National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [ID 838]

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Boehringer Ingelheim	Yes.	Comment noted. No action required.
	British Thoracic Society	Yes it is appropriate	Comment noted. No action required.
	Lilly UK	Yes	Comment noted. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Yes	Comment noted. No action required.
	Roche	Yes	Comment noted. No action required.
Wording	Boehringer Ingelheim	Yes	Comment noted. No action required.

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	Lilly UK	Yes	Comment noted. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Yes	Comment noted. No action required.
	Roche	Yes	Comment noted. No action required.
Timing Issues	Boehringer Ingelheim	NA	Comment noted. No action required.
	Lilly UK	There are currently limited second-line treatment options available for patients with NSCLC, especially squamous patients.	Comment noted. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Randomised phase 3 data is now available and should be assessed (REVEL, Garon et al, The Lancet, June 2014)	Comment noted. The company is expected to include all relevant evidence on the technology in its submission to NICE. No action required.
	Roche	-	No action required.
Additional	British Thoracic	The British Thoracic Society welcomes this appraisal.	Comment noted. No

Section	Consultee/ Commentator	Comments	Action
comments on the draft remit	Society		action required.
	NCRI / RCP / RCR / ACP / BTOG	no	Comment noted. No action required.
	Roche	-	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Lilly UK	No comment	No action required.
	NCRI / RCP / RCR / ACP / BTOG	The staging system has changed since the data quoted. Patients with stage 3b disease (pleural/pericardial efusions) are now classed as stage 4 and more patients therefore present with stage 4 disease. NICE also recommends Cisplatin and Pemetrexed for non-squamous NSCLC in the 1st line setting	Comment noted. The background section aims to provide a short account of the disease and its clinical management. Therefore, further explanation of the staging system is not needed. The scope has been amended to include the NICE recommendation

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			for pemetrexed plus cisplatin (TA181).
	Roche	-	No action required.
The technology/ intervention	Boehringer Ingelheim	Yes.	Comment noted. No action required.
	Lilly UK	Yes – as outlined in the description ramucirumab is a fully human immunoglobulin G1 monoclonal antibody that specifically blocks the vascular endothelial growth factor receptor-2, which plays an important role in angiogenesis (formation of new blood vessels) in tumours	Comment noted. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Yes	Comment noted. No action required.
	Roche	-	No action required.
Population	Boehringer Ingelheim	Of note: possible differential efficacy of ramucirumab in non-squamous and squamous patients (based on sub-group analysis of the REVEL study); cost effectiveness may need to be examined separately for different histologies. Although the study was not powered for subgroup analysis, it is important to note that the overall survival improvement in squamous patients was not statistically significant. The trial included predominantly patients with a non-squamous histology (72.8%) and the efficacy results in the overall patient population may therefore have been driven by these patients.	Comment noted. Scoping workshop attendees heard that the clinical trial for ramucirumab was designed to assess treatment in all patients whether they have squamous or non-squamous tumour, and

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			that the results were consistent across subgroups. It was agreed that no subgroups needed special consideration.
	Lilly UK	No comment	No action required.
	NCRI / RCP / RCR / ACP / BTOG	Yes	Comment noted. No action required.
	Roche	-	No action required.
Comparators	Lilly UK	Best supportive care is not a suitable comparator as it is considered an option for people who are unlikely to tolerate chemotherapy. If patients do not tolerate docetaxel chemotherapy, they are not eligible for ramucirumab /docetaxel combination therapy. Erlotinib is not considered a suitable comparator since ramucirumab plus docetaxel is a second-line option for patients with ECOG performance score 0 or 1, whereas erlotinib is generally offered to those with poor fitness (an ECOG status of 2). Specifically, NICE (ID438) recently published a Final Appraisal Determination (FAD) for Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. Page 30 of the FAD explains that people considered to be fit (ECOG performance score of 0 or 1) are offered docetaxel as a second-line treatment, while those with poor fitness (an ECOG status of 2) are offered erlotinib. On this basis, the appraisal committee concluded that docetaxel alone was the only	Comment noted. The scope has been amended to remove best supportive care as a comparator. The scope should be inclusive and cover all potentially relevant comparators for ramucirumab. With this in mind, scoping workshop attendees did not feel that it was

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		appropriate comparator to nintedanib plus docetaxel (page 31) Nintedanib has been approved for use in locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy. It is awaiting final guidance at present. Following the availability of nintedanib in the NHS, its use in this patient population is expected to increase.	appropriate to exclude erlotinib because some patients receive it for this indication. The clinical experts at the workshop agreed that nintedanib plus docetaxel would represent established clinical practice for this indication at the time of the appraisal.
	NCRI / RCP / RCR / ACP / BTOG	PD-1 PDL-1 therapies have emerging promising data in this 2nd line area. Studies are not yet published in peer reviewed journals (only conference presentations), but data will almost certainly be published during the appraisal period. Nivolumab is likely to be the 1st of this class of drugs to be licensed in this setting.	Comment noted. The scope has been amended to include nivolumab for people with squamous tumour histology (subject to ongoing NICE appraisal).
	Roche	Appropriate	Comment noted. No action required.
Outcomes	Lilly UK	Yes	Comment noted. No action required.

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	NCRI / RCP / RCR / ACP / BTOG	Yes	Comment noted. No action required.
	Roche	Appropriate	Comment noted. No action required.
Economic analysis	Lilly UK	The economic analysis will be conducted in line with the NICE reference case. A life time horizon will be employed.	Comment noted. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Appropriate	Comment noted. No action required.
	Roche	Appropriate	Comment noted. No action required.
Equality and Diversity	Lilly UK	No comment	No action required.
	NCRI / RCP / RCR / ACP / BTOG	Nothing to add	Comment noted. No action required.
	Roche	-	No action required.
Innovation	Lilly UK	There are limited options for treating locally advanced or metastatic NSCLC that has progressed after platinum chemotherapy. There is a need for treatments that are efficacious independent of baseline histology.	Comment noted. The company is encouraged to describe

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		REVEL is the first study evaluating the addition of a new agent to standard second-line chemotherapy to demonstrate a statistically significant and clinically meaningful improvement in progression-free and overall survival across all histologies. A consistent treatment effect was observed in patients regardless of squamous or nonsquamous histology. A robust clinical trial programme for ramucirumab has proven it to be an effective treatment in combination with docetaxel. This technology can provide meaningful health-related benefits to a very sick population who have limited options. This represents a step change in clinical practice.	the innovative nature of ramucirumab in combination with docetaxel in their evidence submission. No action required.
	NCRI / RCP / RCR / ACP / BTOG	Ramicirumab is similar to nintedanib in many ways (which has recently received a positive NICE appraisal) therefore not a step change for the adenocarcinoma population of NSCLC. It does however offer an improvement in outcomes for patients with Squamous cell NSCLC for whom the standard of care therapy remains docetaxel.	Comment noted. Consultees are encouraged to describe the innovative nature of ramucirumab in combination with docetaxel in their evidence submission. No action required.
	Roche	Ramucirumab provides an alternative treatment option for this patients with locally advanced or metastatic NSCLC	Comment noted. Consultees are encouraged to describe the innovative nature of ramucirumab in combination with docetaxel in their

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			evidence submission. No action required.
Other considerations	Lilly UK	No comment	No action required.
	NCRI / RCP / RCR / ACP / BTOG	Nil	No action required.
	Roche	-	No action required.
NICE Pathways	Lilly UK	Based on the anticipated licence we would expect ramucirumab to fit under the 'second-line chemotherapy for advanced or metastatic non-small-cell lung cancer' section of the treatment for non-small-cell lung cancer pathway. Ramcuirumab is expected to be licensed across the full NSCLC patient population. Under this section currently there is guidance relating to erlotinib (NICE TA162), docetaxel monotherapy, pemetrexed (NICE TA124), crizotinib (NICE TA296) and gefitinib (NICE TA175). There is also a Lung cancer clinical guideline (CG121)	Comment noted. No action required.
Questions for consultation	Lilly UK	*Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic non-small-cell lung cancer that has progressed after platinum-based chemotherapy?* Docetaxel and erlotinib are the two NICE recommended treatment options in the second-line NSCLC setting. Nintedanib was recently approved by NICE for use in combination with docetaxel in the adenocarcinoma patient	The scope should be inclusive and cover all potentially relevant comparators for ramucirumab. With this in mind, scoping workshop attendees

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		population that has progressed after first-line chemotherapy. *How should best supportive care be defined?* In UK clinical practice best supportive care (BSC) is likely to vary between patients receiving active second-line treatment and those on BSC only. In the REVEL trial, palliative and supportive care was administered for disease-related symptoms and for toxicity associated with treatment. These included, but were not limited to: antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, bone-modifying agents, and granulocyte and erythroid growth factors**.** *Are there any subgroups of people in whom ramucirumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?* An improvement in OS and PFS was consistently observed across all pre-specified subgroups	agreed to: • remove best supportive care • add nivolumab for people with squamous tumour histology only (subject to ongoing NICE appraisal) • add crizotinib (for people with ALK-positive non-small-cell lung cancer only). Scoping workshop attendees agreed not to consider subgroups in the scope.
	Roche	-	No action required.
Additional comments on the draft scope	Roche	-	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:
1.	Remove Afiya Trust from the matrix of consultees and commentators	NICE Secretariat		Removed	This organisation is no longer engaging with NICE technology appraisals. The Afiya Trust has been removed from the matrix of consultees and commentators under 'Patient/Carer Groups'.

2.	Remove Equalities National Council	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Equalities National Council has been removed from the matrix of consultees and commentators under 'Patient/Carer Groups'.
3.	Add Primary Care Respiratory Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Primary Care Respiratory Society has been added to the matrix of consultees and commentators under 'Professional Groups'.

4.	Add Bristol Myers Squibb	NICE Secretariat		Added	This organisation has a technology which meets the definition for a comparator technology as outlined in the scope. Bristol-Myers Squibb has therefore been added to the matrix under 'comparator companies'
5.	Add Pfizer	NICE Secretariat		Added	This organisation has a technology which meets the definition for a comparator technology as outlined in the scope. Pfizer has therefore been added to the matrix under 'comparator companies'