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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

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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][c]	[redacted][c]
Western Europe subgroup	[redacted]	[redacted]
EGFR Western Europe subgroup		
ORR difference (95% CI)		
ITT population	Not reported	
EGFR subgroup	[redacted][c]	
Western Europe subgroup	[redacted]	
EGFR Western Europe subgroup		
ORR: odds ratio (95% CI)		
ITT population	Not reported	
Western Europe subgroup	[redacted]	
EGFR subgroup	[redacted][c]	
EGFR Western Europe subgroup	[redacted]	

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.