National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Response
Appropriateness	Roche Products Ltd	Yes , as far as is known at this time	Comment noted
Wording			
Timing Issues			
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultees	Comments	Response
Background information	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	Accurate and complete.	Comment noted.
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	CRUK provides more recent incidence and mortality figures, reporting that there were 33,450 new cases on lung cancer in England and Wales in 2006, and in 2007 there were 29,574 deaths. Other figures appear accurate.	Comment noted. The scope has been amended accordingly.
	NCRI/RCP/RCR /ACP/JCCO	We believe more up to date figures for lung cancer incidence show that there were 38,596 cases in 2005 with 33,629 deaths (these 2005 figures would concur with the 24,536 (75 %) of cases being of stage IIIB or IV quoted in Para 2). Pemetrexed has been omitted as a third generation drug in Para 3. We do not believe that the license for erlotinib stipulates that first line chemotherapy should contain a platinum drug.	Comment noted. The scope has been amended accordingly. Pemetrexed has been included as one of the treatment options in accordance with the recommendations of Technology Appraisal 181. The background section describes current clinical guidelines for the management of people with NSCLC
	Royal College of Nursing	The information appears to be accurate and complete.	Comment noted.

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The technology/ intervention	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	Yes.	Comment noted.
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	The technology is described accurately.	Comment noted.
	Eli Lilly	The scope does not state explicitly that erlotinib is not yet licensed for maintenance treatment of advanced NSCLC.	Comment noted. The scope has been amended accordingly.
	Royal College of Nursing	Yes	Comment noted.
Population	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	The population is appropriate. In 'other considerations' comment is made about possible subgroup analysis by performance status, histology and smoking status. EGFR mutation status is known to influence response to EGFR TK inhibitors. If the evidence allows, the efficacy of Erlotinib according to mutation status should also be considered.	Comment noted. The subgroup defined by EGFR mutational status has been added to the scope.
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	The population appears to be defined appropriately. Analyses could be stratified by EGFR status.	Comment noted. The subgroup defined by EGFR mutational status has been added to the scope.
	Eli Lilly	Ethnicity Smoking status	Comment noted. A number of these subgroups have been

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		Histology Disease stage (IIIB vs IV) ECOG Performance status (PS 0 vs PS1) Response status prior to maintenance treatment (response to induction treatment prior to randomisation to maintenance phase) First-line regimen First platinum treatment (cisplatin vs carboplatin) Biomarker status (EGFR / KRAS)	included in the scope and should be considered if evidence allows.
	NCRI/RCP/RCR /ACP/JCCO	If use of erlotinib immediately following completion of first line chemotherapy with progressive disease as the best response is not considered 'maintenance' therapy the population then the interpretation in the scope is correct.	Comment noted. People considered for maintenance treatment are those whose disease has not progressed following first-line treatment.
	Royal College of Nursing	Yes the population is defined appropriately. Groups to be considered separately are covered in other considerations.	Comment noted.
	Royal College of Pathologists	The issue from a pathology standpoint is that current evidence suggests that EGFR TKI drugs are far more effective in patients with certain gene mutations, most of which are adenocarcinomas (in the UK). NICE need to consider (a) whether the drug should be limited to those with gene mutations associated with response (b) if so, how these gene studies would be funded and (c) whether testing should be limited to those with non-squamous histology.	Comment noted. The subgroup defined by EGFR mutational status has been added to the scope.
Comparators	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	Yes	Comment noted.
	Commissioning Support Unit (NHS Cornwall and Isles of	Comparators appear appropriate. Placebo should be added, as there is an ongoing placebo controlled clinical trial (with best supportive care offered in both arms). Maintenance chemotherapy, for example with gemcitabine, should be considered as a comparator.	Comment noted. Best supportive care with watchful waiting has been added to the scope as a comparator.

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	Scilly/NHS Dudley)	As a technology appraisal is currently underway for maintenance treatment using erlotinib plus bevacizumab, the combination could potentially be used as a comparator.	Neither gemcitabine nor erlotinib in combination with bevacizumab have been identified as routine or best practice at this time and have therefore not been included as comparators in the scope. The ongoing appraisal of erlotinib plus bevacizumab for the maintenance treatment of NSCLC is not anticipated to begin until early August 2010 (expected date of issue 2011).
	Eli Lilly	The current standard of care / best alternative care in the NHS for maintenance treatment of NSCLC is 'watch and wait' plus best supportive care (BSC). Pemetrexed is licensed for the maintenance treatment of NSCLC only in patients with other than predominantly squamous (i.e. non-squamous) NSCLC. Therefore, comparators should be as follows: Pemetrexed monotherapy (in patients with non-squamous NSCLC only) 'Watch and wait' (since BSC is available to both treatment arms)	Comment noted. The scope has been amended accordingly (pemetrexed monotherapy [in people with non-squamous NSCLC]). Best supportive care with watchful waiting has been added to the scope as a comparator.
	NCRI/RCP/RCR /ACP/JCCO	The comparators should include: - Pemetrexed maintenance monotherapy - Docetaxel pemetrexed or erlotinib monotherapy upon progression as second line therapy - Best supportive care	Comment noted. Pemetrexed and best supportive care are included as comparators in the scope. The remit of this scope is maintenance treatment (and does not include second line treatment in patients who

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			progress after first line treatment).
	Roche Products Ltd	The request to include pemetrexed as a comparator could proove challenging from a methodology perspective. At present the standard of care in the situation under appraisal is observation plus supportive care. Roche and Lilly have both identified this as an area of therapeutic need and undertaken placebo controlled RCTs. Pemetrexed recently received regulatory approval in this indication in a sub-population. NICE is currently reviewing pemetrexed as a maintenance therapy and if recommended, may restrict its use to a sub-population of those covered by its Marketing Authorisation. The STA process was designed to allow rapid appraisal of new drugs where information is limited and as an alternative to the more exhaustive MTA process. Given the novelty of pemetrexed and the related lack of information in the public domain plus the possibility any recommendation may be for use in a sub-group of patients for whom there are curerntly no data in the public domain. Furthremoe Roche as a competitor company are not in a position to seek from Lilly such data. Although Roche will attempt to comply with NICE's request of such a comparison we would hope that NICE would be mindful of the difficulty that will arise as a consequence of the comparison being requested. The appropriateness of including comparators within STAs interventions that are themselves new, not part of standard care and subject to separate, ongoing STA processes may warrant furtehr discussion and clarification.	Comment noted.
	Royal College of Nursing	Pemetrexed monotherapy is not widely used as yet. Best supportive care and careful monitoring of symptoms is the standard treatment at present but we feel that neither can be described as best alternative care.	Comment noted. A NICE Technology Appraisal of pemetrexed for the maintenance treatment of NSCLC is currently in progress therefore it has it has

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			been included at this stage as a potential comparator. Best supportive care with watchful waiting has been added to the scope as a comparator.
Outcomes	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	Yes	Comment noted.
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	The outcomes appear appropriate but insufficient. It is essential to assess overall survival rather than simply progression-free survival, and absolute benefits rather than just relative benefits (e.g. hazard ratios). As the comparator for oral erlotinib monotherapy is pemetrexed, which is administered intravenously, a measure of patient preference could potentially be included.	Comment noted. Overall survival is included as an outcome. The outcomes of the appraisal should capture all health related cost and benefits of treatment for both the intervention and comparator arm. Patient preference for different treatment options should be included in health related quality of life.
	Eli Lilly	These should be measured from date of initiation of the maintenance phase.	Comment noted.
	Royal College of Nursing	Yes	Comment noted.
Economic analysis	British Thoracic Society Lung Cancer and Mesothelioma	Appropriate	Comment noted.

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	Specialist Advisory Group		
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	It is essential to assess overall survival rather than simply progression-free survival, as a basis for understanding the cost-effectiveness of this technology in terms of opportunities foregone i.e. opportunity costs. This is vital information for service commissioners. Differences are likely to exist between erlotinib and pemetrexed in resource utilisation due to their differing modes of administration (oral vs. IV), therefore costs associated with this resource utilisation should be considered in the economic model. The time horizon should long enough to capture any effects on the timing of second line treatment.	Comment noted. Overall survival is included as an outcome. The outcomes of the appraisal should capture all health related cost and benefits of treatment for both the intervention and comparator arm. This will include differences in the administration costs of different technologies. The time horizon will be sufficiently long enough to reflect any differences in costs or outcomes between the technologies being compared.
	Eli Lilly	If populations are defined by EGFR or other biomarker status, any associated costs should be included in the economic analysis.	Comment noted.
	Roche Products Ltd	The encessry indirect analysis to inform the ICER estimate will be subject to the uncertiantites and data limitation outlined above with repsect to a pemetrexed comparison.	Comment noted.
	Royal College of Nursing	Yes it is necessary to consider Social cost in addition to NHS cost.	Comment noted.
Equalities	Roche Products Ltd	If NICE recommends pemetrexed within its licensed maintenance indication (patients with predominantly non-squamous histology) but fails to recommend erlotinib (where squamous histology is not expected to be an exclusion in the anticipated Marketing Authorisation), this could be seen as discriminating	Comment noted.

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		against those groups with a higher incidence of squamous tumours	
Other considerations	British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	See above point re EGFR mutation subgroup.	Comment noted.
	Commissioning Support Unit (NHS Cornwall and Isles of Scilly/NHS Dudley)	This technology appraisal could be combined with the technology appraisals of permetrexed, or erlotinib plus bevacizumab for maintenance therapy.	Comment noted. All 3 technologies have different anticipated dates of marketing authorisation therefore for NICE to able to produce timely guidance to the NHS the 3 technologies need to be appraised separately.
	Eli Lilly	If populations are defined by EGFR or other biomarker status, aspects of this testing should be considered. These may include cost, feasibility, availability, standards across institutions, time to obtain results and sensitivity/specificity.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	Subgroups should include: subgroups defined by best response to first line chemotherapy (Complete response/ Partial response/ Stable disease). It is important to consider EGFR and RAS mutational status where available.	Comment noted. The subgroups defined by response to first-line treatment and EGFR status have been added to the scope.
Questions for consultation	Eli Lilly	British Oncology Pharmacists Association (BOPA) needs to be added to the matrix	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	The technology appraisal on 'Pemetrexed for first line treatment of advanced or metastatic non-small cell lung cancer' is not in progress but has been released as TA No 181 (September 2009).	Comment noted. The scope has been amended accordingly.

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

NHS Quality Improvement Scotland
RICE - The Research Institute for the Care of Older People (formerly the Research Institute for the Care of the Elderly
UK Oncology Nursing Society
Welsh Assembly Government
Department of Health
National Public Health Service for Wales