Appendix C

National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small-cell lung cancer

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Roche Products	In Roche's view this appraisal is appropriate.	Comment noted. No action required.
	AstraZeneca UK	None	No action required.
	Roy Castle Lung Cancer Foundation	Yes. Past experience shows that access to new therapies or therapy indications, is very difficult without a positive NICE appraisal.	Comment noted. No action required.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	This is an appropriate topic. The issue is virtually identical to TA192 where gefitinib was recommended for this exact indication. The question will be whether erlotinib is more efficacious or less expensive (or both).	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	This topic is appropriate.	Comment noted. No action required.
	Royal College of Pathologists	This is an appropriate topic and it should be appraised.	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Yes the remit is appropriate for NICE appraisal.	Comment noted. No action required.

Section	Consultees	Comments	Action
	National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP) and the Joint Collegiate Council for Oncology (JCCO)	Yes, this is appropriate for EGFR mutant non-small cell lung cancer (NSCLC), as per the proposed marketing authorisation.	Comment noted. No action required.
Wording	Roche Products	It does.	Comment noted. No action required.
	AstraZeneca UK	None	No action required.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Non-small cell lung cancers are probably more like 10-15% of the total, rather than 20%.	Comment noted. Small-cell lung cancer accounts for approximately 10-15% of all lung cancers. The background section of the scope has been updated to state that non-small cell lung cancer accounts for 85-90% of the total population with lung cancer rather than 80%.
	Commissioning Support Appraisals Service (CSAS)	This is appropriate. The population in the remit could be more accurately specified as epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation positive patients, as in the similar appraisal for gefitinib and the population definition.	Comment noted. During the scoping workshop the consultees agreed that the remit should be amended to specify that the population includes patients with EGFR-TK mutations. The remit has been updated accordingly.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Yes	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.

Section	Consultees	Comments	Action
Timing Issues	Roche Products	The timing appears appropriate.	Comment noted. No action required.
	AstraZeneca UK	In our view, there is no particular urgency for this proposed appraisal.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Roy Castle Lung Cancer Foundation	Dependent on timing of new licence indication.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Not urgent as gefitinib is already recommended for this indication.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Royal College of Pathologists	Yes - There are ongoing trials of erlotinib in this setting that should provide data to aid this appraisal.	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	A drug in the same class with similar action and side effect profile (gefitinib) has already been approved for this patient group and is in clinical use. Therefore the appraisal is not extremely urgent. It has been appropriately restricted to patients with an EGFR mutation.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	NCRI/RCP/RCR/ACP/JCCO	Satisfactory	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Roche Products	No comment	No action required.
	AstraZeneca UK	None	No action required.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Accurate	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	This is accurate. Cancer Research UK currently states that small cell accounts for a slightly lower percentage - around 12% rather than 20%.	Commented noted. The background section of the scope has been updated in line with comments from consultees, to state that non-small cell lung cancer accounts for 85-90% of the total population with lung cancer.
	Royal College of Pathologists	Accurate	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	It is unclear whether the figures in the 1st paragraph of the background are referring to the UK or international. Not all patients with Stage IV disease have distant disease (e.g. pleural effusion)	Comment noted. The background section of the scope provides a brief description of the disease. A more detailed exploration of the disease and the incidence in the UK will be included in the manufacturer's submission. The background section of the scope has been updated to include pleural effusion as one of the descriptors of Stage IV disease.
	NCRI/RCP/RCR/ACP/JCCO	OK	Comment noted. No action required.
The technology/ intervention	Roche Products	No. The scope incorrectly details the clinical trials ongoing for erlotinib in patients with an EGFR mutation. The paragraph stating 'It is being studied as monotherapy in clinical trials compared with	Comment noted. The paragraph describing the trials in the scope has been amended to state that erlotinib has been studied as monotherapy in clinical trials compared with gemcitabine or docetaxel in combination with platinum

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		gefitinib or docetaxel in combination with platinum based chemotherapy (cisplatin or carboplatin) in adults with advanced NSCLC with the EGFR-TK mutation' should be replaced with: 'Erlotinib is being studied as monotherapy in clinical trials compared with platinum-doublet chemotherapy in the first line treatment of adults with advanced NSCLC whose tumours harbour an activating EGFR-TK mutation.'	based chemotherapy (cisplatin or carboplatin) in adults with advanced NSCLC whose tumours have an activating EGFR-TK mutation.
	AstraZeneca UK	We are not aware of any direct comparative trial of gefitinib (the current standard of care for mutation positive patients) and erlotinib	Comment noted. The paragraph describing the trials in the scope has been amended to state that erlotinib has been studied as monotherapy in clinical trials compared with gemcitabine or docetaxel in combination with platinum based chemotherapy (cisplatin or carboplatin) in adults with advanced NSCLC whose tumours have an activating EGFR-TK mutation.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Accurate	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Yes, though information could be given on erlotinib's current license "use as a second-line alternative to docetaxel for patients with NSCLC" (TA162, 2008).	Comment noted. The technology section only provides a brief description of the technology and the anticipated marketing authorisation in the population being considered. If the technology does not have a marketing authorisation, a brief description of clinical trials in the proposed indication is included. Marketing authorisations for other

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			indications are generally not included. A comprehensive description of the technology, including all of its licensed indications will be included in the evidence submission from the manufacturer.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Yes	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	OK	Comment noted. No action required.
Population	Roche Products	The population appears to be appropriately defined.	Comment noted. No action required.
	AstraZeneca UK	None	Comment noted. No action required.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Yes	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	This states that erlotinib is being studied in "adults with advanced NSCLC with the EGFR-TK mutation". It should be pointed out that several activating EGFR mutations have been identified (with varying levels of prediction of disease response). More recently inactivating EGFR mutations have been reported.	Comment noted. The population in the table describes the population which should be considered in the appraisal. The scope is only intended to provide a brief overview of the condition and its current clinical management within the NHS, therefore details of the different EGFR mutations have not been included. A comprehensive description of the disease, will be included in the evidence

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			submission from the manufacturer.
	NCRI/RCP/RCR/ACP/JCCO	OK	Comment noted. No action required.
Comparators	Roche Products	Following the issuance of positive NICE guidance in TA192 the vast majority of patients diagnosed with EGFR mutation positive mNSCLC currently receive gefitinib. Roche market research indicates gefitinib is currently used in nearly 75% of patients with an identified EGFR mutation (December 2010). Furthermore this research indicates that this proportion is continuing to grow as NICE guidance becomes more widely implemented. Of the doublet chemotherapies named gemcitabine/carboplatin and pemetrexed/cisplatin are the most widely used regimens in a non-EGFR mutation targeted population. However given the outcome of TA192 and the market research highlighted above it would appear that gefitinib should be the prime comparator of interest in mNSCLC patients with an activating EGFR mutation and not the numerous doublet chemotherapy combinations detailed in the scope.	Comment noted. During the scoping workshop the consultees agreed that gefitinib is the most appropriate comparator for this appraisal. It was noted that platinum doublet chemotherapy would only be considered for patients with EGFR mutations that are not sensitive to tyrosine kinase inhibitors, which represents less than 5% of patients. Therefore consultees considered that platinum-based chemotherapy should not be included as a comparator. For people with non-squamous non-small cell lung cancer of adenocarcinoma or large cell carcinoma histology, consultees considered that pemetrexed in combination with platinum-containing therapy (i.e. cisplatin or carboplatin) would be appropriate as a comparator. The scope has been amended accordingly.
	AstraZeneca UK	Gefitinib is currently the only Tyrosine Kinase inhibitor which has 1) A license as first line treatment of patients with EGFR mutation positive NSCLC. 2) NICE recommendation as an option for the first line treatment of patients with EGFR mutation positive NSCLC	Comment noted. During the scoping workshop the consultees agreed that the comparators should not include platinum-based chemotherapy and that they should include only gefitinib and pemetrexed in combination with cisplatin or carboplatin. The scope has been amended accordingly.

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	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Yes	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	These are appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Yes, as far as I am aware, although I am not an oncologist.	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Yes. In this population Gefitinib is the best alternative care.	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes, these are standard treatments. The 'best alternate care' is gefitinib as per TA192.	Comment noted. No action required.
Outcomes	Roche Products	These appear appropriate.	Comment noted. No action required.
	AstraZeneca UK	Yes, as long as NICE is reasonably assured of the quality of monitoring and recording of outcomes within the included clinical trials.	Comment noted. No action required.
	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Yes	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	These are appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Yes, as far as I am aware, although I am not an oncologist.	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Yes	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
Economic analysis	Roche Products	This appears appropriate.	Comment noted. No action required.
	AstraZeneca	None	No action required.

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	Roy Castle Lung Cancer Foundation	Will the cost of EGFR mutation diagnostic testing be included in this economic analysis?	Comment noted. During the scoping workshop the consultees agreed that the cost of EGFR mutation diagnostic testing will be included in the economic analysis.
	Commissioning Support Appraisals Service (CSAS)	None	No action required.
	Royal College of Pathologists	Outside my area of expertise.	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	The QALY calculation may not take into account the convenience, patient preference and marked lower toxicity of oral therapy compared to intravenous platinum-based chemotherapy. The human advantage of not waiting in hospitals for many hours for chemotherapy will not be taken into account	Comment noted. During an appraisal any potential health-related benefits that have not been included in the economic model will be discussed by the Committee.
Equality considerations	British Thoracic Society (Lung Cancer and Mesothelioma Specialist Advisory Group)	Drugs such as gefitinib and erlotinib are much less toxic than standard chemotherapy. This means that their use allows elderly patients to benefit from treatment they might otherwise be denied.	Comment noted. The Committee will consider the health needs of the population under consideration in the appraisal. No action required.
	Royal College of Pathologists	None.	No action required.
	Commissioning Support Appraisals Service (CSAS)	No issues	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Nil additional	Comment noted. No action required.
Innovation	Roche Products	Compared to gefitinib If the EURTAC study reports positively erlotinib will be the first, and only, EGFR TKI to have phase 3 randomised evidence demonstrating efficacy in the first line treatment of European	Comment noted. During an appraisal any potential health-related benefits that have not been included in the economic model will be discussed by the Committee.

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		EGFR M+ mNSCLC patients. Compared to doublet chemotherapies As erlotinib is an oral EGFR TKI it offers advantages over traditional platinum doublet based chemotherapy which may be difficult to incorporate formally in any economic analysis undertaken. Unlike doublet chemotherapy erlotinib is oral rather than IV administered. It can be taken by patients in their own homes with no requirement to attend a chemotherapy infusion suite. Whilst the reduced cost of infusions will be taken into account in any analysis comparing erlotinib to doublet chemotherapy the reduced patient burden associated with a switch to an oral therapy is unlikely to be incorporated (i.e. patient loss of time, patient transport costs etc). Furthermore many studies have demonstrated that patients generally have a preference for oral over IV therapy (Liu et al. 1997; Kopec et al. 2007; Borner et al. 2002; Twelves et al. 2005). Similarly it may be that many patients would prefer erlotinib to platinum doublet based treatment simply due to the stigma associated with chemotherapy. Whilst patient choice is at the centre of the current NHS agenda such 'softer' benefits of	

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		new technologies are often overlooked by the 'Cost per QALY' metric typically utilised.	
	AstraZeneca UK	AstraZeneca does not consider this technology as significantly innovative as gefitinib already has a licence and positive NICE recommendation for EGFR mutation positive NSCLC patients.	Comment noted. No action required.
	Medical Research Council Clinical Trials Unit	Not a step-change in management as similar drug already available.	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Erlotinib is innovative in potential. Perhaps the most substantial impact comes from enabling systemic anti-cancer therapy to be offered to those patients who would not otherwise be fit for chemotherapy. By enabling such patients to get effective palliation and appropriate therapy (eg performance status 3-4), then a significantly larger number of patients would benefit from treatment.	Comment noted. No action required.
Other considerations	Roche Products	No comment.	No action required.
	AstraZeneca UK	None	No action required.
	Commissioning Support Appraisals Service (CSAS)	None	No action required.
	Royal College of Pathologists	None	No action required.
	Medical Research Council Clinical Trials Unit	How to identify patients with activating EGFR mutations.	Comment noted. Consultees at the scoping workshop confirmed that in clinical practice, mutational testing is not conducted for all patients with non-small-cell lung cancer. During the appraisal,

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			the Committee will discuss who should have a mutation analysis and whether it is feasible to routinely test all patients with non-small-cell lung cancer in order to decide on the most appropriate treatment option. .
Questions for consultation	AstraZeneca UK	None that we are aware of. None As the current NICE recommendation on erlotinib is for 2nd Line use in an unselected population of patients with NSCLC, it is important to ensure this is clearly excluded from the scope of this appraisal.	Comment noted. The remit of the scope states that this appraisal will consider the first-line use of erlotinib in people with EGFR-TK mutation positive NSCLC. No action required.
	Commissioning Support Appraisals Service (CSAS)	As above	Comment noted. No action required.
	Royal College of Pathologists	A key question to consider is whether erlotinib is more effective than gefitinib in this setting, when balanced against cost and potential side effects, but the technology has potential to make a substantial impact Outside my areas of expertise	Comment noted. The Committee will consider the clinical and cost-effectiveness of erlotinib compared with gefitinib and compared with pemetrexed plus cisplatin (or carboplatin).
	NCRI/RCP/RCR/ACP/JCCO	The QALY calculation may not take into account the convenience, patient preference and marked lower toxicity of oral therapy compared to intravenous platinum-based chemotherapy. The very real human advantage of not waiting in hospitals for many hours for chemotherapy will not be taken into account.	Comment noted. During an appraisal any potential health-related benefits that have not included in the economic model will be discussed by the Committee.
Additional	Royal College of Pathologists	From a cost perspective, how is the funding of	Comment noted. Consultees at the

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comments on the draft scope.		mutation testing going to be provided - this has been an issue with gefitinib as the NHS has had to fund the mutation analysis now there is NICE approval? If an appraisal occurs, it should look at who exactly should be targeted for mutation analysis, with appropriate reference to current pathology guidelines, so that money is not wasted on unnecessary testing.	scoping workshop confirmed that in clinical practice, mutational testing is not conducted for all patients with non-small-cell lung cancer. During the appraisal, the Committee will discuss who should have a mutation analysis and whether it is feasible to routinely test all patients with non-small-cell lung cancer in order to decide on the most appropriate treatment option.

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

Association of Respiratory Nurse Specialists
British Thoracic Oncology Group (BTOG)
Department of Health
Eli Lilly and Company
Healthcare Improvement Scotland (formerly NHS Quality Improvement Scotland)
MHRA
Royal College of Nursing
Welsh Government