National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Thoracic Society	Yes it is appropriate	Thank you for your comments. No action required.
	Eli Lilly and Company	Yes, this is an appropriate topic for appraisal. Lung cancer is one of the most common and serious types of cancer, accounting for more than 1 in 5 cases of cancer deaths in the UK. Lung cancer is a heterogeneous disease, with squamous non-small-cell lung cancer (NSCLC) being a distinct disease from non-squamous NSCLC. There has been limited treatment advances specifically for squamous NSCLC in the past two decades, not least because there are no relevant oncogenic drivers that can inform treatment development decisions (e.g. EGFR M+ and ALK+) in non-squamous NSCLC. There are currently no targeted therapies available for first-line treatment of	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		squamous NSCLC.	
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	Yes. Necitumumab has shown statistically signficant improvement in survival, in combination with system cheotherapy, for patients with advanced squamous cell carcinoma of the lung. It is appropriate that this is assessed by NICE.	Thank you for your comments. No action required.
	National Lung cancer Forum for Nurses	Yes	Thank you for your comments. No action required.
	Pierre Fabre	Yes appropriate	Thank you for your comments. No action required.
Wording	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Yes	Thank you for your comments. No action required.
	National Cancer Research	Yes	Thank you for your comments. No action

Section	Consultee/ Commentator	Comments [sic]	Action
	Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)		required.
	National Lung cancer Forum for Nurses	Reflects the issue	Thank you for your comments. No action required.
	Pierre Fabre	With reference to the clinical trials (INSPIRE & SQUIRE) we belive that this appraisal should be focused solely on the EGFR +ve patient population as necitumumab is a fully human IgG1 monoclonal antibody that is designed to block the ligand binding site of the human EGFR.	Thank you for your comments. No action required.
Timing Issues	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	There are currently no targeted first-line squamous NSCLC treatment options available.	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group /	Necitumumab has yet to receive a European licence for use. In addition, the clinical benefits demonstrated in the registration study are modest. Consequently although the NICE appraisal remains relevant there is not a pressing clinical urgency.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Thoracic Oncology Group (BTOG)		
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
Additional comments on the draft remit	British Thoracic Society	The British Thoracic Society welcomes this appraisal.	Thank you for your comments. No action required.
	Eli Lilly and Company	No comment	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	No comment	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	No comment	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	In practice there are more than 4 types of non-small cell lung cancer (NSCLC) because 'NSCLC not otherwise specified' is a valid pathological diagnosis. Furthermore, Large Cell carcinoma is not consistently referred to as 'undifferentiated' and I would suggest removing this and just leaving 'Large Cell'. 'Minor wording error noted in the 1st 'background' paragraph. The sentence beginning 'advanced stage…' is incomplete and needs re-wording (however	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		there is no factual error in the content)	
	National Lung cancer Forum for Nurses	Appears accurate	Thank you for your comments. No action required.
	Pierre Fabre	Clarity may be required that platinum-based chemotherapy refers to platinum combination chemotherapy, as NICE guideline 121 recommends platinum combination chemotherapy as an option for people with untreated stage III or IV NSCLC and good performance status. In terms of completeness we believe it should be made clear that pemetrexed is not the only option for adenocarcinoma or large-cell carcinoma. Docetaxel, paclitaxel, vinorelbine and gemcitabine were also approved in these patients.	Thank you for your comments. No action required.
The technology/ intervention	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Yes the description is accurate. [redacted] Intervention: Patients will be treated with necitumumab in combination with gemcitabine plus cisplatin for up to six cycles of treatment followed by necitumumab as a single agent in patients whose disease has not progressed until disease	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		progression or unacceptable toxicity.	
	National Lung cancer Forum for Nurses	Nil to add	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	Yes	Thank you for your comments. No action required.
	Pierre Fabre	The paragraph does not reflect that the technology, necitumumab, has also been studied in combination with pemetrexed and cisplatin in non squamous NSCLC patients (INSPIRE). Therefore a statement summarising INSPIRE would be appropriate.	Thank you for your comments. No action required.
Population	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Yes	Thank you for your comments. No action required.
	National Cancer	Correct identification of the population group. No sub-groups require separate	Thank you for your

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	Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	consideration.	comments. No action required.
	National Lung cancer Forum for Nurses	It appears to be	Thank you for your comments. No action required.
	Pierre Fabre	Given the way in which necitumumab works as an inhibitor of EGFR the population being considered should be those that are EGFR +ve.	Thank you for your comments. No action required.
Comparators	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	There are currently no targeted first- line treatments available for squamous NSCLC. NICE Clinical Guideline 121 for the diagnosis and treatment of lung cancer states that chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. The most common first-line chemotherapy regimen for patients with NSCLC in the UK is gemcitabine plus a platinum drug. We therefore consider	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		gemcitabine plus platinum to be the main comparator for this proposed appraisal.	
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	Yes no changes required	Thank you for your comments. No action required.
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	With regard to vinorelbine it should be noted that it is available in both oral and IV presentations and this impacts on Healthcare Economic evaluations.	Thank you for your comments. No action required.
Outcomes	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Yes	Thank you for your comments. No action required.
	National Cancer	Yes	Thank you for your

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	Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)		comments. No action required.
	National Lung cancer Forum for Nurses	Appropriate over view	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
Economic analysis	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	The economic analysis will be conducted in line with the NICE reference case. A life time horizon will be employed.	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group /	This is appropriately worded and no changes are needed.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Thoracic Oncology Group (BTOG)		
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	This should also consider the NHS cancer reform strategy which aims to keep treatment closer to home. For patients QOL it should be reflected the time of going to the hospital and time spent there receiving an IV versus being at home with an oral treatment. Cost of administration (nursing & pharmacy time), capacity and time spent in hospital should also be considered in the economic analysis.	Thank you for your comments. No action required.
Equality and Diversity	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	No comment	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic	I have no concerns	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Oncology Group (BTOG)		
	National Lung cancer Forum for Nurses	Yes	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
Innovation	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	If licensed, necitumumab will offer an innovative first-line treatment option for patients with advanced squamous NSCLC. Patients with NSCLC 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. SQUIRE is the first and only study in patients with advanced squamous NSCLC to demonstrate benefit in overall survival (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.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Necitumumab is an add-on treatment up to a maximum of six cycles, and will be given with the current dosing schedule of days 1 and 8 for 21 days. Therefore, there is no additional administrative burden for the first 6 cycles, after which necitumumab will continued as a single agent in patients whose disease has not progressed until disease progression or unacceptable toxicity.	
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	The opinion below are based on the phase 3 registration trial published in Lancet Oncology (Thatcher et al., 2014). Metastatic squamous cell lung cancer is difficult to treat and so any technology that increases survival is significant. There is a need to improve outcomes in this disease area, and necitumumab is the first agent to achieve this in a large scale phase 3 trial. The clinical data indicates that necitumumab in combination with chemotherapy improves overall survival (OS) by 1.6 months, compared to giving chemotherapy alone. The benefit occurs early in treatment, demonstrated by early and consistent separation of the Kaplan-Meier OS surves, and reaches statistical significance. There is also a statistically significant improvement in progression free survival (PFS), with a hazard ratio of 0.85. An important question is whether these findings are clinically significant. It must be borne in mind that metatstatic squamous cell lung cancer has a very poor prognosis, is difficult to treat, and to date no novel agents have been able to achieve an increase in survival compared to chemotherapy alone. It is of note that this study included patients with an ECOG performance status of 2, therefore representing a more realistic patient population that that seen in other clinical trials in this setting. Therefore any improvements in outcome is potentially significant.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The 1.6 month improvement in OS seen with necitumumab is modest and is on the borderline of clinical significance. The difference in DFS is not clinically meanginful. As such this technology represents a small step-forward in the management of advanced squamous cell carcinoma of the lung, but is not a paradigm shift in the treatment of this disease. The side effects associated with necitumumab and chemotherapy are principally related to the chemotherapy components, with only hypomagnasemia and rash being more common and directly attributable to necitumumab. Consequently it is safe to conclude that necitumumab is well tolerated and its addition to standard chemotherapy is not at the cost of greater overall toxicity and quality of life. There are no other benefits apparent to me that are not likely to be included in the QALY calculations.	
	National Lung cancer Forum for Nurses	Nil to add	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
Other considerations	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	No comment	Thank you for your comments. No action

Section	Consultee/ Commentator	Comments [sic]	Action
			required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	No comment	Thank you for your comments. No action required.
	National Lung cancer Forum for Nurses	Nil to add	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
NICE Pathways	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Based on the anticipated licence we would expect necitumumab to fit under the 'first-line and maintenance chemotherapy for advanced or metastatic non-small-cell lung cancer' section of the treatment for non-small-cell lung cancer pathway. Necitumumab is expected to be licensed in the squamous NSCLC patient population.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	Necitumumab would fit in with existing NICE guidance under the management of advanced NSCLC. For example, where the current recommendation is made of the use of pemetrexed for patients with non-squamous histology, (assuming NICE approval were granted) the recommendation would be for the addition of necitumumab to gemcitabine and cisplatin in the management of squamous disease.	Thank you for your comments. No action required.
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your comments. No action required.
Questions for consultation	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	Which treatments are considered to be established clinical practice in the NHS for advanced, untreated, metastatic, squamous non-small-cell lung cancer? There is currently no specific treatment pathway for patients with squamous NSCLC in the UK as treatment guidance is focussed on patients with NSCLC as a whole. How should best supportive care be defined?	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		In UK clinical practice best supportive care (BSC) is likely to vary between patients receiving active first-line treatment and those on BSC only. In the SQUIRE trial, palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients on the trial. Supportive care measures included but were not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Are there any subgroups of people in whom necitumumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? No subgroups have been identified.	
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	1. Current standard of treatment, for those well enough to receive chemotherapy, would be platinum-based chemotherapy (carboplatin or cisplatin) combined with either gemcitabine, docetaxel, vinorelbine or paclitaxel. The combination of gemcitabine and carboplatin is perhaps the commonent regimen used in the UK, but it is important to appreciate that there is no evidence to support one combinaiton over another and individual practice varies between oncologists. No additional chemotherapy (i.e. triplet therapy) has been shown to be effective, and maintenance chemotherapy is not NICE approved nor widely practised in the UK for squamous cell carcinoma. The addition of other EGFR targeting agents (e.g. cetuximab) or anti-angiogenic agents (e.g. bevacizumab) not NICE approved and are not routinely used. Beyond the treatment above, patients may require palliative radiotherapy (e.g. for painful bone metastases or for the treatment of haemoptysis). 2. Best supportive care (BSC) should be offered to all patients, whether or not	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		they are receiving any active cancer therapy. It involves active management of the patient's symptoms. This will vary between patients but will include analgesia, anti-emetics, palliative radiotherapy, blood transfusions, occupational therapy, physiotherapy, emotional and psychological support, and end-of-life care. BSC can be provided via a number of routines including day-case and inpatient hospice care, primary care, secondary care inpatients and outpatients, voluntary sector, and charity providers. 3. On the basis of the data provided, there is no difference in benefit from necitumumab between patient groups and so no subset needs separate analysis. The clinical data makes note of a greater OS benefit for those with a higher EGFR H-score, however this does not reach statistical significance and it is not suggested that this patient group requires separate analysis. 4. Necitumumab would fit in with existing NICE guidance under the management of advanced NSCLC. For example, where the current recommendation is made of the use of pemetrexed for patients with non-squamous histology, (assuming NICE approval were granted) the recommendation would be for the addition of necitumumab to gemcitabine and cisplatin in the management of squamous disease. 5. I can find no evidence or risk of discrimination or inequality in the scope. 6. Other questions covered in section above.	
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.
	Pierre Fabre	No comment	Thank you for your

Section	Consultee/ Commentator	Comments [sic]	Action
			comments. No action required.
Additional comments on the draft scope	British Thoracic Society	No comment	Thank you for your comments. No action required.
	Eli Lilly and Company	No comment	Thank you for your comments. No action required.
	National Cancer Research Institute (NCRI) Lung Clinical Studies Group / British Thoracic Oncology Group (BTOG)	The chemotherapy arm was gemcitabine and cisplatin. A range of different chemotherapy agents are used in the first line treatment of squamous cell lung cancer (see comments above). It will be important to decide whether the benefits of necitumumab are restricted to combination with gemcitabine and cisplatin only, or whether they are application to any platinum based first line chemotherapy. This is pertinant because gemcitabine and cisplatin is less commonly used than other chemotherapy combinations in the UK.	Thank you for your comments. No action required.
	National Lung cancer Forum for Nurses	No comment	Thank you for your comments. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Thoracic Oncology Group
Department of Health
Royal College of Nursing

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
	Remove Afiya Trust from patient/carer group consultees.	NICE Secretariat		Removed	The Afiya Trust is no longer actively engaging with NICE and has therefore been removed from the matrix.
	Remove Equalities National Council from patient/carer group consultees.	NICE Secretariat		Removed	The Equalities National Council has confirmed that they no longer wish to participate in appraisals of this indication therefore this organisation has been removed from the matrix.
	Add Primary Care Respiratory Society to professional group consultees.	NICE Secretariat		Added	Primary Care Respiratory Society meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.