National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)

Response to consultee and commentator comments on the draft scope and provisional matrix

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	AstraZeneca UK	There is not a high unmet need in 2nd line treatment. According to NICE CG121, all EGFR M+ patients should receive EGFR-TKI first line. In England and Wales, EGFR mutation testing is routinely carried out and the majority of patients with advanced/metastatic EGFR positive NSCLC receive a TKI as a first-line treatment. In exceptional cases, EGFR positive NSCLC patients may receive doublet chemotherapy as a first-line treatment regimen, which is then followed by a TKI treatment at second-line. This tends to occur when the results of the EGFR mutation testing are not available quickly enough to meet the NHS target times for the start of first-line treatment, but this is not best practice. Therefore, in most cases, patients with advanced/metastatic EGFR positive NSCLC in England and Wales do not receive a TKI as a second-line treatment. As an alternative approach we would recommend having a EGFR M+ MTA giving guidance on the treatment pathway from diagnosis to 1st line, 2nd and 3rd line treatments. The Background information reports that around 85%-90% of people with lung cancer are diagnosed with NSCLC. This may overestimate the target population. The National Lung Cancer Audit 2011 reports that 85.2% (n=840) of patients were diagnosed with lung cancer excluding small cell and mesothelioma. Of these patients 70.5% (n=592) were diagnosed with NSCLC. The proportion of patients in England & Wales with NSCLC is likely to represent around 60% of the lung cancer population.	Commented noted. The background has been updated. This is a multiple technology appraisal reviewing erlotinib and gefitinib for treating NSCLC that has progressed following prior chemotherapy. Therefore, first-line treatment options are not relevant to this technology appraisal. The proportion of patients in England and Wales has been updated to reflect the National Lung Cancer Audit report (2012).

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		NICE CG121 states that chemotherapy should only be offered to patients with good performance status (WHO 0,1 or a Karnofsky score of 80-100). This is an important consideration that should be expanded in the background section. On average only 30% of patients in England & Wales with histologically confirmed stage IIIB/IV NSCLC have good performance status (PS 0,1) and fewer than 60% of these good performance status patients go on to receive chemotherapy. (National Lung Cancer Audit Report 2011.) This highlights that a significant proportion of patients in England & Wales diagnosed with stage IIIB/IV NSCLC are unsuitable for chemotherapy and receive palliative care only.	
	Health Improvement Scotland (1)	In description of stage distribution, locally advanced should be both stage IIIA and B. Split in Scotland is now 25:25:50 rather than 30:30:40, with about a third of stage I/II and at least half of stage III having undiagnosed stage IV disease. Standard first line therapy for advanced disease seems outdated. - first line for adeno- or large cell carcinoma now usually cisplatin and pemetrexed.	Commented noted. The background has been updated. This is a multiple technology appraisal reviewing erlotinib and gefitinib for treating NSCLC that has progressed following prior chemotherapy. Therefore, first-line treatment options are not relevant to this technology appraisal.
	Health Improvement Scotland (2)	Accurate summary of current position with regards to NICE approval of the various drug options for second line therapy.	Comment noted. No action required.
	Liverpool Reviews and Implementation Group (LRiG)	The scope states that CG121 recommends a combination of docetaxel, gemcitabine, paclitaxel or vinorelbine plus carboplatin or cisplatin as first-line treatment options. However, NICE also recommends pemetrexed for patients with non-squamous disease and erlotinib and gefitinib for patients with EGFR M+ status as first-line treatment options.	Commented noted. This is a multiple technology appraisal reviewing erlotinib and gefitinib for treating NSCLC that has progressed following

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		The importance of EGFR status is described in the background section, would it be appropriate to mention ALK in the background also?	prior chemotherapy. Therefore, first-line treatment options are not relevant to this technology appraisal. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib.
	National Lung Cancer Forum for Nurses	Accurate	Comment noted. No action required.
	Pfizer UK	No comments.	Comment noted. No action required.
	Roche Products Ltd	This appears accurate	Comment noted. No action required.
	Royal College of Physicians	As erlotinib is now licensed for first line use in EGFR mutation positive patients the remit should be widened to include this indication. Differentiation between EGFR mutated and non-mutated patients is included but not all EGFR mut negative patients who might not have much to gain from EGFR TKIs over docetaxel are fit to receive Docetaxel but are fit to receive EGFR TKIs. These should be considered separately	Commented noted. This is a multiple technology appraisal reviewing erlotinib and gefitinib for treating NSCLC that has progressed following prior chemotherapy. Therefore, first-line treatment options are not relevant to this technology appraisal.

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			The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
The technology/ intervention	AstraZeneca UK	We agree that erlotinib and gefitinib should be the interventions. It should be clarified that gefitinib is also an orally active EGFR-TKI	Commented noted. The technology section has been updated.
	Health Improvement Scotland (1)	Crizotinib has only been used in patients with alk rearrangements and I do not think can be compared with erlotinib and gefitinib. For erlotinib and gefitinib the population needs to be predefined as one with EGFR-mutant, EGFR-wild type or EGFR-unknown cancers. If NICE cannot quantify this effect, it has a role in mandating this research be done. There is evidence in stage I-III populations that unselected use of EGFR-TKIs may be harmful, and this appears to be in those patients referred to above who have undiagnosed stage IV disease. With regard to histology, I would expect very little contemporary use of these agents in patients with squamous cell cancer.	Comment noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal.
	Health Improvement Scotland (2)	Correctly outlines UK licensing for erlotinib and gefitinib. However the proposed MTA specifically refers to the use of these two agents as second line therapy after prior chemo. Gefitinib does not have a specific license for secondline therapy and indeed license is restricted to those patients who have EGFR muations so these patients will generally have had EGFR TKI as first	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology

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		line therapy. Cannot see how this MTA is feasible on basis of current gefitinib license - is there also a proposal from the company to change the licensed indication ?.	appraisal. The population specified in the final scope is “adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy”. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Liverpool Reviews and Implementation Group (LRiG)	The scope lists erlotinib and gefitinib as interventions. Erlotinib and gefitinib can be used in combination with other treatments – are both monotherapy and combination therapies to be considered? The scope lists erlotinib as having a UK marketing authorisation for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Please note that erlotinib is also indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations and as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy.	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal. The population specified in the final scope is “adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy”.
	National Lung Cancer Forum for Nurses	yes	Comment noted. No action required.
	Pfizer UK	It may be worth clarifying the gefitinib's license is not specific to the line of therapy in which it is used.	The treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal.

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	Roche Products Ltd	This appears accurate	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
Population	AstraZeneca UK	The target population for gefitinib will be restricted to adults with aNSCLC harboring EGFR mutations that have been previously treated with platinum-based chemotherapy.	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal.
	Health Improvement Scotland (1)	See above. Mutation status is critical, and because mutations are so rare in squamous cancers, patients with these tumours rarely now receive EGFR-TKI. Within the subgroup of mutation-positive patients, gender, performance status and current smoking behaviour may still be important.	Commented noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Health Improvement Scotland (2)	Population proposed here is any adult with locally advanced NSCLC following prior chemo. As EGFR mutation positive patients will have received TKI first line usually then is it the intention of this MTA to focus on EGFR mutation negative patients at second line ? If so need to make this clear. Also only erlotinib and not gefitinib has license for this.	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Liverpool Reviews and Implementation Group (LRiG)	The population is unclear and needs to be better defined. In the scope, the population is defined as “adults with locally advanced or metastatic NSCLC following prior chemotherapy”. Does this mean that NICE is interested in the effectiveness of erlotinib and gefitinib in a single population only (e.g. adults with NSCLC) or in subgroups (e.g. squamous, non-squamous, EGFR M+,	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology

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		ALK+)? If so, this should be explicitly stated. The term "following prior chemotherapy" is unclear – does this mean after one chemotherapy treatment or after two chemotherapy treatments? Also, there is no mention of maintenance treatments in the scope – does 'after prior treatment' also mean after maintenance treatments?	appraisal. The population specified in the final scope is "adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy". The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	National Lung Cancer Forum for Nurses	yes	Comment noted. No action required.
	Pfizer UK	As both of the interventions target EGFR mutations (and gefitinib is licensed for use specifically in patients with EGFR mutations), it would be appropriate to reflect this in the population.	Comment noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Roche Products Ltd	The population description is accurate. We believe the following subgroups should be considered: 1) Patients who are EGFR wild type (i.e. patients without an EGFR mutation) 2) Patients unsuitable for docetaxel 3) Patients with unknown EGFR status	Comment noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Royal College of Nursing	The population is defined appropriately and we consider that the histological subgroups would be a valuable population to consider	Comment noted. No action required.
Comparators	AstraZeneca UK	The target population for gefitinib will be restricted to adults with aNSCLC	Comment noted. It was

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		harboring EGFR mutations that have been previously treated with platinum-based chemotherapy. Crizotinib would not be a relevant comparator in this population as it is not currently a standard-of-care for the 2nd-line treatment of EGFR mutation positive aNSCLC. Crizotinib as a comparator in the scope refers to adults positive for anaplastic lymphoma kinase fusion (ALK) genes, which data suggests are mutually exclusive from adults with EGFR positive mutations, the relevant population for gefitinib. Best supportive care should be included as a relevant comparator given the majority of patients diagnosed with stage IIIb/IV NSCLC are currently unsuitable for chemotherapy due to poor performance status (PS 3/4) and other considerations. Although not NICE recommended as a 2nd-line treatment option, pemetrexed may be considered as a potential comparator in light of new data that has been published comparing gefitinib to pemetrexed as a 2nd -line treatment for NSCLC (please see 'questions for consultation' section below).	decided that NICE technology appraisal guidance 124 (pemetrexed) should be moved to the static guidance list. During a previous consultation held in 2011, consultees indicated that the availability of new data was unlikely to change the 'not recommended' guidance of TA 124. Therefore, pemetrexed is not considered to be an intervention of interest in this multiple technology appraisal. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. Best supportive care has been added to the comparators.
	Health	The mutation pattern of EGFR and ALK rearrangements makes the EGFR-TKI-	Comment noted. Following

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	Improvement Scotland (1)	sensitive and crizotinib- sensitive patients are almost mutually exclusive. Docetaxel is standard second line, but the side effect profile of the EGFR TKIs means they may be used in patients for whom second line chemotherapy is contraindicated, rendering Best Supportive Care an appropriate comparator.	consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. Best supportive care has been added to the comparators.
	Health Improvement Scotland (2)	Comparators chosen make little sense.Crizotinib application still pending I understand but would expect that approval would be for first line therapy of alk positive patients. Certainly would not view crizotinib as an option for second line therapy generally as its action is restricted to very small percentage patients who are alk pos and would treat these upfront. Also pemetrexed is licensed as second line although not approved by NICE but in terms of licensed indications and data would make a more sensible comparator at second line. Currently erlotinib, docetaxel and pemetrexed all have second line license independent of EGFR whereas gefitinib license only first line EGFR mutation Given that response rates to secondline therapy are less than 10% and robust QoL data lacking it would certainly be worth including as comparator a supportive care only option which could include any medication /radiotherapy but not alternative chemo.	Comment noted. It was decided that NICE technology appraisal guidance 124 (pemetrexed) should be moved to the static guidance list. During a previous consultation held in 2011, consultees indicated that the availability of new data was unlikely to change the 'not recommended' guidance of TA 124. Therefore, pemetrexed is not considered to be an intervention of interest in this multiple technology appraisal.

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			Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal.
	Liverpool Reviews and Implementation Group (LRiG)	Docetaxel is an appropriate comparator. However, we are unclear as to why crizotinib is listed as a comparator as it is currently undergoing appraisal (comparators include erlotinib and docetaxel after previous treatment). Crizotinib is unlikely to require a comparison with gefitinib as mutations in EGFR and ALK are considered to be mutually exclusive in patients with NSCLC. In addition, crizotinib, unlike docetaxel and gefitinib, does not have a licence for "patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy" as it is licensed, with conditions, for "adults with previously treated ALK-positive advanced NSCLC".	Comment noted. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal.
	National Lung Cancer Forum for Nurses	yes	Comment noted. No action required.
	Pfizer UK	We suggest that crizotinib should not be considered a comparator, as its license for the treatment of 2nd-line NSCLC is specific to those with ALK-	Comment noted.

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		positive NSCLC. This separates it from the populations relevant to this appraisal, and therefore removes it as a relevant comparator. Gefitinib, as noted in the scope, is licensed specifically for use in patients with activating mutations of EGFR-TK. Because EGFR and ALK mutations tend to be mutually exclusive, it is extremely unlikely that a patient would be simultaneously eligible for both gefitinib and crizotinib. Although erlotinib is licensed for use in "unselected" 2nd-line patients (i.e., those in whom EGFR status is not known), it would very usual for a patient to have been tested for the ALK mutation but not have been tested for th EGFR mutation. Again, because of the mutually exclusive nature of the ALK/EGFR mutations (coupled with emerging evidence that erlotinib in EGFR wild type patients has limited efficacy), it is also extremely unlikely that a patient would be simultaneously eligible for both erlotinib and crizotinib. Given the above considerations, crizotinib is not an appropriate comparator for either of the technologies included in the scope. Ref: Garassino M.C. TAILOR: A phase III trial comparing erlotinib with docetaxel as the second-line treatment of NSCLC patients with wild-type (wt) EGFR. J Clin Oncol 2012;30(Suppl.) [Abstract LBA7501].	Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal.
	Roche Products Ltd	Erlotinib is used in seven out of ten patients who are treated in second line NSCLC, it therefore should be viewed as the standard treatment used in the NHS. We believe that only cytotoxic chemotherapy (docetaxel - for patients fit enough to receive it) and Best Supportive Care (BSC) (for patients unsuitable for docetaxel) are relevant comparators in this MTA. Crizotinib is the subject of an ongoing STA with erlotinib, docetaxel and BSC as comparitors. The outcome of the STA will report prior to this MTA.	Comment noted. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and

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		Therefore the addition of crizotinib to this MTA would provide no additional guidance. In the second line setting there are no group of patients who are eligible to receive gefitinib and therefore inclusion as a comparitor would not seem to be an efficient use of resource. The full rational for not including crizotinib and gefitinib as compartors is provided in the "questions for consultation" section below.	gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. Best supportive care has been added to the comparators.
	Royal College of Nursing	These seem appropriate comparators however, we are aware that in some areas, Crizotinib and Gefitinib are not widely used routinely as 2nd line therapy. The use of "best supportive care" may also be compared i.e any supportive systemic therapy which does not have an anti cancer action but does improve symptoms. Radiotherapy may also be included in best supportive care.	Comment noted. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. Best supportive care has been added to the comparators.
	Royal College of Physicians	Erlotinib and gefitinib should not be compared with each other, as there is no phase 3, appropriately powered, head-to-head trial data. Also gefitinib is licensed for the treatment of EGFR M+ patients only, whereas erlotinib is licensed for the treamtent of NSCLC (in the post chemotherapy setting) regardless of EGFR M+ status. Also NICE has only reviewed and approved the use of gefitinib in EGFR M+ patients in the chemotherapy naive (1st line setting). Whilst trials of gefitinib vs docetaxel in mixed (EGFR M+ and M-) patients have been performed, gefitinb is only licensed for EGFR M+ patients.	Comment noted. The available evidence will be presented and critiqued in the manufacturers and Assessment Group's submissions. The potential to make robust comparisons between gefitinib and alternative technologies will be

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		In view of this it is not relevant to incuilde gefitinb in the rescoping exercise. It is appropriate to compare erlotinib with docetaxel as per TA162 It is inappropriate to compare either gefitinib or erlotinib with crizotinib. There have been no head-to-head trials, and neither would it make medical sense to do so, as the indiciations for their use are disparate. Best supportive care should not be used as a comparator, as this comparison of therapies is for patients that are fit for active oncological treatment and not best supportive care. The subgroups are approprioate but should consider patients with EGFR M+ that did not received 1st line erlotinib or gefitinib as per TA258 and TA192.	considered by the appraisal Committee. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
Outcomes	Health Improvement Scotland (1)	Overall survival and Health-related Quality of Life are most important. The value of progression-free survival is debatable. It is a marker of drug activity, but has no independent clinical utility over and above the other two endpoints.	Comment noted. No action required.
	Health Improvement Scotland (2)	If such a comparison being done then overall survival is most appropriate outcome with adverse effects and QoL as next most important. Progression free survival and response rates do not predict for overall survival and are fairly meaningless outcomes to patients in this context.	Comment noted. No action required.
	National Lung Cancer Forum for Nurses	yes	Comment noted. No action required.
	Pfizer UK	No comments.	Comment noted. No action required.
	Roche Products Ltd	Yes	Comment noted. No action required.

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	Royal College of Nursing	Yes	Comment noted. No action required.
	Royal College of Physicians	Appropriate	Comment noted. No action required.
Economic analysis	Health Improvement Scotland (1)	In the context of relapsed stage IV NSCLC, time frames are such that all remaining life should be used for economic assessment.	Comment noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The length and quality of life are important aspects in the calculation of the quality-adjusted life year (QALY) and will be considered in the appraisal.
	Health Improvement Scotland (2)	This is fair.	Comment noted. No action required.
	National Lung Cancer Forum for Nurses	appears appropriate	Comment noted. No action required.
	Pfizer UK	No comments.	Comment noted. No action required.
	Roche Products Ltd	No comment.	Comment noted. No action required.

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Equality and Diversity	Health Improvement Scotland (1)	Evidence suggests these drugs maybe more frequently of use in women and those of South/East Asian ethnicity.	Comment noted. Equality issues and implications of access to the different patient groups will be considered by the appraisal Committee.
	National Lung Cancer Forum for Nurses	no suggestions	Comment noted. No action required.
	Pfizer UK	No comments.	Comment noted. No action required.
	Roche Products Ltd	No comment.	Comment noted. No action required.
	Royal College of Nursing	In our view, the considerations for offering the above technologies should be based on histology, stage of disease, prior treatment and patients' fitness to tolerate the therapy. Support should be provided to all patients who fall into the above category to enable them to understand and make informed decisions regarding their acceptance or not of the treatment, therefore promoting equality.	Comment noted. Equality issues and implications of access to the different patient groups will be considered by the appraisal Committee.
Innovation	AstraZeneca UK	We consider that gefitinib is an innovative treatment for patients with stage IIIB/IV NSCLC with EGFR mutations that have been previously treated with platinum-based doublet chemotherapy and offers a substantial impact on health-related benefits including higher objective response rates, significantly longer PFS, improved tolerability and quality-of-life over current standard-of-care. However, it must be acknowledged that data on the use of gefitinib in the target population is currently limited and there may be insufficient evidence to enable a robust comparison against the alternative technologies to be made. Overall survival data from the 2nd-line trials is likely to have been confounded by patient cross-over.	Comment noted. The potential innovative nature of the technologies will be considered by the appraisal Committee. The available evidence will be presented and critiqued in the manufacturers and Assessment Group's submissions. The potential to make robust comparisons between gefitinib and

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		Adjusting for patient cross-over given the limited sample sizes in the EGFR mutation positive subgroups will be challenging. If this is not possible, the QALY calculation is likely to underestimate the health-related benefits associated with this technology.	alternative technologies will be considered by the appraisal Committee.
	Roche Products Ltd	Yes. Erlotinib provided a step change in the treatment of NSCLC when NICE approved it in TA162. It is an oral product that allows patients to be treated at home at the end of life. This releases capacity in chemotherapy suites, reduces the burden of intravenous infusions and allows patients to spend their last months with their loved ones.	Comment noted. The potential innovative nature of the technologies will be considered by the appraisal Committee.
Other considerations	Health Improvement Scotland (2)	Very important to focus on efficacy by histology as the treatment options vary between squamous and non-squamous. Also hard to see how you can justify this comparison without including EGFR mutation status which will make large difference to likely efficacy of therapy	Commented noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Liverpool Reviews and Implementation Group (LRiG)	If NICE is interested in subgroups of patients, it would be appropriate to add EGFR mutation positive and ALK positive populations to the subgroups stated in the scope (squamous and non-squamous).	The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	National Lung Cancer Forum for Nurses	no suggestions	Comment noted. No action required.
	Pfizer UK	No comments.	Comment noted. No action required.
	Roche Products Ltd	This appraisal should explicitly consider societies preference for incremental QALY gains provided to patients with a high burden of illness and few existing treatment options. Regarding the end of life criteria, we believe that the Guidance Executive, and the Committee for this Appraisal, should consider whether the number of	Comment noted. The potential innovative nature of the technologies will be considered by the appraisal Committee.

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		patients indicated for erlotinib is of consequence to societies valuation of the health gain it provides. This is particularly relevant in patients unsuitable for docetaxel in which erlotinib is the only treatment option.	The end of life criteria considered by the Committee in technology appraisals is available on the NICE website.
Questions for consultation	AstraZeneca UK	Data on the 2nd-line use of gefitinib versus docetaxel in patients with locally advanced or metastatic NSCLC with EGFR mutations is available from 2 phase III clinical trials: INTEREST (EGFR mutation+ subgroup n=44 [Kim Lancet 2008;Gefitinib EPAR])]) and V-15-32 (EGFR mutation+ subgroup n=31 [Maruyama et al JCO 2008;Sekine 2007]). Data on the use of gefitinib versus best supportive care (placebo) in previously treated patients with refractory advanced NSCLC that have EGFR mutations is available from ISEL [Thatcher et al Lancet 2005] (EGFR mutation+ subgroup n=26). A Korean study [KCSG-LU08-01, Sun et al Cancer 2012] has been published comparing gefitinib to pemetrexed as a 2nd-line treatment for NSCLC (EGFR mutation+ subgroup n=33. We are aware of two other RCTs assessing the use of gefitnib (ISTANA, Lee et al 2010; SIGN, Cufer et al 2006), however mutation status was not addressed. We are aware of 1 ph3 RCT [TITAN) that has assessed the efficacy and tolerability of erlotinib as a 2nd line treatment for advanced NSCLC (Cieleanu et al Lancet Oncol 2012). The comparators in this trial were docetaxel and pemetrexed.The EGFR mutation+ subgroup comprised of 11 patients. There is limited published information regarding the HORG study (Vamvakas et al 2010) which is also potentially relevant. A biomarker analysis of BR21 phIII trial that compared erlotinib to placebo in previously treated patients with advanced NSCLC has been reported [Zhu et al	Comment noted. No action required.

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		JCO 2008]. The EGFR mutation positive subgroup was restricted to Exon 19 or 21 mutations (n=37	
	Health Improvement Scotland (1)	I would expect current evidence to limit use of these drugs to those with mutation-positive tumours, between 3-10% of population. If this is demonstated, this would avoid toxicity in a substantial number who currently receive the drug, and substantially reduce the resource required for the drug. However about one quarter to one third of lung cancer patients never have a biopsy, so some consideration needs given to those with clinical indications of likely benefit (gender, ethnicity, smoking habit, performance status, disease - free interval) Appropriate comparators for second line use are docetaxel and best supportive care; the latter would have to include any treatment not involving systemic therapy. As alluded to above, gender, ethnicity and smoking habit, in addition to mutation status and histology, are all relevant to EGFR-TKI activity and use, and preformance status warrants consideration in any assessment of a cancer treatment. I think the major impact of this assessment is likley to be to refine the use of these agents to groups who have a higher chance of benefit compared to the unrestricted use now allowed.	Comment noted. The resource consequences of treatments specified in the scope will be explored in the economic analysis. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows. Best supportive care has been added to the comparators.
	Health Improvement Scotland (2)	I cannot understand at all the purpose of this proposed MTA - gefitinib not licensed for second line or for EGFR mutation negative. For EGFR mutation positive patients most will have had TKI as first line therapy so what is the intended population here ? Definitely makes no sense to have crizotinib as comparator as this is not second line and is intended for very small specific subgroup in population. If plan is to look at TKIs generally as second line therapy in all comers or mutation negative then probably need to include pemetrexed which has second line license for non-squamous.	Comment noted. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal. The population specified in the final scope is “adults with locally advanced or metastatic non-small-cell lung cancer that

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			has progressed following prior chemotherapy". Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. It was decided that NICE technology appraisal guidance 124 (pemetrexed) should be moved to the static guidance list. During a previous consultation held in 2011, consultees indicated that the availability of new data was unlikely to change the 'not recommended' guidance of TA 124. Therefore, pemetrexed is not considered to be an intervention of interest in this multiple technology appraisal.
	National Lung	Has the potential to make a big difference to a small groups of patients.	Comment noted. No action

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	Cancer Forum for Nurses	Medication should be stopped if any signs of disease progression.	required.
	Pfizer UK	Responses included in above comments.	Comment noted. No action required.
	Roche Products Ltd	Q1: Have the most appropriate comparators for erlotinib and gefitinib for the treatment of NSCLC following prior chemotherapy been included in the scope? A1: Crizotinib Crizotinib has recently received regulatory approval for the small group of patients (4-7%) with relapsed NSCLC bearing the EML4-ALK fusion oncogene. It is the subject of an ongoing STA in this indication, whose scope lists comparators as docetaxel, erlotinib and best supportive care. The first Apparisal Committee Meeting for this STA is scheduled for February 2013, therefore it is assumed that there will be guidance on its cost and clinical effectiveness shortly before publication of this proposed MTA. The only additional comparator included in this MTA and not in the crizotinib STA is gefitinib. However, gefitinib is licensed only for patients with tumours bearing activating EGFR mutations, which are mutually exclusive with EML4-ALK fusion oncogenes. Therefore, gefitinib and crizotinib are not appropriate comparators for each other. In summary, including crizotinib in this MTA will duplicate the work of the STA, complicate the MTA and not produce any further guidance. Gefitinib as comparator In recent years, multiple clinical trials have indicated that for the 10% or so of patients with activating EGFR mutations requiring systemic therapy for inoperable NSCLC, a specific EGFR tyrosine kinase inhibitor (EGFR TKi; gefitinib or erlotinib) offers a much better treatment option than non-specific chemotherapy in terms of efficacy, tolerability and quality of life. These targeted therapies are also cost effective with NICE endorsing both gefitinib	Comment noted. Following consultation, it has been highlighted that people with NSCLC with an ALK fusion gene mutation do not harbour EGFR mutations. ALK fusion genes may be associated with resistance to EGFR-TK inhibitors such as erlotinib and gefitinib. Therefore, crizotinib has been removed as a comparator from the final scope of this multiple technology appraisal. All treatments will be appraised within their licensed indications, relevant to the final remit of this technology appraisal. The population specified in the final scope is “adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy”. The subgroups have been updated. EGFR mutational status will be explored, if the

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		(TA175) and erlotinib (TA162) for use in this way. The advantages of EGFR TKi therapy in this situation is so clear that testing for the mutation and treating with a TKi if found is now standard practice During TA192, NICE accepted the Manufacturer's argument that the only relevant comparator for a first-line EGFR TKi is anotherTKi (despite the inclusion of non-specific chemotherapy as a comparator in the Scope). Similarly, at the recent Scoping Meeting for afatanib in the first-line treatment of EGFR mutatant NSCLC, the sole comparators proposed by NICE were the other two EGFR TKi's licensed in this indication. Consequently, patients with detectable EGFR mutation positive disease will arrive at second-line therapy having already received the appropriate targeted therapy. Since such treatment normally continues until disease progression or (rarely) unacceptable toxicity, there is no scope for second-line treatment of these patient populations with existing targeted agents. Under these circumstances, the second-line treatment population consists of: -Patients who have tested negative for EGFR mutations who will have received cytotoxic chemotherapy at first line. At second line, gefitinib (which is only licensed for EGFR mutation-positive disease) is not a treatment option. -Patients with an identified EGFR mutation who received first-line treatment with a TKI (gefitinib or erlotinib) and will have now exhausted treatment with these agents (outside of a clinical trial). Gefitinib is not a treatment option. -Patients where it has been impossible to determine their EGFR status because of a lack of suitable biopsy material. Since knowledge of these characteristics is considered central to good patient care, every reasonable effort is likely to have already been made to do this at first-line and their EFGR mutation status is likely to remain unknown. In the absence of a confirmed EGFR mutation gefitinib is not indicated and it is not a treatment option. In summary, the inclusion of gefitinib in this MTA would be wasteful of time and resources since there is no group of patients who would be suitable to receive gefitinib as a second-line treatment. This presumably explains the failure of its	evidence allows. Best supportive care has been added to the comparators.

Section	Consultees	Comments	Action
		manufacturer to submit evidence during the STA of gefitinib in the second-line treatment of NSCLC that led to TA175. Conclusion Only cytotoxic chemotherapy (docetaxel - for patients fit enough to receive it) and Best Supportive Care (for patients unsuitable for docetaxel) are relevant comparators in this MTA Q2: Should best supportive care be included as a comparator? If applicable how should it be defined? A2: Yes, many patients are not fit enough to be treated with docetaxel and for this population, best suportive care is likely to be their only option. Best supportive care is very difficult to define, since, by definition it comprises of whatever treatments are required to alleviate the physical and psychological impact of advanced cancer. Such treatment must, of course, be provided to all patients (including those receiving active anticancer therapy) so when considering it as a comparator "Best Supportive Care alone" is a more appropriate description. However consumption of various elements of the care package can be expected to be reduced in patients receiving effective systemic anticancer therapy. Best supportive care is generally considered to exclude therapies administered with aim of cure or prolonging life (e.g.radical surgery, radiotherapy, systemic anticancer drug therapy). However, there is a complex interplay between Supportive Care and survival, with recent research demonstrating that early referral to a Supportive care team extends survival.	
	Royal College of Nursing	Docetaxel and Erlotinib are widely used for 2nd line therapy and this should provide clearer guidance and efficacy/tolerability in order to aid both health care professionals and patient with decision making.	Comment noted. No action required.
Additional comments on	AstraZeneca UK	There is not a high unmet need in 2nd line treatment. According to NICE CG121, all EGFR M+ patients should receive EGFR-TKI first line. As an	Comment noted. This is a multiple technology appraisal

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the draft scope.		alternative approach we would recommend having a EGFR M+ MTA giving guidance on the treatment pathway from diagnosis to 1st line, 2nd and 3rd line treatments. The draft scope reports that the appraisal should consider the implications of mutational testing. We agree with this and would like to refer the project team to the in process diagnostic appraisal - Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer	reviewing erlotinib and gefitinib for treating NSCLC that has progressed following prior chemotherapy.
	Royal College Of Pathologists	I agree that the questions at the end in relation to the relevance and mutation status and histology tumour subtypes (adenocarcinoma, versus squamous, versus nonc-small cell carcinoma, not otherwise specified) are important.	Comment noted. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.
	Royal College of Physicians	Overall, the scope must emphasise that it relates to second line Rituximab. Our experts also wish to highlight the following important aspects: a) patients with mutations now get first line erlotinib or gefitinib b) neither is known to be superior, but gefitinb is licensed for first line only c) if patients' mutation status is negative or not known they may have erlotinib second line as the main BR21 study does show benefit for all subgroups d) supportive care is not a valid comparator as these are fit patients and in many UK practices may receive docetaxel or pemetrexed as second line therapy e) many patients do not want further chemotherapy so an oral effective therapy is invaluable as an option f) the toxicity from erlotinib is significantly less than docetaxel The inclusion of a section on whether or not patients have been tested for activating EGFR mutations should be considered. This is because it may influence secondline treatment decision making The scope does not mention the CG 121 guidance about referring to the use of	This is a multiple technology appraisal reviewing erlotinib and gefitinib for treating NSCLC that has progressed following prior chemotherapy. The subgroups have been updated. EGFR mutational status will be explored, if the evidence allows.

Section	Consultees	Comments	Action
		firstline gefitinib (TA192) and firstline pemetrexed (TA181) in adenocarcinoma patients, which are both relevant and most reflective of current practice. Some experts believe that the inclusion of appropriate staging and restaging to assess therapy response is potentially important. They feel that this would save costs and reduce inappropriate treatment.	

Comment 2: the provisional matrix

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 CANCERactive from patient/carer group consultees.	NICE Secretariat		Removed	CANCERactive have now closed, and therefore been removed from the matrix.
2.	Remove Chinese National Healthy Living Centre from patient/carer group consultees.	NICE Secretariat		Removed	Chinese Healthy Living Centre have requested that they only be contacted about Chinese-related business (BME topics, Hep B, vaccination, retaining organs)
3.	Remove Sue Ryder Care from Patient/carer group consultees.	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria Sue Ryder Care has not been included in the matrix of consultees and commentators.

4.	Add Allied Health Professionals Federation to general group commentators.	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
5.	Add Society and College of Radiographers to professional groups.	NICE Secretariat		Added	The Society and College of Radiographers 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.
6.	Add the Health Research Authority to research groups	NICE Secretariat		Added	The Health Research Authority meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.
7.	Add the Independent Cancer Patients' Voice to patient/carer groups	NICE Secretariat		Added	The Independent Cancer Patients' Voice meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.