National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Cetuximab for the first-line treatment of advanced and/or metastatic non-small cell lung cancer

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

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	BTSLC and MSAG	No Comment	No action required.
	Eli Lilly	This section provides comprehensive background information. Whilst we have not commented in previous consultations, we feel it would be helpful going forward if this section were to be referenced. This would enable consultees to comment more fully on the accuracy and completeness of the information provided as the data sources could be checked to ensure they provide the most up to date data available.	Comment noted. No action required.
	Merck Serono	We feel that the background should first describe EGFR expression, and report that there are two groups of patient: low EGFR and high EGFR expressers. High EGFR expression represents approximately 25% of patients. As per cetuximab mechanism of action, it binds onto the extracellular structure of EGFR, therefore, the more EFGR is expressed the more cetuximab is likely to bind and exert its treatment effect.	Comment noted. The background section of the scope is supposed to give a brief outline of the disease and of current practice. No action required.
	NCRI	Large cell lung cancer should not be diagnosed on anything other than a resected specimen so should be stated or the subtype excluded from this section; we don't think the section on CXR diagnosis is necessary or relevant since even these patients may have advanced disease. 33% operable is nonsense! It is 20% at most in the UK..	Comment noted. The scope has been amended accordingly.
The technology/ intervention	BTSLC and MSAG	There is no mention of how EGFR expression is to be measured and whether it is quanitiative or qualitative. Does assessment use exisiting technologies used in the NHS (EGFR mutation status) or is a new test required?	Comment noted. The scope has been amended accordingly. The PICO table in

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			the scope states that the cost of any additional testing not currently routinely undertaken that is required for this treatment should be considered in the economic analysis.
	Eli Lilly	The intervention states that cetuximab, in combination with other chemotherapy, will be appraised as a first-line treatment. In addition to referring to the first-line study in combination with cisplatin and vinorelbine versus cisplatin and vinorelbine alone (i.e. the FLEX study, NCT00148798), page 2 of the draft scope mentions that cetuximab has been studied in combination with docetaxel or pemetrexed versus docetaxel or pemetrexed alone. As far as Lilly is aware, this latter study refers to a Lilly sponsored study (NCT00095199) in the second-line setting. If this appraisal is intended to appraise cetuximab in the first-line setting the draft scope should be amended to clarify that the study in combination with docetaxel or pemetrexed was in the second-line setting.	Comment noted. The scope has been amended to include only those studies relating to first-line treatment of NSCLC with cetuximab.
	Merck Serono	The description of the mechanism of action of the technology is correct (i.e. "Cetuximab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Cetuximab prevents the proliferation of cells by binding to the extracellular structure of EGFR and preventing autophosphorylation of the intracellular region. This stops cells from dividing. Cetuximab may also make the cancer cells more sensitive to chemotherapy.") Merck Serono would like to amend the sentence "*Cetuximab has been studied in clinical trials in people with EGFR-TK expressing* ...". Cetuximab is not an EGFR-TK inhibitor like gefitinib but specifically binds the EFGR expressed on the cells surface. Merck Serono proposes the following alternative: "*Cetuximab has been studied in clinical trials in people with EGFR expressing, advanced and/or metastatic NSCLC in combination with platinum standard doublet therapy.* As a result, Merck Serono would like to highlight that cetuximab has a different	Comment noted. The technology section of the scope has been amended accordingly.

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		mechanism of action than the EGFR tyrosine kinase (TK) inhibitors such as gefitinib and erlotinib. Cetuximab has an additional licensed indication that was omitted for the treatment of squamous cell carcinoma of the head and neck (see licensed indication below). NB: Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer: • in combination with irinotecan-based chemotherapy or FOLFOX-4, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. Additionally, Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck: • in combination with radiation therapy for locally advanced disease, • in combination with platinum-based chemotherapy for recurrent and/or metastatic disease	
	NCRI	Yes	Comment noted. No action required.
Population	BTSLC and MSAG	The text does not state clearly enough how the EGFR status affects suitability for the drug. For example, the terms EGFR-expressing and EGFR-overexpressing seem to be used interchangably.	Comment noted. Guidance will only be issued in accordance with the marketing authorisation. No action required.
	Eli Lilly	The population stated in the draft scope is not clearly defined as the draft remit/appraisal objective refers to over expression of 'EGFR-TK', whereas the population refers only to over expression of 'EGFR'. The draft scope states that cetuximab has been studied in clinical trials in people 'with EGFR-TK expressing' advanced/metastatic NSCLC. However, the inclusion criteria for the FLEX study states 'immunohistochemical evidence of EGFR expression on tumour tissue', rather than 'EGFR-TK'. A recent press release referring to a retrospective analysis of the FLEX study	Comment noted. The scope has been amended accordingly.

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		refers to 'over expression of EGFR', not 'EGFR-TK' as refered to in the draft remit/appraisal objective. (Ref: http://www.eurekalert.org/pub_releases/2011-07/iaft-hee062811.php) The specific nomenclature used within the draft remit and population needs to be clarified or justified and aligned with the expected and/or any subsequent marketing authorisation.	
	Merck Serono	The appropriate population definition is patients with locally advanced and/or metastatic non small-cell lung cancer which highly expresses EGFR.	Comment noted. Guidance will only be issued in accordance with the marketing authorisation. No action required.
	NCRI	yes but the patients who respond best are those with a calculated overexpression of >200 rather than all with overexp is quantify.	Comment noted. Guidance will only be issued in accordance with the marketing authorisation. No action required.
Comparators	BTSLC and MSAG	Gefitinib would only be used first line in patients with EGFR mutations (approx 7% of all NSCLC in UK populations).	Comment noted. No action required.
	Eli Lilly	For the first-line setting the comparators listed in the draft scope are appropriate. In addition to the comparators listed in the draft scope, if erlotinib gains a licence in first-line NSCLC with EGFR-TK positive mutation this should also be considered as a comparator for this appraisal. Bevacizumab, in combination with platinum-based chemotherapy, for NSCLC other than predominantly squamous cell histology should not be included as a comparator. Whilst it may be used in private practice, it is not approved by NICE for use in the NHS due to non-submission, and to date, there do not appear to have been any requests for use in NSCLC through the Cancer Drugs Fund. Market share data suggests that there is little or no use of bevacizumab in this indication.	Comments noted. Comparators are included if they are usually used in current clinical practice in the NHS. No changes to the scope required.

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	Merck Serono	We agree that platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine are the most appropriate comparators for cetuximab. Additionally, for people with non-squamous non small-cell lung cancer of adenocarcinoma or large cell carcinoma histology we acknowledge as per NICE TA181 that pemetrexed in combination with cisplatin or carboplatin is an appropriate comparator. We feel that EGFR-TK inhibitors such as gefitinib and erlotinib are not appropriate comparators to cetuximab as the selection criteria for eligible patients are different. Furthermore, in light with NICE TA227, we believe that erlotinib is not a standard of care within the NHS, consequently will not be considered as a comparator.	Comments noted. Comparators are included if they are usually used in current clinical practice in the NHS. No changes to the scope required.
	NCRI	no to gefitinib as it is for mutated patients, not those overexpressing EGFR; standard platinum-based doublets are comparators; no need to add bevacizumab as it is not approved or used, even in private practice.	Comments noted. Comparators are included if they are usually used in current clinical practice in the NHS. No changes to the scope required.
Outcomes	BTSLC and MSAG	No Comment	No action required.
	Eli Lilly	In order to be consistent with the ongoing consultation for the draft scope of crizotinib in NSCLC, in addition to the outcomes stated in the draft scope, response rate and duration of response should also be considered.	Comment noted. Response rate and duration of response have now been included in the scope.

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	Merck Serono	We would like “response rate” outcome added to the current outcome list. We would therefore agree that overall survival, progression-free survival, response rate, health related quality of life and adverse effects of treatment are relevant outcomes to consider.	Comment noted. Response rate and duration of response have now been included in the scope.
	NCRI	see above - need to get rid of the large cell statement as it is inaccurate; also, squamous cell NSCLC need to be included in this analysis - see below.	Comment noted. The scope has been amended from the following: ‘For people with non-squamous NSCLC of adenocarcinoma or large cell carcinoma histology’ to ‘For people with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology’
Economic analysis	BTSLC and MSAG	No Comment	No action required.
	Eli Lilly	No Comment	No action required.
	Merck Serono	Merck Serono endeavours to meet the NHS reference case and will express the cost effectiveness of cetuximab in terms of incremental cost per quality-adjusted life year. The time horizon will be sufficiently long to reflect any differences in costs or outcomes between the compared technologies.	Comment noted. No action required.
	NCRI	Ok	Comment noted. No action required.
Equality and Diversity	BTSLC and MSAG	No Comment	No action required.

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	Eli Lilly	No Comment	No action required.
	Merck Serono	We have no further suggestion.	Comment noted. No action required.
	NCRI	Ok	Comment noted. No action required.
Innovation	BTSLC and MSAG	-	No action required.
	Eli Lilly	-	No action required.
	Merck Serono	[redacted] Given the innovative nature of this product and the associated biomarker, we feel that NICE should review this medication as close to CHMP opinion as possible.	Comment noted. This NICE technology appraisal will take place in line with the usual process.
	NCRI	-	No action required.
Other considerations	BTSLC and MSAG	No Comment	No action required.
	Eli Lilly	Immunohistochemistry (IHC), was used in the FLEX study to provide evidence	Comment noted. No action

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		of EGFR expression to meet the study's inclusion criteria. If a licence is granted for this indication, a diagnostic test will be required to identify tumours with over expression of EGFR. Any test should be fully validated and reproducible. Since IHC is standard practice within the UK, the addition of a specific antibody, to test for over expression of EGFR in NSCLC, should only have mimimal resource implications for the NHS.	required.
	Merck Serono	Cetuximab will focus [redacted] where it provides a significant effective treatment option improving statistically and clinically patient overall survival. As stated in the background section, data from the subgroup analysis was not available at the time of the randomised controlled study recruitment.	Comment noted. The scope states that guidance will only be issued in accordance with the marketing authorisation, and that if evidence allows, subgroups of patients defined by histology or other relevant factors, will be considered. No action required.
	NCRI	none; these are important/fine	Comment noted. No action required.
Questions for consultation	BTSLC and MSAG	yes	Comment noted. No action required.
	Eli Lilly	No comment	No action required.
	Merck Serono	The appropriate comparators for this technology are outlined above (see comparator section). The comparators not appropriate against this technology are erlotinib (due to a different selection of eligible patient NICE TA162 and NICE TA227) and bevacizumab (not recommended by NICE TA148 and not a therapy routinely used in the NHS).	Comment noted. Erlotinib and bevacizumab have not been included in the scope. No action required.

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	NCRI	certainly innovative in view of the best effect seen in squamous NSCLC for which there are currently fewer treatment options	Comment noted. No action required.
Additional comments on the draft scope.	BTSLC and MSAG	None	No action required.
	Eli Lilly	None	No action required.
	Merck Serono	• In the "Related NICE recommendations" section, we would also add: o Technology Appraisal No. 145, Cetuximab for the treatment of head and neck cancer June 2008 o MTA Colorectal cancer (metastatic) 2nd line – cetuximab, bevacizumab and panitumumab (review of TA150 and part review of TA118). Review date TBC • We have the following key data for NSCLC and Erbitux. 1. FLEX study. Pirker et al. The Lancet Vol 373 May 2009. [redacted] 2. LUCAS study. Rosell et al Annals of Oncology October 2007 3. BMS 100 study. Butts et al. JCO Vol 25 No. 36 December 2009 4. BMS 099 study. Lynch et al JCO Vol 28 No 6. February 2010. 5. A meta-analysis of all 4 of these studies. Nick Thatcher et al. WCLC in 2009. (Abstract A3.7)	Comment noted. The scope has been amended to include these technology appraisals in the 'Related NICE recommendations' section of the scope. Comment noted. No action required.

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	NCRI	None	No action required.

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

Department of Health
MHRA
Primary Care Respiratory Society UK
Royal College of Nursing
Royal College of Pathologists