)

Phase	Item	Therapy/Effect	N	LS Mean	SE	p-value*a	p-value*b
Necitumumab Maintenance Phase and Post-Treatment Phase for Chemo only Arm	Visual Analogue Score	Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	Index Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visual Analogue Score	Necitumumab Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	
		Necitumumab plus Chemo Arm - Chemo Only Arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*a - p-value for each treatment arm is for testing mean of within group change equal 0; for treatment comparison is based on ANCOVA LS means.
*b - Mann-Whitney-Wilcoxon test p-value

Appendix 8. Response to question A18a/c/d.

Table 56 Data available in the included studies for the NMA

Trial Reference	Intervention	OS: Median (95% CI)	OS: HR (95% CI)	PFS: Median (95% CI)	PFS: HR (95% CI)
Ref ID 806 Thatcher et al. 2014 Phase III	gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2 (n = 545)	9.9 (8.9, 11.1)		5.5 (4.8-5.6)	
	necitumumab 800 mg/day + cisplatin 75 mg/m^2 (n = 545)	11.5 (10.4,12.6)	0.84 (0.74-0.96)	5.7 (5.6-6.0)	0.85 (0.74-0.98)
	gemcitabine 1250 mg/m^2 +		p=0.012		p=0.020
Ref ID 1266 Hoang et al. 2013 Phase III	gemcitabine 1250 mg/m^2 + cisplatin 80 mg/m^2 (n = 50)	9.4 (5.7-15.6)	NR	4.3 (3.3 - 6.6)	NR
	paclitaxel 135 mg/m^2 + cisplatin 75 mg/m^2 (n = 60)	6.9 (5.3 - 9.4)	NR	2.6 (1.7-4.2)	NR
	docetaxel 75 mg/m^2 + cisplatin 70 mg/m^2 (n = 56)	8.1 (5.5-11.2)	NR	3.1 (2.4-5.0)	NR
	paclitaxel 225 mg/m^2 + carboplatin mg/m^2 (n = 57)	9.3 (7.3-12.1)	NR	3.7 (3.0- 5.0)	NR
		p=0.18			

Trial Reference		Intervention	OS: Median (95% CI)	OS: HR (95% CI)	PFS: Median (95% CI)	PFS: HR (95% CI)
					p=0.20	
Ref ID 1263 Morabito et al. 2013 Phase III		gemcitabine 1200 mg/m^2 (n = 9) gemcitabine 1000 mg/m^2 + cisplatin 60 mg/m^2 (n = 10)	100%* 70%* *% dead at study end	0.32 (0.10-0.98)	100%* 80%* *% progressed at study end	0.28 (0.09-.86)
Ref ID 858 Pirker et al. 2009 Phase III		vinorelbine 25 mg/m^2 + cisplatin 80 mg/m^2 (n = 187) cetuximab 400/250 mg/m^2 + vinorelbine 25 mg/m^2 + cisplatin 80 mg/ m^2 (n = 190)	8.9 (7.8-9.8) 10.2 (8.2-12.0)	NR 0.80 (0.64-1.00)	NR NR	NR NR
Ref ID 1089 Tan et al. 2009	Phase III	docetaxel 75 mg/m^2 + cisplatin 80 mg/m^2 (n=64)	9.8 (8.4-12.2)	NR	4.2 (3.8-4.6)	NR
Phase III		vinorelbine i.v./oral 30 mg/m^2 + cisplatin 80 mg/m^2 (n=65)	8.9 (6.4-12.8)	NR	3.2 (2.8-4.6)	NR
Ref ID 1336 Yoshioka et al. 2013 Phase III		paclitaxel 200 mg/m^2 + carboplatin AUC 6 (n = 59) oral S-1 40 mg 2*/day + carboplatin AUC 6 (n = 55)	10.6 (8.7-12.6) 14.0 (11.4-16.7)	0.71 (0.48-1.07)	4.87 (3.98-5.72) 4.4 (3.7-5.8)	0.94 (0.64-1.37)

Trial Reference	Intervention	OS: Median (95% CI)	OS: HR (95% CI)	PFS: Median (95% CI)	PFS: HR (95% CI)
Ref ID 1027 Socinski et al. 2012 Phase III	sb paclitaxel 200 mg/m^2 + carboplatin AUC 6 (n = 229)	9.5		5.7	0.87 (0.68-1.10)
	nab paclitaxel 200 mg/m^2 + carboplatin AUC 6 (n = 221)	10.7	0.89 (0.72-1.0) p=0.284	5.6	p=0.235
Ref ID 1115 Treat et al. 2010 Phase III	paclitaxel 225 mg/m^{2+} + carboplatin AUC 6 (n = 61)	10.3 (8.7 - 12.0)		5.7 (4.6-6.9)	
	gemcitabine 1000 mg/m^2 + carboplatin AUC 5 (n = 67)	6.6 (5.1 - 9.5)	1.36 (0 .93-1.99) p=.11	4.3 (3.8-5.1)	1.33 (0 .91-1.94) p=.14
	gemcitabine 1000 mg/m^2 + paclitaxel 200 mg/m^2 (n = 74)	10.2 (7.7 - 13.7)	1.08 (0.75-1.55) p=.67	5.0 (3.9-6.6)	1.17 (0.82-1.67) p=0.38
Ref ID 603 Kubota et al. 2008 Phase III	paclitaxel 225 mg^2 + carboplatin AUC 6 (n = 30)	NR		NR	
	gemcitabine 1000 mg^2 + vincitabine 25 mg/m^2 (n = 46)	NR	0.94 (0.56-1.57) p=.80	NR	1.04 (0.65-1.68) p=0.86
Ref ID 655	paclitaxel 200 mg/m^2 +	NR	NR	5.1	

Trial Reference	Intervention	OS: Median (95% CI)	OS: HR (95% CI)	PFS: Median (95% CI)	PFS: HR (95% CI)
Lilenbaum et al. 2008 Phase III	carboplatin AUC 6 (n = 8) erlotinib 150 mg/day (n = 11)	NR	NR	2.1	3.45 (1.11-10.72) p=.024
Ref ID 171 Chen et al. 2012 Phase II	vinorelbine 60/80 mg/m^2 (n = 12) erlotinib 150 mg/day (n=19)	NR NR	NR NR	1.47 4.07 p=0.15	NR NR

Table 57 Summary of Squamous Outcomes Reported in Trials

REF ID	Authors	Pub Year	Reference Regimen	Comparator Regimen	OS	PFS	Safety	QoL
Gemcitabine plus cisplatin (gem-cis)								
806	Thatcher et al	2014, 2015	gemcitabine-cisplatin	gemcitabine-cisplatin + necitumumab	M/HR	M/HR	☑	
1266	Hoang et al.	2013	gemcitabine-cisplatin	paclitaxel-carboplatin	M	M		
1266	Hoang et al. (Arm 3)		gemcitabine-cisplatin	paclitaxel-cisplatin	M	M		
1266	Hoang et al. (Arm 4)		gemcitabine-cisplatin	docetaxel-cisplatin	M	M		
1263	Morabito et al.	2013	gemcitabine-cisplatin	gemcitabine monotherapy	HR	HR		
Paclitaxel plus carboplatin								
1115	Treat et al.	2010	paclitaxel-carboplatin	gemcitabine-carboplatin	M/HR			
1115	Treat et al (3rd Arm)	2010	paclitaxel-carboplatin	gemcitabine-paclitaxel	M/HR			

[a] safety data for squamous population reported in secondary publication (Novello et al., 2009).

REF ID	Authors	Pub Year	Reference Regimen	Comparator Regimen	OS	PFS	Safety	QoL
603	Kubota et al.	2008	paclitaxel-carboplatin	vinorelbine-gemcitabine + docetaxel	HR	HR		
655	Lilenbaum et al.	2008	paclitaxel-carboplatin	erlotinib mono (o)		M/HR		
1027	Socinski et al.	2012	sb-paclitaxel-carboplatin	nab-paclitaxel-carboplatin	M/HR			
Vinorelbine plus cisplatin (vin-cis)								
858	Pirker et al.	2009	vin-cis	vinorelbine-cisplatin + cetuximab	M/HR			

1089	Tan et al.	2009	vin-cis	docetaxel-cisplatin	M
Other agents and combinations					
171	Chen, Y. M., et al.	2012	erlotinib	vinorelbine	M

Abbreviations: HR, Hazard Ratio; M, median; o, oral; i.v., intravenous; sb, solvent-based; nab, nanoparticle albumin-bound.

Appendix 9. Response to question A20

Table 58 Baseline Patient Characteristics of studies included in the NMA

Study & Reference	Study Drugs	Dose	Squamous patients	Age (median)	Sex (% male)	St IV (%)	PS 0 (%)	PS 1 (%)	PS 2 (%)
Ref ID 171	vinorelbine	60-80 mg/m^2	13	77	80	82	4	70	27
Chen et al. 2012 Phase II	erlotinib	150 mg/day	19	78	83	75	4	77	19
Ref ID 1266 Hoang et al. 2013 Phase III	paclitaxel + cisplatin	135 mg/m^2 75 mg/m^2	60	62	64	89	29	65	6
	gemcitabine + cisplatin	1000 mg/m^2 100 mg/m^2	50	64	62	86	33	62	5
	docetaxel + cisplatin	75 mg/m^2 75 mg/m^2	56	63	63	86	32	62	6
	paclitaxel + carboplatin	225 mg/m^2 AUC 6	57	63	62	86	28	67	5
Ref ID 603 Kubota et al. 2008 Phase III	paclitaxel + carboplatin	225 mg/m2 AUC 6	30	65	69	83	40	60	0
	gemcitabine + vinorelbine +	1000 mg/m^2 25 mg/m2	46	64	73	83	40	60	0

Study & Reference	Study Drugs	Dose	Squamous patients	Age (median)	Sex (% male)	St IV (%)	PS 0 (%)	PS 1 (%)	PS 2 (%)
	docetaxel	40 mg/m2							
Ref ID 655	paclitaxel +	200 mg/m^2	8	-	55	86	0	0	100
Lilenbaum et al.	carboplatin	AUC 6							
2008									
Phase II	erlotinib	150 mg/day	11	-	44	87	0	0	100
Ref ID 1263	gemcitabine	1200 mg/m^2	9	63	82	93	0	0	100
Morabito et al.									
2013	gemcitabine +	1000 mg/m^2	10	63	82	93	0	0	100
Phase III	cisplatin	60 mg/m^2							
	paclitaxel +	200 mg/m^2	12	63	63	89	32	68	0
	carboplatin +	AUC 6							
	conatumumab	15 mg/m^2							
Ref ID 858	vinorelbine	25 mg/m^2	187	60	71	94	21	60	18
Pirker et al.	cisplatin +	80 mg/m^2							
2009									
Phase III	vinorelbine +	25 mg/m^2	190	59	69	94	24	60	17
	cisplatin +	80 mg/m^2							
Ref ID 1027	sb -paclitaxel	200 mg/m^2	221	60	75	79	21	78	0
Socinski et al.	carboplatin	AUC 6							
2012									
Phase III	nab-paclitaxel +	100 mg/m^2	229	60	75	79	26	74	0
	carboplatin	AUC 6							
Ref ID 1089	docetaxel +	75 mg/m^2	64	62	76.4	NR	38	38	24

Study & Reference	Study Drugs	Dose	Squamous patients	Age (median)	Sex (% male)	St IV (%)	PS 0 (%)	PS 1 (%)	PS 2 (%)
Tan et al. 2009 Phase III	cisplatin (vinorelbine iv then oral) + cisplatin	75 mg/m^2 30 mg/m^2 80 mg/m^2 80 mg/m^2	65	59	73.2	NR	38	42	20
Ref ID 806 Thatcher et al. 2014 Phase III	gemcitabine + cisplatin	1250 mg/m^2 75 mg/m^2	548	62	84	100	33	58	9
	gemcitabine + cisplatin + necitumumab	1250 mg/m^2 75 mg/m^2 800 mg	545	62	83	100	30	61	9
Ref ID 1115 Treat et al. 2010 Phase III	gemcitabine + carboplatin	1000 mg/m^2 AUC 5.5	67	64	58	90	33	67	0
	gemcitabine + Paclitaxel	1000 mg/m^2 200 mg/m^2	74	64	63	90	42	57	1
	paclitaxel + carboplatin	225mg/m^2 AUC 6	61	64	61	89	38	61	0
Ref ID 1336 Yoshiaka et al 2013 Phase III	paclitaxel + carboplatin	200 mg/m^2 AUC 6	59	65	86	54	33	66	0
	oral S-1 + carboplatin	40 mg twice daily AUC 5	55	66	87	64	24	76	0

Abbreviations: St, stage; TRT, thoracic radiation treatment; mg, milligrams; m, meters; m^2, meters squared; AUC, area under the curve.

Appendix 10. Response to question A21

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 59 PEDro Methodological Quality Review Results

Ref ID	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
171	Chen et al.	2012	[redacted]											
1266	Hoang et al.	2013	[redacted]											
603	Kubota et al.	2008	[redacted]											
655	Lilenbaum et al.	2008	[redacted]											
1263	Morabito et al.	2013	[redacted]											
858	Pirker et al.	2009	[redacted]											
1027	Socinski et al.	2012	[redacted]											
1089	Tan et al.	2009	[redacted]											
806	Thatcher	2014	[redacted]											
1115	Treat et al.	2010	[redacted]											
1336	Yoshioka et al.	2013	[redacted]											

Q1) Were eligibility criteria specified?

Q2) Were subjects randomly allocated to groups?

Q3) Was allocation concealed?

Q4) Were groups similar at baseline?

Q5) Was there blinding of all subjects?

Q6) Was there blinding of all therapists administering therapy?

Q7) Was there blinding of all assessors?

Q8) Were measures of key outcomes obtained from more than 85% of subjects initially allocated to groups?

Q9) Did all subjects for whom outcome measures were available receive treatment as allocated?

Q10) Were results of between-group statistical comparisons reported for at least one key outcome?

Q11) Did the study provide both point and variabilities for at least one key outcome?

Table 60 Cochrane Risk of Bias Review Results

Ref ID	Authors	Year	Q1	Q2	Q3	Q4	Q5	Q6
171	Chen et al.	2012	[redacted]					
1266	Hoang et al.	2013						
603	Kubota et al.	2008						
655	Lilenbaum et al.	2008						
1263	Morabito et al.	2013						
858	Pirker et al.	2009						
1027	Socinski et al.	2012						
1089	Tan et al.	2009						
806	Thatcher et al.	2014						
1115	Treat et al.	2010						
1336	Yoshioka et al.	2013						

Selection bias

1) inadequate generation of a randomized sequence for patient allocation to groups

2) inadequate concealment of allocations prior to group assignment

Performance bias

3) inadequate blinding of allocated interventions by study participants and personnel

Detection bias

4) inadequate blinding of allocated interventions by outcome assessors

Attrition bias

5) amount, nature, or handling of incomplete outcome data

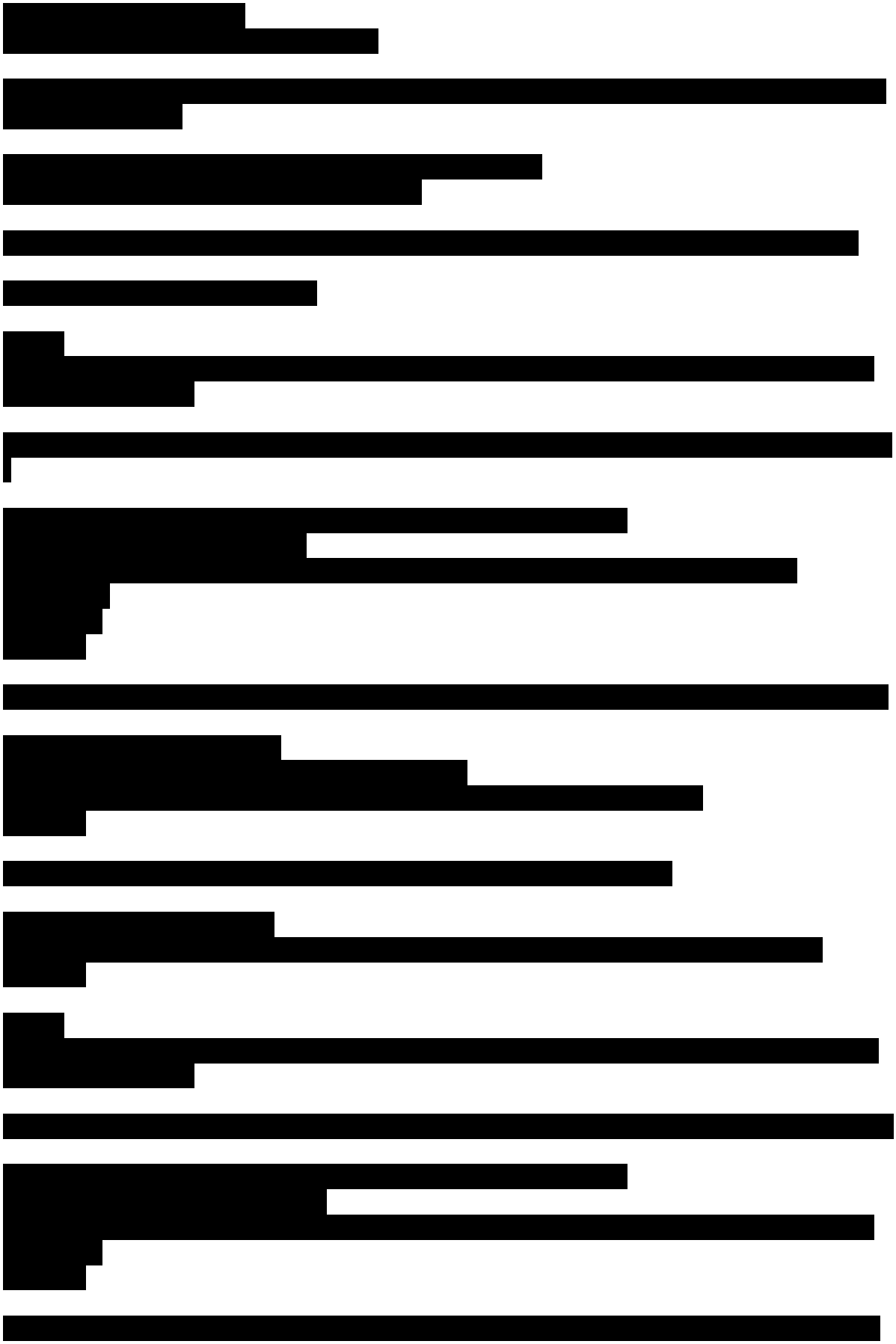
6) reporting bias due to selective outcome reporting

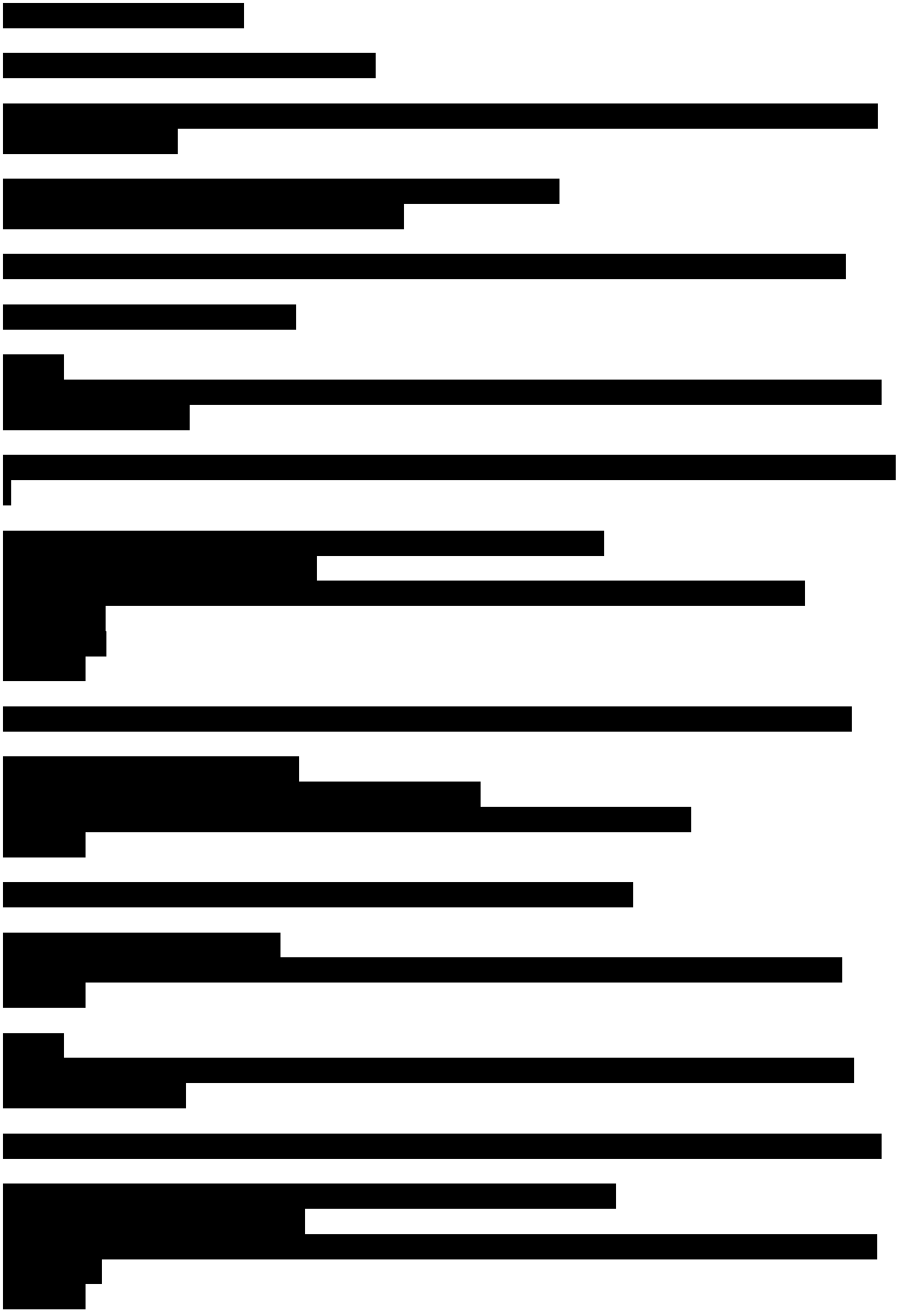
Other

7) other problems not covered elsewhere

Appendix 11. Response to question A22

OpenBUGS codes (Please see 4 sets of codes below).





Appendix 12.Response to question B2

Table 61 OS Kaplan-Meier Outputs for ITT by 1-week Cycle Including Hall-Wellner Simultaneous Confidence Intervals and Survival Standard Error

ITT

CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	0	0	1		.	.	0	0	0	0	548
GC	1	1	0.9872	LOGLOG	0.2928936	0.9998645	0	0.0128	0.00481	7	539
GC	2	2	0.9835	LOGLOG	0.5607644	0.9995227	0	0.0165	0.00545	9	537
GC	3	2.7143	0.9744	LOGLOG	0.7732657	0.9973794	0	0.0256	0.00676	14	531
GC	4	4	0.9688	LOGLOG	0.8106639	0.9952352	0	0.0312	0.00744	17	525
GC	5	4.8571	0.9559	LOGLOG	0.8408856	0.9883332	0	0.0441	0.0088	24	516
GC	6	6	0.9466	LOGLOG	0.8455663	0.9822108	0	0.0534	0.00965	29	509
GC	7	7	0.9392	LOGLOG	0.8453179	0.9768318	0	0.0608	0.0103	33	505
GC	8	8	0.928	LOGLOG	0.8414537	0.9681799	0	0.072	0.0111	39	498
GC	9	8.8571	0.9205	LOGLOG	0.837456	0.9620962	0	0.0795	0.0116	43	492
GC	10	9.8571	0.9187	LOGLOG	0.8363306	0.9605414	0	0.0813	0.0118	44	491
GC	11	11	0.8981	LOGLOG	0.8217904	0.9428016	0	0.1019	0.013	55	478
GC	12	12	0.8905	LOGLOG	0.8157998	0.9360972	0	0.1095	0.0135	59	472
GC	13	13	0.8792	LOGLOG	0.8063835	0.9258712	0	0.1208	0.0141	65	466
GC	14	14	0.8716	LOGLOG	0.7998799	0.9189554	0	0.1284	0.0144	69	461
GC	15	15	0.8584	LOGLOG	0.7881836	0.90671	0	0.1416	0.0151	76	454
GC	16	16	0.8395	LOGLOG	0.7709434	0.8889468	0	0.1605	0.0159	86	443

ITT

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	17	16.8571	0.8281	LOGLOG	0.7603959	0.878183	0	0.1719	0.0163	92	437
GC	18	18	0.8167	LOGLOG	0.7497354	0.8673573	0	0.1833	0.0167	98	431
GC	19	18.8571	0.811	LOGLOG	0.7443699	0.8619244	0	0.189	0.0169	101	428
GC	20	18.8571	0.811	LOGLOG	0.7443699	0.8619244	0	0.189	0.0169	101	428
GC	21	20.8571	0.8016	LOGLOG	0.7353827	0.8528434	0	0.1984	0.0173	106	423
GC	22	21.7143	0.7921	LOGLOG	0.7263234	0.843713	0	0.2079	0.0176	111	417
GC	23	23	0.775	LOGLOG	0.7099007	0.8272031	0	0.225	0.0181	120	407
GC	24	24	0.7578	LOGLOG	0.6933438	0.810601	0	0.2422	0.0186	129	398
GC	25	25	0.7407	LOGLOG	0.6766789	0.7939224	0	0.2593	0.019	138	388
GC	26	26	0.7235	LOGLOG	0.6599277	0.7771814	0	0.2765	0.0194	147	379
GC	27	26.8571	0.7101	LOGLOG	0.6468619	0.7641346	0	0.2899	0.0197	154	372
GC	28	28	0.6967	LOGLOG	0.6337521	0.7510542	0	0.3033	0.02	161	364
GC	29	29	0.6756	LOGLOG	0.6130123	0.7303884	0	0.3244	0.0204	172	352
GC	30	30	0.6603	LOGLOG	0.5978954	0.7153334	0	0.3397	0.0206	180	344
GC	31	31	0.641	LOGLOG	0.5789276	0.6964577	0	0.359	0.0209	190	333
GC	32	31.8571	0.6276	LOGLOG	0.5656214	0.6832218	0	0.3724	0.0211	197	326
GC	33	33	0.6122	LOGLOG	0.5504009	0.6680847	0	0.3878	0.0212	205	318
GC	34	33.8571	0.6025	LOGLOG	0.5408616	0.6586027	0	0.3975	0.0213	210	312
GC	35	34.7143	0.5948	LOGLOG	0.5332163	0.651006	0	0.4052	0.0214	214	308
GC	36	36	0.5736	LOGLOG	0.5121796	0.6301052	0	0.4264	0.0216	225	297
GC	37	36.8571	0.56	LOGLOG	0.4987555	0.616775	0	0.44	0.0217	232	289

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	38	37.4286	0.5503	LOGLOG	0.4891482	0.6072385	0	0.4497	0.0217	237	284
GC	39	38.8571	0.5348	LOGLOG	0.4737721	0.5919766	0	0.4652	0.0218	245	276
GC	40	40	0.5271	LOGLOG	0.4660824	0.5843444	0	0.4729	0.0218	249	272
GC	41	40.2857	0.5193	LOGLOG	0.4583919	0.5767113	0	0.4807	0.0218	253	268
GC	42	42	0.5096	LOGLOG	0.4487776	0.5671692	0	0.4904	0.0219	258	263
GC	43	43	0.498	LOGLOG	0.4372394	0.5557178	0	0.502	0.0219	264	257
GC	44	43.8571	0.4864	LOGLOG	0.4257003	0.5442657	0	0.5136	0.0219	270	251
GC	45	44.5714	0.4825	LOGLOG	0.4218539	0.5404483	0	0.5175	0.0219	272	249
GC	46	46	0.4728	LOGLOG	0.4122378	0.5309048	0	0.5272	0.0218	277	244
GC	47	46.5714	0.467	LOGLOG	0.4064682	0.5251787	0	0.533	0.0218	280	240
GC	48	47.5714	0.4631	LOGLOG	0.4026037	0.5213475	0	0.5369	0.0218	282	238
GC	49	48.8571	0.4514	LOGLOG	0.3910011	0.5098474	0	0.5486	0.0218	288	231
GC	50	49.7143	0.4456	LOGLOG	0.3851765	0.5040798	0	0.5544	0.0218	291	228
GC	51	50.8571	0.4377	LOGLOG	0.377411	0.4963902	0	0.5623	0.0217	295	224
GC	52	52	0.428	LOGLOG	0.3677053	0.4867794	0	0.572	0.0217	300	219
GC	53	53	0.4182	LOGLOG	0.3580013	0.47717	0	0.5818	0.0216	305	214
GC	54	53.7143	0.4104	LOGLOG	0.3502396	0.4694837	0	0.5896	0.0216	309	210
GC	55	55	0.3908	LOGLOG	0.330842	0.4502741	0	0.6092	0.0214	319	200
GC	56	56	0.3889	LOGLOG	0.3289028	0.4483537	0	0.6111	0.0214	320	199
GC	57	56.7143	0.3752	LOGLOG	0.3153092	0.4348975	0	0.6248	0.0213	327	191
GC	58	58	0.3693	LOGLOG	0.3094605	0.4291147	0	0.6307	0.0212	330	188

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	59	58.7143	0.3634	LOGLOG	0.3036133	0.4233333	0	0.6366	0.0211	333	185
GC	60	59.7143	0.3595	LOGLOG	0.2997161	0.4194798	0	0.6405	0.0211	335	183
GC	61	61	0.3555	LOGLOG	0.2958196	0.415627	0	0.6445	0.021	337	181
GC	62	62	0.3536	LOGLOG	0.2938716	0.4137008	0	0.6464	0.021	338	180
GC	63	62.7143	0.3497	LOGLOG	0.2899763	0.4098491	0	0.6503	0.021	340	178
GC	64	63.8571	0.3457	LOGLOG	0.2860819	0.405998	0	0.6543	0.0209	342	176
GC	65	64.8571	0.3418	LOGLOG	0.2821883	0.4021478	0	0.6582	0.0209	344	174
GC	66	66	0.3339	LOGLOG	0.274404	0.3944499	0	0.6661	0.0207	348	170
GC	67	67	0.33	LOGLOG	0.2705133	0.3906023	0	0.67	0.0207	350	168
GC	68	67.4286	0.3143	LOGLOG	0.2549615	0.3752218	0	0.6857	0.0204	358	160
GC	69	68.4286	0.3084	LOGLOG	0.2491346	0.3694586	0	0.6916	0.0203	361	156
GC	70	70	0.2985	LOGLOG	0.2393096	0.3597816	0	0.7015	0.0202	366	150
GC	71	70.5714	0.2885	LOGLOG	0.2294639	0.3500938	0	0.7115	0.02	371	145
GC	72	71.8571	0.2766	LOGLOG	0.2176639	0.3384823	0	0.7234	0.0197	377	138
GC	73	72.1429	0.2746	LOGLOG	0.2156816	0.336538	0	0.7254	0.0197	378	135
GC	74	73.7143	0.2705	LOGLOG	0.2116102	0.3325861	0	0.7295	0.0196	380	130
GC	75	75	0.26	LOGLOG	0.2011114	0.3225254	0	0.74	0.0194	385	123
GC	76	76	0.2557	LOGLOG	0.1968926	0.3184923	0	0.7443	0.0193	387	121
GC	77	77	0.2515	LOGLOG	0.1926772	0.3144623	0	0.7485	0.0192	389	119
GC	78	77.7143	0.2452	LOGLOG	0.1863609	0.3084236	0	0.7548	0.0191	392	116
GC	79	79	0.2366	LOGLOG	0.1778554	0.3003353	0	0.7634	0.0189	396	107

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	80	80	0.2344	LOGLOG	0.1756062	0.2982529	0	0.7656	0.0188	397	104
GC	81	80.4286	0.2322	LOGLOG	0.1733309	0.2961588	0	0.7678	0.0188	398	102
GC	82	81.7143	0.2299	LOGLOG	0.1710287	0.294053	0	0.7701	0.0187	399	100
GC	83	82.8571	0.223	LOGLOG	0.1640129	0.2876913	0	0.777	0.0186	402	96
GC	84	83.7143	0.2206	LOGLOG	0.1616254	0.2855516	0	0.7794	0.0186	403	93
GC	85	85	0.2157	LOGLOG	0.1566156	0.2811817	0	0.7843	0.0185	405	88
GC	86	85	0.2157	LOGLOG	0.1566156	0.2811817	0	0.7843	0.0185	405	86
GC	87	86.8571	0.2057	LOGLOG	0.146207	0.2723189	0	0.7943	0.0183	409	80
GC	88	87.5714	0.2005	LOGLOG	0.1408729	0.2678575	0	0.7995	0.0182	411	77
GC	89	87.5714	0.2005	LOGLOG	0.1408729	0.2678575	0	0.7995	0.0182	411	75
GC	90	89.5714	0.1978	LOGLOG	0.138017	0.2655776	0	0.8022	0.0181	412	72
GC	91	90.4286	0.1951	LOGLOG	0.1351124	0.2632892	0	0.8049	0.0181	413	71
GC	92	91.5714	0.1923	LOGLOG	0.1322135	0.261006	0	0.8077	0.018	414	69
GC	93	91.5714	0.1923	LOGLOG	0.1322135	0.261006	0	0.8077	0.018	414	68
GC	94	93.7143	0.1895	LOGLOG	0.1291419	0.2586912	0	0.8105	0.018	415	66
GC	95	93.7143	0.1895	LOGLOG	0.1291419	0.2586912	0	0.8105	0.018	415	65
GC	96	96	0.1835	LOGLOG	0.1227561	0.254038	0	0.8165	0.0179	417	61
GC	97	96.7143	0.1775	LOGLOG	0.1162608	0.2493998	0	0.8225	0.0178	419	59
GC	98	96.7143	0.1775	LOGLOG	0.1162608	0.2493998	0	0.8225	0.0178	419	58
GC	99	98.8571	0.1683	LOGLOG	0.1063639	0.2424978	0	0.8317	0.0177	422	55
GC	100	98.8571	0.1683	LOGLOG	0.1063639	0.2424978	0	0.8317	0.0177	422	53

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	101	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	52
GC	102	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	51
GC	103	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	50
GC	104	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	49
GC	105	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	47
GC	106	100.7143	0.1652	LOGLOG	0.1029122	0.2402154	0	0.8348	0.0176	423	47
GC	107	106.4286	0.1581	LOGLOG	0.0949811	0.2357541	0	0.8419	0.0176	425	44
GC	108	108	0.1509	LOGLOG	0.0868944	0.2314342	0	0.8491	0.0175	427	41
GC	109	108.2857	0.1436	LOGLOG	0.0786504	0.2273077	0	0.8564	0.0174	429	37
GC	110	109.2857	0.1358	LOGLOG	0.0699069	0.2235618	0	0.8642	0.0173	431	35
GC	111	109.2857	0.1358	LOGLOG	0.0699069	0.2235618	0	0.8642	0.0173	431	35
GC	112	111.5714	0.1319	LOGLOG	0.0656221	0.2217775	0	0.8681	0.0172	432	34
GC	113	112.4286	0.1281	LOGLOG	0.0614012	0.2200602	0	0.8719	0.0172	433	33
GC	114	112.4286	0.1281	LOGLOG	0.0614012	0.2200602	0	0.8719	0.0172	433	33
GC	115	115	0.1239	LOGLOG	0.0568219	0.2186433	0	0.8761	0.0171	434	30
GC	116	115.5714	0.1198	LOGLOG	0.0523383	0.2173304	0	0.8802	0.017	435	29
GC	117	115.5714	0.1198	LOGLOG	0.0523383	0.2173304	0	0.8802	0.017	435	29
GC	118	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	28
GC	119	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	28
GC	120	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	27
GC	121	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	27

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	122	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	27
GC	123	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	25
GC	124	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	25
GC	125	118	0.1157	LOGLOG	0.0479586	0.2161338	0	0.8843	0.0169	436	24
GC	126	125.4286	0.1108	LOGLOG	0.0424881	0.2161415	0	0.8892	0.0169	437	23
GC	127	125.4286	0.1108	LOGLOG	0.0424881	0.2161415	0	0.8892	0.0169	437	23
GC	128	125.4286	0.1108	LOGLOG	0.0424881	0.2161415	0	0.8892	0.0169	437	22
GC	129	128.7143	0.1058	LOGLOG	0.036852	0.2168751	0	0.8942	0.0169	438	21
GC	130	128.7143	0.1058	LOGLOG	0.036852	0.2168751	0	0.8942	0.0169	438	19
GC	131	128.7143	0.1058	LOGLOG	0.036852	0.2168751	0	0.8942	0.0169	438	19
GC	132	128.7143	0.1058	LOGLOG	0.036852	0.2168751	0	0.8942	0.0169	438	17
GC	133	132.2857	0.0996	LOGLOG	0.0292981	0.221506	0	0.9004	0.017	439	16
GC	134	132.2857	0.0996	LOGLOG	0.0292981	0.221506	0	0.9004	0.017	439	14
GC	135	132.2857	0.0996	LOGLOG	0.0292981	0.221506	0	0.9004	0.017	439	14
GC	136	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	13
GC	137	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	11
GC	138	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	10
GC	139	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	9
GC	140	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	8
GC	141	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	8
GC	142	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	8

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	143	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	144	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	145	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	146	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	147	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	148	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	7
GC	149	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	5
GC	150	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	5
GC	151	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	5
GC	152	135.1429	0.0925	LOGLOG	0.02087	0.2310898	0	0.9075	0.0172	440	5
GC	153	152.7143	0.074	LOGLOG	0.0005672	0.4036643	0	0.926	0.0215	441	4
GC	154	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	3
GC	155	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	3
GC	156	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	3
GC	157	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	3
GC	158	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	3
GC	159	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	2
GC	160	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	2

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	161	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	2
GC	162	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	2
GC	163	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	1
GC	164	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	1
GC	165	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	1
GC	166	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	1
GC	167	153.4286	0.0555	LOGLOG	7.6934E-09	0.63918	0	0.9445	0.0227	442	1
GC	168	153.4286	.		.	.	0	.	.	442	0
GC+N	0	0	1		.	.	0	0	0	0	545
GC+N	1	1	0.9926	LOGLOG	1.4486E-09	0.9999973	0	0.00737	0.00367	4	538
GC+N	2	1.8571	0.9852	LOGLOG	0.4539419	0.9997203	0	0.0148	0.00518	8	534
GC+N	3	2.7143	0.9742	LOGLOG	0.7737515	0.997335	0	0.0258	0.00681	14	528
GC+N	4	4	0.9686	LOGLOG	0.8107134	0.9951697	0	0.0314	0.00749	17	522
GC+N	5	4.5714	0.963	LOGLOG	0.8291465	0.9924582	0	0.037	0.00811	20	517
GC+N	6	5.8571	0.9537	LOGLOG	0.8421832	0.987007	0	0.0463	0.00904	25	510
GC+N	7	7	0.9462	LOGLOG	0.8451724	0.9819895	0	0.0538	0.00972	29	504
GC+N	8	7.7143	0.9368	LOGLOG	0.8443871	0.9751216	0	0.0632	0.0105	34	498

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	9	8.7143	0.9312	LOGLOG	0.8424745	0.9707511	0	0.0688	0.0109	37	493
GC+N	10	10	0.9255	LOGLOG	0.8398336	0.9662156	0	0.0745	0.0113	40	487
GC+N	11	11	0.9179	LOGLOG	0.8354771	0.9599481	0	0.0821	0.0119	44	482
GC+N	12	11.7143	0.9083	LOGLOG	0.8291131	0.9518691	0	0.0917	0.0125	49	476
GC+N	13	13	0.893	LOGLOG	0.817497	0.9384607	0	0.107	0.0134	57	467
GC+N	14	13.8571	0.8854	LOGLOG	0.8112586	0.9316042	0	0.1146	0.0138	61	463
GC+N	15	14.8571	0.8835	LOGLOG	0.8096613	0.9298735	0	0.1165	0.0139	62	461
GC+N	16	16	0.8796	LOGLOG	0.8064313	0.9263977	0	0.1204	0.0141	64	459
GC+N	17	17	0.8681	LOGLOG	0.796483	0.9158543	0	0.1319	0.0147	70	452
GC+N	18	17.8571	0.8585	LOGLOG	0.7879635	0.906963	0	0.1415	0.0151	75	447
GC+N	19	18.4286	0.8566	LOGLOG	0.7862398	0.9051754	0	0.1434	0.0152	76	445
GC+N	20	20	0.8489	LOGLOG	0.7792704	0.8979823	0	0.1511	0.0156	80	441
GC+N	21	21	0.8354	LOGLOG	0.7668753	0.8852892	0	0.1646	0.0161	87	433
GC+N	22	22	0.8258	LOGLOG	0.7578877	0.876146	0	0.1742	0.0165	92	427
GC+N	23	23	0.8219	LOGLOG	0.7542626	0.8724699	0	0.1781	0.0167	94	425
GC+N	24	24	0.8103	LOGLOG	0.7433208	0.8614038	0	0.1897	0.0171	100	419
GC+N	25	25	0.7987	LOGLOG	0.7322891	0.8502842	0	0.2013	0.0175	106	412
GC+N	26	26	0.789	LOGLOG	0.7230217	0.8409678	0	0.211	0.0178	111	407
GC+N	27	26.7143	0.7812	LOGLOG	0.7155775	0.833496	0	0.2188	0.0181	115	403
GC+N	28	27.8571	0.7677	LOGLOG	0.7024951	0.8203856	0	0.2323	0.0185	122	396
GC+N	29	29	0.756	LOGLOG	0.6912341	0.8091172	0	0.244	0.0188	128	390

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	30	30	0.7444	LOGLOG	0.6799361	0.7978242	0	0.2556	0.0191	134	384
GC+N	31	30.8571	0.7347	LOGLOG	0.6704803	0.7883831	0	0.2653	0.0193	139	378
GC+N	32	32	0.7269	LOGLOG	0.6628928	0.7808131	0	0.2731	0.0195	143	374
GC+N	33	32.7143	0.7211	LOGLOG	0.6571947	0.7751304	0	0.2789	0.0196	146	370
GC+N	34	34	0.7016	LOGLOG	0.6381038	0.7561118	0	0.2984	0.02	156	360
GC+N	35	35	0.6958	LOGLOG	0.6323658	0.7503985	0	0.3042	0.0202	159	357
GC+N	36	35.8571	0.6802	LOGLOG	0.6170435	0.7351479	0	0.3198	0.0204	167	349
GC+N	37	36.8571	0.6704	LOGLOG	0.6074534	0.7256061	0	0.3296	0.0206	172	344
GC+N	38	38	0.6548	LOGLOG	0.5920904	0.7103252	0	0.3452	0.0209	180	336
GC+N	39	39	0.647	LOGLOG	0.5844012	0.7026789	0	0.353	0.021	184	332
GC+N	40	40	0.6256	LOGLOG	0.5632333	0.6816344	0	0.3744	0.0212	195	321
GC+N	41	41	0.608	LOGLOG	0.5458593	0.6643724	0	0.392	0.0214	204	311
GC+N	42	42	0.5904	LOGLOG	0.5284431	0.6470764	0	0.4096	0.0216	213	302
GC+N	43	43	0.5728	LOGLOG	0.5110143	0.6297706	0	0.4272	0.0217	222	293
GC+N	44	43.8571	0.5591	LOGLOG	0.4974516	0.6163049	0	0.4409	0.0218	229	286
GC+N	45	44.8571	0.5494	LOGLOG	0.4877608	0.6066841	0	0.4506	0.0219	234	281
GC+N	46	45.8571	0.5396	LOGLOG	0.4780679	0.5970615	0	0.4604	0.0219	239	276
GC+N	47	46.7143	0.5259	LOGLOG	0.4644946	0.5835873	0	0.4741	0.022	246	269
GC+N	48	48	0.52	LOGLOG	0.4586767	0.5778119	0	0.48	0.022	249	265
GC+N	49	48.5714	0.5122	LOGLOG	0.4508857	0.5700851	0	0.4878	0.022	253	261
GC+N	50	50	0.4926	LOGLOG	0.4314058	0.5507662	0	0.5074	0.022	263	251

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	51	51	0.4808	LOGLOG	0.4197171	0.5391742	0	0.5192	0.022	269	245
GC+N	52	52	0.4769	LOGLOG	0.4158208	0.5353102	0	0.5231	0.022	271	243
GC+N	53	52.4286	0.4729	LOGLOG	0.4119245	0.5314462	0	0.5271	0.022	273	241
GC+N	54	54	0.4671	LOGLOG	0.4060802	0.5256502	0	0.5329	0.022	276	238
GC+N	55	54.8571	0.4553	LOGLOG	0.394392	0.5140588	0	0.5447	0.022	282	232
GC+N	56	56	0.4454	LOGLOG	0.3845943	0.5043562	0	0.5546	0.0219	287	225
GC+N	57	56.5714	0.4335	LOGLOG	0.3727915	0.4926791	0	0.5665	0.0219	293	219
GC+N	58	57.8571	0.4296	LOGLOG	0.3688577	0.4887871	0	0.5704	0.0218	295	217
GC+N	59	59	0.4276	LOGLOG	0.3668909	0.4868412	0	0.5724	0.0218	296	216
GC+N	60	60	0.4197	LOGLOG	0.3590138	0.4790505	0	0.5803	0.0218	300	211
GC+N	61	60.8571	0.4137	LOGLOG	0.3530827	0.4731907	0	0.5863	0.0217	303	208
GC+N	62	61.8571	0.4038	LOGLOG	0.3431997	0.4634259	0	0.5962	0.0217	308	203
GC+N	63	62.8571	0.3958	LOGLOG	0.3352952	0.4556159	0	0.6042	0.0216	312	199
GC+N	64	63.2857	0.3938	LOGLOG	0.3333194	0.4536637	0	0.6062	0.0216	313	198
GC+N	65	64.7143	0.3878	LOGLOG	0.3273693	0.4477909	0	0.6122	0.0215	316	194
GC+N	66	66	0.3818	LOGLOG	0.3214087	0.4419109	0	0.6182	0.0215	319	191
GC+N	67	66.1429	0.3778	LOGLOG	0.3174358	0.4379916	0	0.6222	0.0214	321	189
GC+N	68	67.8571	0.3658	LOGLOG	0.305459	0.4261938	0	0.6342	0.0213	327	182
GC+N	69	69	0.3557	LOGLOG	0.2954733	0.4163598	0	0.6443	0.0212	332	177
GC+N	70	69.8571	0.3497	LOGLOG	0.2894845	0.4104616	0	0.6503	0.0211	335	174
GC+N	71	70.5714	0.3417	LOGLOG	0.2815026	0.4026004	0	0.6583	0.021	339	167

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	72	72	0.3314	LOGLOG	0.2713188	0.392637	0	0.6686	0.0209	344	162
GC+N	73	72.5714	0.3294	LOGLOG	0.2692829	0.3906451	0	0.6706	0.0208	345	159
GC+N	74	73.5714	0.3253	LOGLOG	0.2651511	0.3866224	0	0.6747	0.0208	347	156
GC+N	75	75	0.3126	LOGLOG	0.2525387	0.3744186	0	0.6874	0.0206	353	148
GC+N	76	75.8571	0.3084	LOGLOG	0.2482807	0.3703181	0	0.6916	0.0205	355	143
GC+N	77	77	0.2954	LOGLOG	0.2352664	0.3578738	0	0.7046	0.0204	361	136
GC+N	78	77.8571	0.2888	LOGLOG	0.2286679	0.3516009	0	0.7112	0.0203	364	130
GC+N	79	79	0.2821	LOGLOG	0.2218881	0.3452267	0	0.7179	0.0201	367	124
GC+N	80	80	0.273	LOGLOG	0.2126576	0.3366271	0	0.727	0.02	371	119
GC+N	81	80.4286	0.2707	LOGLOG	0.2103345	0.3344698	0	0.7293	0.02	372	117
GC+N	82	80.4286	0.2707	LOGLOG	0.2103345	0.3344698	0	0.7293	0.02	372	115
GC+N	83	82.7143	0.2683	LOGLOG	0.2078833	0.3322476	0	0.7317	0.0199	373	112
GC+N	84	83.8571	0.2635	LOGLOG	0.2029846	0.3278064	0	0.7365	0.0199	375	110
GC+N	85	84.8571	0.2611	LOGLOG	0.2005373	0.3255876	0	0.7389	0.0198	376	109
GC+N	86	85.4286	0.2563	LOGLOG	0.1956176	0.3211399	0	0.7437	0.0198	378	103
GC+N	87	86.7143	0.2538	LOGLOG	0.1930538	0.3188689	0	0.7462	0.0197	379	101
GC+N	88	88	0.2513	LOGLOG	0.1904261	0.3165706	0	0.7487	0.0197	380	99
GC+N	89	88.4286	0.2437	LOGLOG	0.1825546	0.3096863	0	0.7563	0.0196	383	95
GC+N	90	89.5714	0.2385	LOGLOG	0.1772462	0.3050768	0	0.7615	0.0195	385	93
GC+N	91	91	0.2334	LOGLOG	0.1719093	0.300461	0	0.7666	0.0194	387	90
GC+N	92	91	0.2334	LOGLOG	0.1719093	0.300461	0	0.7666	0.0194	387	89

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	93	91	0.2334	LOGLOG	0.1719093	0.300461	0	0.7666	0.0194	387	87
GC+N	94	91	0.2334	LOGLOG	0.1719093	0.300461	0	0.7666	0.0194	387	86
GC+N	95	94.1429	0.2307	LOGLOG	0.1690615	0.2980891	0	0.7693	0.0194	388	85
GC+N	96	95.8571	0.2252	LOGLOG	0.1632865	0.2933239	0	0.7748	0.0193	390	81
GC+N	97	96.7143	0.2196	LOGLOG	0.1574319	0.2885418	0	0.7804	0.0192	392	78
GC+N	98	97.4286	0.2168	LOGLOG	0.1544089	0.2861265	0	0.7832	0.0192	393	76
GC+N	99	97.4286	0.2168	LOGLOG	0.1544089	0.2861265	0	0.7832	0.0192	393	74
GC+N	100	99.5714	0.2108	LOGLOG	0.1480421	0.2812219	0	0.7892	0.0191	395	71
GC+N	101	101	0.2048	LOGLOG	0.1415111	0.2762981	0	0.7952	0.019	397	67
GC+N	102	101.2857	0.2017	LOGLOG	0.1382237	0.2738391	0	0.7983	0.019	398	66
GC+N	103	102.2857	0.1986	LOGLOG	0.134944	0.271387	0	0.8014	0.0189	399	62
GC+N	104	102.2857	0.1986	LOGLOG	0.134944	0.271387	0	0.8014	0.0189	399	61
GC+N	105	105	0.1953	LOGLOG	0.1312875	0.2688879	0	0.8047	0.0189	400	58
GC+N	106	105.5714	0.192	LOGLOG	0.1275539	0.266391	0	0.808	0.0189	401	57
GC+N	107	105.5714	0.192	LOGLOG	0.1275539	0.266391	0	0.808	0.0189	401	57
GC+N	108	108	0.1885	LOGLOG	0.1237389	0.2638996	0	0.8115	0.0189	402	53
GC+N	109	108.1429	0.185	LOGLOG	0.1197325	0.2614151	0	0.815	0.0188	403	51
GC+N	110	108.1429	0.185	LOGLOG	0.1197325	0.2614151	0	0.815	0.0188	403	48
GC+N	111	110.4286	0.1811	LOGLOG	0.1152548	0.2589631	0	0.8189	0.0188	404	47
GC+N	112	110.4286	0.1811	LOGLOG	0.1152548	0.2589631	0	0.8189	0.0188	404	46
GC+N	113	112.8571	0.1732	LOGLOG	0.1059428	0.2541787	0	0.8268	0.0188	406	42

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	114	113.1429	0.169	LOGLOG	0.1010933	0.2518699	0	0.831	0.0188	407	40
GC+N	115	113.1429	0.169	LOGLOG	0.1010933	0.2518699	0	0.831	0.0188	407	40
GC+N	116	116	0.1647	LOGLOG	0.0959093	0.2496833	0	0.8353	0.0188	408	38
GC+N	117	116	0.1647	LOGLOG	0.0959093	0.2496833	0	0.8353	0.0188	408	38
GC+N	118	116	0.1647	LOGLOG	0.0959093	0.2496833	0	0.8353	0.0188	408	36
GC+N	119	116	0.1647	LOGLOG	0.0959093	0.2496833	0	0.8353	0.0188	408	34
GC+N	120	119.8571	0.1599	LOGLOG	0.089828	0.247858	0	0.8401	0.0189	409	32
GC+N	121	119.8571	0.1599	LOGLOG	0.089828	0.247858	0	0.8401	0.0189	409	32
GC+N	122	122	0.1549	LOGLOG	0.083544	0.2462394	0	0.8451	0.019	410	31
GC+N	123	122.7143	0.1399	LOGLOG	0.0654033	0.2420347	0	0.8601	0.019	413	28
GC+N	124	122.7143	0.1399	LOGLOG	0.0654033	0.2420347	0	0.8601	0.019	413	25
GC+N	125	124.1429	0.1343	LOGLOG	0.0584786	0.2417371	0	0.8657	0.019	414	23
GC+N	126	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	22
GC+N	127	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	21
GC+N	128	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	20
GC+N	129	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	20
GC+N	130	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	20
GC+N	131	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	20
GC+N	132	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	18
GC+N	133	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	16
GC+N	134	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	15

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	135	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	15
GC+N	136	125.5714	0.1284	LOGLOG	0.0513264	0.2421249	0	0.8716	0.0191	415	15
GC+N	137	137	0.1186	LOGLOG	0.0351836	0.2570827	0	0.8814	0.02	416	12
GC+N	138	137	0.1186	LOGLOG	0.0351836	0.2570827	0	0.8814	0.02	416	12
GC+N	139	137	0.1186	LOGLOG	0.0351836	0.2570827	0	0.8814	0.02	416	12
GC+N	140	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	9
GC+N	141	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	8
GC+N	142	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	8
GC+N	143	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	8
GC+N	144	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	8
GC+N	145	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	7
GC+N	146	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	5
GC+N	147	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	4
GC+N	148	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	149	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	150	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	151	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	152	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	153	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	154	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	155	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	156	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	157	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	158	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	159	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	3
GC+N	160	139.7143	0.0988	LOGLOG	0.0122054	0.2964218	0	0.9012	0.021	418	1
GC+N	161	139.7143	.		.	.	0	.	.	418	0
GC+N	162	139.7143	.		.	.	0	.	.	418	0
GC+N	163	139.7143	.		.	.	0	.	.	418	0
GC+N	164	139.7143	.		.	.	0	.	.	418	0
GC+N	165	139.7143	.		.	.	0	.	.	418	0
GC+N	166	139.7143	.		.	.	0	.	.	418	0
GC+N	167	139.7143	.		.	.	0	.	.	418	0
GC+N	168	139.7143	.		.	.	0	.	.	418	0
Overall	0	0	1		.	.	0	0	0	0	1093
Overall	1	1	0.9899	LOGLOG	0.546437	0.9998293	0	0.0101	0.00303	11	1077
Overall	2	2	0.9844	LOGLOG	0.8000909	0.9988893	0	0.0156	0.00376	17	1071
Overall	3	2.7143	0.9743	LOGLOG	0.8768564	0.9948419	0	0.0257	0.0048	28	1059
Overall	4	4	0.9687	LOGLOG	0.8862792	0.9916743	0	0.0313	0.00528	34	1047
Overall	5	4.8571	0.9595	LOGLOG	0.8900425	0.9854029	0	0.0405	0.00599	44	1033
Overall	6	6	0.9501	LOGLOG	0.8876745	0.9782875	0	0.0499	0.00661	54	1019
Overall	7	7	0.9427	LOGLOG	0.8837643	0.9721866	0	0.0573	0.00707	62	1009

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	8	8	0.9324	LOGLOG	0.8768398	0.9633957	0	0.0676	0.00764	73	996
Overall	9	8.8571	0.9258	LOGLOG	0.8718442	0.9576113	0	0.0742	0.00798	80	985
Overall	10	10	0.9221	LOGLOG	0.8688369	0.9542447	0	0.0779	0.00817	84	978
Overall	11	11	0.9079	LOGLOG	0.8568832	0.9413369	0	0.0921	0.00882	99	960
Overall	12	12	0.8994	LOGLOG	0.8493429	0.9334225	0	0.1006	0.00919	108	948
Overall	13	13	0.8861	LOGLOG	0.8372536	0.9209284	0	0.1139	0.00971	122	933
Overall	14	14	0.8785	LOGLOG	0.8302065	0.9137162	0	0.1215	0.01	130	924
Overall	15	15	0.8709	LOGLOG	0.8230779	0.9064572	0	0.1291	0.0103	138	915
Overall	16	16	0.8594	LOGLOG	0.8122612	0.895494	0	0.1406	0.0106	150	902
Overall	17	17	0.848	LOGLOG	0.8013334	0.8844628	0	0.152	0.011	162	889
Overall	18	18	0.8375	LOGLOG	0.7912412	0.8743035	0	0.1625	0.0113	173	878
Overall	19	18.8571	0.8337	LOGLOG	0.7875574	0.8706004	0	0.1663	0.0114	177	873
Overall	20	20	0.8299	LOGLOG	0.7838626	0.8668891	0	0.1701	0.0115	181	869
Overall	21	21	0.8184	LOGLOG	0.7727389	0.8557283	0	0.1816	0.0118	193	856
Overall	22	22	0.8088	LOGLOG	0.7634165	0.8463883	0	0.1912	0.0121	203	844
Overall	23	23	0.7983	LOGLOG	0.7531117	0.8360756	0	0.2017	0.0123	214	832
Overall	24	24	0.7839	LOGLOG	0.7390077	0.8219745	0	0.2161	0.0127	229	817
Overall	25	25	0.7695	LOGLOG	0.7248538	0.8078359	0	0.2305	0.013	244	800
Overall	26	26	0.756	LOGLOG	0.7115885	0.7945954	0	0.244	0.0132	258	786
Overall	27	26.8571	0.7454	LOGLOG	0.7011491	0.7841797	0	0.2546	0.0134	269	775
Overall	28	28	0.732	LOGLOG	0.687838	0.7709038	0	0.268	0.0136	283	760

ITT

CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	29	29	0.7156	LOGLOG	0.6716196	0.7547371	0	0.2844	0.0139	300	742
Overall	30	30	0.7021	LOGLOG	0.6582429	0.7414069	0	0.2979	0.0141	314	728
Overall	31	31	0.6876	LOGLOG	0.6438704	0.7270902	0	0.3124	0.0143	329	711
Overall	32	32	0.6769	LOGLOG	0.6333114	0.7165751	0	0.3231	0.0144	340	700
Overall	33	33	0.6663	LOGLOG	0.6227453	0.7060541	0	0.3337	0.0146	351	688
Overall	34	34	0.6518	LOGLOG	0.6082918	0.6916684	0	0.3482	0.0147	366	672
Overall	35	35	0.645	LOGLOG	0.6015412	0.6849502	0	0.355	0.0148	373	665
Overall	36	36	0.6265	LOGLOG	0.5832102	0.6667087	0	0.3735	0.015	392	646
Overall	37	36.8571	0.6149	LOGLOG	0.5716146	0.6551722	0	0.3851	0.0151	404	633
Overall	38	38	0.6023	LOGLOG	0.5590417	0.642665	0	0.3977	0.0151	417	620
Overall	39	39	0.5906	LOGLOG	0.5474328	0.6311172	0	0.4094	0.0152	429	608
Overall	40	40	0.576	LOGLOG	0.532918	0.6166793	0	0.424	0.0153	444	593
Overall	41	41	0.5634	LOGLOG	0.5203267	0.6041564	0	0.4366	0.0154	457	579
Overall	42	42	0.5498	LOGLOG	0.506749	0.5906549	0	0.4502	0.0154	471	565
Overall	43	43	0.5352	LOGLOG	0.4921991	0.5761871	0	0.4648	0.0155	486	550
Overall	44	43.8571	0.5225	LOGLOG	0.4795877	0.563647	0	0.4775	0.0155	499	537
Overall	45	44.8571	0.5157	LOGLOG	0.4727965	0.5568943	0	0.4843	0.0155	506	530
Overall	46	46	0.506	LOGLOG	0.4630943	0.5472471	0	0.494	0.0155	516	520
Overall	47	46.7143	0.4963	LOGLOG	0.4533917	0.5375996	0	0.5037	0.0155	526	509
Overall	48	48	0.4914	LOGLOG	0.44853	0.5327671	0	0.5086	0.0155	531	503
Overall	49	48.8571	0.4816	LOGLOG	0.4387809	0.5230809	0	0.5184	0.0155	541	492

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	50	50	0.4689	LOGLOG	0.4260846	0.5104703	0	0.5311	0.0155	554	479
Overall	51	51	0.4591	LOGLOG	0.4163185	0.50077	0	0.5409	0.0155	564	469
Overall	52	52	0.4522	LOGLOG	0.4094824	0.49398	0	0.5478	0.0155	571	462
Overall	53	53	0.4454	LOGLOG	0.4026465	0.4871902	0	0.5546	0.0154	578	455
Overall	54	54	0.4385	LOGLOG	0.3958108	0.4804006	0	0.5615	0.0154	585	448
Overall	55	55	0.4229	LOGLOG	0.3801878	0.4648826	0	0.5771	0.0154	601	432
Overall	56	56	0.417	LOGLOG	0.3743095	0.4590477	0	0.583	0.0153	607	424
Overall	57	56.7143	0.4042	LOGLOG	0.3615474	0.4463847	0	0.5958	0.0153	620	410
Overall	58	58	0.3993	LOGLOG	0.3566283	0.4415059	0	0.6007	0.0152	625	405
Overall	59	59	0.3953	LOGLOG	0.3526933	0.4376031	0	0.6047	0.0152	629	401
Overall	60	60	0.3894	LOGLOG	0.3467856	0.4317449	0	0.6106	0.0152	635	394
Overall	61	61	0.3845	LOGLOG	0.3418538	0.4268562	0	0.6155	0.0151	640	389
Overall	62	62	0.3785	LOGLOG	0.3359362	0.4209903	0	0.6215	0.0151	646	383
Overall	63	62.8571	0.3726	LOGLOG	0.3300193	0.4151251	0	0.6274	0.0151	652	377
Overall	64	63.8571	0.3696	LOGLOG	0.3270611	0.4121927	0	0.6304	0.015	655	374
Overall	65	64.8571	0.3647	LOGLOG	0.3221193	0.4072965	0	0.6353	0.015	660	368
Overall	66	66	0.3577	LOGLOG	0.3151976	0.4004396	0	0.6423	0.0149	667	361
Overall	67	67	0.3538	LOGLOG	0.3112429	0.3965218	0	0.6462	0.0149	671	357
Overall	68	67.8571	0.3399	LOGLOG	0.2973671	0.3827838	0	0.6601	0.0148	685	342
Overall	69	69	0.3319	LOGLOG	0.2894304	0.3749281	0	0.6681	0.0147	693	333
Overall	70	70	0.3239	LOGLOG	0.2814587	0.3670465	0	0.6761	0.0146	701	324

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	71	70.5714	0.3149	LOGLOG	0.2724818	0.3581736	0	0.6851	0.0145	710	312
Overall	72	72	0.3038	LOGLOG	0.2613832	0.3472362	0	0.6962	0.0144	721	300
Overall	73	72.5714	0.3018	LOGLOG	0.2593565	0.3452413	0	0.6982	0.0144	723	294
Overall	74	73.7143	0.2977	LOGLOG	0.2552281	0.3411976	0	0.7023	0.0143	727	286
Overall	75	75	0.2861	LOGLOG	0.243626	0.3299022	0	0.7139	0.0142	738	271
Overall	76	76	0.2819	LOGLOG	0.2393684	0.3257684	0	0.7181	0.0141	742	264
Overall	77	77	0.2733	LOGLOG	0.2307633	0.3174402	0	0.7267	0.014	750	255
Overall	78	77.8571	0.2669	LOGLOG	0.2242835	0.3111775	0	0.7331	0.0139	756	246
Overall	79	79	0.2592	LOGLOG	0.2165572	0.3037627	0	0.7408	0.0138	763	231
Overall	80	80	0.2536	LOGLOG	0.2108551	0.2983494	0	0.7464	0.0137	768	223
Overall	81	80.4286	0.2513	LOGLOG	0.2085487	0.2961683	0	0.7487	0.0137	770	219
Overall	82	81.7143	0.2501	LOGLOG	0.2073769	0.2950664	0	0.7499	0.0137	771	215
Overall	83	82.8571	0.2455	LOGLOG	0.2025987	0.2906042	0	0.7545	0.0136	775	208
Overall	84	83.8571	0.2419	LOGLOG	0.1989657	0.2872289	0	0.7581	0.0136	778	203
Overall	85	85	0.2383	LOGLOG	0.1952544	0.2838087	0	0.7617	0.0136	781	197
Overall	86	85.4286	0.2359	LOGLOG	0.1927686	0.2815224	0	0.7641	0.0135	783	189
Overall	87	86.8571	0.2296	LOGLOG	0.1863137	0.2756751	0	0.7704	0.0135	788	181
Overall	88	88	0.2258	LOGLOG	0.1823639	0.2721271	0	0.7742	0.0134	791	176
Overall	89	88.4286	0.2219	LOGLOG	0.1783807	0.2685631	0	0.7781	0.0134	794	170
Overall	90	89.5714	0.218	LOGLOG	0.1742845	0.2649435	0	0.782	0.0133	797	165
Overall	91	91	0.214	LOGLOG	0.1701508	0.2613074	0	0.786	0.0133	800	161

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	92	91.5714	0.2127	LOGLOG	0.1687668	0.2600928	0	0.7873	0.0133	801	158
Overall	93	91.5714	0.2127	LOGLOG	0.1687668	0.2600928	0	0.7873	0.0133	801	155
Overall	94	93.7143	0.2113	LOGLOG	0.1673156	0.2588475	0	0.7887	0.0132	802	152
Overall	95	94.1429	0.2099	LOGLOG	0.165853	0.2575974	0	0.7901	0.0132	803	150
Overall	96	96	0.2042	LOGLOG	0.1598461	0.2525325	0	0.7958	0.0132	807	142
Overall	97	96.7143	0.1985	LOGLOG	0.153757	0.2474398	0	0.8015	0.0131	811	137
Overall	98	97.4286	0.197	LOGLOG	0.1522081	0.2461573	0	0.803	0.0131	812	134
Overall	99	98.8571	0.1926	LOGLOG	0.1475069	0.2422923	0	0.8074	0.013	815	129
Overall	100	99.5714	0.1896	LOGLOG	0.1442608	0.2396786	0	0.8104	0.013	817	124
Overall	101	101	0.1849	LOGLOG	0.1392795	0.2357263	0	0.8151	0.013	820	119
Overall	102	101.2857	0.1834	LOGLOG	0.1376097	0.2344075	0	0.8166	0.013	821	117
Overall	103	102.2857	0.1818	LOGLOG	0.1359224	0.2330844	0	0.8182	0.0129	822	112
Overall	104	102.2857	0.1818	LOGLOG	0.1359224	0.2330844	0	0.8182	0.0129	822	110
Overall	105	105	0.1801	LOGLOG	0.1340923	0.2317232	0	0.8199	0.0129	823	105
Overall	106	105.5714	0.1784	LOGLOG	0.1321941	0.2303475	0	0.8216	0.0129	824	104
Overall	107	106.4286	0.175	LOGLOG	0.1284042	0.2276021	0	0.825	0.0129	826	101
Overall	108	108	0.1698	LOGLOG	0.1226095	0.2234754	0	0.8302	0.0129	829	94
Overall	109	108.2857	0.1643	LOGLOG	0.116501	0.2193174	0	0.8357	0.0128	832	88
Overall	110	109.2857	0.1606	LOGLOG	0.1122982	0.2165443	0	0.8394	0.0128	834	83
Overall	111	110.4286	0.1586	LOGLOG	0.1100969	0.2151552	0	0.8414	0.0128	835	82
Overall	112	111.5714	0.1567	LOGLOG	0.1078626	0.2137687	0	0.8433	0.0128	836	80

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	113	112.8571	0.1508	LOGLOG	0.1011516	0.2096401	0	0.8492	0.0128	839	75
Overall	114	113.1429	0.1488	LOGLOG	0.0988566	0.2082751	0	0.8512	0.0127	840	73
Overall	115	115	0.1467	LOGLOG	0.096429	0.2069218	0	0.8533	0.0127	841	70
Overall	116	116	0.1424	LOGLOG	0.091548	0.2042443	0	0.8576	0.0127	843	67
Overall	117	116	0.1424	LOGLOG	0.091548	0.2042443	0	0.8576	0.0127	843	67
Overall	118	118	0.1403	LOGLOG	0.0890417	0.2029273	0	0.8597	0.0127	844	64
Overall	119	118	0.1403	LOGLOG	0.0890417	0.2029273	0	0.8597	0.0127	844	62
Overall	120	119.8571	0.138	LOGLOG	0.0863671	0.2016473	0	0.862	0.0127	845	59
Overall	121	119.8571	0.138	LOGLOG	0.0863671	0.2016473	0	0.862	0.0127	845	59
Overall	122	122	0.1357	LOGLOG	0.0835715	0.2004074	0	0.8643	0.0127	846	58
Overall	123	122.7143	0.1287	LOGLOG	0.0752854	0.1967875	0	0.8713	0.0127	849	53
Overall	124	122.7143	0.1287	LOGLOG	0.0752854	0.1967875	0	0.8713	0.0127	849	50
Overall	125	124.1429	0.1261	LOGLOG	0.0721356	0.1957586	0	0.8739	0.0127	850	47
Overall	126	125.5714	0.1207	LOGLOG	0.0655163	0.1939703	0	0.8793	0.0127	852	45
Overall	127	125.5714	0.1207	LOGLOG	0.0655163	0.1939703	0	0.8793	0.0127	852	44
Overall	128	125.5714	0.1207	LOGLOG	0.0655163	0.1939703	0	0.8793	0.0127	852	42
Overall	129	128.7143	0.1179	LOGLOG	0.0618919	0.193334	0	0.8821	0.0127	853	41
Overall	130	128.7143	0.1179	LOGLOG	0.0618919	0.193334	0	0.8821	0.0127	853	39
Overall	131	128.7143	0.1179	LOGLOG	0.0618919	0.193334	0	0.8821	0.0127	853	39
Overall	132	128.7143	0.1179	LOGLOG	0.0618919	0.193334	0	0.8821	0.0127	853	35
Overall	133	132.2857	0.1145	LOGLOG	0.0572962	0.1934682	0	0.8855	0.0128	854	32

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	134	132.2857	0.1145	LOGLOG	0.0572962	0.1934682	0	0.8855	0.0128	854	29
Overall	135	132.2857	0.1145	LOGLOG	0.0572962	0.1934682	0	0.8855	0.0128	854	29
Overall	136	135.1429	0.1105	LOGLOG	0.0514796	0.1949414	0	0.8895	0.0129	855	28
Overall	137	137	0.1059	LOGLOG	0.0442538	0.1986027	0	0.8941	0.0132	856	23
Overall	138	137	0.1059	LOGLOG	0.0442538	0.1986027	0	0.8941	0.0132	856	22
Overall	139	137	0.1059	LOGLOG	0.0442538	0.1986027	0	0.8941	0.0132	856	21
Overall	140	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	17
Overall	141	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	16
Overall	142	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	16
Overall	143	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	15
Overall	144	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	15
Overall	145	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	14
Overall	146	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	12
Overall	147	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	11
Overall	148	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	10
Overall	149	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	8
Overall	150	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	8
Overall	151	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	8
Overall	152	139.7143	0.0958	LOGLOG	0.0291598	0.2110524	0	0.9042	0.0137	858	8
Overall	153	152.7143	0.0839	LOGLOG	0.0064071	0.2962938	0	0.9161	0.0164	859	7
Overall	154	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	6

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	155	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	6
Overall	156	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	6
Overall	157	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	6
Overall	158	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	6
Overall	159	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	5
Overall	160	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	3
Overall	161	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	2
Overall	162	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	2
Overall	163	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	1
Overall	164	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	1
Overall	165	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	1
Overall	166	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	1
Overall	167	153.4286	0.0719	LOGLOG	0.0004426	0.4075893	0	0.9281	0.0179	860	1
Overall	168	153.4286	.		.	.	0	.	.	860	0

Program: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\km_hw_stderr

Data: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\final_restricted\data\shared\adam

Output: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\tfl_output\km_hw_stderr.xls

Run date: 06NOV2014:16:54

Table 62 PFS Kaplan-Meier Outputs for ITT by 1-week Cycle Including Hall-Wellner Simultaneous Confidence Intervals and Survival Standard Error

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	0	0	1		.	.	0	0	0	0	548
GC	1	1	0.9865	LOGLOG	0.3550818	0.9998219	0	0.0135	0.00506	7	512
GC	2	2	0.9827	LOGLOG	0.5987659	0.9994035	0	0.0173	0.00573	9	510
GC	3	2.7143	0.973	LOGLOG	0.7844327	0.9969249	0	0.027	0.00711	14	505
GC	4	4	0.9634	LOGLOG	0.8285536	0.9926314	0	0.0366	0.00824	19	499
GC	5	5	0.944	LOGLOG	0.8453612	0.9804348	0	0.056	0.0101	29	486
GC	6	6	0.8971	LOGLOG	0.820578	0.9421302	0	0.1029	0.0134	53	453
GC	7	7	0.8512	LOGLOG	0.7810832	0.9003121	0	0.1488	0.0158	76	422
GC	8	8	0.8391	LOGLOG	0.7698837	0.8889139	0	0.1609	0.0163	82	413
GC	9	8.8571	0.8309	LOGLOG	0.7623157	0.881259	0	0.1691	0.0166	86	409
GC	10	9.8571	0.8269	LOGLOG	0.7585033	0.8774146	0	0.1731	0.0168	88	406
GC	11	11	0.8044	LOGLOG	0.7372657	0.8561072	0	0.1956	0.0177	99	393
GC	12	12	0.7818	LOGLOG	0.715496	0.834425	0	0.2182	0.0184	110	377
GC	13	13	0.7255	LOGLOG	0.6605224	0.7800723	0	0.2745	0.02	137	344
GC	14	14	0.7106	LOGLOG	0.6459018	0.7656957	0	0.2894	0.0204	144	335
GC	15	15	0.7	LOGLOG	0.6354077	0.7553874	0	0.3	0.0206	149	329

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	16	15.7143	0.6936	LOGLOG	0.6290743	0.7491733	0	0.3064	0.0208	152	324
GC	17	16.8571	0.6893	LOGLOG	0.6248347	0.7450169	0	0.3107	0.0209	154	322
GC	18	18	0.6572	LOGLOG	0.592918	0.7137518	0	0.3428	0.0215	169	302
GC	19	19	0.5993	LOGLOG	0.5350371	0.6575562	0	0.4007	0.0224	195	266
GC	20	20	0.5632	LOGLOG	0.4988738	0.6225528	0	0.4368	0.0228	211	250
GC	21	21	0.5452	LOGLOG	0.4807817	0.605043	0	0.4548	0.0229	219	242
GC	22	22	0.5362	LOGLOG	0.4717018	0.5962629	0	0.4638	0.023	223	237
GC	23	23	0.5203	LOGLOG	0.4557918	0.5808826	0	0.4797	0.0231	230	230
GC	24	24	0.4769	LOGLOG	0.4120858	0.5387595	0	0.5231	0.0232	249	207
GC	25	25	0.3884	LOGLOG	0.3228839	0.4532929	0	0.6116	0.0229	287	163
GC	26	26	0.3716	LOGLOG	0.3058618	0.4371714	0	0.6284	0.0228	294	154
GC	27	26.8571	0.3449	LOGLOG	0.2789239	0.4117309	0	0.6551	0.0225	305	141
GC	28	28	0.3277	LOGLOG	0.2615392	0.3954073	0	0.6723	0.0223	312	133
GC	29	29	0.313	LOGLOG	0.24659	0.381396	0	0.687	0.0221	318	127
GC	30	30	0.2931	LOGLOG	0.2265576	0.3626755	0	0.7069	0.0218	326	118
GC	31	31	0.2578	LOGLOG	0.1908654	0.3296734	0	0.7422	0.0211	340	98
GC	32	32	0.2341	LOGLOG	0.1668827	0.3080507	0	0.7659	0.0206	349	89
GC	33	33	0.2288	LOGLOG	0.1615809	0.303271	0	0.7712	0.0205	351	87
GC	34	33.8571	0.221	LOGLOG	0.1536503	0.2961218	0	0.779	0.0203	354	84

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	35	35	0.2131	LOGLOG	0.1457485	0.2889997	0	0.7869	0.02	357	81
GC	36	36	0.1971	LOGLOG	0.1298247	0.2747761	0	0.8029	0.0196	363	74
GC	37	36.4286	0.1757	LOGLOG	0.1086977	0.2560292	0	0.8243	0.0189	371	65
GC	38	37.4286	0.1676	LOGLOG	0.1007575	0.2490733	0	0.8324	0.0186	374	62
GC	39	39	0.1568	LOGLOG	0.0902827	0.2399142	0	0.8432	0.0181	378	58
GC	40	39	0.1568	LOGLOG	0.0902827	0.2399142	0	0.8432	0.0181	378	58
GC	41	40.5714	0.154	LOGLOG	0.0876215	0.2376398	0	0.846	0.018	379	56
GC	42	40.5714	0.154	LOGLOG	0.0876215	0.2376398	0	0.846	0.018	379	54
GC	43	42.8571	0.1455	LOGLOG	0.0792836	0.2308568	0	0.8545	0.0177	382	51
GC	44	43.5714	0.1398	LOGLOG	0.0737958	0.2264114	0	0.8602	0.0174	384	49
GC	45	44.7143	0.1341	LOGLOG	0.068372	0.2220372	0	0.8659	0.0172	386	46
GC	46	44.7143	0.1341	LOGLOG	0.068372	0.2220372	0	0.8659	0.0172	386	46
GC	47	46.1429	0.1312	LOGLOG	0.0655995	0.2198869	0	0.8688	0.0171	387	45
GC	48	47.7143	0.1283	LOGLOG	0.0628475	0.2177602	0	0.8717	0.0169	388	44
GC	49	48.4286	0.1253	LOGLOG	0.0601174	0.2156591	0	0.8747	0.0168	389	43
GC	50	49.2857	0.1166	LOGLOG	0.0520718	0.2095295	0	0.8834	0.0164	392	40
GC	51	50.7143	0.1136	LOGLOG	0.0493397	0.2075827	0	0.8864	0.0162	393	38
GC	52	50.7143	0.1136	LOGLOG	0.0493397	0.2075827	0	0.8864	0.0162	393	38
GC	53	50.7143	0.1136	LOGLOG	0.0493397	0.2075827	0	0.8864	0.0162	393	38

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	54	50.7143	0.1136	LOGLOG	0.0493397	0.2075827	0	0.8864	0.0162	393	38
GC	55	55	0.1076	LOGLOG	0.043976	0.2038176	0	0.8924	0.0159	395	36
GC	56	55.5714	0.1046	LOGLOG	0.0413491	0.2020075	0	0.8954	0.0157	396	35
GC	57	55.5714	0.1046	LOGLOG	0.0413491	0.2020075	0	0.8954	0.0157	396	35
GC	58	57.1429	0.1016	LOGLOG	0.0387621	0.2002519	0	0.8984	0.0156	397	34
GC	59	58.1429	0.0987	LOGLOG	0.0362179	0.1985563	0	0.9013	0.0154	398	33
GC	60	60	0.0927	LOGLOG	0.0312701	0.1953706	0	0.9073	0.015	400	31
GC	61	60.2857	0.0866	LOGLOG	0.0264025	0.1926347	0	0.9134	0.0147	402	28
GC	62	61.2857	0.0835	LOGLOG	0.0240015	0.1914891	0	0.9165	0.0145	403	27
GC	63	62.2857	0.0804	LOGLOG	0.0216758	0.1904739	0	0.9196	0.0142	404	26
GC	64	62.2857	0.0804	LOGLOG	0.0216758	0.1904739	0	0.9196	0.0142	404	26
GC	65	64.2857	0.0773	LOGLOG	0.0194312	0.1896064	0	0.9227	0.014	405	25
GC	66	64.2857	0.0773	LOGLOG	0.0194312	0.1896064	0	0.9227	0.014	405	24
GC	67	64.2857	0.0773	LOGLOG	0.0194312	0.1896064	0	0.9227	0.014	405	23
GC	68	67.8571	0.0706	LOGLOG	0.0146155	0.1895857	0	0.9294	0.0136	407	21
GC	69	67.8571	0.0706	LOGLOG	0.0146155	0.1895857	0	0.9294	0.0136	407	21
GC	70	67.8571	0.0706	LOGLOG	0.0146155	0.1895857	0	0.9294	0.0136	407	21
GC	71	67.8571	0.0706	LOGLOG	0.0146155	0.1895857	0	0.9294	0.0136	407	21
GC	72	67.8571	0.0706	LOGLOG	0.0146155	0.1895857	0	0.9294	0.0136	407	21

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	73	72.1429	0.0672	LOGLOG	0.0124171	0.190019	0	0.9328	0.0134	408	19
GC	74	72.1429	0.0672	LOGLOG	0.0124171	0.190019	0	0.9328	0.0134	408	18
GC	75	75	0.0635	LOGLOG	0.0099809	0.1921255	0	0.9365	0.0131	409	17
GC	76	75.4286	0.0598	LOGLOG	0.0077979	0.1948852	0	0.9402	0.0129	410	16
GC	77	75.4286	0.0598	LOGLOG	0.0077979	0.1948852	0	0.9402	0.0129	410	16
GC	78	75.4286	0.0598	LOGLOG	0.0077979	0.1948852	0	0.9402	0.0129	410	16
GC	79	75.4286	0.0598	LOGLOG	0.0077979	0.1948852	0	0.9402	0.0129	410	13
GC	80	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	12
GC	81	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	12
GC	82	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	12
GC	83	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	12
GC	84	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	12
GC	85	79.5714	0.0552	LOGLOG	0.0051145	0.2036585	0	0.9448	0.0127	411	10
GC	86	85.4286	0.0496	LOGLOG	0.0024246	0.2237333	0	0.9504	0.0126	412	9
GC	87	86.5714	0.0441	LOGLOG	0.0008914	0.2499061	0	0.9559	0.0123	413	8
GC	88	86.5714	0.0441	LOGLOG	0.0008914	0.2499061	0	0.9559	0.0123	413	8
GC	89	86.5714	0.0441	LOGLOG	0.0008914	0.2499061	0	0.9559	0.0123	413	8
GC	90	89.1429	0.0386	LOGLOG	0.0002174	0.2848997	0	0.9614	0.0119	414	7
GC	91	89.1429	0.0386	LOGLOG	0.0002174	0.2848997	0	0.9614	0.0119	414	7

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	92	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	93	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	94	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	95	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	96	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	97	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	98	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	99	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	5
GC	100	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	101	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	102	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	103	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	104	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	105	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	106	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	107	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	108	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	109	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	110	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	111	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	112	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	113	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	114	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	115	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	116	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	117	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	118	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	119	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	120	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	121	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	122	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	123	91.8571	0.0322	LOGLOG	9.8714E-06	0.3589469	0	0.9678	0.0116	415	4
GC	124	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3
GC	125	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	126	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3
GC	127	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3
GC	128	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3
GC	129	123.8571	0.0241	LOGLOG	8.647E-11	0.5496068	0	0.9759	0.0111	416	3
GC	130	129.4286	0.0161	LOGLOG	2.269E-34	0.8024101	0	0.9839	0.0099	417	2
GC	131	129.4286	0.0161	LOGLOG	2.269E-34	0.8024101	0	0.9839	0.0099	417	1
GC	132	129.4286	0.0161	LOGLOG	2.269E-34	0.8024101	0	0.9839	0.0099	417	1
GC	133	129.4286	.		.	.	0	.	.	417	0
GC	134	129.4286	.		.	.	0	.	.	417	0
GC	135	129.4286	.		.	.	0	.	.	417	0
GC	136	129.4286	.		.	.	0	.	.	417	0
GC	137	129.4286	.		.	.	0	.	.	417	0
GC	138	129.4286	.		.	.	0	.	.	417	0
GC	139	129.4286	.		.	.	0	.	.	417	0
GC	140	129.4286	.		.	.	0	.	.	417	0
GC	141	129.4286	.		.	.	0	.	.	417	0
GC	142	129.4286	.		.	.	0	.	.	417	0
GC	143	129.4286	.		.	.	0	.	.	417	0
GC	144	129.4286	.		.	.	0	.	.	417	0

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC	145	129.4286	.		.	.	0	.	.	417	0
GC+N	0	0	1		.	.	0	0	0	0	545
GC+N	1	1	0.9903	LOGLOG	0.0191014	0.9999758	0	0.00975	0.00434	5	508
GC+N	2	1.8571	0.9805	LOGLOG	0.6687045	0.9990375	0	0.0195	0.0061	10	503
GC+N	3	2.7143	0.9669	LOGLOG	0.8173693	0.9943843	0	0.0331	0.0079	17	496
GC+N	4	4	0.9591	LOGLOG	0.8360481	0.9902914	0	0.0409	0.00875	21	492
GC+N	5	5	0.9435	LOGLOG	0.84491	0.9801075	0	0.0565	0.0102	29	484
GC+N	6	6	0.9121	LOGLOG	0.8313091	0.9552158	0	0.0879	0.0125	45	458
GC+N	7	7	0.8879	LOGLOG	0.8128723	0.9340926	0	0.1121	0.014	57	437
GC+N	8	7.7143	0.8818	LOGLOG	0.8077612	0.928595	0	0.1182	0.0143	60	432
GC+N	9	8.7143	0.8737	LOGLOG	0.8007557	0.9211818	0	0.1263	0.0148	64	428
GC+N	10	10	0.8655	LOGLOG	0.7935843	0.9136977	0	0.1345	0.0152	68	423
GC+N	11	10.7143	0.8573	LOGLOG	0.7862596	0.9061361	0	0.1427	0.0156	72	419
GC+N	12	12	0.8285	LOGLOG	0.7597232	0.8791755	0	0.1715	0.0169	86	401
GC+N	13	13	0.7931	LOGLOG	0.7259864	0.8454591	0	0.2069	0.0182	103	373
GC+N	14	13.8571	0.7803	LOGLOG	0.7136099	0.833207	0	0.2197	0.0186	109	365
GC+N	15	15	0.776	LOGLOG	0.7094491	0.8290967	0	0.224	0.0188	111	362
GC+N	16	16	0.7674	LOGLOG	0.7010891	0.8208481	0	0.2326	0.0191	115	357
GC+N	17	16.5714	0.7588	LOGLOG	0.6926998	0.8125795	0	0.2412	0.0193	119	353

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	18	18	0.7286	LOGLOG	0.6631168	0.783482	0	0.2714	0.0202	133	337
GC+N	19	19	0.6587	LOGLOG	0.5938718	0.7157242	0	0.3413	0.0217	165	299
GC+N	20	19.4286	0.6499	LOGLOG	0.5850992	0.7071638	0	0.3501	0.0218	169	294
GC+N	21	21	0.6321	LOGLOG	0.5673603	0.6898916	0	0.3679	0.0221	177	284
GC+N	22	22	0.6232	LOGLOG	0.558471	0.6812401	0	0.3768	0.0223	181	280
GC+N	23	22.7143	0.6188	LOGLOG	0.5540248	0.6769132	0	0.3812	0.0223	183	278
GC+N	24	24	0.5763	LOGLOG	0.5116073	0.6356699	0	0.4237	0.0228	202	257
GC+N	25	25	0.4727	LOGLOG	0.4076296	0.5348499	0	0.5273	0.0233	248	209
GC+N	26	26	0.4455	LOGLOG	0.3804084	0.5084789	0	0.5545	0.0232	260	197
GC+N	27	27	0.4297	LOGLOG	0.3645367	0.493102	0	0.5703	0.0232	267	190
GC+N	28	28	0.4184	LOGLOG	0.3532042	0.4821223	0	0.5816	0.0231	272	185
GC+N	29	28.2857	0.4139	LOGLOG	0.3486724	0.4777315	0	0.5861	0.0231	274	183
GC+N	30	30	0.3889	LOGLOG	0.3236718	0.4535335	0	0.6111	0.0229	285	170
GC+N	31	31	0.334	LOGLOG	0.2686688	0.4004613	0	0.666	0.0222	309	145
GC+N	32	32	0.3132	LOGLOG	0.2479533	0.3805207	0	0.6868	0.0219	318	136
GC+N	33	33	0.3063	LOGLOG	0.2410589	0.3738834	0	0.6937	0.0218	321	133
GC+N	34	33.5714	0.304	LOGLOG	0.2387621	0.3716721	0	0.696	0.0217	322	132
GC+N	35	35	0.2971	LOGLOG	0.2318759	0.3650421	0	0.7029	0.0216	325	129
GC+N	36	36	0.2649	LOGLOG	0.1998375	0.33419	0	0.7351	0.0209	339	115

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	37	36.8571	0.2418	LOGLOG	0.1769971	0.3122264	0	0.7582	0.0203	349	104
GC+N	38	37.8571	0.2302	LOGLOG	0.1655346	0.3012452	0	0.7698	0.02	354	99
GC+N	39	39	0.2232	LOGLOG	0.1586772	0.2946754	0	0.7768	0.0198	357	96
GC+N	40	39.2857	0.2208	LOGLOG	0.1563639	0.2924748	0	0.7792	0.0197	358	94
GC+N	41	41	0.2138	LOGLOG	0.1494364	0.2858847	0	0.7862	0.0195	361	91
GC+N	42	42	0.2067	LOGLOG	0.1425289	0.2793138	0	0.7933	0.0193	364	88
GC+N	43	43	0.1715	LOGLOG	0.1083738	0.246838	0	0.8285	0.018	379	73
GC+N	44	43.4286	0.1644	LOGLOG	0.1016411	0.2404432	0	0.8356	0.0177	382	69
GC+N	45	44.8571	0.1596	LOGLOG	0.0970402	0.2361674	0	0.8404	0.0175	384	66
GC+N	46	45.4286	0.1572	LOGLOG	0.0947247	0.2340323	0	0.8428	0.0174	385	65
GC+N	47	46.1429	0.1548	LOGLOG	0.0924151	0.2319036	0	0.8452	0.0173	386	64
GC+N	48	48	0.1427	LOGLOG	0.0809677	0.2213687	0	0.8573	0.0168	391	59
GC+N	49	49	0.1207	LOGLOG	0.0605558	0.2029874	0	0.8793	0.0157	400	48
GC+N	50	49.5714	0.1157	LOGLOG	0.0559739	0.1990586	0	0.8843	0.0155	402	46
GC+N	51	49.5714	0.1157	LOGLOG	0.0559739	0.1990586	0	0.8843	0.0155	402	46
GC+N	52	49.5714	0.1157	LOGLOG	0.0559739	0.1990586	0	0.8843	0.0155	402	46
GC+N	53	49.5714	0.1157	LOGLOG	0.0559739	0.1990586	0	0.8843	0.0155	402	46
GC+N	54	54	0.1131	LOGLOG	0.0537067	0.1971237	0	0.8869	0.0153	403	45
GC+N	55	55	0.1056	LOGLOG	0.0470109	0.1914547	0	0.8944	0.0149	406	42

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	56	55	0.1056	LOGLOG	0.0470109	0.1914547	0	0.8944	0.0149	406	42
GC+N	57	57	0.1031	LOGLOG	0.044818	0.1896163	0	0.8969	0.0148	407	41
GC+N	58	57	0.1031	LOGLOG	0.044818	0.1896163	0	0.8969	0.0148	407	41
GC+N	59	57	0.1031	LOGLOG	0.044818	0.1896163	0	0.8969	0.0148	407	41
GC+N	60	60	0.0981	LOGLOG	0.0404978	0.1860297	0	0.9019	0.0145	409	39
GC+N	61	60.7143	0.088	LOGLOG	0.0321621	0.1792962	0	0.912	0.0138	413	35
GC+N	62	60.7143	0.088	LOGLOG	0.0321621	0.1792962	0	0.912	0.0138	413	35
GC+N	63	60.7143	0.088	LOGLOG	0.0321621	0.1792962	0	0.912	0.0138	413	35
GC+N	64	60.7143	0.088	LOGLOG	0.0321621	0.1792962	0	0.912	0.0138	413	35
GC+N	65	60.7143	0.088	LOGLOG	0.0321621	0.1792962	0	0.912	0.0138	413	35
GC+N	66	66	0.0855	LOGLOG	0.0301518	0.1777252	0	0.9145	0.0137	414	34
GC+N	67	66.1429	0.0805	LOGLOG	0.0262342	0.1747509	0	0.9195	0.0133	416	31
GC+N	68	66.1429	0.0805	LOGLOG	0.0262342	0.1747509	0	0.9195	0.0133	416	30
GC+N	69	69	0.0778	LOGLOG	0.0241261	0.1735403	0	0.9222	0.0131	417	29
GC+N	70	69.5714	0.0751	LOGLOG	0.0220717	0.1724238	0	0.9249	0.013	418	27
GC+N	71	70.4286	0.0723	LOGLOG	0.0199544	0.1715635	0	0.9277	0.0128	419	26
GC+N	72	70.4286	0.0723	LOGLOG	0.0199544	0.1715635	0	0.9277	0.0128	419	26
GC+N	73	72.2857	0.0695	LOGLOG	0.0179094	0.1708405	0	0.9305	0.0126	420	25
GC+N	74	72.2857	0.0695	LOGLOG	0.0179094	0.1708405	0	0.9305	0.0126	420	25

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	75	74.2857	0.0667	LOGLOG	0.0159423	0.1702743	0	0.9333	0.0124	421	23
GC+N	76	74.2857	0.0667	LOGLOG	0.0159423	0.1702743	0	0.9333	0.0124	421	23
GC+N	77	74.2857	0.0667	LOGLOG	0.0159423	0.1702743	0	0.9333	0.0124	421	23
GC+N	78	74.2857	0.0667	LOGLOG	0.0159423	0.1702743	0	0.9333	0.0124	421	23
GC+N	79	78.5714	0.0637	LOGLOG	0.0137695	0.1704884	0	0.9363	0.0122	422	20
GC+N	80	78.5714	0.0637	LOGLOG	0.0137695	0.1704884	0	0.9363	0.0122	422	19
GC+N	81	78.5714	0.0637	LOGLOG	0.0137695	0.1704884	0	0.9363	0.0122	422	19
GC+N	82	82	0.0568	LOGLOG	0.0089376	0.1748751	0	0.9432	0.0118	424	16
GC+N	83	82	0.0568	LOGLOG	0.0089376	0.1748751	0	0.9432	0.0118	424	16
GC+N	84	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	85	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	86	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	87	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	88	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	89	83.1429	0.0533	LOGLOG	0.0067992	0.1785019	0	0.9467	0.0116	425	15
GC+N	90	89.8571	0.0497	LOGLOG	0.0049586	0.1830855	0	0.9503	0.0113	426	14
GC+N	91	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13
GC+N	92	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13
GC+N	93	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13

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CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	94	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13
GC+N	95	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13
GC+N	96	90.2857	0.0462	LOGLOG	0.0034271	0.188879	0	0.9538	0.0111	427	13
GC+N	97	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	11
GC+N	98	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	10
GC+N	99	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	10
GC+N	100	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	10
GC+N	101	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	10
GC+N	102	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	10
GC+N	103	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	9
GC+N	104	96.2857	0.0426	LOGLOG	0.0022086	0.1962284	0	0.9574	0.0108	428	9
GC+N	105	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	8
GC+N	106	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	8
GC+N	107	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	8
GC+N	108	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	7
GC+N	109	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	6
GC+N	110	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	6
GC+N	111	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	6
GC+N	112	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	5

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	113	104.5714	0.0379	LOGLOG	0.0008365	0.2204216	0	0.9621	0.0106	429	5
GC+N	114	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	4
GC+N	115	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	3
GC+N	116	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	3
GC+N	117	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	2
GC+N	118	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	2
GC+N	119	114	0.0303	LOGLOG	0.0000119	0.340153	0	0.9697	0.0108	430	2
GC+N	120	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	121	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	122	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	123	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	124	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	125	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	126	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	127	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	128	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	129	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	130	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	131	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
GC+N	132	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	133	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	134	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	135	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	136	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	137	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	138	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	139	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	140	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	141	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	142	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	143	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	144	119.8571	0.0151	LOGLOG	2.68E-214	0.9649326	0	0.9849	0.012	431	1
GC+N	145	119.8571	.		.	.	0	.	.	431	0
Overall	0	0	1		.	.	0	0	0	0	1093
Overall	1	1	0.9884	LOGLOG	0.6639001	0.9996661	0	0.0116	0.00334	12	1020
Overall	2	2	0.9816	LOGLOG	0.8376873	0.9980522	0	0.0184	0.00418	19	1013
Overall	3	2.7143	0.97	LOGLOG	0.8846344	0.9924403	0	0.03	0.00531	31	1001
Overall	4	4	0.9612	LOGLOG	0.8897462	0.9867121	0	0.0388	0.00601	40	991

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	5	5	0.9438	LOGLOG	0.8841754	0.9731409	0	0.0562	0.00718	58	970
Overall	6	6	0.9046	LOGLOG	0.8537185	0.9384026	0	0.0954	0.00917	98	911
Overall	7	7	0.8695	LOGLOG	0.8214927	0.905398	0	0.1305	0.0106	133	859
Overall	8	8	0.8604	LOGLOG	0.8128031	0.8966457	0	0.1396	0.0109	142	845
Overall	9	8.8571	0.8522	LOGLOG	0.8050118	0.8888234	0	0.1478	0.0111	150	837
Overall	10	10	0.8461	LOGLOG	0.7991366	0.8829369	0	0.1539	0.0113	156	829
Overall	11	11	0.8308	LOGLOG	0.7843242	0.8681338	0	0.1692	0.0118	171	812
Overall	12	12	0.8051	LOGLOG	0.7592209	0.8431428	0	0.1949	0.0125	196	778
Overall	13	13	0.7592	LOGLOG	0.7139841	0.7983062	0	0.2408	0.0136	240	717
Overall	14	14	0.7454	LOGLOG	0.7002724	0.7847659	0	0.2546	0.0139	253	700
Overall	15	15	0.7379	LOGLOG	0.6928521	0.7774439	0	0.2621	0.014	260	691
Overall	16	16	0.7304	LOGLOG	0.6853999	0.7700947	0	0.2696	0.0141	267	681
Overall	17	16.8571	0.724	LOGLOG	0.6789968	0.7637825	0	0.276	0.0143	273	675
Overall	18	18	0.6928	LOGLOG	0.6479372	0.7331814	0	0.3072	0.0148	302	639
Overall	19	19	0.6289	LOGLOG	0.5839712	0.6704158	0	0.3711	0.0156	360	565
Overall	20	20	0.6066	LOGLOG	0.5616351	0.6485382	0	0.3934	0.0158	380	544
Overall	21	21	0.5888	LOGLOG	0.5436748	0.6309604	0	0.4112	0.016	396	526
Overall	22	22	0.5798	LOGLOG	0.5346685	0.6221499	0	0.4202	0.0161	404	517
Overall	23	23	0.5697	LOGLOG	0.5245299	0.6122326	0	0.4303	0.0161	413	508

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	24	24	0.5268	LOGLOG	0.4813919	0.5700901	0	0.4732	0.0163	451	464
Overall	25	25	0.4307	LOGLOG	0.3846417	0.4758262	0	0.5693	0.0164	535	372
Overall	26	26	0.4086	LOGLOG	0.3623731	0.4542091	0	0.5914	0.0163	554	351
Overall	27	27	0.3876	LOGLOG	0.3412087	0.4336803	0	0.6124	0.0162	572	331
Overall	28	28	0.3735	LOGLOG	0.3270242	0.4199402	0	0.6265	0.0161	584	318
Overall	29	29	0.3641	LOGLOG	0.3175521	0.4107691	0	0.6359	0.0161	592	310
Overall	30	30	0.3417	LOGLOG	0.2949698	0.3889288	0	0.6583	0.0159	611	288
Overall	31	31	0.2963	LOGLOG	0.2491739	0.3448274	0	0.7037	0.0154	649	243
Overall	32	32	0.2744	LOGLOG	0.2270204	0.3236425	0	0.7256	0.0151	667	225
Overall	33	33	0.2683	LOGLOG	0.2208749	0.3177655	0	0.7317	0.015	672	220
Overall	34	33.8571	0.2634	LOGLOG	0.2159614	0.3130666	0	0.7366	0.0149	676	216
Overall	35	35	0.2561	LOGLOG	0.2085965	0.3060231	0	0.7439	0.0148	682	210
Overall	36	36	0.2316	LOGLOG	0.1839786	0.2825215	0	0.7684	0.0144	702	189
Overall	37	36.8571	0.2095	LOGLOG	0.1618231	0.2614054	0	0.7905	0.0139	720	169
Overall	38	37.8571	0.1996	LOGLOG	0.1519032	0.2519956	0	0.8004	0.0137	728	161
Overall	39	39	0.1909	LOGLOG	0.1432458	0.243784	0	0.8091	0.0135	735	154
Overall	40	39.2857	0.1896	LOGLOG	0.1420007	0.2426077	0	0.8104	0.0134	736	152
Overall	41	41	0.1846	LOGLOG	0.1370047	0.2378975	0	0.8154	0.0133	740	147
Overall	42	42	0.1808	LOGLOG	0.1332035	0.2343423	0	0.8192	0.0132	743	142

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	43	43	0.1579	LOGLOG	0.1103987	0.2130855	0	0.8421	0.0126	761	124
Overall	44	43.5714	0.1515	LOGLOG	0.1041138	0.2072321	0	0.8485	0.0124	766	118
Overall	45	44.8571	0.1464	LOGLOG	0.0990202	0.2025387	0	0.8536	0.0123	770	112
Overall	46	45.4286	0.1451	LOGLOG	0.0977274	0.2013609	0	0.8549	0.0122	771	111
Overall	47	46.1429	0.1425	LOGLOG	0.0951458	0.1990095	0	0.8575	0.0121	773	109
Overall	48	48	0.1346	LOGLOG	0.0874363	0.1919935	0	0.8654	0.0119	779	103
Overall	49	49	0.1214	LOGLOG	0.0746048	0.1804225	0	0.8786	0.0114	789	91
Overall	50	49.5714	0.1148	LOGLOG	0.0681492	0.1747053	0	0.8852	0.0112	794	86
Overall	51	50.7143	0.1134	LOGLOG	0.066845	0.1735682	0	0.8866	0.0111	795	84
Overall	52	50.7143	0.1134	LOGLOG	0.066845	0.1735682	0	0.8866	0.0111	795	84
Overall	53	50.7143	0.1134	LOGLOG	0.066845	0.1735682	0	0.8866	0.0111	795	84
Overall	54	54	0.1121	LOGLOG	0.0655439	0.1724346	0	0.8879	0.0111	796	83
Overall	55	55	0.1053	LOGLOG	0.0590875	0.1668257	0	0.8947	0.0108	801	78
Overall	56	55.5714	0.104	LOGLOG	0.0578068	0.1657169	0	0.896	0.0108	802	77
Overall	57	57	0.1026	LOGLOG	0.0565301	0.1646127	0	0.8974	0.0107	803	76
Overall	58	57.1429	0.1013	LOGLOG	0.0552573	0.1635136	0	0.8987	0.0106	804	75
Overall	59	58.1429	0.0999	LOGLOG	0.0539886	0.1624196	0	0.9001	0.0106	805	74
Overall	60	60	0.0945	LOGLOG	0.0489583	0.1581001	0	0.9055	0.0104	809	70
Overall	61	60.7143	0.0863	LOGLOG	0.0414593	0.1518344	0	0.9137	0.00999	815	63

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	62	61.2857	0.085	LOGLOG	0.0402221	0.1508204	0	0.915	0.00992	816	62
Overall	63	62.2857	0.0836	LOGLOG	0.0389917	0.1498161	0	0.9164	0.00985	817	61
Overall	64	62.2857	0.0836	LOGLOG	0.0389917	0.1498161	0	0.9164	0.00985	817	61
Overall	65	64.2857	0.0822	LOGLOG	0.0377686	0.148822	0	0.9178	0.00979	818	60
Overall	66	66	0.0808	LOGLOG	0.0365219	0.1478467	0	0.9192	0.00972	819	58
Overall	67	66.1429	0.078	LOGLOG	0.034054	0.1459334	0	0.922	0.00958	821	54
Overall	68	67.8571	0.0751	LOGLOG	0.0314474	0.1441479	0	0.9249	0.00944	823	51
Overall	69	69	0.0737	LOGLOG	0.0301431	0.1432914	0	0.9263	0.00937	824	50
Overall	70	69.5714	0.0722	LOGLOG	0.028852	0.1424553	0	0.9278	0.0093	825	48
Overall	71	70.4286	0.0707	LOGLOG	0.0275331	0.1416669	0	0.9293	0.00923	826	47
Overall	72	70.4286	0.0707	LOGLOG	0.0275331	0.1416669	0	0.9293	0.00923	826	47
Overall	73	72.2857	0.0677	LOGLOG	0.0249431	0.1401679	0	0.9323	0.00908	828	44
Overall	74	72.2857	0.0677	LOGLOG	0.0249431	0.1401679	0	0.9323	0.00908	828	43
Overall	75	75	0.0645	LOGLOG	0.0221845	0.1390033	0	0.9355	0.00893	830	40
Overall	76	75.4286	0.0629	LOGLOG	0.0208155	0.1385104	0	0.9371	0.00885	831	39
Overall	77	75.4286	0.0629	LOGLOG	0.0208155	0.1385104	0	0.9371	0.00885	831	39
Overall	78	75.4286	0.0629	LOGLOG	0.0208155	0.1385104	0	0.9371	0.00885	831	39
Overall	79	78.5714	0.0611	LOGLOG	0.0192879	0.1383	0	0.9389	0.00877	832	33
Overall	80	79.5714	0.0592	LOGLOG	0.0175646	0.1385289	0	0.9408	0.0087	833	31

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	81	79.5714	0.0592	LOGLOG	0.0175646	0.1385289	0	0.9408	0.0087	833	31
Overall	82	82	0.0553	LOGLOG	0.0142088	0.1395341	0	0.9447	0.00855	835	28
Overall	83	82	0.0553	LOGLOG	0.0142088	0.1395341	0	0.9447	0.00855	835	28
Overall	84	83.1429	0.0534	LOGLOG	0.0125936	0.1403598	0	0.9466	0.00847	836	27
Overall	85	83.1429	0.0534	LOGLOG	0.0125936	0.1403598	0	0.9466	0.00847	836	25
Overall	86	85.4286	0.0512	LOGLOG	0.0108493	0.1419759	0	0.9488	0.0084	837	24
Overall	87	86.5714	0.0491	LOGLOG	0.0092229	0.1438755	0	0.9509	0.00832	838	23
Overall	88	86.5714	0.0491	LOGLOG	0.0092229	0.1438755	0	0.9509	0.00832	838	23
Overall	89	86.5714	0.0491	LOGLOG	0.0092229	0.1438755	0	0.9509	0.00832	838	23
Overall	90	89.8571	0.0448	LOGLOG	0.0063485	0.1487153	0	0.9552	0.00812	840	21
Overall	91	90.2857	0.0427	LOGLOG	0.0051118	0.1517774	0	0.9573	0.00801	841	20
Overall	92	91.8571	0.0404	LOGLOG	0.0039165	0.1561718	0	0.9596	0.0079	842	18
Overall	93	91.8571	0.0404	LOGLOG	0.0039165	0.1561718	0	0.9596	0.0079	842	18
Overall	94	91.8571	0.0404	LOGLOG	0.0039165	0.1561718	0	0.9596	0.0079	842	18
Overall	95	91.8571	0.0404	LOGLOG	0.0039165	0.1561718	0	0.9596	0.0079	842	18
Overall	96	91.8571	0.0404	LOGLOG	0.0039165	0.1561718	0	0.9596	0.0079	842	18
Overall	97	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	16
Overall	98	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	15
Overall	99	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	15

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Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	100	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	14
Overall	101	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	14
Overall	102	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	14
Overall	103	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	13
Overall	104	96.2857	0.0382	LOGLOG	0.0028961	0.1613446	0	0.9618	0.00777	843	13
Overall	105	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	12
Overall	106	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	12
Overall	107	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	12
Overall	108	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	11
Overall	109	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	10
Overall	110	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	10
Overall	111	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	10
Overall	112	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	9
Overall	113	104.5714	0.0353	LOGLOG	0.0016038	0.1757119	0	0.9647	0.00771	844	9
Overall	114	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	8
Overall	115	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	7
Overall	116	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	7
Overall	117	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	6
Overall	118	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	6

ITT

CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	119	114	0.0313	LOGLOG	0.0004094	0.2149569	0	0.9687	0.00778	845	6
Overall	120	119.8571	0.0261	LOGLOG	6.8753E-06	0.3269849	0	0.9739	0.00805	846	5
Overall	121	119.8571	0.0261	LOGLOG	6.8753E-06	0.3269849	0	0.9739	0.00805	846	5
Overall	122	119.8571	0.0261	LOGLOG	6.8753E-06	0.3269849	0	0.9739	0.00805	846	5
Overall	123	119.8571	0.0261	LOGLOG	6.8753E-06	0.3269849	0	0.9739	0.00805	846	5
Overall	124	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	125	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	126	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	127	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	128	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	129	123.8571	0.0209	LOGLOG	7.19E-10	0.491239	0	0.9791	0.00796	847	4
Overall	130	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	3
Overall	131	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	2
Overall	132	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	2
Overall	133	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	134	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1

ITT

CP11-0806

Treatment	Timelist	Time (weeks)	Survival Distribution Function Estimate	Transform for Survival Confidence Interval	Hall-Wellner Band Lower 95.00% Limit	Hall-Wellner Band Upper 95.00% Limit	Censoring Indicator	Failure	Survival Standard Error	Number Failed	Number Left
Overall	135	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	136	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	137	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	138	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	139	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	140	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	141	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	142	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	143	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	144	129.4286	0.0157	LOGLOG	3.212E-22	0.7053704	0	0.9843	0.00749	848	1
Overall	145	129.4286	.		.	.	0	.	.	848	0

Program: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\km_hw_stderr

Data: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\final_restricted\data\shared\adam

Output: H:\lillyce\prd\ly3012211\i4x_ie_jfcc\ho1\programs_stat\tfl_output\km_hw_stderr.xls

Run date: 06NOV2014:16:54

Appendix 13. Response to question B4

EQ-5D

Table 63 Pre-progression EQ-5D Score in patients with EGFR expressing tumours (total population) Using UK Weights

	GCis+N	GCis	Overall
	N=462	N=473	N=935
Over the study			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Chemotherapy Phase			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Maintenance Phase			
No. of patients, n (%)	[redacted]		[redacted]
No. of non-missing EQ-5D Scores	[redacted]		[redacted]
Mean EQ-5D	[redacted]		[redacted]
SD/SE	[redacted]		[redacted]

Off Treatment			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]

Table 64 Pre-progression EQ-5D Score in patients with EGFR expressing tumours (Western European subpopulation) Using UK Weights

	GCis+N	GCis	Overall
	N=145	N=155	N=300
Over the study			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Chemotherapy Phase			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Maintenance Phase			
No. of patients, n (%)	[redacted]		[redacted]
No. of non-missing EQ-5D Scores	[redacted]		[redacted]
Mean EQ-5D	[redacted]		[redacted]
SD/SE	[redacted]		[redacted]
Off Treatment			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing EQ-5D Scores	[redacted]	[redacted]	[redacted]
Mean EQ-5D	[redacted]	[redacted]	[redacted]

SD/SE	[redacted]	[redacted]	[redacted]

Table 65 Pre-progression VAS Score in patients with EGFR expressing tumours (total population)

	GCis+N	GCis	Overall
	N=462	N=473	N=935
Over the study			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Chemotherapy Phase			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Maintenance Phase			
No. of patients, n (%)	[redacted]		[redacted]
No. of non-missing VAS Scores	[redacted]		[redacted]
Mean VAS	[redacted]		[redacted]
SD/SE	[redacted]		[redacted]
Off Treatment			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]

No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]

Note: Patients with EGFR-expressing tumour only include patients with EGFR H-score>0.
Abbreviations: VAS, Visual analogue scale; Gem-Cis+Neci, gemcitabine-cisplatin + necitumumab; Gem-Cis, gemcitabine-cisplatin; SD, Standard deviation; SE, Standard error; ITT, intention to treat.

Table 66 Pre-progression VAS Score in patients with EGFR expressing tumours (Western European subpopulation)

	GCis+N	GCis	Overall
	N=145	N=155	N=300
Over the study			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Chemotherapy Phase			
No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]
Maintenance Phase			
No. of patients, n (%)	[redacted]		[redacted]
No. of non-missing VAS Scores	[redacted]		[redacted]
Mean VAS	[redacted]		[redacted]
SD/SE	[redacted]		[redacted]
Off Treatment			

No. of patients, n (%)	[redacted]	[redacted]	[redacted]
No. of non-missing VAS Scores	[redacted]	[redacted]	[redacted]
Mean VAS	[redacted]	[redacted]	[redacted]
SD/SE	[redacted]	[redacted]	[redacted]

Note: Patients with EGFR-expressing tumour only include patients with EGFR H-score>0.
Western European Countries: Germany, France, Spain, Greece, Italy, UK, Portugal, Austria, and Belgium.
Abbreviations: VAS, Visual analogue scale; Gem-Cis+Neci, gemcitabine-cisplatin + necitumumab; Gem-Cis, gemcitabine-cisplatin; SD, Standard deviation; SE, Standard error; ITT, intention to treat.

Appendix 14. Response to question C5

Table 67 Results of proportional hazards (PH) assumption assessment

Study number	Included trial	Comparators	Reconstructed hazard ratio and 95% confidence interval	P-value for PH
1115	Treat et al. 2010	carboplatin+paclitaxel vs gemcitabine+carboplatin	1.232 (0.857-1.775)	0.056
1115	Treat et al. 2010	carboplatin+paclitaxel vs gemcitabine + paclitaxel	1.106 (0.762-1.603)	0.289
1027	Socinski et al. 2012	carboplatin+paclitaxel vs carboplatin+nab-paclitaxel	0.908 (0.732-1.126)	0.949

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of Necitumumab for untreated advanced or metastatic Squamous Non Small Cell Lung Cancer (NSCLC).

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, cure is not a treatment option.
For patients with squamous cell histology, of good performance status, current standard first line treatment would be with Cisplatin combination chemotherapy. 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. Available active treatment options are limited for this histological patient group. Overall outcomes remain poor. And so, 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
   Necitumumab is given in combination with Cisplatin and Gemcitabine in previously untreated patients with advanced or metastatic squamous cell NSCLC. It is administered intravenously on days 1 and 8 of a 21-day cycle.

2. Side effect profile
   Necitumumab appears to be generally well tolerated. Common side effects are noted to be skin rash and those of magnesium deficiency (muscular weakness, seizure, and can lead to cardiopulmoinary arrest). Monitoring of serum electrolytes, magnesium, potassium and calcium is necessary. Patients will, of course experience side effects associated with the Cisplatin/Gemcitabine combination.

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 SQUIRE trial of 1,093 patients, which showed a 1.6 month improvement in overall survival when Necitumumab was added to the Cisplatin/Gemcitabine combination. The median overall survival was reported as 11.5 months for the Necitumumab containing arm, compared with 9.9 months for the Cisplatin/Gemcitabine doublet arm. We note the median progression free survival of 5.7 months when Necitumumab is added, compared with 5.5 months for the doublet alone.

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 are in a particularly devastating situation. There is a need for new improved therapy options.

[redacted] **RCLCF.**

January 2016.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? xx
- 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)

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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.

The British Thoracic Society welcomes this appraisal and has no specific issues to raise.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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?

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.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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)?

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.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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: National Lung Cancer Forum for Nurses (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)?

- ✓
- 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)?

Macmillan Lung Cancer Nurse Specialist

- other? (please specify)

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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.

Other than units accessing clinical trials; there should not be geographical variations in practice.

The subgroup of patients advanced metastatic squamous NSCLC.

This type of medication will be given in secondary care within a specialist clinic environment. I am not familiar with the administrative requirements for this particular drug.

No further comments

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?

Inappropriate to answer as insufficient knowledge/experience of se 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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for treating advanced, metastatic, squamous non-small cell lung cancer [ID835]

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)?

Lack of knowledge of this particular drug not in position to answer question

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for untreated metastatic squamous non-small-cell lung cancer [ID835]

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: Prof Gary Willam Middleton

Name of your organisation University of Birmingham and University Hospital, Birmingham

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- 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.)? NO
- other? (please specify)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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?

Squamous cell carcinoma of the lung (sq-NSCLC) remains a huge area of unmet therapeutic need. Whilst the advent of targeted therapy has significantly improved the outcome of certain patients with advanced non-squamous NSCLC, there are no recognised active targeted agents for patients with squamous disease and the standard of care has remained largely unchanged over 25 years – the use of platinum-containing chemotherapy doublet. Randomised data (Scagliotti, JCO, 2008) show that Gemcitabine/Cisplatin significantly improved outcome compared with pemetrexed/cisplatin in patients with sq-NSCLC and this doublet remains the registration standard of care as comparator in first line randomised trials. Although, other regimens are also utilised in the UK, for such patients the majority of clinicians use gemcitabine/platinum and no other doublet utilised has proved superior in terms of efficacy, toxicity or cost.

The survival even with chemotherapy is extremely poor for sq-NSCLC patients. In the Scagliotti study median OS was just 10.8 months for gemcitabine/platinum treated patients and in the SQUIRE study which forms the basis of the current submission this figure remains largely unchanged with the control arm median OS of 9.9 months. Thus novel therapies to improve this parlous state of affairs are desperately needed, for this group of patients that represent 25-30% of all lung cancer. The addition of the EGFR monoclonal antibody Necitumumab to gemcitabine/cisplatin is the first ever drug to significantly improve survival when added to gemcitabine/cisplatin compared to the same chemotherapy alone. Even fairly modest survival benefits to patients are critically important when survival is less than a year.

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?

Many patients with lung cancer are simply to poorly to benefit from chemotherapy. Those that are fit enough with an ECOG performance status of 0-2 are the target population for this technology and it is known that PS 2 patients fare less well than their PS0/1 counterparts. Thus, it is reassuring and important to know that the SQUIRE study not only included PS 2patients but stratified the patients PS0/1 vs 2. In the planned sub-set analysis PS 2 patients had numerically a greater benefit for the addition of necitumumab with an hazard ratio of 0.78.

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)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

This is a cancer therapy that will be seen by consultant oncologists in the hospital setting and delivered by specialist chemotherapy nurses in appropriately equipped and monitored facilities

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?

N/A

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.

The ASCO guidelines remain the global benchmark for the management of lung cancer. They were most recently updated in 2015 (Masters et al, JCO, 2015) and gemcitabine/platinum remains one of the recommended (and FDA-approved) regimens for sq-NSCLC.

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?

There are no current alternatives unfortunately as there are no other agents which improve survival when added to gemcitabine/cisplatin.

The delivery of necitumumab is intravenous give d1 and day 8 of each 3 week cycle. This implies no resource issue during the time it is delivered concomitantly with chemotherapy but in the SQUIRE study 50% of patients went onto maintenance montherapy with necitumamb for a median of 4 cycles. This will require a median of 8 hospital visits with cannulation and drug delivery over 12 weeks. This needs to be factored in to the health economics of the treatment. However, maintenance therapy is very commonly given to patients with non-squamous NSCLC who receive pemetexed maintenance again given intravenously and again for a median of 4 cycles.This represents a larger group of patients and certainly from a capacity point of view has no had any significant repercussions on units delivering this therapy. From a patient acceptability perspective patients understand the importance of the maintenance component of their treatment and every cycle is only delivered after careful evaluation of the risk:benefit for that cycle particularly considering the physical and emotional effect of that therapy.

In the SQUIRE study there was no significant differences in the febrile neutropenia rate or grade 3/4 anaemia or thrombocytopenia. This is important as these toxicities have significant resource implications for hospitalisations, antibiotic usage and blood product transfusions.

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Single Technology Appraisal (STA)

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.

Patients will only continue to receive necitumamb if CT scanning demonstrates continuing disease stabilisation with acceptable tolerability. CT scanning during induction will not be altered by the addition of necitumamb. During the maintenance phase patients will be scanned on average every three months and given the median of four maintenance cycles this amounts to only one extra scan in 50 of the patients.

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?

The SQUIRE study was a large adequately powered randomised trial with an entirely appropriate primary end-point, overall survival. The trial was not blinded because rash is a class effect of these drugs and intravenous placebo maintenance is not ethically acceptable. The study was reflective of UK practice, including PS 2 patients with no age restriction: the oldest patient treated was 86.

Overall survival remains the key end-point for trials in this population given the very poor outcomes and the fact that this is the only truly reliable measurable outcome. The study showed a significant benefit for the addition of necitumumab to gemcitabine/cisplatin with an HR of 0.84 with no significant evidence of any sub-group effect. There was no difference in the delivery of subsequent therapies. The disease modifying benefit of necitumumab was supported by a significant improvement in progression free survival.

An important analysis of outcome by region was performed. This was done because there is a clear difference in incidence and mortality in patients with lung cancer living in different regions and indeed across Europe. Highly pertinent here, in regards to applicability of the trial results to UK practice, is the survival data for the EU5 patients (UK, France, Italy, Spain and Germany): the median survival was 12.3 months for patients receiving all three drugs, the first time the 12 month median OS barrier has been broken. The addition of necitumamb gave a highly important 3.8 month survival benefit with an OS HR of 0.68. These are highly meaningful survival benefits of great relevance to UK patients. Such analyses are rarely performed but they are critical in determining the real impact of translating a technology to our English population

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?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab is an EGFR monoclonal antibody and this class of drugs have been in use for more than 10 years. The most significant side-effect is the class effect, rash. This is usually easily managed and there are clear guidel;ines fo the prophylactic management of this side-effect and dose modification guidelines should it occur. It is important to note that there was only a 7% grade 3 rash rate with necitumumab, entirely in line with other EGFR monoclonals in routine clinical use in England.

The only other relevant class effect is hypomagnesaemia seen in 9.5% (grade 3) in this trial. This is picked up on routine chemistry testing and easily managed with magnesium supplementation.

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:

- 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 disabilitiesPlease tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I have no concerns re E & D. This was a global study representing all races with no age limit. It is highly relevant to all English patients receiving chemotherapy in the UK.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

This is the only randomised study of the addition of necitumumab to chemotherapy in squamous cell lung cancer patients.

It is however worth noting the differential effect of cetuximab by histology in the first line registration study in NSCLC (Pirker et al, Lancet, 2009). The OS HR for the addition of cetuximab to navelbine/cisplatin was 0.80 in patients with squamous cell cancer compared with only 0.93 in non-squamous patients. Merck Serono never applied for a licence in the purely squamous population and performed no subsequent squamous validation studies.

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 additional resources have been mentioned above. There will be very little need for additional training as this class of drugs have been in the clinic for greater than 10 years and standardised management pathways are in place in all accredited units delivering these treatments.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Necitumumab for untreated metastatic squamous non-small-cell lung cancer [ID835]

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 Thomas Newsom-Davis

Name of your organisation: National Cancer Research Institute (NCRI) Lung Clinical Study Group (CSG)

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)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I have no links, direct or indirect, with the tobacco industry

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

The technology applies to patients with advanced (stage IV, metastatic) squamous cell lung cancer. These patients are currently treated with chemotherapy and the aim is palliative, not curative, with a focus on quality of life as much as prolongation of survival. Prognosis is sadly very poor, with clinical trial data suggesting an average (median) survival of 8-10 months. Patients with poor performance status (ECOG >2) have a markedly worse outcome than those with ECOG 0-2, and chemotherapy is therefore largely reserved for the latter group. There are no other subgroups in which prognosis or treatment significantly differs.

First line platinum doublet chemotherapy is the standard-of-care: cisplatin or carboplatin, in combination with gemcitabine, vinorelbine, paclitaxel or docetaxel. There is variation across the world and the United Kingdom with respect to which combination is preferred, but there is no consistent difference in efficacy or toxicity between regimens. Consequently all drugs are recognised in current NICE guidelines (CG121, 2011) and local practice tends to reflect personal preference and experience of the treating oncologist. Perhaps the commonest combination used in the United Kingdom is gemcitabine and carboplatin.

Despite advances in other types of lung cancer, there has been little progress in the treatment of advanced squamous cell carcinoma since these drug combinations were established in 2002. For example, the use of targeted drugs such as EGFR tyrosine kinase inhibitors instead of chemotherapy is not possible because squamous cell carcinomas very rarely harbour the necessary EGFR mutations for these agents to be effective. Newer chemotherapy agents, such as pemetrexed, are not effective in squamous cell carcinoma. Meanwhile the addition of a third compound, for example bevacizumab, is only licensed for non-squamous tumour types due to concerns about toxicity.

There are no current alternatives to the technology beyond standard chemotherapy.

All treatment for this patient group would be under the care of lung cancer oncology department, supervised by a medical or clinical oncologist. Chemotherapy is given as a day-case in local or regional chemotherapy units, with close input from oncology clinical nurse specialists and chemotherapy nurses.

Necitumumab is not currently available in the United Kingdom. It is not included in any current clinical guidelines.

The advantages and disadvantages of the technology

<u>Advantages of Necitumumab:</u>
The clinical trial (SQUIRE) from which the evidence for Necitumumab comes was large, well designed, and completed planned recruitment. The inclusion criteria included patients with a performance status of 0-2 and as such, within the bounds of

clinical trials, is representative of the patient group currently considered eligible for first line chemotherapy-based treatment.
The primary end-point was overall survival, which is usually regarded as the most important outcome measure. The trial was presented in the plenary session of the largest oncology conference (ASCO) and published in a high impact factor peer-reviewed clinical journal (Lancet Oncology).
Necitumumab is the only agent that has been shown to improve survival for patients with advanced squamous cell carcinoma of the lung, when added to standard chemotherapy. The importance of this should not be underestimated because squamous cell carcinoma is very difficult to treat, and repeated efforts over the years to improve survival by addition or substitution of other drugs have failed. Squamous cell carcinoma patients are excluded from many of the new and exciting developments in the treatment of lung cancer (for example EGFR and ALK targeting tyrosine kinase inhibitors).
The SQUIRE study demonstrated an overall survival benefit for those patients treatment with chemotherapy and Necitumumab, compared to those treated with chemotherapy alone. This advantage extended to all sub-groups, although the benefit for those aged ≥70 years is uncertain. Progression free survival and response rates were also improved for patients receiving Necitumumab.
The survival benefits of Necitumumab did not come at the expense of markedly worse toxicity. There was a statistically significant increase in the incidence and severity of hypomagnesaemia and rash, but no increase in serious adverse events leading to death. There was no negative impact on quality of life with the addition of Necitumumab. From my experience of treating patients as part of the trial, the skin rash was manageable and did not cause significant problems. There were few other Nicetumumab related side effects that impacted on quality of life
The study protocol involved Necitumumab added to existing, standard, platinum-based chemotherapy and Necitumumab was given on the same days as gemcitabine and cisplatin. No additional treatments were required during the chemotherapy phase, and no additional testing of the tumour or other biomarkers is required in order for Necitumumab to be given.
Although Necitumumab was administered until evidence of disease progression, the nature of advanced 1st line squamous cell carcinoma is that the disease progresses soon after chemotherapy has finished. Therefore prolonged treatment with Necitumumab is not a likely financial burden: the median number of Necitumumab cycles after chemotherapy had finished was 4. Deciding when to stop Necitumumab is clear, as routine cross-sectional imaging (most likely CT) is standard of care in this patient group.

<u>Disadvantages:</u>
Although the addition of Necitumumab to chemotherapy resulted in a statistically significant increase in survival, the benefits are modest and of questionable clinical significance. For example the median overall survival increased by less than 2 months. The hazard ratios for overall survival and progression free survival were 0.84 and 0.85 respectively, which is disappointing, whilst the increase in response rates was similarly modest. The statistical significance in part reflects the large number of patients that took part in the SQUIRE study.
There is no biomarker that allows identification of a sub-group that would particularly benefit from Necitumumab. A high EGFR H-score showed a trend towards greater

overall survival compared to those patients with a low H-score, however this did not reach statistical significance.
Addition of Necitumumab did not improve quality of life. Quality of life is one of the fundamental reasons to treat patients with advanced squamous cell lung cancer, and although it is important that quality of life did not fall, it is equally significant that it did not rise.
The evidence behind Necitumumab involved its combination with cisplatin and gemcitabine, which is a less common regimen in the United Kingdom. Its benefit with carboplatin and gemcitabine, and other more commonly used regimens, is therefore unknown and it is not possible to assume that the same survival benefit extends to the use of Necitumumab with these chemotherapies. This is of particular relevance because patients are often unable to receive cisplatin due to poor renal function and carboplatin is the only platinum agent open to them.
Necitumumab was given until disease progression and therefore often continued after 4-6 cycles of chemotherapy. This will have an impact on patients and chemotherapy units, as people will continue to receive intravenous treatment for 2 out of every 3 weeks. Chronic hypomagnesaemia, a side effect that is more common with Necitumumab, usually requires regular and ongoing treatment with intravenous magnesium (given over 4-6 hours) which will have further impact on chemotherapy day-unit workloads.

Conclusion:
A well-designed and executed clinical trial has demonstrated a statistically significant survival benefit following the addition of Necitumumab to standard chemotherapy in this hard-to-treat and often neglected patient group. Although this comes with only minor additional toxicity, the overall clinical benefit is modest and there is no improvement in quality of life. The statistical significance of the survival advantage is not matched by a similar degree of clinical significance, and there is no identifiable sub-group in whom Necitumumab is found to be especially efficacious.

Equality and Diversity

I do not believe that this appraisal:
- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Necitumumab will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Any additional sources of evidence

N/A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

If NICE were to approve the use of Necitumumab, it is likely that existing oncology services could provide it without significant problems.
Necitumumab is a monoclonal antibody given as an intra-venous infusion. In this respect it is a common treatment modality and no additional training of staff is anticipated. The additional demand on facilities is likely to be modest, reflecting that squamous cell carcinoma only represents the minority of lung cancer patients and treatment with Necitumumab beyond completion of chemotherapy usually only continues for a maximum of 3-4 months. No additional equipment is anticipated, and the side effect profile is unlikely to present new and complex demands on current oncology services.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors
Karen Pickett, Research Fellow, SHTAC
Micah Rose, Research Fellow, SHTAC
Jill Colquitt, Senior Reviewer / Partner, Effective Evidence LLP
Emma Loveman, Senior Reviewer / Partner, Effective Evidence LLP
Geoff Frampton, Senior Research Fellow, SHTAC
Andy Clegg, Senior Reviewer / Partner, Effective Evidence LLP
Joanne Lord, Professorial Fellow in Health Economics, SHTAC

Correspondence to
Karen Pickett
Southampton Health Technology Assessments Centre
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed 24 March 2016

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/69/01.

Acknowledgements

We would like to thank a consultant oncologist, who has requested not to be named, for providing clinical advice and commenting on a draft of this report. We would also like to thank: Karen Welch, Information Scientist, SHTAC, for appraising the literature search strategies in the company's submission, running updates of the company's clinical and cost-effectiveness searches and searching for ongoing studies; and Jonathan Shepherd, Principal Research fellow, for acting as internal editor for the ERG report.

Declared competing interests of the authors

None from the authors. The consultant oncologist who advised the ERG declared all potential competing interests.

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:

Pickett K, Rose M, Colquitt J, Loveman E, Frampton G, Clegg A, Lord J. Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2015.

Contributions of authors

K Pickett (Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and project managed the review. M Rose (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. J Colquitt (Senior Reviewer / Partner, Effective Evidence LLP) and E Loveman (Senior Reviewer / Partner, Effective Evidence LLP) critically appraised the clinical effectiveness systematic review and drafted the report. G Frampton (Senior Research Fellow) critically appraised the clinical effectiveness systematic review and the network meta-analysis (NMA), drafted the report and is the project guarantor. A Clegg (Senior Reviewer / Partner,

Effective Evidence LLP) critically appraised the NMA and drafted the report. J Lord (Professorial Fellow in Health Economics) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report.

Word count: 48,669

Key to colour highlighting used in report

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow.

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LIST OF ABBREVIATIONS

A&E	Accident and Emergency
AE	Adverse event
ASBI	Average Symptom Burden Index
BIC	Bayesian information criterion
BSA	Body surface area
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CR	Complete response
CS	Company's submission
CSR	Clinical study report
DCarbo	Docetaxel plus carboplatin
DCis	Docetaxel plus cisplatin
DIC	Deviance Information Criterion
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOL	End-of-life
ERG	Evidence Review Group
FDA	Food and Drug Administration
GCarbo	Gemcitabine plus carboplatin
GCis	Gemcitabine plus cisplatin
GCis + N	Necitumumab in combination with gemcitabine plus cisplatin
GP	General Practitioner
G + P	Gemcitabine in combination with paclitaxel
HR	Hazard ratio
HRQoL	Health-related quality of life
H-score	Immunohistochemistry score
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ITT	Intention-to-treat
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
Nab-PCarbo	Nab-paclitaxel plus carboplatin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCarbo	Paclitaxel plus carboplatin
PCis	Paclitaxel plus cisplatin
PFS	Progression free survival
PR	Partial response
PS	Partitioned survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
S-1Carbo	S-1 plus carboplatin
SmPC	Summary of Product Characteristics
TA	Technology Assessment
TK	Tyrosine kinase
TTD	Time to discontinuation
TTF	Time to treatment failure
UKCRN	UK Clinical Research Network
VCarbo	Vinorelbine plus carboplatin
VCis	Vinorelbine plus cisplatin
VCis + C	Vinorelbine plus cisplatin and cetuximab
VEGF	Vascular endothelial growth factor
VGD	Vinorelbine in combination with gemcitabine and docetaxel
WHO	World Health Organisation

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of this appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to appraise the clinical and cost-effectiveness of necitumumab within its marketing authorisation for the treatment of untreated advanced, metastatic, squamous non-small-cell lung cancer (NSCLC). The necitumumab marketing authorisation states that necitumumab in combination with gemcitabine and cisplatin (GCis + N) is indicated for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous NSCLC who have not received prior chemotherapy. The company's original evidence submission for this appraisal did not include analyses of the efficacy, safety or cost-effectiveness of GCis + N among patients with EGFR expressing squamous NSCLC. The company, however, supplied additional clinical and cost-effectiveness analyses for this patient population during the appraisal, in their response to clarification questions from NICE and the Evidence Review Group (ERG). The submission assesses the clinical and cost-effectiveness of GCis + N compared with five of the eight comparator combination drug regimens specified in NICE's scope:

- Cisplatin in combination with gemcitabine (GCis)
- Cisplatin in combination with paclitaxel (PCis)
- Carboplatin in combination with gemcitabine (GCarbo)
- Carboplatin in combination with paclitaxel (PCarbo)
- Cisplatin in combination with docetaxel (DCis)

Insufficient evidence was available to enable a comparison with the remaining three:

- Carboplatin in combination with docetaxel (DCarbo)
- Cisplatin in combination with vinorelbine (VCis)
- Carboplatin in combination with vinorelbine (VCarbo)

Summary of submitted clinical effectiveness evidence

The company's submission to NICE included:

- A systematic literature review of direct evidence, which included one Phase III randomised controlled trial (RCT) (the SQUIRE trial[1]).
- A systematic review to inform a network meta-analysis (NMA), which included a total of 10 RCTs in four networks to provide direct and indirect evidence of the efficacy of GCis + N compared to GCis alone and the other squamous NSCLC treatments specified in

the scope (where evidence was available). The outcomes in the four networks were median OS, hazard ratio of OS, median PFS and hazard ratio of PFS.

The SQUIRE trial was a large (N = 1093), open-label, multicentre RCT carried out in 26 countries, including the UK [redacted]. It compared the efficacy of GCis + N to GCis alone in people with stage IV squamous NSCLC who had not received prior chemotherapy for advanced NSCLC. The trial included patients with Eastern Cooperative Oncology Group (ECOG) performance statuses of 0-2. The drug doses of necitumumab, gemcitabine and cisplatin used in the trial matched those specified in the necitumumab and gemcitabine marketing authorisations. In line with the marketing authorisation, participants treated with necitumumab received treatment with GCis + N, followed by, where appropriate, maintenance treatment with necitumumab alone. The scope-relevant outcomes the trial assessed were overall survival (OS), progression free survival (PFS), objective response rates (ORR), health-related quality of life (HRQoL) and adverse events (AEs). The company supplied the results of these outcomes in its submission for the intention-to-treat population (ITT; defines as all randomised patients) and some of these outcomes for three trial subgroups:

- a post-hoc Western European subgroup (including patients from Germany, France, Spain, Greece, Italy, UK, Portugal, Austria and Belgium);
- a post-hoc subgroup of patients with EGFR expressing squamous NSCLC (the subgroup most relevant to the licensed indication) from the ITT population;
- a post-hoc subgroup of patients with EGFR expressing squamous NSCLC from the Western European subgroup.

The company stated that the Western European subgroup was a more generalisable population to patients in England than the ITT population, but did not provide a clear rationale for this or demonstrate a statistically significant treatment interaction for this subgroup.

The SQUIRE trial showed that GCis + N resulted in a median OS benefit compared with GCis of an additional 1.7, 1.6, [redacted] and [redacted] months, respectively, in the EGFR expressing subgroup, ITT population, Western Europe subgroup and the EGFR expressing Western Europe subgroup. The associated hazard ratios (HRs) were statistically significant for all populations. Median PFS was statistically significantly slightly longer with GCis + N compared to GCis in the EGFR expressing and ITT populations, but not the two Western Europe subgroups. Objective response rates were statistically significantly higher with GCis + N than with GCis in the EGFR Western Europe subgroup only (statistical significance not reported for the ITT population).

[redacted]. The proportion of patients experiencing at least one serious adverse event (AE) was marginally higher during the treatment phase with GCis + N than during treatment with GCis. Venous thromboembolic events were experienced more frequently in those treated with GCis + N than GCis alone for any grade. In the ITT population, the GCis + N group also experienced rashes, hypomagnesaemia, and conjunctivitis more frequently than the GCis group alone. In the EGFR expressing subgroup from the ITT population, patients treated with GCis experienced higher rates of hypomagnesaemia than patients treated with GCis in the ITT population. Rates of any grade of rash were lower in the both treatment arms in the EGFR expressing subgroup than in the ITT population.

The company's systematic review conducted for the NMA identified enough evidence to enable comparisons of GCis + N against PCarbo, GCis, PCis, DCis and GCarbo on the OS and PFS outcomes only (no evidence was available for HRQoL or toxicity, which are the other outcomes specified in the inclusion criteria for the review). A comparison with VCis could only be made for median OS data analyses. The NMA mainly included subgroup analyses of patients with squamous NSCLC from trials including patients with other histological subtypes of NSCLC. Only one trial (the SQUIRE trial) included in the NMA focused exclusively on patients with squamous NSCLC. The NMA is broader than the licensed population in that it did not focus solely on patients with EGFR expressing squamous NSCLC.

[redacted]

Summary of submitted cost effectiveness evidence

The company's submission to NICE includes:

1. A review of published economic evaluations.
2. A report of a model developed by the company to estimate the cost-effectiveness of GCis + N compared with GCis, GCarbo, PCarbo and DCis for previously untreated patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment.

Ten papers were identified from the review of economic evaluations, but none were considered suitable for the NICE decision problem. After completion of the systematic review, a US

economic evaluation based on the SQUIRE trial results was identified. The company expressed concern about the applicability of this study in the UK, and did not discuss or critique it further.

The CS reported an economic evaluation conducted for the appraisal, based on a de novo model. This was generally consistent with the specified decision problem and with the NICE reference case. A revised version of the model submitted during the assessment focussed on patients with EGFR expressing tumours, in line with the marketing authorisation. The analysis excluded some comparators specified in the scope: vinorelbine combinations and DCarbo because HR estimates were not available from the company's NMA; and PCis as the company argued that it is infrequently used in practice. Some utility values used in the model did not conform to NICE's preferred methods for the measurement and valuation of health-related quality of life.

The model structure reflected the process of treatment and disease progression for a cohort of patients starting first-line induction treatment with GCis + N or conventional chemotherapy. It was a Markov-type model, with five health states: three prior to progression, for patients on induction treatment, maintenance treatment and off treatment; a post-progression state and death. The model used a one week time step. After completion of induction treatment with GCis + N, patients were assumed to proceed to maintenance treatment with necitumumab alone. Induction and maintenance treatment could terminate at any time due to adverse events or patient choice, disease progression or death. AEs were not modelled explicitly, but costs and effects associated with common AEs (>2.5% of patients and febrile neutropenia) were estimated. Similarly, second line treatments and palliative care were not modelled explicitly, but costs were included for proportions of patients after disease progression.

Rates of treatment discontinuation, disease progression and mortality for GCis + N and GCis were based on data from SQUIRE. PFS and OS for the other comparators were modelled using HRs from the NMA, relative to the survival curves for GCis + N. SQUIRE provided Kaplan-Meier PFS and OS estimates for up to three years following randomisation, and parametric survival functions were then used to extrapolate to the end of the model horizon (lifetime). Alternative functional forms were considered for extrapolation of PFS and OS. The company argued that the best approximations the Kaplan-Meier curves were provided by log-logistic survival functions, fitted separately for the two treatment groups. But to make use of the NMA results for the indirect comparisons, the proportional hazards assumption is necessary.

The company concluded that, of the proportional hazards survival functions tested, Weibull provided the best fit. There was no need to extrapolate estimates for Time to Treatment Discontinuation (TTD), since nearly all patients in SQUIRE had stopped treatment by the end of follow up. TTD estimates were not available from the NMA, so for the indirect comparisons it was assumed that the HRs for treatment discontinuation would match the HRs for PFS. Data from SQUIRE was used to estimate AE risks for GCis + N and GCis, and for the indirect comparisons it was assumed that the relative risks of AEs would equal those for GCis versus GCis + N from SQUIRE.

In order to calculate QALYs, health-related quality of life values ('utilities') were attached to the pre-progression and post-progression health states, and 'disutilities' to the included AEs. EQ-5D data were collected before progression for SQUIRE trial participants. As the company found no between-group differences in EQ-5D, they pooled data for GCis + N and GCis. A systematic review was used to identify sources for utility in the post - progression health state and for AE disutilities.

The model included costs for drugs used in first-line and second-line treatment, drug administration, disease monitoring and management, treatment of AEs and palliative care. Health care resource use was estimated based on a retrospective medical chart review, and consultation with clinical experts. Unit costs of healthcare items were based on national tariffs and data sources.

The company's preferred analysis was based only on direct evidence from the SQUIRE trial for the Western European subgroup of patients with EGFR expressing tumours: which yielded an Incremental Cost Effectiveness Ratio (ICER) of £57,725 per QALY gained for GCis + N compared with GCis. Including other comparators from the NMA for this same patient group, they cited an ICER of £116,344 for GCis + N compared with PCarbo, which was the the next-best, non-dominated alternative.

These results were based on deterministic versions of the model. The company did conduct a Probabilistic Sensitivity Analysis (PSA), but did not report ICERs from this. However, they did use graphical methods to illustrate the wide uncertainty around the estimated incremental costs and effects, and the low probability that GCis + N would be cost-effective below a willingness-to-pay threshold of around £200,000 per QALY. Deterministic analysis was used to show that the

ICER was most sensitive to estimates of OS, and to a lesser extent to PFS and TTD for GCis+N. The estimated ICER was shown to be much higher for the ITT population with EGFR expressing tumours (a figure of £151,152 per QALY gained was cited by the company, but we believe the correct estimate from the company model to be £110,248). Results were also sensitive to the methods used to extrapolate beyond the Kaplan-Meier OS curves; ICERs were in the region of £80,000 per QALY gained using Weibull or exponential functions, or a five-year time horizon, which effectively cuts off the tail of the survival function.

It should be noted that none of these estimates include a cost for the test of EGFR expression that would be required to comply with the marketing authorisation. Thus in practice, the cost of the GCis + N arm (and hence the ICER) would be rather higher than estimated.

Commentary on the robustness of submitted evidence

Strengths

- The company's searches for the systematic reviews of direct and indirect evidence and the reviews of cost-effectiveness studies and data used appropriate search techniques, although they were out-of-date (having been conducted in August 2015, January 2015 and April/May 2014, respectively). The company appears to have included all relevant phase III RCTs in its systematic review; the ERG's update searches for the systematic review of direct evidence (conducted for the period from January 2015 to February 2016) did not identify any other relevant RCTs, although the searches did identify four conference abstracts relating to the SQUIRE trial published before August 2015 that were not identified in the company's searches.
- The inclusion criteria for the systematic reviews of direct evidence and for the NMA generally reflect NICE's scope and the company's decision problem.
- The company's systematic review of direct evidence included a large phase III trial that provided direct evidence of the efficacy of GCis + N compared with GCis, which is one of the most commonly used platinum doublets in clinical practice. The patients included in the trial are representative of those seen in practice.
- The company has, on the whole, appropriately synthesised the evidence in its systematic review of direct evidence.
- The company's economic model is well designed and appropriate for the decision problem.

- Most model parameters are estimated from best-available evidence. The Kaplan-Meier survival estimates from the SQUIRE trial were based on a large patient population, with long follow up, which was not subject to cross over or other serious sources of bias. Systematic searches were used to identify post-progression and AE utility values. And the costing was very thorough, including a retrospective case note review. Although we are critical of some of the methods of used to analyse AE and EQ-5D data, the resulting parameter estimates appear to be reasonable.
- The model is also well implemented. We identified few errors or inconsistencies, and none that made any sizeable difference to the results.
- The model also provides a good platform for exploring parametric and structural uncertainties, including the patient population and methods for extrapolating survival curves.

Weaknesses and areas of uncertainty

- The risk of systematic error in the company's clinical effectiveness systematic reviews is uncertain. The searches for the NMA review were one year out-of-date and the company made post-hoc exclusions of studies from the NMA, not all of which the ERG agrees with.
- The ERG's quality assessment of the included SQUIRE trial differed to the company's assessment. The ERG identified that HRQoL data reported from SQUIRE in the CS are at risk of selective outcome reporting bias, as a number of analyses of HRQoL detailed in the clinical study report (CSR) provided by the company as part of its submission were not reported in the CS. The ERG also noted that subgroup analyses results by age, ECOG performance status [redacted] were not presented in the CS in line with the pre-specified comparison categories.
- The OS results supplied for the EGFR expressing subgroup do not match those reported for this subgroup in a publicly available Food and Drug Administration (FDA) briefing document about necitumumab. [redacted].
- The ERG considers that that company's argument that the Western European subgroup is a more generalisable population to patients in England than the ITT population is not inadequately justified. The ERG considers the EGFR expressing subgroup to be the most relevant population for this appraisal, as this is in line with the marketing authorisation treatment indication. The ERG did not identify a clinical justification for why

data from particular geographical regions rather than the total trial population would be more relevant to England. Furthermore the company did not find a statistical interaction for efficacy effects by region. Clinical expert advice to the ERG was that the baseline characteristics of patients in the ITT population in the SQUIRE trial are representative of those seen in clinical practice.

- The company does not report what a clinically meaningful change in OS would be in the CS; therefore it is unclear if the OS benefits seen with GCis + N in comparison to GCis are clinically meaningful. Clinical expert advice to the ERG is that the improvement in OS in the EGFR expressing subgroup (the population most relevant to the licensed indication) is clinically meaningful.
- The treatment effect estimates from the NMA networks are highly uncertain, as: it is unclear how similar the studies included in the NMA networks were in terms of length of follow-up; the proportion of patients with an ECOG performance status of 2 differed across the studies, and this might have modified treatment outcomes as the analyses were unadjusted; the NMA included mainly subgroup analyses that were likely to be underpowered; the company appears to have made some inappropriate post-hoc exclusions of studies from the NMA; and, most of the comparisons were based on indirect evidence, so consistency with direct evidence could not be assessed.
- The company only presents cost-effectiveness results for the Western European subgroup. As argued above, we do not believe that this is justified.
- The extrapolations of OS curves beyond the three-year follow-up available from SQUIRE are influential on modelled estimates of QALY gain, and are subject to considerable uncertainty. The company's base case estimates rely on log-logistic curves, which have a long tail compared with Weibull curves. Evidence of goodness of fit is similar for these two functional forms.
- We also question the method of extrapolating from the last observations from the SQUIRE data. This places undue emphasis on the tails of the Kaplan-Meier curves, which are based on very small numbers of patients and so are subject to very wide confidence ranges. In the company preferred base case, this has the effect of separating the tails of the extrapolated curves, increasing the estimates of QALY gains.
- We also question whether the long-term survival predictions from the log-logistic extrapolated curves are realistic for the SQUIRE population: 7% and 1% at five years with GCis + N and GCis, respectively, in the company preferred base case.

- The company presents ICERs estimated from the deterministic version of the model, rather than using the correct approach based on mean incremental costs and mean incremental QALYs estimated from the PSA. The deterministic ICERs are lower for the PSA-based ICERs (due to the skew in QALY estimates as illustrated on the cost-effectiveness scatterplots).
- The company does not present correct incremental analyses, but instead presents pairwise comparisons for GCis + N with other included comparators.

Summary of additional work undertaken by the ERG

The ERG conducted verification checks on the model. We started by reviewing the model structure and formulae to look for errors or inconsistencies; cross-checked the model assumptions and inputs against those reported in the CS, and with the cited data sources (where available); compared that the results and sensitivity analyses reported in the CS and clarification report with model outputs. The model included a rather complex system of interacting input sheets and intermediate calculations, and some complicated macros. We therefore chose to replicate the model in a separate Excel file, to check that the calculations and macros yielded the expected intermediate and final results. We found a small number of minor errors and inconsistencies, none of which led to big changes in the model results.

We then conducted a range of additional analyses to test the robustness of the company model to changes in structural assumptions. This included an alternative 'base case' reflecting our best judgement about the most plausible set of assumptions. We then used this base case to explore other possible scenarios and uncertainties over key parameters. The key changes that we made to the company model in our base case were:

- ITT population with EGFR expressing tumours.
- Indirect comparators included, based on the NMA. Despite uncertainty over the completeness and robustness of the NMA, we believe this to provide the best-available evidence relevant to the specified decision problem.
- We added PCis, which was included in the company NMA but not in the model.
- Kaplan-Meier curves were extrapolated from the point at which the number of patients remaining in each arm had declined to 20 or fewer.
- Weibull curves were used for the extrapolations of PFS and OS.

- Results of the PSA were used to calculate ICERs for our base case and all scenario and sensitivity analyses.

This resulted in an estimated ICER of £169,612 per QALY gained for GCis + N compared with GCis (which was the next-best, non-dominated comparator in the incremental analysis). We note that the probabilistic version of the company model including indirect comparisons yielded an ICER of similar magnitude for the ITT (EGFR-expressing) population: £154,024 compared with GCis and £189,779 compared with PCarbo (the best-best, non-dominated option in this case). In our version of the model, the estimated probability that GCis + N would be the most cost-effective treatment option was near to zero below cost-effectiveness thresholds of £100,000 per QALY.

We conducted 16 scenario or sensitivity analyses, selected as those that had proved to be influential in the company analyses and to explore other uncertainties that we had. These analyses further highlighted the sensitivity of results to the way in which OS was extrapolated beyond the Kaplan-Meier data, and the absolute levels of OS for GCis + N and GCis. Results were also somewhat sensitive to PFS and time to discontinuation of GCis + N. However, in all cases the estimated ICER remained high: above £100,000 per QALY except for the most optimistic scenario that we tested, using log-logistic curves for GCis + N and Weibull for GCis, which maximises the separate between the tails of the two curves, and gave an ICER of £84,188 per QALY gained.

As with the company reported ICER estimates, our estimates do not include the cost of a test for EGFR expression that would be required to meet the marketing authorisation. This would further increase the estimated ICERs.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Eli Lilly and Company on the clinical effectiveness and cost effectiveness of necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer (NSCLC). It identifies the strengths and weaknesses of the CS. A clinical expert was consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by NICE and the ERG on 17th February 2016. A response from the company via NICE was received by the ERG on 4th March 2016 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

The ERG considers that the CS provides a clear and accurate overview of the prevalence, cause and prognosis of both lung cancer and, more specifically, squamous NSCLC, as well as the impact of lung cancer on patients and society (CS p. 31 to p. 34). A clinical expert consulted by the ERG advised that most patients with squamous NSCLC are referred to secondary care by their general practitioner (GP) through the two week wait referrals pathway, and in line with the company's statement in the CS, median survival in this patient population is poor (typically less than one year).

The ERG notes that the company has provided limited background information about epidermal growth factor receptor (EGFR) expression in squamous NSCLC. This is an important consideration in this appraisal, as the summary of product characteristics (SmPC)[2] states that necitumumab is indicated for patients with locally advanced or metastatic EGFR expressing squamous NSCLC. The CS details that around 82% to 95% of patients with squamous NSCLC have tumours with EGFR protein expression, with the 82% estimate referring to the proportion with intermediate to high EGFR expression (CS p. 26). The ERG notes that the company has not discussed in the CS how tumour overexpression of the EGFR protein is related to patient prognosis either generally or when treated with an anti-EGFR monoclonal antibody, such as

necitumumab. The clinical expert consulted by the ERG stated that there is currently no reliable evidence linking EGFR expression to drug efficacy generally.

2.2 Critique of company's overview of current service provision

The CS provides a generally clear and accurate overview of how squamous NSCLC is currently managed in clinical practice. As is noted on CS p. 34, NICE clinical guideline (CG) 121[3] provides recommendations for good practice in the management of lung cancer in England. There is currently no guidance specific to the management of squamous NSCLC. The CS correctly notes that NICE CG 121[3] recommends chemotherapy for patients with stage III or IV NSCLC who have a good performance status using a platinum doublet. As stated in the CS, CG 121[3] recommends that either cisplatin or carboplatin is combined with one of the following third-generation drugs: docetaxel, gemcitabine, vinorelbine or paclitaxel. The CS also correctly notes that a single third-generation drug may be used in patients who are unable to tolerate a platinum doublet. In line with the clinical pathway presented in CS Figure 1 (p. 36), the clinical expert consulted by the ERG stated that patients with stages IIIB or IV disease receive first-line treatment with chemotherapy. The ERG's expert stated that patients with stage IIIA disease can receive radiotherapy or chemoradiotherapy, with some receiving chemotherapy. As noted in the CS (p. 35), NICE CG 121[3] emphasises that the aim of chemotherapy treatment is to control the patient's symptoms, to improve their quality of life and to extend their life. The clinical expert consulted by the ERG concurred, stating that chemotherapy can provide palliation and symptom control (if the patient is sufficiently fit to tolerate toxicity) and is given for quality of life reasons, so it is important to know if it is working at an early stage. The expert emphasised that quality of life is a key consideration when treating this patient population.

The ERG notes that the SmPCs for docetaxel,[4] gemcitabine[5] and paclitaxel[6] state that these drugs are to be administered in combination with cisplatin for treating NSCLC. The clinical expert consulted by the ERG indicated, however, that in clinical practice, each of these third generation drugs is used in combination with either cisplatin or carboplatin. The SmPC for vinorelbine[7] states that it can be used with either cisplatin or carboplatin for combination treatment of NSCLC. The expert indicated that carboplatin is quicker to administer and has fewer side effects than cisplatin.

The clinical expert consulted by the ERG stated that in clinical practice, cisplatin in combination with gemcitabine (GCis) or carboplatin in combination with gemcitabine (GCarbo) are the most commonly used platinum doublets. This concurs with the company's statement on CS p. 37 that gemcitabine is the most commonly used first-line treatment for squamous NSCLC in the UK and the company's statement in the decision problem (CS Table 1, p. 15) that GCis and GCarbo are the current standard of care in the National Health Service (NHS). The clinical expert consulted by the ERG stated that all the platinum doublet combinations are equally efficacious, therefore all the combinations are used in practice and all are the current standard of care. The choice of which to use is usually governed by expectations of what patients will be able to tolerate and their quality of life.

The CS (p. 29 and p. 35) states that patients receive chemotherapy for four to six cycles, but does not state the cycle length. Clinical expert advice to the ERG is that patients receive chemotherapy in three-week cycles. Patients undergo two cycles and then have a scan to check that the treatment is working. If it is, they then receive another two cycles of treatment. A full course of treatment takes 12 to 18 weeks (i.e. patients receive four to six cycles in 12 to 18 weeks). In line with the CS, the clinical expert advised that patients may receive between four to six cycles. Therefore, as acknowledged on CS p. 30, the introduction of necitumumab, which will require up to six cycles of treatment in the induction phase (mean 4.6 cycles in the SQUIRE trial, CS Table 6 p. 29) and then maintenance treatment (mean 6 cycles in the SQUIRE trial,[8] CS Table 6 p. 29) (please see section 2.3 below for a description of the induction and maintenance treatment phases), will be associated with additional costs to the NHS, including up to an extra two cycles of treatment in the induction phase.

The necitumumab SmPC states that it is indicated for patients who have epidermal growth factor (EGFR) expressing squamous NSCLC. The company has not, however, discussed in the CS current clinical practice regarding testing patients for EGFR expression nor how the introduction of necitumumab might impact on service provision regarding this. The cost of testing for EGFR expression was not included in the company's cost-effectiveness analyses. The ERG's clinical expert advised that patients are not currently routinely tested for EGFR expression. They are only currently tested for mutations in the EGFR gene. Patients would need to be tested for EGFR expression prior to administration of necitumumab and this would be a new test. The ERG's clinical expert commented that it is unclear how the costs of this would be funded.

As part of the submitted economic model for this appraisal of necitumumab, the company has included the costs of second-line treatment (with either docetaxel or erlotinib). In the overview of current service provision in the CS, the company has stated that patients with NSCLC receive second-line treatment with either docetaxel or erlotinib, as recommended in NICE CG 121[3] and Technology Assessment (TA) 162,[9] respectively. The ERG concurs with the company that docetaxel is recommended for second-line treatment in CG 121.[3] The CS states that TA 162[9] recommends erlotinib for all patients with NSCLC. The ERG notes, however that TA 162[9] has been updated and replaced by TA 374.[10] TA 374 recommends erlotinib as a second-line treatment only in patients who test positive for the EGFR-tyrosine kinase (TK) mutation and who have had non-targeted chemotherapy due to a delay in confirmation of mutation status, or where a patient's EGFR-TK status is unknown, under particular circumstances. The clinical expert consulted by the ERG stated that in clinical practice patients tend to receive second-line treatment with docetaxel given in six doses over three weeks or nivolumab in the context of a clinical trial given indefinitely [nivolumab is licensed but not funded; it is currently undergoing two separate NICE technology appraisals for the treatment of patients with metastatic squamous NSCLC (ID811) and locally advanced or metastatic non-squamous NSCLC (ID900) NSCLC]. The ERG additionally notes that ramucirumab is currently being appraised by NICE as a second-line treatment for patients with metastatic NSCLC (ID838). The ERG's clinical expert estimated that around 40% of patients who receive first-line treatment receive second-line treatment.

2.3 Critique of the company's definition of the decision problem

Population

The population specified in the company's decision problem is people with "locally advanced/metastatic (stage IV)" (CS Table 1, p. 15) squamous NSCLC who have not received prior chemotherapy for this condition. The patient population matches the final scope issued by NICE and is in line with the SmPC indication for necitumumab, in that it is indicated for patients with locally advanced or metastatic disease who have not received prior chemotherapy. Where the population specified by the company does not fully match the SmPC, is that the SmPC more specifically states that necitumumab is indicated for patients who have EGFR expressing squamous NSCLC (as discussed above). The company acknowledges on CS p. 15 that the

population specified in the decision problem is not fully consistent with the SmPC indication, but does not explain why. The ERG therefore believes that the population specified in the decision problem is not appropriate for the potential use of necitumumab in the NHS and that the most appropriate population would be people with locally advanced or metastatic EGFR expressing squamous NSCLC. The company provided clinical effectiveness and cost-effectiveness results for subgroups of patients with EGFR expressing tumours in response to clarification questions from NICE and the ERG (please see discussion under Subgroups below) to reflect the SmPC indication (clarification response A1).

The ERG notes that the Food and Drug Administration (FDA) has approved necitumumab in combination with GCis (GCis + N) for the first-line treatment of metastatic squamous NSCLC, but the FDA has not limited the indication to patients with EGFR expressing squamous NSCLC nor specified locally advanced NSCLC.[11]

As mentioned above, the patient population specified by the company matches the SmPC indication for necitumumab in terms of patients' prior treatment (patients who have not received prior chemotherapy). The final scope specifies that the population should be those "untreated" for advanced, metastatic disease. While the company has more specifically stated that the population is those who have "not received prior chemotherapy", the ERG's clinical expert advised that clinically this is the same as "untreated advanced" disease. The ERG's expert advised that some people may have had resected or irradiated cancer before chemotherapy, but this is essentially the same as presenting with untreated metastatic disease.

Intervention

In accordance with the final scope, the intervention described in the decision problem is GCis + N (necitumumab's brand name is Portrazza). Necitumumab is a monoclonal antibody that works by targeting EGFR-1. In December 2015, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for necitumumab, and this has now been granted. As outlined in the CS, the SmPC recommends that necitumumab is given to patients at a flat dose of 800 mg via intravenous infusion over 60 minutes on days one and eight of each 3-week chemotherapy cycle, for up to six cycles. The company states that a gemcitabine dose of 1250 mg/m^2 is to be administered through intravenous infusion on days one and eight of each cycle, with a cisplatin dose of 75mg/m^2 administered on day one of each cycle. The ERG notes that these stated doses of gemcitabine and cisplatin match those

specified in the gemcitabine SmPC[5] for combination therapy for NSCLC. The ERG further notes the gemcitabine SmPC[5] states that gemcitabine should be given as a 30-minute intravenous infusion. Cisplatin is also given by intravenous infusion.[12] The CS states that following induction combination therapy, patients who have not experienced disease progression receive necitumumab monotherapy at a flat dose of 800 mg on days one and eight of each three-week cycle until the patients experience disease progression or unacceptable toxicity. The ERG notes that this matches the SmPC. Overall, the intervention described in the decision problem is appropriate for the NHS.

Comparators

The CS decision problem includes all eight platinum doublets that are currently used in the NHS and which were specified in the final scope (i.e. carboplatin or cisplatin in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine). In the economic analysis, however, the company has included (as outlined on CS p. 162):

- GCis,
- GCarbo,
- Carbopatin in combination with paclitaxel (PCarbo), and
- Cisplatin in combination with docetaxel (DCis).

The company did not identify any relevant clinical evidence to be able to include carboplatin in combination with docetaxel (DCarbo) or carboplatin in combination with vinorelbine (VCarbo). The evidence identified for assessing the comparative efficacy of cisplatin in combination with vinorelbine (VCis) was unsuitable for use in the model and so VCis is also not included in the model. The ERG considers the company's justification for not including these comparators is reasonable. Although data were available for cisplatin in combination with paclitaxel (PCis), the company excluded this from their economic model. In response to a clarification question, the company stated that this was due to its infrequency of use in UK practice (assumed that less than [redacted] of patients receive PCis, based on market share data). The clinical expert consulted by the ERG confirmed that PCis is not widely used in the UK and that, in practice, its use is limited to clinical trials. Nevertheless, PCis was included in the scope, so the ERG believes it should have been included in the company model. Table 1 summarises the comparators specified in the scope and those included in the economic model.

Overall, the comparators specified in the decision problem are appropriate for the NHS.

Table 1 The eight comparators specified in NICE's final scope and those included in the economic model

Scope specified comparator	Comparator included in the company's economic model (✓indicates 'yes')
GCis	✓
GCarbo	✓
DCis	✓
DCarbo	
PCis	
PCarbo	✓
VCis	
VCarbo	

GCis, cisplatin in combination with gemcitabine; GCarbo, carboplatin in combination with gemcitabine; DCis, cisplatin in combination with docetaxel; DCarbo, carboplatin in combination with docetaxel; PCis, cisplatin in combination with paclitaxel; PCarbo, carboplatin in combination with paclitaxel; VCis, cisplatin in combination with vinorelbine; VCarbo, carboplatin in combination with vinorelbine.

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem:

- Overall survival (OS)
- Progression free survival (PFS)
- Response rates
- Adverse events (AEs)
- Health-related quality of life (HRQoL)

These outcomes are appropriate and clinically meaningful to patients. The ERG considers that the company has included all important outcomes in the decision problem. Given that the ERG's clinical expert advised that treatment of this patient population is palliative with a focus on patients' quality of life, the ERG suggests that HRQoL is a particularly clinically important outcome. Clinical expert advice to the ERG is that the aim of chemotherapy is to improve or maintain quality of life.

Economic analysis

The economic analysis specified in the decision problem largely matches the final scope and is appropriate for the NHS. The company have conducted a cost-utility analysis with a lifetime horizon. This is an appropriate time horizon when considering differences in costs and outcomes between treatments for patients with squamous NSCLC. Utility estimates for the main health states in the model are based on EQ-5D data from patients, valued by a representative sample of the UK population (UK tariff). However, disutility estimates for adverse events are derived from patients by direct valuation (standard gamble). Costs are considered from the NHS

and Personal Social Services perspective. Discount rates of 3.5% per year are applied to health outcomes (QALYs) and costs.

[redacted].

Other relevant factors

Subgroups

The final scope does not specify any patient subgroups for examination in this appraisal and the company has not specified any in their decision problem in the CS. The company has, however, argued that a post-hoc subgroup of patients from Western Europe in the SQUIRE trial is a more generalisable population to patients in England than the ITT population (all randomised patients). The company provided trial results for both the ITT population and the Western Europe subgroup in the CS but based efficacy and cost-effectiveness conclusions on the results of the Western European subgroup analyses. The Western European subgroup included patients from Germany, France, Spain, Greece, Italy, UK, Portugal, Austria and Belgium.

In the CS, the company state in their decision problem (CS Table 1 p. 15) that additional analysis would be provided to NICE at a later stage to reflect the SmPC population. In response to NICE and the ERG's clarification request about this (clarification response A1), the company provided clinical effectiveness results for two further post-hoc subgroups:

1. Patients with EGFR expressing tumours from the total SQUIRE trial population
2. Patients with EGFR expressing tumours from the Western Europe subgroup of the SQUIRE trial

The company supplied additional cost-effectiveness analyses and a revised economic model, which used data from the EGFR expressing tumours Western European subgroup as the base case. The four groups of patients included in the company's submission and clarification response are summarised in Table 2.

Table 2 Summary of populations and subgroups

Population	Source	Used in company's analyses	Used in ERG's analyses
ITT population All randomised patients in SQUIRE trial	Original CS	Clinical effectiveness only	Clinical effectiveness only
Western European subgroup	Original CS	Clinical effectiveness Base case in original CS	Clinical effectiveness subgroup analysis only
EGFR expressing subgroup of ITT population (the licensed indication)	Clarification response	Clinical effectiveness only	Clinical effectiveness **ERG's preferred base case**
EGFR expressing Western European subgroup	Clarification response	Clinical effectiveness **Base case in updated analysis**	ERG's scenario analysis

CS, company submission.; EGFR, epidermal growth factor receptor; ERG, evidence review group; ITT, Intention-to-treat.

The company does not provide a clear rationale for why patients from countries in Western Europe are considered to be the most generalisable to patients in England. The ERG notes that the SQUIRE trial included patients from other countries, such as Australia, the US and Canada, who might also be considered similar to the patient population in England, and who could have been included in the relevant subgroup, but the company has not discussed why these countries have not been included. The company has also not included Eastern European countries (such as Hungary and Poland) in the subgroup considered generalisable to England. The company states in the CS that patients in Hungary and Poland performed better in the GCis than the GCis + N arm in the trial, and that there were no differences between arms in patient demographics, characteristics, prognostic factors or treatment received that explained this difference (CS p. 21 to p. 22). Instead the company suggests this finding may be due to "unobserved treatment effect modifiers" (CS p. 22), including the disease burden of squamous NSCLC and environmental causes of the disease, including heavy smoking. The ERG considers this explanation unconvincing, since these factors would likely equally affect both arms in the trial due to patient randomisation and no rationale is given as to why these factors would result in worse outcomes with necitumumab.

NICE and the ERG sought further clarification from the company on the rationale for the choice of countries included in the Western Europe subgroup, and asked why other countries such as Australia and Canada had not been included. In response, the company stated that all countries in Europe that were not included in the pre-specified Eastern Europe subgroup were included in

the post-hoc Western Europe subgroup, and that Australia and Canada were not included as they are not part of Europe. The company also stated that it is believed that the Western Europe subgroup is more generalisable to clinical practice in England than the populations across Australia, Canada and Europe combined (clarification response A6), however no additional information was provided.

Clinical expert advice to the ERG is that data from patients from all geographical regions would be representative of patients in England, with perhaps the exception of Asia (8% of the ITT population). Patients in Asia have a higher frequency of EGFR mutations, which would make an EGFR receptor drug more effective. The ERG also notes that the company stated that there was not a statistically significant treatment interaction between the post-hoc Western Europe subgroup and other patients in the SQUIRE trial (CS p. 229). Overall, the ERG considers that the company's use of the Western Europe subgroup in the base case is not sufficiently justified. The ERG considers the subgroup of patients with EGFR expressing tumours from the ITT population is the most relevant patient group to the marketing authorisation and to patients in England.

On CS pp. 68 to 69, the company additionally lists a number of planned subgroup analyses by geographical region and countries with an enrolment >40 patients, but has not provided the results of these in the CS. These were requested by NICE and the ERG, and while subgroup analyses by region were provided in clarification response A6c Appendix 6, the regions analysed differed to those pre-specified.

The company also provides details of other planned subgroup analyses on CS p. 69, including:

- age (<70 versus ≥70 years; and <65 versus ≥65 years);
- gender (women versus men);
- race (White versus non-White);
- ECOG PS (0 versus 1 versus 2 and 0-1 versus 2); and,
- smoking history [never smoker (non-smoker and light ex-smoker combined) versus smoker].

CS Table 11 p. 51 also states that patients who displayed a rash within the first cycle was a pre-specified subgroup, however results are not presented in the CS.

Results of the subgroup analyses by age, gender, race, ECOG performance status and smoking history are provided in CS Figure 9 (p. 70) for the ITT population only. However, the presentation of the results for the age and ECOG performance status analyses is not entirely in line with the pre-specified comparison categories. Clinical expert advice to the ERG is that EGFR receptor drugs are more efficacious in women, people of an Asian ethnicity and smokers. The ERG's expert also advised that a patient's performance status can impact treatment efficacy. The ERG therefore considers that while these subgroup analyses are appropriate, the deviation in how the results are presented from those pre-specified means the results may be at risk of selective reporting bias. The results of the subgroup analyses by age and performance status are not, however, used in the company's economic model.

The CS also presents pre-specified subgroup analyses of OS and PFS by EGFR expression status, classified by immunohistochemistry score (H-score) on a scale of 0-300[1] (H-score of <200 and H-score ≥200) for the ITT population (CS pp. 71 to 73). The CS does not provide a rationale for using an H-score of 200 as the cut-off, although the trial publication[1] refers to a previously reported study, the FLEX trial of cetuximab in NSCLC.[13] An FDA Briefing Document[14] about necitumumab identified by the ERG notes that the cutpoint value of 200 was chosen based on a post-hoc subgroup analysis of the FLEX study, in which patients with NSCLC who had an EGFR H-score >200 experienced greater improvement in OS with cetuximab compared to patients with an H-score <200.

The FDA Briefing Document states that additional analyses were undertaken to evaluate all patients with EGFR expressing squamous NSCLC together (H-score > 0) and those with no detectable EGFR expression (H-score=0, where H-score=0 is defined as 100% of cells with undetectable EGFR staining).[14] Results of these analyses are not reported in the CS but were provided in the company's clarification response. The ERG has reproduced the results from the FDA briefing in section 3.3, along with the results provided by the company in the clarification response. This is because the results the company provided for the EGFR expressing subgroup differ slightly to those reported in the FDA document. The company only provided a brief comment on the results for the subgroup of patients with no detectable EGFR expression without provding supporting data, although these data are available in the FDA document.

The ERG and the clinical expert consulted by the ERG did not identify any other key subgroups that should have been considered.

Equality issues

The final scope does not identify any equity or equality issues related to the implementation of GCis + N in the NHS and the company has not specified any in its decision problem. The ERG and the ERG's clinical expert have also not identified any equity or equality issues.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The ERG considers that the searches for the main systematic review of direct evidence, the systematic review informing the network meta-analysis (NMA), and the reviews of cost-effectiveness studies and data were appropriate. There was one minor typographical error and slight inconsistencies in approach across the searches, but the ERG considers that these would not impact the results. As the main systematic review and the cost-effectiveness searches were out-of-date (conducted in August 2015 and April/May 2014, respectively), the ERG ran update searches for these relating to necitumumab on the following databases: Embase, Medline and Medline in Process and other Indexed Citations via the Ovid Platform. The search for the review to inform the NMA was also out-of-date, having been conducted in January 2015, but the ERG did not elect to update these searches. No new trials or cost-effectiveness publications were identified. The ERG's searches (conducted from January 2015 to February 2016) for the main systematic review, however, found four conference abstracts reporting analyses appertaining to the SQUIRE trial, which were not identified in the company's searches. These were screened by two ERG reviewers who considered that two of the abstracts[15 16] were relevant to the appraisal and met the company's main systematic review inclusion criteria (please see section 3.1.3 of this report for details). Clinicaltrials.gov is documented in the CS as searched for recently completed and not yet published studies. The ERG elected to widen the ongoing study searches to incorporate UK Clinical Research Network (UKCRN), World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), ISRCTN, and clinicaltrials.gov. The ERG search results were screened by one reviewer. The results yielded two relevant trials of GCis + N (please see section 3.1.3 for details).

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The company clearly states the inclusion and exclusion criteria for both the main systematic review of studies evaluating GCis + N (in CS Table 9, p. 39) and the systematic review underpinning the NMA (in CS Table 21, p. 85). The ERG's critique of the eligibility criteria used in the review for the NMA and details about the studies identified for inclusion are provided in section 3.1.7.

The main systematic review of direct evidence included trials of first-line treatment with GCis + N for patients with locally advanced or metastatic squamous NSCLC who were naïve to treatment, compared with a platinum doublet (i.e. GCarbo, GCis, DCarbo, DCis, PCarbo, PCis, VCarbo or VCis). Trials had to assess OS, PFS, response rates, HRQoL or safety to be included. Inclusion was limited to Phase III and IV randomised controlled trials (RCTs) and English language references. The company did not specify treatment setting as an inclusion criterion nor place any limits on inclusion relating to the quality of the RCTs, which is appropriate. The inclusion criteria reflect the decision problem, the licensed indication for necitumumab (although drug doses are not specified in the criteria), current service provision and the potential use of GCis + N in the NHS. Overall, the ERG considers the inclusion criteria reasonable, but suggests that the company could have considered including phase II RCTs for efficacy and safety data. The company, however, did not restrict study eligibility for inclusion in the systematic review that informed the NMA by RCT phase and so any relevant phase II RCTs are likely to have been identified by the review for NMA (the review identified none; please see section 3.1.7).

The CS includes a flow diagram showing the number of studies included and excluded at each stage of the main systematic review (CS Figure 2, p. 41). The flowchart for the main systematic review does not provide reasons for the exclusion of six publications at the full text screening stage of the main review; however these were provided in clarification response A2 and the exclusions appear justified.

Overall, the ERG considers that the eligibility criteria used in the main systematic review were appropriate and matched the company's decision problem.

3.1.3 Identified studies

The main systematic review identified one relevant Phase III RCT of GCis + N – the SQUIRE trial[1] (shown in Table 3) – reported in one publication. In the CS, the company has also referred to supplementary information, in addition to the primary publication. The company did not identify any non-RCTs, as they restricted inclusion to RCTs only. Details of the studies identified in the systematic review underpinning the NMA are provided in section 3.1.7.

Table 3 Details of the included SQUIRE RCT[1]

Design, patient population and legth of follow-up	Intervention	Comparator
Design: Phase III, open-label, multicentre RCT carried out in 26 countries, including the UK [redacted] *Patient population:* Adults with stage IV squamous NSCLC, who had not received previous chemotherapy for advanced NSCLC. ECOG PS 0-2. N=1093 (545 GCis + N; 548 GCis). *Median length of follow-up:* GCis + N arm: 25.2 months; GCis arm: 24.8 months.	A maximum of six 3-week cycles of gemcitabine 1250 mg/m^2 (administered intravenously over 30 min on days 1 and 8 of each cycle) and cisplatin 75 mg/m^2 (administered intravenously over 120 min on day 1), plus necitumumab 800 mg (administered intravenously on days 1 and 8 over a minimum of 50 min). At the end of chemotherapy, patients who had not experienced disease progression received necitumumab alone as a maintenance therapy until disease progression, AEs leading to discontinuation, or consent withdrawal.	A maximum of six 3-week cycles of gemcitabine 1250 mg/m^2 (administered intravenously over 30 min on days 1 and 8 of each cycle) and cisplatin 75 mg/m^2 (administered intravenously over 120 min on day 1).

ECOG, Eastern Cooperative Oncology Group; GCis, gemcitabine plus cisplatin; GCis + N, Necitumumab with gemcitabine plus cisplatin; NSCLC, non-small-cell lung cancer; RCT, randomised controlled trial; PS, performance status.

The company supplied the ERG with electronic copies of the SQUIRE trial primary publication[1] and the clinical study report (CSR). The trial was sponsored by Eli Lilly and Company.

The ERG agrees that the SQUIRE trial meets the systematic review inclusion criteria and is relevant to the final scope and the company's decision problem. The trial only included patients with metastatic (stage IV) squamous NSCLC, so no data on the efficacy or safety of GCis + N were available in the company's systematic review for people with locally advanced (stage III) disease. The population is therefore narrower than that outlined in the scope and included in the

SmPC indication (GCis + N is indicated for patients with stage III and IV disease). The ERG notes that the trial used the drug doses and regimens outlined in the necitumumab draft SmPC and the gemcitabine SmPC,[5] except that necitumumab was delivered for a minimum of 50 minutes, while the draft SmPC states it should be delivered for a minimum of one hour.

The trial patient population, however, is wider than the licensed indication, as the SQUIRE trial was not limited to patients with EGFR expressing NSCLC, which is the licensed indication. The CS provides subgroup analyses of OS and PFS according to whether patients had high or low expressing EGFR tumours (defined as H-scores of ≥200 and <200, respectively), but does not provide a combined subgroup analysis of all patients with EGFR expressing NSCLC compared with patients without EGFR expressing NSCLC. The ERG identified results from this analysis in a FDA Briefing Document[14] and has presented these findings in section 3.3. As noted above, the company provided subgroup analysis results for patients with EGFR expressing tumours in the SQUIRE trial, in its response to NICE and the ERG's clarification questions (clarification response A1 Appendix 1). The company also provided a comment in clarification response A7 that a subgroup analysis of patients without EGFR expression (H-score = 0) was carried out but did not present data.

The CS provides an overview of the SQUIRE trial design and interventions used (CS p. 42 and p. 45 to 46). The patient inclusion and exclusion criteria are provided on CS p. 42 to 43. In clarification response A8 the company stated that the SQUIRE exclusion critieria incorporated prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor; or previous chemotherapy for advanced NSCLC (patients who had received adjuvant chemotherapy were eligible if the last administration of the prior adjuvant regimen occurred at least one year prior to randomisation). Clinical expert advice to the ERG is that it was reasonable for the SQUIRE trial to include patients who had received adjuvant chemotherapy. Baseline characteristics for both the ITT and Western European populations are reported in the CS (Table 13 on CS p. 58 and p. 59). Race characteristics are missing for the Western European population and were requested by NICE and the ERG. These are provided in clarification response A6b Appendix 5, but are for the EGFR expressing Western European subgroup only and not the whole Western European subgroup from the ITT population. The data provided showed that race characteristics were balanced across arms.

The CS provides a CONSORT flowchart (Figure 3, p. 55) showing the number of patients randomised, treated and the number who completed each stage of the trial or discontinued. The number of patients eligible for the trial is not reported. [redacted]There appears to have been no participant cross-over (treatment switching) in the trial. The CS details the primary and secondary outcomes assessed (CS p. 52 and p. 53, including the definitions of each outcome and the HRQoL measures used. The sample size and power calculation (for the primary outcome of OS) are provided on CS p. 53, subgroup analyses are detailed on CS p. 49 to p.50 and the ITT population is defined on CS p. 18. The CS details how the statistical analyses of the primary and secondary outcomes were performed on pp. 52 to 53, except how HRQoL data were analysed.

Baseline characteristics

The CS states that baseline patient characteristics were similar across treatment arms within the SQUIRE trial in the ITT population (CS p. 57), and the ERG agrees with this conclusion. The ERG also agrees with the company that there are differences in age and ECOG performance status between the trial arms in the Western Europe population. As the CS notes, the proportion of patients aged ≥ 70 years was higher in the GCis + N arm than in the GCis arm (23% versus 14%). The GCis arm had a higher proportion of patients with an ECOG performance status of 2 than the GCis + N arm (7% versus 2%). Clinical expert advice to the ERG is that performance status can affect treatment outcomes and that the fittest patients are best suited to treatment with GCis. The ERG suggests that the performance status differences between trial arms may have marginally favoured the GCis + N arm in the post-hoc Western European subgroup analyses. Clinical expert advice to the ERG is that prognosis is determined by disease stage and ECOG performance status more than by age.

The CS does not report on the proportion of patients who had EGFR expressing tumours at baseline, but provided these data in clarification response A7. The company clarified that of the patients in the SQUIRE trial with tumour samples available (90%), 95% had tumours expressing EGFR protein. The company also provided patients' baseline characteristics for the main EGFR expressing subgroup and the EGFR expressing Western Europe subgroup in their clarification response A1 Appendix 1. The ERG notes that baseline characteristics were similar between treatment arms in the main EGFR expressing subgroup. In the EGFR expressing Western Europe subgroup (similarly to the overall Western Europe subgroup) proportionally fewer patients in the GCis + N arm were aged ≥18 - <65 years [redacted] than in the GCis arm

[redacted] and proportionally fewer patients in the GCis + N arm had an ECOG performance status of two [redacted] than in the GCis arm [redacted].

The CS states that the patient baseline characteristics in the SQUIRE trial were representative of patients with advanced, squamous NSCLC, and the ERG agrees. The clinical expert consulted by the ERG stated that the baseline characteristics for both the ITT and Western Europe populations are broadly representative of patients seen in practice in England. The SQUIRE trial included fewer patients with an ECOG performance status of 2 than 0 or 1, and the ERG's clinical expert advised that this reflects the patient population treated in practice.

ERG's appraisal of whether all relevant studies were included in the review

The CS appears to have included all relevant Phase III RCTs. The ERG's searches did not identify any other relevant studies, but did identify four conference abstracts[15-18] reporting results from the SQUIRE trial that were not included in the company's systematic review. All these abstracts were published between November 2014 and May 2015. The company did not appear to find these publications during their searches (which were undertaken in August 2015), as they are not listed among the 34 excluded references listed by the company in their clarifications response. Of the four abstracts identified by the ERG, the ERG considered that two met the company's inclusion criteria for the systematic review:

- One[15] reported on the planned ECOG performance status subgroup analyses, in line with all the pre-planned categories. The ERG has summarised the results from these analyses in section 3.3 of our report.
- One[16] reported on the safety and efficacy of treatment with necitumumab alone during the maintenance phase following treatment with GCis + N; this reported the proportions of patients receiving maintenance treatment, the median OS, and PFS, and two-year survival (these outcomes were not reported in the CS), and adverse events of special interest [reported in the CS, apart from the proportion of patients experiencing venous thrombolic events (2.5%)].

Ongoing studies

The CS lists six ongoing Phase I and II trials of necitumumab for treating squamous and non-squamous NSCLC (CS pp. 136 to 137). The CS provides the trial identifiers and details about the patient populations. All but one of the trials are single arm studies of the safety and efficacy of necitumumab used in combination with other drugs, including standard chemotherapy with

PCarbo and with experimental agents. The trials include patients with either stage IV NSCLC or squamous NSCLC, or, in one trial, patients with EGFR mutation-positive stage IV or recurrent NSCLC who have progressed after previous treatment with an EGFR-TK inhibitor.

The ERG searched for ongoing trials and identified one additional relevant RCT (NCT01763788; not listed among the ongoing studies identified by the company on CS p. 136-137). This is an open-label RCT of GCis + N versus GCis in people with Stage IV squamous NSCLC. The study has two phases: Phase 1b is a dose escalation study (gemcitabine 1000 or 1250 mg/m^2) to determine the recommended dose for the subsequent Phase 2 portion of the study. Phase 2 evaluates efficacy. Estimated enrolment is 189 and study completion date is June 2017. In addition, one single arm, open label, phase II study of GCis + N in people with Stage IV squamous NSCLC was identified (NCT01788566) (also not listed on CS p. 136-137), with a study completion date of December 2015.

Summary

The CS appears to include all relevant RCTs of GCis + N for treating squamous NSCLC; there appears to be only one relevant RCT available (the SQUIRE trial). As the ERG identified two conference abstracts from the ERG's searches that met the company's inclusion criteria for the main systematic review that were not identified in the CS or listed among the studies excluded in the company's clarification response, it is uncertain if the company's searches identified all relevant publications relating to the SQUIRE trial.

3.1.4 Description and critique of the approach to validity assessment

The CS includes a quality assessment of the SQUIRE trial (CS Table 12 p. 56), but not of the trials included in the NMA. In response to a request by NICE and the ERG, the company provided quality assessment for trials included in the NMA (clarification response A21 Appendix 10), and the ERG discusses this further in section 3.1.7.

The company's quality assessment of the SQUIRE trial is presented in tabular format containing detailed factual information, although judgement or discussion on the criteria by the company is limited. The company used the criteria suggested by NICE for quality assessment of the SQUIRE trial, and the ERG agrees with most of the company's assessment (please see Table 4). However, the ERG notes that whilst the ITT population was similar in both trial arms at the

outset of the study in terms of prognostic factors, there were differences in the post hoc Western Europe subgroup (used in the company's base-case analysis) with respect to age group (≥18 to <65 years GCis+N [redacted], GCis [redacted]; ≥70 years, GCis+N [redacted], GCis [redacted]) and ECOG performance status (ECOG performance status 1 GCis+N [redacted], GCis [redacted]; ECOG performance status 2 GCis+N [redacted], GCis [redacted]).

SQUIRE was an open label study, with outcome assessors at Eli Lilly blinded to treatment assignment, except for serious adverse event (SAE) data. In response to a question from NICE and the ERG, the company clarified that the assessment of progressive disease or toxicity to define whether maintenance therapy was given was completed by investigators who were not blinded to treatment allocation (clarification response A9). The trial is therefore at risk of performance bias and detection bias on these measures. The ERG notes, however, that the trial paper states that safety data were assessed by an independent data monitoring committee. [8] The company confirmed that an independent review of the assessment of PFS, ORR and time to treatment failure (TTF) was not conducted (clarification response A10), meaning that the results for these outcomes are also at risk of detection bias. Limited HRQoL data are presented in the CS. The ERG also notes that a number of the analyses and corresponding results of the Lung Cancer Symptom Scale (LCSS) detailed in the CSR are not reported in the CS. Furthermore, subgroup analyses by age, ECOG performance status and region were not presented in the CS and the company's clarification response in accordance with the pre-planned analyses. The ERG therefore considers there to be a risk of bias due to selective outcome reporting in the CS.

Table 4 Company and ERG assessment of trial quality

NICE QA Criteria for RCT	CS response (selected information from CS Table 12 p. 56)	ERG response
1. Was the method used to generate random allocations adequate?	Description given but judgement not provided	Yes
2. Was the allocation adequately concealed?	Description given but judgement not provided	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Yes (ITT population)[a]
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Care providers and participants not blinded. Outcome assessors at Eli Lilly blinded to treatment assignment with the	Care providers and participants: no Outcome assessors: no[c]

	exception of SAE data.	
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes[b]
7. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Primary analyses include all randomised patients following the ITT principle, regardless of compliance with the treatment regimen and protocol.	Yes (OS, PFS, ORR and TTF analyses, but not the HRQoL analyses),[d] yes

[a] For the Western Europe subgroup, there were imbalances in age group (≥18 to <65 years GCis+N [redacted], GCis [redacted]; ≥70 years, GCis+N [redacted], GCis [redacted]) and ECOG performance status (ECOG PS 1 GCis+N [redacted], GCis [redacted]; ECOG performance status 2 GCis+N [redacted], GCis [redacted]).
[b] Limited HRQoL data were presented in the CS. The ERG notes the CSR also reports [redacted]. The ERG also notes that subgroup analyses by patients' age and ECOG performance status presented in the CS and subgroup analyses by region presented in Appendix 6 of the company's response to clarifications questions from NICE and the ERG are not presented in line with the pre-specified analyses.
[c] CS p. 42 states that the company had blinded access to the clinical data provided to it during the trial (except for SAEs), but it is unclear who assessed patient outcomes. Based on information provided in the SQUIRE trial paper, [8] and the company's clarifications question response to NICE and the ERG (clarification responses A9 and A10), outcome assessors (the investigators) were not blinded to treatment allocation for assessments of any outcome (clarification response A9), although safety data were assessed by an independent data monitoring committee.[8]
[d] AE analyses were conducted in the safety population.

3.1.5 Description and critique of company's outcome selection

The NICE scoped outcomes were OS, PFS, response rates, AEs and HRQoL. The outcomes in the decision problem addressed by the company (CS p. 15) are the same as in the NICE scope. The primary outcome in the SQUIRE trial was OS, with secondary outcomes including PFS, objective response rate (ORR), time to treatment failure (TTF), safety and HRQoL. The company used the results from the analyses of the OS, PFS, AE and HRQoL (EQ-5D data) outcomes from the SQUIRE trial in the economic models submitted with the CS and the model submitted in the company's clarifications response.

OS was defined as the time from the date of randomisation to the date of death from any cause, and PFS was defined as the time from randomisation until the first radiographic documentation of objective progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.0, or death from any cause (CS Table 11, p. 50). An independent review of the assessment of PFS, ORR and TTF was not conducted (clarification response A10). For OS, patients who did not die or who were lost to follow-up were censored at the last date they were

known to be alive. For PFS, the CS states that patients were censored from the PFS analysis at the date of their last radiographic tumour assessment if they did not experience disease progression or if they were lost to follow-up. Patients were also censored at the date of their last radiographic assessment if they died or experienced disease progression after two missing assessment visits or if they began using a different cancer treatment before disease progression.

ORR was defined as the proportion of patients achieving a best overall response of confirmed partial or complete response according to RECIST Version 1.0 from the start of treatment until disease progression or recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

HRQoL was measured using the LCSS and EQ-5D-3L (visual analogue scale and health index score) prior to treatment (within 14 days of randomisation), prior to the first infusion of Cycles 1-6, and every 6 weeks (± 3 days) thereafter (i.e. concurrent with radiological evaluation after discontinuation of chemotherapy) until progressive disease. The LCSS is a self-reported disease and lung cancer specific instrument consisting of nine items including six major lung cancer symptoms and three global measures of symptom distress, activity and quality of life. Each item is assessed with a 100-mm visual analogue scale with higher ratings equating to poorer quality of life. The CS does not define a clinically meaningful difference, however in the CSR p. 63 this is defined as a ≥15 mm change from baseline.

The CS states that the instruments were completed where there was a validated language/cultural translation in a language/culture in which the patient was fluent. Other lung cancer-specific instruments are available, such as EORTC Quality of Life Questionnaire 30 item core instrument (QLQ C30) or FACT-L (Functional Assessment of Cancer Therapy – lung cancer module); however, the CS does not provide a rationale for selecting the LCSS.

The CS presents time to deterioration of LCSS and time to deterioration of ECOG performance status (CS Figure 14 p. 77), but does not provide a definition for these. In the CSR p.63 deterioration in LCSS was defined as a ≥15 mm increase from baseline in LCSS score, but assessment of deterioration of ECOG PS was not defined. Deterioration of ECOG performance status is not a NICE scoped outcome.

The ERG notes that the CSR also reports that a number of other analyses of the LCSS were undertaken, but the results of these analyses are not reported in the CS. This means there is a risk of selective outcome reporting in the data presented in the CS.

The CS also reports TTF (not a NICE scoped outcome), defined as the time from randomisation to the first observation of progressive disease, death due to any cause, early discontinuation of treatment or initiation of new anticancer therapies. As TTF is not a NICE scoped outcome, we do not consider it further in our report.

Treatment-emergent adverse events (TEAEs) were defined as: those with an onset date that occurred any time during or after the administration of the first dose of study treatment or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment); or those that occurred prior to the date of first dose and worsened while on therapy or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment). A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required inpatient hospitalisation or caused prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; required intervention to prevent permanent impairment/damage; and/or was an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardize the patient, or may require intervention to prevent one of the aforementioned serious outcomes).

Overall the ERG considers that the outcomes listed in the NICE scope are appropriately addressed by the CS.

3.1.6 Description and critique of the company's approach to trial statistics

The company confirmed in the clarification response to NICE and the ERG that data for the EGFR expressing subgroup and ITT population in SQUIRE were analysed using the same methods (clarification response A1). Below, we summarise and critique the company's approach to summarising the trial statistics in the CS for each outcome.

Overall survival

The CS reports trial results for OS (CS p. 59-61) presenting the numbers, numbers censored, the stratified log-rank p-value, the stratified HR and 95% CI. The HR for OS was estimated from a stratified Cox proportional hazards model; the stratification factors were ECOG PS (0-1 vs 2) and geographic region (North America, Europe and Australia vs South America, South Africa and India vs Eastern Asia). A Kaplan-Meier (KM) curve for the ITT population is presented in CS figure 4 and outcomes of median OS and survival rates (6-month, 1-year, 18-months, 2-year) are presented together with 95% CIs in CS Table 14.

The trial publication for SQUIRE[1] concurs with the CS that censoring for OS was based on the last date that the patient was known to be alive.

The trial publication for SQUIRE[1] it states that a Cox proportional hazards model was fitted for OS to formally test the proportional hazards assumption, with the following predictors: treatment, and an interaction term of treatment and log of event time.

We note that CS p. 53 reports the power calculation for the trial which was adequately powered to detect a statistically significant difference on OS.

Progression free survival

The CS reports trial results for PFS (CS pp. 63 to 65), presenting the number of patients in the analysis, the number censored, the stratified log-rank p-value, the stratified hazard ration (HR) and 95% confidence intervals (CIs). The HR for PFS was estimated from a stratified Cox proportional hazards model; the stratification factors were the same as for OS. A KM curve for the ITT population is presented in CS Figure 6 (p. 64) and outcomes of median PFS and 3-month and 6-month PFS are presented with 95% CIs in CS Table 15 (p. 79).

Objective response rate

For ORR (CS pp. 65 to 66) the CS reports trial results for the ITT population as numbers and proportions, 95% CIs (from the Wilson test) as appropriate and p-values based on the Cochran-Mantel-Haenszel test adjusted for the stratification factors. The treatment effect for the ITT population is not provided in the CS despite the CS stating on page 53 that the stratified OR (Group B over Group A) and the estimated difference (A minus B) in ORR are presented along with the corresponding 95% CIs.

Analysis population for OS, PFS and ORR

The ITT population was used for OS, PFS, and ORR and included all randomly assigned patients. The CS states on page 54 that all analyses are based on the observed data. On page 52 of the CS it states that additional analyses were completed for PFS on a per protocol population, however, the outcomes from these analyses are not reported. For PFS analyses, page 52 of the CS states that additional analyses using unstratified log-rank tests were performed; however, the results of these are also not presented in the CS. In addition, the CS states (pp. 52 to 53) that sensitivity analyses for PFS, using alternative censoring rules, were performed according to rules specified in the statistical analysis plan. No further details or results from these sensitivity analyses are presented.

Health-related quality of life

HRQoL outcomes are presented as HRs and 95% CIs for time to deterioration (undefined – see Section 3.1.5) for the LCSS scale items and composite scores, and as descriptive statistics also for the LCSS scales and for the EQ-5D-3L. These reported analyses reflect those in the CSR. It is unclear in the CS what the pre-specified analysis plan for HRQoL was and therefore whether what is reported is in line with the analysis plan. In response to a question from NICE and the ERG, the company clarified that no formal statistical test of difference between arms was planned for EQ-5D (clarification response A13). Summary statistics, including change from baseline, for the index score (using UK weights) and the VAS for each assessment visit in the chemotherapy phase (up to cycle 6) by treatment arm were planned. These are not presented in the CS, but the company supplied the results in Appendix 7 of the clarifications response. The CS described the analysis as being undertaken on all patients with a baseline value and at least one post-baseline value. Patients without baseline and/or post-baseline assessments were censored at the randomisation date (clarification response A12). The CSR also states, that HRs for time to deterioration in LCSS (the outcome presented in the CS, see Section 3.1.5) were estimated using Cox proportional hazards. For EQ-5D, the CSR reports only that summary statistics were used.

Subgroups

The CS states that the SQUIRE trial had pre-planned exploratory subgroup analyses for OS and PFS (which is consistent the with trial publication). These included analyses by geographic region (five subgroup comparisons): Korea and Taiwan combined vs. all others; Eastern Asia

vs. all others; Eastern Europe vs. Eastern Asia vs. all others; Eastern Europe vs. all others; Each non-Eastern country with >40 patients randomized vs. Eastern Asia vs. all others; Each country with >40 patients randomized vs. all others. Subgroup analyses were also conducted by age, gender, race, ECOG performance status, smoking history and EGFR expression (by H-score values <200 or ≥200, see Section 3.1.5 for description of H-score). Each analysis was completed using the same methodology as for the primary analyses except that tests were unstratified. Results for these subgroups (other than geographical region) are presented in a forest plot (CS figure 9, p. 70) which concurs with the trial publication, and for the EGFR expression groups in various Kaplan-Meier plots (CS pp 71 - 73) which concurs with the CSR (see Section 2.3 for further discussion of these subgroups). As discussed in section 2.3 above, the subgroup analyses by age and ECOG performance status are not fully presented in line with the pre-specified categories. That is, ECOG performance status results are presented for 0, 1 and 2 only and not for a combined 0-1 category (which was also planned). The ERG identified a conference abstract reporting the pre-planned subgroup analyses during its searches[15] – please see section 3.1.3 of this report for details and section 3.3 for a summary of the results. The age results are not presented for patients aged <70 versus ≥70 years and <65 versus ≥65 years (as planned), but are instead provided for subgroups of patients aged <65 years, ≥65 to <70 years, and ≥70 years. Results from the age and ECOG performance status subgroups are not, however, used in the economic model.

Results of the pre-planned subgroup analyses by geographic region are not presented in the CS and were requested by NICE and the ERG. Clarification response A6c Appendix 6 presents subgroup analyses by geographic region but not in the groupings stated on CS pp. 68 to 69.

Post hoc subgroup analyses were completed for patients in countries classified by the CS as being in Western Europe (includes participants from Austria, Belgium, Germany, France, Greece, Italy, Portugal, Spain and UK, see Section 2.3 'Subgroups' for further details). Results are presented from analyses using the same approaches as the ITT analyses described above. Results are presented in the CS following the presentation of each of the ITT analyses for the outcomes of OS, PFS, ORR and TTF (CS pp. 61 to 62 for OS; pp. 64 to 65 for PFS; p. 66 for OR; pp. 67 to 68 for TTF). Please see Section 2.3 for ERG's critique of this post hoc subgroup.

Clinical significance

The CS does not discuss the clinical significance of the results seen for the OS and PFS outcomes, other than commenting that the OS difference in the Western European subgroup could be considered clinically significant. The company, however, did not define what a clinically meaningful change would be. The ERG is unclear what the minimally clinically important differences are on these outcomes for patients with NSCLC. The clinical expert consulted by the ERG stated that previous trials that have found an improvement in survival of around one month have been considered practice changing, although the expert was unable to comment on precisely what would be a clinically meaningful difference. The CSR reports that a clinically meaningful difference on the scales of the LCSS is a change of ≤ 15 mm, and this was used to categorise patients as having either improved, stable or worsened status in the LCSS results presented in the CS.

Summary

The ERG considers the trial statistics to be appropriate for survival outcomes, response rates and the pre-planned subgroup analyses. The ERG has reservations about the reliability of the post hoc Western European subgroup analysis (see also Section 2.3) and believe it is unclear if the OS benefits reported in the CS are clinically meaningful for all the populations included in the CS and clarification response.

3.1.7 Description and critique of the company's approach to the evidence synthesis

SQUIRE trial

Given that only one trial (SQUIRE) was included comparing necitumumab with one of the scoped comparators (GCis), a pairwise meta-analysis was not feasible.

A narrative review of the evidence from the SQUIRE RCT is presented in the CS. Where possible, the ERG has checked key data presented in the CS against those in the publication [8] and CSR. CS Table 40 p. 125 has an error in the number of Grade 3, 4 and 5 arterial thrombotic events. The correct data from the publication is reproduced in the ERG report. Otherwise, the adverse events results in the CS are consistent with those in the trial publication. [redacted]

[redacted]

Network meta-analysis

To enable comparison of necitumumab against scoped comparators for which there is no direct evidence, the company conducted a NMA comprising four networks to capture indirect evidence:

- An analysis of OS HR data
- An analysis of OS median data
- An analysis of PFS HR data
- An analysis of PFS median data.

The systematic review conducted for the NMA appears to broadly follow conventional guidelines for systematic review (e.g. a systematic search for evidence was undertaken). However, the searches were out-of-date (conducted in January 2015). As mentioned in section 3.1.4, the CS does not include a quality assessment of the included studies. In response to a request by NICE and the ERG, the company provided a quality assessment for trials included in the NMA (clarification response A21 Appendix 10); however, this is presented in tabular format only, without a summary of the overall quality of the evidence base as requested.

Inclusion and exclusion of studies

The company clearly states the inclusion and exclusion criteria for the systematic review underpinning the NMA (CS Table 21, p. 85). To be included in the NMA, studies had to be RCTs that included patients with squamous NSCLC and that evaluated any first-line chemotherapy or concurrent radiation therapy and chemotherapy treatment in each trial arm. Study inclusion was not limited to just the scope and decision problem specified intervention (i.e. GCis + N) and comparators. To be eligible, RCTs had to report results for OS, PFS, toxicity or HRQoL. RCTs including patients with other histological subtypes of NSCLC in addition to patients with squamous NSCLC were eligible, but had to provide a separate analysis for patients with “advanced or metastatic (Stage IV)” (CS p. 85) squamous NSCLC on at least one outcome of interest. In response to a question from NICE and the ERG, the company clarified that only patients with advanced or metastatic squamous NSCLC (stages IIIB and IV) were

included in the NMA (clarification response A5). Inclusion was restricted to English language publications, published from 1995 onwards. Setting was not used as an eligibility criterion and no restrictions were placed on the quality of the RCTs for inclusion in the review.

At the final analysis stage of the NMA systematic review, after full text screening, a second set of eligibility criteria was applied and the company excluded studies of agents that are not used to treat NSCLC (n=1); those used only in non-squamous NSCLC (n=6) and those that did not contain a comparator that enabled connection to a common comparator in the NMA networks (n=5). The company additionally excluded trials of unapproved experimental agents and agents without a marketing authorisation in any country (but not necessarily limited by histology) (n=10), although those recommended by clinical treatment guidelines and/or used off-label for the first-line treatment of advanced or metastatic squamous NSCLC were included (clarification response A4a). One additional trial was excluded as it compared two dosing schedules of the same regimen.

The ERG considers that the company's wide inclusion criterion related to the intervention (evaluation of any first-line chemotherapy) is appropriate, even though this meant that studies including interventions outside the scope in at least one trial arm could be included. It is appropriate to include these studies if they contribute evidence to the network, as long as they are clinically relevant (i.e. include the same patient groups and outcomes as other studies included in the network). The ERG, though, does not agree with all the exclusions the company made on the basis of studies using experimental or unapproved agents at the second screening stage. The ERG also does not agree with some of the other post-hoc exclusions of studies. Please see 'Identified studies' sub-section below for a further discussion. Overall, however, the ERG considers that the eligibility criteria adequately reflect the decision problem, except that response rate was not specified as an outcome of interest, so evidence for this outcome was not included.

The CS includes a flow diagram showing the number of studies included and excluded at each stage of inclusion for the systematic review for the NMA (CS Figure 22, p. 86). The flow diagram does not reflect the number of publications (n = 23) subsequently excluded from the NMA (as described above), but the company has summarised reasons for these exclusions in the CS text and provided a list of the 23 excluded studies excluded in CS Appendix 5. The ERG agrees with

the exclusions of trials comparing different doses of the same regimens. The ERG, however, considers that the following exclusions were insufficiently justified:

- Lynch et al. (2012) was excluded due to not having a comparator similar enough to the other trials in the network to enable connection with the network. The ERG notes, however, that CS Table 6 in Appendix 5 indicates that PCarbo was a comparator arm, and, based on this information, it appears that the trial could have been connected to the network via this arm.
- Eight of the 10 trials excluded due to using experimental or unapproved agents potentially could have been connected to the network through the PCarbo (Heymach et al., 2008; Langer et al., 2014; Lara et al, 2011; Novello et al., 2014; Paz-Ares et al., 2013; Reck et al., 2013; and, Scagliotti et al., 2010) and GCarbo arms (Spigel et al., 2013) of these studies. As these studies were included based on the initial inclusion criteria for the NMA, they would appear to be clinically relevant [i.e. include the same patient group (patients with squamous NSCLC) and outcomes as other studies included in the network]. NICE and the ERG requested additional clarification on the reasons for excluding these studies. However, the company re-iteratated that these studies investigated agents without market authorisation for the first-line treatment of patients with advanced or metastatic squamous NSCLC, but not necessarily limited by histology, without further details (clarification response A4b).
- Four of the six trials excluded due to one of the treatment arms receiving a drug limited to the treatment of patients with non-squamous NSCLC (Sandler et al, 2010; Scagliotti et al 2008, Johnson et al, 2007, and Zhang et al, 2013). Again, as these studies were included based on the initial inclusion criteria, they would appear to include patients with squamous NSCLC (or at least a subgroup) and to have measured relevant outcomes. The ERG considers that these studies could potentially have been connected to the network through the PCarbo (Johnson et al, 2007; Sandler et al, 2010) and GCis (Scagliotti et al, 2008; Zhang et al, 2013) arms.
- One trial (Lee et al, 2009) was excluded due to one of the treatment arms using a regimen not used in patients with NSCLC. Similar to above, having been included at the initial screening stage, the ERG suggests that this trial could potentially have been connected to the network through the GCis + placebo arm.

The ERG therefore considers that the efficacy estimates derived from the NMA may be subject to greater uncertainty, as not all relevant trials appear to have been included in the network. This may particularly affect the treatment effect estimates for comparisons against PCarbo and

GCis. This may impact the cost-effectiveness results for comparisons of GCis + N with PCarbo, as the base case uses the OS and PFS results from the NMA networks.

Identified studies

The systematic review for the NMA identified 10 RCTs (reported in 12 publications) that met the eligibility criteria (stated in the CS as 11 RCTs in 13 publications, but corrected in clarification response A19). The company lists the studies and comparisons included in the NMA in CS Tables 22 (pp. 93 to 94) and 23 (p. 96). However there are a number of discrepancies between these tables. In response to a question from NICE and the ERG, the company provided clarification on the studies and data included in the NMA (clarification questions A17 to A19, clarification Appendix 8). One of the 11 studies listed as included in the NMA was actually excluded (Yoshioka et al. 2013 assessing S-1, which is a combination of three drugs: tegafur, a fourth generation pro-drug of 5-fluorouracil; gimeracil; and oteracil); the company stated it was not included in the NMA as it is not relevant to countries outside of Japan (clarification reponse A19). The ERG does not believe that exclusion of this study was appropriate, because, as discussed above, the ERG considers that it is appropriate to include studies of unapproved or experimental agents if they are clinically relevant and contain a scope-specified treatment arm that could be connected to the network. The ERG considers that Yoshioka et al 2013 could potentially have been connected to the network through its PCarbo arm. The ERG has summarised the studies included in the NMA networks of OS (n = 6) and PFS (n = 7) using HR data in Table 5 and Table 6. We have not presented thestudies included in the two networks for median OS and median PFS here, as the data were not used in the economic model.

The ERG has not checked the company's quality assessment of trials included in the NMA, but notes that all trials have been judged to have a high risk of bias on at least one domain of bias.

The ERG notes that some of the arms of the trials included in the NMAs used drug doses that are not specified in the drugs' SmPCs. Clinical expert advice to the ERG is that although some of the drug doses are low, none of the doses used would likely adversely impact efficacy.

None of the included studies, apart from the SQUIRE trial, measured AEs and HRQoL in the squamous population, so NMA networks could only be formed for the OS and PFS outcomes.

Table 5 Trials included in the OS network using HR data

Trial	Interventions
SQUIRE	GCis + N GCis
Morabito 2013	GCis Gemcitabine
Hoang 2013[a]	GCis PCis DCis PCarbo
Socinski 2012	Sb-PCarbo Nab-PCarbo
Treat 2010	PCarbo GCarbo G + P
Kubota 2008	PCarbo VGD

[a] Not explicitly stated for this study, but assumed that the company calculated HRs by digitization of survival curves. DCis, docetaxel plus cisplatin; GCarbo, gemcitabine plus carboplatin; GCis, Gemcitabine plus cisplatin; GCis + N, necitumumab in combination with gemcitabine plus cisplatin; G + P, gemcitabine in combination with paclitaxel; Nab, nanoparticle albumin-bound; PCarbo, paclitaxel plus carboplatin; PCis, paclitaxel plus cisplatin; Sb, solvent-based; VGD, vinorelbine in combination with gemcitabine and docetaxel.

Table 6 Trials included in the PFS network using HR data

Trial	Interventions
SQUIRE	GCis + N GCis
Morabito 2013	GCis Gemcitabine
Hoang 2013[a]	GCis PCis DCis PCarbo
Socinski 2012	Sb-PCarbo Nab-PCarbo
Treat 2010	PCarbo GCarbo G + P
Kubota 2008	PCarbo VGD
Lilenbaum 2008	PCarbo Erlotinib

[a] Not explicitly stated for this study, but assumed that the company calculated HRs by digitization of survival curves. DCis, docetaxel plus cisplatin; GCarbo, gemcitabine plus carboplatin; GCis, Gemcitabine plus cisplatin; GCis + N, necitumumab in combination with gemcitabine plus cisplatin; G + P, gemcitabine in combination with paclitaxel; Nab, nanoparticle albumin-bound; PCarbo, paclitaxel plus carboplatin; PCis, paclitaxel plus cisplatin; Sb, solvent-based; VGD, vinorelbine in combination with gemcitabine and docetaxel.

Similarity of included studies

The CS does not present summary baseline characteristics from the 10 studies included in the NMA or provide other details (e.g. length of follow-up) that would enable a comparison of how similar the studies included were. Baseline data on age, sex, proportion of patients with stage IV disease and ECOG performance status 0, 1 and 2 were provided in response to a request by NICE and the ERG (clarification response A20 Appendix 9). However other requested details [race, region (proportion from Western Europe) and length of follow-up were not provided].

Squamous participants were a subgroup of about 15% to 44% of the arms in all the trials in the NMA networks, other than the SQUIRE trial. The ERG notes there were slight imbalances in baseline characteristics between the arms in some trials (clarification response Appendix 9). The trials in the NMA networks were reasonably similar with respect to patients' mean age, around 60 to 65 years, although this was about 78 years in the Chen et al. 2012 study of vinorelbine. The proportions with other characteristics in the trial arms ranged as follows: men 44% to 84%, stage IV 75% to 100%, performance status 0 4% to 42%, performance status 1 0% to 78%, and performance status 2 0% to 100%. The ERG therefore does not agree with the company's statement on CS p. 89 that covariates were similar across studies in all but two studies.

Company's approach to conducting the NMA

The CS states that networks were analysed for the outcomes of OS and PFS, respectively, through calculation of HRs as the primary analysis. The CS states that HRs were extracted from the text of the publications, calculated from available data, or, where possible, extracted from the KM plot following digitisation of the curve. Also, the CS states that a secondary analysis assessed median time to death for OS, median time to progression for PFS and as a ratio of median time to event. It is unclear how the secondary analysis was conducted. Data on HRs and 95% confidence intervals were extracted, or calculated using data or KM plots, from included studies. Where KM curves were the source, the submission reports that the

proportional hazards assumption was applied and appropriately tested through correlating the scaled Schoenfeld residuals with the default transformation of time (and by visual inspection of patterns of residuals that may indicate non-proportionality not identified by tests of non-zero slopes). Median time to event data were log transformed. Where standard errors for HRs were not available, they were estimated using the standard error for the median time to event adopting an exponential distribution of survival time and log HR or from the number of subjects with events. Fixed- and random-effects models were planned, along with adjustment for influential covariates and extensive sensitivity analyses to assess the robustness of the models. Sensitivity analyses would investigate the effects of the method of analysis (i.e. Bayesian versus frequentist), different survival outcome measures, geographical location, disease severity, patient age, study design, study quality and risk of bias.

The models adopted a Bayesian framework through the BATMAN tool, which uses the JAGS software program for the Bayesian analysis of hierarchical models. The BATMAN tool was developed in collaboration with the company to undertake NMA using a Bayesian approach through Markov Chain Monte Carlo simulation. The CS indicates that models developed in BATMAN were validated through independent replication in OpenBUGS software. All models were estimated using two chains with a 10,000 iteration burn-in and 2,000 iterations for estimating the posterior distribution. Clarifications from the company corrected the burn-in iterations to 1,000 (clarification response A24). Convergence was assessed using trace plots and autocorrelation plots (clarification response A25). Heterogeneity was planned to be explored through use of forest plots and consistency through comparison of outcomes from any closed loops in the network and through density plots of posterior distributions. Model fit was to be assessed through the variance, between-study standard deviation, residual deviance and deviance information criterion, where possible. In practice, the company did not assess model fit. The deviance information criterion (DIC) was provided for information only, but not discussed.

Table 7 shows the ERG's critical appraisal of the company's NMA. Despite the CS providing a basic outline of the approach taken to the NMAs, specific issues limit its usefulness. The main concern is the sparse nature of the evidence identified, which affects the analysis that was possible. Although the evidence networks included all the interventions in the scope except vinorelbine in combination with a platinum drug, most comparisons only involved one study, and outcomes could be produced for only six of the eight specified comparisons. Despite the

inclusion of some comparators that were outside the scope to provide additional information to inform the NMA, the evidence base remained limited.

The submission planned to produce fixed- and random-effects models for the NMAs, however the lack of evidence meant that random-effects models would not converge (confirmed in clarification response A23). As a result, only fixed-effect models are presented, which may result in narrower credible intervals. With some of the credible intervals from the fixed-effect models being close to unity, estimation of random-effects models might have resulted in wider credible intervals that included unity, affecting the interpretation of the outcome. Only unadjusted analyses could be estimated as the inclusion of covariates could not be supported by the evidence available, with models failing to converge. Of the eight pre-planned sensitivity analyses, only two were conducted due to fragmentation of the networks. The limited evidence available will have affected the assessment of heterogeneity and consistency between direct and indirect evidence due to a lack of contributing studies that can be compared through forest plots, density plots, direct and indirect evidence for closed loops and comparisons of between-study variance. The company did not comment on how their results compared with those of other published NMAs. For example, the ERG notes that Brown et al. 2013[19] conducted mixed treatment comparison of the clinical effectiveness of first-line chemotherapy for patients with locally advanced or metastatic NSCLC. The results of the company's NMA could have been compared with those of the Brown et al. 2013 mixed treatment comparison.

In addition, the CS provides limited details of some aspects of the approach taken. Although a proportional hazards assumption is applied to the HR and tested for, only the results for a limited number of included studies are discussed. These identified some concerns around violation of the proportion hazards assumption (clarification response A26) and the company submission indicates that conclusions regarding appropriateness of the proportional hazards assumption should not be drawn across all studies in the network.

Apart from the sample OpenBUGS code provided in appendix 8 of the submission, there is no discussion regarding the prior values used for treatment effects or for the prior distributions for the variance component (i.e. alternative priors used). It is unclear if any sensitivity analyses were undertaken around the different priors. Clarification from the company outlined the OpenBUGS code for the different models (clarification response A22); however, no clarification was provided regarding sensitivity analyses on prior values or distributions. It was evident from

the OpenBUGS code and the clarifications (clarification response A24) that vague priors were used. Similarly, none of the diagnostic plots to assess convergence, autocorrelation, heterogeneity or consistency are presented or discussed. Only trace plots are used to assess convergence (Brooks-Gelman-Rubin plots would have provided further clarity as to whether convergence had occurred). These limitations make it difficult to judge whether there was a sufficient period of burn-in or additional iterations to allow model convergence. This is particularly important given the limited numbers of iterations used for burn-in and estimation of the posterior distribution. Finally, results from the frequentist analysis and validation analysis in OpenBUGS are not presented or discussed.

Summary and key caveats:

Overall, the ERG considers that the sparse evidence base and the lack of clarity around the NMA indicates that there is considerable uncertainty and the outcomes should be viewed with caution, something identified in the CS itself. Other key caveats are:

- The post-hoc exclusion of studies that the ERG considers relevant and which could have been connected to the network.
- It is unclear if the included studies were similar enough to combine as the company provided limited information about participants' baseline characteristics and the company did not provide information about length of follow-up.
- The ERG considers that the fixed effects model was not a plausible model choice and the company have not adequately explored the possibility of using a random effects model, so there is uncertainty in the model.
- The company has used a model unadjusted for covariates.

Table 7 ERG appraisal of the NMA approach

Checklist	Response (yes/no)
Does the MS present an MTC?	Yes (NMA)
Are the NMA results used to support the evidence for the clinical effectiveness of the intervention	Yes
Are the NMA results used to support the evidence for the cost-effectiveness of the intervention	Yes
Homogeneity	
1. Is homogeneity considered?	Yes, with caveats. The NMA clearly specifies the participants that will be included in the systematic review and it undertakes a limited assessment of heterogeneity (see below). However there is no discussion of how similar the studies are in terms of intervention characteristics or outcome measures. Most of the studies included patients with non-squamous histology and only data from the subset of squamous patients were used, which was <30% of the study population in most cases. Similarity of the squamous subgroup between arms within the trials was not considered.
2. Are the studies homogenous in terms of patient characteristics and study design?	Unclear. Limited baseline characteristics were provided in clarification response A20 Appendix 9. The proportion of squamous patients in each trial arm ranged from 15% to 44% and was 100% in the SQUIRE trial. Median age ranged from 59 to 78 years; the proportion male ranged from 44% to 84%; and the proportion with stage IV disease ranged from 75% to 100%.The PS varied considerably among trials, with the proportion of patients classed as PS0, PS 1 and PS2 ranging, respectively, from 0% to 42%, 0% to 78%, and 0% to 100%.
3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	No (visual inspection of forest plots only). Due to the limited number of studies and small patient numbers the random effects heterogeneity variance became inestimable and the random effects models did not converge in all instances. Therefore all analyses were conducted using a fixed effects model.
4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. subgroup analysis, sensitivity analysis, meta-regression)	Partially. Homogeneity: The majority of comparisons were populated with only one study. Heterogeneity was identified by wide credible intervals for one study (Morabito 2013) in the OS HR analysis and two studies (Morabito 2013, Lilenbaum 2008) in the PFS HR analysis. These studies were not central to the network connections for each of the OS and PFS analyses and could be removed without affecting the results versus the necitumumab region, therefore post hoc sensitivity analyses were undertaken. The CS does not comment on heterogeneity (identified by wide confidence intervals) for studies that were central to the network connections.
Similarity	
1. Is the assumption of similarity stated?	No

2. Have they justified their assumption?	No
Consistency	
1. Does the analysis explicitly assess consistency of direct and indirect evidence?	Not applicable (the CS states (p. 119) that the consistency assumption could not explored due to the lack of closed loops that included GCis + N).
2. Does the method described include a description of the analyses/ models/ handling of potential bias/ inconsistency/ analysis framework?	Not applicable
3. Are patient or trial characteristics compared between direct and indirect evidence trials?	Not applicable
4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	Not applicable

3.2 Summary statement of the company's approach

The ERG's quality assessment of the CS is summarised in Table 8. The quality of the company's systematic reviews is suboptimal and there is a chance of systematic error in the reviews. The company appears to have included all relevant RCTs in the main systematic review. The company, however, did not identify four conference abstracts related to the SQUIRE trial in their searches, which were published before the company conducted the searches for the main systematic review (in August 2015) and that were subsequently identified by the ERG's update searches conducted from January 2015 to present. The company's searches for the systematic review underpinning the NMA was conducted in January 2015, therefore any relevant studies published in the past year will have been missed. Eligibility criteria were reported for the main systematic review and NMA review, however inappropriate post-hoc exclusions were performed for the NMA review. The process for study selection, data extraction and quality assessment are not described in the CS, but details were provided in clarification response A3 and are appropriate. In addition, limited details of study characteristics are reported for those trials included in the NMA.

The submitted evidence generally reflects the decision problem. However, the only head-to-head comparison was with GCis. Comparisons with DCis, PCis, GCarbo and PCarbo were made through an NMA, although there were a number of limitations with this due to the sparse network. Comparisons could not be made with DCarbo or VCarbo, and comparison with VCis

could only be made for OS analyses based on median data (which could not be used in the economic model).

Table 8 Quality assessment (CRD criteria) of CS review

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partial. Criteria for the main systematic review are reported in CS Table 9 p. 39. Eligibility criteria for the NMA are reported in CS Table 21 p. 85, however some studies were excluded post hoc.
2. Is there evidence of a substantial effort to search for all relevant research? ie all studies identified	Partial. The search strategy for the systematic review of GCis + N was appropriate, but not all relevant publications relating to the SQUIRE trial were identified and searches were 5-6 months out of date. However, no relevant studies were missed by these searches. The search strategy for the NMA was appropriate but last updated in January 2015 therefore any studies published in the last year will have been missed.
3. Is the validity of included studies adequately assessed?	Partial. The CS uses the NICE recommended criteria and the ERG generally agrees with the company's assessment of the SQUIRE RCT (see section 3.1.4). Quality assessment of the trials included in the NMA was not provided in the CS but was provided on request from NICE and the ERG in clarification response Appendix 10. The company assessed trial validity using the PEDRO tool and Cochrane Risk of bias tool which are appropriate, although the company does not explicitly discuss whether or how their quality assessment results informed their NMA analyses and conclusions.
4. Is sufficient detail of the individual studies presented?	Partial. Details are provided for the SQUIRE RCT on methodology (CS p. 42-51), statistical analysis (CS p. 52-54), and participant flow (p. 54-55). Limited details were provided for the trials included in the NMA, but were provided on request from NICE and the ERG in clarification response Appendix 10.
5. Are the primary studies summarised appropriately?	Partial. Results of the SQUIRE RCT are presented in narrative form with tabulation of data. The synthesised results from the studies included in the NMA are highly uncertain (as discussed in section 3.1.7).

3.3 Summary of submitted evidence

Summary of evidence

During the appraisal, in response to clarification question A1, the company supplied results for the EGFR expressing subgroup of patients in the SQUIRE trial for all outcomes except HRQoL. Below, we present the EGFR expressing subgroup (n = 935) results first for each outcome, as this is the SmPC population, followed by the ITT population results. We have summarised the

results for all four patients populations included in the CS and company's clarification response in the subsection 'Summary of results for all populations', including the Western Europe subgroups results. We present results for the Western Europe subgroups these are used to inform the company's base case cost-effectiveness analysis. Where possible, the ERG has checked data with the published data. The CS also reports that pharmacokinetics and immunogenicity of necitumumab were secondary outcomes. These do not meet the decision problem and are not discussed further here.

Summary overall survival results

EGFR expressing subgroup

As shown in Table 9, in the EGFR expressing population, the median OS was 11.7 months [redacted] in the GCis + N group; and 10 months [redacted] in the GCis group: a modest improvement in OS of 1.74 months. The HR showed a statistically significant survival benefit in the GCis + N group compared with the GCis group (HR 0.79 (95% CI 0.69, 0.92), p=0.002). The number of deaths was [redacted] out of [redacted] participants in the GCis + N group and [redacted] out of [redacted] in the GCis group. Twelve month and 24 month survival rates were not reported in the clarification response.

Table 9 Overall survival in the EGFR expressing subgroup, as reported in the company's clarification response

	GCis + N, N = 462	**GCis, N=473**
OS results presented in the CS		
Number of deaths, n (%)	[redacted]	[redacted]
Number censored, n (%)	[redacted]	[redacted]
Median survival[a], months (95% CI)	11.73 [redacted]	9.99 [redacted]
Stratified Hazard Ratio (95% CI), p-value[b]	0.79 (0.69, 0.92) p=0.002	
12 month survival rate, % (95% CI)	NR	NR
24 month survival rate,% (95% CI)	NR	NR

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin; NR: not reported
[a]Kaplan-Meier estimated
[b]Stratified log-rank p-value

Table 10 shows the OS results from the SQUIRE trial for patients with and without detectable EGFR expression (H-scores of > 0 and = 0, respectively) reported in a FDA Briefing Document[14] identified by the ERG. [redacted]

[redacted]. A small proportion of participants in the SQUIRE trial (GCis + N = 24; GCis= 23) lacked detectable EGFR expression (H-score = 0). There was no statistically significant difference in OS (HR 1.86) between treatment arms for participants with an H-score of 0. The company commented in their clarification response A7 that results of a subgroup analysis of patients without detectable EGFR expression showed that these patients may not benefit from the addition of necitumumab to GCis.

Table 10 OS by % positive EGFR expression, as reported in a FDA briefing document identified by the ERG

	Percent positive >0		Percent positive = 0[a]	
	GCis + N n=462	GCis n=473	GCis + N n=24	GCis n=23
Overall survival				
Median, months	11.73	9.99	6.47	17.35
HR (95% CI)	0.81 (0.70, 0.93)		1.86 (0.94, 3.65)	
P value	0.004		0.072	
Interaction p value	0.018			

Source: FDA Briefing Document[14]
[a]0 % positive is equivalent to H-score=0 for EGFR staining

ITT population

Overall survival was longer with GCis + N than with GCis (Table 11). Median OS was 11.5 months (95% CI 10.4, 12.6) among 545 participants in the GCis + N group and 9.9 months (95% CI 8.9, 11.1) among 548 participants in the GCis group. The stratified hazard ratio (HR) was 0.84 (95% CI 0.74, 0.96) suggesting a 16% reduction in risk with GCis + N. At 1 year, the survival rate was 48% (95% CI 43, 52) with GCis + N versus 43% (95% CI 39, 47) with GCis. At 2 years the survival rate was 20% (95% CI 16, 24) with GCis + N compared with 17% (95% CI 13, 20) with GCis. The median follow-up time was 25.2 months (95% CI 23.7, 27.1) in the GCis + N group and 24.8 months (95% CI 22.8, 28.3) in the GCis group. Loss to follow-up and withdrawals of consent for follow-up for OS was low and similar across both groups (GCis + N 39 (7.2%); GCis 35 (6.4%)).

A conference abstract[16] from the SQUIRE trial identified by the ERG's searches that reported on the efficacy of treatment with necitumumab alone during the maintenance phase (i.e. following treatment with GCis + N) found a two-year survival rate of 27.5% among the 51% of the GCis + N patients receiving maintenance treatment.

Table 11 Overall survival (ITT population)

	GCis + N, N = 545	GCis, N=548
Number of deaths, n (%)	418 (77)	442 (81)
Number censored, n (%)	127 (23)	106 (19)
Median survival[a], months (95% CI)	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Stratified Hazard Ratio (95% CI), p-value[b]	0.84 (0.74, 0.96) p=0.01	
12 month survival rate[a], % (95% CI)	48 (43, 52)	43 (39, 47)
24 month survival rate[a],% (95% CI)	20 (16, 24)	17 (13, 20)

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]Kaplan-Meier estimated
[b]Stratified log-rank p-value (stratified by ECOG PS and geographic region).

Summary of progression-free survival results

EGFR expressing subgroup

PFS in the EGFR expressing subgroup was slightly longer with GCis + N than with GCis (Table 12). Median PFS was 5.7 months [redacted] in the GCis + N group and 5.5 months [redacted] in the GCis group. The HR for PFS was 0.84 (95% CI, 0.72, 0.97), p=0.018.

Table 12 Progression-free survival in the EGFR expressing subgroup, as reported in the company's clarification response

	GCis + N, N = 462	GCis, N=473
Number of events, n (%)	[redacted]	[redacted]
Number censored, n (%)	[redacted]	[redacted]
Median PFS[a], months (95% CI)	5.72 ([redacted]	5.49 [redacted]
Stratified Hazard ratio (95% CI), p-value[b]	0.84 (0.72, 0.97) p=0.018	
3 month PFS rate[a], % (95% CI)	NR	NR
6 month PFS rate[a],% (95% CI)	NR	NR

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin; NR: not reported
[a]Kaplan-Meier estimated
[b]Stratified log-rank p-value

Table 13 shows the PFS results from the SQUIRE trial for patients with and without detectable EGFR expression (H-scores of > 0 and = 0, respectively) reported in the FDA Briefing Document[14] identified by the ERG. [redacted]. The was no statistically significant difference in PFS (HR 1.19) between treatment arms for participants with an H-score of 0.

Table 13 PFS by % positive EGFR expression, as reported in a FDA briefing document identified by the ERG

	Percent positive >0		Percent positive = 0[a]	
	GCis + N n=462	GCis n=473	GCis + N n=24	GCis n=23
Progression-free survival				
Median, months	5.72	5.49	4.24	5.59
HR (95% CI)	0.83 (0.72, 0.97)		1.19 (0.61, 2.30)	
p-value	0.015		0.611	
Interaction p value	0.305			

Source: FDA Briefing Document[14]
[a]0 % positive is equivalent to H-score=0 for EGFR staining

ITT population

PFS was slightly longer with GCis + N than with GCis (Table 14). Median PFS was 5.7 months (95% CI, 5.6, 6.0) in the GCis + N group and 5.5 months (95% CI, 4.8, 5.6) in the GCis group (HR for progression or death 0.85; 95% CI 0.74, 0.98). At 3 months, the PFS rate was 79% (95% CI, 76, 83) with GCis + N versus 73% (95% CI, 68, 76) with GCis. At 6 months, the PFS rate was 45% (95% CI, 40, 49) with GCis + N versus 37% (95% CI, 33, 42) with GCis. It is not clear to the ERG what the median follow-up time was for the assessment of PFS, but the ERG notes that the number of events in the GCis group is lower than the number of deaths in this group, as presented in Table 11 above.

Table 14 Progression-free survival (ITT population)

	GCis + N, N = 545	GCis, N=548
Number of events, n (%)	431 (79)	417 (76)
Number censored, n (%)	114 (21)	131 (24)
Median PFS[a], months (95% CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Stratified Hazard ratio (95% CI), p-value[b]	0.85 (0.74, 0.98) p=0.02	
3 month PFS rate[a], % (95% CI)	79 (76, 83)	73 (68, 76)
6 month PFS rate[a],% (95% CI)	45 (40, 49)	37 (33, 42)

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]Kaplan-Meier estimated
[b]Stratified log-rank p-value (stratified by ECOG PS and geographic region).

EGFR expressing subgroup

In the EGFR expressing subgroup, the difference in ORR between the GCis + N and GCis groups was [redacted] (Table 15). The disease control rate in this subgroup was [redacted] in the GCis + N group [redacted] than in the GCis group [redacted].

Table 15 Objective response rate in the EGFR expressing subgroup

n (%)	GCis + N, N = 462	GCis, N=473
Objective response (CR+PR) rate, n (%), 95% CI	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
OR (95% CI), p-value	[redacted]	
Disease control rate (CR+PR+SD) (95% CI)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
OR (95% CI), p-value	[redacted]	
Best overall response, n (%):		
Complete response (CR)	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable/No assessment[b]	[redacted]	[redacted]

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin [redacted]

[b]Calculated by ERG from 'not evaluable' and 'no assessment'.

ITT population

ORR was higher with GCis + N than with GCis, however this was not statistically significant (p=0.40) (**Table** 16). The ORR was 31% (95% CI, 27, 35) in the GCis + N group and 29% (95% CI, 25, 33) in the GCis group. The disease control rate was also reported in the CS, this was significantly higher in the GCis + N group than in the GCis group (**Table** 16).

Table 16 Objective response rate (ITT population)

n (%)	GCis + N, N = 545	GCis, N=548
Objective response (CR+PR) rate (95% CI)	170 (31) (27, 35)	158 (29) (25, 33)
p-value (stratified Cochran-Mantel-Haenszel[a])	0.40	
Disease control rate (CR+PR+SD) (95% CI)	446 (82) (78, 85)	422 (77) (73, 80)
p-value (stratified Cochran-Mantel-Haenszel[a])	0.043	
Best overall response, n (%):		
Complete response (CR)	0	3 (<1)
Partial response (PR)	170 (31)	155 (28)
Stable disease (SD)	276 (51)	264 (48)
Progressive disease (PD)	41 (8)	55 (10)
Not evaluable/No assessment[b]	58 (11)	71 (13)

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]stratified by ECOG PS and geographic region.
[b]calculated by ERG from not evaluable and no assessment in CS Table 16

Summary of Health related quality of life (ITT population only)

The CS presents data from the SQUIRE trial on the LCSS. For the LCSS the CS presents the time to deterioration for lung symptoms based on each of six symptom questions (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, pain) together with the Average Symptom Burden Index (ASBI). The CS also reports three global items (overall symptoms, interference with normal activities, quality of life) together with a global 3-item composite score. Finally, a total LCSS score is presented. On the LCSS each item is assessed with a 100-mm visual analogue scale with higher ratings corresponding to poorer quality of life. The CS reports that 88.3% of participants in the GCis + N group and 88% of participants in the GCis group had a baseline and at least one post baseline assessment of the LCSS. The CS reports summary data for the nine individual items of the LCSS at baseline for both treatment groups (CS Table 20, p. 74) and data for the time to deterioration in a forest plot (CS Figure 14, p. 77). This includes the number of events for each item by treatment group, and the HR and 95% CI. No items on the LCSS were significantly different between treatment groups, with all confidence intervals from the reported HRs crossing 1.0. As stated in section 3.1.5, a number of other analyses of the LCSS were undertaken, but the results of these analyses are not reported in the CS.

The CS also presents data on the EQ-5D-3L. Data were reported for the EQ-5D index at baseline, cycles 2-6 and end of therapy in a series of figures illustrating the percentage of patient responses for each response option for each EQ-5D dimension (CS figures 15-17, pp. 79 to 81) and in a series of figures illustrating the percentage of patient responses at each visit (CS figure 21, p. 83). The CS reports that [redacted] of participants in the GCis + N group and [redacted] of participants in the GCis group had a baseline and at least one post baseline assessment of the EQ-5D. The CS reports on page 78 that most patients in both arms experienced no or some problems in each of the five dimensions and that fewer than 6.5% in each arm experienced extreme problems on any of the five dimensions.

The CS also reports ECOG PS time to deterioration, and an analysis of severity of LCSS as predictor of OS. These analyses are post hoc and are therefore not summarised by the ERG (see CS p. 77 to 78).

Pre-specified sub-group analysis results (ITT population only)

There were no subgroups noted as relevant in the NICE scope or the decision problem. Pre-specified subgroup analyses (described in CS Section 4.8 pp. 68 to 73) were planned of the OS and PFS outcomes by:

- geographical region (see section 3.1.6 for a list of the pre-planned analyses)
- age (<70 vs. ≥70 years; and <65 vs. ≥65 years).
- gender (female vs. male).
- race (White vs. non-White).
- ECOG PS (0 vs. 1 vs. 2 and 0-1 vs. 2).
- smoking history (never smoker [non-smoker and light ex-smoker combined] vs. smoker).

Except for the pre-specified analyses by geographical region (provided in clarification response A6c, Appendix 6 but in different groupings to those stated above), results were presented for these subgroups in Figure 9 in the CS (p. 70). These concur with results seen in the CSR with the exception of the age subgroup analyses. In the CS and clarification response Appendix 6, the subgroups (including those by geographical region) show a similar pattern on outcomes of OS and PFS, generally favouring treatment with GCis + N (please see Figure 1, Figure 2 and Figure 3).

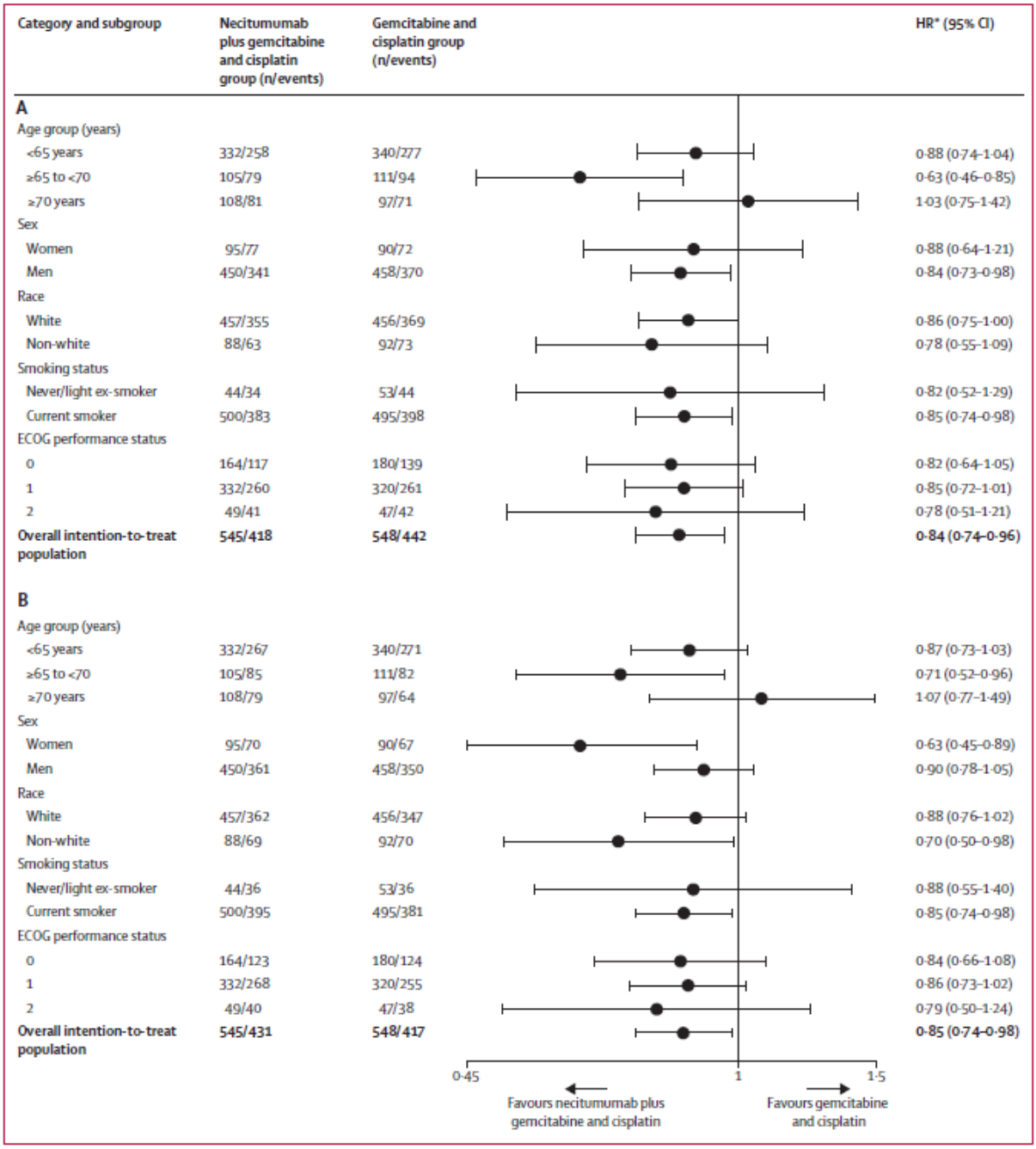


Figure 1 Forest plot of subgroup analyses results in ITT population Panel A shows OS results; panel B shows PFS results.

Panel A shows OS results; panel B shows PFS results. Figure reproduced from Appendix 6, p. 61, of the company's clarification response.

Source: Thatcher et al. 2015.

Figure 2 OS Subgroup analyses results by geographical region.

Figure reproduced from Appendix 6, p. 61 of the company's clarification response.

Figure 3 PFS Subgroup analyses results by geographical region

Figure reproduced from Appendix 6, p. 62, of the company's clarification response.

As discussed in section 2.3 above, the age and ECOG performance status results were not presented in the CS entirely in line with the pre-specified groupings of patients. The ERG therefore considers the age and performance status results presented in the CS to be at risk of selective reporting bias.

The ERG identified a conference abstract[15] through its searches that reports the results of analyses of patients with a performance status of 0-1; results that were not reported in the CS. This showed that patients treated with GCis + N who had an ECOG performance score of 0-1 experienced statistically significantly better OS [HR 0.85 (95% CI: 0.74 to 0.98; p = 0.026) and PFS [HR 0.86 (95% CI: 0.75 to 0.99; p = 0.035) than patients treated with GCis alone, while patients treated with GCis + N with a PS score of 2 did not [OS: HR 0.78 (95% CI: 0.51 to 1.21; p = 0.275); PFS: HR 0.79 (95% CI: 0.50, 1.24; p = 0.292)].

The CS (and trial publication) also report pre-specified exploratory analysis of tumour EGFR expression, categorising participants into high (H-score ≥200) and low (H-score <200) EGFR expression groups. This was undertaken to establish whether H-scores were predictive of a differential effect of the addition of necitumumab on OS and PFS. No significant differences were seen in HRs for OS or PFS between the two H-score groups (see CS pp. 71 to 73).

Summary of results for all populations

In Table 17, the ERG has summarised the OS, PFS and ORR results reported for all four populations included in the CS and the company's clarifications response. As Table 17 shows, [redacted]. These were the population subgroups used in the company's economic model base case. The CS states that although the improvement in OS in the Western Europe subgroup [redacted] is moderate, it is clinically significant in the squamous NSCLC populations. The company did not comment on the clinical significance of the results for the other populations. The difference in median OS in the EGFR expressing subgroup (the subgroup the ERG considers to be most relevant to the SmPC indication and this appraisal) was 1.74 months, favouring GCis + N (HR 0.79 (0.69, 0.92).

There were statistically significant differences between the treatment arms in OS for all four populations. GCis + N resulted in statistically significantly better PSF outcomes than GCis in the ITT population and EGFR expressing population. There were, however, no statistically

significant differences in PFS between GCis + N and GCis in either of the Western Europe subgroups.

Table 17 Summary of results for all SQUIRE trial populations presented in the CS and the company's clarifications response

	GCis + N	GCis
Median survival, months (95% CI)		
ITT population	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
EGFR subgroup	11.73 [redacted]	9.99 [redacted] [a]
Western Europe subgroup	[redacted] [a]	[redacted]
EGFR Western Europe subgroup	[redacted]	
OS: stratified HR (95% CI) [b]		
ITT population	0.84 (0.74, 0.96); p=0.01	
EGFR subgroup	0.79 (0.69, 0.92); p=0.002	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup		
Median PFS, months (95% CI)		
ITT population	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
EGFR subgroup	5.72 [redacted]	5.49 [redacted]
Western Europe subgroup	[redacted] [a]	[redacted] [a]
EGFR Western Europe subgroup		
PFS: stratified HR (95% CI) [b]		
ITT population	0.85 (0.74, 0.98); p=0.02	
EGFR subgroup	0.84 (0.72, 0.97); p=0.018	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup		
ORR, % (95% CI)		
ITT population	31 (27, 35)	29 (25, 33)
EGFR subgroup	[redacted]	[redacted]
Western Europe subgroup	[redacted] [c]	[redacted] [c]
EGFR Western Europe subgroup		
ORR difference (95% CI)		
ITT population	Not reported	
EGFR subgroup	[redacted] [d]	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup	[redacted] [c]	
ORR: odds ratio (95% CI)		
ITT population	Not reported	
Western Europe subgroup	[redacted]	
EGFR subgroup	[redacted]	
EGFR Western Europe subgroup	[redacted] [c]	

EGFR, epidermal growth factor receptor; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin; ITT, intention-to-treat.

[a] CIs extracted by the ERG from the CSR

[b] unstratified analysis for EGFR Western Europe subgroup

[c] the company's clarification response Appendix 1 states that these results were for the Western Europe subgroup, but the ERG believes that this is a typo and that these results are for the EGFR expressing Western Europe subgroup.

[redacted]

[e] calculated by the ERG.

Mixed Treatment Comparison results

The CS presents results from the NMA as median HR and mean HR for OS and PFS HRs (Table 18). The means were utilised in the CS economic evaluation. The CS also presents results from the secondary analyses; however, these are not used in the economic evaluation and are not reported here. As stated in section 3.1.7, the spare evidence base and lack of clarity around the NMA indicates there is considerable uncertainty and the outcomes should be viewed with caution.

Overall Survival

The NMA for OS allows comparisons of GCis + N with five comparators in the decision problem (PCarbo; GCis; PCis; DCis; GCarbo). No evidence was identified that allowed pairwise comparisons with the remaining three comparators in the decision problem (DCarbo; VCarbo; VCis), although there is evidence for VCis in the secondary NMA analysis of median survival. The credible intervals for GCis + N with all comparators are overlapping, suggesting that this NMA does not provide evidence of a hierarchy of effectiveness between comparators.

Table 18 NMA overall survival estimates, fixed effect model

Intervention	Comparator				
	PCarbo	GCis	PCis	DCis	GCarbo
Median OS HR (from CS Table 25)					
GCis + N	[redacted]				
Mean OS HR[a] (from CS Table 26)					
GCis + N	[redacted]				

CrI: Credible interval; DCis: Docetaxel + cisplatin; GCarbo: Gemcitabine + carboplatin; GCis: Gemcitabine + cisplatin; GCis + N: Necitumumab + gemcitabine + cisplatin; PCarbo: Paclitaxel + carboplatin; PCis: Paclitaxel + cisplatin; VCis: Vinorelbine + cisplatin.
[a]95% credible intervals were obtained from the median HR analyses which the CS states is reasonable given they are taken from the same distribution

Progression-Free Survival

The NMA for PFS allows comparisons of GCis + N with the same comparators as in the OS analyses (PCarbo; GCis; PCis; DCis; GCarbo). There are no PFS HR comparisons available for DCarbo; VCarbo or VCis. In all analyses the HRs are favourable for GCis + N. For the comparison with GCis, PCis and GCarbo the 95% CrI do not include unity, indicative of a treatment effect for GCi + N on PFS (Table 19).

Table 19 NMA progression-free survival HR results, fixed effect model

Intervention	Comparator				
	PCarbo	GCis	PCis	DCis	GCarbo
Median PFS HR (from CS Table 28)					
GCis + N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean PFS HR[a] (from CS Table 29)					
GCis + N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI: Credible interval; DCis: Docetaxel + cisplatin; GCarbo: Gemcitabine + carboplatin; GCis: Gemcitabine + cisplatin; GCis + N: Necitumumab + gemcitabine + cisplatin; PCarbo: Paclitaxel + carboplatin; PCis: Paclitaxel + cisplatin.
[a]95% credible intervals were obtained from the median HR analyses which the CS says is reasonable given they are taken from the same distribution, ERG notes upper bound CrI for GCis + N vs. PCarbo, and lower bound CrI for GCis + N vs. GCarbo are slightly different.

Summary of adverse events

Here we have summarised the AE results for the safety population from the SQUIRE trial, followed by a comment on how similar the AE results for the EGFR expressing subgroup, as provided in the company's clarification response Appendix 1, are to those observed in the safety population.

Safety population

For the safety population in the SQUIRE trial,[1] any participants who received at least one dose of therapy were included in the analyses. The CS states (p. 121) that there was a longer observation phase for those in the GCis + N group because the treatment phase was longer due to this group receiving maintenance therapy. To represent the difference in observation phases the CS states (page 121) that it presents safety data as overall for each group, and also separately for the chemotherapy and maintenance phases for the GCis + N group. The CS presents the chemotherapy phase and the maintenance phase and the overall safety set in different tables, although these are not always clearly identified. Where possible, the ERG has presented results from chemotherapy phases and maintenance phases separately unless these were not distinguished in the CS or CSR.

Treatment emergent adverse events (TEAEs) were defined in the SQUIRE trial as detailed in section 3.1.5. The frequency of deaths, including fatal cases of disease progression, that occurred as a result of TEAEs was similar between groups in the chemotherapy phase (GCis + N 9.3% vs GCis 10.5%) (Table 20). In the maintenance phase (i.e. necitumumab monotherapy) there were 5.8% TEAE related deaths. TEAEs with outcome of death, excluding fatal cases of disease progression, were also similar between groups in the chemotherapy phase (see Table

20). Most participants reported at least one TEAE and the rates during the chemotherapy phases were similar between groups (>97%).

The proportion of participants reporting at least one treatment-emergent serious adverse event (SAE, defined in section 3.1.5) in the chemotherapy phase was 42.6% in the GCis + N group compared with 37.5% in the GCis group. These values concur with the CSR data; however, the publication for the SQUIRE trial[1] reports that serious adverse events were reported in 48% of participants in the GCis + N group. The CS also differs from the published data on the proportion of participants with grade 3 or worse TEAEs in the GCis + N group (67.7% in the CS, 72% in the publication). On checking the CSR, the data in the trial publication were found to correspond to the overall safety set, which includes the maintenance phase for the GCis + N treatment group. The proportion of participants discontinuing the allocated treatments due to at least one TEAE was similar between the two arms of the SQUIRE trial (13.8% and 14.8% respectively).

The CS does not report details about which specific treatment emergent SAEs the participants in the SQUIRE trial experienced. NICE and the ERG requested details about these from the company. The company referred to detailed information about SAEs available in the CSR in its response to this clarification question (clarification response A14). The ERG has reproduced the SAEs reported in the CSR that occurred in ≥2% of patients in the GCis + N arm and where there was a ≥1% difference between arms in Table 21. The GCis + N arm had higher rates of anemia, pulmonary embolism and vomiting than the GCis arm.

A number of adverse events were classified as being of special interest (not defined) in the CS and these are presented as composite categories in CS Tables 40, 41, 42 and 43. The ERG presents a summary of thromboembolic events for any grade and grade ≥3 in Table 22.

Table 20 Summary of treatment-emergent adverse events

	GCis + N	GCis

	Chemotherapy phase N = 538	Maintenance phase N = 275	Chemotherapy phase N = 541
At least one TEAE, all grades, %	99.1	77.5	97.8
TEAEs with outcome of death including fatal cases of disease progression,%	9.3	5.8	10.5
TEAEs with outcome of death excluding fatal cases of disease progression, %	5.9	3.6	6.8
Patients with ≥1 treatment emergent SAE, %	42.6	17.1	37.5
Patients with ≥1 Grade ≥3 TEAE	67.7	28.7	61.6
Discontinued study drug due to ≥1 TEAE, n (%)	74 (13.8)		80 (14.8)
Discontinued at least one of the combination treatments due to AEs, n (%) [a]	[redacted] (31)		[redacted] (25)

GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a] from CS p. 123 and CSR section 12.3.3.1

Table 21 Treatment emergent serious adverse events

[redacted], n (%)	GCis + N N = 538	GCis N = 541
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin

Venous thromboembolic events were experienced more frequently in the chemotherapy phase in those treated with GCis + N than GCis alone for any grade (8.2% vs [redacted] respectively) and ≥ grade 3 (4.3% vs [redacted] respectively). Rates of arterial thromboembolic events in the chemotherapy phase were more similar between groups. The CS states there were no differences between treatment groups with respect to fatal thromboembolism (arterial or

venous) (<1% in both groups). Other adverse events of special interest that were experienced more frequently in the GCis + N group than GCis group alone were rashes, hypomagnesaemia, and conjunctivitis (Table 22). Rates of haematological toxicities were similar between the groups.

Treatment emergent adverse events were also reported in CS Table 38 for grade 3, grade 4 and grade 5 events. These were for the overall safety sets (for the GCis + N group including the maintenance phase). The events presented included the haematological toxicities, rash, hypomagnesemia and fatigue (as presented in CS Tables 42 and 43) and other adverse events of asthenia, pulmonary embolism, nausea and vomiting. For the events that were also reported in CS Tables 42 (and CS Table 43 for the GCis group) the number of events of grade 3, 4 and 5 do not correspond. The ERG considers the data from CS Tables 42 and 43 as accurate as we have checked these data against the CSR.

EGFR expressing subgroup

Adverse events for the EGFR expressing subgroup were provided by the company in clarification response Appendix 1. The rates of AEs in the EGFR-expressing subgroup generally reflect those seen in the ITT population (reported above) and as such are not reproduced here. Exceptions are that in the GCis group the rates of any grade hypomagnesaemia are higher in the EGFR expressing population [redacted] than in the ITT population (15.7%); and rates of any grade rash for both treatment groups in the EGFR expressing group are lower than in the ITT population (GCis + N [redacted] versus 76.2%; GCis [redacted] versus 10.2%). The reasons for these discrepancies are unclear. The company also provided AE results for the EGFR expressing Western European population in clarification response Appendix 1 (not shown here).

Table 22 Adverse events of special interest

Adverse event of specicial interest experienced in at least one participant unless stated, n (%)	GCis + N				GCis	
	Chemotherapy phase N = 538		Maintenance phase N = 275		Chemotherapy phase N = 541	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Thromboembolic events						
Venous thromboembolic events[a]	44 (8.2)	23 (4.3)	[redacted]	[redacted]	29 (5.4)	14 (2.6)
Arterial thromboembolic events[a]	23 (4.3)	16 (3.0)	[redacted]	[redacted]	21 (3.9)	11 (2.0)
Haematologic toxicity events						
Neutropenia	235 (43.7)	131 (24.3)	[redacted]	[redacted]	248 (45.8)	149 (27.5)
Febrile neutropenia	4 (0.7)	3 (0.6)	[redacted]	[redacted]	8 (1.5)	7 (1.3)
Anaemia	216 (40.1)	56 (10.4)	[redacted]	[redacted]	248 (45.8)	59 (10.9)
Thrombocytopenia	116 (21.6)	55 (10.2)	[redacted]	[redacted]	146 (27.0)	58 (10.7)
Fatigue	219 (40.7)	37 (6.9)	[redacted]	[redacted]	230 (42.5)	38 (7.0)
Skin reactions						
Rash[b]	405 (75.3)	30 (5.6)	[redacted]	[redacted]	55 (10.2)	2 (0.4)
Hypomagnesaemia	162 (30.1)	48 (8.9)	[redacted]	[redacted]	85 (15.7)	6 (1.1)
Hypersensitivity / infusion-related reactions	8 (1.5)	2 (0.4)	[redacted]	[redacted]	11 (2.0)	0
Conjunctivitis[c]	30 (5.6)	0	[redacted]	[redacted]	12 (2.2)	0
Interstitial lung disease (pneumonitis)	4 (0.7)	1 (0.2)	[redacted]	[redacted]	4 (0.7)	3 (0.6)

GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]Events experience in at least 2 participants
[b]The category of 'Rash' is a subset of the category 'Skin Reactions'.
[c]Conjunctivitis equates to 'eye disorders'

3.4 Summary

The systematic review of direct evidence in the CS identified one trial comparing GCis + N to GCis as a first-line treatment for patients with metastatic (stage IV) squamous NSCLC (the SQUIRE trial). The trial did not include patients with locally advanced disease (stage III). The CS reports OS and PFS results for both the ITT population and a post-hoc subgroup analysis of patients from Western Europe, as well as other results for the ITT population only. The company also provided results from the SQUIRE trial of post-hoc subgroup analyses of patients with EGFR expressing tumours from the ITT population and Western European subgroups in response to NICE and the ERG's clarifications questions, to reflect the population specified in the indication for necitumumab in the SmPC (clarification response A1). In the CS, the company argues that the Western Europe subgroup is more generalisable to patients in England than the ITT population. The company used data from the Western Europe EGFR expressing subgroup in their updated economic model submitted with the clarifications response. The SQUIRE trial was of a reasonable quality, although there is a risk of performance and detection bias due to lack of blinding of participants, care providers and outcome assessors.

The CS also presents an NMA comparing GCis + N with some of the scoped comparators.

The SQUIRE trial showed that GCis + N resulted in statistically significant greater improvements than GCis in OS and PFS in [redacted] in the total ITT population. Objective response rates did not differ significantly between the trial arms in the ITT population and [redacted]. The CS states that HRQoL was similar between treatment arms over time during the trial in the ITT population, although limited HRQoL data are presented. HRQoL results were not provided for the EGFR expressing subgroup. In the ITT population, the proportion of patients experiencing at least one serious adverse event was marginally higher during the treatment phase with GCis + N than during treatment with GCis. Venous thromboembolic events of any grade were experienced more frequently in those treated with GCis + N than GCis alone. The GCis + N group also experienced rashes, hypomagnesaemia, and conjunctivitis more frequently than the GCis group. In the EGFR expressing subgroup from the ITT population, rates of AEs were similar to those reported for the total ITT population, although, in the GCis group rates of any grade hypomagnesaemia were higher in the EGFR expressing group than in the ITT population. In addition, rates of any grade rash for both treatment groups in the EGFR expressing group appeared to be lower than in the ITT population. The reasons for this are unclear. Subgroup

analyses suggest that GCis + N has little benefit for people without EGFR expressing NSCLC (H-score = 0).

The ERG considers that the main systematic review in the CS based on the SQUIRE trial matches the decision problem, but that the treatment effect estimates are subject to some bias. The company's interpretation of the evidence is not fully appropriate and justified. The ERG has identified the following concerns and uncertainties:

- The patient population in the SQUIRE trial does not fully match the SmPC for GCis + N, which states GCis + N is indicated only for patients with EGFR expressing squamous NSCLC. The company supplied a post-hoc subgroup analysis for this population in response to NICE's and the ERG's clarification questions.
- The results for the EGFR expressing subgroup do not match those reported in an FDA document[14] for this subgroup. [redacted].
- The OS and PFS results from the EGFR expressing, Western Europe and EGFR expressing Western Europe subgroup analyses are at risk of bias, as these were post-hoc analyses.
- The company does not present a clear rationale for why the Western Europe subgroups are considered more relevant to the UK than the ITT population. The company did not demonstrate a significant treatment interaction for this subgroup. The company's rationale for excluding patients from Eastern Europe from the subgroup considered relevant to the UK is not convincing. The company has also not provided a clear rationale for why patients from other regions that may be similar to England (e.g. North America) were not included in the subgroup considered relevant to England. Additionally, there was an imbalance between the trial arms in ECOG performance status in the Western Europe subgroup at baseline which may have marginally favoured GCis + N. The ERG considers that the EGFR expressing subgroup from the ITT population is the most appropriate population on which to base efficacy conclusions, as this is the licensed indication. Participant baseline characteristics were balanced in the EGFR expressing subgroup between treatment arms.
- It is uncertain if the OS benefits associated with GCis + N compared to GCis in the SQUIRE trial are clinically meaningful, as the company did not define what a clinically meaningful improvement would be. The company only commented that the OS benefit in

the Western Europe group was clinically significant. Clinical expert advice to the ERG is that the improvement in OS in the EGFR expressing subgroup (the population most relevant to the licensed indication) was clinically meaningful.

- Direct efficacy data (i.e. from the SQUIRE trial) were only available for patients with stage IV disease. It is unclear whether the relative effectiveness of GCis + N and GCis would differ for patients with stage III and IV disease.

The company's systematic review conducted for the NMA of OS and PFS identified evidence to enable comparisons of GCis + N against PCarbo, GCis, PCis, DCis and GCarbo, but not against other comparators specified in the final scope and decision problem (DCarbo and VCarbo). A comparison with VCis could only be made for secondary OS median data analyses. All the studies included in the NMA were assessed by the company as having a high risk of bias on at least one quality assessment domain. The NMA showed that median OS was improved when patients were treated with GCis + N compared with GCis and PCis, but not PCarbo, DCis or GCarbo. PFS was longer with GCis + N compared with GCis, PCis and GCarbo, but not the other included comparators.

The ERG also considers that the NMA treatment effect estimates are highly uncertain for the reasons that follow:

- The company appears to have made some inappropriate post-hoc exclusions of studies.
- As acknowledged in the CS, the OS and PFS efficacy estimates from the NMA (which are used in the economic model) are uncertain due to the sparse evidence available to inform the network.
- The limited evidence base meant that: only fixed effects models could be analysed, resulting in narrow credible intervals; only unadjusted analyses could be estimated; only two of the eight pre-planned sensitivity analyses could be undertaken; and the appropriateness of the proportional hazards assumptions could not be determined for all studies in the network.
- Based on limited participant baseline characteristics provided by the company, the ERG does not agree with the company's statement on CS p. 89 that covariates were similar across studies in all but two studies.
- The company did not supply information about the length of follow-up in the studies included in the NMA, so it is unclear if this is comparable across the studies (i.e. that they are similar enough to combine).

- Most of the comparisons were based on indirect evidence, so consistency with direct evidence could not be assessed.
- The NMA was based on mainly potentially underpowered subgroup analyses.

4 COST-EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

1. a review of published economic evaluations of GCis + N compared with GCis for previously untreated patients with locally advanced or metastatic squamous NSCLC. (Section 5.1 of the CS, p. 139).
2. a report of an economic evaluation undertaken for the NICE STA process. The de novo model estimates the cost-effectiveness of GCis + N compared with GCis, GCarbo, PCarbo and DCis for previously untreated patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment. (CS, p. 142).

At the clarification stage, the company submitted a revised version of the de novo economic evaluation in order to be consistent with the SmPC indication (patients with advanced or metastatic EGFR expressing squamous NSCLC tumours). The clarification response included revised tables and figures relating to model inputs and results for the Western European population with EGFR expressing tumours (clarification response Appendix 1). A revised version of the executable Excel model was also submitted. The description, critique and analysis presented below is based on this revised version of the CS model.

4.2 Company's review of published economic evaluations

A systematic literature review was conducted by the company to identify studies that assessed the cost-effectiveness of GCis + N compared to GCis. The search was conducted using Embase, Medline (including Medline-R In-Process), EconLit and the NHS EED databases. Inclusion and exclusion criteria are reported in Table 47 (p. 139) in the CS, which is adapted below in Table 23 with modified inclusion criteria consistent with the text on p. 139 of the CS. The company conducted initial searches that included a wide population of all NSCLC patients, but at full text screening this population was narrowed to studies having <80% of the population having adenocarcinoma or non-squamous histology. This narrowing of the population was not included in the company's Table 47 (p. 139) where inclusion and exclusion criteria are listed.

Table 23 Cost-effectiveness review eligibility criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated NSCLC patients with less than 80% combined adenocarcinoma and non-squamous histology.	Small cell lung cancer patients, non-lung cancer patients (mesothelioma), previously treated patients
Intervention	GCis + N	
Comparator	GCis	
Outcome	Cost per QALY gained, Cost per LY gained	
Study Design	Economic Evaluations (cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-minimisation analyses)	RCTs, observational data, Budget Impact Assessments

GCis, gemcitabine plus cisplatin; GCis + N, necitumumab in combination with gemcitabine plus cisplatin.
Note: Table adapted from CS Table 47, p. 139.

After de-duplication, 718 potentially relevant studies were identified by title and abstract screening. Of these, 44 were identified for full-text screening. Full-text screening was conducted in two iterative passes. In the first pass, studies assessing any NSCLC population were included, whilst in the second pass only studies with less than 80% of patients who had adenocarcinoma or non-squamous histology were included. At first pass 17 studies were included. The second pass reduced this number to 10 studies.

There were 503 studies excluded for study design (19 at full text-screening), 107 for 'not first-line treatment' (6 at full-text screening), and 96 for study population (7 at full-text screening). There were also two papers that were excluded due to being duplicate studies of those found in a grey literature search. No methods or results were reported for this grey literature search. One of the excluded studies, Brown et al. 2013[19] was frequently cited in the model for resource use and cost data.

The 10 papers that were identified for extraction were assessed using the Drummond checklist (reported in Appendix 10 of the CS). None of the studies was deemed suitable for the NICE decision problem and a *de novo* cost-utility analysis model was constructed.

After completion of the systematic review, an additional economic evaluation by Goldstein et al. 2015[20] was identified. This paper reported an economic evaluation of GCis + N compared to GCis using USA Medicare reimbursement rates. The company expressed concern over the generalisability of Goldstein et al. 2015 to a UK NHS context, and did not discuss or critique it

further. The ERG agrees that the cost and cost-utility results from Goldstein et al. are unlikely to be applicable in the UK. However, Goldstein et al. was a well-conducted economic evaluation relevant to the necitumumab scope, and the modelled estimates of clinical benefits (life years gained and QALYs gained) for GCis + N compared with GCis do provide a means of cross-validating the results of the company economic model: see section 4.3.10.4 below for further discussion.

The primary limitation of the systematic review of cost-effectiveness evidence is the potential restrictiveness of the exclusion criteria with regards to study design. The inclusion criteria do not explicitly include cost-consequence analyses, a type of economic analysis where the results are disaggregated. The exclusion criteria also specifically exclude RCTs, observational studies, and budget impact analyses. Economic evaluations that are conducted alongside trials and observational studies are often cost-consequence analyses. Additionally, many budget impact analyses are equivalent to cost-minimisation analyses. This lack of clarity on inclusion and exclusion criteria for study design leaves the 503 studies excluded for study design open to question.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The NICE reference case requirements have been considered for critical appraisal of the submitted economic evaluation in Table 24.

The CS has a number of inconsistencies and potential issues with regard to the NICE reference case. The model population in the CS is consistent with the NICE Reference case, but not with the SmPC. However, the company submitted a revised model and results for the licensed population as part of their clarification response (Clarification Response A1 Appendix 1). Not all comparators were included in the NMA, and therefore could not be included in the model (see section 3.1.7 for discussion of the NMA). Studies reporting results for vinorelbine platinum doublets were excluded, and data were not available for docetaxel plus carboplatin. The model also excluded PCis, which was included in the NMA, as the company argued that this combination is used rarely in NHS practice (Clarification Response B3, p. 11).

Table 24 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	The SmPC indication is narrower than the NICE scope or CS model, but the revised model submitted with the company's clarification response is consistent with the SmPC.
Comparator: As listed in the scope developed by NICE	?	Vinorelbine plus cisplatin, a comparator listed in the scope, was only included in the NMA for median OS, and therefore could not be included in the economic model (*Discussed in section 4.3.4*). PCis was also excluded from the model, as the company argued that it is little used in UK practice.
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	A fully incremental analysis was not reported, but the ERG has created this analysis from the model.
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	?	Not all utility values were derived from EQ-5D, all adverse events were derived from standard gamble methods. *(Discussed in section 4.3.6)*
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	?	Utility decrements for adverse events were derived from members of the general public. Health status measured by EQ-5D was derived from patients. *(Discussed in section 4.3.6)*
Source of preference data: Representative sample of the UK population	?	EQ-5D data used the UK tariff. It is unclear whether studies for adverse events have representative samples. *(Discussed in section 4.3.6)*

NICE reference case requirements:	Included in submission	Comment
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No	Treatment assessed for end of life criteria.
Discount rate: 3.5% pa for costs and health effects	Yes	
Notes: ? = uncertain; N/A=not applicable		

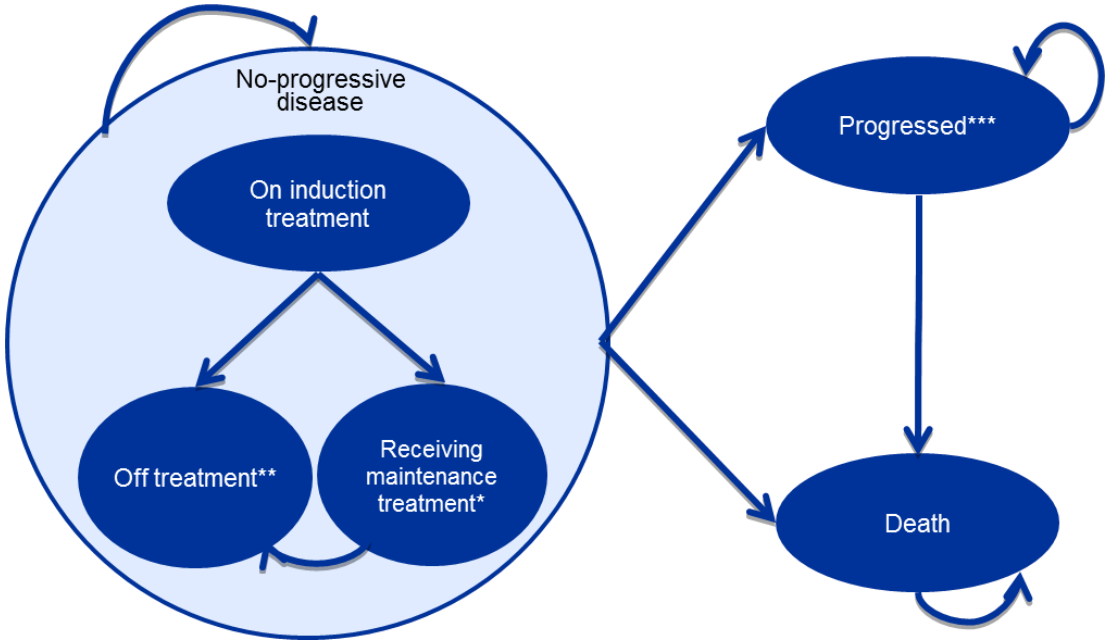
A common thread throughout Table 24 relates to quality of life measurement. The current NICE Guide to the Methods of Technology Appraisal (Methods Guidance)[21] states that utility in cost-utility analyses should be measured using EQ-5D, with patients submitting health state scores and valuation done by the general UK public. The utility values for modelled health states use EQ-5D data measured in accordance with NICE preferences, but the utility decrements used for adverse events are not in accordance with NICE preferred methods.

The company does not present a standard incremental analysis. Instead they present a series of pairwise comparisons between GCis + N and each included comparator. However, the company does report disaggregated costs and QALYs for most interventions, and the model contains full disaggregated results. We have therefore calculated fully incremental results tables (see section 4.3.8 below).

The company has used mostly appropriate methods but their analysis has a number of limitations: due to lack of available data vinorelbine doublets and PCis were excluded from the modelling; utility decrements for adverse events are inconsistent with NICE methodological guidance; and analyses are presented in a pairwise manner that obfuscates cost-effectiveness conclusions.

4.3.2 Model structure and methodological approach

The company model is a state transition model, which reflects the progress of a cohort of patients through the stages of first-line treatment and disease progression to death. The structure is illustrated in Figure 4 below.



* Patients who completed up to six cycles of first-line treatment and are receiving maintenance treatment.

** Patients who discontinued induction treatment or maintenance treatment due to AEs, or physician or patient preference.

*** At least a 20% increase in the sum of the longest diameter of target lesions or unequivocal increase in the size of non-target lesions or the appearance of one or more new lesions.

Figure 4 Company model structure

Note: This figure is a direct reproduction of CS Figure 36, p. 144.

4.3.2.1 Choice of health states and transitions

There are three main health states in the model: no progressive disease (NPD); progressed disease (PD); and death. Patients start in the NPD state at initiation of first-line treatment. Each week, patients may remain in NPD, move to PD as they develop progressive disease, or die. After progression, patients may remain in the PD state for some time but will eventually die.

Within the NPD state, there are three sub-states that reflect the process of first-line treatment: on induction treatment (NPD-induction); maintenance treatment (NPD-maintenance); and off treatment (NPD-discontinued). Patients start in NPD-induction, receiving chemotherapy in three-week cycles. With conventional chemotherapy, patients remain on induction until completion (usually after 4-6 treatment cycles), or they may discontinue early due to unacceptable adverse

effects, patient choice, because of disease progression or death. Patients who complete induction treatment with a platinum doublet move into the NPD-discontinued state, where they remain until progression or death. However, after completion of induction with GCis + N patients move into NPD-maintenance, where they continue to receive necitumumab every three weeks until discontinuation, progression or death.

This broad model structure is appropriate for the decision problem. The three main states and transitions between them reflect the progressive and usually terminal nature of advanced NSCLC, and the three sub-states and transitions are consistent with current and recommended practice for first-line chemotherapy, and with the draft SmPC use of necitumumab.

4.3.2.2 Method for estimating transitions between states

A partitioned survival (or area under the curve) approach was used to estimate the proportion of the cohort in each of the five states at each weekly cycle. The distribution of the cohort between the NPD, PD and Dead states is illustrated in Figure 5. Here the distribution is governed by two survival curves for each treatment: PFS and OS. At each time point (t), the proportion of the cohort who are dead is 1 - OS(t); the proportion in the PD state is OS(t) – PFS(t); and the proportion in the NPD state is just PFS(t).

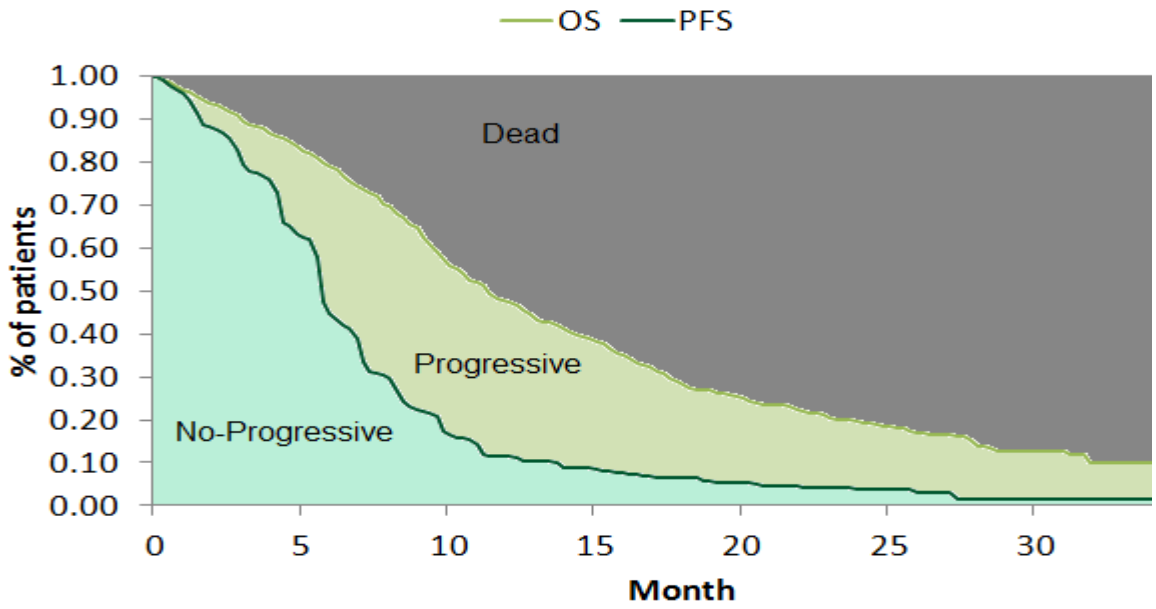


Figure 5 Illustration of health states derived from OS and PFS curves

Note: This figure is a direct reproduction of CS Figure 51, p. 164.

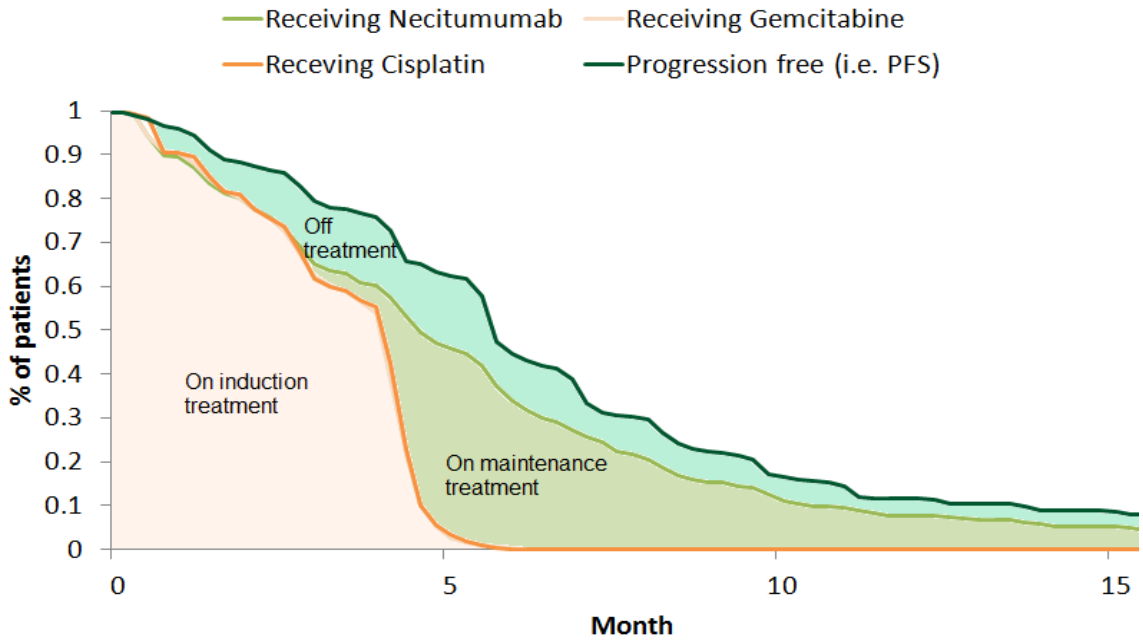


Figure 6 Illustration of sub-states for patients without progressive disease

Note: This figure is a direct reproduction of CS Figure 52, p. 164.

A similar approach was used to split the patients in the NPD state between the induction, maintenance and discontinued sub-states, as illustrated in Figure 6. In this case, the calculations are a little more complicated:

- For the GCis treatment arm, there are three survival curves to consider: PFS and the times to discontinuation of gemcitabine (TTD_g) and cisplatin (TTD_c). At any time (t), the proportion of patients in the induction phase is the proportion who have not yet discontinued both gemcitabine and cisplatin: the maximum of $TTD_g(t)$ and $TTD_c(t)$. The proportion of patients who have stopped treatment but not yet progressed is then the difference between PFS(t) and the proportion on induction.
- For the GCis + N treatment arm, there is an additional survival curve to consider: the time to discontinuation of necitumumab (TTD_n). The proportion of patients in the induction phase is still the maximum of $TTD_g(t)$ and $TTD_c(t)$. The proportion of patients on maintenance treatment is the difference between the proportion who have not discontinued necitumumab and the proportion who have discontinued both gemcitabine and cisplatin: $TTD_n(t)$ minus the minimum of $TTD_g(t)$ and $TTD_c(t)$. The proportion of patients who are off treatment but not yet progressed is the difference between PFS(t) and the proportion on induction or maintenance.

Table 25 Distribution of cohort between states

Health State	Methodology
NPD-induction	Derived from the survival curves for TTD for each treatment arm and treatment compound. Defined as the maximum of the proportion of patients receiving gemcitabine or cisplatin and less or equal to the proportion of patients who were progression-free.
NPD - discontinued	Patients that remain progression-free and are not receiving maintenance or induction treatment. This is calculated by subtracting the proportion of patients on treatment from the proportion of patients in the progression-free disease state.
NPD - maintenance	The proportion of patients on maintenance treatment was estimated as the proportion of patients on treatment minus those on induction treatment. By definition, the proportion on maintenance treatment was zero for the platinum doublet treatments.
PD	All patients surviving (OS) minus those who remain progression-free (OS-PFS).
Death	(1-OS)

Note: Adapted from CS Table 53, p. 165.

This partitioned survival method is convenient for conventional three-state cancer models, as it uses survival results that are usually reported anyway for clinical purposes (PFS and OS). As seen above (Table 25), the method can be extended for models with more than three states,

provided they are acyclic (patients cannot return to a state that they have left). There is some controversy over the validity of Partitioned Survival compared with the more usual Markov method, in which direct estimates of transition probabilities are used to derive the flow of a cohort between states. [22 23] However, a recently published economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC found very similar results with Partitioned Survival and Markov models.[24]

The ERG concludes that the Partitioned Survival method is theoretically reasonable, and that there is no evidence to believe that different results would have been found with an equivalent Markov model. Of course the ability of the model to reflect real-life patient flows depends on the data and methods used to fit and extrapolate the various survival curves. These data and methods are described and critiqued below: for OS see section 4.3.5.1, PFS section 4.3.5.2, and treatment discontinuation section 4.3.5.3. We also assess the consistency of the modelled times on treatment, PFS and OS in comparison with SQUIRE results and external evidence (section 4.3.10).

4.3.2.3 Treatment duration

The protocol for the SQUIRE trial specified up to six, three-week cycles of treatment for induction therapy with GCis and with GCis + N. The duration of treatment was modelled using KM survival curves from SQUIRE. In this study, some patients stopped before six cycles, spending less than 18 weeks on induction therapy, while others spent longer than 18 weeks on induction, due to delays in administration and 'treatment holidays'. To avoid overestimating costs for the latter group, the model included an adjustment for the intensity of treatment incurred within each three-week period. See section 4.3.5.4 for a discussion of how this adjustment factor was calculated. For indirect comparators, the HR of treatment discontinuation was set equal to the HR of PFS. PFS was considered the most suitable proxy for continuation of therapy as only progression-free patients can remain on treatment. Duration of necitumumab maintenance therapy was also modelled using KM survival curves from SQUIRE.

4.3.2.4 Adverse events associated with first-line treatment

TEAEs were not modelled explicitly as health states. This is acceptable if the model captures impacts of the TEAEs on treatment discontinuation, costs and utilities in a way that is reflective

of current NHS practice and any differences between the comparators. The impact of TEAEs on first-line treatment discontinuation was modelled via the TTD survival curves, which regulate transitions out of the NPD-induction and NPD-maintenance states. The model also included direct estimates of costs and disutilities for TEAEs that occurred in at least 2.5% of the total patient population in the SQUIRE trial, and grade 3 and 4 febrile neutropenia. The frequency of these events for GCis and GCis + N comparators was estimated from the observed rates in SQUIRE (see 4.3.5.5, p.102). For other comparators, it was assumed that the relative risks of TEAEs would be the same as for GCis versus GCis + N. Assumptions were also made about the costs of treating the included TEAEs (section 4.3.7) and associated utility decrements (section 4.3.6).

4.3.2.5 Second-line treatment and palliative care

The company model does not explicitly map out subsequent treatment or palliative care after progression. One would not expect such treatments to have an effect on survival, although they may impact on quality of life and costs. The model includes estimates of second-line treatment and palliative care costs in the PD state. Utility impacts of any treatments received after progression are implicitly incorporated in the post-progression utility. This approach is reasonable, provided that the evidence used to underpin the cost and utility estimates in the PD state are reflective of current practice in the NHS, and of any differential impacts of first-line treatment on the use or effects of treatment that patients receive after progression (see section 4.3.6 for a discussion of the PD utility data and section 4.3.7 for resource use and costs).

4.3.2.6 Other assumptions

The model includes a half-cycle correction, assuming that utilities and costs were spread throughout each week cycle. It is stated in the model ('Model design' sheet) that the half-cycle correction was not applied to first-line treatment and administration costs, since the drugs are usually administered at the beginning of the cycle, but in practice it was.

The company provided a summary of methodological and structural assumptions in their model (CS Table 74, p. 212). This is reproduced below, together with comments from the ERG (Table 26). A summary of model parameters is provided in CS Table 73 (pp. 206 to 211). This

includes the mean values used in the base case analysis, 95% confidence intervals and distributions used in the Probabilistic Sensitivity Analysis (PSA).

Table 26 Summary of assumptions in the company model

Assumption	Description	Company justification	ERG position
Patient Population	The Western European subgroup of the SQUIRE trial is representative of the UK NSCLC patient population.	The SQUIRE trial has reported a difference in the clinical efficacy of necitumumab across regions. Statistical analysis has determined that this is not due to a difference in baseline characteristics or treatment received during the SQUIRE trial, but is likely due to potential unobserved treatment effect modifiers including difference in the disease burden associated with NSCLC and environmental causes of cancer including social and cultural practices such as heavy smoking. The literature suggests that this is likely to have resulted in higher incidence and mortality rates for lung cancer patients in Eastern Europe than in Western Europe. The unobserved treatment effect modifiers in the SQUIRE trial may have contributed to an overall varying impact on health outcomes geographically for necitumumab. Therefore, it is considered appropriate to employ data which has been generated from a patient population reflective of the disease burden of NSCLC patients in England. As a result, the economic evidence presented in this submission is reflective of the Western Europe subgroup of the SQUIRE trial as it is considered the most appropriate population for decision making regarding the NHS. The Western European subgroup of patients consists of patients from Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain and UK.	We disagree. There is no evidence of significant differences in treatment effects (OS or PFS) between geographical regions in the subgroup analyses or in the post-hoc Western Europe analysis (see Appendix 6 p. 61-2 of the CS clarification response). There was no statistically significant interaction between Western Europe and the remaining patients in the SQUIRE trial (CS p. 229).
Maximum of 6 cycles of induction treatment	It is assumed that patients receive induction treatment for a maximum of 6 cycles.	The SQUIRE clinical trial data allowed patients to continue induction treatment for a maximum of 6 cycles before initiating necitumumab maintenance treatment. While this varies from UK clinical practice in which patients typically only receive 4 cycles, it has been assumed that this discrepancy has no impact on the outcomes associated with treatment.	We agree. Up to 6 cycles is consistent with the SmPC, and expert advice suggests that 4-6 cycles of treatment is common in the UK.
BSA	The average body surface area (BSA) was considered to be 1.85 m^2. This was used to calculate the cost for all comparators.	The BSA from the trial was slightly lower than the average UK patient found in Sacco et al. 2010 for NSCLC patients.[25] Therefore, it was determined to use the BSA of the average UK NSCLC patient rather than the average BSA from the trial.	We agree with the company approach.

Assumption	Description	Company justification	ERG position
Second-line therapies	It is assumed that the second-line therapies reported in the SQUIRE trial have the same efficacy and utility as those assumed to be routinely used in UK clinical practice.	A number of the treatments used in the SQUIRE trial are not representative of UK clinical practice. However, the rates of use are similar in both arms therefore OS should not differ by arm due to second-line therapy.	This is a reasonable assumption, in the absence of evidence to the contrary. Effects of second-line treatments were not modelled explicitly, but are implicitly included in the SQUIRE results. It would therefore be difficult to model an alternative second-line treatment regimen.
Choice of second-line therapy	Second-line therapies in the model are docetaxel and erlotinib	Brown et al. 2013 assumed that docetaxel and erlotinib are used equally in the second-line setting for NSCLC patients. Positive NICE appraisals for each of these treatments support their choice as second-line therapy in the UK.	NICE Guidance has changed since Brown et al. 2013. Erlotinib is now only recommended for patients who have the EGFR-TK mutation. Expert opinion also indicated that nivolumab is used in second-line therapy.
Duration of subsequent treatment	The duration of subsequent treatment is the median duration of each therapy received in SQUIRE	To determine the number of infusions of each subsequent treatment received, the median duration was used in combination with the cycle length and number of administrations per cycle. Median duration was preferred over the mean, as many patients had not completed subsequent treatment which would result in an underestimated duration if the mean was used. Data was not available to inform use and duration of subsequent treatments for the indirect comparators. Therefore the use and duration of subsequent treatments for indirect comparators was assumed to be equivalent to those observed in the GCis arm. This assumption was tested in scenario analysis.	Although the mean would be preferred for costing, it is reasonable to use the median in this case, due to truncated follow up of second-line treatment. It is reasonable to assume similar second-line treatment patterns following other first-line platinum doublets as for GCis.
End-of-life (EOL) Care	All patients are assumed to receive 2 weeks of EOL care	EOL care is assumed to occur for 2 weeks and is can be provided at home by Macmillan Nurse, in Hospice or a Hospital according to Brown et al. 2013	We agree.

Assumption	Description	Company justification	ERG position
Utility following progression	The utility value for patients that have progressed following first-line treatment is based on Khan et al. 2015	Post-progression health state utilities were obtained from the literature as the SQUIRE trial only conducted EQ-5D assessments until disease progression. For the post-progression health state, the values by Khan et al. 2015 were used because they are values obtained during a RCT of patients that had an active treatment until progression and valued based on UK weights applied to the EQ-5D-3L.	We agree that this is the best available estimate. However, there are questions over its applicability, since the Khan et al. 2015 study included only elderly patients who were considered unfit for chemotherapy.
NMA AE	The rate of AEs for indirect comparators is set equal to AEs observed in the GCis arm.	In the base-case analysis the relative safety profile of indirect comparators versus GCis + N was assumed to be equivalent to the relative safety profile of GCis versus GCis + N. This was because the systematic literature review did not identify AE data specific to the squamous population for these comparators. To examine the impact of this assumption two extreme scenarios were tested, where the risk of AEs for all indirect comparators was set to 0 or to double that associated with the GCis + N arm.	This is a reasonable approach.

Note: Summary adapted from CS Table 74 pp. 212 to 213.

4.3.3 Population

The model submitted with the CS assesses a patient population that is generally consistent with the decision problem. However, the SmPC restricts the indication to first-line treatment of advanced or metastatic EGFR expressing squamous NSCLC. The revised version of the model is appropriate for this indication.

The company model relies on the SQUIRE trial for estimates of OS, PFS and TTD for GCis + N and GCis. As discussed in clinical effectiveness section 3.1.3 above, the population in SQUIRE was somewhat narrower than that in the decision problem, since this study only included patients with stage IV squamous NSCLC, excluding patients with stage IIIB disease. It is unclear whether the relative effectiveness of GCis + N and GCis would differ for patients with stage IIIB and IV disease.

The results of the economic model reported in the CS, and the revisions in the clarification response were based on analysis of the Western Europe subgroup of patients in the SQUIRE trial. Results for the whole ITT sample were only reported in summary form as a scenario analysis (Table 38 of the clarification response). As noted in 2.3 above, the rationale for the use of this subgroup is not robust. Statistical tests did not show a significant difference in treatment effects for this post-hoc subgroup or for the other pre-specified subgroups. The results for the Western Europe subgroup are more favourable to GCis + N than those for the ITT population, so it is likely to have biased the cost-effectiveness results reported by the company. Both the original and revised versions of the submitted models include data for the SQUIRE ITT population and EGFR expressing subgroup from the ITT population, respectively, and so we have conducted further analyses to estimate cost-effectiveness using these data (see section 4.4 below).

Effectiveness for comparator treatments was primarily derived from the NMA. Systematic searches were conducted to populate the NMA (see section 3.1.7) and in these searches studies were excluded based on whether results were reported separately for squamous histology. This approach is consistent with the scope.

Bottom-line summary of ERG view on patient group

The patient population for the economic model generally reflects the scope, but some studies were excluded from the NMA using post-hoc exclusion criteria (see section 3.1.7). Additional analyses including data from the patients in these studies (where studies could have connected to the network) would have been appropriate.

4.3.4 Interventions and comparators

The model includes GCis + N as the intervention, and four of the eight comparators specified in the decision problem: GCis, GCarbo, PCarbo and DCis. The modelled doses and adminstration schedules are broadly in line with UK practice and relevant SmPC criteria.

The CS omits vinorelbine platinum doublets, DCarbo and PCis from their economic evaluation. The company did not identify any evidence relating to the vinorelbine combinations to include in their NMA of OS HR or PFS OR (the NMA data used in the model). DCarbo was also omitted from the economic model, as HR estimates were not available from the NMA. As discussed in 3.1.7, the ERG considers the results from the company's NMA highly uncertain; please see that section for a summary of the key caveats regarding the NMA. The model omitted the PCis combination, for which evidence was available from the NMA. In response to a clarification question (B3), the company noted that market share data suggests that PCis is not typically used in clinical practice in England. The ERG has included PCis against other comparators in the sensitivity analysis in section 4.4.

4.3.5 Treatment effectiveness and extrapolation

4.3.5.1 Overall survival

In the company's base-case analysis, only GCis + N and GCis are compared. For this analysis KM data were used until end of follow-up (36 months), and then parametric regression was used to extrapolate from the last point. This approach gives greater weight to the tails of the KM curves, which are estimated from small numbers of patients, and may introduce error into the survival estimates. In the Western European patients with EGFR expressing tumours, the population used for the base case analysis, there were four patients remaining at the end of follow up.

The company reported that they had used a selection process, based on the NICE Decision Support Unit (DSU) technical support document 14,[26] to select appropriate parametric survival functions (CS p.149). They tested six functional forms: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma, although it was stated that the Gompertz curve was not included as it did not converge. Functions were fitted separately to the trial arms, without predictors. The use of a joint distribution, with a treatment interaction term was also considered. Methods for model selection included: assessment of goodness of fit within the observed period with Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and plots of Cox-Snell residuals; inspection of hazard functions to assess the plausibility of the proportional hazards assumption; visual inspection of the fit against the KM function; and assessment of the tail of the parametric function in comparison with long term survival estimates.The specific methods used to assess suitability of parametric survival curves are given in Table 27.

Table 27 Methods for assessing parametric survival model suitability

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 KM function
	Kernel-smoothed hazard function	Assess the behaviour of the hazard function and the plausibility of the proportional hazards assumption
	Visual inspection	Assess how closely a parametric function follows the KM 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) concurs with any available external longer term data or clinically expected outcomes

Note: This table is a direct reproduction of CS Table 49, p. 149. KM, Kaplan-Meier.

The company provided diagnostic plots for the Cox-Snell residuals and kernel-smoothed hazard functions for the EGFR subgroup in their clarification response Appendix 1. The OS KM survival curve for the EGFR subgroup (ITT population) is shown in Figure 7.

Figure 7 Kaplan- Meier OS survival for EGFR expressing tumours (ITT Population)

Note: This is a direct reproduction of clarification response, Appendix 1, Figure 1

Parametric model fit was assessed by the company using AIC and BIC statistics for the EGFR expressing Western European subgroup of the SQUIRE trial (base case) (clarification response A1, Appendix 1), reproduced below (Table 28). The company also produced a variety of diagnostic plots for this subgroup, which were evaluated in the CS by visual inspection. They concluded that the proportional hazards assumption was not valid, and that the log-logistic curve was the best-fitting distribution.

Table 28 Estimates of model fit for OS in the EGFR expressing Western European subgroup

	AIC	BIC
GCis + N		
Weibull	391.893	397.847
Log-normal	392.795	398.748
Log-logistic	**385.977**	**391.931**
Exponential	395.275	398.252
Generalized Gamma	390.397	399.327
GCis		
Weibull	**416.062**	**422.149**
Log-normal	433.06	439.147
Log-logistic	**416.941**	**423.028**
Exponential	426.513	429.556
Generalized Gamma	417.003	426.134

Note: This is a direct reproduction of Table 18, clarification response Appendix 1

Diagnostic fit was not assessed in the CS for the ITT population. The ERG considers this to be inappropriate, in the absence of evidence supporting the Western European subgroup.

Based on the available diagnostic assessments for the Western European subgroup, the log-logistic curve has the lowest AIC and BIC for the GCis + N group (indicating a better fit), and it has a good visual fit. The log-logistic also provides a reasonable fit for the GCis group, although the AIC and BIC were slightly lower than for the Weibull curve, which also has a good visual fit. The hazard function plots presented in the CS to justify the rejection of the proportional hazards assumption are difficult to assess, due to the small numbers of patients remaining in the unstable portions of the graphs. Statistical tests for proportional hazards were not presented in the CS, and the analysis for the larger ITT population might have been informative.

The diagnostic statistics and curves presented are not definitive, and the visual fit was similar between the log-logistic, Weibull, and generalised gamma distributions. The choice of curve should also be predicated on clinical plausibility. The log-logistic curve has a heavy tail, so predicts that a proportion of patients survive for a long time. This may be questionable for the stage IV NSCLC population in the SQUIRE trial. Relative expected survival from Cancer Research UK shows stage IIIB patients having a 5-year survival rate of around 6.32%,[27] whilst

extrapolation using the company methods estimates 5-year survival of 7% for GCis + N and 2% for GCis. Estimates from United States SEER data indicated that patients with stage IV disease have expected 5-year survival of approximately 1%.[28] Comparator trials used a mixed population of stage IIIB and stage IV patients, so it is likely that expected survival for these comparators at five years is between 1% and 7%.

Trial KM estimates of OS with alternative extrapolations (log-logistic and Weibull curves) are shown in Figure 8**Error! Reference source not found.** for the Western European subgroup with EGFR expressing tumours. It can be seen that the area between the curves (the estimated life years gained from GCis + N compared with GCis) is greater when log-logistic curves are used for extrapolation than when Weibull curves are used. Note that the start point of the parametric extrapolations (which are fitted on the whole KM dataset) are adjusted to meet the final KM endpoints, which are estimated from a small number of patients remaining in the analysis at that time.

In the analysis that included the remaining treatment regimens (PCarbo, PCis, GCarbo and DCis) OS was modelled using HR derived from the fixed-effects NMA with GCis + N used as the baseline survival curve. To enable comparison via NMA, proportional hazards were assumed – indicating that non proportional hazards survival functions (such as the log-logistic) would not be appropriate. Of the candidate proportional hazards survival curves tested, as described above, the company selected the Weibull curve, as it is the best fitting curve that can be used in a proportional hazards model, but with reservations on whether proportional hazards assumptions were justified. The ERG does not find fault with assuming proportional hazards. Additionally, since GCis + N is the new treatment, it is easier to interpret its comparative effectiveness if GCis is used as the baseline survival curve.

Figure 8 SQUIRE OS KM and fitted curves; Western European subgroup with EGFR expressing tumours

4.3.5.2 Progression free survival

Disease progression was based on PFS, which was defined by the time from randomisation until first radiographic documentation of objective progression, or death from any cause. PFS for GCis + N and GCis was estimated based on KM data from SQUIRE. Extrapolation using a log-logistic parametric survival curve was used for the remainder of patients who had not progressed at the end of the trial (4% of patients). The log-logistic curve was chosen in the same manner as for OS (Table 27), diagnostic plots for model fit in EGFR expressing tumour patients were reported in the Clarification Response (Appendix 1). The PFS survival curve for the EGFR subgroup (ITT population) is provided in Figure 9.

The PFS curve used in the base case of the company EGFR expressing model is given in Figure 10. The ITT curves for the EGFR expressing population appear to converge earlier than the curves and extrapolation for the EGFR expression Western European subgroup used in the company model, and the overall PFS benefit for GCis + N compared to GCis appears smaller. PFS in the original model submitted by the company (which includes patients without EGFR expression reported) was externally validated against Hoang et al. 2013.[29] In Hoang et al. 2013 GCis patients had an expected PFS time of 4.3 months (3.3 - 6.6 months), which is similar to the estimate of 4.37 months from the separately fitted log-logistic curve for GCis using SQUIRE data.

4.3.5.3 Time to treatment discontinuation

A KM analysis was conducted on the safety population of the SQUIRE trial (all patients who received at least one dose of the study drug) to estimate time to treatment discontinuation. No parametric estimation was necessary as >99% of patients had discontinued treatment at the end of the trial.

As none of the trials included in the NMA reported treatment discontinuation specific to the squamous population, the HR of treatment discontinuation was assumed to be the same as the HR of PFS. The company states that clinical experts were consulted to validate this assumption.

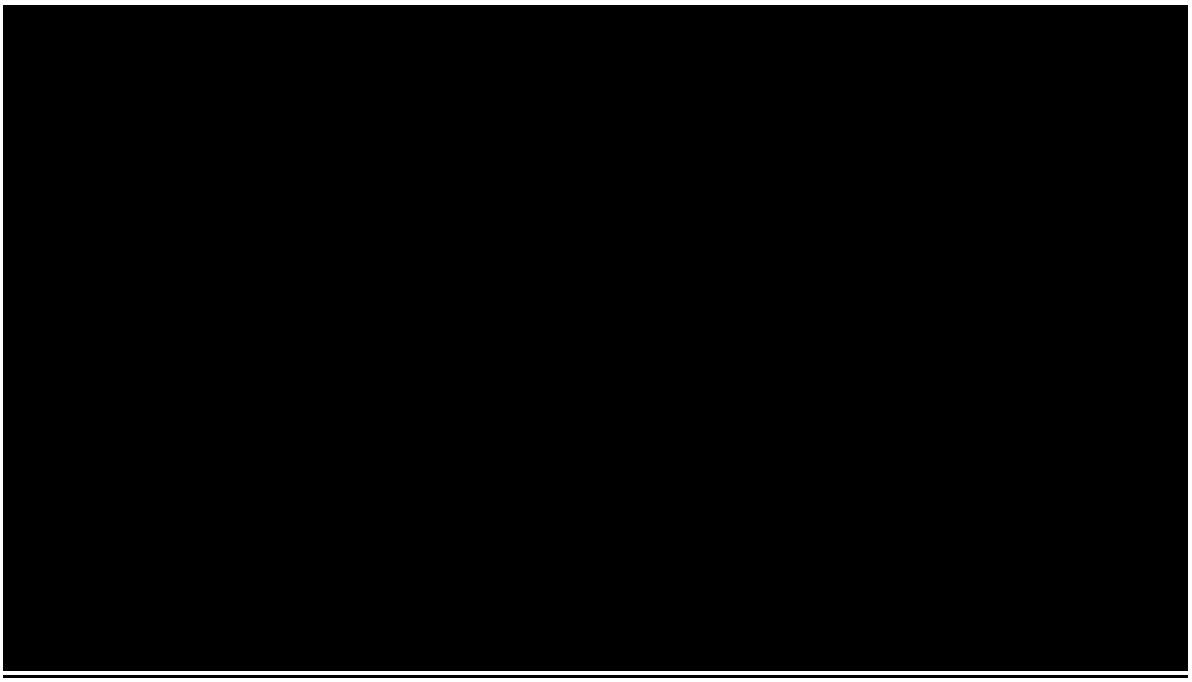


Figure 9 Kaplan-Meier PFS for EGFR expressing tumours (ITT population)

Note: This figure is a direct reproduction of clarification response, Appendix 1, Figure 3

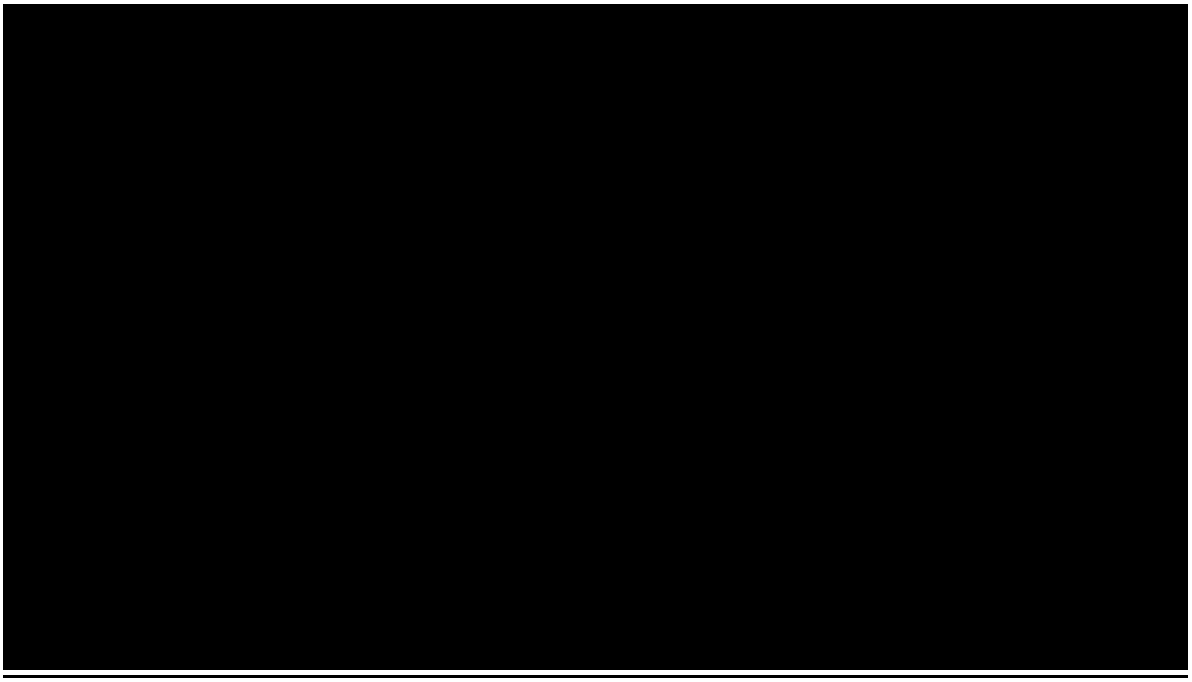


Figure 10 Kaplan-Meier and extrapolation of PFS in patients with EGFR expressing tumours (Western European subgroup)

4.3.5.4 Treatment duration adjustment

Because patients experienced delays in treatment due to AEs or personal reasons, a proportion of patients remained on induction therapy beyond 18 weeks. Without adjustment the time on treatment is overestimated: 15.5 days of treatment for GCis + N compared to 13.6 observed, and 8.96 days of treatment for GCis vs 7.4 observed. To adjust for this, ratios were applied to the costs for the drugs in the model, 0.88 for GCis + N and 0.83 for GCis. Treatment intensity was assumed identical to GCis for all other comparators. Where treatment holidays are due to adverse events, treatments with lower adverse event rates could be made less expensive by this assumption. Expert advice indicated that carboplatin based regimens have less toxicity.

4.3.5.5 Adverse events

The incidence and duration of AEs for GCis + N and GCis were derived from the SQUIRE trial. Treatment emergent adverse events were included if they occurred in 2.5% or more of the total patient population. Because febrile neutropenia is considered to have important cost and utility consequences, it was also included in the analysis. Probilities of adverse event occurrence were converted into one week probabilities, adjusted for when they occurred (induction or maintenance). Induction corresponded to 13.6 weeks for GCis + N and 12.8 weeks for GCis. Maintenance continued until 21.7 weeks for GCis + N.

Apart from the SQUIRE trial, none of the studies included in the NMA reported AEs specifically for the squamous population. Therefore, the company assumed that the relative risk of adverse events for comparators was the same as the relative risk for GCis versus GCis + N. The company stated that this assumption was validated with clinical experts. Given that no studies included in the NMA compared AEs in squamous and non-squamous patients, there is insufficient data to conclude that histology drives AEs. It might therefore have been more appropriate to consider all evidence on AEs, independent of histotype. The RCT evidence base for AEs for the comparator treatments is substantial, as nearly every trial reports safety data.

As the company assumes that adverse event rates are identical for GCis, GCarbo, PCarbo, and DCis, the per cycle calculations in the model should produce identical results. They do not. There are small discrepancies in the rates of adverse events, and their utility decrements and costs. Between GCis and the other comparators, the rate of hyponatraemia is lower in GCarbo, PCarbo and DCis. However, the utility decrements per cycle are higher for GCarbo, PCarbo, and DCis. Similarly, AE costs are higher in GCarbo, PCarbo, and DCis

Bottom-line summary of ERG view on clinical effectiveness

Primary clinical effectiveness data for GCis + N and GCis was derived from the good quality SQUIRE RCT.[8] The approach taken by the company was generally appropriate, with the important caveat of the use of the Western European subgroup, rather than the ITT dataset.

In order to extend the model to a lifetime horizon some extrapolation was required. The method of extrapolation, modelling from the last follow-up observation, emphasises the tail of the KM curve based on sparse data, and appears to favour GCis + N. The choice of the log-logistic curve for extrapolation had good fit, but may not be the most clinically plausible curve for OS, as it predicts 7% OS at five years in a stage IV NSCLC population, which is higher than estimated 6.32% 5-year survival for stage IIIB patients from Cancer Research UK using data from the East Anglia Cancer Network.[27] Data for stage IV patients was not available in the East Anglia Cancer Network from Cancer Research UK, but SEER data from the United States estimated five year survival for stage IV at approximately 1%.[28] However, trials for other comparators included mixed stage IIIB and stage IV populations, therefore the 5-year OS in the stage IIIB and stage IV NSCLC patients should be expected to be between 1% and 7%.

Evidence for the effectiveness of GCarbo, PCarbo and DCis were derived from the NMA via HRs. For these analyses a proportional hazards assumption was used, with Weibull curves fitted to GCis + N and GCis survival data from SQUIRE, and hazard ratios applied in comparison to GCis + N.

4.3.6 Health related quality of life

Quality of life data enters the model as utility scores assigned to the following health states: NPD-induction, NPD-maintenance (this health state only applies to GCis + N), NPD-discontinued, PD, and death. Death has a utility score of 0 by definition. Utility decrements were used to represent the effects AEs have on patient quality of life. The company derived quality of life data from the SQUIRE trial and from a systematic review of the literature. SQUIRE collected EQ-5D-3L utility data from patients at baseline, at each chemotherapy session (approximately every three weeks) and then every six weeks after discontinuation of treatment for each treatment arm. The systematic review identified further quality of life data.

Utility scores for the NPD-induction, NPD-maintenance (this health state only applies to GCis + N), and NPD-discontinued health states were derived from the SQUIRE trial.{Thatcher, 2015 #29} Utility data was pooled between the treatment arms during the induction treatment phase, and after discontinuation. All utilities from the SQUIRE trial are in accord with NICE preferred methods for utility measurement in economic evaluations: they use EQ-5D, health status reported by patients, and valuation from the UK general public (UK EQ-5D-3L tariff).[21]

Table 29 Criteria for company systematic review of HRQoL

	Inclusion criteria	Exclusion criteria
Population	Adult patients with metastatic or advanced NSCLC	Small-cell lung cancer; not advanced or metastatic; stage I, II, III only
Intervention	Not restricted	
Comparator	Not restricted	
Outcomes	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)
Language	English	Non-English
Date	2000 onwards [b]	Prior to 2000 [b]

Notes: This tabe is a direct reproduction of CS Table 55, p. 168. 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] 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.[30] 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 year 2013 were excluded.

The utility score for progressive disease and all utility decrements for adverse events in the CS were identified through a systematic review of the literature. The systematic review searched the following databases: PubMed, EMBASE, MEDLINE, Cochrane Library, NHS Economic Evaluation Database (NHS EED), Cost-effectiveness Analysis Registry from the Centre for the Evaluation of Value and Risk in Health, and EconLit. The inclusion and exclusion criteria are

reported in Table 29. Health state utility scores derived from SQUIRE and the systematic review of HRQoL are presented in Table 30.

Table 30 Utility values used in the CS economic model EGFR expressing (Western European subgroup)

Health state or adverse event	Mean	Lower CI	Upper CI	Distribution in PSA	Source
Utility scores for health states in the economic model					
Pre-progression and on induction treatment	[redacted]	[redacted]	[redacted]	Beta	SQUIRE
Pre-progression and off treatment	[redacted]	[redacted]	[redacted]	Beta	SQUIRE
Pre-progression and receiving maintenance treatment	[redacted]	[redacted]	[redacted]	Beta	SQUIRE
Relapsed progressive disease	0.55	0.52	0.58	Beta	Khan et al. 2015

Note: Data in this table were derived from Table 21 in clarification response Appendix 1.

The systematic review of HRQoL publications identified 833 references, of which 27 were selected for data extraction. Of these 27 studies, three studies provided utility scores for a squamous NSCLC population.[31-33] All three of these studies used EQ-5D-3L data. The three studies were quality assessed according to the NICE Technical Support Document for assessment of health state specific utility studies.[34]

Four of the studies identified in the systematic review of HRQoL included information on disutilities related to adverse events. The company assessed the disutilities for these studies for inclusion in the economic model. Utility decrements were selected from two of the four studies, Nafees et al. 2008[35] and Doyle et al. 2008.[36] Neither of these studies follow NICE Reference Case preferred methods. In the current NICE Guide to the Methods of Technology Appraisal[21] preferred methods are provided for measuring HRQoL: the preferred preference based utility questionnaire is the EQ-5D, health status data should be collected from patients, and health state valuations should be from the UK general public. Where EQ-5D data is not available, and validated preference-based utility scores are not used, NICE prefers that utility data be collected using the time trade-off method. Where these methods are not available, NICE recommends the

use of mapping algorithms. Any other methods of measuring utility may be considered appropriate, but require further justification, and should be considered for sensitivity analyses, according to NICE.[21] Nafees et al. 2008[35] and Doyle et al. 2008[36] do not use EQ-5D, health status is not collected from patients, and the standard gamble method of utility measurement is used. To account for the effect of pulmonary embolisms on HRQoL, an additional study, Locadia et al. 2004[37] was identified. Similar to adverse event utility decrements identified in other studies, the methods in Locadia et al. 2004[37], do not follow NICE Methods Guidance preferences for utility measurement. Locadia et al. 2004[37] did not use EQ-5D, and did not value states using the general public, but did derive utility scores from patients using the time trade-off method. Utility decrements for adverse events reported in the CS are presented in Table 31.

The utility data collection schedule in the SQUIRE trial means that patients who received necitumumab have, on average, a greater number of data points due to more frequent observation. They also have a health state that corresponds to the period directly after discontinuation of platinum doublets (NPD-maintenance). Patient utilities were averaged across the length of time spent in the respective treatment states. This means that patients in the off-treatment health state in the GCis + N arm are further removed from discontinuing platinum doublet therapy and further along in their disease, on average, than patients in the GCis arm. The difference in measurement timing has the potential to bias the utility estimates in favour of GCis + N. In order to address this potential bias, the ERG requested utility scores reported by arm, for each time point that was recorded with adjustment for baseline imbalances. This data would allow the comparison of HRQoL in the two treatment arms by time, rather than by potentially biased health states. This data was not supplied as requested in the company's response to clarification questions.

Table 31 Utility decrements and duration of effect for AEs in company model

Adverse event	Mean	Lower CI	Upper CI	PSA distribution	Source
Neutropenia	0.09	0.05	0.13	Beta	Nafees et al. 2008
Anaemia	0.07	0.04	0.12	Beta	Nafees et al. 2008
Thrombocytopenia	0.09	0.05	0.13	Beta	Nafees et al. 2008
Hypomagnesaemia	0.09	0.06	0.12	Beta	Nafees et al. 2008
Pulmonary Embolism	0.32	0.12	0.57	Beta	Locadia et al. 2004
Asthenia	0.07	0.04	0.12	Beta	Assumption
Leukopenia	0.09	0.05	0.13	Beta	Assumption
Rash	0.03	0.02	0.05	Beta	Nafees et al. 2008
Fatigue	0.07	0.04	0.12	Beta	Nafees et al. 2008
Nausea1	0.05	0.02	0.09	Beta	Nafees et al. 2008
Vomiting1	0.05	0.02	0.09	Beta	Nafees et al. 2008
Hypokalaemia2	-	0.00	0.00	Beta	Assumption
Hyponatraemia2	-	0.00	0.00	Beta	Assumption
Febrile neutropenia	0.09	0.06	0.12	Beta	Nafees et al. 2008
Dyspnoea	0.05	0.02	0.10	Beta	Doyle 2008
Pneumonia	0.07	0.04	0.12	Beta	Assumption
Utility decrement duration for AEs grade 3/4 (days)					
Neutropenia	7.00				
Anaemia	7.00				
Thrombocytopenia	7.00				
Hypomagnesaemia	12.30				
Pulmonary Embolism	30.44				
Asthenia	7.00				
Leukopenia	7.00				
Rash	12.30				
Fatigue	32.00				
Nausea[a]	2.50				
Vomiting[a]	2.50				
Hypokalaemia[b]	7.00				
Hyponatraemia[b]	7.00				
Febrile neutropenia	7.00				
Dyspnoea	7.00				
Pneumonia	7.00				

[a]Nausea and vomiting combined into one state in the model
[b]No adverse utility in the model, decrement listed in CS Table 60

Note: Table derived from CS Table 73, pp. 208 to 209.

No imputation methods were reported for the analysis of SQUIRE EQ-5D data. Approximately [redacted] across both arms had baseline utility data and at least one completed post-baseline assessment in the ITT population as reported in section 4.9 of the CS. However, the data used in the model is not from the ITT population in the base case, it is from the Western European population, so the amount of missing data is unclear. The ERG requested data on utility scores collected at each follow-up with the number of patients missing. This data was not provided by the company, so the amount of data gathered and the amount of data missing over the length of the SQUIRE trial is unclear.

Using the Western European population for utilities was not justified in the CS. It is possible within the model to use utility values from the ITT population. Table 32 reports the SQUIRE trial ITT pre-progression health state utility values from the company's model. The utility value for the progressed state is derived from Khan et al. 2015[33] and remains unchanged from the Western European (base case) analysis. The utility scores for the ITT population are lower than those found in the Western European (base case) analysis in general, but have the greatest difference for maintenance therapy. Because of this, they adversely affect the cost-effectiveness of GCis + N, as the maintenance state is exclusive to GCis + N.

Table 32 Pre-progression utility scores from the SQUIRE EGFR expressing ITT population (company model)

Health State	Utility Score (mean)	Standard Error
On induction treatment	[redacted]	[redacted]
Off treatment	[redacted]	[redacted]
Receiving maintenance treatment	[redacted]	[redacted]

There are several limitations in the company's approach to measuring quality of life. They went through considerable effort to add utility decrements for adverse events to the economic model. However, it might be argued that this was unnecessary, as the patients in the SQUIRE trial will have included adverse events in their assessment of their own quality of life during the trial.

The assumption that the treatment arms produce the same utility for the progression free on induction and progressed states is unnecessary. It might have been more appropriate to adjust the arms for baseline imbalances and allow them to have different utilities over time. Another

method of handling utility scores would be to assign them to cycles in the model instead of to health states. This would allow more granular utility data and eliminate potential biases due to differential measurement timings.

Bottom-line summary of ERG view on patient outcomes

The data from the SQUIRE trial appears to have been collected in an appropriate manner, but has not been used to its full potential. There is little reporting on missing data and the base case analysis used utility scores from the Western European subgroup. AEs in the model were derived from sources that have poor compliance with NICE's preferred methods of HRQoL measurement methods[21] and using this data is a form of double counting.

4.3.7 Resource use and costs

4.3.7.1 Resource Use

The model included resource use for drug administration, disease monitoring and management, adverse events, and for active treatment and palliative care following disease progression. Resource use for drug administration, disease monitoring and supportive care was obtained from a retrospective medical chart review (Table 33) and validated by expert opinion. In addition to the retrospective chart review, a systematic review and consultations with experts were undertaken to identify further resource use. Clinical experts were consulted to confirm resource use assumptions.

Table 33 Retrospective medical chart review methodology

objective	**To assess treatment patterns among patients with a diagnosis of metastatic squamous NSCLC and who are receiving first-line treatment with a platinum-based doublet regimen in the UK.**
Study design	This study was carried out using a retrospective, non-interventional observational review of medical records for patients with a confirmed diagnosis of metastatic squamous NSCLC (i.e., Stage IIIB with pleural effusions according to the 6th edition of the AJCC guidelines or Stage IV according to the 6th or 7th edition of the AJCC guidelines; or initially diagnosed with a more limited stage and progressed to metastatic disease). In this study, physicians served as the direct data abstractors, allowing for efficient and accurate interpretation of their own notes and records. Participating physicians selected patients who met the screening criteria and abstracted the requested data elements which existed in the patient's chart at the time of abstraction. Physicians then entered the abstracted data into a web-based DCF, which was compiled into a patient-level analytic file. As patient chart data may contain highly sensitive and private personal health information, only anonymous data were collected for use in this study. The patient's physician was the only entity who had access to potentially sensitive patient data.
Sample size	Due to the retrospective, descriptive nature of this study, the study size was not based on formal statistical considerations. A sample of 54 physicians in the UK participated in the study with 203 patients in the UK.
Physician Selection	Physicians recruited to perform the patient-level medical record abstractions must have been located in the UK, with a case load of at least 6 patients with metastatic squamous NSCLC treated in the past 12 month. They must have also been in practice for 5 to 30 years after completion of formal training or board certification and a medical specialty of medical oncology, clinical oncology, haematology-oncology, pulmonology, or internal medicine specialized in pulmonology.
Patient Selection	The patients must have a confirmed diagnosis of metastatic squamous NSCLC, aged at least 18 years on the date of diagnosis of metastatic squamous NSCLC, initiated systemic treatment after diagnosis of metastatic disease with a platinum-based doublet regimen (i.e., cisplatin or carboplatin in combination with another agent) and stopped first-line systemic treatment and stopped maintenance therapy (if any maintenance therapy was received after first-line treatment). Maintenance therapy was defined as either the continuation of one first-line therapy agent or a switch to another single agent before any disease progression occurred.
Outcomes Measured	Overall treatment patterns, systematic therapy and supportive care

Note: This table is a direct reproduction of CS Table 65, p. 191.

The systematic review search strategy expanded search strategies conducted as part of the erlotinib STA (TA 258) and crizotinib STA (TA 296) related to advanced or metastatic lung cancer. Medline, Medline In Process and EMBASE were searched using the OVID platform. An

expanded strategy was adopted for the NHS EED and NICE technology appraisals. For the update of the resource use systematic literature review, the date limits were restricted to 2012 onwards to account for the time elapsed since the searches performed for erlotinib and crizotinib. The inclusion and exclusion criteria for the resource use systematic review are reported in Table 34.

Table 34 Resource use systematic review inclusion/exclusion criteria

Population	**Adult patients with metastatic or advanced lung cancer**
Interventions	Any
Comparators	Any
Outcomes	Resource use from a UK NHS perspective
Study Design	Any
Exclusion Criteria	Not in metastatic/advanced lung cancer Not UK specific Not regarding resource use Publications prior to 2012

Note: This table is a direct reproduction of CS Table 61, p. 245.

In addition to studies identified by the update search, the studies identified in the original TA 258 and TA296 searches were evaluated. In total 19 studies, including 10 NICE STAs and 9 publications, were identified. Among these studies, only Brown et al. 2013[19] was utilised. Brown et al. 2013[19] provided data on AE costs and palliative care costs.

The identification of resource use data appeared to be well conducted and comprehensive. The restrospective chart review had a thorough description and was conducted in a squamous NSCLC population, which is directly relevant to this STA. Brown et al. 2013[19] and other studies identified in the systematic review of resource use did not directly compare resource use in squamous populations. The justification for selecting Brown et al. 2013[19] for resource use was not provided, but it appears to be appropriate.

4.3.7.2 Unit costs

Unit costs were derived from the drugs and pharmaceutical electronic market information tool (eMit) (December 2014), the British National Formulary (BNF) 68 (2015), NHS Reference Costs (2013/14), and Personal and Social Services Research Unit (PSSRU) costs (2014).[38-41] EMit

costs were used for all pharmacological treatments with the exception of erlotinib and dietary supplements, which were obtained from the BNF. NHS Reference Costs were used for outpatient administration of chemotherapy, medical oncology outpatient appointments, palliative care specialists, biochemistry tests, CT scans, chest x-rays, radiation therapy, red blood cell transfusions, hospitalisations and Accident and Emergency outpatient visits. PSSRU costs were used for GP visits, clinical nurse specialists, GP home visits and community nurse visits. In general, the most recent unit cost data was used, but the use of more recent eMit data (which was published in November 2015[42]) would allow the analysis to be conducted in 2015 GBP (£) instead of 2014 GBP (£).

Drug costs

The acquisition costs for treatment are reported in Table 35 and Table 36. Drug costs were derived from the company for GCis + N, whilst eMit prices were used for comparators, and the BNF was used for erlotinib second-line therapy. The cost of administration was derived from NHS Reference Costs for delivering complex chemotherapy at first attendance, and for subsequent administrations. The cycle length and number of administrations for each treatment were obtained from the appropriate SmPC. After discontinuing first-line treatment, patients were either off treatment or receiving second-line therapy of docetaxel or erlotinib.

Proportions of patients receiving second-line therapy were based on the SQUIRE trial. Patients on GCis + N and GCis received different mixes of second-line therapies. The CS states that 47.3% of patients in the GCis + N arm and 44.7% of patients in the GCis arm received second-line therapy. For GCis + N, 30.6% of patients received second-line docetaxel and 10.5% received erlotinib. For GCis, 23.2% received second-line docetaxel and 13.7% received erlotinib. The company's estimated cost for each daily erlotinib administration is £67.78, £1,423.46 per 3 week cycle. The cost per docetaxel administration is £54.53 and is given every three weeks. The company indicated that, according to their market data, 70% of lung cancer patients receiving second-line therapy receive docetaxel, and 30% receive erlotinib.

Table 35 Drug costs

Regimen	Technology	Recommended Dose	Cycle Length	Unit Cost	Source
First-line treatment					
GCis + N	Necitumumab	800 mg on Days 1 and 8	3 weeks	800mg vial=£1,450 [redacted]	
	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	eMit December 2014
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	eMit December 2014
GCis	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	eMit December 2014
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	eMit December 2014
GCarbo	Gemcitabine	1250 mg/m^2 on Days 1 and 8	3 weeks	200mg/2ml=£5.11; 1g/10ml=£12.71; 2g/20ml=£29.03	eMit December 2014
	Carboplatin	400 mg/m^2 on day 1	3 weeks	450mg/45ml=£19.07; 150mg/15ml=£7.71; 50mg/5ml=£3.51	eMit December 2014
PCarbo	Paclitaxel	175 mg/m^2	3 weeks	150mg/25ml=£12.71; 30mg/5ml=£3.78	eMit December 2014
	Carboplatin	400 mg/m^2 on day 1	3 weeks	450mg/45ml=£19.07; 150mg/15ml=£7.71; 50mg/5ml=£3.51	eMit December 2014
DCis	Docetaxel	75 mg/m^2	3 weeks	80mg/ml=£25.73; 20mg/1ml=£7.45; 140mg/7ml=£54.60	eMit December 2014
	Cisplatin	75 mg/m^2 on day 1	3 weeks	100mg/100ml=£15.60; 10mg/10ml=£3.71; 50mg/50ml=£8.09	eMit December 2014
Second-line treatment costs					
D	Docetaxel monotherapy	75 mg/m^2	3 weeks	80mg/ml=£25.73; 20mg/1ml=£7.45; 140mg/7ml=£54.60	eMit December 2014
E	Erlotinib	150 mg	3	25mg=£378; 100mg=£1,324;	BNF 68

monotherapy	weeks	150mg=£1,632 *All strengths are provided as 30 tablets	March 2015

Note: This table was adapted from Table 66 and Table 67 in the CS.

Table 36 Cost of chemotherapy administration

Description	Unit Cost	Reference
Deliver Complex Chemotherapy, at First Attendance	£401	NHS Reference Cost 2013-2014. Chemotherapy administration. Day Case. Currency Code SB14Z.
Deliver subsequent elements of a chemotherapy cycle	£328	NHS Reference Cost 2013-2014. Chemotherapy administration. Day Case. Currency Code SB15Z.

Note: This is a direct reproduction of CS Table 68, p. 195.

It would have been more appropriate to use this marketing data in the model. As currently modelled, the make-up of second-line therapy favours GCis + N, and it is unclear if this would be replicated in UK general practice. The ERG believes that the quantity of patients receiving second-line treatment and the duration of that treatment are appropriately derived from SQUIRE, but that the make-up of therapies received by patients on second-line therapy should be equivalent between arms. However, it should be noted that whilst the methods used in the company model are appropriate, NICE guidance on second-line erlotinib treatment has changed. Erlotinib is now only recommended for second-line treatment in patients with EGFR-TK mutation. Additionally, expert advice indicated that nivolumab is also used in second-line therapy.

Treatment intensity was adjusted using SQUIRE data for GCis + N and GCis and assuming comparators were equivalent to GCis. Drug wastage was included by default.

Health state costs

Beyond chemotherapy, patients in the model receive supportive and palliative care. Table 37 reports resource use and costs for patients on active therapy, whilst Table 38 reports resource use and costs for patients receiving supportive care.

The retrospective medical chart review determined that patients receiving active therapy require the following resource use: medical oncologist outpatient visits, GP visits, clinical nurse specialists, biochemistry tests, full blood count tests, CT scans, Chest X-rays, red blood cell

transfusions, opiate analgesics, antiemetics, accident and emergency (A&E) visits and oral dietary supplements. This resource use was determined to be appropriate for all patients receiving active treatment, even if they had previously progressed (includes patients on second-line therapy).

For patients who have progressed and are only receiving supportive care, the retrospective medical chart review determined the following resource use: medical oncologist outpatient appointments, GP home visits, district nurse visits, clinical nurse specialist home visits, chest x-rays opiate analgesics, antibiotics and A&E visits.

For patients who are within the last two weeks of life and receiving palliative care, the model assumes that 55.8% of patients receive palliative care in hospital, 16.9% will receive palliative care in hospice and 27.3% will receive palliative care at home with the aid of a Macmillan nurse, community nurse and GP home visits based on Brown et al. 2013.[19] Table 39 reports resource use for patients on palliative care at the end of life.

Table 37 Health state unit costs for patients receiving active therapy

Resource Required	Frequency	Unit Cost	Reference
Outpatient Visit with medical oncologist	100%; Once every 3 weeks	£147	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
GP Visit	100%; Once monthly	£35	Resource use: Brown (2013), Appendix 1 NICE CG81 Cost: PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Surgery consultation lasting 11.7 minutes.
Clinical Nurse Specialist	100%; Once every 3 weeks	£22	Resource use: Clinical Expert Opinion Cost: PSSRU 2014. 10.7 Nurse advanced (includes lead specialist, clinical nurse specialist, and senior specialist). £22 per surgery consultation (excluding qualification cost).
Complete	100%;	£3	Resource use:

Resource Required	Frequency	Unit Cost	Reference
Blood Count	Once per week		Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Haematology. Currency Code DAPS05.
Biochemistry (Renal and Liver Function)	100%; Once per week	£2	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Clinical Biochemistry. Currency Code DAPS04.
CT-Scan(Chest)	100%; once every 6 weeks	£110	Resource use: Retrospective Medical Chart Review Cost: NHS Reference Cost 2013/2014. Weighted average of computerised tomography scan with outpatient service description. Currency Code (RA08A, RA09A, RA10Z-RA14Z, RA50Z).
Chest X-ray	100%; once every 3 weeks	£30	Resource use: Retrospective Medical Chart Review Unit Cost: NHS Reference Cost 2013/2014. Directly Accessed Diagnostic Services. Direct Access Plain Film (Currency Code DAPF).
Opiate analgesics (30mg of codeine 4 times daily)	30%; daily	£0.11 per day	Resource use: Retrospective Medical Chart Review Unit Cost: EMIT December 2014. Codeine 30mg tablets/Pack size 100=£2.86
Antiemetic's (16mg ondansetron daily)	100%; 3 day of every cycle	£0.36 per day	Resource use: Clinical Expert Opinion Cost: EMIT December 2014. Ondansetron 8mg tablets / Pack size 10=£1.82
Red blood cell transfusion	21%; two units every 3 months	£195 per transfusion	Resource use: Retrospective Medical Chart Review Cost: NHS Reference Cost 2013/2014. Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over. Procedures in Outpatients (Currency Code SA13A)
Accident & Emergency visit	11%; once every 12 weeks	£88	Resource use: Retrospective Medical Chart Review Cost: Non-Consultant led Outpatient Attendances. Non-admitted Face to Face Attendance, First. Currency Code (WF01B). Accident & Emergency.

Resource Required	Frequency	Unit Cost	Reference
Antibiotics	25%; 7 days in every cycle	£1.71 per day	Resource use: Retrospective Medical Chart Review Cost: 500 mg of levofloxacin once daily for 7 days. Levofloxacin 500mg/pack size 10=£17.19
Oral dietary supplement (200 ml Ensure daily)	11%; daily while on	£2.02 per day	Resource use: Retrospective Medical Chart Review Cost: Ensure Plus. Liquid. Bottle, 200ml=£2.02

Note: Adapted from CS Table 69, pp. 197 to 199.

Table 38 Resource use and costs for patients receiving supportive care

Resource Required	Frequency	Unit Cost	Reference
Outpatient Visit with medical oncologist	100%; Once every 3 weeks	£147	Resource use: Clinical Expert Opinion Cost: NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
District Nurse	100%; Twice monthly	£19	Resource Use: Brown (2013) Cost: PSSRU 2014. 10.1 Community nurse (includes district nursing sister, district nurse.) £57 per hour of patient related work. Excluding qualifications costs. (Assuming each visit has a 20 minute duration according to Brown et al. 2013)
GP home Visit	100%; Twice monthly	£35.00	Resource use: Brown (2013), Appendix 1 NICE CG81 Cost: PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Surgery consultation lasting 11.7 minutes.

Note: Adapted from CS Table 70.

Table 39 Unit costs for end-of-life palliative care

Description	Resource Use	Unit Cost	Source
Palliative Care- Hospital	55.8%	£4,153	Resource use: Brown (2013) Cost: NHS Reference Cost 2013/2014: Non-elective inpatient (long stay). Respiratory Neoplasms with CC Score 11+. Currency Code DZ17E.
Palliative Care- Hospice	16.9%	£5,191	Resource use: Brown (2013) Cost: Brown (2013) assumed hospice was a 25% increase in hospital inpatient cost. NHS Reference Cost 2013/2014: Non-elective inpatient (long stay). Respiratory Neoplasms with CC Score 11+. Currency Code DZ17E.
Palliative Care- Home	27.3%	Community Nurse Visit: £266	Resource use: Brown (2013) Cost:

Description	Resource Use	Unit Cost	Source
		GP Home visit: £70 Macmillan Nurse: £1901	Community Nurse Visit- PSSRU 2014. 10.1 Community nurse (includes district nursing sister, district nurse.) £57 per hour of patient related work. Excluding qualifications costs. (Assuming each visit has a 20 minute duration and occurs for 14 days during terminal care according to Brown et al. 2013) GP Home Visit- PSSRU 2014. 10.8b General practitioner — unit costs. Excluding qualification costs and direct care staff costs. Home visit lasting 11.4 minutes. (Assuming occurs weekly- twice in 14 days) Macmillan Nurse-PSSRU 2014. Brown (2013) assumed a Macmillan nurse was 66.7% of the cost of a community nurse (£57 per hour). Also assumed would be required for 50 hours for terminal care.

Note: This is a direct reproduction of CS Table 71, p. 202

Adverse Events

AE costs were also included for grade three and four AEs related to treatment. The resource use associated with AEs were derived from Brown et al. 2013,[19] and the NICE DSU document on febrile neutropenia. Costs were obtained from NHS Reference Costs, eMit and the NICE DSU document on febrile neutropenia. The company indicated that resource use estimates were validated with clinical opinion. Table 40 reports the resource use and costs used for adverse events in the model.

Bottom-line summary of ERG view on resource use and costs

The company did a comprehensive search for appropriate costs, updating systematic reviews in previous NSCLC STAs and performing a comprehensive and well-reported chart review of relevant squamous patients. The cost categories included were reasonable and well-reported. EMit cost data used for the price of comparator drugs was not up to date, and the variance data reported with eMit data was not used to inform the PSA.

Overall, the company's analysis of resource use and costs was appropriate and comprehensive.

Table 40 Calculation of resource use and cost of adverse events

Description	Unit Cost	Reference
Neutropenia	£349.34	NHS Reference Cost 2013/2014. Weighted average of mean costs for HRG code WA02W (disorders of immunity without HIV/AIDS with complicating condition) across non-elective long- and short-stay episodes and day-case admissions.
Anaemia	£755.53	NHS Reference Cost 2013/2014. Weighted average of Iron Deficiency Anaemia with CC Score 0-14+ (Currency Code SA04G, H, J, K, L) non-elective inpatient long stay, non-elective inpatient short stay and day case.
Thrombocytopenia	£195	NHS Reference Cost 2013/2014. Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over. Procedures in Outpatients (Currency Code SA13A)
Hypomagnesaemia	£590.00	EMIT December 2014. Magnesium sulphate 10% solution for infusion 20mmol IV over a 6 hour period for a maximum of 5 days. (£9.68/day, totalling £48.42). NHS Reference Cost 2013/2014. Assumed the infusion given as a non-elective inpatient short stay as a Neoplasm Related Admission with CC Score 0-3+ (Currency Code WA17A-WA17D) (£541.80 (£319.70, £612.30)
Pulmonary embolism	£654.84	NHS Reference Cost 2013/2014: Weighted average of Deep Vein Thrombosis with CC Score 0-12+ (Currency Code YQ51A-YQ51E) inpatient long stay, short stay and day case.
Skin rash	£147.39	NHS Reference Cost 2013/2014. Weighted average of Consultant Led Outpatient appointments- Non-admitted face to face, first time appointments with service code 370 (medical oncology) and Non-admitted face to face, follow-up appointments with service code 370 (medical oncology).
Fatigue	£3008.41	NHS Reference Cost 2013/2014. Weighted average of the non-elective long-stay. Neoplasm Related Admission with CC Score 0 to 3+). Currency code WA17A-WA17D.
Nausea	£1494.00	NHS Reference Cost 2013/2014. Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over as a non-elective short-stay episode. Currency Code FZ13C. Each hospitalisation cost £747 (£459, £833) with two hospital admissions typically required during chemotherapy.
Febrile Neutropenia	£4,402.87	The NICE Decision Support Unit report (2007) on the cost of febrile neutropenia as an inpatient estimated the cost to be £2572.44 (89). The cost from 2007 has been inflated to 2015 using the CPI from the ONS to £3144.19 Brown (2013) assume 1.4 episodes per patient during the four cycles (12 weeks) of chemotherapy.

Note: This table is a direct reproduction of CS Table 72, p. 204.

4.3.8 Cost-effectiveness results

Deterministic results from the company's base case economic model are presented in section *5.7* (pp. 214 to 220) of the CS. These relate to the Western European subgroup, including patients without EGFR expressing tumours. The company's clarification response included revised tables for patients with EGFR expressing tumours within the Western European subgroup (CS clarification response Appendix 1). In this section we report the revised results from the clarification response. Results from the company's sensitivity analyses are discussed below in section 4.3.9. This includes probabilistic results, one-way sensitivity analyses, and scenario analyses (which include estimates for the ITT population).

The company base case estimates for GCis + N compared with GCis in the Western European population with EGFR expressing tumours are shown below (Table 41). These are based on a deterministic analysis for the direct comparison only, using data from the SQUIRE trial (with KM survival functions for OS and PFS, extrapolated from the KM endpoint with log-logistic survival functions, fitted separately to each study arm). The company noted the modelled benefits of GCis + N: a mean gain in OS of 0.54 years (6.5 months), corresponding to a mean gain of 0.34 QALYs per patient. Given the higher estimated cost (a mean increase of £19,516 per patient), the ICER was £57,725 per QALY gained.

Table 41 Base case cost-effectiveness results – Direct comparison (deterministic) (Western European EGFR expressing population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCis	[redacted]	[redacted]	[redacted]				
GCis + N	[redacted]	[redacted]	[redacted]	£19,516	0.544	0.338	£57,725

Note: this table is directly reproduced from Table 22 in the clarification response Appendix 1, p. 36.

Results presented by the company for the other comparisons are shown in Table 42. These are deterministic results, with survival functions for OS and PFS estimated from SQUIRE data for GCis + N and GCis (KM survival functions extrapolated from the endpoint using separately fitted Weibull models); and hazard ratios from the NMA for other comparators versus GCis + N. The results for GCis + N are slightly different to those reported for the above direct comparison (Table 41) because of the use of different parametric survival curves for extrapolation – Weibull instead of log-logistic. Note that the ICERs in this table are for GCis + N compared separately

with each comparator – it is not a fully incremental analysis – and the company did not report results for GCis in this table.

Table 42 Base case cost-effectiveness results – Indirect comparisons (deterministic) (Western European EGFR expressing population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCis + N	[redacted]	[redacted]	[redacted]				
GCarbo	[redacted]	[redacted]	[redacted]	£20,316	0.523	0.344	£59,031
DCis	[redacted]	[redacted]	[redacted]	£19,948	0.482	0.312	£63,982
PCarbo	[redacted]	[redacted]	[redacted]	£20,036	0.236	0.172	£116,344

Note: this table is directly reproduced from Table 23 in the clarification response Appendix, p.37. LYG, life years gained.

To aid interpretation, we have extracted the results for GCis from the submitted company model and conducted an incremental analysis. Table 43 suggests PCarbo would have a lower mean cost and greater mean QALY than DCis or GCis. When an intervention is less effective and more expensive as DCis and GCis are in the base case incremental analysis, they are referred to as dominated. Comparing GCis + N with the next best, non-dominated option (PCarbo), the estimated ICER is over £116,000. However, we note that the absolute differences in costs and QALYs between the four included platinum doublets are all small and that there is a question over the robustness of the NMA. Based on the direct evidence from the SQUIRE trial with Weibull endpoint extrapolations, the results from this analysis suggest an ICER of £80,912 per QALY for GCis + N compared with GCis.

Table 43 Incremental analysis – direct and indirect comparisons (deterministic) (Western European EGFR expressing population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCarbo	[redacted]	[redacted]	[redacted]				
PCarbo	[redacted]	[redacted]	[redacted]	£280	0.287	0.172	£1,628
DCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis + N	[redacted]	[redacted]	[redacted]	£20,036	0.237	0.172	£116,488

LYG, life years gained.

4.3.9 Assessment of uncertainty

The company used probabilistic and one-way deterministic analyses to explore the impact of uncertainties around input parameters, and scenario analyses to examine structural uncertainties.

4.3.9.1 Probabilistic sensitivity analysis

The company reported the results of their probabilistic base case analysis in section 5.8 (pp. 220 to 223) of the CS. They noted that these results were based on 2,000 PSA iterations, and that they had checked the stability of the cost-effectiveness results by running up to 10,000 iterations. The PSA included the following sets of parameters that were subject to uncertainty:

Nonparametric survival curves (KM)

A random process was used in the PSA to introduce variation to the KM curves to reflect sampling uncertainty over the SQUIRE data. The process used a single random number per curve, per PSA iteration, to shift the curves vertically in proportion to the reported standard errors for the KM estimates at each time point. The PSA value for the proportion of the cohort surviving in the first week $S^*(t_1)$ was drawn randomly from a lognormal distribution based on the KM mean μ_1 and point standard error σ_1 at time t_1: $S^*(t_1) \sim LN(\mu_1, \sigma_1)$. Survival at the next time point t_2 was then calculated by adjusting the KM estimate : $S^*(t_2) = [S^*(t_1) - \mu_1]^* (\sigma_2/ \sigma_1)$. And so on for successive time points.

Parametric survival curves (log-logistic, Weibull, etc)

Random sampling was also used to draw PSA values for the parametric survival models which were used to extrapolate OS and PFS beyond SQUIRE follow up. The related sets of parameters, such as the scale and the shape parameters for the Weibull distribution, were drawn from mulitvariate normal distributions with mean and variance-covariance matrices from the regressions used to fit the models to the SQUIRE data. This process introduces variation in the position and shape of the sampled curves between PSA iterations.

Hazard ratios for indirect comparators

The effectiveness of the indirect comparators entered the model in the form of hazard ratios for OS and PFS compared with GCis + N. Values for these hazard ratios were sampled from independent lognormal distributions, based on means and 95% confidence intervals estimated

from the NMA. This approach does not account for correlations between estimates for the different comparators within the NMA.

Incidence of adverse events

The proportions of patients experiencing the included AEs for the GCis + N and GCis arms were sampled from beta distributions, according to the observed proportions reporting these events in the SQUIRE trial and the numbers of patients within the relevant treatment arm.

Relative risks of adverse events

For the indirect comparators, it was assumed that the relative risks of TEAEs compared with GCis + N would equal those for GCis. For the PSA, these relative risks were sampled from lognormal distributions, based on mean and 95% confidence intervals estimated from SQUIRE. Values for each comparator (GCarb, GCarbo and DCis) and for each included TEAE were sampled independently.

Health state utilities and adverse event utility decrements

PSA values for utilities and utility decrements were sampled from beta distributions. Means and standard errors for the health state utilities prior to progression were taken from the SQUIRE trial, and those for the post-progression state from literature. Means and standard errors for disutilities associated with the included adverse events were taken from the literature.

Resource use and costs

Unit costs of drugs (£ per mg or ml) were not varied in the PSA. However, the cost of drugs per administration was variable, due to variation in the treatment duration adjustment and wastage rates (for drugs other than necitumumab): the treatment duration adjustment was sampled from a beta distribution (see section 4.3.5 above); and wastage depended on body surface area, which was sampled from a normal distribution. Uncertainty over the cost of drugs after progression was included by sampling the proportions of patients assumed to receive erlotinib and docetaxel (from a beta distribution) and the duration of that treatment (from a gamma distribution). Other costs, including the costs of drug administration, other resource use, and one-off costs for palliative care and death were sampled directly from gamma distributions, with subjective estimates of variation (standard errors set at 30% of the mean).

The methods used in the company model PSA were generally of a good standard. Uncertainty over the key effectiveness parameters of overall and progression-free survival was captured appropriately, based on variance in the SQUIRE trial. Uncertainty related to the outputs from the NMA (hazard ratios for OS and PFS) was included, but did not account for correlations of estimates between comparators. Conventional methods were used to incorporate uncertainty around other input parameters, with variance based on empirical sources or reasonable subjective estimates.

The CS summarises the results of the PSA in the form of Cost-effectiveness Acceptability Curves (CEAC) and cost-effectiveness scatterplots. No numerical results are provided in the CS. A revised version of the CEAC based on the Western European subgroup with EGFR expressing tumours was provided in the company's clarification response (CS Appendix 1, Figure 21 p. 44), this is reproduced below (Figure 11, top). The ERG notes that the company's submitted CEAC suggests that GCis + N does not have the greatest probability of being the most cost-effective option unless the willingness to pay threshold is above about £400,000 per QALY. This appears inconsistent with the deterministic results summarised above (e.g. see Table 43). It also appears inconsistent with the equivalent PSA results calculated from the submitted model by the ERG (Figure 11, bottom).

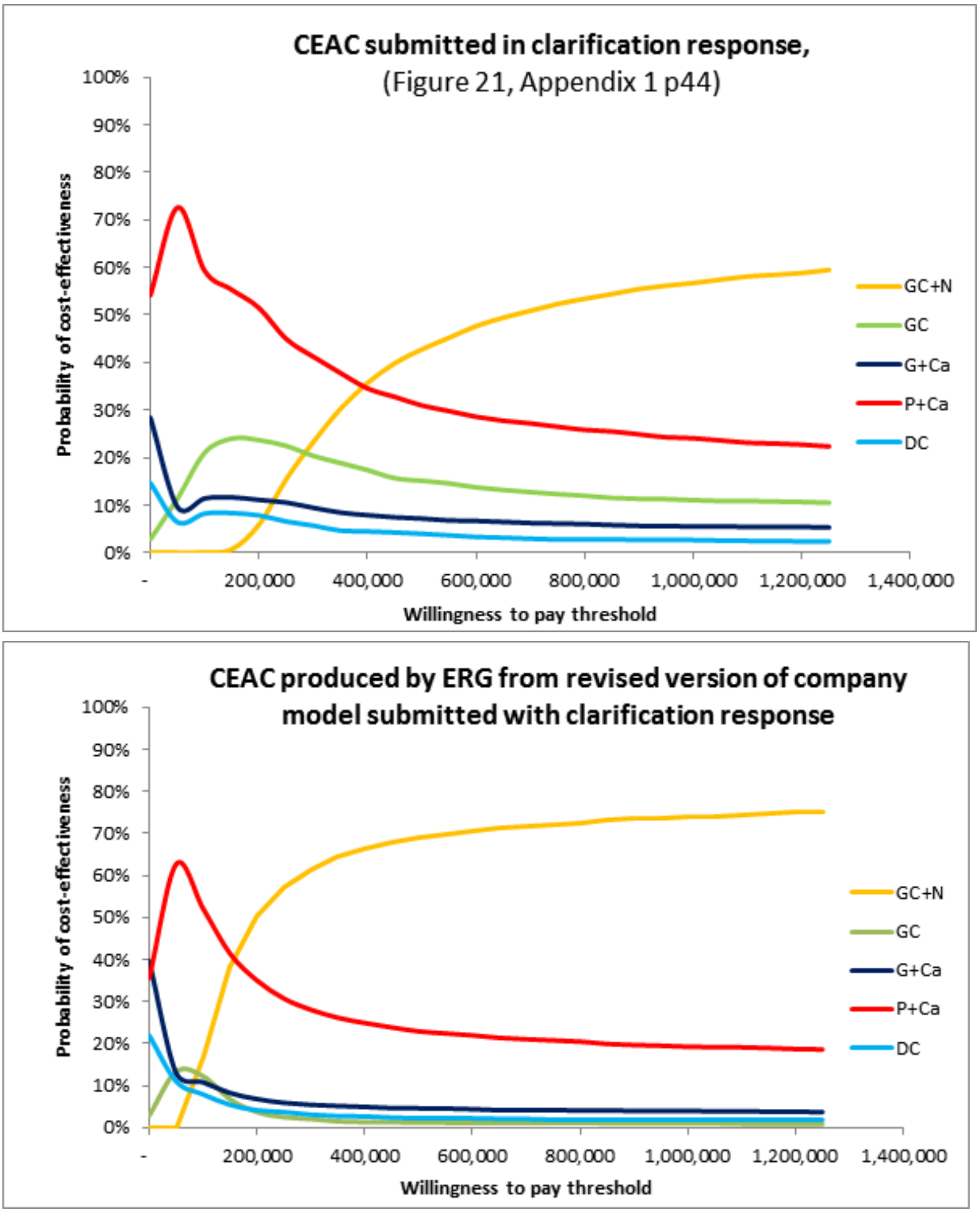


Figure 11 Cost-Effectiveness Acceptability Curve in patients with EGFR expressing tumours (Western European subgroup)

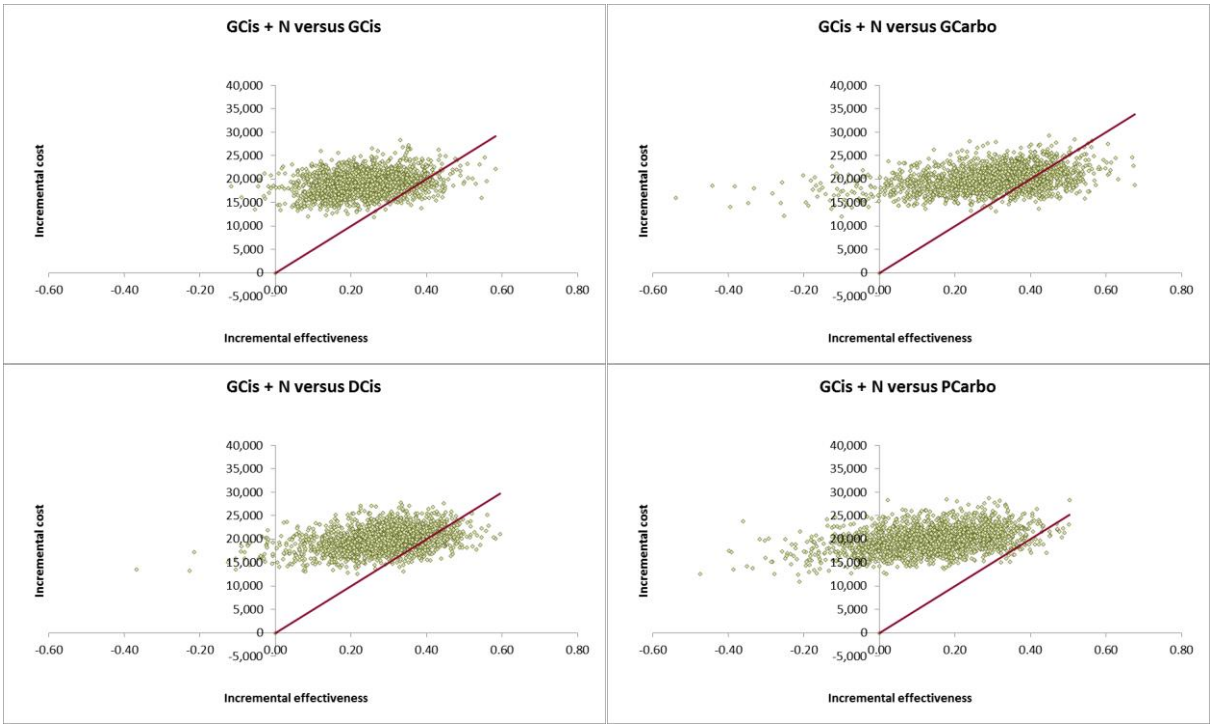
Numerical results from the revised model submitted as part of the clarification response are presented below in Table 44. These relate to the Western European subgroup of patients with EGFR expressing tumours, and are based on KM estimates of OS and PFS extrapolated from the endpoint with separately fitted Weibull curves for GCis and GCis + N, and adjusted by NMA hazard ratios for other comparators. This estimated ICER for GCis + N versus the next best non-dominated alternative (PCarbo) is £144,737 per QALY. If we restrict the analysis to the direct comparison between GCis + N and GCis, the ICER is £80,634.

Table 44 Incremental analysis – direct and indirect comparisons (PSA results) (Western European EGFR expressing subgroup)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCarbo	[redacted]	[redacted]	[redacted]				
PCarbo	[redacted]	[redacted]	[redacted]	£134	0.265	0.160	£839
DCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis + N	[redacted]	[redacted]	[redacted]	£19,868	0.181	0.137	£144,737

LYG, life years gained.

Cost-effectiveness scatterplots for the included comparisons in this analysis are shown below (Figure 12). The spread of dots illustrates the extent of uncertainty over the relative costs and effects of GCis + N in relation to the included comparators. It can be seen that uncertainty over the incremental effects (QALYs gained) is lower for the direct comparison with GCis than for the other, indirect comparisons estimated from the NMA. The slope of the red lines in these graphs shows a cost-effectiveness threshold of £50,000 per QALY gained. It can be seen that the probability that GCis + C is cost-effective (the proportion of dots below and to the right of the diagonal line) is low for all comparators.



The slope of the red lines indicates a cost-effectiveness threshold of £50,000 per QALY

Figure 12 Cost-effectiveness scatterplots– direct and indirect comparisons (PSA results) (Western European EGFR expressing subgroup)

4.3.9.2 Deterministic sensitivity analyses

The company conducted deterministic sensitivity analyses to test the impact of uncertainty around key model parameters on the cost-effectiveness results. This analysis was only conducted on the deterministic version of the model for the direct comparison (GCis + N versus GCis), and for the Western European subgroup. Parameters were varied one at a time, between defined lower and upper limits, and the resulting ICERs were recorded. The results are reported on pp. 223 to 226 of the CS, and revised results for Western European patients with EGFR expressing tumours were provided in the clarification response [clarification Appendix 1: Table 37 (p. 45) and Figure 22 (p. 47)]. The parameters included in this analysis were:

- **Survival curves** - OS, PFS and TTD estimates for GCis + N and GCis were varied (separately) at all time points between 95% confidence limits.
- **Adverse event risks, costs and utility decrements** – varied by 30% around the base case
- **Utilities for health states** – varied between 95% confidence limits.

- **Drug costs** – varied by 20% for necitumumab and 30% for other drugs.
- **Other costs** – varied by 50% around the base case.

The variables included and ranges of variation are reasonable.

Results are presented in the tornado diagram below (Figure 13). The company noted that the key drivers (among variables tested) for cost-effectiveness were: OS and PFS estimates for GCis +N and GCis, TTD for GCis + N, and the acquisition cost for necitumumab.

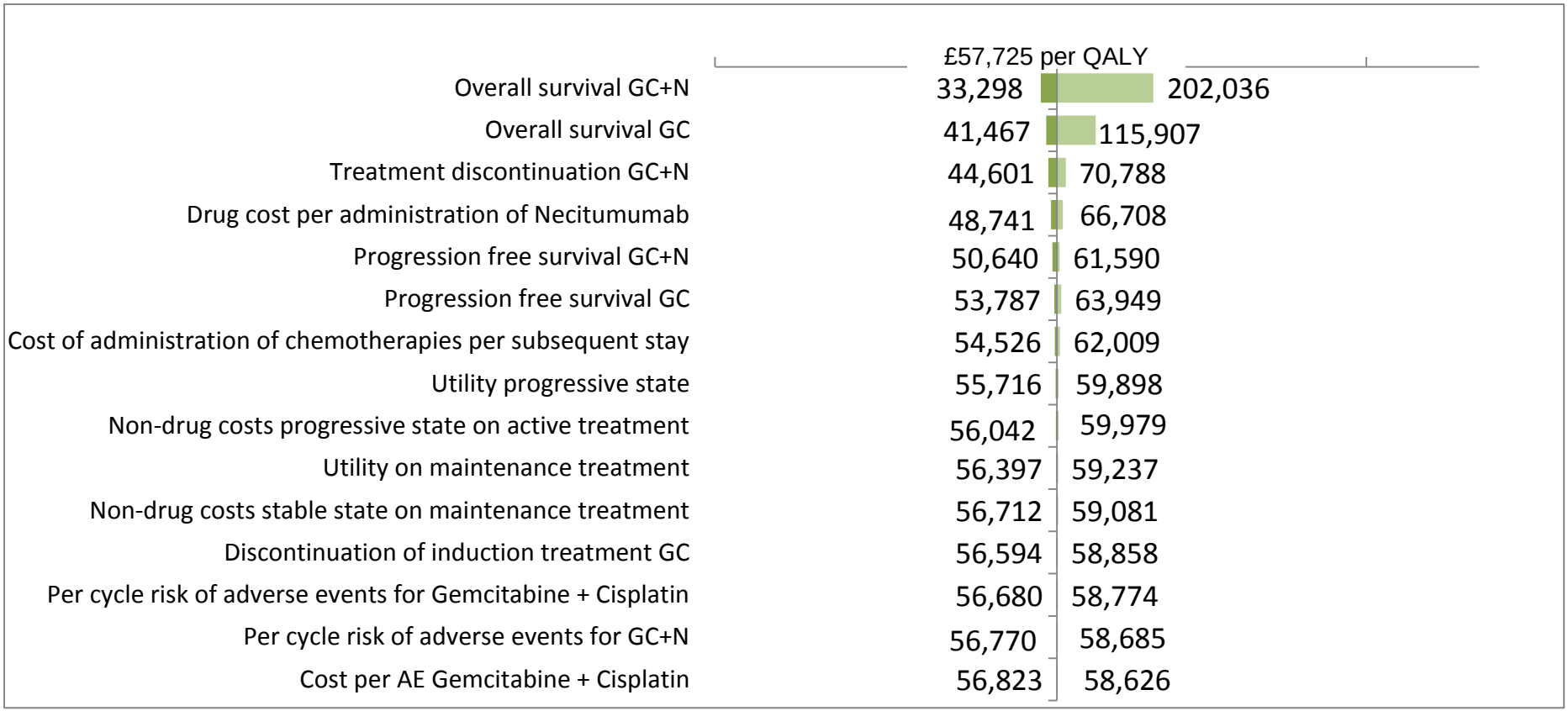


Figure 13 Tornado diagram for ICER (£ per QALY) – Western European patients with EGFR expressing tumours

Note: Reproduced for revised version of model submitted with clarification responses.

4.3.9.3 Scenario Analysis

The company conducted scenario analyses around key issues of structural uncertainty, see CS pp. 226 to 228. The analyses were deterministic, and only performed for the direct comparison (GCis + N versus GCis). The issues considered were:

- **Population** – the company's base case analysis relates to Western European patients with EGFR expressing tumours. A scenario analysis was conducted including results for all patients randomised in the SQUIRE trial with EGFR expressing tumours from the ITT population.
- **Functional forms for OS** – the company's base case analysis used KM estimates for OS, with separately fitted log-logistic curves used to extrapolate beyond the last OS observation for the GCis + N and GCis groups. They tested three different methods for extrapolation beyond the last OS observation: separately fitted Weibull functions for both groups; log-logistic for GCis + N and Weibull for GCis; and separately fitted exponential distributions.
- **Definition of PFS** – in the company's base, PFS was defined as radiographic documentation of progression (RECIST 1.0 criteria) or death. A scenario was conducted including symptomatic deterioration as well as radiographic progression and death.
- **Time horizon** – the base case assumed a time horizon of 18.5 years (effectively lifetime for this population. A shorter time horizon (5 years) was tested in order to assess the impact of the long tail of the log-logistic distribution, used to extrapolate OS and PFS in the base case model.
- **Time to treatment discontinuation** – due to the lack of reporting on discontinuation rates for studies in the NMA, assumptions were required to model TTD for comparators other than GCis. In the base case, it was assumed that hazard ratios for treatment discontinuation were equal to hazard ratios for PFS for each of the indirect comparators. A scenario analysis was conducted in which hazard ratios for treatment discontinuation for all comparators were assumed to be equal to those for GCis.
- **Source of utility estimates** – in the base case, utilities for the three pre-progression substates were estimated from the SQUIRE EQ-5D data (both arms pooled), post-

progression utility was taken from Khan et al 2015[33], and adverse event disutilites were taken from a variety of sources.[35-37] Two other senarios were tested: 1) state utilities from Chouaid et al. 2013[31] and AE decrements from Nafees et al. 2008; and 2) post-progression utility from Chouaid et al. 2013.[31]

The results of the company's scenario analyses for the Western European subgroup with EGFR expressing tumours were presented in the clarification response (Appendix 1, Table 38, p.48) and are reproduced below. The company noted that the model results were most affected by uncertainty in the methods used to extrapolate the OS and PFS survival curves. This is demonstrated by the scenarios testing alternative functional forms for OS (scenarios 5, 6 and 7), as well as the use of a truncated, 5-year time horizon (scenario 8).

The company did not comment on the impact of using the ITT patient population (scenario 4), but argued that the Western European subgroup is most applicable for the NHS.

Table 45, below, is derived from the company clarification response, and contains errors. For analyses 4-9 the company model assumes that time to treatment discontinuation is the same as GCis instead of the assumption from the base case, that time to treatment discontinuation for indirect comparators is equivalent to PFS.

Table 45 Scenario analysis results (GCis + N vs. GCis) in patients with EGFR expressing tumours (Western European subgroup)

Scenario	Description	Company ICER	Corrected ICER
Base-case	Base Case results	£57,725	£57,725
1)	Utilities from Chouaid et al. and AE decrements from Nafees et al.	£57,788	£57,788
2)	Utility post-progression from Chouaid et al.	£55,751	£55,751
3)	Time to treatment discontinuation assumed same as GCis for all indirect comparators	£64,713	£64,713
4)	Using ITT as patient population	£151,152	£110,248
5)	Using separate Weibull for OS	£87,543	£79,412
6)	Using Log-logistic for OS in GCis + N and Weibull in GCis arm	£53,433	£49,802
7)	Using separate Exponential distributions for OS	£78,868	£73,194
8)	5 year time horizon	£83,205	£76,744
9)	Symptomatic deterioration considered progression	£64,251	£57,354

Note: Adapted from clarification response, Appendix 1, Table 38, p.48.

The above scenario analyses are quite a narrow selection of the potential scenario analyses, and quite limited. Some important structural assumptions were not investigated in the CS. In particular, other methods for modelling the overall and PFS curves are appropriate for testing: other functional forms; use of purely parametric survival functions (rather than relying on the KM curves for SQUIRE follow up); use of jointly-fitted curves for GCis+ N and GCis (with a treatment interaction term); and methods for attaching the parametric extrapolation to the last KM estimates. It is also important to analyse the impact of influential scenarios and parameters under PSA (not just with the deterministic version of the model). These options are considered further in the ERG's additional analyses (section 4.4).

4.3.10 Model validation

The company noted (CS p.229-230) that as recommended by international methodological guidelines,[43] they used the following methods to test the validity of their model.

4.3.10.1 Face validity

The company noted that external clinical and economic advisors in the UK were consulted to validate that the model structure and modelling assumptions reflect the clinical pathway of patients with locally advanced or metastatic squamous NSCLC in England. The advisory panel comprised four NHS consultant oncologists, three UK academic health economists and two UK academic statisticians (CS p.165). The discussion guide for consultations is provided in the CS (Appendix 17, p.193). The company state that all of the recommendations from their experts have been addressed, although no further details are given.

The ERG also discussed some key assumptions in the model with a clinical expert, who agreed that they were generally plausible for a UK population and context.

4.3.10.2 Verification

Methods used to verify the model are reported on pp. 229 to 230 of the CS. The structure and programming of the model was checked by two modelling experts who were not involved in developing the model, but worked in the organisation commissioned by the company to develop the model. It is reported that they conducted stress tests – to check that the model behaved as expected when inputs were changed – and that debugging was conducted where necessary.

The ERG has also conducted a range of independent verification checks on the model:

- Reviewing the model structure and formulae;
- Checking that the model assumptions and inputs are consistent with those reported in the CS, and with the cited data sources (where available);
- Checking that the results and sensitivity analyses reported in the CS and clarification report are consistent with model outputs;

- Replicating the model in a separate Excel file to check that the calculations and macros yielded the same intermediate and final results;
- And investigating the impact of our own sensitivity and scenario analyses, and checking that the changes in results are consistent with expectations (see section 4.4 below).

We found a small number of minor errors and inconsistencies (Table 46), although none of these led to big changes in the model results.

Table 46 Inconsistencies identified by ERG in company model

Issue	Location in model	Effect on results	Action taken by ERG
1) Sum of incident cases of progression is greater than population size.	'Comp1Model' and 'Comp2Model' sheets, columns AG	Small increase in costs (about £200) for treatment after progression, for all comparators.	Corrected in ERG version of model used for additional analysis, although this formula might have related to the company's assumption that all patients entered the PD state before death.
2) Wrong denominator used for duration of second-line erlotinib use (whole SQUIRE population, rather than selected subgroup).	'Wastage' sheet cells D156 and J156.	Very small increase in costs (by about £20) for all comparators.	Corrected.
3) Denominator for calculation of AE risks differs between GCis and other chemotherapies, despite assumption of same relative risk.	'Per Cycle calculations' cells E45-G45.	Very small change in number of estimated AEs.	Corrected.
4) Cost for administration of chemotherapy in week 2 for DCis included, although costs for drugs are not included.	'Drug Costs' sheet cell K77, and Table 66 (p194 CS).	Increases cost of DCis arm by about £1,000.	Corrected.

4.3.10.3 External validity

The company compared their modelled estimates of median overall and progression-free survival with results from the two RCTs that had been used to inform model efficacy parameters:

- SQUIRE trial[8]: see CS Table 77, and revised Table 24 in the clarification response (Appendix 1 p. 37), and
- Eastern Cooperative Oncology Group study E1594[29 44]: see CS Table 92 (p. 230).

These results are reproduced in Table 47 below. They show a good level of concordance between the model estimates and SQUIRE results. This is not surprising since these data were used as inputs for the model, and so this might more properly be seen as a form of 'internal validity', a check of correct model assumptions and coding. Concordance with E1594 results was also reasonable, although somewhat less good than with the SQUIRE data. Again, this is not surprising, since these data were included in the NMA, but alongside other studies.

Table 47 Comparison of model results with other sources of evidence

Outcome	Time (months)		Source
	Model Result	External estimate	
GCis + N			
PFS (median)	5.52	5.6 (5.4, 6.2)	SQUIRE
OS (median)	11.73	11.7 (9.6, 13.6)	SQUIRE
GCis			
PFS (median)	4.37	4.5 (4.2, 5.3)	SQUIRE
OS (median)	8.74	8.9 (8.1, 11.1)	SQUIRE
PFS (median)	4.60	4.3	E1594 (1)
OS (median)	10.35	9.4	E1594 (1)
PCarbo			
PFS (median)	4.6	3.7	E1594 (1)
OS (median)	10.35	9.3	E1594 (1)
DCis			
PFS (median)	4.14	3.1	E1594 (1)
OS (median)	8.97	8.1	E1594 (1)
US Markov model			
Life years gained	0.544	0.154	Goldstein et al. 2015
QALYs gained	0.338	0.111	

Note: This table is adapted from CS Table 92 and clarification response Appendix 1, Table 24, p. 37.

4.3.10.4 Cross validity

The CS does not report on cross validity. An independent NIH-funded economic evaluation has recently been published by Goldstein and colleagues.[20] They used a Markov model to estimate the cost-effectiveness of GCis + N compared with GCis for first-line treatment of patients with metastatic squamous NSCLC in a US context. Although the costs are not likely to be reflective of UK practice, and absolute rates of survival may differ between the US and UK, it is not unreasonable to compare the estimates of incremental effects (life years and QALYs gained), between the CS and Goldstein models (see section 4.3.10.4 above).

4.3.10.5 Predictive validity

As stated in the CS, assessment of predictive validity is not possible at this time.

4.4 Additional work undertaken by the ERG

We conducted a range of additional analyses to further test the robustness of the company model to changes in structural assumptions. This included an alternative 'base case' that reflects the ERG's judgement about the most plausible set of assumptions on which to base cost-effectiveness estimates for the decision problem (see section 4.4.1 below). We then used this base case to explore other possible scenarios and uncertainty over key parameters (section 4.4.2).

4.4.1 SHTAC base case analysis

Differences between our preferred set of assumptions and the company's are summarised in Table 48. Our base case analysis was conducted using our replication of the company model. This version of the model included corrections for the minor inconsistencies noted in Table 46 above, and avoided the need to edit the complicated code and many data input sheets in the submitted model.

Table 48 Base case specifications

	Company base case	**SHTAC base case**
Population	Western European (WE) EGFR expressing The company believes that results for the WE subgroup are more applicable for UK patients.	ITT EGFR expressing We do not believe that use of the WE subgroup is justified. It is a post hoc analysis, a significant treatment-subgroup interaction has not been shown for this (or for other prespecified regional sugroups), and there is no clear explanation for why the relative effects of treatment should differ in this selection of countries in particular.

	Company base case	**SHTAC base case**
Comparators	Direct comparison preferred (GCis+N vs. GCis only), due to weakness of NMA and robustness of SQUIRE dataset. Indirect comparison was also conducted, including GCis, PCarbo, GCarbo and DCis. The company explained in their response to clarification questions from NICE and the ERG that they had excluded PCis as marketing data suggested that it is used infrequently in the UK.	There is considerable uncertainty over the robustness of the NMA. However, we prefer to include the full range of comparators specified in the decision problem, and to incorporate uncertainty through probabilistic sensitivity analysis. We included all comparators for which data were available: GCis, GCarbo, PCarbo, DCis and PCis. We have received clinical advice that PCis is rarely used, but still consider that it should be included for completeness.
OS / PFS	KM curves extrapolated from last observation. For the direct comparson, the extrapolation was based on log-logistic survival curves, fitted separately to the SQUIRE arms. The indirect comparison used separately fitted Weibull curves, which were the best-fitting distribution subject to the proportional hazards assumption required for integration of NMA results.	KM extrapolated from the last timepoint with more than 20 patients remaining in each arm. This avoids undue weight on survival estimates based on very small numbers of patients. In our base case, we used separately fitted Weibull distributions, but also tested other parametric functions, including log-logistic curves for a direct comparsion of GCis+N and GCis.
TTD	KM curves from SQUIRE for GCis + N and GCis. Follow up was complete, so extrapolation was not needed. For indirect comparisions, the company assumed that HRs for TTD would equal those for PFS. And they tested the effect of assuming that TTD HRs for other comparators would equal those for GCis.	We used the same assumptions as in the company base case.
Adverse events	Risks estimated from SQUIRE for GC+N and GCis. For other comparators, it was assumed that the relative risks of AEs (versus those for GCis+N) would equal the GCis relative risks from SQUIRE.	Same approach used. Although the absolute numbers of some events were small, SQUIRE represents the best available data. Uncertainty over absolute and relative AE risks are reflected in the PSA.

	Company base case	**SHTAC base case**
2nd line therapy	For costing purposes, it was assumed that a proportion of patients would receive active treatment after progression with either erlotinib or docetaxel. These treatments were the most frequently used at second-line in SQUIRE. The proportions of patients on erlotonib and docetaxel were based on SQUIRE data, estimated separately by trial arm.	For our base case we followed the company's approach, but tested the assumption that both arms would have the same proportions of patients receiving erlotonib and docetaxel. We have received advice that use of erlotinib in this patient population would be rare in the UK. However, the effects of second-line treatment is implicitly built into the SQUIRE effectiveness data. It is therefore consistent to estimate the costs of this treatment.
Costs	Detailed costings based on data from SQUIRE on utilisation and appropriate unit cost data.	The company's approach to costing was thorough and appropriate. The only main exception is that they did not include a cost for a test for EGFR expression, that would be required to be consistent with the SmPC indication. We have not been able to identify a cost for this test, as it is not currently routinely available.
Utilities	SQUIRE data for the pre-progression health states. EQ-5D tariff scores were pooled across arms, but estimated separately for ITT EGFR and Western Europe EGFR subgroups. Khan et al. for post-progression utility. Various sources for AE disutilities.	For our base case analysis we followed the company approach. SQUIRE does represent the best available source of utility data that is consistent with the NICE reference case, and applicable to the patient population. Data presented in the CS and response to clarification questions does show similar utility scores between GCis and GCis+N groups. The utility estimates for the post-progression and adverse events are less robust for the current decision problem and are tested in sensitivity analysis.
Time horizon	Lifetime	Lifetime
Discounting	3.5% per year for costs and effects	3.5% per year for costs and effects
Analysis	Deterministic	Probabilistic

Key outputs from the company and SHTAC versions of the model are presented in Table 49. To aid comparison, results are presented for both versions based on the ITT analysis of the SQUIRE data for patients with EGFR expressing tumours. In other respects, the company and SHTAC results follow their respective base cases. The results are broadly similar. Both produce equivalent estimates of median, one year and two year OS and PFS – since they use the same KM data for this duration of follow up. The differences in modelled five year and mean OS and PFS, and hence in estimated QALYs relate to different assumptions about extrapolation beyond the KM data. Cost estimates are very similar for the two versions of the model.

Table 49 Model outputs: ITT EGFR expressing population

	Company model			SHTAC base case		
	GCis + N	GCis	Difference	GCis + N	GCis	Difference
Modelled OS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	3.69	[redacted]	[redacted]	2.25
One year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year OS	4.9%	2.4%	2.5%	0.5%	0.3%	0.3%
Modelled PFS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year PFS	0.5%	0.4%	0.1%	0.0%	0.0%	0.0%
QALYs (undiscounted)						
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (undiscounted)						
Pre-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean costs and effects for the six interventions from the SHTAC base case model are shown in

Figure 14. In terms of effectiveness estimates, the interventions fell into three groups: GCis + N, which had the highest estimated QALY; GCis and PCarbo, which had similar, intermediate QALY estimates; and PCis, DCis and GCarbo, with the lowest estimated QALYs. This ranking reflects the more favourable estimates from the NMA for PCarbo and GCis, than for PCis, DCis and DCarbo. However, the confidence intervals around the modelled QALY estimates were broad, and overlapped for all interventions. Further, although confidence intervals around the NMA HRs were incorporated in the PSA, correlations between NMA estimates and structural uncertainties about the conduct of the NMA and biases in the literature are not reflected in the results below.

Figure 14 Estimated costs and effects: SHTAC base case analysis

Estimated costs were similar for all options, except for GCis + N which was a lot more expensive. In all of the incremental analyses conducted by the ERG, the relevant comparator for GCis + N was either GCarbo or GCis. The third set of comparators (PCis, DCis and GCarbo) offered fewer estimated QALYs for no or very small cost savings.

Cost-effectiveness results for the SHTAC base case analyses are shown in Table 50. These suggest an ICER of £169,612 per QALY, in comparison with the next best non-dominated comparator (in this case GCis). The related CEAC in Figure 15 illustrates the very high level of uncertainty over which treatment is most likely to be cost-effective. However, it does suggest a negligible probability that GCis + N is more cost-effective than the comparators at cost-effectiveness thresholds below £100,000 per QALY.

Table 50 Cost-effectiveness: SHTAC base case (ITT EGFR subgroup)

Technologies	Total		Incremental		ICER (£ per QALY)	Comparison
	Costs	QALYs	Costs	QALYs		
PCis	[redacted]	[redacted]			-	
DCis	[redacted]	[redacted]			-	Dominated
PCarb	[redacted]	[redacted]	£1,001	0.135	£7,429	vs PCis
GCarb	[redacted]	[redacted]			-	Dominated
GCis	[redacted]	[redacted]	£1,579	0.013	£124,663	vs DCis
GCis + N	[redacted]	[redacted]	£19,993	0.118	£169,612	vs GCis

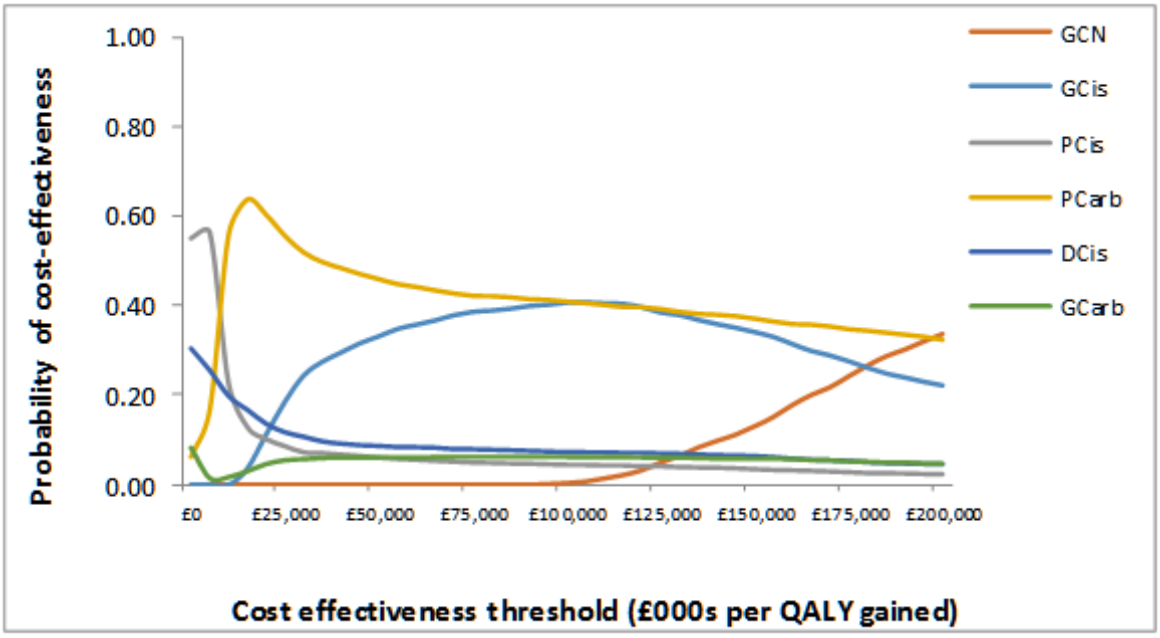


Figure 15 Cost-effectiveness acceptability curve: SHTAC base case analysis

4.4.2 Scenario and sensitivity analyses

The ERG conducted a range of sensitivity and scenario analyses on our base case version of the model (Table 51). We focussed on assumptions and parameter values to which the company model had been shown to be sensitive (CS pp. 223 to 232, and replacement Table 38 and Figure 22 in the clarification response A1):

- The SQUIRE subgroup used: the company model yielded a much higher estimated ICER for the ITT population than for their preferred Western Europe subgroup.
- The survival functions used to extrapolate OS beyond the KM data: Weibull curves have a shorter 'tail' than the log-logistic curves, producing a smaller QALY gain after the end of follow up at around three years, and hence a higher ICER. The use of exponential curves, or truncating the model after a time horizon of five years had a similar effect. Conversely, the use of a log-logistic model for GCis + N and Weibull for GCis had the effect of separating the tails of the survival curves, reducing the ICER.
- The results were very sensitive to parameter uncertainty over the OS, and to a lesser extent PFS, estimates: with higher ICERs at the upper 95% confidence limits for GCis + N, and lower ICERs at the lower 95% limits for GCis.
- Results were also somewhat sensitive to the time to treatment discontinuation in the GCis+N arm: in the model, a shorter duration of treatment had the effect of reducing costs with little impact on QALYs, resulting in a lower ICER.

In addition to these factors, the ERG was keen to test the timing of the transition from the KM curves to the parametric extensions. In particular, we were worried about basing very long extensions of OS and PFS (from about 3 to over 18 years) on the very small numbers of patients remaining in the SQUIRE trial at the end of follow up. As noted above, we set a prior criterion that the KM curves for OS and PFS would be used up to the time when more than 20 patients remained in both groups. However, this is an arbitrary cut-off, so we tested the effect of using the KM data directly to the final observation (as in the company model).

Changes to model assumptions relating to adverse event risks, utilities and resource use had minimal impact on cost-effectiveness results.

Table 51 shows summary results of additional analyses conducted by the ERG. The company's preferred analysis (scenario **C0**) yields an ICER of £57,725 per QALY gained for GCis + N compared with GCis. Introducing indirect comparisons, and changing the survival functions from log-logistic to Weibull to fit the proportional hazards assumption required for use of HRs from the NMA (scenario **C1**), increases the estimated ICERs for GCis + N compared with both

GCis and PCarbo. Changing from the Western European to ITT population (scenario **C2**) further increases the ICERs. The probabilistic version of this analysis (scenario **C3**) is similar to the SHTAC base case analysis (**S0**), although the latter does include further changes relating to the transition from KM to parametric survival curves, an additional comparator (PCis) and some minor corrections to the company version of the model.

The SHTAC base case (**S0**) yields an estimated ICER of £169,612 per QALY gained compared with GCis, which is the appropriate incremental comparator in this case. Scenarios **S1 to S8** illustrate the effect of different approaches to extrapolating the tail of the OS and PFS curves (or cutting the tail off by adopting a shorter time horizon in **S1**). The only scenario that makes an appreciable difference to the estimated ICER is **S8**, which adopts log-logistic tails for the GCis + N arm and Weibull for GCis. This reduces the ICER to £84,188 per QALY gained compared with GCis, or £109,214 with respect to the (correct incremental) comparator, PCarbo. The company have argued that this combination of survival curves presents a good fit for the two arms of the SQUIRE trial, but that it is inconsistent to use different functions. We are less concerned about the appropriateness of using different functions, given the decision to fit the parametric survival functions separately for the two arms, but are not convinced that this extrapolation provides a realistic estimate of longer-term survival within this population.

The final set of scenarios (**S9 to S16**), illustrate again the sensitivity of the ICER to changes in the OS, PFS and TTD estimates – re-iterating the conclusions of the company's tornado diagram (company clarification response A1 Figure 22).

Table 51 Summary of ERG additional analyses

		GCis+N versus GCis			GCis+N versus next best comparator			
		Incremental			Incremental			
Analysis		Cost	QALYs	ICER	Cost	QALYs	ICER	*Comp-arator*
C0	**Company - base case direct analysis**	**£19,516**	**0.3381**	**£57,725**				
C1	Company – direct and indirect analysis	£18,918	0.234	£80,912	£20,036	0.172	£116,344	*PCarbo*
C2	Company – C1 with ITT EGFR subgroup	£20,584	0.134	£153,947	£22,148	0.142	£155,654	*PCarbo*
C3	Company - C2 probabilistic	£20,591	0.134	£154,024	£21,999	0.116	£189,679	*PCarbo*
S0	**SHTAC - base case**	**£19,993**	**0.118**	**£169,612**	**£19,993**	**0.118**	**£169,612**	*GCis*
S1	SHTAC – five year time horizon	£19,976	0.117	£170,755	£19,976	0.117	£170,755	*GCis*
S2	SHTAC – KM for OS and PFS to final endpoint	£20,474	0.134	£153,085	£22,018	0.142	£154,569	*PCarbo*
S3	SHTAC – KM + Weibull OS and PFS (joint)	£20,037	0.123	£163,154	£21,596	0.132	£163,340	*PCarbo*
S4	SHTAC – KM + log-logistic OS and PFS (separate)	£20,571	0.149	£138,018	£20,571	0.149	£138,018	*GCis*
S5	SHTAC – KM + log-logistic OS and PSS (joint)	£20,608	0.156	£132,263	£20,608	0.156	£132,263	*GCis*
S6	SHTAC – Weibull OS & PFS (separate), no KM	£19,903	0.119	£167,233	£19,903	0.119	£167,233	*GCis*
S7	SHTAC – Log-logistic OS & PFS (separate), no KM	£20,514	0.142	£144,432	£20,514	0.142	£144,432	*GCis*
S8	SHTAC – Log-logistic GCis+N and Weibull GCis	£21,152	0.251	£84,188	£22,368	0.205	£109,214	*PCarbo*
S9	SHTAC – GCis OS at lower 95% limit	£20,427	0.185	£110,177	£21,572	0.131	£165,250	*PCarbo*
S10	SHTAC – GCis OS at upper 95% limit	£19,516	0.043	£457,474	£19,516	0.043	£457,474	*GCis*
S11	SHTAC – GCis+N OS at lower 95% limit	£19,337	0.039	£493,999	£19,337	0.039	£493,999	*GCis*
S12	SHTAC – GCis+N OS at upper 95% limit	£20,666	0.200	£103,574	£21,816	0.145	£150,426	*PCarbo*
S13	SHTAC – GCis+N PFS at lower 95% limit	£19,805	0.110	£180,194	£19,805	0.110	£180,194	*GCis*
S14	SHTAC – GCis+N PFS at upper 95% limit	£20,106	0.126	£159,862	£21,690	0.132	£163,922	*PCarbo*
S15	SHTAC – GCis+N TTD at lower 95% limit	£17,591	0.116	£151,908	£17,591	0.116	£151,908	*GCis*
S16	SHTAC – GCis+N TTD at upper 95% limit	£21,943	0.120	£183,597	£21,943	0.120	£183,597	*GCis*

4.5 Conclusions of cost-effectiveness

Overall, the company model provides a good foundation for assessing the cost-effectiveness of necitumumab for first line treatment of advanced squamous NSCLC. The model structure is appropriate and well implemented, with no major coding errors or inconsistencies that we could find. The key effectiveness estimates are based on a good quality RCT, and most other parameter estimates were of a good quality – or at least of best available quality. We agree with most of the assumptions in the company's base case analysis, with two notable exceptions. Firstly, we believe that the best available estimates of OS and PFS are from the ITT population in the SQUIRE trial. The company has argued for a narrower subgroup of Western European patients, based on post hoc analysis, but has not provided statistical evidence or a plausible explanation for whether and why necitumumab was more effective when added to conventional treatment for patients from this particular selection of countries.

The second set of assumptions in the company's base case analysis that we question, are those around the methods for extrapolating overall and progression-free survival beyond the observed RCT data. In particular, we question the particular choice of survival functions, and the way in which these have been attached to the sparse data at the end of follow-up. We believe that the methods used by the company exaggerate the proportion of patients likely to survive in the longer term, and therefore overestimate the projected estimates of QALYs gained. The company did provide alternative methods for extrapolation, and examined these in scenario analyses, and we have further explored these and some other plausible scenarios.

Our final, best estimate of the ICER for necitumumab compared with conventional platinum based chemotherapy for first line treatment of advanced squamous NSCLC is £169,612 per QALY gained. Although considerably higher than the company's base case estimate of £57,725, the company model yielded an ICER of £110,248 for the ITT (EGFR) population, with higher estimates based on less favourable assumptions about long-term survival.

Probabilistic analysis highlighted considerable uncertainty over the optimum choice of treatment for this group of patients, but the estimated probability of necitumumab being cost-effective was negligible below a cost-effectiveness threshold of less than £100,000 per QALY gained. Other uncertainties could not be quantified, including uncertainty over the completeness and robustness of the NMA, and the omission of relevant comparators. We are also concerned that

none of the estimated ICERs include the cost of testing patients for EGFR expression, as would be required to meet the SmPC indication. This cost was not included in the company model, and we have been unable to identify an estimate of the cost of this test, as it is not currently in routine use.

5 End of life

The company argues that necitumumab meets NICE's criteria in the 'Supplementary Advice for Appraising life-extending, end of life treatments'. The company states that expected survival in this patient population is less than 24 months (6.5 to 9.4 months, depending on the treatment used). The company further states that in the Western European subgroup, the modelled mean OS benefit for the Western Europe subgroup was 5.75 months for GCis + N compared with GCis alone. The company also indicates the treatment is indicated for an estimated small population of 2,575 patients in England with locally advanced or metastatic squamous NSCLC.

The ERG agrees that the company's estimate of the population size (CS Table 93, p. 233) appears reasonable, except that it includes all squamous NSCLC patients, not restricted to the EGFR expressing group (which is the SmPC indication). Therefore the patient population may be smaller than estimated.

The ERG agrees with the company that expected average survival in this population is less than 24 months. The ERG, however, does not agree with the company that GCis + N confers an additional survival benefit of 5.75 months compared with GCis alone. The company has used data from the Western European subgroup to support its argument, and the ERG believes that the company's rationale for basing efficacy conclusions on the Western European subgroup is unjustified. The ERG believes that the EGFR expressing subgroup from the ITT population is the most relevant population to the SmPC indication and this appraisal. Using the EGFR expressing subgroup data in the company's model (submitted in the clarifications response), the company's model showed a mean survival difference between GCis + N and GCis of 3.69 months, favouring GCis + N. The SHTAC base case analysis resulted in a mean survival difference of 2.25 months, favouring GCis + N. Therefore, when using the SHTAC base case, GCis + N does not meet this criterion in NICE's end of life criteria.

6 DISCUSSION

6.1 Summary of clinical effectiveness issues

The company identified one phase III trial in its review that was relevant to the decision problem. This was a well conducted, open-label, large trial including patients that are representative of those seen in clinical practice, based on clinical expert advice to the ERG. It provides direct evidence of the efficacy of GCis + N compared with GCis alone, the current gold standard treatment used in practice (for the fittest patients). The company argued that the results from a post-hoc Western European subgroup are the most generalisable to patients in England and used results from the SQUIRE trial from this population in the submitted economic model. The ERG, however, considers the company's rationale for this unjustified. The ERG considers the results from the EGFR expressing patient subgroup from the total population to be the most relevant population for this appraisal, as this is the SmPC indication. The company supplied additional analyses for this population during the appraisal.

The company also provided an NMA including 10 RCTs, which provided indirect and direct evidence for GCis + N versus PCarbo, GCis, PCis, DCis and GCarbo. Insufficient evidence was available to compare GCis + N with DCarbo, VCarbo and VCis. The NMA included patients with squamous NSCLC and was not limited by region or EGFR expression. Enough evidence was available for the company to conduct analyses of OS and PFS, but not HRQoL or AEs (which were also specified as outcomes in its inclusion criteria). The results from the OS and PFS analyses were used in the economic model. The ERG considers the treatment effects derived from the NMA are highly uncertain due to the lack of details provided about the studies included in the analysis and a number of methodological issues with how the NMA was conducted.

6.2 Summary of cost effectiveness issues

The company developed a model to estimate the cost-effectiveness of necitumumab in the context of the decision problem. This used a conventional model structure for cancer, with three main health states: pre-progression; post-progression and death. Before progression, patients were divided into three groups: those on induction treatment; those on maintenance with necitumumab (for the GCis + N arm); and those who have discontinued treatment but not yet progressed. The model included costs and utility impacts of adverse events, and costs for

active treatment and palliative care after progression. We believe this to be an appropriate model structure, and the model was implemented in a robust fashion. The effectiveness of GCis + N compared with GCis was based on good quality data from the SQUIRE trial, including: OS, PFS, TTD, AE risks and pre-progression utilities. Relative effects on OS and PFS for the other comparators were drawn from the NMA, and assumptions over TTD and AEs. Other parameters were estimated from the literature, and case note review.

Although the methods used for the company's economic evaluation were generally of a good quality, we do have some important reservations. In particular, the survival estimates that drive the cost-effectiveness results are based on a post-hoc subgroup analysis of SQUIRE, which we believe to be inappropriate. The company cite a much lower ICER (£57,725 per QALY gained) for this Western European subgroup than for the ITT population (£110,248 per QALY). We have further reservations about the methods that the company has used to extrapolate survival beyond the three years of follow-up that is available from SQUIRE. First, they extrapolate from the final endpoint of the KM data, which is based on a small number of patients and hence is subject to a high level of uncertainty. The company also choose a functional form for the extrapolation that gives a relatively wide separation between the tails of the survival curves (log-logistic), rather than another functional form (Weibull) that has a similar fit to the available data. This has the effect of increasing the estimated gain in life years, and hence in QALYs, from adding necitumumab to GCis. The company shows that alternative assumptions result in higher ICER estimates: for example, £79,412 per QALY gained if Weibull distributions are used to extrapolate beyond the OS KM endpoints.

The ERG's preferred set of modelling assumptions included use of the ITT (EGFR-expressing) patient group and Weibull extrapolations from points on the KM with more than 20 patients remaining per arm. This resulted in an estimated ICER of £169,612 per QALY gained. Sensitivity and scenario analysis showed considerable variation around this ICER. However, it remained high, and the estimated probability that GCis + N presents a cost-effective treatment option for first-line treatment for squamous NSCLC for patients with EGFR-expressing tumours is very low unless the maximum acceptable ICER is more than £100,000 per QALY gained.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Necitumumab for untreated metastatic squamous non-small-cell lung cancer [ID835]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 7 April 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 necitumumab marketing authorisation states that necitumumab in combination with gemcitabine and cisplatin (GCis + N) is indicated for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous NSCLC who have not received prior chemotherapy"	We propose the following amendment "The necitumumab marketing authorisation states that necitumumab in combination with gemcitabine and cisplatin (GCis + N) is indicated for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous NSCLC who have not received prior chemotherapy for this condition"	This statement is a factual inaccuracy.	We agree with the company's proposed amendment and have changed this sentence to the wording suggested by the company. As the company notes, the SmPC does more specifically state that the indication for necitumumab is patients "… who have not received prior chemotherapy for this condition".

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 – "Only one trial (the SQUIRE trial) included in the NMA focused exclusively on patients with squamous NSCLC. The NMA is broader than the licensed population."	We propose the following amendment: "Only one trial (the SQUIRE trial) included in the NMA focused exclusively on patients with squamous NSCLC. The NMA is broader than the licensed population as necitumumab is the only drug with a marketing authorisation for patients with locally advanced or metastatic EGFR expressing squamous NSCLC."	The NMA is broader than the licensed population as necitumumab is the only drug with a marketing authorisation for patients with locally advanced or metastatic EGFR expressing squamous NSCLC.	This is not a factual inaccuracy, no change needed. Our statement on page 11 that "The NMA is broader than the licensed population in that it did not focus solely on patients with EGFR expressing squamous NSCLC" is correct and clarifies the patient population included in the NMA for the reader.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 – "After completion of induction treatment with GCis + N, patients were assumed to proceed to maintenance treatment with necitumumab alone"	We propose the following amendment "After completion of induction treatment with GCis + N, patients without progressive disease were assumed to proceed to maintenance treatment with necitumumab alone"	This statement is a factual inaccuracy. Only those without progressive disease were eligible to proceed to maintenance therapy	This is not a factual inaccuracy, no change needed. The following sentence on page 12 of the ERG report states: "Induction and maintenance treatment could terminate at any time due to … disease progression…" Thus patients who progress while on induction will not complete induction treatment.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15– "The OS results supplied for the EGFR expressing subgroup do not match those reported for this subgroup in a publicly available Food and Drug Administration (FDA) briefing document about necitumumab."	We propose removing this statement from the ERG report or provide the justification.	In the FDA report, the primary analysis presented the unstratified analysis whereas, the EMA and company submission include stratified analysis.	This is not a factual inaccuracy, no change needed. We have checked the FDA report and note it does not state that the analysis of OS in the EGFR expressing subgroup was unstratified. We acknowledge the company's explanation here for the difference in the OS results presented in their submission, but this is not a factual

			inaccuracy.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 - “most of the comparisons were based on indirect evidence, so consistency with direct evidence could not be assessed”	We propose the following amendment: “Most of the comparisons were based on indirect evidence. Consistency with direct evidence could not be assessed due to lack of studies in squamous NSCLC”	The consistency with direct evidence could not be assessed due to a lack of studies in squamous NSCLC. As mentioned in the main submission and in clarification response document (response A4a), we excluded studies investigating agents without market authorisation in any country for the first-line treatment of patients with advanced or metastatic advanced squamous NSCLC	This is not a factual inaccuracy, no change needed. Our original text and the company’s proposed amendment have the same meaning: it was not possible to assess consistency between indirect and direct evidence.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 – “In line with the CS, the clinical expert advised that patients may receive between four to six cycles. Therefore, as acknowledged on CS p. 30, the introduction of necitumumab, which will require up to six cycles of treatment in the induction	We propose to remove last sentence.	The statement is a factual inaccuracy as the clinical expert advised that patients may receive between four to six cycles. Therefore, providing necitumumab for a maximum of six cycles is in line with clinical practice and will not	We agree that this is a factual inaccuracy. We have amended the text as follows: “In line with the CS, the clinical expert advised that patients may receive between four to six cycles. As described in section

phase (mean 4.6 cycles in the SQUIRE trial, CS Table 6 p. 29) and then maintenance treatment (mean 6 cycles in the SQUIRE trial,8 CS Table 6 p. 29) (please see section 2.3 below for a description of the induction and maintenance treatment phases), **will be associated with additional costs to the NHS, including up to an extra two cycles of treatment in the induction phase."**		be associated with additional cost to the NHS of an extra two cycles of treatment in the induction phase.	2.3 below, the necitumumab SmPC states that patients treated with necitumumab can receive up to six cycles of treatment in the induction phase (patients received a mean of 4.6 cycles in the SQUIRE trial, CS Table 6 p. 29). Therefore, providing necitumumab for a maximum of six cycles is in line with current clinical practice. The SmPC states that following induction treatment, patients who have not experienced disease progression can receive necitumumab maintenance treatment (mean 6 cycles in the SQUIRE trial,[2] CS Table 6 p. 29). As acknowledged on CS p. 30, this maintenance treatment will be associated with additional costs to the NHS."

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 – "Patients would need to be tested for EGFR expression prior to administration of necitumumab and this would be a	We propose the following amendment: "An EGFR test using an IHC kit from Dako was used in the SQUIRE trial to test for EGFR	A test is available to test for EGFR expression and is currently used in clinical practice in other disease	The company's response here has highlighted to us that our original wording of this point did

new test.”	expression. The cost of the kit is £1,459 for 35 tests which equates to £42 per kit (NICE TA176). There are also in house tests that have been developed as alternatives to the Dako test. No companion diagnostic is required with the label.”	areas.	not adequately convey our meaning. We did not mean that a test for EGFR expression is not currently available, but that patients with squamous NSCLC are not currently routinely tested for EGFR expression and that testing them for this would be a change to current practice. We have therefore reworded this sentence on page 21 to read as follows: “Patients would need to be tested for EGFR expression prior to administration of necitumumab and this would be a change to current practice.” We thank the company for this further information about the costs of tests for EGFR expression. We have not, however, updated the report with these costs, as suggested by the company in their proposed amendment to the text, as this information was not supplied in the company’s submission and we are making a point on page 21 and elsewhere in our report that the costs of testing for EGFR expression have not been included in the company’s economic model.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22 – "The company acknowledges on CS p. 15 that the population specified in the decision problem is not fully consistent with the SmPC indication, but does not explain why."	We propose the following amendment: The company acknowledges on CS p. 15 that the population specified in the decision problem is not fully consistent with the SmPC indication. This is because the label was unexpectedly amended by the EMA following the NICE decision problem meeting.	We communicated this with NICE in advance as soon as we were aware of the implication.	This is not a factual inaccuracy, no change needed. In the decision problem presented in CS Table 1 on p. 15, it is stated that the specified population "is not consistent with the indication provided in the summary of product characteristics for necitumumab. Additional analysis will be provided to NICE at a later stage to reflect this population". No explanation for why the populations differ is given.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 – "The ERG notes that the Food and Drug Administration (FDA) has approved necitumumab in combination with GCis (GCis + N) for the first-line treatment of metastatic squamous NSCLC, but the FDA has not limited the indication to patients with EGFR expressing squamous NSCLC nor specified locally	We propose making the following amendment: "The FDA and EMA have differing indications for necitumumab."	FDA did not restrict their recommendation according to EGFR expression status and as a result have a different indication to the EMA. The EMA requested an amendment to the label to restrict licensing to patients with EGFR expressing tumours (95.2% of the SQUIRE trial population).	This is not a factual inaccuracy, no change needed. It is implicit in our text that the FDA and EMA indications for necitumumab differ, as we have noted the indication for which necitumumab has been approved by the FDA and as we have detailed the SmPC

advanced NSCLC.[11] ”			indication in the preceding paragraph of the ERG report,

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23– “While the company has more specifically stated that the population is those who have “not received prior chemotherapy”, the ERG’s clinical expert advised that clinically this is the same as “untreated advanced” disease”	We propose the following amendment “While the company has more specifically stated that the population is those who have “not received prior chemotherapy for this indication”, the ERG’s clinical expert advised that clinically this is the same as “untreated advanced” disease”	This statement is a factual inaccuracy.	We agree that this is a factual inaccuracy and that the text should more specifically state that the company states that the population is those who have “not received prior chemotherapy for this condition”, in accordance with the company’s text on CS p. 15. We have corrected page 23. Please note that the company states “…for this condition” on CS p. 15, which is why we have corrected the ERG report text to this wording rather than “… for this indication”, as suggested by the company.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 – "Patients in Asia have a higher frequency of EGFR mutations, which would make an EGFR receptor drug more effective."	We propose removing this statement.	This statement refers to EGFR mutations, not EGFR expression. EGFR mutations and EGFR expressions are not interchangeable. Necitumumab is indicated for patients with an EGFR expression.	We have removed this statement as suggested by the company. We have also removed the statement "with perhaps the exception of Asia (8% of the ITT population)" from the following preceding sentence: "Clinical expert advice to the ERG is that data from patients from all geographical regions would be representative of patients in England, with perhaps the exception of Asia (8% of the ITT population)." Although the clinical expert commented that Asian populations have more frequent EGFR mutations it is not fully clear whether this would affect necitumumab efficacy, therefore we have removed this sentence.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 – "The ERG notes that	We propose adding this justification in the ERG	This change in duration of	We thank the company for this

the trial used the drug doses and regimens outlined in the necitumumab draft SmPC and the gemcitabine SmPC,[5] except that necitumumab was delivered for a minimum of 50 minutes, while the draft SmPC states it should be delivered for a minimum of one hour. “	report.	administration was made during regulatory interactions and label negotiations.	information, but this is not a factual inaccuracy, so no change is needed. This information was not available to the ERG when we wrote our report.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60, In the EGFR expressing subgroup, the difference in ORR between the GCis + N and GCis groups was [redacted]…..	The upper CI should be [redacted].	There were factual inaccuracies in the information provided in the CS.	We have corrected this, as suggested by the company.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61, Table 15, ‘objective response (CR + PR) difference (95% CI)[redacted] Footnote of Table 15 ‘[redacted]	The upper CI should be [redacted]. We propose removal of the statement.	There were factual inaccuracies in the information provided in the CS.	We have corrected this and removed the associated footnote, as suggested by the company.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 17, Median survival results for EGFR Western Europe subgroup GCis [redacted]	The upper CI should be [redacted].	This information is a factual inaccuracy.	We agree that this is a factual inaccuracy and we have now corrected this.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 17, ORR difference results for EGFR Western Europe subgroup: [redacted][d] ORR, odds ratio results for EGFR subgroup [redacted]	The correct CI is ([redacted]). The correct CI is ([redacted]).	There were factual inaccuracies in the information provided in the CS.	We have corrected both confidence intervals, as suggested by the company, and removed the associated footnotes explaining that the CI as reported in the company's clarification appendix A1 contains sign error(s). We note, though, that the ORR difference of [redacted] relates to the EGFR subgroup in Table 17 and not the EGFR Western Europe subgroup as stated by the company here. As the company has not requested that we amend the subgroup label in Table 17, we assume that the label we originally used

			is correct.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – "Exceptions are that in the GCis group the rates of any grade hypomagnesaemia are higher in the EGFR expressing population ([redacted]) than in the ITT population ([redacted]); and rates of any grade rash for both treatment groups in the EGFR expressing group are lower than in the ITT population (GCis + N [redacted] versus [redacted]; GCis [redacted] versus [redacted]). The reasons for these discrepancies are unclear"	The correct figures are as follows: Rates of any grade hypomagnesaemia in the EGFR expressing population: [redacted] and Rates of any grade rash for both treatment groups in the EGFR expressing group are: GCis + N [redacted]; GCis [redacted]	There were factual inaccuracies in the information provided in the CS (Table 10). Please find the correct table below.	We have amended this. Given the corrected data supplied by the company, our statement on page 73 that there were differences between the EGFR expressing population and the ITT population in rate of any grade hypomagnesaemia and any grade rash is no longer correct. We have therefore amended page 73 by removing the following text: "Exceptions are that in the GCis group the rates of any grade hypomagnesaemia are higher in the EGFR expressing population ([redacted]) than in the ITT population ([redacted]); and rates of any grade rash for both treatment groups in the EGFR expressing group are lower than in the ITT population (GCis + N [redacted] versus 76.2%; GCis [redacted] versus 10.2%). The reasons for these discrepancies are unclear."

			As a result of the company supplying this corrected information, we have now also updated page 75 where we additionally summarise these results, to reflect that rates of all AEs were similar between the EGFR expressing and ITT populations. To do this, we have removed the following text: ", although, in the GCis group rates of any grade hypomagnesaemia were higher in the EGFR expressing group than in the ITT population. In addition, rates of any grade rash for both treatment groups in the EGFR expressing group appeared to be lower than in the ITT population. The reasons for this are unclear." We have also updated page 11, where these results are summarised too, to reflect this, by removing the following text: "In the EGFR expressing subgroup from the ITT population, patients treated with GCis experienced higher rates of hypomagnesaemia than patients treated with GCis in the ITT population. Rates of any grade of rash were lower in the both

			treatment arms in the EGFR expressing subgroup than in the ITT population.”

Preferred Term	GCis+N N = 456 n (%)		GCis N = 468 n (%)	
	Any grade	Gr. ≥3	Any grade	Gr. ≥3
Patients with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 - “The trial did not include patients with locally	We propose adding this justification in the ERG	For patients with stage IIIB and stage IV NSCLC, the 5-year survival rates	We thank the company for this further information, but this is

advanced disease (stage III).”	report.	as calculated from the National Cancer Institute’s SEER database, based on people who were diagnosed with NSCLC between 1998 and 2000, are approximately 5% and 1%, respectively (ACS 2016). The current European evidence-based clinical practice guidelines for the treatment of patients with NSCLC evaluated as unresectable in stage IIIb (locally advanced disease) recommend concurrent chemoradiotherapy as the treatment of choice (Bezjak et al. 2015; Eberhardt et al. 2015). In clinical practice, it is common for patients with locally advanced disease and considered unfit for concurrent chemoradiotherapy to be offered 1st-line therapy for advanced (stage IV; metastatic) disease. With known poor survival and a noncurative treatment intent in both patient groups, the treatment pattern of locally advanced and metastatic NSCLC is therefore much the same in clinical practice. On this basis, Necitumumab is indicated for both patient groups.	not a factual inaccuracy, so no change is needed. We note that this statement is made on page 74 of our report and not page 75, as stated by the company here. The trial did not include patients with locally advanced disease (stage III). We have stated this in our report on page 74 to make the trial population clear to the reader.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82 – "The company does not present a standard incremental analysis. Instead they present a series of pairwise comparisons between GCis + N and each included comparator."	Please add "the economic model included these incremental analyses".	An incremental analysis is presented in "Results (2)" tab on the top of the efficiency frontier figure in the economic model provided to the ERG.	We agree that the submitted model did include a facility to calculate the incremental comparisons, although the submitted report did not. We have clarified this on page 82, as follows: "The company does not present a standard incremental analysis in their submission. Instead they present a series of pairwise comparisons between GCis + N and each included comparator. However, the company does report disaggregated costs and QALYs for most interventions, and the model contains full disaggregated results and an incremental analysis. We present incremental results tables (see section 4.3.8 below).

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 – “Patients who complete induction treatment with a platinum doublet move into the NPD-discontinued state, where they remain until progression or death.”	We propose the following amendment: “Patients who complete induction treatment with a platinum doublet that do not progress move into the NPD-discontinued state, where they remain until progression or death.”	This statement is a factual inaccuracy.	This is not a factual inaccuracy, as the preceding sentence makes it clear that patients who progress do not complete induction treatment. However, we note that there is a typo in this sentence, which we have corrected: “With conventional chemotherapy, patients remain on induction until completion (usually after 4-6 treatment cycles), or they may discontinue early due to unacceptable adverse effects, patient choice, disease progression or death.”

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97 – “The log-logistic also provides a reasonable fit for the GCis group, although the AIC and BIC were slightly lower than for the Weibull curve, which also has a good visual fit. “	We propose the following amendment: “The log-logistic also provides a reasonable fit for the GCis group, although the AIC and BIC were slightly higher than for the Weibull curve, which also has a good visual fit.”	This statement is a factual inaccuracy.	Thank you, this was an error. We have corrected this sentence as follows: “The log-logistic also provides a reasonable fit for the GCis group, although the AIC and BIC were only slightly higher than for the Weibull curve,

			which also has a good visual fit.”

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 127 – “It can be seen that the probability that GCis + C is cost-effective (the proportion of dots below and to the right of the diagonal line) is low for all comparators.”	We propose the following amendment: “It can be seen that the probability that GCis + N is cost-effective (the proportion of dots below and to the right of the diagonal line) is low for all comparators.”	The ERG report states GCis + C, which is a factual inaccuracy.	Thank you, this was a typing error, which we have corrected as suggested.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 148 – “The ERG, however, does not agree with the company that GCis + N confers an additional survival benefit of 5.75 months compared with GCis alone.”	We propose the following amendment: “The ERG, however, does not agree with the company that GCis + N confers an additional survival benefit of 6.5 months compared with GCis alone.”	This statement is a factual accuracy as the 5.75 months refers to the Western Europe subpopulation of the ITT population.	This is not a factual inaccuracy. In the CS ‘End of life criteria’ section (CS p. 134), the company states that “The modelled mean OS benefit for the Western Europe subpopulation was 5.76 months for GCis + N (19.82 months) when compared to GCis (14.06 months).” The company did not provide a new ‘End of life’ criteria section to its submission when reporting the additional analyses based on

			the EGFR expressing and Western Europe EGFR expressing subgroups in its clarifications response (although, we acknowledge that this was not requested). We therefore referred to the 'End of life' section in the CS, which presented the survival benefit in the Western Europe subgroup to demonstrate how NICE's criteria in the 'Supplementary Advice for Appraising life-extending, end of life treatments' have been met. We do acknowledge, though, that it would be appropriate to additionally report in this section the modelled mean OS benefit for the Western Europe EGFR expressing population, and so we have now added this alongside the modelled mean OS benefit in the Western Europe population in both the first and third paragraphs. We also note that there was a typographical error in our report: "5.75 months" should read "5.76 months". We have now corrected this.

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Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 – "The SQUIRE trial showed that GCis + N resulted in a median OS benefit compared with GCis of an additional 1.7,……"	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 – "[redacted]."	Please mark this information as academic in confidence.	This is unpublished information that will be submitted as an abstract to EU ISPOR	The ERG has not updated the confidentiality marking. NICE is in the

		2016.	process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 – "The associated hazard ratios (HRs) were statistically significant for all populations. Median PFS was statistically significantly slightly longer with GCis + N compared to GCis in the EGFR expressing and ITT populations, but not the two Western Europe subgroups. Objective response rates were	Please remove the confidential marking.	The text referring to confidential information is not considered confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

statistically significantly higher with GCis + N than with GCis in the EGFR Western Europe subgroup only (statistical significance not reported for the ITT population)."			

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 – "a number of analyses of HRQoL detailed in the clinical study report (CSR) provided by the company as part of its submission were not reported in the CS."	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 – "race characteristics were balanced across arms."	Please remove the confidential marking.	The text referring to confidential information is not considered confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 and 35 – "….(similarly to the overall Western Europe subgroup) proportionally fewer patients in the GCis + N arm were aged ≥18 - <65 years ([redacted]) than in the GCis arm ([redacted]); and proportionally fewer patients in the GCis + N arm had an ECOG performance status of two ([redacted]) than in the GCis arm ([redacted])."	Please remove the confidential marking.	The text referring to confidential information is not considered confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39, "The CS does not define a clinically meaningful difference, however in the CSR p. 63 this is defined as a ≥15 mm change from baseline" "In the CSR p.63 deterioration in LCSS was defined as a ≥15 mm increase from baseline in LCSS score, but assessment of deterioration of ECOG PS was	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

not defined.”			

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40, “The ERG notes that the CSR also reports that a number of other analyses of the LCSS were undertaken, but the results of these analyses are not reported in the CS. This means there is a risk of selective outcome reporting in the data presented in the CS.”	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42, “The CSR also states, that HRs for time to deterioration in LCSS (the outcome presented in the CS, see Section3.1.5) were estimated using Cox proportional hazards. For EQ-5D, the CSR reports only that summary statistics were used.”	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44, “The CSR reports that a clinically meaningful difference on the scales of the LCSS is a change of ≤ 15 mm, and this was used to categorise patients as having either improved, stable or worsened status in the LCSS results presented in the CS. ”	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57 – “As shown in Table 9, in the EGFR expressing population, the median OS was 11.7 months …….10 months …. in OS of 1.74 months……(HR 0.79 (95% CI 0.69, 0.92), p=0.002)….”	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57 – Table 9, median OS	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the

survival of 11.73 months for GCis + N and 9.99 months for GCis and HR.			confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – "Median PFS was 5.7 months…… and 5.5 months…… The HR for PFS was 0.84 (95% CI, 0.72, 0.97), p=0.018"	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – Table 12, median PFS of 5.72 months for GCis + N and 5.49 months for GCis arm and HR.	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is

			complete.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62 – “As stated in section 3.1.5, a number of other analyses of the LCSS were undertaken, but the results of these analyses are not reported in the CS.”	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67 – “was 1.74 months, favouring GCis + N (HR 0.79 (0.69, 0.92). “	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67 and 68 – "There were statistically significant differences between the treatment arms in OS for all four populations. GCis + N resulted in statistically significantly better PSF outcomes than GCis in the ITT population and EGFR expressing population. There were, however, no statistically significant differences in PFS between GCis + N and GCis in either of the Western Europe subgroups. "	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 17 – Median OS for EGFR subgroup for both arms – 11. 73 and 9.99 months; OS HR for EGFR subgroup 0.79 (0.69, 0.92); p=0.002; median PFS for EGFR subgroup for both arms – 5.72 and 5.49 months, PFS HR 0.84 (0.72, 0.97); p=0.018	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 – "occurred as a result of TEAEs was similar between groups in the chemotherapy phase (GCis + N 9.3% vs GCis 10.5%) .."	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page – 71 – "..5.8% ..", "..42.6%..", "..37.5% ..", "…67.7% .."	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, Table 20, results from	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the

first row to that of 'Patients with ≥1 Grade ≥3 TEAE'			confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 45

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, "…than GCis alone for any grade (8.2% …….≥ grade 3 (4.3% …."	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 46

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – "…15.7%...", "76.2%", "10.2%"	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is

			complete.

Issue 47

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74, Table 22 – results for continuation phase	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – "The SQUIRE trial showed that GCis + N resulted in statistically significant greater improvements than GCis in OS and PFS in the EGFR expressing subgroup from the ITT population and in the total ITT population. Objective response rates did not differ significantly between the trial arms in the ITT population and in the EGFR expressing subgroup from the ITT population"	Please remove the confidential marking.	This information is not confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96, Figure 7 Page 101, Figure 9	Please mark this information as academic in confidence.	This is unpublished information.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 50

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100, Table 33	Please mark this information as academic in confidence.	This is unpublished information.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 51

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 121, "..0.54 years (6.5 months), corresponding to a mean gain of 0.34 QALYs per patient. Given the higher estimated cost (a mean increase of £19,516 per patient),…."	Please remove the confidential marking.	The incremental results are no longer considered confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

Issue 52

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 121, Table 41 Page 122, Table 42 and Table 43 Page 143, Table 50	Please remove the confidential marking.	The incremental results are no longer considered confidential.	The ERG has not updated the confidentiality marking. NICE is in the process of reviewing the confidentiality marking with the company and has agreed to update the marking in the ERG report once the review is complete.

(please cut and paste further tables as necessary)

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer

ERRATUM

Replacement pages following the factual accuracy check by Eli Lilly

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors
Karen Pickett, Research Fellow, SHTAC
Micah Rose, Research Fellow, SHTAC
Jill Colquitt, Senior Reviewer / Partner, Effective Evidence LLP
Emma Loveman, Senior Reviewer / Partner, Effective Evidence LLP
Geoff Frampton, Senior Research Fellow, SHTAC
Andy Clegg, Senior Reviewer / Partner, Effective Evidence LLP
Joanne Lord, Professorial Fellow in Health Economics, SHTAC

Correspondence to
Karen Pickett
Southampton Health Technology Assessments Centre
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Erratum date 13 April 2016

Version 1

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of this appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to appraise the clinical and cost-effectiveness of necitumumab within its marketing authorisation for the treatment of untreated advanced, metastatic, squamous non-small-cell lung cancer (NSCLC). The necitumumab marketing authorisation states that necitumumab in combination with gemcitabine and cisplatin (GCis + N) is indicated for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous NSCLC who have not received prior chemotherapy for this condition. The company's original evidence submission for this appraisal did not include analyses of the efficacy, safety or cost-effectiveness of GCis + N among patients with EGFR expressing squamous NSCLC. The company, however, supplied additional clinical and cost-effectiveness analyses for this patient population during the appraisal, in their response to clarification questions from NICE and the Evidence Review Group (ERG). The submission assesses the clinical and cost-effectiveness of GCis + N compared with five of the eight comparator combination drug regimens specified in NICE's scope:

- Cisplatin in combination with gemcitabine (GCis)
- Cisplatin in combination with paclitaxel (PCis)
- Carboplatin in combination with gemcitabine (GCarbo)
- Carboplatin in combination with paclitaxel (PCarbo)
- Cisplatin in combination with docetaxel (DCis)

Insufficient evidence was available to enable a comparison with the remaining three:

- Carboplatin in combination with docetaxel (DCarbo)
- Cisplatin in combination with vinorelbine (VCis)
- Carboplatin in combination with vinorelbine (VCarbo)

Summary of submitted clinical effectiveness evidence

The company's submission to NICE included:

- A systematic literature review of direct evidence, which included one Phase III randomised controlled trial (RCT) (the SQUIRE trial[1]).

A systematic review to inform a network meta-analysis (NMA), which included a total of 10 RCTs in four networks to provide direct and indirect evidence of the efficacy of GCis + N compared to GCis alone and the other squamous NSCLC treatments specified in

[redacted] The proportion of patients experiencing at least one serious adverse event (AE) was marginally higher during the treatment phase with GCis + N than during treatment with GCis. Venous thromboembolic events were experienced more frequently in those treated with GCis + N than GCis alone for any grade. In the ITT population, the GCis + N group also experienced rashes, hypomagnesaemia, and conjunctivitis more frequently than the GCis group alone.

The company's systematic review conducted for the NMA identified enough evidence to enable comparisons of GCis + N against PCarbo, GCis, PCis, DCis and GCarbo on the OS and PFS outcomes only (no evidence was available for HRQoL or toxicity, which are the other outcomes specified in the inclusion criteria for the review). A comparison with VCis could only be made for median OS data analyses. The NMA mainly included subgroup analyses of patients with squamous NSCLC from trials including patients with other histological subtypes of NSCLC. Only one trial (the SQUIRE trial) included in the NMA focused exclusively on patients with squamous NSCLC. The NMA is broader than the licensed population in that it did not focus solely on patients with EGFR expressing squamous NSCLC. [redacted].

Summary of submitted cost effectiveness evidence

The company's submission to NICE includes:

1. A review of published economic evaluations.
2. A report of a model developed by the company to estimate the cost-effectiveness of GCis + N compared with GCis, GCarbo, PCarbo and DCis for previously untreated patients with locally advanced or metastatic squamous NSCLC eligible for first-line treatment.

The clinical expert consulted by the ERG stated that in clinical practice, cisplatin in combination with gemcitabine (GCis) or carboplatin in combination with gemcitabine (GCarbo) are the most commonly used platinum doublets. This concurs with the company's statement on CS p. 37 that gemcitabine is the most commonly used first-line treatment for squamous NSCLC in the UK and the company's statement in the decision problem (CS Table 1, p. 15) that GCis and GCarbo are the current standard of care in the National Health Service (NHS). The clinical expert consulted by the ERG stated that all the platinum doublet combinations are equally efficacious, therefore all the combinations are used in practice and all are the current standard of care. The choice of which to use is usually governed by expectations of what patients will be able to tolerate and their quality of life.

The CS (p. 29 and p. 35) states that patients receive chemotherapy for four to six cycles, but does not state the cycle length. Clinical expert advice to the ERG is that patients receive chemotherapy in three-week cycles. Patients undergo two cycles and then have a scan to check that the treatment is working. If it is, they then receive another two cycles of treatment. A full course of treatment takes 12 to 18 weeks (i.e. patients receive four to six cycles in 12 to 18 weeks). In line with the CS, the clinical expert advised that patients may receive between four to six cycles. As described in section 2.3 below, the necitumumab SmPC states that patients treated with necitumumab can receive up to six cycles of treatment in the induction phase (patients received a mean of 4.6 cycles in the SQUIRE trial, CS Table 6 p. 29). Therefore, providing necitumumab for a maximum of six cycles is in line with current clinical practice. The SmPC states that following induction treatment, patients who have not experienced disease progression can receive necitumumab maintenance treatment (mean 6 cycles in the SQUIRE trial,[2] CS Table 6 p. 29). As acknowledged on CS p. 30, this maintenance treatment will be associated with additional costs to the NHS.

The necitumumab SmPC states that it is indicated for patients who have epidermal growth factor (EGFR) expressing squamous NSCLC. The company has not, however, discussed in the CS current clinical practice regarding testing patients for EGFR expression nor how the introduction of necitumumab might impact on service provision regarding this. The cost of testing for EGFR expression was not included in the company's cost-effectiveness analyses. The ERG's clinical expert advised that patients are not currently routinely tested for EGFR expression. They are only currently tested for mutations in the EGFR gene. Patients would need to be tested for EGFR expression prior to administration of necitumumab and this would be a

change to current practice. The ERG's clinical expert commented that it is unclear how the costs of this would be funded.

population specified in the decision problem is not fully consistent with the SmPC indication, but does not explain why. The ERG therefore believes that the population specified in the decision problem is not appropriate for the potential use of necitumumab in the NHS and that the most appropriate population would be people with locally advanced or metastatic EGFR expressing squamous NSCLC. The company provided clinical effectiveness and cost-effectiveness results for subgroups of patients with EGFR expressing tumours in response to clarification questions from NICE and the ERG (please see discussion under Subgroups below) to reflect the SmPC indication (clarification response A1).

The ERG notes that the Food and Drug Administration (FDA) has approved necitumumab in combination with GCis (GCis + N) for the first-line treatment of metastatic squamous NSCLC, but the FDA has not limited the indication to patients with EGFR expressing squamous NSCLC nor specified locally advanced NSCLC.[3]

As mentioned above, the patient population specified by the company matches the SmPC indication for necitumumab in terms of patients' prior treatment (patients who have not received prior chemotherapy). The final scope specifies that the population should be those "untreated" for advanced, metastatic disease. While the company has more specifically stated that the population is those who have "not received prior chemotherapy for this condition" (CS p. 15), the ERG's clinical expert advised that clinically this is the same as "untreated advanced" disease. The ERG's expert advised that some people may have had resected or irradiated cancer before chemotherapy, but this is essentially the same as presenting with untreated metastatic disease.

Intervention

In accordance with the final scope, the intervention described in the decision problem is GCis + N (necitumumab's brand name is Portrazza). Necitumumab is a monoclonal antibody that works by targeting EGFR-1. In December 2015, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for necitumumab, and this has now been granted. As outlined in the CS, the SmPC recommends that necitumumab is given to patients at a flat dose of 800 mg via intravenous infusion over 60 minutes on days one and eight of each 3-week chemotherapy cycle, for up to six cycles. The company states that a gemcitabine dose of 1250 mg/m^2 is to be administered through intravenous infusion on days one and eight of each cycle, with a cisplatin dose of 75mg/m^2 administered on day one of each cycle. The ERG notes that these stated doses of gemcitabine and cisplatin match those

the post-hoc Western Europe subgroup, and that Australia and Canada were not included as they are not part of Europe. The company also stated that it is believed that the Western Europe subgroup is more generalisable to clinical practice in England than the populations across Australia, Canada and Europe combined (clarification response A6), however no additional information was provided.

Clinical expert advice to the ERG is that data from patients from all geographical regions would be representative of patients in England. The ERG also notes that the company stated that there was not a statistically significant treatment interaction between the post-hoc Western Europe subgroup and other patients in the SQUIRE trial (CS p. 229). Overall, the ERG considers that the company's use of the Western Europe subgroup in the base case is not sufficiently justified. The ERG considers the subgroup of patients with EGFR expressing tumours from the ITT population is the most relevant patient group to the marketing authorisation and to patients in England.

On CS pp. 68 to 69, the company additionally lists a number of planned subgroup analyses by geographical region and countries with an enrolment >40 patients, but has not provided the results of these in the CS. These were requested by NICE and the ERG, and while subgroup analyses by region were provided in clarification response A6c Appendix 6, the regions analysed differed to those pre-specified.

The company also provides details of other planned subgroup analyses on CS p. 69, including:

- age (<70 versus ≥70 years; and <65 versus ≥65 years);
- gender (women versus men);
- race (White versus non-White);
- ECOG PS (0 versus 1 versus 2 and 0-1 versus 2); and,
- smoking history [never smoker (non-smoker and light ex-smoker combined) versus smoker].

CS Table 11 p. 51 also states that patients who displayed a rash within the first cycle was a pre-specified subgroup, however results are not presented in the CS.

Table 13 PFS by % positive EGFR expression, as reported in a FDA briefing document identified by the ERG

	Percent positive >0		Percent positive = 0[a]	
	GCis + N n=462	GCis n=473	GCis + N n=24	GCis n=23
Progression-free survival				
Median, months	5.72	5.49	4.24	5.59
HR (95% CI)	0.83 (0.72, 0.97)		1.19 (0.61, 2.30)	
p-value	0.015		0.611	
Interaction p value	0.305			

Source: FDA Briefing Document[4]
[a]0 % positive is equivalent to H-score=0 for EGFR staining

ITT population

PFS was slightly longer with GCis + N than with GCis (Table 14). Median PFS was 5.7 months (95% CI, 5.6, 6.0) in the GCis + N group and 5.5 months (95% CI, 4.8, 5.6) in the GCis group (HR for progression or death 0.85; 95% CI 0.74, 0.98). At 3 months, the PFS rate was 79% (95% CI, 76, 83) with GCis + N versus 73% (95% CI, 68, 76) with GCis. At 6 months, the PFS rate was 45% (95% CI, 40, 49) with GCis + N versus 37% (95% CI, 33, 42) with GCis. It is not clear to the ERG what the median follow-up time was for the assessment of PFS, but the ERG notes that the number of events in the GCis group is lower than the number of deaths in this group, as presented in Table 11 above.

Table 14 Progression-free survival (ITT population)

	GCis + N, N = 545	GCis, N=548
Number of events, n (%)	431 (79)	417 (76)
Number censored, n (%)	114 (21)	131 (24)
Median PFS[a], months (95% CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Stratified Hazard ratio (95% CI), p-value[b]	0.85 (0.74, 0.98) p=0.02	
3 month PFS rate[a], % (95% CI)	79 (76, 83)	73 (68, 76)
6 month PFS rate[a],% (95% CI)	45 (40, 49)	37 (33, 42)

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]Kaplan-Meier estimated
[b]Stratified log-rank p-value (stratified by ECOG PS and geographic region).

EGFR expressing subgroup

In the EGFR expressing subgroup, the difference in ORR between the GCis + N and GCis groups was [redacted] (**Error! Reference source not found.**). The disease control rate in this subgroup was [redacted] in the GCis + N group [redacted] than in the GCis group [redacted].

Table 15 Objective response rate in the EGFR expressing subgroup

n (%)	GCis + N, N = 462	GCis, N=473
Objective response (CR+PR) rate, n (%), 95% CI	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
OR (95% CI), p-value	[redacted]	
Disease control rate (CR+PR+SD) (95% CI)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
OR (95% CI), p-value	[redacted]	
Best overall response, n (%):		
Complete response (CR)	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable/No assessment[a]	[redacted]	[redacted]

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]Calculated by ERG from 'not evaluable' and 'no assessment'.

ITT population

ORR was higher with GCis + N than with GCis, however this was not statistically significant (p=0.40) (**Error! Reference source not found.**). The ORR was 31% (95% CI, 27, 35) in the GCis + N group and 29% (95% CI, 25, 33) in the GCis group. The disease control rate was also reported in the CS, this was significantly higher in the GCis + N group than in the GCis group (**Error! Reference source not found.**).

Table 16 Objective response rate (ITT population)

n (%)	GCis + N, N = 545	GCis, N=548
Objective response (CR+PR) rate (95% CI)	170 (31) (27, 35)	158 (29) (25, 33)
p-value (stratified Cochran-Mantel-Haenszel[a])	0.40	
Disease control rate (CR+PR+SD) (95% CI)	446 (82) (78, 85)	422 (77) (73, 80)
p-value (stratified Cochran-Mantel-Haenszel[a])	0.043	
Best overall response, n (%):		
Complete response (CR)	0	3 (<1)
Partial response (PR)	170 (31)	155 (28)
Stable disease (SD)	276 (51)	264 (48)
Progressive disease (PD)	41 (8)	55 (10)
Not evaluable/No assessment[b]	58 (11)	71 (13)

CI = confidence interval; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin
[a]stratified by ECOG PS and geographic region.

[b]calculated by ERG from not evaluable and no assessment in CS Table 16

[redacted]

Table 17 Summary of results for all SQUIRE trial populations presented in the CS and the company's clarifications response

	GCis + N	GCis
Median survival, months (95% CI)		
ITT population	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
EGFR subgroup	11.73 [redacted] [a]	9.99 [redacted] [a]
Western Europe subgroup	[redacted]	[redacted]
EGFR Western Europe subgroup		
OS: stratified HR (95% CI) [b]		
ITT population	0.84 (0.74, 0.96); p=0.01	
EGFR subgroup	0.79 (0.69, 0.92); p=0.002	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup		
Median PFS, months (95% CI)		
ITT population	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
EGFR subgroup	5.72 [redacted] [a]	5.49 [redacted] [a]
Western Europe subgroup	[redacted]	[redacted]
EGFR Western Europe subgroup		
PFS: stratified HR (95% CI) [b]		
ITT population	0.85 (0.74, 0.98); p=0.02	
EGFR subgroup	0.84 (0.72, 0.97); p=0.018	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup		
ORR, % (95% CI)		
ITT population	31 (27, 35)	29 (25, 33)
EGFR subgroup	[redacted]	[redacted]
Western Europe subgroup	[redacted] [c]	[redacted] [c]
EGFR Western Europe subgroup		
ORR difference (95% CI)		
ITT population	Not reported	
EGFR subgroup	[redacted]	
Western Europe subgroup	[redacted] [c]	
EGFR Western Europe subgroup		
ORR: odds ratio (95% CI)		
ITT population	Not reported	
Western Europe subgroup	[redacted]	
EGFR subgroup	[redacted]	
EGFR Western Europe subgroup	[redacted] [c]	

EGFR, epidermal growth factor receptor; GCis: gemcitabine + cisplatin; GCis + N: necitumumab + gemcitabine + cisplatin; ITT, intention-to-treat.

[a] CIs extracted by the ERG from the CSR

[b] unstratified analysis for EGFR Western Europe subgroup

[c] the company's clarification response Appendix 1 states that these results were for the Western Europe subgroup, but the ERG believes that this is a typo and that these results are for the EGFR expressing Western Europe subgroup.

[d] calculated by the ERG.

and conjunctivitis (Table 22). Rates of haematological toxicities were similar between the groups.

Treatment emergent adverse events were also reported in CS Table 38 for grade 3, grade 4 and grade 5 events. These were for the overall safety sets (for the GCis + N group including the maintenance phase). The events presented included the haematological toxicities, rash, hypomagnesemia and fatigue (as presented in CS Tables 42 and 43) and other adverse events of asthenia, pulmonary embolism, nausea and vomiting. For the events that were also reported in CS Tables 42 (and CS Table 43 for the GCis group) the number of events of grade 3, 4 and 5 do not correspond. The ERG considers the data from CS Tables 42 and 43 as accurate as we have checked these data against the CSR.

EGFR expressing subgroup

Adverse events for the EGFR expressing subgroup were provided by the company in clarification response Appendix 1. The rates of AEs in the EGFR-expressing subgroup generally reflect those seen in the ITT population (reported above) and as such are not reproduced here. The company also provided AE results for the EGFR expressing Western European population in clarification response Appendix 1 (not shown here).

CS reports OS and PFS results for both the ITT population and a post-hoc subgroup analysis of patients from Western Europe, as well as other results for the ITT population only. The company also provided results from the SQUIRE trial of post-hoc subgroup analyses of patients with EGFR expressing tumours from the ITT population and Western European subgroups in response to NICE and the ERG's clarifications questions, to reflect the population specified in the indication for necitumumab in the SmPC (clarification response A1). In the CS, the company argues that the Western Europe subgroup is more generalisable to patients in England than the ITT population. The company used data from the Western Europe EGFR expressing subgroup in their updated economic model submitted with the clarifications response. The SQUIRE trial was of a reasonable quality, although there is a risk of performance and detection bias due to lack of blinding of participants, care providers and outcome assessors.

The CS also presents an NMA comparing GCis + N with some of the scoped comparators.

The SQUIRE trial showed that GCis + N resulted in statistically significant greater improvements than GCis in OS and PFS [redacted] in the total ITT population. Objective response rates did not differ significantly between the trial arms in the ITT population and [redacted]. The CS states that HRQoL was similar between treatment arms over time during the trial in the ITT population, although limited HRQoL data are presented. HRQoL results were not provided for the EGFR expressing subgroup. In the ITT population, the proportion of patients experiencing at least one serious adverse event was marginally higher during the treatment phase with GCis + N than during treatment with GCis. Venous thromboembolic events of any grade were experienced more frequently in those treated with GCis + N than GCis alone. The GCis + N group also experienced rashes, hypomagnesaemia, and conjunctivitis more frequently than the GCis group. In the EGFR expressing subgroup from the ITT population, rates of AEs were similar to those reported for the total ITT population. Subgroup analyses suggest that GCis + N has little benefit for people without EGFR expressing NSCLC (H-score = 0).

NICE reference case requirements:	Included in submission	Comment
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No	Treatment assessed for end of life criteria.
Discount rate: 3.5% pa for costs and health effects	Yes	
Notes: ? = uncertain; N/A=not applicable		

A common thread throughout **Error! Reference source not found.** relates to quality of life measurement. The current NICE Guide to the Methods of Technology Appraisal (Methods Guidance)[5] states that utility in cost-utility analyses should be measured using EQ-5D, with patients submitting health state scores and valuation done by the general UK public. The utility values for modelled health states use EQ-5D data measured in accordance with NICE preferences, but the utility decrements used for adverse events are not in accordance with NICE preferred methods.

The company does not present a standard incremental analysis in their submission. Instead they present a series of pairwise comparisons between GCis + N and each included comparator. However, the company does report disaggregated costs and QALYs for most interventions, and the model contains full disaggregated results and an incremental analysis. We present incremental results tables (see section **Error! Reference source not found.** below).

The company has used mostly appropriate methods but their analysis has a number of limitations: due to lack of available data vinorelbine doublets and PCis were excluded from the modelling; utility decrements for adverse events are inconsistent with NICE methodological guidance; and analyses are presented in a pairwise manner that obfuscates cost-effectiveness conclusions.

1.1.1 Model structure and methodological approach

The company model is a state transition model, which reflects the progress of a cohort of patients through the stages of first-line treatment and disease progression to death. The structure is illustrated in **Error! Reference source not found.** below.

effects, patient choice, disease progression or death. Patients who complete induction treatment with a platinum doublet move into the NPD-discontinued state, where they remain until progression or death. However, after completion of induction with GCis + N patients move into NPD-maintenance, where they continue to receive necitumumab every three weeks until discontinuation, progression or death.

This broad model structure is appropriate for the decision problem. The three main states and transitions between them reflect the progressive and usually terminal nature of advanced NSCLC, and the three sub-states and transitions are consistent with current and recommended practice for first-line chemotherapy, and with the draft SmPC use of necitumumab.

1.1.1.1 Method for estimating transitions between states

A partitioned survival (or area under the curve) approach was used to estimate the proportion of the cohort in each of the five states at each weekly cycle. The distribution of the cohort between the NPD, PD and Dead states is illustrated in **Error! Reference source not found.**. Here the distribution is governed by two survival curves for each treatment: PFS and OS. At each time point (t), the proportion of the cohort who are dead is 1 - OS(t); the proportion in the PD state is OS(t) – PFS(t); and the proportion in the NPD state is just PFS(t).

Table 1 Estimates of model fit for OS in the EGFR expressing Western European subgroup

	AIC	BIC
GCis + N		
Weibull	391.893	397.847
Log-normal	392.795	398.748
Log-logistic	**385.977**	**391.931**
Exponential	395.275	398.252
Generalized Gamma	390.397	399.327
GCis		
Weibull	**416.062**	**422.149**
Log-normal	433.06	439.147
Log-logistic	**416.941**	**423.028**
Exponential	426.513	429.556
Generalized Gamma	417.003	426.134

Note: This is a direct reproduction of Table 18, clarification response Appendix 1

Diagnostic fit was not assessed in the CS for the ITT population. The ERG considers this to be inappropriate, in the absence of evidence supporting the Western European subgroup.

Based on the available diagnostic assessments for the Western European subgroup, the log-logistic curve has the lowest AIC and BIC for the GCis + N group (indicating a better fit), and it has a good visual fit. The log-logistic also provides a reasonable fit for the GCis group, although the AIC and BIC were only slightly higher than for the Weibull curve, which also has a good visual fit. The hazard function plots presented in the CS to justify the rejection of the proportional hazards assumption are difficult to assess, due to the small numbers of patients remaining in the unstable portions of the graphs. Statistical tests for proportional hazards were not presented in the CS, and the analysis for the larger ITT population might have been informative.

The diagnostic statistics and curves presented are not definitive, and the visual fit was similar between the log-logistic, Weibull, and generalised gamma distributions. The choice of curve should also be predicated on clinical plausibility. The log-logistic curve has a heavy tail, so predicts that a proportion of patients survive for a long time. This may be questionable for the

stage IV NSCLC population in the SQUIRE trial. Relative expected survival from Cancer Research UK shows stage IIIB patients having a 5-year survival rate of around 6.32%,[6] whilst

Numerical results from the revised model submitted as part of the clarification response are presented below in Table 2. These relate to the Western European subgroup of patients with EGFR expressing tumours, and are based on KM estimates of OS and PFS extrapolated from the endpoint with separately fitted Weibull curves for GCis and GCis + N, and adjusted by NMA hazard ratios for other comparators. This estimated ICER for GCis + N versus the next best non-dominated alternative (PCarbo) is £144,737 per QALY. If we restrict the analysis to the direct comparison between GCis + N and GCis, the ICER is £80,634.

Table 2 Incremental analysis – direct and indirect comparisons (PSA results) (Western European EGFR expressing subgroup)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
GCarbo	[redacted]	[redacted]	[redacted]				
PCarbo	[redacted]	[redacted]	[redacted]	£134	0.265	0.160	£839
DCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis	[redacted]	[redacted]	[redacted]	Dominated			
GCis + N	[redacted]	[redacted]	[redacted]	£19,868	0.181	0.137	£144,737

LYG, life years gained.

Cost-effectiveness scatterplots for the included comparisons in this analysis are shown below (**Error! Reference source not found.**). The spread of dots illustrates the extent of uncertainty over the relative costs and effects of GCis + N in relation to the included comparators. It can be seen that uncertainty over the incremental effects (QALYs gained) is lower for the direct comparison with GCis than for the other, indirect comparisons estimated from the NMA. The slope of the red lines in these graphs shows a cost-effectiveness threshold of £50,000 per QALY gained. It can be seen that the probability that GCis + N is cost-effective (the proportion of dots below and to the right of the diagonal line) is low for all comparators.

none of the estimated ICERs include the cost of testing patients for EGFR expression, as would be required to meet the SmPC indication. This cost was not included in the company model, and we have been unable to identify an estimate of the cost of this test, as it is not currently in routine use.

2 End of life

The company argues that necitumumab meets NICE's criteria in the 'Supplementary Advice for Appraising life-extending, end of life treatments'. The company states that expected survival in this patient population is less than 24 months (6.5 to 9.4 months, depending on the treatment used). The company further states that in the Western European subgroup, the modelled mean OS benefit for the Western Europe subgroup was 5.76 months for GCis + N compared with GCis alone. The ERG notes that the modelled mean OS benefit in the Western Europe EGFR expressing population, used in the company's model submitted with its clarification response, was 6.5 months. The company also indicates the treatment is indicated for an estimated small population of 2,575 patients in England with locally advanced or metastatic squamous NSCLC.

The ERG agrees that the company's estimate of the population size (CS Table 93, p. 233) appears reasonable, except that it includes all squamous NSCLC patients, not restricted to the EGFR expressing group (which is the SmPC indication). Therefore the patient population may be smaller than estimated.

The ERG agrees with the company that expected average survival in this population is less than 24 months. The ERG, however, does not agree with the company that GCis + N confers an additional survival benefit of 5.76 months (6.5 months in the Western Europe EGFR expressing population) compared with GCis alone. The company has used data from the Western European subgroup to support its argument, and the ERG believes that the company's rationale for basing efficacy conclusions on the Western European subgroup is unjustified. The ERG believes that the EGFR expressing subgroup from the ITT population is the most relevant population to the SmPC indication and this appraisal. Using the EGFR expressing subgroup data in the company's model (submitted in the clarifications response), the company's model showed a mean survival difference between GCis + N and GCis of 3.69 months, favouring GCis + N. The SHTAC base case analysis resulted in a mean survival difference of 2.25 months,

favouring GCis + N. Therefore, when using the SHTAC base case, GCis + N does not meet this criterion in NICE's end of life criteria.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer

ADDENDUM

Additional information requested by the National Institute for Health and Care Excellence

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Addendum date 26 April 2016

Key to colour highlighting used in report

Commercial in confidence (CIC) information in blue

TABLE OF CONTENTS

1 Introduction

This is an addendum to the Evidence Review Group (ERG) report for the single technology appraisal (STA) of necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer (NSCLC). At the request of the National Institute for Health and Care Excellence (NICE), the ERG has provided the following additional information to inform the Appraisal Committee Meeting:

- The modelled mean overall survival (OS) benefit associated with necitumumab in combination with gemcitabine plus cisplatin (GCis + N) compared with cisplatin in combination with gemcitabine (GCis) alone in patients with epidermal growth factor receptor (EGFR)-expressing NSCLC from the whole SQUIRE trial population, derived from the ERG's economic model when applying a log-logistic extrapolation to the Kaplan-Meier (KM) curves. The ERG's base case, presented in our original report, used a Weibull extrapolation, and NICE was interested in the results of our analyses when a log-logistic extrapolation was used instead.
- The results (ICERs and modelled mean OS benefits) of sensitivity analyses that explore the effect of different extrapolation start points (i.e. with different numbers of patients remaining at risk) on the Kaplan-Meier (KM) curves, when using a log-logistic extrapolation on data from patients with EGFR-expressing NSCLC from the whole trial population in the ERG's economic model.
- The modelled mean OS benefit for the EGFR-expressing (whole trial) population when no extrapolation has been used, when using the ERG's economic model.

In response to a query from NICE, we have corrected Table 50 on page 143 of the ERG report, which contained errors in the 'Comparison' column. In addition, we include a corrected version of Table 49 of the ERG report (p. 141), in which we reported the modelled estimates of mean OS, PFS, costs and QALYs from the company model with discounting applied. The undiscounted estimates in the corrected table below provide a better comparison between the clinical outcomes from the company and SHTAC base case versions of the model, in the whole trial population with EGFR expressing tumours.

2 Additional information

Table 1 shows the estimated ICERs and modelled mean and median OS benefits associated with GCis + N compared with GCis for patients with EGFR-expressing NSCLC from the total trial population when using different extrapolation assumptions in the ERG's economic model (scenarios **S0a to S17**). For comparison, we have also provided the results of the company's preferred analysis (base case direct analysis) when using data from the EGFR-expressing Western Europe population (**C0a**) and when using data from the EGFR-expressing (total trial, intention-to-treat; ITT) population (**C0b**).

Scenario **S0a** is our base case, as presented in the ERG report, that used Weibull extrapolations from the points on the OS KM curves with more than 20 patients remaining per arm (from week 126 in the GCis + N arm and from week 129 in the GCis arm). Scenario **S4a** is our scenario S4 reported in the ERG report. As shown in Table 1, the results of this scenario demonstrate that when a log-logistic extrapolation is used with more than 20 patients remaining in each arm, the modelled mean benefit for the EGFR-expressing patients from the whole trial population is 2.84 months, favouring GCis + N. Altering the point at which the log-logistic extrapolation was applied to the KM curves (in sensitivity analyses), to either one patient (scenario **S4b**) or more than 30 patients (scenario **S4c**) left at risk, resulted in modelled mean OS benefits of 4.16 and 3.57 months, respectively, favouring GCis + N. The associated ICERs were £110,567 and £123,905, respectively.

We note that the direction of impact on the ICER from reducing the time to extrapolation is not consistent or obviously predictable: a reduction from full trial follow-up (scenario S4b: extrapolation from week 161 and 168 for GCis + N and GCis respectively) to the point where at least 20 patients remain in each arm (scenario S4a: from weeks 126 and 129) leads to an increase in the ICER; but a further reduction to the point where at least 30 patients remain in each arm (scenario 4c: from weeks 122 and 115) then leads to a decrease in the ICER. This can be understood with reference to the graphs reproduced from the company model in Figure 8 of the ERG report (p. 99). It can be seen that the vertical distance between the OS KM curves from the two SQUIRE trial arms is variable, particularly after about two years of follow up. This means that attaching the extrapolated tails at different times might either increase or decrease the total area between the modelled OS curves, and hence increase or decrease the estimated QALY difference.

The modelled mean OS benefit for the EGFR-expressing (whole trial) population when no extrapolation was used (scenario **S17**) was 2.04 months. As might be expected, this three year time horizon provided a higher estimated ICER (£183,649 per QALY gained) compared with that for the five year time horizon reported in scenario S1 in the ERG report (£170,755 per QALY gained).

Table 1. Modelled mean and median OS benefits and associated ICERs from the company's and the ERG's economic model when using different extrapolation assumptions

Base scenario	Population	OS model	Extrapolated from n left (week)		ICER GCis+N vs GCis (£ per QALY)	Incremental Modelled OS (months, undiscounted)	
			GCis+N	GCis		Median	Mean
C0a	WE (EGFR)	Log-logistic	n=1 (160)	n=1 (163)	£57,725	[redacted]	7.53
C0b	ITT (EGFR)	Log-logistic	n=1 (161)	n=1 (168)	£110,248	[redacted]	4.16
S0a	ITT (EGFR)	Weibull	n>20 (126)	n>20 (129)	£169,612	[redacted]	2.25
S4a	ITT (EGFR)	Log-logistic	n>20 (126)	n>20 (129)	£138,018	[redacted]	2.84
S4b	ITT (EGFR)	Log-logistic	n=1 (161)	n=1 (168)	£110,567	[redacted]	4.16
S4c	ITT (EGFR)	Log-logistic	n>30 (122)	n>30 (115)	£123,905	[redacted]	3.57
S17	ITT (EGFR)	3 year time horizon (no extrapolation)			£183,649	[redacted]	2.04

Note: all ICERs and survival estimates are from deterministic analyses. Our base case and scenario analysis results (S0 to S16) presented in our original ERG report were stated to be from a Probabilistic Sensitivity Analysis, but this is an error, and the results were from deterministic analyses. Scenario S17 is a new, additional scenario analysis to those reported in the ERG report, which we ran in response to NICE's additional information request. Scenarios S4b and S4c were new sensitivity analyses that we also carried out in response to NICE's request for additional information. EGFR, epidermal growth factor receptor; GCis, cisplatin in combination with gemcitabine; GCis + N, necitumumab in combination with gemcitabine plus cisplatin; ICER, Incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life year; OS, overall survival; WE, Western Europe.

3 Corrected Table 49

The results of the company model reported in Table 49 of the ERG report (p. 141) were incorrect: we reported discounted estimates of the modelled mean OS, PFS, costs and QALYs for the company model, rather than the undiscounted estimates that were reported for the SHTAC base case model. The corrected table with undiscounted results for both versions of the model is show below (Table 2).

Table 2 Model outputs (undiscounted): ITT EGFR expressing population (amended Table 49 from ERG report p141).

	Company model			SHTAC base case		
	GCis + N	GCis	Difference	GCis + N	GCis	Difference
Modelled OS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	4.16	[redacted]	[redacted]	2.25
One year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year OS	4.9%	2.4%	2.5%	0.5%	0.3%	0.3%
Modelled PFS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year PFS	0.5%	0.4%	0.1%	0.0%	0.0%	0.0%
QALYs (undiscounted)						
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (undiscounted)						
Pre-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 Corrected Table 50

Table 3 below is a corrected table to replace Table 50 in the ERG report. The original Table 50 contained errors. In the original table, DCis was described as 'dominated' and we have now amended this to 'extendedly dominated'. We have also corrected the table to show that GCis was compared to carboplatin in combination with paclitaxel (PCarb) and not with cisplatin in combination with docetaxel (DCis).

Table 3. SHTAC base case – ITT EGFR subgroup (amended Table 50 from the ERG report)

Technologies	Total		Incremental		ICER (£ per QALY)	Comparison
	Costs	QALYs	Costs	QALYs		
PCis	[redacted]	[redacted]			-	
DCis	[redacted]	[redacted]			-	Ext. dominated
PCarb	[redacted]	[redacted]	£1,001	0.135	£7,429	vs PCis
GCarb	[redacted]	[redacted]			-	Dominated
GCis	[redacted]	[redacted]	£1,579	0.013	£124,663	vs PCarb
GCis+N	[redacted]	[redacted]	£19,993	0.118	£169,612	vs GCis

DCis, cisplatin in combination with docetaxel; GCarb, carboplatin in combination with gemcitabine; GCis, cisplatin in combination with gemcitabine; GCIs + N, necitumumab in combination with gemcitabine plus cisplatin; ICER, incremental cost-effectiveness ratio; PCarb, carboplatin in combination with paclitaxel; PCis, cisplatin in combination with paclitaxel; QALY, quality-adjusted life year.