4-year surveillance 2016 - Lung cancer (2011) NICE guideline CG121

Decision matrix

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Access to services and referral			
121 – 01 **Access to services and referral (1.1.1)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	A randomised controlled trial (RCT)[1] (n=493) tested a strategy of a straight-to-test model of computerised tomography (CT) in patients referred to a fast-track lung cancer pathway. Outcomes were number of CTs performed, use of specialist time and staff acceptability. The findings indicated that giving GPs direct access to CT did not change the number of CTs performed but significantly reduced chest physician time per patient. A meta-analysis[2] (46 studies, 23 in narrative synthesis, 23 in meta-analysis) found that patients with lung cancer living in more socioeconomically deprived circumstances were less likely to receive any type of treatment, surgery, and chemotherapy. The association remained when stage was taken into account for receipt of surgery, and was found in both universal (28 studies) and non-universal (18 studies) health care systems.	Topic expert feedback indicated the importance of the 'route to diagnosis' pathway. (Note, from National Cancer Intelligence Network data, that 39% of lung cancer patients are diagnosed via the emergency route – all cancers, 23%. One year survival for those diagnosed via emergency route is 8.9%, for those diagnosed via the GP route, it is 39.8%). There is ongoing research into this and an updated guideline will need to implement strategies to effect change. No ongoing studies were cited. Topic expert feedback also highlighted that there is wide variation in access to care in	No new evidence was identified that would affect recommendations. Further studies may be required to confirm RCT evidence identified at the 4 year review, on a straight-to-test model of CT in patients referred to a fast-track lung cancer pathway, and on reciprocal peer review with supported quality improvement in multidisciplinary teams. Recommendations for lung cancer referral are covered in related guidance NICE guideline NG12 suspected cancer: recognition and referral. Evidence from a meta-analysis identified at the 4 year review indicates a possible inequality in access to services by socioeconomic status. There was no evidence identified on risk prediction models to identify people who should be referred for lung cancer.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		lung cancer, including specialist palliative care. The strongest evidence is for inequality between patients who are first referred to a centre with many specialised services on site compared with those who are not. Since the latter group represents 70% of the lung cancer population, this is important. There is an over twofold variation in provision of curative treatment throughout the UK. No studies were cited. Further topic expert feedback highlighted the need to update the guideline in the area of risk prediction models to identify people who should be referred for lung cancer. Evaluation of composite risk models were excluded from the original scope. The topic expert stated that there was over reliance on a single small study from a single area with one of the lowest incidences of lung cancer and some unusual features, including double the rates of small cell lung cancer. No Studies were cited.	Although this was excluded from the original scope, it was highlighted as a significant area by topic expert feedback. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
121 – 02 **Referral and indications for chest radiography (1.1.2-1.1.6)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Communication			
121 – 03 **For patients with lung cancer and their carers, what is the effectiveness of communication methods to support decisions regarding treatment options? (1.2.1-1.2.10)**			
2-year Evidence Update (2012) No relevant evidence identified.	**Multidisciplinary education** An RCT[3] (n=60) found significantly lower fatigue scores in patients with lung cancer who received a multidisciplinary education program in self-care during chemotherapy treatment. An RCT[4] (n=212) evaluated whether a theory-based primary care intervention increased timely consulting of individuals with symptoms of lung cancer. The intervention comprised a single nurse consultation at participants' general practice and a self-help manual. The main outcomes were consultations within target times for individuals with new chest symptoms and intentions about consulting with chest symptoms at 1 and 6 months. The findings indicated that the behavioural intervention in primary care shortened the time individuals at high risk of lung disease took before consulting with new chest symptoms. However,	Topic expert feedback indicated that, since CG121 was published, the area of patient information has focused on patient decision aids. It was felt there may be value in considering patient experience within an update. No studies were cited to support this view. Further feedback indicated a need to update the guideline on public awareness of lung cancer signs and symptoms, encouraging GP attendance with appropriate symptoms. No studies were cited, but the campaign 'Be Clear on Cancer – Lung Cancer' was highlighted.	New evidence is unlikely to impact on guideline recommendations or research recommendation RR-08. Further evidence may be required to confirm the benefits reported in limited RCT evidence identified at the 4 year review on: • Multidisciplinary education for self-care during chemotherapy treatment. • Primary care behavioural interventions to reduce time to consultation for individuals at high risk of lung disease. Topic expert feedback also highlighted the importance of early diagnosis via public awareness of lung cancer signs and symptoms, and encouraging GP attendance with appropriate symptoms. • A comprehensive Health Enhancement Support System (CHESS) over Internet based support in relieving physical symptom distress in patients with non-

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	increases in consultation rates and the proportions of consultations within target times were not statistically significant. **Internet based support** An RCT[5] (n=285) examined the effectiveness of an online support system (Comprehensive Health Enhancement Support System [CHESS]) versus the Internet in relieving physical symptom distress in patients with non-small cell lung cancer. Findings indicated that caregivers in the CHESS arm consistently reported lower patient physical symptom distress than caregivers in the Internet arm. The effect on survival was non-significant.		small cell lung cancer. **Surveillance decision** This review question should not be updated.
Diagnosis and staging; Effectiveness of diagnostic and staging investigations; Sequence of investigations; Organisational factors relevant to diagnosis and staging			
121 – 04 **How effective are diagnostic and staging investigations in patients with suspected/confirmed lung cancer? (1.3.1-1.3.11)** 121 – 05 **What clinical factors and information from sequential tests determine the choice of next test for diagnosis and/or staging? (1.3.12-1.3.29)**			
2-year Evidence Update (2012) **Autofluorescence versus white light bronchoscopy** CG121 does not specify the type of light source to use in fibreoptic bronchoscopy. A meta-analysis[6] (14 studies, n= 1358) compared autofluorescence bronchoscopy (AFB) with white light bronchoscopy (WLB) for detection of cancerous or dysplastic lesions in people with suspected lung cancer.	**Endobronchial ultrasound (EBUS) Fine Needle Aspiration (FNA)** NICE interventional procedure guidance IPG254: Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses recommends EBUS for the investigation of mediastinal masses. An RCT[13] (n=125) evaluated if endobronchial needle aspiration may increase the sensitivity of bronchoscopy for diagnosing central airways neoplasms when added to conventional diagnostic	Topic expert feedback stated that CG121 assessed cost effectiveness on the basis of non-RCT data and modelling was used to come up with indicative costs. Health Economic data from the ASTER study provides RCT evidence to inform an update of the health economic model. Topic expert feedback indicated	**EBUS-FNA** New evidence was identified that may change guideline recommendations. The evidence identified at the 4 year review on EBUS has potential impact on recommendation 1.3.18 which advises offering EBUS-guided TBNA, or EUS-guided FNA, or non-ultrasound-guided TBNA as the first test for patients with an intermediate probability of mediastinal malignancy. Intermediate probability is

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The pooled sensitivity for AFB was 0.90 and for WLB it was 0.66. The pooled specificity for AFB was 0.56 and for WLB it was 0.69. In the summary receiver operating characteristic curve, the area under the curve (AUC) was 0.84 for AFB and 0.72 for WLB, which the authors concluded was due to a slightly better diagnostic performance of AFB. Another meta-analysis[7] (21 studies, n=3266) examined WLB plus AFB versus WLB alone for the diagnosis of intraepithelial neoplasia and invasive lung cancer, with histopathology as the reference standard. The authors postulated that only WLB may be needed for detecting invasive cancer because the RR for sensitivity gained with both AFB and WLB was much smaller than the RR for sensitivity gained when detecting intraepithelial neoplasia. The lower specificity of AFB was noted as problematic because more biopsies would be needed. The evidence suggests that AFB may have better sensitivity than WLB especially for detecting dysplastic lesions. The specificity of AFB seems to be lower than that of WLB, so the benefits of higher detection rates might be limited by the need to do additional	methods (forceps biopsy, brushing and bronchial washing), and if rapid on-site evaluation may be beneficial in patients undergoing endobronchial needle aspiration. Results showed that needle aspiration increased the sensitivity of bronchoscopy when added to conventional diagnostic methods, with a further significant improvement when guided by rapid on-site evaluation. An RCT[14] (n=160) examined combined sequential application of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in lung cancer staging. The diagnostic values and patient satisfaction were not different between the EBUS-centred and endoscopic ultrasound (EUS)-centred groups, but EBUS-transbronchial needle aspiration (EBUS-TBNA) was considered to be the better primary procedure, due to the necessity for EBUS-TBNA following EUS. A meta-analysis[15] (8 studies, n=822) found that combining EBUS-TBNA plus EUS-FNA achieved a higher sensitivity than EBUS-TBNA or EUS-FNA alone for mediastinal lymph node staging of lung cancer. An RCT[16] (n=108) found that rapid on-site cytologic evaluation during EBUS-TBNA in the diagnosis of lung cancer was associated with a significantly lower need for additional bronchoscopic procedures and puncture number. No significant	that diagnostic testing, particularly EGFR testing, has become integral to the lung cancer pathway since the last Guideline. There is a need to ensure guidance on EGFR and anaplastic lymphoma kinase (ALK) testing. No studies were cited. Additional topic expert feedback highlighted the need for the guideline to include: • Tools to help GPs better identify those patients requiring investigation of symptoms, and screening programmes to assist in early diagnosis. No studies were cited to support this view. However, screening is outside the remit of NICE and will not be incorporated into an update of the guideline. • New high level data about the role of EBUS in diagnostic pathways has been published. The cited study[18] is included in the summary of new evidence.	defined as lymph nodes between 10 and 20 mm maximum short axis on CT. Recommendation 1.3.22 advises that combined EBUS and EUS should be considered for initial staging of the mediastinum as an alternative to surgical staging. Firstly, cost effectiveness evidence from the ASTER RCT, also highlighted by topic expert feedback, indicates that EBUS-guided TBNA in combination with EUS-FNA is more effective and less expensive than standard surgical staging alone. New evidence from several RCTs also indicates that EBUS-TBNA may have superior diagnostic value to standard staging alone. There is therefore a potential impact, although none of the new studies specified the probability of mediastinal malignancy of included patients at abstract level. CG121 recommendation 1.3.18 defines intermediate probability as lymph nodes between 10 and 20 mm maximum short axis on CT. Secondly, new evidence indicates that combining EBUS-guided TBNA and EUS-guided FNA may achieve higher sensitivity than EBUS-TBNA or EUS-FNA alone, but that the sequence of primary and secondary procedure yields similar results. This new data may also potentially impact

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biopsies. The new evidence was not considered likely to impact CG121, which does not specify the type of light to use in fibreoptic bronchoscopy. **Fine-needle aspiration versus core-needle biopsy** A systematic review[8] (11 studies, n= 16640 assessed fine needle aspiration (FNA) versus core-needle biopsy (CNB) in people with undiagnosed lung nodule or mass seen on imaging for 3 outcomes: diagnosis, complication rates, and obtaining sufficient samples. The authors found that the design and reporting of most of the included studies was poor. Potential sources of bias included the recruitment of people with thoracic lesions (which may not be diagnosed by FNA as well as lung cancer), differences in study type (fully paired, randomised, or indirect comparison), and lack of blinding. The authors concluded that the evidence is insufficient to guide choice of FNA, CNB or both, in practice, and that the best technique is influenced by the local expertise in biopsy technique and sample interpretation. The new evidence from the evidence	difference was detected in sensitivity and accuracy, however. An RCT[17] (n=115) found no evidence of any benefit derived from the practice of applying suction (capillary sampling) to EBUS-guided biopsies, regardless of lymph node size. An RCT[18] (n=133) found that the time to treatment decision was significantly shorter with EBUS-TBNA than with conventional diagnosis and staging. An RCT[19] (n=145) found that for peripheral pulmonary lesions smaller than 30 mm, EBUS plus fluoroscopy guidance provided significantly greater diagnostic performance than fluoroscopy alone. A systematic review[20] (190 studies, n=16,181) investigated the complication rate of endosonography (EUS and EBUS) in the analysis of mediastinal/hilar nodal or central intrapulmonary lesions. The results indicated that serious adverse events (SAE) were more frequent in patients investigated with EUS than in those investigated with EBUS. Infectious SAE were most prevalent (0.07%) and predominantly occurred in patients with cystic lesions and sarcoidosis. In lung cancer patients, complications were rare. However, the true incidence of SAE might be higher as accurate documentation of complications was missing in most studies. A cost effectiveness analysis[21] of the Aster RCT reported the country-specific survival, quality of life and cost effectiveness up to 6 months, of		on recommendation 1.3.22, which advises that combined EBUS and EUS should be considered for initial staging of the mediastinum as an alternative to surgical staging. The recommendation may require stronger wording in the light of the new evidence. **PET-CT scanning** New evidence is consistent with guideline recommendations. In CG121, PET-CT is recommended (1.3.17-1.3.29), for mediastinal lymph node staging in patients whose disease is potentially suitable for treatment with curative intent, such as those with low probability of mediastinal malignancy (lymph nodes up to 10 mm maximum short axis on CT). It is also an option for staging in people with intermediate probability of mediastinal metastases and for confirming distant metastases. The new systematic review evidence identified in the evidence update and 4 year surveillance review is consistent with this. Inconclusive evidence was identified on the following forms of PET for NSCLC staging: • FDG-PET imaging for diagnosing malignant pleural effusions and distant metastases • The two main makes of PET-CT

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
update was considered to be consistent with the recommendations in CG121 around choice of biopsy technique and the need for local audits of test performance. **Positron-emission tomography (PET) in staging PET for radiotherapy treatment planning** A meta-analysis[9] assessed 14 studies (n=2550) of PET-CT for mediastinal lymph node staging in people with non-small-cell lung cancer (NSCLC). The pooled weighted sensitivity of PET-CT in studies with patient-based analysis was 0.76 and pooled specificity was 0.88. In the summary receiver operating characteristic curve, the AUC was 0.90, indicating good diagnostic performance of PET-CT. The results of this meta-analysis were considered in the Evidence Update to be consistent with CG121, which recommends PET-CT for mediastinal lymph node staging in people with disease suitable for potentially curative treatment. A systematic review[10] examined 18 studies analysing the cost effectiveness of PET-CT versus conventional imaging in people with NSCLC or solitary	combined EBUS−TBNA and EUS−FNA (followed by surgical staging if endosonography was negative), compared with standard surgical staging alone, in patients with NSCLC. Survival in the two arms of the study was similar. In all three countries, including the UK (n=28), the endosonography strategy had slightly higher quality-adjusted life years over 6 months, and was cheaper. **Bronchoscopy and Endosonography** A meta-analysis[22] (6 studies) compared AFB versus WLB in the detection of lung cancers and precancerous lesions. The sensitivity of AFB was found to be higher than that of WLB, while the specificity of AFB was lower than that of WLB. The overall diagnostic performance of AFB was slightly better than that of WLB. An RCT[23] (n=350) found that virtual bronchoscopic navigation assisted ultrathin bronchoscopy but did not improve the diagnostic yield for peripheral pulmonary lesions. However, the method improved the diagnostic yield for lesions in the subcategories (right upper lobe, invisible, peripheral third). **PET-CT scanning** A meta analysis[24] (32 studies) found that CT scanning had relatively high sensitivity and moderate specificity for the diagnosis of solitary pulmonary nodules. A meta analysis[25] (13 studies n=1035) investigated the diagnostic value of PET and PET/CT for the detection of lung cancer recurrence. PET/CT and		scanners • dual time-point (DTP) 18F-FDG PET/CT compared with single time-point (STP) imaging, for detecting mediastinal nodal metastases in patients with NSCLC, and for diagnosing pulmonary nodules • whole-body PET/CT for the overall assessment of distant malignancies **Autofluorescence versus white light bronchoscopy** New evidence is unlikely to impact on guideline recommendations. The new evidence from the evidence update and 4 year surveillance review is not likely to impact CG121, which does not specify the type of light to use in fibreoptic bronchoscopy. **Fine-needle aspiration versus core-needle biopsy** New evidence is consistent with guideline recommendations. The new evidence from the evidence update is consistent with the recommendations 1.3.8-1.3.11 in CG121 around choice of biopsy technique and the need for local audits of test performance. **MRI** New evidence is unlikely to impact on

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pulmonary nodules, one of which was the full version of the 2005 NICE clinical guideline on lung cancer. 13 studies focusing on staging in NSCLC were included with a median assumption of mediastinal disease prevalence of 31%, and assumptions of PET-CT having a median sensitivity of 91% and median specificity of 91%. Costs were converted to 2010 US dollars. Most of the included studies found that the additional information gained from PET-CT staging of newly diagnosed lung cancer and diagnosis of indeterminate solitary pulmonary nodules is cost effective, which is consistent with CG121. A systematic review[11] (22 studies, n=1663) assessed the use of PET-CT in the staging of small cell lung cancer (SCLC). None of the included studies were randomised. Adequate clinical or pathological correlation of imaging findings was reported in 11 studies. The authors reported that PET-CT could change the management of disease compared with conventional staging in 28% of people if including radiotherapy portal changes. Most available studies reported adequate correlation of PET-CT findings with clinical or pathological results. A successful randomised trial	PET were found to be superior modalities to conventional imaging techniques for the detection of recurrent lung cancer, and PET/CT was superior to PET. A meta analysis[26] (9 studies n=780) evaluated the accuracy of (18) fluorodeoxyglucose (FDG) PET-CT for diagnosis of distant metastases in lung cancer patients. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and weighted area under curve collectively indicated a strong diagnostic performance. The type of lung cancer was not specified in the abstract, however. A meta analysis[27] (14 studies, n=407) assessed FDG-PET imaging for diagnosing malignant pleural effusions. Semiquantitative readings indicated only moderate diagnostic accuracy, with sensitivity significantly lower than visual assessments. A meta-analysis[28] (45 studies) aimed to determine the diagnostic accuracy of integrated PET-CT for mediastinal staging of patients with suspected or confirmed NSCLC that is potentially suitable for treatment with curative intent. The findings indicated that accuracy of PET-CT is insufficient to allow management based on PET-CT alone. The results also indicated that the apparent difference between the two main makes of PET-CT scanner is important and may influence the treatment decision in some circumstances. Two meta-analyses[29,30], both covering 8 studies, evaluated the diagnostic performance of dual time-		guideline recommendations. Further evidence may be needed on the diagnostic performance of diffusion-weighted MRI in differentiating between benign and malignant lung lesions, nodules and masses, and in lymph node staging. The comparative diagnostic performance of short time inversion recovery imaging and diffusion weighted MRI may also require further research. **Diagnostic biomarkers** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that the detection of MicroRNAs as biomarkers, particularly a combination of multiple MicroRNAs has potential diagnostic value. New evidence from a randomised validation study suggested that a clinical diagnostic model for the malignancy probability of pulmonary nodules is accurate, but further research may be required to verify the findings. New systematic review evidence also indicates potential diagnostic value of the following biomarkers: • Serum HE4 and serum • Serum anti-p53 antibody

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
was thought to be unlikely because of the large number of patients needed. CG121 does not specify whether the use of PET-CT in staging applies to NSCLC or SCLC, so this evidence was considered to be consistent with current guidance. **PET for radiotherapy treatment planning** CG121 recommends PET-CT in staging lung cancer, but does not provide specific recommendations about how radiotherapy should be planned. A systematic review[12] (28 studies, n=1054) examined PET-CT used in the planning of radiotherapy, mostly prospective observational studies. Only one randomised controlled trial was identified. All studies assessed NSCLC, with some additionally including people with SCLC or unspecified lung cancer. In 11 studies reporting change in gross tumour volume, PET-CT was associated with a mean decrease of 14–71% (median 40.5%). In 10 studies reporting changes in planning target volume, PET-CT was associated with a mix of increases and decreases in planning target volume. PET-CT resulted in the detection of distant metastases in 8–25% of patients (median 17.5%) across 6	point (DTP) 18F-FDG PET/CT compared with single time-point (STP) imaging, for detecting mediastinal nodal metastases in patients with NSCLC, and for diagnosing pulmonary nodules. The results showed that DTP PET/CT performed better than STP imaging in evaluating the lymph node status of NSCLC patients. For pulmonary nodules, DTP and STP were similar, although DTP had higher specificity. However, the small sample sizes and large heterogeneity may weaken the strength of the results. A meta-analysis[31] (41 studies n=4305) assessed the accuracy of whole-body PET/CT for the overall assessment of distant malignancies in patients with various cancers. The sensitivity and specificity were high for lung cancer diagnosis, but it should be noted that the number of included studies on lung cancer was not reported in the abstract. An RCT[32] (n=143) assessed whether coregistered whole brain (WB) magnetic resonance imaging(MRI)-PET would increase the number of correctly upstaged patients compared with WB PET-computed tomography (PET-CT) plus dedicated brain MRI in patients with NSCLC. Although both staging tools allowed greater than 20% correct upstaging compared with conventional staging methods, coregistered MRI-PET did not appear to help identify significantly more correctly upstaged patients than PET-CT plus brain MRI. **Magnetic resonance imaging (MRI)**		• Isocitrate dehydrogenase 1 • Circulating tumour DNA (ctDNA) for the detection of EGFR mutation status. **EGFR Testing** New evidence is unlikely to impact on guideline recommendations. CG121 does not make recommendations on EGFR mutation testing, but this area is covered by EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC (2013) NICE diagnostics guidance DG9. The recommended tests are relevant to the CG121 diagnosis and staging recommendations. The NICE lung cancer pathway includes the recommended tests and lists DG9 as source guidance. New systematic review evidence indicates that: • immunohistochemistry alone may be sufficient for the detection of EGFR mutations if the result is positive. • Blood samples appear insufficient as a substitute to tumour tissues. • Current evidence does not appear to demonstrate greater accuracy of one single EGFR mutation test over the other tests. Topic expert feedback highlighted the need for guidance on ALK testing, although no

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studies. The intent of radiotherapy changed from curative to palliative in 8–41% of patients across 11 studies. The Evidence Update noted that this review suggests that PET-CT has benefits over CT in planning radiotherapy for people with lung cancer. PET-CT is recommended in CG121 for staging in people with lung cancer, but no specific recommendations are made for radiotherapy planning. However, the Evidence Update reported the fact that PET-CT imaging detected metastasis or identified that the cancer was at a more advanced stage in some people provides some limited evidence in support of using this imaging in staging. How PET-CT imaging should be used for radiation planning in UK clinical practice, where PET-CT for staging is already established, is not clear.	Three meta-analyes[33-35] covering 11, 17 and 10 studies respectively, evaluated the diagnostic performance of diffusion-weighted MRI in differentiating between benign and malignant lung lesions, nodules and masses. Diffusion weighted MRI was found to be accurate in differential diagnosis. However, variable study quality, possible publication bias and heterogeneity weaken the strength of the results. A further meta-analysis[36] (9 studies) found that MRI showed high specificity in NSCLC lymph node staging, with short time inversion recovery imaging demonstrating a greater diagnostic odds ratio than diffusion weighted MRI. Further studies were considered necessary to confirm these findings and to establish consistent diagnostic criteria. **Diagnostic Biomarkers** Two meta-analyses[37,38] covering 20 studies (n=1563) and 13 studies, respectively, found that the detection of microRNAs as biomarkers, particularly a combination of multiple microRNAs, has potential value in the diagnosis of non-small cell lung cancer. Two further meta-analyses[39,40] covering 11 and 7 studies respectively, assessed the diagnostic accuracy and clinical value of serum microRNA-21 in the diagnosis of lung cancer. Results indicated that the single microRNA-21 may not be sufficient to identify lung cancer and that more microRNAs should be used.		studies were cited or retrieved in the evidence update or 4 year surveillance review. **Sentinal node biopsy** New evidence is unlikely to impact on guideline recommendations. Further studies may be needed to confirm new systematic review evidence indicating the feasibility of Sentinel node mapping using radiotracers for mediastinal lymph node staging of NSCLC patients. **Risk Prediction** New evidence is unlikely to impact on guideline recommendations. The new evidence on risk prediction indicates that a new model in general practice may be more effective in early diagnosis than the original CG24 guideline. This evidence was included in NICE guideline NG12 suspected cancer: recognition and referral, which CG121 cross refers to. Topic expert feedback confirmed the need for risk prediction tools in general practice, now covered by NG12. **Surveillance decision** Topic expert feedback indicated that there is extensive literature building on prognostic and predictive biomarkers. It was considered an emerging area, but with

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	A meta-analysis[41] covering 7 studies found that serum human epididymis protein 4 is a potential tool in the diagnosis of lung cancer, although high heterogeneity and potential publication bias weakened the strength of the findings. A meta-analysis[42] (17 studies, n=4221) found that Cyfra21-1 was a useful biomarker for diagnosis of NSCLC. However, significant publication bias was detected, which weakened the strength of the findings. Two meta-analyses[43,44] (16 studies and 100 studies) found that anti-p53 antibody has potential as an assistant marker in diagnosing lung cancer, particularly NSCLC. The number of lung cancer studies was not reported in the abstract for the second meta-analysis, however. An RCT[45] (n=1422) found that isocitrate dehydrogenase 1 can be used as a plasma biomarker for the diagnosis of NSCLCs, particularly lung adenocarcinoma, with relatively high sensitivity and specificity. A meta-analysis[46] (22 studies) found that the diagnostic accuracy of sputum DNA as a biomarker for NSCLC was not strong enough for clinical application. A randomised validation study[47] (n=3358) of a clinical diagnostic model for the malignancy probability of pulmonary nodules found that the accuracy of the model was high, based on validation with the randomised test set.		insufficient evidence to result in new recommendations. Further topic expert feedback indicated the need for recommendations on EGFR status testing. These are already available through EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC (2013) NICE diagnostics guidance DG9. This review question should not be updated.

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	Epidermal Growth Factor Receptor (EGFR) Testing CG121 does not make recommendations on EGFR mutation testing, but this area is covered by NICE Diagnostic guidance DG9 EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC and is included in the NICE lung cancer pathway. A meta-analysis[48] (15 studies) assessed the diagnostic accuracy of EGFR mutation-specific antibodies in NSCLC. The results indicated that immunohistochemistry alone may be sufficient for the detection of EGFR mutations if the result is positive. Molecular-based analyses were stated as being necessary only in the event of negative anti-E746-A750 antibody results. Three meta-analyses[49-51] (13, 25 and 26 studies respectively) were performed to determine whether blood samples could serve as substitutes for tissue specimens in detecting the EGFR mutation status. Blood samples had a high specificity but relatively low sensitivity for detecting EGFR mutations compared to tumour tissues, indicating that blood samples may be insufficient as a substitute. In one of the meta-analyses[50], the risk ratio for objective response and hazard ratio for progression-free survival (PFS) and overall survival (OS) were similar for blood serum as for tumour tissue and higher than that for plasma. A systematic review and cost-effectiveness		

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	analysis[52] compared the performance and cost-effectiveness of EGFR-TK mutation tests used to identify previously untreated adults with locally advanced or metastatic NSCLC, who may benefit from first-line treatment with tyrosine kinase inhibitors. Results showed similar estimates of accuracy across studies and did not show greater accuracy of any one EGFR mutation test over other tests. A limitation of the study was the assumption that the differences in outcomes between the results of the trials were solely attributable to the different mutation tests used to distinguish between patients; this assumption ignores other factors that might explain this variation. This study was incorporated into NICE Diagnostic guidance DG9 EGFR‑TK mutation testing in adults with locally advanced or metastatic NSCLC. A meta-analyis[53] (27 studies, n=3110) found that circulating tumour DNA (ctDNA) was an effective biomarker for the detection of EGFR mutation status, particularly in terms of specificity and area under ROC. **Sentinal node biopsy** A meta-analysis[54] (47 studies) assessed the accuracy of sentinel node biopsy in the staging of non-small cell lung carcinomas. Sentinel node mapping using radiotracers was found to be a feasible technique for mediastinal lymph node staging of NSCLC patients. However, the		

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	diagnostic accuracy data was only reported for the overall pooled detection and was not reported for individual techniques in the abstract, thereby weakening the impact of the results. **Risk prediction** A clinical risk validation study[55] (n=132,805) examined a risk prediction model in general practice, developed using variables that were independently associated with lung cancer up to 4 months before diagnosis. Clinical and socio-demographic features that were independently associated with lung cancer were patients' age, sex, socioeconomic status and smoking history. Results indicated that the model performed better in risk prediction than the CG24 NICE referral guideline and all comparable models. This study was incorporated into NICE guideline NG12 suspected cancer: recognition and referral.		
121 – 06 **Organisational factors relevant to diagnosis and staging (1.3.30-1.3.34)**			
2-year Evidence Update (2012) No relevant evidence identified.	An RCT[56] (n=30 teams) found that reciprocal peer review with supported quality improvement in multidisciplinary teams was feasible and effective in stimulating quality improvement activity, but resulted in only modest improvements in lung cancer treatment rates and patient experience. An RCT[57] (n=131) found that a 6 week multidisciplinary intervention to improve the 5 domains of quality of life increased the overall quality of life at week 4. The 6 month follow up of	Topic expert feedback highlighted the need for better multidisciplinary team (MDT) working. Multidisciplinary working has been key to improvement in lung cancer treatment and care. Almost all lung cancer patients are discussed by the MDT. However, the topic experts felt that some	The new evidence identified was consistent with recommendations 1.3.31 and 1.3.32 relating to multidisciplinary teams (MDTs). Topic expert feedback highlighted the need for recommendations on quality MDT working, but no research was cited. Further research may be needed to confirm the benefits of reciprocal peer review in MDTs with supported quality improvement, and on multidisciplinary interventions to improve

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	10 brief telephone counselling sessions did not result in any significant change. It should be noted that only 13% of patients in the sample had lung cancer, and the type of lung cancer was not specified. The components of the multidisciplinary intervention were not reported in the abstract.	aspects remain unclear including the quality of the MDT, its optimal specialism and decision making processes. On that basis, they felt there would be value in revisiting several aspects of MDTs including: • The overall number of MDTs • Effectiveness of each MDT • Quality MDT working Topic experts cited the following project: Improving Lung Cancer Outcomes Project (LCOP), hosted by the Royal College of Physicians. The RCT on reciprocal peer review stemming from this project is included in the 4 year surveillance review[58]. Topic expert feedback also stated that recent major structural changes to the NHS need to be reflected in the guideline. Local commissioning and specialist commissioning in lung cancer need to be defined. No studies were cited. The Welsh Assembly Government and Department of Health recommendations from which CG121 recommendation	quality of life. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		1.3.30 were derived appear to remain extant. These stipulate that patients should be treated within 31 days of the decision to treat and within 62 days of their urgent referral.	
Treatment: Smoking cessation			
121 – 07 **Does pre-operative smoking cessation/pre-operative pulmonary rehabilitation improve outcomes following lung cancer surgery? (1.4.1-1.4.4)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	Topic expert feedback stated that there may be new evidence on benefits of stopping smoking whilst receiving treatment. No studies were cited.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Treatment: Selection of patients with non-small-cell lung cancer for treatment with curative intent			
121 – 08 **Do exercise tests, lung function tests and/or global/other risk scores predict post-operative morbidity and mortality in patients with resectable lung cancer? (1.4.5-1.4.19)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Treatment: Curative treatment options for patients with NSCLC; What is the most effective treatment for patients with resectable non-small cell lung cancer?			
121 – 09 **Surgery with curative intent for non-small-cell lung cancer: Effectiveness of surgery for treatment of NSCLC. (1.4.20-1.4.23)** This chapter of the guideline has no review questions associated with it in the evidence review document			
2-year Evidence Update (2012) CG121 recommends lobectomy as first choice surgical treatment for NSCLC, and that more extensive surgery, including pneumonectomy, should be offered only when needed to obtain clear margins. However, the guidance also states 'do not offer neo-adjuvant chemotherapy outside a clinical trial' for patients with NSCLC who are suitable for surgery. A meta-analysis[58] (27 studies, n=2126) of perioperative mortality after pneumonectomy following neo-adjuvant chemotherapy or chemoradiation therapy for NSCLC found that left pneumonectomy after neo-adjuvant treatment was justifiable in terms of 30-day and 90-day mortality, but the risk–benefit profile of right pneumonectomy is less clear. Additionally it was not clear whether the increase in mortality between 30 and 90 days was due to the neo-adjuvant treatment, changes in cardiopulmonary function after	**Sublobar resection – lobectomy, segmentectomy and wedge resection** A secondary analysis of an RCT[59] (n=210) found that, in patients with early stage lung cancer for whom lobectomy was inappropriate, wedge resection was associated with a smaller parenchymal margin and a lower yield of lymph nodes and rate of nodal upstaging when compared with segmentectomy. A meta-analysis[60] (12 studies n=2745) compared the OS and disease-free survival (DFS) outcomes of patients who underwent sublobar resections who were also eligible for lobectomy procedures with those who underwent lobectomy. There were no significant differences in OS or DFS between the two treatment arms. In addition, no significant OS difference was detected for patients who underwent segmentectomies compared to lobectomies. **Sleeve lobectomy versus pneumonectomy** A meta-analysis[61] (19 studies n=3878) compared sleeve lobectomy versus pneumonectomy for NSCLC and found that sleeve lobectomy resulted in lower mortality and greater long term survival.	Topic expert feedback highlighted the potential impact of minimally invasive resection, which includes VATS, on outcomes. This topic is becoming very important in thoracic surgery and many UK thoracic surgical units are undertaking more and more VATS surgery. The option for VATS in appropriate patients is a vital part of the treatment and the new evidence that it is at least equally effective as open thoracotomy in terms of lymph node clearance and recurrence is of great importance and needs to be considered for inclusion in a future guideline update. An ongoing UK based study comparing open thoracotomy vs VATS was cited (VIOLET study). However the results from this are unlikely to be available for	**Video-assisted thoracoscopic surgery** New evidence was identified that may change recommendations. The new systematic review evidence on VATS lobectomy for stage 1 NSCLC indicates that VATS may be superior to thoracotomy in terms of 5 year survival, recurrence, intra-operative blood loss, chest drainage time, hospital stay and complication incidence. However, thoracotomy may be superior in terms of lymph node sampling. CG121 does not make recommendations on the use of VATS as a minimally invasive technique for lobectomy, and there is therefore a potential need for a new recommendation in this area, or an amendment to recommendation 1.4.20. This advises that for patients with NSCLC who are medically fit and suitable for treatment with curative intent, lobectomy should be offered (either open or thoracoscopic) as the treatment of first choice. Further research, including the results of

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
pneumonectomy, or complications taking longer to lead to death. The evidence suggests that risk of death is higher in right-side than in left-side pneumonectomy after neo-adjuvant treatment. Because CG121 recommends lobectomy unless pneumonectomy is needed for clear margins, this evidence was not considered to have a potential impact on current recommendations. The evidence also does not address the efficacy of neo-adjuvant chemotherapy, thus limiting the impact further.	An RCT[62] (n=385) found that the sequence of pulmonary vessel ligation, during anatomic resection, did not significantly affect long-term survival in patients with NSCLC. **Video-assisted thoracoscopic surgery (VATS)** Two meta-analyses[63,64] compared VATS lobectomy with thoracotomy for stage I NSCLC. In the first[63] (20 studies n=3457) VATS was found to achieve advantages over thoracotomy in terms of intra-operative blood loss, chest drainage time, hospital stay and complication incidence. In the second[64] (n=5389) VATS was found to result in significantly lower recurrence. In both meta-analyses, the 5 year survival rate of the VATS groups was also significantly higher than in the thoracotomy groups. A meta-analysis[65] (24 studies, n=5265) investigated whether VATS could achieve equivalent lymph node (LN) evaluation efficacy to thoracotomy. The findings showed that the same number of total and mediastinal LN stations could be harvested by VATS and thoracotomy, while less total and mediastinal LNs could be harvested by VATS. A secondary analysis[66] (n=1018) of an RCT evaluated survival and patterns of recurrence after surgical resection for early stage lung cancer. Propensity-score matched analysis showed no significant difference in survival between patients undergoing VATS and open lobectomy.	several years. Additional topic expert feedback stated that VATS is more available because of the training and interest of an increasing numbers of surgeons. It was felt that NICE recommendations for use of VATS could be beneficial in increasing the training and development of specialist thoracic surgeons. The topic expert felt that improved results described for VATS are probably explainable by a selection bias in favour of VATS for the technically easier cases with smaller tumours, but that this does not diminish its importance as a less traumatic intervention than open thoracotomy. The topic expert felt that VATS will inevitably have non-measurable benefits if it is done properly. The topic expert felt that the VIOLET trial has the best chance of answering the comparative question for NICE to make a firm recommendation, and so awaiting the results of the trial is sensible. Further topic expert feedback	the ongoing VIOLET study, may be required to inform this. **Sublobar resection – lobectomy, segmentectomy and wedge resection** New evidence is consistent with guideline recommendations. New evidence from the Evidence Update was not considered to have a potential impact on current recommendations, because CG121 recommends lobectomy unless pneumonectomy is needed to obtain clear margins (1.4.20-1.4.21). The evidence was also not considered to address the efficacy of neo-adjuvant chemotherapy, thus limiting the impact further. The new evidence identified at the 4 year surveillance review was consistent with recommendation 1.4.20 to offer lobectomy as first choice surgical treatment for NSCLC, and that more extensive surgery, including pneumonectomy, should be offered only when needed to obtain clear margins. RCT evidence indicates that wedge resection may be inferior to segmentectomy, but further systematic review evidence may be needed to confirm this before a definite impact can be established on recommendation 1.4.20 which advises either operation to be

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Mediastinal lymph node dissection A meta-analysis[67] (n=1,791) found similar results for OS, local recurrence rate, and distant metastasis rate between mediastinal lymph node dissection and mediastinal lymph node sampling in early stage NSCLC patients. There was no evidence of increased complications from mediastinal lymph node dissection. An RCT[68] (n=202) found that complete and minimal mediastinal lymph node dissection had similar surgical risks and mediastinal staging effects in patients with NSCLC. Minimal dissection was considered sufficient for early stage high-differentiation tumours. A meta-analysis[69] found that lymphatic vessel invasion was significantly associated with worse relapse free survival and OS for surgically managed patients with NSCLC.	stated that increasing resection and other curative treatment rates leads to improved survival. No studies were cited.	considered for patients with borderline fitness and smaller tumours. **Mediastinal lymph node dissection** New evidence is consistent with guideline recommendations. New systematic review evidence indicates similar OS, local recurrence rate, and distant metastasis rate between mediastinal lymph node dissection and mediastinal lymph node sampling in early stage NSCLC patients. This is consistent with recommendation 1.4.22, which advises either approach for patients undergoing surgery with curative intent. **Surveillance decision** Some topic expert feedback indicated that there is sufficient existing evidence to form a recommendation. However, additional topic expert feedback indicated that further research, including the results of the ongoing VIOLET study, may be required to inform this. It was felt that publishing a recommendation on the basis of current evidence could potentially prevent recruitment to the trial. The review question should be considered for a future update, following publication of the VIOLET study. This study is in the recruiting stage and updating the question now could potentially impact on the

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			recruitment process. The surveillance team will track the findings of the VIOLET study.
121 – 10 **Radiotherapy with curative intent for non-small-cell lung cancer: Which NSCLC patients are eligible for radiotherapy? (1.4.24-1.4.28)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
121 – 11 **Radiotherapy with curative intent for non-small-cell lung cancer: Effectiveness of radiotherapy as treatment for NSCLC. (1.4.27-1.4.30)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) A meta-analysis[70] (34 observational studies, n=2587) investigated stereotactic ablative radiotherapy ([SABR]; previously known as Stereotactic body radiation therapy [SBRT]) for treating stage I NSCLC. Patients' outcomes were compared by the biologically effective dose, which was categorised, according to quartiles of the included studies, as low (<83.2 Gy), medium (83.2–106 Gy), medium to high (106–146 Gy) or high (>146 Gy). At 1 year, OS, cancer specific survival, and local control rate were not significantly different for any comparison of biologically effective dose, in either the uncorrected or corrected analyses. At 2 years, in corrected analyses, OS in the medium biologically effective dose group was significantly higher than that of the low dose group and the high dose group; the medium to high dose group had significantly higher OS compared with the high dose group. The proportion of grade 3–5 adverse events were significantly different only in the comparison of low dose and high	**Radiotherapy with curative intent for non-small-cell lung cancer** A meta-analysis[72] (40 studies, n=4850) compared treatment outcomes of SABR with those of surgery in stage I NSCLC. Results showed that, after adjusting for differences in age and operability, OS and DFS did not differ significantly between SABR and surgery in patients with operable stage I NSCLC. However, the statistical significance data were not reported in the abstract. A prospective RCT was recommended to confirm the findings. A meta-analysis[73] (6 studies n=864) compared the efficacy of SABR versus surgery for early-stage NSCLC. Surgery was associated with a better long-term OS. However, the difference in 1-year and 3-year cancer specific survival, DFS, local control and distant control was not significant. A meta-analysis[74] (3 studies, n=1005) found that hyperfractionated radiotherapy did not improve OS of patients suffering from NSCLC compared to conventional fractionated radiotherapy. A subgroup analysis[75] (n=163) of an RCT found that significantly superior local control was achieved by continuous hyperfractionated accelerated radiotherapy-weekend less (CHARTWEL) compared to conventional radiotherapy in NSCLC patients. Gross tumour	Topic expert feedback stated that SABR has become an established treatment now routinely commissioned for treatment of stage I NSCLC. The NHS Commissioning Board is routinely commissioning SABR for a subset of patients with early stage, inoperable NSCLC, and it is now routinely used for this indication, as set out in NHS Commissioning Board (2013) Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult)	New evidence was identified that may change current recommendations**.** CG121 recommends (1.4.27-1.4.30) continuous hyperfractionated accelerated radiotherapy (CHART) for medically inoperable stage I and II NSCLC suitable for radical radiotherapy. Conventionally fractionated radiotherapy is recommended if CHART is not available. However, the recommendations for radiotherapy were based on data assessed for the 2005 NICE guideline on lung cancer. In the 2011 review of the guideline these recommendations were not formally re-assessed, however a footnote was added recognising the advances in radiotherapy techniques since 2005 and that centres would reasonably wish to offer these techniques (such as SABR) to patients. The new evidence identified in the Evidence Update may help to establish optimum dosing regimens for SABR, and was considered to have a potential impact on CG121. New systematic review evidence identified at the 4 year surveillance review indicates that surgery may be superior to SABR for early stage operable NSCLC in terms of OS, but similar

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
dose groups. Although this study does not compare SABR with CHART or conventional radiotherapy, the authors noted that a previous meta-analysis of SABR showed 5-year OS of 42% compared with 20% for conventional radiotherapy. The new evidence may help to establish optimum dosing regimens for SABR, and was considered to have a potential impact on CG121. A meta-analysis[71] (10 studies, n= 2685) of individual patient data compared hyperfractionated or accelerated radiotherapy (modified radiotherapy) with conventional radiotherapy for NSCLC (8 studies) and SCLC (2 studies) patients. For NSCLC, overall results were based on 2000 patients with a median follow-up of 6.9 years and 1849 deaths. Modified radiotherapy was associated with an absolute increase in survival of 3.8% at 3 years and at 5 years. Across trials, the risk of death was significantly reduced. This increase in survival was not significantly different for groups receiving chemotherapy compared with those who did not. No subgroup of patients, stratified by age, sex, histology or stage, had significantly better response to	volume had a significant effect on locoregional control after conventional fractionation, an effect that was not significant with CHARTWEL.		for other outcomes. Additional systematic review evidence suggests that surgery and SABR are not significantly different in terms of OS and DFS. This is a different subset of patients to the one by recommendation 1.4.27, which advises that patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered the CHART regimen. However, the NHS Commissioning Board is routinely commissioning SABR for a subset of patients with early stage, inoperable NSCLC, and it is now routinely used for this indication. New systematic review evidence, although not directly affecting the use of CHART, suggests that modified fractionation is generally better than conventional fractionation, although another meta-analysis suggested that hyperfractionated radiotherapy did not improve OS. New RCT evidence suggests that CHART-weekend less (CHARTWEL) may achieve superior local control compared to conventional radiotherapy in NSCLC patients, but further research may be required to confirm this. The collective evidence, clinical feedback and NHS commissioning policy indicate that the recommendations may require updating, to incorporate the use of SABR in

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
radiotherapy. For SCLC, overall results were based on 685 people with a median follow-up of 12.1 years and 622 deaths. Modified radiotherapy was not associated with a significant increase in survival. People with poor performance status benefitted significantly less from modified radiotherapy than those with good performance status. Modified radiotherapy for NSCLC significantly increased the likelihood of acute severe oesophageal toxicity, which was highest for 'very accelerated radiotherapy'. Platelet toxicity was significantly reduced with modified radiotherapy; however, no severe platelet toxicity was seen in people who did not have chemotherapy. In people with SCLC, modified radiotherapy was associated with increased acute oesophageal toxicity and reduced platelet toxicity. CG121 recommends CHART (which is both hyperfractionated and accelerated) for medically inoperable stage I and II NSCLC suitable for radical radiotherapy. The Evidence Update concluded that although this evidence does not directly affect use of CHART, it suggests that modified fractionation is generally better			inoperable early stage NSCLC and its optimum dosing regimens. **Surveillance decision** Topic expert feedback confirmed that the NHS Commissioning Board is routinely commissioning SABR for the subset of patients with early stage, inoperable NSCLC, and it is now routinely used for this indication. It was therefore considered necessary for CG121 to be updated to reflect this. Further clinical feedback indicated that patient travel and planning costs may be offset by delivering SABR in fewer factions and availability of equipment. Cost was not therefore considered to impede access to SABR. This review question should be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
than conventional fractionation.			
121 – 12 **What is the most effective combination treatment for patients with NSCLC? (1.4.31-1.4.39)**			
2-year Evidence Update (2012) **Chemotherapy plus best supportive care** In a Cochrane review[76] (16 trials,	**Chemoradiotherapy** ***First-line chemoradiation*** A systematic review and meta-analysis[77] (19 studies) examined the clinical effectiveness of first-	Topic expert feedback indicated that: • cetiximab is not licensed for lung cancer. There is nothing on new drugs online about a	**Chemoradiotherapy** New evidence is unlikely to impact on guideline recommendations. CG121 does not specify age groups, and

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
n=2714) the Non-Small Cell Lung Cancer Collaborative Group assessed the effect of supportive care or supportive care plus chemotherapy on survival in people with advanced NSCLC whose disease was not suitable for surgery or radical radiotherapy and who had not previously received chemotherapy. The definition of supportive care included palliative radiotherapy, antibiotics, corticosteroids, analgesics, antiemetics, transfusions and psychological support. Supportive care plus chemotherapy was associated with a significant survival benefit. No significant differences were seen for type of chemotherapy drugs used, or in single drug versus combination regimens, or in subgroups of patients defined by age, sex, stage, histology or performance status. The authors noted that their previous Cochrane review in this topic had led to discussion about whether the side-effects of chemotherapy were worthwhile for the small increase in survival. However, the data for quality of life were not sufficient to assess this outcome.	line chemoradiation for adult patients with locally advanced NSCLC who are suitable for potentially curative treatment. The results showed a statistically significant OS advantage for concurrent/consolidation chemoradiation treatment over sequential treatment. However, trial quality was generally poor and suffered from a lack of reporting of all important clinical findings, including OS. The 19 trials included in the systematic review were considered too disparate to form any conclusions as to the effectiveness of individual chemoradiation agents or types of radiotherapy. ***Older patients*** An RCT[78] (n=200) found that for patients over 70 years with locally advanced NSCLC, combination chemoradiotherapy provided a clinically significant benefit over radiotherapy alone. ***High dose radiation plus chemotherapy*** An RCT[79] (n=166) found that high dose 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than standard 60 Gy plus concurrent chemotherapy for patients with stage III NSCLC, in terms of OS and was more harmful. Addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in OS. An RCT[80] (n=102) found that the addition of cetuximab to radiotherapy and concurrent cisplatin did not improve disease control or OS in patients with locally advanced NSCLC.	licence being pursued for this indication. • MHRA drug safety update Cetuximab: new safety information available • Tegafur/uracil was discontinued in the UK in March 2013. • MHRA Drug Safety Update on erlotinib Erlotinib: new safety information	new RCT evidence on chemoradiotherapy for NSCLC patients over 70 years old is unlikely to impact on recommendation 1.4.32, which advises that potential benefit in survival should be balanced with the risk of additional toxicities. New systematic review evidence indicates that: • Injection of brucea javanica oil emulsion plus chemoradiotherapy may improve response rate and quality of life, but poor trial quality indicates the need for further research to confirm this. Brucea javanica oil is not listed on MHRA list of Herbal medicines granted a traditional herbal registration or on MHRA list of Banned and restricted herbal ingredients. • There may be an OS advantage for concurrent/consolidation chemoradiation treatment over sequential treatment, but poor trial quality indicates the need for further research to confirm this. • There is insufficient evidence to determine the effectiveness of individual chemoradiation agents or types of radiotherapy. New RCT evidence indicates that for patients with advanced NSCLC: • High dose radiation with concurrent chemotherapy may not improve OS and

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Postoperative chemoradiotherapy An RCT[81] (n=140) found that, compared with postoperative chemotherapy alone, postoperative concurrent radiochemotherapy increased both local/regional and distant DFS rate of the patients with IIIA-pN2 NSCLC, but not the OS rate. ***Low dose gemcitabine plus radiotherapy*** An RCT[82] (n=111) found no evidence of an improvement in event-free survival with the addition of weekly low dose gemcitabine to radical radiotherapy for patients with early stage NSCLC unfit for surgery. The study was underpowered however with entry terminated due to low accrual. ***Sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy*** The SOCCAR RCT[83] (n=130) compared sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III NSCLC. Treatment was given either sequentially or concurrently with three to four cycles of cisplatinum and vinorelbine. No significant differences in treatment related mortality, toxicity or survival were observed. The reported two year survival indicated that a four week regime of radiotherapy should be compared with conventionally fractionated radiotherapy in an adequately powered randomised controlled phase III trial. ***Amifostine to carboplatin and paclitaxel based chemoradiation***		may be more harmful. • The addition of cetuximab to chemoradiotherapy may not improve disease control or OS. • Compared with postoperative chemotherapy alone, postoperative concurrent radiochemotherapy may increase both local/regional and distant DFS rate of the patients with IIIA-pN2 NSCLC, but not the OS rate. • Sequential and concurrent chemotherapy (cisplatinum and vinorelbine) with radical hypofractionated radiotherapy in patients with inoperable stage III NSCLC appear similar in mortality, toxicity or survival outcomes. • The addition of amifostine to carboplatin and paclitaxel based chemoradiation in locally advanced NSCLC may not result in any significant difference in OS, DFS or long-term toxicity. • Different schedules of gemcitabine may be no different when combined with cisplatin as induction chemotherapy, followed by radiation therapy concurrent with cisplatin and etoposide. • There may be no difference in OS with the administration of tecemotide (L-BLP25) after chemoradiotherapy compared with placebo. Topic expert feedback confirmed that development

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Long term follow up results of the Radiation Therapy Oncology Group (RTOG 9801) RCT[84] (n=243) showed that the addition of amifostine to carboplatin and paclitaxel based chemoradiation in locally advanced NSCLC did not result in any significant difference in OS, DFS or long-term toxicity. The incidence of chemoradiation-induced esophagitis, and the ability of amifostone to prevent this, was not reported in the abstract. ***Gemcitabine induction chemotherapy*** An RCT[85] (n=106) of patients with confirmed inoperable non-metastatic NSCLC compared gemcitabine in two different schedules and cisplatin - as induction chemotherapy, followed by radiation therapy concurrent with cisplatin and etoposide. There were no statistically significant differences in response rate, PFS or OS between two different schedules. ***Brucea javanica oil injection*** A meta-analysis[86] (21 studies, n=1619) found that injection of brucea javanica oil emulsion plus chemoradiotherapy yielded a significant difference in response rate and quality of life, but did not report the data for survival outcomes. The trial quality was considered to be poor. ***Tecemotide (L-BLP25) after chemoradiotherapy*** An RCT[87] (n=1513) found no significant difference in OS with the administration of tecemotide (L-BLP25) after chemoradiotherapy compared with placebo for all patients with unresectable stage III		of this drug has been discontinued. • Combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel maintenance therapy, may not improve clinical outcomes in terms of OS and PFS. • There may be no difference in OS between sequential radiochemotherapy versus radiochemotherapy with epoetin alfa. • Further research may be required in these areas to confirm the findings and establish potential impact on CG121 recommendations. **Preoperative Chemotherapy** New evidence is unlikely to impact on guideline recommendations. No new evidence was identified that would affect recommendations. New systematic review evidence indicates that preoperative chemotherapy for resectable NSCLC may result in significant improvement in OS, including the subpopulation of patients with stage III disease. However RCT evidence conflicted with this and further studies may be needed to establish firm conclusions. CG121 did not update the recommendation in CG24 section 1.8.2.7 which advises that Patients with stage I, II or IIIA NSCLC who are suitable for resection should not be

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	NSCLC. ***Combined paclitaxel, carboplatin, and radiation therapy*** An RCT[88] (n=220) found that combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel maintenance therapy, did not improve clinical outcomes in terms of OS and PFS. ***Epoetin alfa*** An RCT[89] (n=385) found no significant difference in OS between sequential radiochemotherapy versus radiochemotherapy with epoetin alfa. The epoetin alfa group experience significantly more thrombovascular events. **Preoperative Chemotherapy** An RCT[90] (n=356) evaluated whether preoperative chemotherapy provides benefits in the survival and prognosis of patients with NSCLC in resectable stages I to IIIA, except T1N0. The results showed that preoperative chemotherapy did not result in improved OS or PFS. A meta-analysis[91] (16 studies, n=3728) found that preoperative chemotherapy for resectable NSCLC resulted in significant improvement in OS. Sensitivity analysis was conducted to address heterogeneity and further analysis showed that 7 studies (n=1447) with low heterogeneity evaluating only stage III disease demonstrated improved OS. An RCT[92] (n=528) found no significant difference in OS or 3 year DFS between patients receiving preoperative and perioperative chemotherapy in		offered preoperative chemotherapy unless it is part of a clinical trial. The new evidence is unlikely to impact on this. **Adjuvant chemotherapy** New evidence is unlikely to impact on guideline recommendations. Recommendation 1.4.36 advises offering a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. New systematic review evidence identified at the 4 year surveillance showed that six-cycle platinum-based adjuvant chemotherapy was shown to be effective in stage 1B NSCLC patients, which is consistent with this. However, it also found that uracil-tagafur alone or in combination with platinum-based therapy was beneficial in terms of OS, but had no advantage in prolonging DFS without platinum based therapy. Further research may be needed however, including tolerability, to establish a definite impact on the guideline. Tegafur/uracil was discontinued in the UK in March 2013, which limits its impact further. New Cochrane systematic review evidence indicates a clear benefit of adjuvant chemotherapy for resected early stage NSCLC patients, irrespective of whether chemotherapy is given in addition to

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	early-stage NSCLC, although compliance was greater in the preoperative group. **Adjuvant chemotherapy** A Cochrane systematic review[93] (47 studies n=11107) demonstrated a clear benefit of adjuvant chemotherapy for resected early stage NSCLC patients, irrespective of whether chemotherapy was given in addition to surgery or surgery plus radiotherapy. The outcomes measured were OS, time to locoregional recurrence, time to distant recurrence and recurrence-free survival. Where toxicity was assessed and mentioned in the publications, it was thought to be manageable. The risk of bias in the included trials was considered to be low. A meta-analysis[94] (16 studies, n=4656) found that Six-cycle platinum-based adjuvant chemotherapy improved OS and DFS in stage IB NSCLC patients. Uracil-tegafur alone or in combination with platinum-based therapy was beneficial to the patients in terms of OS, but uracil-tegafur had no advantage in prolonging DFS, unless it was administered with platinum-based therapy. An RCT[95] (n=140) found that third-generation (gemcitabine-vinorelbine-cisplatin) drugs were similar to second-generation drugs (mitomycine-ifosfamide-cisplatin) as neoadjuvant chemotherapy before surgery in NSCLC, but had significantly higher costs. The TREAT RCT[96] (n=132) found that in patients		surgery or surgery plus radiotherapy. The outcomes measured were OS, time to locoregional recurrence, time to distant recurrence and recurrence-free survival. This is consistent with CG121, which recommends postoperative chemotherapy in patients with good performance status (1.4.34-1.4.35), but does not specify surgery or surgery plus chemotherapy in combination with this. New RCT evidence indicated higher costs but similar performance of third generation chemotherapy drugs compared to second generation drugs as neoadjuvant chemotherapy before surgery in NSCLC. Further research may be needed to establish any impact on recommendation 1.4.37, which advises that neoadjuvant therapy should not be offered outside a clinical trial. New RCT evidence indicated that adjuvant chemotherapy with cisplatin and pemetrexed may have less toxicity and superior dose delivery compared with cisplatin and vinorelbine, without decreasing pulmonary function. New systematic review and RCT evidence suggests that chemo-immunotherapy with activated killer T cells and dendritic cells in patients with resected NSCLC can improve outcomes over 2,3 and 5 years. CG121

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	with completely resected stages IB-pT3N1 NSCLC, adjuvant chemotherapy with cisplatin and pemetrexed had significantly less toxicity and superior dose delivery compared with cisplatin and vinorelbine. A secondary analysis[97] (n=132) of the TREAT RCT found that adjuvant chemotherapy with cisplatin and pemetrexed did not result in a decrease of pulmonary function parameters. A post hoc analysis[98] (n=1867) of an RCT found that adjuvant cisplatin-based chemotherapy significantly reduced the risk of local relapse and of nonbrain metastasis, thereby improving survival. This treatment exerted no significant residual effect on mortality during the first 5 years, but a higher risk of noncancer mortality was found thereafter. **Chemoimmunotherapy** A meta-analysis[99] (6 studies) and an RCT[100] (n=103) found that chemotherapy in combination with immunotherapy (dendritic cells with a subset of natural killer T lymphocytes termed cytokine-induced killer cells) increased the 2-year, 3-year and 5-year survival rates and PFS in patients with NSCLC compared to those treated with chemotherapy alone. An RCT[101] (n=157) found that gemcitabine plus platinum combined with dendritic cell-cytokine induced killer immunotherapy significantly improved the immune cell function in the postoperative NSCLC patients, in addition to reducing postoperative tumour recurrence and		does not make recommendations on chemoimmunotherapy, and further studies may be needed to confirm these findings before a potential impact on the guideline can be established. **Chemotherapy plus best supportive care** CG121 did not make recommendations on chemotherapy plus best supportive care. It concluded that it is likely that chemotherapy as an adjunct to best supportive care for patients with NSCLC is cost effective, but that estimates of cost-effectiveness are contingent on the estimated changes in overall health-related quality of life and that more research would be needed in this area. New systematic review evidence indicates that chemotherapy plus best supportive care increased the OS and reduced the 6-month, 12-month, and 2-year mortality in patients with NSCLC. However, quality of life and side effect outcomes were not reported and further research may be needed on these to establish any impact on the guideline. **Adjuvant Brachytherapy** New evidence is unlikely to impact on guideline recommendations. New RCT evidence does not support the use of adjuvant brachytherapy, and is

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	prolonging the survival time of patients with NSCLC, in terms of DFS, cumulative recurrence rate and cumulative survival rate over 36 months. **Chemotherapy plus best supportive care** A meta-analysis[102] (16 studies, n=4135) found that chemotherapy plus best supportive care increased the OS and reduced the 6-month, 12-month, and 2-year mortality in patients with NSCLC. **Adjuvant brachytherapy** An RCT[103] (n=224) found that adjuvant brachytherapy following sublobar resection did not significantly affect local recurrence or 3 year OS in patients with NSCLC.		consistent with CG121 which does not recommend adjuvant brachytherapy following surgery. **Surveillance decision** This review question should not be updated.
121 – 13 **Chemotherapy for non-small-cell lung cancer: Which NSCLC patients are eligible for chemotherapy? (1.4.40-1.4.43)**			
2-year Evidence Update (2012) No relevant evidence identified.	**Prognostic biomarkers** ***XRCC1 Arg399Gln polymorphism*** A meta-analysis[104] (17 studies n=2256) found that XRCC1 Arg399Gln is related with the sensitivity of NSCLC patients to platinum-based treatment. The subgroup of AA genotype patients with advanced NSCLC presented higher response rates toward platinum drug treatment compared with G model (GG+GA) patients. An RCT[105] (n=142) found that serum protein test status was predictive of differential benefit in OS for erlotinib versus chemotherapy in the second-line NSCLC treatment. Patients classified as likely to have a poor outcome had better outcomes on	Clinical feedback indicated that there is extensive literature building on prognostic and predictive biomarkers. It was considered worthy of inclusion in an update to the guideline, but unlikely to result in new recommendations. No studies were cited.	**Prognostic biomarkers** New evidence is unlikely to impact on guideline recommendations. CG121 does not make specific recommendations on the use of prognostic biomarkers in assessing eligibility for chemotherapy, but recommends (1.4.40) chemotherapy on the basis of performance status and stage of disease. However, biomarkers were stipulated as within the scope of this area, which was not updated in CG121. Further research may be needed in the following areas, where new systematic

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	chemotherapy than on erlotinib. ***EGFR status*** A secondary analysis[106] (n=743) of an RCT found that patients with KRAS wild-type or EGFR mutation-positive NSCLC derived PFS but not OS benefits from bevacizumab plus erlotinib. However, EGFR immunohistochemistry, EGFR fluorescence in-situ hybridization (FISH), and EGFR or KRAS mutation status were not strongly predictive of survival. Two meta-analyses[107, 108] were identified comparing chemotherapy and EGFR-TKIs in the second-line treatment of NSCLC, in the context of EGFR mutational status. However, guidance on the EGFR inhibitors covered in the two meta-analyses, erlotinib and gefitinib, is the subject of an ongoing technology appraisal – [ID620] Lung cancer (non-small cell) - erlotinib & gefitinib (post chemotherapy) (rev TA162, TA175) This information will be passed onto the TA team for consideration. ***Post-treatment neutrophil-to-lymphocyte ratio*** A secondary analysis[109] (n=199) of an RCT found that a high posttreatment neutrophil-to-lymphocyte ratio, an inflammatory-immunological marker, was associated with a significantly increased risk of death in advanced lung adenocarcinoma. ***Rapamycin*** A meta-analysis[110] (10 studies), found no		review evidence indicates the following: ***XRCC1 Arg399Gln polymorphism*** XRCC1 Arg399Gln is related to the sensitivity of NSCLC patients to platinum-based treatment. The subgroup of AA genotype patients with advanced NSCLC may have higher response rates toward platinum drug treatment compared with G model (GG+GA) patients. ***Rapamycin*** There appears to be no association between the potential prognostic marker of rapamycin and phosphorylated mTOR expression and NSCLC patients' prognosis. ***Thymidylate Synthase*** There appears to be a significant association between thymidylate synthase (TS) expression and survival outcomes (PFS and OS) of pemetrexed-based chemotherapy for NSCLC. TS expression may be a potential predictor of sensitivity to pemetrexed-based chemotherapy, with an increased level appearing to be an independent risk factor of potential resistance against pemetrexed and worse outcomes. ***CD44-V6 Overexpression*** Overexpression of CD44-V6 may be associated with tumour differentiation, tumour histological type, clinical TMN stage

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	statistically significant association between the potential prognostic marker of rapamycin and phosphorylated mTOR expression and NSCLC patients' prognosis. ***Thymidylate synthase (TS)*** Two meta-analyses[111,112] covering 8 and 11 studies (second study n=798) found a significant association between TS expression and survival outcomes (PFS and OS) of pemetrexed-based chemotherapy for NSCLC. An increased level of TS was probably an independent risk factor of potential resistance against pemetrexed. Low/negative TS was significantly associated with better response rate and survival outcomes. ***CD44-V6 overexpression*** A meta-analysis[113] (23 studies n=1772) found that overexpression of CD44-V6 was significantly associated with tumour differentiation, tumour histological type, clinical TMN stage and lymph node metastasis. However, there was no significant association between CD44-V6 and tumour size. A secondary analysis[114] (n=524) found that TP53 mutations were not significant predictors of outcome in an RCT of cisplatin-based chemotherapy, although a specific class of structural mutations may be associated with a tendency towards worse outcomes upon treatment. ***Vascular endothelial growth factor (VEGF)*** An RCT[115] (n=303) found that baseline and/or		and lymph node metastasis. However, there may be no association between CD44-V6 and tumour size. ***Single Nucleotide Polymorphisms*** Positive/high ERCC1 expression may be a prognostic factor in SCLC patients receiving platinum-based chemotherapy, especially for LS-SCLC. ERCC1 C118T, ERCC2 Asp312Asn, and Lys751Gln single nucleotide polymorphisms may be associated with poor OS and PFS outcomes and serve as useful biomarkers to predict the clinical outcomes of platinum-based chemotherapy in NSCLC patients. Platinum-based chemotherapy sensitivity may be significantly associated with polymorphism of ERCC1 C118T and MDR1 C3435T single-nucleotide polymorphism in advanced NSCLC patients. ***Protein expression analysis*** Protein expression analysis for therapeutic decision making in newly diagnosed NSCLC patients suggests that if RRM1 and ERCC1 protein levels are low, patients may have better PFS with gemcitabine and carboplatin than with docetaxel/carboplatin or gemcitabine/docetaxel. ***Beta-tubulin (TUBB3) expression*** For patients receiving taxane/vinorelbine-

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	dynamic changes in plasma basic fibroblast growth factor, E-selectin, intercellular adhesion molecule-1, placental growth factor, VEGFR-1 and VEGFR-2, and tumour biomarkers did not correlate statistically with treatment outcomes for bevacizumab plus chemotherapy. Only baseline plasma VEGF-A was significantly correlated with progression-free survival/OS. A secondary analysis[116] of an RCT found that four genetic variants of VEGF-A and VEGFR-1 were associated with bevacizumab treatment outcome. Three variants in VEGF-A were associated with increased best overall response, one variant in VEGFR-1 was associated with worse progression-free survival/OS. These associations were not statistically significant after correction for multiple testing. No genetic variant was associated with significantly higher risk of hypertension. A meta-analysis[117] (22 studies) found that xeroderma pigmentosum group D (XPD) polymorphisms (Lys751Gln and Asp312Asn) may function as a predictive biomarker on platinum-based chemotherapy in NSCLC. The Lys751Gln polymorphisnm was not associated with response to platinum based-chemotherapy or survival. However, the XPD 312Asn allele was significantly associated with poor response to Pt-chemotherapy compared with the Asp312 allele. Additionally, the variant genotype of XPD Asp312Asn polymorphism was associated with favourable survival in Caucasian but unfavourable survival in		based chemotherapy, class III beta-tubulin (TUBB3) expression may be associated with a poorer ORR, an unfavourable OS, and a worse event-free survival compared a negative or low level of TUBB3 expression. This may also apply by ethnic subgroup (Asian and Caucasian), chemotherapy regimen (taxane-based and vinorelbine-based), TUBB3 detection method (IHC and PCR), and treatment strategy. ***EGFR status*** New systematic review evidence on the EGFR inhibitors in the context of EGFR mutational status is covered by an ongoing technology appraisal – [ID620] Lung cancer (non-small cell) - erlotinib & gefitinib (post chemotherapy) (rev TA162, TA175). Patients with KRAS wild-type or EGFR mutation-positive NSCLC may derive PFS but not OS benefits from bevacizumab plus erlotinib. However, EGFR IHC, EGFR FISH, and EGFR or KRAS mutation status do not appear to be strongly predictive of survival. ***Xeroderma pigmentosum group D*** Xeroderma pigmentosum group D (XPD) polymorphisms (Lys751Gln and Asp312Asn) may function as a predictive biomarker on platinum-based chemotherapy in NSCLC but this does not

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Asians. A secondary analysis[118] (n=316) of an RCT found that low pre-treatment plasma levels of VEGF were predictive of a positive effect of celecoxib on survival in advanced NSCLC patients. ***Single nucleotide polymorphisms*** A systematic review[119] (11 studies) found that platinum-based chemotherapy sensitivity was significantly associated with polymorphism of ERCC1 C118T and MDR1 C3435T single-nucleotide polymorphism in advanced NSCLC patients. A meta-analysis[120] (9 studies, n=1129) found that positive/high ERCC1 expression was associated with unfavourable OS and PFS. Subgroup analysis according to disease stage suggested the significant relationship was found in limited stage SCLC, but not in extensive stage SCLC. However, no significant association was found between ERCC1 expression and overall response rate (ORR). The analysis suggested ERCC1 expression may be a prognostic factor in SCLC patients receiving platinum-based chemotherapy, especially for LS-SCLC. A meta-analysis[121] (46 studies, n=9407) found that ERCC1 C118T, ERCC2 Asp312Asn, and Lys751Gln single nucleotide polymorphisms were significantly associated with poor OS and PFS outcomes. ***Beta-tubulin (TUBB3) expression***		appear to be associated with response to platinum based-chemotherapy or survival. However, the XPD 312Asn allele may be significantly associated with poor response to platinum based-chemotherapy compared with the Asp312 allele. Additionally, the variant genotype of XPD Asp312Asn polymorphism may be associated with favourable survival in Caucasian but unfavourable survival in Asians. New RCT evidence indicates the following: ***Serum protein test status*** The serum protein test status may be predictive of differential benefit in OS for erlotinib versus chemotherapy in the second-line NSCLC treatment. Patients classified as likely to have a poor outcome may have better outcomes on chemotherapy than on erlotinib. ***Post-treatment neutrophil-to-lymphocyte ratio*** The high inflammatory-immunological marker of posttreatment neutrophil-to-lymphocyte ratio may be associated with a significantly increased risk of death in advanced lung adenocarcinoma. ***TP53 mutations*** TP53 mutations do not appear to be significant predictors of outcome in an RCT of cisplatin-based chemotherapy, although

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	A meta-analysis[122] (28 studies, n=2401) found that for patients receiving taxane/vinorelbine-based chemotherapy, class III beta-tubulin (TUBB3) expression was associated with a poorer ORR, an unfavourable OS, and a worse event-free survival compared a negative or low level of TUBB3 expression. The statistically significant associations between TUBB3 and chemotherapy responses were also observed in the stratified subgroup analysis, which included the analysis by ethnic subgroup (Asian and Caucasian), chemotherapy regimen (taxane-based and vinorelbine-based), TUBB3 detection method (IHC and PCR), and treatment strategy. ***Protein expression analysis*** An RCT[123] (n=275) conducted protein expression analysis for therapeutic decision making in newly diagnosed NSCLC patients. The intervention group received gemcitabine/carboplatin if RRM1 and ERCC1 protein levels were low, docetaxel/carboplatin if RRM1 was high and ERCC1 was low, gemcitabine/docetaxel if RRM1 was low and ERCC1 was high, and docetaxel/vinorelbine if both were high. The control group received gemcitabine/carboplatin. There were no statistically significant differences between the groups. A subset analysis revealed that patients with low levels for both proteins who received the same treatment in both treatment arms had a statistically better PFS in the control arm compared with the experimental arm.		a specific class of structural mutations may be associated with a tendency towards worse outcomes upon treatment. ***VEGF Status*** Baseline and/or dynamic changes in plasma basic fibroblast growth factor, E-selectin, intercellular adhesion molecule-1, placental growth factor, VEGFR-1 and VEGFR-2, and tumour biomarkers do not appear to correlate with treatment outcomes for bevacizumab plus chemotherapy. Only baseline plasma VEGF-A appears to correlate significantly with progression-free survival/OS. Four genetic variants of VEGF-A and VEGFR-1 do not appear to be significantly associated with bevacizumab treatment outcome. Three variants in VEGF-A may be associated with increased best overall response, one variant in VEGFR-1 with worse progression-free survival/OS. These associations do not appear to be statistically significant after correction for multiple testing. Low pre-treatment plasma levels of VEGF may be predictive of a positive effect of celecoxib on survival in advanced NSCLC patients. ***Age and gender factors*** Tumour biomarker analysis demonstrates

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Age and gender biomarkers A secondary analysis[124] (n=255) of an RCT examined outcomes and biomarker profiles of elderly pre-treated NSCLC patients. Tumour biomarker analysis demonstrated sex and age variations, with older men gaining significant survival benefits from specific targeted agents (sorafenib and vandetanib).		sex and age variations in NSCLC patients, indicating that older men may gain survival benefits from specific targeted agents (sorafenib and vandetanib). Further research on specific subgroups may be needed to confirm these findings. Topic expert feedback indicated that neither sorafinib nor vandetinib are licensed currently for lung cancer. **Surveillance decision** Topic expert feedback indicated that there is extensive literature building on prognostic and predictive biomarkers. It was considered an emerging area, but with insufficient evidence to result in new recommendations. Further topic expert feedback indicated the need for recommendations on EGFR status testing. These are already available through related diagnostic guidance and technology appraisals. This review question should not be updated.
121 – 14 **Chemotherapy for non-small-cell lung cancer: Effectiveness of chemotherapy as treatment for NSCLC. (1.4.40-1.4.43)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) **Chemotherapy for advanced NSCLC** **Pemetrexed**	**Chemotherapy for advanced NSCLC** **First Line Chemotherapy** A health technology assessment[128] (23 studies,	Topic expert feedback indicated: • The role of maintenance therapy is becoming more important.	New evidence was identified that may change current recommendations. **Combination Chemotherapy**

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
A meta-analysis[125] (4 randomised controlled trials, n=2518) assessed first-line pemetrexed plus cisplatin or carboplatin compared with third-generation drugs plus cisplatin (1 trial) or carboplatin (4 trials) in stage III or IV NSCLC. The third-generation drugs used in comparisons were gemcitabine or docetaxel. The OS was greater with pemetrexed plus platinum, and no significant heterogeneity between studies was noted. In patients with non-squamous disease (defined as adenocarcinoma or large-cell carcinoma, n=1792) the OS benefit of pemetrexed plus platinum was greater than for all NSCLC cancers. The survival benefit was marginally greater when only the pemetrexed plus cisplatin data were analysed. No significant increase in progression-free survival was seen. Pemetrexed plus platinum was associated with significantly less grade 3 and 4 neutropenia and leukopenia, but more nausea compared with other platinum-based chemotherapy. The authors recognised that their results should be interpreted with caution because of the small number of trials and	n>11000), identified as ongoing at the time of CG121 development, evaluated the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic NSCLC. However, the treatments assessed are the subject of several completed or ongoing technology appraisals, and this information will be passed on to the TA team for consideration when the topics undergo the review proposal process. **Pralatrexate** An RCT[129] (n=201) found that pralatrexate demonstrated a trend toward improved OS relative to erlotinib in patients with advanced NSCLC. However, the authors did not report whether the trend was significant. **Pemetrexed** ***First line pemetrexed and cisplatin*** A meta-analysis[128] and an RCT[130] were identified evaluating the use of pemetrexed in the first line treatment of patients with NSCLC. The guideline includes a cross referral to the technology appraisal TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer (September 2009) which is also included in the lung cancer NICE pathway. TA181 has been moved to the static list of technology appraisals. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal	• Concurrent chemotherapy for NSCLC is becoming increasingly important. Published randomised studies include RTOG 0617, SOCCAR both studies are included in this review. • The 2011 update did not include chemotherapy for NSCLC due to uncertainty about the results of multiple technology appraisals. A section on chemotherapy for NSCLC would make the guideline more complete. This should include first, second line and maintenance indications. • New combination therapies have emerged. No studies were cited. • Pralataxate is not licensed for use in lung cancer in the UK. It has EMEA orphan drug status for some cancers but not lung cancer. • Generic versions of gemcitabine and vinorelbine are available following UK patent expiry. • Ombrabulin is not licensed in the UK for lung cancer. It is an EMEA orphan drug for	New evidence was identified that may change current recommendations CG121 recommends (1.4.41) combination chemotherapy for advanced NSCLC using a third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (cisplatin or carboplatin). Dosing regimens are not specified. A single third-generation drug may be used for people unable to tolerate combination chemotherapy (1.4.42). The new evidence from the Evidence Update suggests that gemcitabine plus paclitaxel may have similar efficacy to and lower toxicity than combination chemotherapy including a platinum-based drug. This was considered to have a potential impact on CG121 for patients who are unable to tolerate platinum-based combination chemotherapy. New RCT evidence also suggests that cisplatin-based chemotherapy is not superior to a platinum-free regimen (ifosfamide-gemcitabine) in advanced NSCLC, which may also potentially impact on recommendation 1.4.42. New systematic review evidence indicates that platinum based doublet chemotherapy may be superior to a single agent therapy, including third-generation cytotoxic drugs, for elderly patients with advanced NSCLC,

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
patients included in the meta-analysis. The new evidence indicating that OS is greater in people with non-squamous NSCLC was considered by the Evidence Update to be consistent with NICE TA181. **Combination chemotherapy** A meta-analysis[126] examined 5 randomised trials (n=940) of paclitaxel-based chemotherapy regimens given once weekly compared with standard 3-weekly dosing in NSCLC. Studied regimens were paclitaxel in combination with carboplatin, or gemcitabine or carboplatin plus cetuximab. No significant differences were found in OS or PFS. Adverse events were not reported uniformly, but the most commonly reported were haematological toxicities, fever and peripheral neuropathy. No significant difference in treatment-related deaths was seen. The authors noted that weekly chemotherapy may be useful for older patients with comorbidities and functional status for whom standard 3-weekly chemotherapy would not be suitable. Current guidance does not include dosing schedules, so this evidence was	process. ***Second line pemetrexed*** Seven RCTs[131-137] and one meta-analysis[138] were identified evaluating the use of pemetrexed in the second line treatment of patients with NSCLC. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA124 Pemetrexed for the treatment of non-small-cell lung cancer (August 2007), which is also included in the lung cancer NICE pathway. TA124 has been moved to the static list of technology appraisals as it is recognised that the availability of new data was unlikely to change the 'not recommended' guidance of TA124. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. **Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin** The PARAMOUNT RCT[139] and 3 secondary analyses[140-142] of this trial were identified evaluating the use of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin in the first line treatment of patients with NSCLC. However, guidance in this area can be found in the technology appraisal TA309: Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung	soft tissue sarcoma • Nedaplatin is not licensed in the UK. • Linifanib is not licensed for lung cancer in the UK.	in terms of OS, time to progression, 1 year survival rate, and overall response rate. This is consistent with the guideline for patients able to tolerate combination chemotherapy. New economic analysis evidence indicates that after chemotherapy drug patent expiry in 2013, gemcitabine plus vinorelbine became the least costly regimen compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced NSCLC patients. There is a potential impact on recommendation 1.4.41 due to changes in health economics for chemotherapy. An update to this section of the guideline would potentially need to encompass health economic modelling. New systematic review evidence indicates that docetaxel-based doublet therapy may be superior to docetaxel monotherapy as a second-line treatment for advanced NSCLC, in terms of OS, ORR and DCR. This has a potential impact on recommendation 1.4.43, which states that docetaxel monotherapy should be considered if second-line treatment is appropriate. New systematic review evidence, which is unlikely to impact on guideline recommendations, indicates that cisplatin plus docetaxel may be superior to cisplatin

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
considered unlikely to impact CG121. A meta-analysis[127] examined 4 trials (n=2186) of gemcitabine plus paclitaxel compared with carboplatin plus gemcitabine or carboplatin plus paclitaxel. Gemcitabine plus paclitaxel did not significantly affect 1-year survival. Grade 3–4 neutropenia, anaemia and thrombocytopenia were lower with gemcitabine plus paclitaxel. This evidence suggests that gemcitabine plus paclitaxel may have similar efficacy to and lower toxicity than combination chemotherapy including a platinum-based drug. This was considered by the Evidence Update to have a potential impact on NICE CG121 for patients who are unable to tolerate platinum-based combination chemotherapy.	cancer (April 2014), which is not mentioned in the guideline but is included in the lung cancer NICE pathway. **Gemcitabine** A meta-analysis[143] (6 studies, n=867) found that fixed dose rate (FDR) infusion of gemcitabine had equal ORR and 1-year survival rate with standard infusion in patients with advanced NSCLC, while FDR infusion was associated with more grade 3/4 haematological and non-haematological toxicities. **Combination chemotherapy** A health technology assessment[128] (23 studies, n>11000) found that vinorelbine was not cost-effective in any comparison in the first line treatment of NSCLC. However, the number of studies relating to vinorelbine was not reported in the abstract. An economic analysis[144] of an RCT of gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced NSCLC found that gemcitabine/vinorelbine was the most expensive regimen but with the lowest toxicity costs. Diagnostic and administration costs did not differ significantly among regimens. By 2013, after chemotherapy drug patent expiry, gemcitabine/vinorelbine became the least costly regimen. The study was conducted in Canadian health care setting. An RCT[145] (n=444) found that vinorelbine and		plus vinorelbine in terms of response rate and 2 year survival rate in advanced NSCLC, with less frequent adverse events, but the 1 year survival rates appear comparable between the two regimens. New RCT evidence, which may require further research to impact on guideline recommendations, suggests that for first line treatment of NSCLC: • Two commonly used regimens of docetaxel/cisplatin and paclitaxel/carboplatin may result in similar PFS and OS outcomes. • Paclitaxel-loaded polymeric micelle in combination with cisplatin appears to be well tolerated, with a non-inferior response rate to that of paclitaxel plus cisplatin. • Vinorelbine and gemcitabine vs vinorelbine and carboplatin are similar in terms of OS. Vinorelbine and gemcitabine may have a slightly better toxicity profile. • Oral vinorelbine and cisplatin may have similar disease control rate, response rates and PFS and OS as with pemetrexed and cisplatin. • Docetaxel/cisplatin dosages of 75/60 and 60/60 mg/m2 may result in similar response rates, indicating non-inferiority of the lower dose with an accompanying better safety profile.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	gemcitabine vs vinorelbine and carboplatin as first-line treatment of advanced NSCLC yielded similar OS. Vinorelbine and gemcitabine had slightly better toxity profile. Infections, health related quality of life (HRQoL) and the use of radiotherapy did not differ significantly between the treatment groups. A systematic review[146] (9 studies, n=1886) found that cisplatin plus docetaxel was significantly superior to cisplatin plus vinorelbine in terms of response rate and 2 year survival rate in advanced NSCLC, with less frequent adverse events, but the 1 year survival rates were comparable between the two regimens. An RCT[147] (n=153) found that oral vinorelbine and cisplatin had similar disease control rate, response rates and PFS and OS as with pemetrexed and cisplatin. Statistical significance was not reported in the abstract. A meta-analysis[148] (10 studies n=2510) found that doublet chemotherapy therapy was superior to a single third-generation cytotoxic agent for elderly patients with advanced NSCLC, in terms of OS, time to progression, 1 year survival rate, and overall response rate. More incidences of grade 3 or 4 anaemia, thrombocytopenia, and neurotoxicity were observed in the doublet combination group. With respect to grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhoea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups.		• Carboplatin-S-1 appears to be non-inferior to carboplatin-paclitaxel, regardless of tumour histology. • In elderly patients, nab-paclitaxel in combination with carboplatin as first-line therapy appears to be well tolerated and may improve the ORR and PFS, with significantly longer OS versus solvent-based paclitaxel. • Adding ombrabulin to a taxane-platinum regimen may not significantly improve PFS. • Combination chemotherapy with carboplatin and pemetrexed may improve survival in patients with an Eastern Cooperative Oncology Group performance status of 2. • Nedaplatin concomitant with other chemotherapy response rates and survival with fewer advers effects. CG121 advises (1.4.41) that either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. Further research may be needed to establish nedaplatin as an alternative. Nedaplatin is not licensed in the UK currently. **Chemotherapy for advanced NSCLC** CG121 recommends chemotherapy for stage III and IV NSCLC in people with good performance status to improve survival,

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Subgroup analysis favoured platinum-based doublet therapy. A meta-analysis[149] (7 studies, n=2219) found that combination chemotherapy, particularly platinum or non-platinum, was more effective than single-agent therapy for treating elderly advanced NSCLC patients, in terms of overall response rate, and was more tolerable. An RCT[150] (n=693) found that cisplatin-based chemotherapy is not superior to a platinum-free regimen (ifosfamide-gemcitabine) in advanced NSCLC, in terms of OS. Toxicity was also found to be favourable in the platinum free regimen. A meta-analysis[151] (12 studies, n=2680) found that docetaxel-based doublet therapy was superior to docetaxel monotherapy as a second-line treatment for advanced NSCLC, in terms of OS, ORR and DCR. A higher incidence of grade 3 or 4 diarrhoea and thrombocytopenia was observed in docetaxel-based doublet therapy. An RCT[152] (n=100) found that two commonly used regimens of Docetaxel/Cisplatin and Paclitaxel/Carboplatin showed statistically similar outcomes in terms of PFS and OS. An RCT[153] (n=306) found that the addition of cediranib 20mg daily to carboplatin/paclitaxel chemotherapy increased response rate and toxicity, but not PFS or OS. An RCT[154] (n=276) found that paclitaxel-loaded polymeric micelle in combination with cisplatin was		disease control and quality of life. The new evidence identified in the Evidence Update is consistent with the recommendation in CG121 to offer chemotherapy in advanced NSCLC to improve survival, disease control and quality of life. **Gemcitabine** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that fixed dose rate infusion of gemcitabine is comparable to standard infusion in patients with advanced NSCLC, but with greater toxicity. This is unlikely to impact on the guideline, which does not stipulate either fixed or standard infusion. The licensed dose in NSCLC is 1250 mg/m2, given by 30 minute intravenous infusion, on days 1 and 8 of each 21 day cycle. Dosage reduction with each cycle or within a cycle may be applied, based upon the amount of toxicity experienced by the patient. **Triplet therapy** New evidence is unlikely to impact on guideline recommendations. New RCT evidence suggests that: The addition of a third chemotherapy agent, ifosfamide, to a standard gemcitabine-

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	well tolerated, and its response rate was noninferior to that of paclitaxel plus cisplatin in patients with advanced NSCLC and who were chemo naive. Paclitaxel-loaded polymeric micelle has circumvented many of the infusion-related difficulties associated with standard solvent-based paclitaxel. A meta-analysis[155] (14 studies, n=6922) found that, compared with chemotherapy alone, combination targeted therapy and chemotherapy significantly increased response rates and PFS, but did not improve OS and was more toxic. A meta-analysis[156] (11 studies, n=607) found that NSCLC patients who relapsed after a first-line platinum-based chemotherapy obtained a significantly higher tumour response from a platinum rechallenge containing pemetrexed or taxane combinations. Taxane combinations resulted in a higher response rate and median PFS than pemetrexed combinations, but OS was similar. An RCT[157] (n=132) found that docetaxel/cisplatin dosages of 75/60 and 60/60 mg/m^2 for the treatment of NSCLC were similar response rates, indicating non-inferiority of the lower dose. The rate and incidence of grade 3-4 neutropenia were significantly higher in the 75/60 group, indicating a better safety profile for the lower dose. An RCT[158] (n=126) of docetaxel-cisplatin combination with weekly docetaxel alone in elderly		based doublet may not improve treatment outcome. Pemetrexed plus carboplatin followed by pemetrexed may result in similar outcomes to paclitaxel plus carboplatin plus bevacizumab followed by bevacizumab, but with differing drug related adverse events. There appear to be differing adverse effects with both interventions. New RCT evidence suggests that linifanib with carboplatin and paclitaxel as first-line therapy of advanced nonsquamous NSCLC may improve PFS but not OS and further research may be needed to establish the trade-off between benefits and increased toxicity. Linifanib is not licensed for lung cancer in the UK. Further research may be needed on triplet therapies to establish effectiveness. **Surveillance decision** This review question should be updated, including a review of first, second line and maintenance indications.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	patients with advanced NSCLC was terminated due to interaction between age and subgroup and treatment arm, which suggested that docetaxel may not represent an adequate control arm regimen for the age subgroup of 70-74. An updated analysis[159] of an RCT found non-inferiority of carboplatin-S-1 compared with carboplatin-paclitaxel for first-line treatment of advanced NSCLC, regardless of tumour histology. An RCT[160] (n=1052) found that in elderly NSCLC patients, nab-paclitaxel in combination with carboplatin as first-line therapy was well tolerated and improved the ORR and PFS, with significantly longer OS versus solvent-based paclitaxel. An RCT[161] (n=176) found that adding ombrabulin to a taxane-platinum regimen for first-line treatment of metastatic NSCLC did not significantly improve PFS. ***Nedaplatin*** A RCT[162] (n=619) found that nedaplatin concomitant with other chemotherapy resulted in significantly higher ORR and DCR than cisplatin concomitant with other chemotherapy, in addition to significantly longer OS. The rates of decreased haemoglobin and increased creatinine, nausea and vomiting were significantly lower in the nedaplatin group. However, the RCT was described as retrospective, which limits the strength of the findings. ***Aflibercept***		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	An RCT[163] (n=913) evaluated the addition of (ziv-) aflibercept, a recombinant human fusion protein targeting the VEGF pathway, to standard docetaxel therapy finding no improvement in OS. In exploratory analyses, secondary efficacy end points did seem to be improved in the (ziv-) aflibercept arm. The study regimen was associated with increased toxicities, consistent with known anti-VEGF and chemotherapy-induced events. ***Triplet Therapy*** An RCT[164] (n=433) compared triplet versus doublet combination chemotherapy, with or without cisplatin, in the first-line treatment of stage IIIB-IV NSCLC patients. Results showed a small but significant difference in OS between vinorelbine and cisplatin. The results also indicated that the addition of a third chemotherapy agent, ifosfamide, to a standard gemcitabine-based doublet did not improve treatment outcome. Two RCTs[165,166] (n=361, n=939) compared the efficacy and safety of the following regimens in patients with NSCLC: • pemetrexed plus carboplatin followed by pemetrexed (Pem+Cb) • paclitaxel plus carboplatin plus bevacizumab followed by bevacizumab (Pac+Cb+Bev) PFS, OS, ORR, and DCR did not differ significantly between the arms. Significantly more drug-related grade 3/4 anaemia and thrombocytopenia were reported for Pem+Cb. Significantly more grade 3/4		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	neutropenia, grade 1/2 alopecia, and grade 1/2 sensory neuropathy were reported for Pac+Cb+Bev. An RCT[167] (n=138) found that linifanib with carboplatin and paclitaxel as first-line therapy of advanced nonsquamous NSCLC significantly improved PFS but not OS, and resulted in increased toxicity reflective of known VEGF/PDGF inhibitory effects. An RCT[168] (n=205) found that combination chemotherapy with carboplatin and pemetrexed significantly improved survival in patients with advanced NSCLC and an Eastern Cooperative Oncology Group performance status of 2.		
Treatment of SCLC; First-line treatment for limited-stage disease small-cell lung cancer			
121 – 15 **Assessing patients with small-cell lung cancer (1.4.44)** This chapter of the guideline has no review questions associated with it in the evidence review document.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
121 – 16 **What is the most effective first line treatment for patients with limited disease small cell lung cancer? (1.4.45-1.4.47)**			
2-year Evidence Update (2012) No relevant evidence identified.	**Early versus late concurrent chemoradiotherapy** An RCT[169] (n=222) found that in LD-SCLC thoracic	Topic expert feedback highlighted that Irinotecan is not licensed for lung cancer in the	**Early versus late concurrent chemoradiotherapy** New evidence was identified that may

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	radiotherapy starting in the third cycle of chemotherapy was noninferior to early thoracic radiotherapy in terms of the complete response rate, OS and PFS, and had a more favourable profile with regard to neutropenic fever. A meta-analysis[170] (3 studies) found no significant differences in the 1-, 2-, 3- and 5-year survival rates between early and late concurrent thoracic radiotherapy with etoposide and cisplatin/carboplatin chemotherapy for LD-SCLC patients. The total incidence of grade 3-4 adverse events, including anaemia, leukopenia, neutropenia, thrombocytopenia, nausea and vomiting, infection, esophageal toxicity, pulmonary toxicity, alopecia and hemorrhage with early concurrent thoracic radiotherapy was significantly higher compared to that with late concurrent thoracic radiotherapy. **Etoposide and cisplatin versus irinotecan and cisplatin** An RCT[171] (n=281) found similar OS between etoposide and cisplatin versus irinotecan and cisplatin in patients with limited disease SCLC (LD-SCLC) treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy.	UK. Topic expert feedback indicated that in current clinical practice, thoracic radiotherapy is usually started in the second cycle of chemotherapy for patients with limited disease SCLC. Further topic expert feedback indicated that the timing of starting thoracic radiotherapy may not be as significant as the evidence suggests. Topic expert feedback indicated that it would be sensible to await the results of the CONVERT trial, which is evaluating once vs twice daily radiotherapy, to update this related aspect of dosing regimen.	change current recommendations CG121 recommendation 1.4.46 advises starting radiotherapy during the first or second cycle of chemotherapy for patients with limited-stage disease SCLC. New systematic review and RCT evidence indicates that thoracic radiotherapy starting in the third cycle of chemotherapy, or after the first 30 days, was noninferior to early thoracic radiotherapy in terms of the complete response rate, OS and PFS, and had a more favourable adverse effect profile. **Etoposide and cisplatin versus irinotecan and cisplatin** New evidence is consistent with guideline recommendations New RCT evidence indicated similar OS between etoposide and cisplatin versus irinotecan and cisplatin following induction etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy. This is consistent with recommendation 1.4.45, with etoposide being the standard combination drug with cisplatin-based chemotherapy. **Surveillance decision** The collective evidence and clinical feedback indicates that the review question

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			should be updated. This review question should be updated, potentially following publication of the results of the CONVERT trial. Both the timing of starting thoracic radiotherapy and its daily dosing schedule should be considered. The surveillance team will track the findings of the CONVERT trial.
121 – 17 **How effective is surgical treatment for patients with small cell lung cancer? (1.4.48)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Treatment of SCLC; First-line treatment for extensive-stage disease small-cell lung cancer			
121 – 18 **What is the most effective regimen of chemotherapy for patients with extensive stage disease small cell lung cancer? (1.4.49-1.4.51)**			
2-year Evidence Update (2012) **Topotecan** NICE TA184 recommends oral topotecan as an option in people with relapsed SCLC for whom re-treatment with the first-line regimen is not appropriate and for whom the combination of cyclophosphamide, doxorubicin and vincristine is contraindicated. Intravenous topotecan is not recommended. Irinotecan is not mentioned for SCLC in	**Thoracic radiotherapy following chemotherapy** An RCT[183] (n=498) found that for patients with extensive stage SCLC, thoracic radiotherapy in addition to prophylactic cranial irradiation (PCI) following any response to chemotherapy resulted in no significant difference in the primary endpoint of 1 year OS. However, in a secondary analysis, 2-year OS, progression and 6 month PFS were significantly different in favour of thoracic radiotherapy in addition to prophylactic cranial	Topic expert feedback highlighted new evidence on palliative consolidation thoracic radiotherapy. An RCT[183] was cited and is included in the decision matrix. The feedback indicated that this is a very important area and good radiotherapy probably improves both symptoms and intermediate survival rates, so should be	**Thoracic radiotherapy following chemotherapy** New evidence was identified that may change recommendations. Recommendation 1.4.51 advises that for patients with extensive-stage disease SCLC, thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
CG121, which recommends platinum-based combination chemotherapy for extensive-stage SCLC, but does not specify the particular drugs to use. At the time of publication of this Evidence Update irinotecan did not have marketing authorisation in the UK for the treatment of lung cancer, and topotecan did not have marketing authorisation in the UK for first-line treatment of SCLC. A systematic review and meta-analysis[172] of camptothecins (topotecan and irinotecan) plus platinum drugs compared with etoposide plus platinum drugs as first-line treatment of extensive disease SCLC. 8 studies (n=3086) were identified: 6 used irinotecan and two used topotecan. Tests for interaction showed significant differences between the efficacy of topotecan and irinotecan, so these regimens were analysed separately. Irinotecan was associated with significantly greater OS than etoposide. This relates to an absolute OS benefit of 1–2 months, based on expected OS of 8–10 months for etoposide-based regimens. Topotecan did not show a significant increase in OS compared with etoposide. Irinotecan was associated with more	irradiation. There were no severe toxic effects. **Chemotherapy** An updated systematic review[173] (5 studies) investigated both the effectiveness of first-line chemotherapy at diagnosis and the effectiveness of second-line chemotherapy at relapse or progression after first-line chemotherapy compared with best supportive care or placebo in prolonging survival. Two of the five included studies suggested that first-line chemotherapeutic treatment (based on ifosfamide) may provide a small survival benefit (less than three months) in comparison with supportive care or placebo infusion in patients with advanced SCLC. ***Topoisomerase inhibitors*** An RCT[174] (n=140) found that sequential administration of topoisomerase inhibitors did not significantly improve overall response rate, PFS or OS of standard platinum-doublet chemotherapy for extensive-stage SCLC. ***Topotecan in combination with chemotherapy*** An RCT[175] (n=795) compared efficacy and safety of topotecan-cisplatin versus topotecan-etoposide versus cisplatin-etoposide in chemo-naive ED-SCLC. Topotecan-cisplatin was found to be noninferior to cisplatin-etoposide in OS and superior in time to progression and overall response rates, but had worse toxicity. ***Lobaplatin plus Etoposide*** An RCT[176] (n=62) found that lobaplatin plus	considered for inclusion in a future update. Topic expert feedback highlighted that the following are not licensed for lung cancer in the UK: • Topotecan-cisplatin • Topotecan-etoposide • Lobaplatin • Amrubicin plus cisplatin (EMEA orphan drug status for small-cell lung cancer, not a marketing authorization) • Obatoclax • Ipilimumab • Picoplatin (this has EMEA orphan drug status for SCLC but not a marketing authorisation) • Aflibercept • Amrubicin (this has EMEA orphan drug status for SCLC but not a marketing authorisation)	the thorax. The new RCT evidence suggests that thoracic radiotherapy following any response to four to six cycles of standard chemotherapy may improve 2 year OS and 6 month PFS. There is therefore a potential impact on recommendation 1.4.51, to extend the thoracic radiotherapy to patients with any response to chemotherapy. **Chemotherapy** New evidence is unlikely to impact on guideline recommendations. Platinum-based combination chemotherapy regimens have been shown to increase complete response rates when compared to non-platinum chemotherapy regimens with no significant difference in survival, and so these are currently the standard first-line treatment for patients with SCLC. CG121 recommends platinum-based combination chemotherapy for extensive-stage SCLC, but does not specify the particular drugs to use, so the new evidence for irinotecan, amrubicin, lobaplatin plus etoposide, and phased ipilimumab is not likely to have an impact on current guidance. New evidence does not support the use of the following drug treatments for the first line treatment of SCLC:

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
grade 3–4 diarrhoea but less grade 3–4 haematological toxicity than etoposide. Toxicities associated with topotecan were heterogeneous so meta-analysis was not done. NICE CG121 recommends platinum-based combination chemotherapy for extensive-stage SCLC, but does not specify the particular drugs to use, so the evidence for irinotecan is not likely to have an impact on current guidance. NICE TA184 recommends topotecan for some patients with relapsed SCLC; the evidence suggests no benefit as first-line treatment, which is also unlikely to have an impact on guidance.	etoposide was non-inferior to a cisplatin plus etoposide regimen in treatment response. Outcomes reported were ORR, DCR, PFS and adverse events. ***Amrubicin plus cisplatin*** An RCT[177] (n=284) found that amrubicin plus cisplatin was inferior to irinotecan plus cisplatin in the treatment of extensive-disease SCLC in terms of OS, PFS but did have a non-significantly higher response rate. **Obatoclax** An RCT[178] (n=155) found that obatoclax was well tolerated when added to carboplatin/etoposide in the first-line treatment of ES-SCLC, but failed to significantly improve ORR, PFS, or OS. **rh-endostatin (Endostar)** An RCT[179] (n=140) found that the addition of rh-endostatin (Endostar) to first-line standard etoposide and carboplatin for the treatment of extensive-stage SCLC had an acceptable toxicity profile, but did not improve OS, PFS, and ORR. **Ipilimumab** An RCT[180] (n=130) found that phased ipilimumab, but not concurrent ipilimumab, significantly improved immune related PFS versus control in SCLC patients. No improvement in PFS or OS was observed. **Bevacizumab** An RCT[181] (n=147) found that administering		• endostar • topoisomerase inhibitors • obatoclax • ifosfamide plus etoposide plus platinum • bevacizumab in combination with chemotherapy NICE TA184 recommends topotecan for some patients with relapsed SCLC; the evidence suggests no benefit as first-line treatment as monotherapy or in combination with chemotherapy, which is also unlikely to have an impact on guidance as topotecan is not licensed for first line treatment. The impact of first-line chemotherapy on quality of life and on the sub-populations of older patients, women and patients with poor prognosis is unclear. Further research will be assessed at the next surveillance review to evaluate the trade-offs between benefits and risks of different chemotherapeutic schedules. **Surveillance decision** **Thoracic radiotherapy following chemotherapy** Topic expert feedback stated that the RCT provides good evidence and oncologists are already adopting this approach.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	bevacizumab after induction chemotherapy did not improve survival outcomes in extensive SCLC patients. **Triplet therapy** A meta-analysis[182] (4 studies n=447) compared the efficacy and safety of ifosfamide plus etoposide plus platinum to that of etoposide plus platinum in patients with previously untreated SCLC. There were no significant differences in overall response, 1 or 2 year survival rate. Ifosfamide plus etoposide plus platinum resulted in a significantly higher incidence of grade 3/4 neutropenia and grade 3/4 vomiting.		However, additional topic expert feedback raised concern over the emphasis placed on this single RCT. This review question should be updated.
121 – 19 **Maintenance treatment for small-cell lung cancer (1.4.52)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	A meta-analysis[184] (14 studies, n=1806) found that maintenance chemotherapy failed to improve survival outcomes of 1 year mortality, OS or PFS in patients with SCLC. However, a significant advantage in terms of PFS was observed for maintenance chemotherapy in patients with extensive disease. An RCT[185] (n=95) found that chemotherapy with maintenance sunitinib was safe and significantly improved PFS in extensive-stage SCLC.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG121 recommends offering maintenance treatment to patients with SCLC only in the context of a clinical trial. The new systematic review evidence does not support the use of maintenance therapy for SCLC for most outcomes, although it may improve PFS in patients with extensive SCLC. New RCT evidence suggests that maintenance sunitinib may improve PFS in extensive-stage SCLC, although further

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			studies may be necessary to confirm the findings. **Surveillance decision** This review question should not be updated.
Treatment of SCLC; Second-line treatment for patients with small-cell lung cancer that has relapsed after first-line treatment			
121 – 20 **Which group(s) of patients with small cell lung cancer are suitable for second line treatment? (1.4.55-1.4.56)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
121 – 21 **Effectiveness of chemotherapy for SCLC (1.4.57)** This chapter of the guideline has no review questions associated with it in the evidence review document.			
2-year Evidence Update (2012) No relevant evidence identified.	An updated systematic review[173] (5 studies) investigated both the effectiveness of first-line chemotherapy at diagnosis and the effectiveness of second-line chemotherapy at relapse or progression after first-line chemotherapy compared with BSC or placebo in prolonging survival for extensive SCLC. Across the 3 included studies covering second line treatment, second-line chemotherapy at relapse or progression (methotrexate-doxorubicin, topotecan, or picoplatin versus symptomatic treatment or BSC) was found	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The limited new evidence on second line chemotherapy, emphasised by an updated Cochrane systematic review, is consistent with recommendation 1.4.56. This states that patients whose disease has not responded to first-line treatment should be advised that there is very limited evidence that second-line chemotherapy will be of benefit.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	to prolong survival for some weeks in relation to BSC. **Topetican in combination Ziv-aflibercept** An RCT[186] (n=189) found that addition of combination therapy to weekly topotecan improved the 3-month PFS in patients who had platinum-refractory SCLC, but its addition increased toxicity. OS was similar with combined ziv-aflibercept and topotecan compared with topotecan. **Amrubicin** An RCT[187] (n=637) found that amrubicin did not improve survival when compared with topotecan in the second-line treatment of patients with SCLC. OS did not differ significantly between treatment groups, although a significant improvement in OS was noted in patients with refractory disease treated with amrubicin. An RCT[188] (n=131) found that second-line oral chemotherapy (lomustine, cyclophosphamide, etoposide) was non-inferior to intravenous therapy (cyclophosphamide, doxorubicin, and vincristine) in patients with relapsed SCLC. However, the statistical significance was not reported in the abstract. A meta-analysis[189] (21 studies, n=1692) found that second-line chemotherapy resulted in significantly superior response rate and OS for patients with chemosensitive disease compared to patients with refractory disease.		Patients with chemosensitive disease appear more likely to benefit than patients with refractory disease. For second line treatment, the new RCT evidence does not support: • Topetican in combination Ziv-aflibercept. • Amrubicin. • Oral chemotherapy (lomustine, cyclophosphamide, etoposide) over intravenous chemotherapy. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Palliative interventions and Supportive and Palliative Care			
121 – 22 **Providing palliative care (1.5.1-1.5.2)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	**Early Palliative care** A qualitative analysis[190] (n=20) was conducted on data from an RCT of patients with newly diagnosed metastatic NSCLC who received early palliative care (PC) integrated with standard oncologic care vs standard oncologic care alone. The results showed that addressing symptoms and coping were the most prevalent components of the PC clinic visits. Initial visits focused on building relationships and rapport with patients and their families and on illness understanding, including prognostic awareness. Discussions about resuscitation preferences and hospice predominantly occurred during later visits. Comparing PC and oncologic care visits around critical time points, both included discussions about symptoms and illness status; however, PC visits emphasised psychosocial elements, such as coping, whereas oncologic care visits focused on cancer treatment and management of medical complications.	Topic expert feedback noted that although the evidence base on early palliative care is from the USA funding is available for similar research in UK.	New evidence is unlikely to impact on guideline recommendations. **Early Palliative care** For provision of supportive and palliative care, CG121 cross refers to Improving supportive and palliative care for adults with cancer (2004) NICE Guideline CSGSP. Recommendation 1.5.2 also states that patients who may benefit from specialist palliative care services should be identified and referred without delay. Qualitative evidence provided via clinical feedback is consistent with the provision of early palliative care. **Surveillance decision** This review question should not be updated.
121 – 23 **Palliative radiotherapy (1.5.3)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012)	**Palliative radiotherapy**	None identified relevant to this	New evidence is unlikely to impact on

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
No relevant evidence identified.	A meta-analysis[191] (5 studies n=1730) found that higher dose (>30 Gy) and lower dose (<30 Gy) radiotherapy provided similar symptom palliation of symptoms and survival in patients with locally advanced lung cancer. An updated meta-analysis[192] (14 studies, n=3576) assessed the effects of different palliative radiotherapy regimens on improving thoracic symptoms in patients with locally advanced or metastatic NSCLC. It also assessed the effects of radiotherapy dose on OS in patients with locally advanced or metastatic non-small cell lung cancer who are not suitable for radical RT given with curative intent. No new studies were identified in the update. The results showed no significant difference in 1-year OS between regimens with fewer radiotherapy fractions compared with regimens with more when patients were stratified by performance status. The results of the meta-analysis of 1-year OS for patients with good performance status (WHO performance status 0-1) showed moderately high heterogeneity and a summary result was not thought meaningful. The results of 1-year OS for patients with poor performance status was non-significant. An RCT[193] (n=191) found that palliative chemoradiation was statistically superior to chemotherapy alone with respect to OS, one year survival and HRQoL, but at the expense of more hospital admissions due to significant toxicity. A subset analysis[194] (n=188) of this RCT found that	question.	guideline recommendations. Recommendation 1.5.3 states that patients who cannot be offered curative treatment, and are candidates for palliative radiotherapy, may either be observed until symptoms arise and then treated, or be treated with palliative radiotherapy immediately. The new systematic review evidence did not favour any specific dose or regimen of radiotherapy for palliation of symptoms, and is unlikely to affect recommendation 1.5.3. The new RCT evidence is insufficient to support palliative chemoradiation currently, due to potential additional harm. Any further studies will be assessed at the next surveillance review to establish more definitive evidence. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	in patients with poor prognosis and inoperable locally advanced non-small-cell lung cancer, large tumour size (>7cm) was not a negative predictive factor and OS and 1 year survival were significantly improved by palliative chemoradiotherapy.		
121 – 24 **Managing endobronchial obstruction: How effective are brachytherapy/(airway) stenting/photodynamic therapy/laser/electrocautery/cryotherapy/(surgical) debulking (via ridig bronchoscope) for treatment of patients with lung cancer with endobronchial obstructions? (1.5.4-1.5.6)**			
2-year Evidence Update (2012) **Cryotherapy** A meta-analysis[195] of 16 studies (n=2355) compared cryotherapy with other treatments including laser therapy, electrocauterisation, brachytherapy, stent insertion and photodynamic therapy to treat airway obstruction in lung or bronchial tumours. One study was a comparative observational study, the rest were case studies. No pooling or meta-analysis of results was undertaken; however, the authors concluded that endoscopic cryotherapy generally showed treatment success in about 80% of cases, with variation by operation methods and target patient groups. The new evidence was considered in the Evidence Update to support the efficacy of cryotherapy and was considered	An updated systematic review[196] (14 studies, n=953) assessed the effectiveness of palliative endobronchial brachytherapy (EBB) compared with external beam radiation therapy (EBRT) or other alternative endoluminal treatments in controlling thoracic symptoms and increasing survival in patients with advanced NSCLC. The systematic review found that the evidence did not provide conclusive results that EBB plus EBRT improved symptom relief over EBRT alone. For the primary endpoint of survival there was no evidence of benefit for EBB compared to EBRT and Nd-YAG laser or for the combination of EBB with chemotherapy. No significant differences were found for fatal hemoptysis as an adverse event of EBB.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG121 recommends (1.5.5) external beam radiotherapy, endobronchial debulking, or stenting as palliative interventions in patients with impending endobronchial obstruction. **Cryotherapy** New evidence is unlikely to impact on guideline recommendations. NICE interventional procedures guidance (IPG) 142 recommends cryotherapy as an option for treating endobronchial obstruction, but stresses that clinicians should ensure that patients know that this intervention is one of several available treatment options. The new evidence supports the efficacy of cryotherapy and is not likely to have an impact on current guidance, because this intervention is currently available as a

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
unlikely to have an impact on current guidance, because this intervention is currently available as a treatment option.			treatment option. **Palliative endobronchial brachytherapy** New evidence is unlikely to impact on guideline recommendations. Updated Cochrane systematic review evidence on palliative endobronchial brachytherapy (EBB) compared with external beam radiation therapy (EBRT) or other alternative endoluminal treatments in controlling thoracic symptoms and increasing survival in patients with advanced NSCLC is inconclusive. This is unlikely to impact on recommendation 1.5.5. **Surveillance decision** This review question should not be updated.
121 – 25 **Other Palliative Treatments (1.5.7-1.5.14)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
121 – 26 **How effective is treatment in the management of brain metastases in lung cancer patients? (1.4.53-1.4.54, 1.5.15-1.5.16)** Prophylactic cranial irradiation in NSCLC Prophylactic cranial irradiation in SCLC			
2-year Evidence Update (2012) No relevant evidence identified.	NICE has been commissioned to develop a guideline on primary brain tumours and cerebral metastases, which may overlap with this question. The provisional publication date is 11/7/18. ***PCI in NSCLC*** A secondary analysis[197] of two RCTs found that PCI was associated with a higher risk of decline in self-reported cognitive functioning at 6 and 12 months in patients with locally advanced NSCLC. Decline on Hopkins Verbal learning test (HVLT)-Recall at 6 and 12 months was also associated with PCI but was not closely correlated with decline in self-reported cognitive functioning at the same time points. A meta-analysis[198] (12 studies, n=1718) found that PCI reduced the risk of BM as compared with non-PCI in NSCLC patients. However, OS was significantly superior longer in non-PCI patients. ***PCI in SCLC*** A meta-analysis[199] (12 studies, n=1547) found that PCI decreased brain metastases incidence and improved 1, 3 and 5 year survival in SCLC patients. **Combination treatment**	Topic expert feedback highlighted that enzastaurin is not licensed for lung cancer in the UK.	**Prophylactic cranial irradiation** New evidence is unlikely to impact on guideline recommendations. The new evidence is consistent with recommendations 1.4.53 and 1.4.54 which advise offering prophylactic cranial irradiation to patients with SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment. **Whole brain radiotherapy plus stereotactic radiosurgery** New evidence is unlikely to impact on guideline recommendations. Recommendation 1.5.16 advises that palliative whole-brain radiotherapy should be considered for patients with symptomatic brain metastases with good performance status (WHO 0 or 1). New evidence indicates a potential benefit in treatment response rates from WBRT plus chemotherapy but at the expense of adverse effects in patients with NSCLC. This is unlikely to impact on the guideline

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Whole brain radiotherapy (WBRT) plus chemotherapy Two meta-analyses[200,201] (19 studies, n=1343 and 6 studies, n=910) found that the combination of chemotherapy plus WBRT in patients with brain metastases originating from NSCLC increased treatment response rates of brain metastases, but resulted in significantly higher incidences of adverse effects. Larger scale trials were recommended by the authors. An RCT[202] (n=126) found that the addition of temozolomide or erlotinib to WBRT and stereotactic radiosurgery in NSCLC patients with 1 to 3 brain metastases did not improve survival and had greater toxicity. However, the trial was underpowered and the findings require confirmation by larger studies. ***Whole brain radiotherapy plus stereotactic radiosurgery*** A secondary analysis[203] (n=331) of an RCT found that WBRT plus stereotactic radiosurgery showed no OS improvement. However, in patients with high graded prognostic assessment (3.5-4), there was a survival advantage regardless of the presence of 1, 2, or 3 brain metastases. This benefit did not extend to patients with lower graded prognostic assessment. The number of lung cancer patients in the study was 211, but the type of lung cancer was not reported in the abstract. ***Combination chemotherapy***		and any further, larger scale trials will be considered at next surveillance review. **Whole brain radiotherapy plus stereotactic radiosurgery** New evidence is unlikely to impact on guideline recommendations. Evidence does not support the addition of WBRT plus stereotactic radiosurgery. A potential survival advantage in the subset of patients with high graded prognostic assessment may need to be confirmed by further research. **Combination chemotherapy** New evidence is unlikely to impact on guideline recommendations. There is insufficient evidence to judge the effectiveness and safety of single agent or combination chemotherapy for the treatment of brain metastases from SCLC. **Enzastaurin** New evidence is unlikely to impact on guideline recommendations. Evidence does not support the use of enzastaurin following whole brain radiotherapy, in slowing the time to progression of brain metastases. **EGFR-TKI therapy** New evidence is unlikely to impact on

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	A systematic review[204] (3 studies n=192) found insufficient evidence to judge the effectiveness and safety of single agent or combination chemotherapy for the treatment of brain metastases from SCLC. No significant differences for OS were reported in any of the trials. While the first trial reported no significant difference in PFS, the second RCT found a significant difference favouring combined therapy group. The second trial also found that patients receiving chemoradiotherapy (teniposide plus whole brain radiotherapy) had a higher complete response rate than those receiving only the topoisomerase inhibitor. ***Surgery versus stereotactic radiosurgery*** A systematic review[205] (18 studies, n=713) found that there was no significant difference in median survival time or OS between patients treated with neurosurgery or stereotactic radiosurgery for single brain metastases in NSCLC. However, the statistical significance was not reported in the abstract. **EGFR-TKI therapy** A meta-analysis[206] (16 studies, n=464) found that EGFR-TKIs significantly increased ORR and DCR in NSCLC patients with brain metastases, particularly in those patients harbouring EGFR mutations who experienced significantly longer PFS and OS. **Enzastaurin**		guideline recommendations. The new systematic review evidence, based on small trials, suggests that EGFR-TKIs are an effective treatment for NSCLC patients with brain metastases, particularly in those patients harbouring EGFR mutations. However, larger trials may be required to confirm the findings to establish any impact on the guideline. **Surgery** New evidence is unlikely to impact on guideline recommendations. New evidence does not favour either neurosurgery or stereotactic radiosurgery for single brain metastasis from NSCLC and is unlikely to impact on the guideline, which does not make any specific recommendations for surgery. **Surveillance decision** This review question should not be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	An RCT[207] (n=107) found that enzastaurin was well tolerated but did not improve time to progression of brain metastases, ORR, OS, PFS, or HRQoL after WBRT in lung cancer patients with brain metastases.		
121 – 27 **Hypercalcaemia, bone pain and pathological fractures (1.5.17)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	**Prevention of skeletal related events** ***Bisphosphonates*** A meta-analysis[208] (12 studies, n=1767) assessed the efficacy of bisphosphonates in preventing skeletal related events (SREs), controlling pain, and OS in patients with bone metastases from lung cancer. Patients treated with zoledronic acid and chemotherapy had fewer SREs than those receiving chemotherapy alone. Pain control improved when a bisphosphonate was added to another treatment modality (chemotherapy or radiotherapy). Bisphosphonate therapy improved survival compared to controls, but the difference failed to reach statistical significance. An RCT[209] (n=180) of NSCLC patients with asymptomatic bone metastases found that zoledronic acid (ZA) alone, strontium-89 alone or both in combination significantly extended time to first skeletal related event and reduced the annual incidence of SREs. OS increased with the combination group and ZA monotherapy, but not with strontium-89 alone, but the statistical	Topic expert feedback highlighted the following MHRA drug safety updates: • Bisphosphonates: atypical femoral fractures • Bisphosphonates: osteonecrosis of the jaw • Bisphosphonates: atrial fibrillation • Denosumab (Xgeva, Prolia): intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk • Denosumab: updated recommendations • Denosumab 60 mg (Prolia) Denosumab: monitoring recommended • Update Intravenous zoledronic acid: adverse	**Prevention of skeletal related events** ***Bisphosphonates*** New evidence is unlikely to impact on guideline recommendations. CG121 does not make recommendations on the use of bisphosphonates, and did not update this section from the CG24 guideline, which concluded that the effect of bisphosphonates in the relief of pain and skeletal morbidity from bone metastasis in lung cancer needs further research. New systematic review evidence suggests that zoledronic acid and chemotherapy may be superior to chemotherapy alone in preventing skeletal related events, and that pain control may improve when a bisphosphonate is added to chemotherapy or radiotherapy. Strontium-89 alone or in combination with zoledronic acid may also extend time to first skeletal related event, but further research may be required to confirm this. The collective evidence

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	significance was not reported in the abstract for this outcome. **Denosumab** A secondary analysis[210] was identified evaluating the use of denosumab in the treatment of patients with NSCLC. However, guidance in this area can be found in the technology appraisal TA265 Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012), which is also included in the lung cancer NICE pathway. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.	effects on renal function Topic expert feedback highlighted that zoledronic acid is not licensed for prevention of skeletal related events in cancer in the UK.	suggests that OS does not improve significantly with bisphosphonates. It is unlikely that the totality of evidence is sufficient to impact on the guideline and further studies will be assessed at the next surveillance review. **Surveillance decision** This review question should not be updated.
121 – 28 **Managing other symptoms: weight loss, loss of appetite, difficulty swallowing, fatigue and depression (1.5.18)** This chapter of the guideline has no review questions associated with it in the **evidence review document**.			
2-year Evidence Update (2012) No relevant evidence identified.	**Nausea and vomiting** ***Aprepitant*** An RCT[211] (n=134) found that triple antiemetic therapy with aprepitant, a 5-HT(3) receptor antagonist, and dexamethasone improved the control of chemotherapy induced nausea and vomiting prevention in NSCLC patients receiving carboplatin and pemetrexed chemotherapy. **Pain** ***Gabapentin*** An RCT[212] (n=104) found no evidence for the superiority of gabapentin over placebo for the	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG121 does not make recommendations for specific interventions but advises (1.5.18) that other symptoms should be managed by multidisciplinary groups that include supportive and palliative care professionals. New RCT evidence, which may require verification by further research, indicates that: • Aprepitant and dexamethasone may improve the control of chemotherapy

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	treatment of acute pain following thoracotomy or for the prevention of persistent post-thoracotomy pain in patients with pulmonary malignancies. **Pulmonary function** ***Breathing exercises*** A meta-analysis[213] (8 studies, n=398) found that breathing exercises significantly improved post-operative pulmonary function and quality of life in patients with lung cancer. The main outcomes, all showing significant improvements, were forced expiratory volume, ability of self-care in daily life, social activities, symptoms of depression and symptoms of anxiety. **Exercise** An RCT[214] (n=131) of a combined hospital plus home exercise programme following curative surgery for NSCLC showed no significant differences in physical activity between the groups 4 weeks after surgery, nor in quality of life outcomes. A meta-analysis[215] (3 studies, n=178) examined the effects of exercise training on exercise capacity in people following lung resection (with or without chemotherapy) for NSCLC. On completion of the intervention period, exercise capacity as measured by the six-minute walk distance was statistically greater in the intervention group compared to the control group. No between-group differences were observed in HRQoL.		induced nausea and vomiting in NSCLC patients. • Diet plus an oral nutritional supplement containing EPA significantly improved energy and protein intake, body composition and decreased fatigue, loss of appetite and neuropathy in patients with NSCLC. • Modafinil may have no effect on cancer-related fatigue in adults with advanced NSCLC. • Gabapentin does not appear to be effective for the treatment of acute pain following thoracotomy in lung cancer patients. • Integrated depression care may improve depression severity in lung cancer patients. New systematic review evidence indicates that breathing exercises may improve post-operative pulmonary function and quality of life in patients with lung cancer, but larger trials may be required to confirm this finding and any potential impact on the guideline. **Exercise Training** New evidence is unlikely to impact on guideline recommendations. CG121 does not make specific recommendations relating to exercise training. Limited new evidence suggesting benefits of exercise training following lung

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Fatigue An RCT[216] (n=92) found that diet plus an oral nutritional supplement containing eicosapentaenoic acid significantly improved energy and protein intake, body composition and decreased fatigue, loss of appetite and neuropathy in patients with NSCLC. An RCT[217] (n=208) found that modafinil had no effect on cancer-related fatigue in adults with advanced NSCLC. **Depression** An RCT[218] (n=142) found that average depression severity was significantly lower in lung cancer patients allocated to integrated depression care. Self-rated depression improvement, anxiety, quality of life, role functioning, perceived quality of care, and proportion of patients achieving a 12-week treatment response were also reported as significantly better in the depression care for people with lung cancer group than in the usual care group, although statistical data was not reported for these outcomes in the abstract.		resection is unlikely to impact on the guideline. **Surveillance decision** This review question should not be updated.
Follow up and patient perspectives			
121 – 29 **What is the most effective follow-up model for lung cancer patients? (1.6.1-1.6.4)**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			updated.
Areas not currently covered in the guideline			
NQ – 01 What is the effectiveness of targeted therapies for NSCLC?			
2-year Evidence Update (2012) **Epidermal growth factor-targeted therapies** 'Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer' (NICE TA258) recommended erlotinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if: they test positive for the epidermal growth factor receptor tyrosine kinase mutation and the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012). Although the Evidence Update found new evidence in this area[219], commentary was not provided because the technology appraisal had been recently issued to be referred to as the latest guidance. A NICE multiple technology appraisal of erlotinib and gefitinib in second-line treatment of lung cancer is currently underway. Although the Evidence Update found new evidence in this area[219,220],	**Vaccines** An RCT[225] (n=176) examined switch maintenance therapy with racotumomab-alum vaccine in advanced NSCLC patients. Vaccinated patients had significantly better overall and PFS compared to placebo. The most common adverse events in the racotumomab-alum arm were burning and pain at the injection site, bone pain, and asthenia, but the frequency was not reported in the abstract. **Antiangiogenic agents** A meta-analysis[226] (13 studies, n=8358) found that the addition of antiangiogenic agents to the standard treatments provided significant improvements in OS in the second line treatment of NSCLC patients who failed their first-line therapy. Subgroup analysis showed that OS benefit was presented only in patients treated with docetaxel plus antiangiogenic agents and patients with non-squamous NSCLC. A meta-analysis[227] (33 studies, n=17 396) found that, compared with non-angiogenesis inhibitors, angiogenesis inhibitors resulted in significant improvement in PFS, OS, ORR and DCR. The AEs associated with angiogenesis inhibitors were reported as generally predictable and manageable.	Topic expert feedback indicated that: • There are many new therapies available and new indications have been identified since publication of the guideline. These include crizotinib, gefitinib, afatinib and nintedanib. • Immunotherapy was highlighted as an emerging area. • Biological treatments represent a rapidly changing area and pathological testing in relation to this is increasingly important. No specific studies were cited. • Bevacizumab is licensed, in addition to platinum-based chemotherapy, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. • Ramucirumab is not licensed	**Targeted therapies** New evidence was identified that may change current recommendations. There are no recommendations on new cytotoxic or biologically targeted agents, which were either not licensed for use in the UK during development of CG121 or were undergoing NICE technology appraisals. There may be a need to establish a new area in the guideline with cross referrals to relevant technology appraisals: TA258: erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer TA162: erlotinib for the treatment of non-small-cell lung cancer [ID44] Lung cancer (non-small-cell, advanced or metastatic maintenance treatment) - erlotinib (in combination with bevacizumab) TA310: Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer TA347: Nintedanib for previously treated

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
commentary was not provided because a technology appraisal (ID620) was in progress. This technology appraisal combines reviews of two existing technology appraisals: 'Erlotinib for the treatment of non-small-cell lung cancer' (NICE TA162), which should be referred to as the latest guidance until the new guidance is issued; and 'Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer' (NICE TA175), which was terminated because no evidence submission was received from the manufacturer or sponsor of the technology. Although the Evidence Update found new evidence on cetuximab in advanced lung cancer[221], commentary was not provided because a NICE single technology appraisal of cetuximab in advanced lung cancer had recently been suspended. **Bevacizumab** Bevacizumab was not evaluated for CG121. A NICE technology appraisal (TA148) of bevacizumab for first-line treatment of locally advanced or metastatic lung cancer was terminated because the manufacturer decided not to launch or promote bevacizumab in this indication; however, bevacizumab has	**Tyrosine kinase inhibitors** ***EGFR targeted therapy in combination with chemotherapy*** A meta-analysis[155] (14 studies, n=6922) found that, compared with chemotherapy alone, combination targeted therapy and chemotherapy (pemetrexed or docetaxel) significantly increased response rates and PFS, but did not improve OS and was more toxic. A meta-analysis[228] (6 studies, n=3337) found that chemotherapy plus multitargeted antiangiogenic TKI was found to have specific advantages over chemotherapy alone in terms of PFS and ORR, but not in OS. The toxicity was comparable between the two therapies. A meta-analysis[229] (15 studies n=11456) found that in patients with advanced NSCLC, the OS was positively correlated with the percentage of patients treated with both platinum-based chemotherapy and EGFR-TKIs. The correlation was significant in the trials in Asian populations but was not statistically significant in the trials in predominantly Caucasian populations. The reason for this phenomenon was not reported in the abstract. A meta-analysis[230] (8 studies n=3363) and an RCT[231] found a significant improvement in PFS when erlotinib plus platinum-based chemotherapy was used compared with platinum-based chemotherapy alone in advanced NSCLC. The	for lung cancer in the UK. New drugs online reports it is in P3 trials in the UK for NSCLC with a possible launch date of 2016. • MHRA drug safety update (2012) has been issued: Epidermal growth factor receptor (EGFR) inhibitors: serious cases of keratitis and ulcerative keratitis • MHRA Drug safety update (2011) Bevacizumab and sunitinib: risk of osteonecrosis of the jaw • Herbal extract elemene injection is not on the MHRA list of banned herbal products or those granted registration. • The erlotinib summary of product characteristics does not include an indication for use with bevacizumab at the moment. The TA was suspended because this indication was not being sought. However, new drugs online states that a licence for erlotinib plus bevacizumab has been applied for in EU – possible indication Q3 2016. • The following drugs are not	locally advanced, metastatic, or locally recurrent non-small-cell lung cancer TA296: Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene TA181/190/192/227/258, Lung cancer (NSC, first line and maintenance treatment) - pemetrexed, gefitinib and erlotinib (combined review). The Evidence Update and current surveillance review include evidence and topic expert feedback in the following areas. ***Vaccines*** New evidence is unlikely to impact on guideline recommendations. New RCT evidence suggests that switch maintenance therapy with racotumomab-alum vaccine in advanced NSCLC patients may result in better OS and PFS, but further research may be needed to confirm the findings and the extent of adverse effects. ***Antiangiogenic agents*** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that, compared with non-angiogenesis inhibitors, angiogenesis inhibitors may improve PFS, OS, ORR and DCR, with

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
marketing authorisation for this indication in the UK. A systematic review and meta-analysis[222] compared bevacizumab plus chemotherapy with chemotherapy alone as first-line treatment for locally advanced or metastatic non-small cell lung cancer. 4 studies (n=2200) of bevacizumab 7.5 mg/kg or 15 mg/kg plus chemotherapy with carboplatin and paclitaxel or cisplatin and gemcitabine were included. In the fixed effects meta-analysis, the progression-free survival was significantlyhigher in those receiving bevacizumab 7.5 mg/kg, and 15 mg/kg compared with chemotherapy alone. OS was also significantly greater in the group receiving the higher dose of bevacizumab but not the lower dose. A random effects model was used because of moderate heterogeneity between studies. The progression-free survival was higher in those receiving bevacizumab 7.5 mg/kg, and 15 mg/kg compared with chemotherapy alone. OS was not significantly different. No absolute data were reported for any outcome. Bevacizumab was associated with	effect on OS and other outcomes was not reported in the abstracts. The significance of adverse effects was not reported in the abstracts. ***EGFR targeted therapy alone versus chemotherapy alone*** Two meta-analyses[107, 108] were identified comparing chemotherapy and EGFR-TKIs in the second-line treatment of NSCLC. However, guidance on the EGFR inhibitors covered in the two meta-analyses, erlotinib and gefitinib, is the subject of an ongoing technology appraisal – [ID620] Lung cancer (non-small cell) - erlotinib & gefitinib (post chemotherapy) (rev TA162, TA175) This information will be passed onto the TA team for consideration. ***Motesanib*** The MONET RCT[232] (n=1090) found that motesanib plus carboplatin/paclitaxel did not significantly improve OS over carboplatin/paclitaxel alone in patients with advanced nonsquamous NSCLC or in the adenocarcinoma subset. The trial was terminated due to failure to meet the primary endpoint of overall survival. A subgroup analysis[233] of the squamous cohort in the MONET1 RCT (n=360) found that first line therapy with motesanib (a small-molecule inhibitor of vascular endothelial growth factor receptors) plus carboplatin/paclitaxel had unacceptable toxicity compared with carboplatin/paclitaxel alone	licensed in the UK for lung cancer: – Cediranib – Aflibercept – Racotumomab-alum vaccine – Motesanib – Sorafenib – Axitinib – Dinaciclib – Pazopanib – Iniparib – Vandetinib – Trametinib – Dacomitinib (undergoing phase 3 trials) – Figitumumab (this drug has been discontinued) – Conatumumab – Survivin inhibitor LY218130 – Endostar – Melatonin – Sunitinib – Eribulin – Figitumumab	manageable adverse effects. Further studies may be needed to explore the predictive biomarkers to identify who may gain utmost benefit from anti-angiogenic therapy, including TKIs and monoclonal antibodies. Further evidence on these classes of biological therapies is summarised below. ***Tyrosine kinase inhibitors*** ***EGFR targeted therapy in combination with chemotherapy*** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that chemotherapy plus multitargeted antiangiogenic TKIs may have specific advantages over chemotherapy alone in terms of PFS and ORR, but not in OS. The toxicity appears comparable between the two therapies. New systematic review evidence also indicated that in patients with advanced NSCLC, platinum-based or docetaxel based chemotherapy in combination with EGFR-TKIs may improve OS in Asian patients but not in Caucasian patients, although the cause of this population specific effect is unclear. Additional systematic review and RCT evidence suggests that erlotinib plus

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
greater toxicity than chemotherapy alone including neutropenia and hypertension. Additionally, bevacizumab 15 mg/kg was associated with more haemoptysis, proteinuria, vomiting, rash or desquamation and bleeding events. Another systematic review and meta-analysis[223] looked at the same trials with the addition of a small study (n=81) of second-line treatment. The drug combinations were therefore as reported above for the overlapping studies, and for second-line chemotherapy docetaxel or pemetrexed were used alone or in combination with bevacizumab. OS was significantly higher in the bevacizumab group. When first-line treatment only was analysed, the results were not significant, similar to the results of the random effects model reported in the first systematic review[222]. However, the second systematic review also estimated the absolute survival benefit as a median of 26 days. The progression-free survival was significantly greater for people treated with bevacizumab. The absolute benefit of bevacizumab was 1.4 months of progression-free survival, assuming 4 months of progression-free survival for	in patients with advanced NSCLC. Median OS was similar between groups. A subset analysis[234] (n=227) of MONET1 of Asian patients found that motesanib plus carboplatin/paclitaxel significantly improved OS, PFS, and ORR versus placebo plus carboplatin/paclitaxel. Grade>3 adverse events were more common in the motesanib plus carboplatin/paclitaxel group. ***Axitinib*** An RCT[235] (n=170) found that axitinib in combination with pemetrexed/cisplatin was generally well tolerated. Axitinib combinations resulted in non-significant differences in PFS and numerically higher ORR compared with chemotherapy alone in advanced NSCLC. ***Gefitinib*** Two RCTs[236,237] and one meta-analysis[238] were identified on the use of gefitinib with or without chemotherapy for NSCLC patients. However, guidance on gefitinib is the subject of an ongoing technology appraisal - [ID6881]. This information will be passed onto the TA team for consideration. An RCT[239] (n=503) found that adjuvant gefitinib did not result in OS or DFS benefits in NSCLC patients with either wild-type tumours or EGFR mutation-positive tumours. ***Iniparib*** An RCT[240] (n=119) found that the addition of iniparib to gemcitabine-cisplatin in metastatic	– Celecoxib – Cetuximab – Onartuzumab – Ramucirumab – Talactoferrin alfa	platinum-based chemotherapy may be superior to platinum-based chemotherapy alone in advanced NSCLC for PFS. However, further research may be needed to elucidate other survival outcomes and adverse effects. ***Motesanib*** New evidence is unlikely to impact on guideline recommendations. motesanib plus carboplatin/paclitaxel may improve OS over carboplatin/paclitaxel alone in Asian patients but not in other subgroups. In all groups the toxicity of motesanib appears unacceptable. Motesanib is not licensed in the UK. ***Aflibercept*** New evidence is unlikely to impact on guideline recommendations. RCT evidence suggests that for patients with advanced NSCLC the addition of (ziv) aflibercept, a recombinant human fusion protein targeting the VEGF pathway, to standard docetaxel therapy may not improve OS, but may improve secondary outcomes. Aflibercept is not licensed for lung cancer in the UK. ***Axitinib*** New evidence is unlikely to impact on guideline recommendations. Axitinib in combination with pemetrexed

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
chemotherapy alone. The toxicities identified as higher in the bevacizumab group included hypertension, bleeding events and febrile neutropenia. Bevacizumab was also associated with an increase in deaths related to treatment, with most deaths in this group attributable to bleeding events, complications of neutropenia, and thromboembolic events. A further meta-analysis[224] of bevacizumab looked specifically at its risk profile, and included the same studies. The relative risk of treatment-related deaths was higher for the bevacizumab 15 mg/kg group but not for the 7.5 mg/kg group compared with control. The authors noted that fatal pulmonary haemorrhage was an important cause of treatment-related death with bevacizumab, but did not provide data to support this statement. Hypertension, bleeding events and neutropenia were again noted to be significantly higher with bevacizumab than with controls, although one of the meta-analyses[224] presented the results by dose of bevacizumab. Only 362 of more than 2000 patients received bevacizumab 7.5 mg/kg, so the results for this dose should be viewed with	NSCLC did not improve ORR over gemcitabine-cisplatin alone. The safety profiles were comparable. ***Erlotinib monotherapy*** Four RCTs[241-244] were identified evaluating the use of erlotinib in the first line treatment of patients with NSCLC. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA258: erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. (June 2012). TA258 has been moved to the static list of technology appraisals and is included in the lung cancer NICE pathway. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. Five meta-analyses[245-249], two RCTs[250,251] and two secondary analyses[252,253] of RCTs were identified evaluating the use of erlotinib monotherapy in the second line treatment of patients with NSCLC. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA162: erlotinib for the treatment of non-small-cell lung cancer. (November 2008), and is included in the lung cancer NICE pathway ***Erlotinib combination therapy*** An RCT[254] (n=124) found that the combination of erlotinib with bevacizumab in unselected first-line advanced non-squamous NSCLC compared with		and cisplatin appears to be non-inferior to chemotherapy alone in advanced NSCLC, in survival outcomes and toxicity. ***Iniparib*** New evidence is unlikely to impact on guideline recommendations. The addition of iniparib to gemcitabine-cisplatin in metastatic NSCLC may not improve ORR over gemcitabine-cisplatin alone. The safety profiles appear comparable. ***Cediranib*** New evidence is unlikely to impact on guideline recommendations. The addition of cediranib 20mg daily to carboplatin/paclitaxel chemotherapy may increase response rate and toxicity, but not PFS or OS. Cediranib is not licensed in the UK for lung cancer. ***Erlotinib combination therapy*** New evidence is unlikely to impact on guideline recommendations Evidence does not support the combination of erlotinib with bevacizumab in unselected first-line advanced non-squamous NSCLC compared with chemotherapy plus bevacizumab, because it was not beneficial in terms of PFS. For the second line treatment of NSCLC

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
caution. These three studies show broad agreement in their conclusions that bevacizumab is associated with a slight increase in progression-free survival and little to no increase in OS, but that the adverse effects of treatment are significant. This evidence was considered unlikely to have any impact on NICE CG121, which did not evaluate bevacizumab in lung cancer.	chemotherapy plus bevacizumab was not beneficial in terms of PFS. ***Erlotinib second line combination therapy*** One RCT[255] was identified evaluating the use of erlotinib with bevacizumab in the maintenance treatment of patients with NSCLC. However, guidance on Erlotinib with bevacizumab was the subject of a suspended technology appraisal - [ID44] Lung cancer (non-small-cell, advanced or metastatic maintenance treatment) - erlotinib (in combination with bevacizumab). This information will be passed onto the TA team for consideration. An RCT[256] (n=133) found that everolimus plus erlotinib in combination was not sufficiently efficacious for the second line treatment of NSCLC patients and resulted in a high occurrence of adverse events. An RCT[257] (n=132) found that the addition of sunitinib to erlotinib as second line treatment did not significantly improve PFS in patients with advanced, platinum-pre-treated NSCLC. An RCT[258] (n=123) found that second line treatment with an intercalated combination of eribulin and erlotinib did not appear to improve treatment outcome in NSCLC patients previously treated with platinum-based chemotherapies. A meta-analysis[259] (5 studies n=2100) found that combination therapy with erlotinib plus another targeted agent significantly improved objective response rate and disease control rate, but not OS,		patients, evidence does not support: • The combination of everolimus plus erlotinib. • The combination of sunitinib and erlotinib. • An intercalated combination of eribulin and erlotinib. • Figitumumab in combination with erlotinib versus erlotinib alone. Clinical development of figitumumab has been discontinued. For the second line treatment of NSCLC patients, evidence suggests that: • Combination therapy with erlotinib plus another targeted agent may improve objective response rate and disease control rate, but not OS, without significant increase in frequency or severity of adverse events. • Combination pemetrexed and erlotinib treatment may improve PFS, OS and time to treatment failure but appears to result in increased grade 3/4 toxicities compared with pemetrexed alone. Further research may be needed to establish definitive conclusions on effectiveness. ***Erlotinib Maintenance therapy*** New evidence is unlikely to impact on guideline recommendations. New RCT evidence indicates that for

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	and induced no significant increase in frequency or severity of adverse events in patients with advanced NSCLC. An RCT[260] (n=583) found that figitumumab in combination with erlotinib versus erlotinib alone did not improve OS in patients with advanced, pre-treated, nonadenocarcinoma NSCLC. Clinical development of figitumumab has been discontinued. An RCT[261] (n=165) found that second line combination pemetrexed and erlotinib treatment significantly improved PFS, OS and time to treatment failure in 2nd line non-squamous NSCLC and was associated with an increase in grade 3/4 toxicities compared with pemetrexed alone. An RCT[262] (n=240) compared pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous NSCLC. Pemetrexed-erlotinib significantly improved PFS compared to either drug alone in this clinically selected population. However, safety analyses showed a higher incidence of drug-related grade 3/4 toxicity in pemetrexed-erlotinib than in pemetrexed or erlotinib, the majority being neutropenia, anaemia, rash and diarrhoea. An RCT[263] (n=464) investigated whether continuation maintenance with gemcitabine or switch maintenance with erlotinib improves clinical outcome compared with observation in patients		patients with advanced NSCLC whose disease was controlled after cisplatin-gemcitabine induction chemotherapy, continuation maintenance therapy of gemcitabine or switch maintenance with erlotinib do not appear to significantly improve clinical outcome compared with observation. ***Vascular endothelial growth factor receptor tyrosine kinase inhibitors*** ***Sorafenib*** New evidence is unlikely to impact on guideline recommendations. New evidence does not support the use of first or second line sorafenib, either as monotherapy or in combination with first line chemotherapy or EGFR-TKIs, and suggests that it increases the risk of mortality. ***Combined inhibition therapy*** New evidence is unlikely to impact on guideline recommendations. New evidence does not support the use of combined inhibition therapy (VEGFR and EGFR) in unselected patients with advanced NSCLC, although it may improve ORR and PFS in certain subgroups. Further research may be needed to establish more definitive conclusions. ***Dinaciclib***

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	with advanced NSCLC whose disease was controlled after cisplatin-gemcitabine induction chemotherapy. Both maintenance strategies resulted in a nonsignificant improvement in OS; patients who received second-line pemetrexed or with a performance status of 0 appeared to derive greater benefit. ***Combined VEGFR and EGFR therapy*** A meta-analysis[264] found no evidence to support the use of combined inhibition therapy (VEGFR and EGFR) in unselected patients with advanced NSCLC, based on non-significant OS. Subgroup analysis revealed that combined inhibition therapy using combination regimens was associated with statistically significant improvement in both ORR and PFS. Toxicity was greater in combined inhibition therapy. ***Afatinib*** Four RCTs[265-268] were identified evaluating the use of afatinib in the first line treatment of patients with NSCLC. However, guidance on afatinib can be found in the technology appraisal TA310: Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (April 2014), which is not mentioned in the guideline but is included in the lung cancer NICE pathway. This information will be passed on to the TA team for consideration when the topics undergo the review proposal process.		New evidence is unlikely to impact on guideline recommendations. New RCT evidence suggests that intravenous dinaciclib is non-superior to erlotinib as second line monotherapy. ***Pazopanib*** New evidence is unlikely to impact on guideline recommendations. RCT evidence suggests that for patients with advanced NSCLC that the combination of pazopanib and pemetrexed in first-line treatment of NSCLC shows some antitumour activity but may have unacceptable levels of toxicity. ***Celecoxib*** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that celecoxib may be beneficial in the treatment of NSCLC in terms of ORR but with increased risk of cardiovascular events. However, further research may be needed on NSCLC population to confirm the benefits. ***Vandetanib*** New evidence is unlikely to impact on guideline recommendations. New RCT evidence suggests that vandetanib plus gemcitabine may increase

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Pazopanib An RCT[269] found that the combination of pazopanib and pemetrexed in first-line treatment of NSCLC showed some antitumour activity but had unacceptable levels of toxicity. ***Sorafenib*** A secondary analysis[270] of an RCT (n=105) found that the observed disease control rate with second line treatment with sorafenib was higher in patients with wild-type EGFR than in patients with EGFR mutation, and in patients with EGFR gene copy number gain (FISH-positive) versus FISH-negative patients. Increased expression of fibroblast growth factor-1, NF-kappaB, and hypoxia pathways were identified potential drivers of sorafenib resistance. A meta-analysis[271] (41 studies, n=14139) found a significantly increased risk of death due to vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) in NSCLC patients. In particular, sorafenib and sunitinib had significant risk of death when compared with control arms. Combination treatment of VEGFR-TKIs with antineoplastic agents also significantly increased the risk of treatment-related deaths. A meta-analysis[272] (6 studies, n=2748) found that sorafinib based first or second line therapy, including monotherapy or in combination with chemotherapy or EGFR-TKI therapy, was not associated with significantly superior DCR,PFS or OS. However, sorafenib monotherapy was		PFS but not OS in the first-line treatment of elderly advanced NSCLC patients, with comparable adverse events. Further research may be needed to confirm the findings. ***Trametinib*** New evidence is unlikely to impact on guideline recommendations. New RCT evidence suggests that trametinib may be non-inferior to docetaxel in PFS and response rate as in patients with previously treated KRAS-mutant-positive NSCLC. Further research may be needed to confirm the findings and establish the extent of adverse effects. ***Dacomitinib*** New evidence is unlikely to impact on guideline recommendations. New RCT evidence does not support the use of dacomitinib with placebo for the second line treatment of advanced NSCLC. ***Figitumumab*** New evidence is unlikely to impact on guideline recommendations. Evidence does not support the use of figitumumab in addition to standard chemotherapy in patients with advanced nonadenocarcinoma NSCLC as it appears to yield significantly more serious adverse

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	significantly superior to sorafenib free controls in DCR and PFS, but failed to show advantage with regard to OS. Grade 3 or greater sorafenib-related adverse events were observed, although statistical significance was not reported. An RCT[273] (n=904) found that sorafenib added to first-line gemcitabine/cisplatin in patients with advanced nonsquamous NSCLC did not improve OS compared to placebo. A meta-analysis[274] (13 studies n=5546) found a significantly increased risk of fatal adverse events in patients with lung cancer (type and number of patients not specified) associated with sorafenib. The most common causes were hemorrhage and thrombus or embolism. Risk varied with tumour type, but appeared independent of therapy regimen. ***Dacomitinib*** Two RCTs[275,276] were identified on the use of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, in patients with advanced NSCLC. However, guidance on dacomitinib is the subject of an ongoing technology appraisal - [ID7819]. This information will be passed onto the TA team for consideration. ***Dinaciclib*** An RCT[277] found that intravenous dinaciclib was well tolerated but was non-superior to erlotinib as monotherapy in previously treated NSCLC,		events. ***Conatumumab*** New evidence is unlikely to impact on guideline recommendations. Evidence does not support the use of conatumumab combined with paclitaxel-carboplatin as first-line treatment for advanced NSCLC did not improve PFS. ***Ramucirumab*** New evidence is unlikely to impact on guideline recommendations. Evidence does not support the use of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic NSCLC did not improve PFS. ***Survivin inhibitor LY2181308*** New evidence is unlikely to impact on guideline recommendations. RCT evidence suggests that for patients with advanced NSCLC Survivin inhibitor LY2181308 plus docetaxel may not improve tumour size or in progression-free survival. ***Endostar*** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that Endostar combined with chemotherapy

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	measured by time to progression and objective response rate. However, the sample size was not reported in the abstract. ***Celecoxib*** A meta analysis[278] (11 studies n=2570) found that celecoxib was beneficial in the treatment of NSCLC in terms of ORR but with increased risk of cardiovascular events. It should be noted that the number of studies and patients covering lung cancer patients was not stipulated in the abstract. ***Vandetanib*** Three meta-analyses[279-281] and three RCTs[253,282,283] were identified evaluating the use of vandetanib in the second line treatment of patients with NSCLC. However, vandetanib was the subject of a technology appraisal: Lung cancer (non-small-cell, second line treatment) - vandetanib (Suspended in November 2009), which was stated as ongoing in the guideline. This information will be passed onto the TA team for consideration. An RCT[284] (n=124) found that vandetanib plus gemcitabine significantly increased PGS but not OS when compared with gemcitabine plus placebo as first-line treatment of elderly advanced NSCLC patients. The rate of patients with >1 treatment-related adverse event was comparable in the two arms, pyrexia, dyspnea, and neutropenia being the most common adverse events. ***Gefitinib first line treatment*** One meta-analysis[128] and two post hoc		compared with chemotherapy alone could increase the objective response rate and DCR. New RCT evidence suggests that Endostar can also improve OS, but further research may be required to confirm this. ***Melatonin*** New evidence is unlikely to impact on guideline recommendations. Melatonin in combination with chemotherapy does not appear to affect survival and adverse events of advanced patients with NSCLC, but may improve HRQoL, particularly in social well-being. **Herbal extracts** New evidence is unlikely to impact on guideline recommendations. New systematic review evidence indicates that the herbal extract elemene injection may be effective as an adjunctive treatment and in treating malignant pleural effusion in both NSCLC and SCLC patients. However, variable reported trial quality indicates the need for further studies to confirm the findings. New systematic review evidence suggests that traditional Chinese medicinal herbs combined with EGFR-TKIs may increase efficacy and reduce toxicity in advanced NSCLC patients. However, publication bias was detected which indicates that the

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	analyses[285,286] of RCTs were identified evaluating the use of gefitinib in the first line treatment of patients with NSCLC. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (July 2010), which is also included in the lung cancer NICE pathway. TA192 has been moved to the static list of technology appraisals. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. ***Gefitinib second line treatment*** Four RCTs[238,287-289] and two secondary analyses[290,291] of RCTs were identified evaluating the use of gefitinib in the second line treatment of patients with NSCLC. However, gefitinib was the subject of a technology appraisal TA175: Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated July 2009), which was terminated because no evidence submission was received from the manufacturer or sponsor of the technology. This information will be passed onto the TA team for consideration. ***Nintedanib*** One RCT[292] was identified on the use of nintedanib in the treatment of NSCLC. However, guidance on Nintedanib can be found in the technology appraisal TA347: Nintedanib for previously treated		results require verification by further larger trials. ***Immunotherapy*** New evidence is unlikely to impact on guideline recommendations. New evidence does not support the use of oral dendritic cell (DC)-mediated immunotherapy with talactoferrin alfa for NSCLC patients. New evidence also does not support the use of recombinant MAGE-A3 protein combined with an immunostimulant in completely resected MAGE-A3-positive stage IB to II NSCLC. **Surveillance decision** There are no recommendations on new cytotoxic or biologically targeted agents, which were either not licensed for use in the UK during development of CG121 or were undergoing NICE technology appraisals. Topic experts agreed that there is a need to establish a new area in the guideline to incorporate or cross refer to relevant technology appraisals. This review question should be updated.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (July 2015). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. ***Crizotinib first line*** One RCT[293] was identified on the use of crizotinib in the first line treatment of NSCLC. However, guidance on crizotinib is the subject of an ongoing technology appraisal - [ID865]. This information will be passed onto the TA team for consideration. ***Crizotinib second line*** Two RCTs[294,295] were identified evaluating the use of crizotinib in the second line treatment of patients with NSCLC. However, guidance in this area can be found in the technology appraisal TA296: Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (September 2013), which is also included in the lung cancer NICE pathway. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. ***Trametinib*** An RCT[296] (n=129) found that trametinib showed similar PFS and a response rate as docetaxel in patients with previously treated KRAS-mutant-positive NSCLC. The most frequent adverse events in over 20% of trametinib patients were rash, diarrhoea, nausea, vomiting, and fatigue. The		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	most frequent grade 3 treatment-related AEs in the trametinib arm were hypertension, rash, diarrhoea, and asthenia. ***Dacomitinib second line treatment*** An RCT[297] (n=480) compared dacomitinib with placebo for the second line treatment of advanced or metastatic NSCLC. Dacomitinib did not increase OS, the primary outcome. **Monoclonal antibodies** ***Cetuximab*** A meta-analysis[298] and an RCT[299] were identified evaluating the use of cetuximab in the second line treatment of patients with NSCLC. However, cetuximab was the subject of a technology appraisal: [ID9] Lung cancer (non-small-cell) - cetuximab (Suspended in September 2012), which was stated as ongoing in the guideline. This information will be passed onto the TA team for consideration. ***Onartuzumab*** An RCT[300] was identified evaluating the use of onartuzumab in the treatment of patients with NSCLC. However, guidance on onartuzumab is the subject of an ongoing technology appraisal - [ID7022]. This information will be passed onto the TA team for consideration. ***Bevacizumab*** A systematic review[301] and 2 meta-analyses[302,303] and 3 RCTs[115,304,305] were identified evaluating the		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	use of bevacizumab in the first and second line treatment of patients with NSCLC. However, bevacizumab was the subject of a terminated technology appraisal TA148: Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal) (terminated June 2008). This information will be passed onto the TA team for consideration. ***Figitumumab*** An RCT[306] (n=681) found that adding figitumumab to standard chemotherapy did not increase OS in patients with advanced nonadenocarcinoma NSCLC and yielded significantly more serious adverse events. ***Conatumumab*** An RCT[307] (n=172) found that conatumumab combined with paclitaxel-carboplatin (PC) as first-line treatment for advanced NSCLC did not improve PFS. ***Ramucirumab*** An RCT[308] found that ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic NSCLC did not improve PFS. An RCT[309] was identified evaluating the use of ramucirumab plus docetaxel in the second line treatment of patients with NSCLC. However, guidance on ramucirumab is the subject of an ongoing technology appraisal – ID838 Lung cancer (non-small cell, metastatic) - ramucirumab (with docetaxel, after platinum chemotherapy). This		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	information will be passed onto the TA team for consideration when the topic undergoes the review proposal process. **Survivin inhibitor LY2181308** An RCT[310] (n=162) found that survivin inhibitor LY2181308 plus docetaxel did not produce any significant difference in tumour size or in progression-free survival. **rh-endostatin (Endostar)** An RCT[311] (n=486) found that the addition of endostar to an platinum-based chemotherapy regimen resulted in a significant improvement in OS, overall response rate and time to progression, with non-significant differences in adverse effects. It should be noted that the effect size for OS was not reported in the abstract. A meta-analysis[312] (14 studies) found that endostar combined with chemotherapy compared with chemotherapy alone significantly increased the objective response rate and DCR. No statistical difference was found in incidence of grade III-IV granulocytopenia risk. Nausea and vomiting and grade III-IV alopecia. Survival data and comparative data on other adverse events were not reported in the abstract. **Melatonin** An RCT[313] (n=unreported) found that melatonin in combination with chemotherapy did not affect survival and adverse events of advanced patients		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	with NSCLC, but did improve HRQoL scores, with a slightly significantly better score being found in social well-being. **Herbal extracts** A meta-analysis[314] (14 studies n=1298) found found a significantly higher objective response rate (ORR) for the herbal extract elemene intrathoracic injection in the treatment of lung cancer patients with malignant pleural effusion, compared with other drug groups. The subgroup analysis by comparator drug demonstrated that elemene was significantly superior to cisplatin in ORR, but equivalent to bleomycin and interleukin-2. A meta-analysis[315] (4 studies, n=1467) found that beta-elemene injection as an adjunctive treatment for NSCLC or SCLC was effective in terms of performance status, tumour control and response rates. Increases in adverse reactions were non-significant. However the authors noted that the results required confirmation by rigorously designed trials. A meta-analysis[316] (19 studies) found that traditional Chinese medicinal herbs combined with epidermal growth factor receptor tyrosine kinase inhibitor significantly increased efficacy and reduced toxicity in advanced NSCLC patients. However, publication bias was detected and the results require verification by further larger trials. **Immunotherapy** An RCT[317] (n=742) found that oral dendritic cell		

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	(DC)-mediated immunotherapy with talactoferrin alfa did not significantly improve OS or PFS for NSCLC patients. An RCT[318] (n=182) assessed recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) in completely resected MAGE-A3-positive stage IB to II NSCLC. No statistically significant improvement in DFI, DFS, or OS was observed. No significant toxicity was observed.		
NICE priority Research recommendations			
RR – 01 Selection of patients with NSCLC for treatment with curative intent			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. **Surveillance decision** This research recommendation should be removed from the NICE version of the

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			guideline and the NICE research recommendations database.
RR – 02 **Effectiveness of surgery with or without multimodality treatment in N2 disease**			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. **Surveillance decision** Clinical feedback indicated that this area does need research and if it is removed from the research recommendations database it may deter others from working on it. This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
RR – 03 Pulmonary rehabilitation, optimisation of drug treatment and enhanced recovery programmes			
2-year Evidence Update (2012) No relevant evidence identified.	**Breathing exercises** A meta-analysis[213] (Liu) (8 studies, n=398) found that breathing exercises significantly improved post-operative pulmonary function and quality of life in patients with lung cancer. The main outcomes, all showing significant improvements, were forced expiratory volume, ability of self-care in daily life, social activities, symptoms of depression and symptoms of anxiety. **Exercise training** An RCT[319] (n=61) found that in patients recently operated for lung cancer, high-intensity endurance and strength training (60 min, three times a week, 20 weeks) was well tolerated and induced clinically significant improvements in peak oxygen uptake, carbon monoxide transfer factor, muscular strength, total muscle mass, functional fitness and HRQoL. **Chest Physiotherapy** An RCT[320] (n=24) found that pulmonary rehabilitation with chest physical therapy reduced serum fibrinogen levels, improved functional parameters, and quality of life of patients with LC and inflammatory lung disease awaiting lung resection.	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New evidence was found that partially answered the research recommendation and it could be useful to wait for additional evidence. Therefore it is proposed to keep this research recommendation. **Surveillance decision** This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.
RR – 04 New regimens for radiotherapy with curative intent			
2-year Evidence Update (2012)	See 121-11	None identified relevant to this	**Proposal on retaining the research**

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
No relevant evidence identified.		question.	**recommendation** This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New evidence was found (See question 121-11) and an update to the guideline is proposed. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. **Surveillance decision** Topic expert feedback stated that this area is probably suitable for further research. This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.
RR – 05 Imaging modalities for monitoring response and recurrent disease			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	**Proposal on retaining the research recommendation** This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. No new relevant evidence has been found since the research recommendation was

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			first made. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. **Surveillance decision** This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.
NICE Research recommendations			
RR – 06 Further research is needed into whether the use of low-dose CT in early diagnosis of patients at high risk of developing lung cancer has an effect on the mortality of lung cancer.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 07 Further research is needed into the symptoms and signs associated with early- and late stage lung cancer and the factors associated with delay in presentation. For patients diagnosed with lung cancer, analysis should be undertaken of the symptoms at presentation, the time between onset of symptoms and presentation, the stage at presentation and the reasons for delay in presentation.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			point.
RR – 08 Evidence that is currently available does not indicate which methods are most effective in helping people to make informed decisions about treatment options. Research comparing different methods of communication is therefore a high priority.			
2-year Evidence Update (2012) No relevant evidence identified.	See 121-03	See 121-03	See 121-03 New evidence is unlikely to impact on guideline recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 09 Consider research into the outcome of treatment of small cell lung cancer with low volume metastases detected by PET-CT.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 10 Consider research into the use of MRI and PET-CT in routine brain imaging prior to treatment with curative intent. Include stratification by stage and other prior imaging modalities.			
2-year Evidence Update (2012) No relevant evidence identified.	An RCT[32] (Yi) (n=143) assessed whether coregistered whole brain (WB) magnetic resonance imaging(MRI)-PET would increase the number of correctly upstaged patients compared with WB	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. Further research may be needed on MRI and PET-CT in routine brain imaging prior

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	PET-computed tomography (PET-CT) plus dedicated brain MRI in patients with NSCLC. Although both staging tools allowed greater than 20% correct upstaging compared with conventional staging methods, coregistered MRI-PET did not appear to help identify significantly more correctly upstaged patients than PET-CT plus brain MRI.		to treatment with curative intent. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 11 Research should be undertaken into the benefits of giving up smoking shortly before surgery. Assess mortality, pulmonary complications, pulmonary function, quality of life (including EQ5D), smoking status after surgery, and survival.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 12 Consider patients suitable for treatment with curative intent for entry into trials of different treatment modalities; include cost effectiveness evaluation.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 13 Consider research into cost effectiveness of different surgical strategies.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision**

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
RR – 14 Research should be conducted into whether NSCLC patients with poor lung function have better survival, morbidity and quality of life when treated with radiotherapy with curative intent alone compared to no treatment or treatment with chemotherapy or chemoradiotherapy.			
2-year Evidence Update (2012) No relevant evidence identified.	See 121-12 Chemoradiotherapy	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG121 does not specify age groups, and new RCT evidence on chemoradiotherapy for NSCLC patients over 70 years old is unlikely to impact on recommendation 1.4.32, which advises that potential benefit in survival should be balanced with the risk of additional toxicities. Further research may be needed on radiotherapy with curative intent alone compared to no treatment or treatment with chemotherapy or chemoradiotherapy. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 15 Research into accelerated radiotherapy fractionations with chemotherapy treatment regimens should be undertaken in patients with NSCLC. Outcomes: mortality, pulmonary complications, pulmonary function, validated quality of life measures. (including EQ5D)			
2-year Evidence Update (2012) A meta-analysis[71] of individual patient data compared hyperfractionated or accelerated radiotherapy (modified radiotherapy) with conventional radiotherapy. A total of 10 studies were included (2 in SCLC and 8 in NSCLC), with 12 comparisons (n=2685). For	See 121-12 Chemoradiotherapy	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
NSCLC, modified radiotherapy was associated with an absolute increase in survival at 3 years and at 5 years. Across trials, the risk of death was significantly reduced. This increase in survival was not significantly different for groups receiving chemotherapy compared with those who did not. CG121 recommends CHART (which is both hyperfractionated and accelerated) for medically inoperable stage I and II NSCLC suitable for radical radiotherapy. The Evidence Update concluded that although this evidence does not directly affect use of CHART, it suggests that modified fractionation is generally better than conventional fractionation.			
RR – 16 Research into combinations of new targeted agents and radiotherapy regimens should be undertaken in patients with NSCLC.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
RR – 17 Research is needed to compare existing adjuvant chemotherapy regimens with newer targeted agents for the treatment of NSCLC. Outcomes: mortality, survival, toxicity.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	Topic expert feedback highlighted that many new therapies are available and new indications identified, since previous lung cancer guideline – e.g,Drugs - Crizotinib, Gefitinib, Afatinib, Nintedanib. Many more drugs are in the immediate pipeline – e.g. Immunotherapies. No studies were cited comparing adjuvant chemotherapy regimens with newer targeted agents.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 18 Consider patients receiving concurrent chemo-radiotherapy treatment for patients with NSCLC for trials of adjuvant, consolidation or maintenance chemotherapy.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 19 Consider trials of prophylactic cranial irradiation in patients with NSCLC.			
2-year Evidence Update (2012) No relevant evidence identified.	A secondary analysis[197] of two RCTs found that PCI was associated with a higher risk of decline in self-reported cognitive functioning at 6 and 12 months in patients with locally advanced NSCLC.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. CG121 does not recommend PCI for prevention or treatment of brain metastases

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	Decline on Hopkins Verbal learning test (HVLT)-Recall at 6 and 12 months was also associated with PCI but was not closely correlated with decline in self-reported cognitive functioning at the same time points. A meta-analysis[198] (12 studies, n=1718) found that PCI reduced the risk of BM as compared with non-PCI in NSCLC patients. However, OS was significantly superior longer in non-PCI patients.		in NSCLC. The new evidence on its effectiveness and adverse effects is inconclusive and is unlikely to impact on the guideline. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 20 Consider trials of radiotherapy in known cerebral metastases incorporating prognostication scores.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 21 The use of surgical resection or stereotactic radiotherapy or radiosurgery in the treatment of cerebral metastasis from a primary lung cancer should be performed in well designed clinical studies or using nationally audited clinical guidelines and considered in patients with good performance status and a low total disease volume at primary or metastatic sites.			
2-year Evidence Update (2012) No relevant evidence identified.	A secondary analysis[203] (n=331) of an RCT found that WBRT plus stereotactic radiosurgery showed no OS improvement. However, in patients with high graded prognostic assessment (3.5-4), there was a survival advantage regardless of the presence of 1, 2, or 3 brain metastases. This benefit did not extend to patients with lower graded prognostic assessment. The number of lung cancer patients in the study was not reported in the abstract.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. Evidence does not support the addition of WBRT plus stereotactic radiosurgery. A potential survival advantage in the subset of patients with high graded prognostic assessment may need to be confirmed by further research. New evidence does not favour either

Conclusions from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	A systematic review[205] (18 studies, n=713) found that there was no significant difference in median survival time or OS between patients treated with neurosurgery or stereotactic radiosurgery for single brain metastases in NSCLC. However, the statistical significance was not reported in the abstract.		neurosurgery or stereotactic radiosurgery for single brain metastasis from NSCLC and is unlikely to impact on the guideline, which does not make any specific recommendations for surgery. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 22 Randomised controlled trials should be conducted examining the value of different follow-up patterns.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 23 The use of prognostic factors to develop risk stratification models to determine the optimal follow-up pattern should be examined as part of large clinical trials.			
2-year Evidence Update (2012) No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Section 1 – References

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