

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of:

TA181: Pemetrexed for the first-line treatment of non-small-cell lung cancer [published September 2009]

TA190: Pemetrexed for the maintenance treatment of non-small-cell lung cancer [published July 2010]

TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer [published July 2010]

TA227: Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer [published June 2011]

TA258: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer [published June 2012]

1. Recommendation

The guidance in TA181, TA190, TA192, TA227 and TA258 should be transferred to the 'static guidance list'. TA192 and TA258 should be flagged for further consideration of a review when the results of the LUX Lung 7 trial are available, currently anticipated to be in 2015. That we consult on this proposal.

2. Original remit(s)

TA181 - To appraise the clinical and cost effectiveness of pemetrexed, within its licensed indications, for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer.

TA190 - To appraise the clinical and cost effectiveness of pemetrexed, within its licensed indications, for maintenance treatment immediately after first-line chemotherapy for non-small cell lung cancer.

TA192 - To appraise the clinical and cost effectiveness of gefitinib, within its licensed indication, for the first-line treatment of locally advanced or metastatic non-small cell lung cancer.

TA227 - To appraise the clinical and cost effectiveness of erlotinib monotherapy within its licensed indication, for the maintenance treatment of non-small cell lung cancer after previous platinum containing chemotherapy

TA258 - To appraise the clinical and cost effectiveness of erlotinib, within its licensed indication, for the first-line treatment of epidermal growth factor receptor (EGFR) tyrosine kinase (TK) mutation positive locally advanced or metastatic non-small-cell lung cancer.

3. Current guidance

TA181

- 1.1. Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.
- 1.2. People who are currently being treated with pemetrexed for NSCLC but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

TA190

- 1.1. Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

TA192

- 1.1. Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:
 - they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**
 - the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

TA227

- 1.1. Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy.
- 1.2. People currently receiving erlotinib monotherapy for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

TA258

- 1.1. Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:
- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**
 - the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).

4. Rationale¹

An independent Health Technology Assessment report has been published on first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer undertaken by the Liverpool Reviews and Implementation Group. The results were supportive of the evidence considered in the appraisal of pemetrexed (TA181), and provided updated results for the evidence considered in the appraisal of gefitinib (TA192).

Generic formulations have become available for gemcitabine, the comparator in TA181, which would be likely to impact on the cost-effectiveness of first-line pemetrexed, and therefore the current recommendation. However, the patent for pemetrexed is anticipated to expire shortly after any review would be undertaken. There is therefore limited value in undertaking a review of TA181, and it is appropriate for the guidance to be transferred to the 'static list'. There has been no new evidence identified which would impact on the recommendations in TA190 and TA227, and therefore it is appropriate to transfer the guidance to the 'static list'.

Since the publication of TA192 and TA258, tyrosine kinase inhibitors (TKIs) targeted specifically for EGFR-TK mutation-positive tumours have become established clinical practice. There is an ongoing clinical trial (LUX-lung 7 trial) comparing gefitinib with afatinib (another TKI which has recently been recommended by NICE). It is therefore considered appropriate to transfer TA192 and TA258 to the 'static guidance list', flagged for further consideration of a review when the results of the LUX-lung 7 trial report.

5. Implications for other guidance producing programmes

CCP are happy with the proposal to move TA181, TA190 and TA227 to the static list, and to defer the consideration of a review of TA192 and TA258. There are currently no plans to update the clinical guideline for lung cancer.

6. New evidence

Search strategies based on the original assessment reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from the following dates onwards were reviewed: January 2009 (TA181); May 2009 (TAs 190 & 192); October 2009 (TA227) and September 2011 (TA258). Additional searches of

¹ A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of on-going and unpublished studies.

7. Summary of evidence and implications for review

The following changes to the evidence base have taken place since the original appraisals were conducted:

- Final results for the IPASS trial (registration trial for first line use of gefitinib), including mature overall survival data, have been published. The results show no statistically significant difference in median overall survival between gefitinib single agent therapy and paclitaxel plus carboplatin combination therapy.
- An independent Health Technology Assessment report on 'first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer' by the Liverpool Review and Implementation Group, Liverpool University has been published (referred to in this paper as 'LRiG 2013'). In this review, evidence synthesis was carried out separately for three sub-populations of people with locally advanced and metastatic lung cancer: squamous, non-squamous and EGFR-TK mutation-positive. In line with the licensed indications for the technologies under consideration here, the relevant results relate to the evidence syntheses for the non-squamous and the EGFR-TK mutation-positive populations. For the non-squamous population, direct and indirect evidence was compared for platinum therapy (cisplatin or carboplatin) in combination with the following: paclitaxel, vinorelbine, docetaxel, gemcitabine or pemetrexed. The review found results which support the evidence already considered in TA181 (that is, a similar overall survival hazard ratio for pemetrexed plus cisplatin compared with gemcitabine plus cisplatin).
- For the EGFR-TK mutation-positive population, direct and indirect evidence was combined in LRiG 2013 for gefitinib single agent therapy compared with carboplatin plus paclitaxel and cisplatin plus docetaxel. The evidence base included the final results from the IPASS trial. Erlotinib was not included as it had not been appraised by NICE at the time. For patients with EGFR-TK mutation positive tumours, the report found no statistically significant differences in overall survival between gefitinib and a paclitaxel plus platinum combination therapy, or between gefitinib and a docetaxel plus platinum combination therapy. However, a statistically significant improvement in progression free survival was found for gefitinib when compared to either of the combination therapies. The review noted that there was significant quantitative heterogeneity between the two trials comparing gefitinib with paclitaxel plus platinum combination therapy. This new evidence requires further consideration of whether a review of TA192 should be recommended (see below).
- Generic versions of gemcitabine (a comparator treatment in TA181) have become available since the appraisal. The acquisition cost of pemetrexed has

not changed since the time of publication of TA181 (however, see below for information on the expected end date for the patent). The price of gemcitabine in the original appraisal was £32.55 per 200mg vial. The Electronic Market Information Tool (eMIT)² suggests that the average price paid by the NHS for gemcitabine is £3.17 per 200mg vial.

Other considerations:

- It is anticipated that the patent for pemetrexed will end in December 2015.
- The LUX-lung 7 trial will provide direct head to head evidence of afatinib (a tyrosine kinase inhibitor) compared with gefitinib for the first-line treatment of patients with EGFR-TK mutation-positive advanced adenocarcinoma of the lung. This phase IIb randomised open-label trial is currently ongoing. This would provide the first head to head comparison of 2 tyrosine kinase inhibitors (TKI).

The implications of these changes in evidence, for each of the appraisals under consideration here, are:

1. TA181 - pemetrexed first line: It is likely that the availability of generic gemcitabine would (unfavourably) change the cost effectiveness of pemetrexed as a first-line therapy. The L RiG 2013 study found that, because of the high price of pemetrexed in relation to the generically available comparators, pemetrexed is only considered cost effective if the willingness to pay is greater than £37,000 per QALY gained (or £50,000 per QALY gained using eMIT prices). However the potential end of the patent for pemetrexed would be likely to occur shortly after an appraisal could be scheduled into the work programme, significantly reducing the value to the NHS of reviewing the guidance. In addition, since the positive recommendation in TA181, pemetrexed in combination with cisplatin has become the standard of care for first-line treatment of non-small cell lung cancer, replacing the comparator at the time of the original appraisal (gemcitabine plus cisplatin). The availability of generic formulations of gemcitabine therefore becomes of limited relevance. For these reasons it is recommended that TA181 should be placed on the static list.
2. TA190 – pemetrexed maintenance treatment: there is no change in the evidence base for this appraisal and nothing to suggest a review of TA190 is required. It is therefore recommended that this piece of guidance be placed on the static list.
3. TA192 – gefitinib first-line: gefitinib was the first TKI to be appraised and as such, was compared with chemotherapies that do not target the EGFR-TK mutation. By the time of the first-line erlotinib appraisal (TA258) the Committee accepted that non-targeted therapies were no longer valid

² Electronic market information tool produced by the Commercial Medicines Unit of the Department of Health, which provides estimated mean product prices for generic medicines drawn from information from about 95% of NHS trusts.

comparators due to their declining use in EGFR-TK mutation-positive non-small cell lung cancer. In the recent appraisal of afatinib, the scope included erlotinib and gefitinib as comparators for the first-line use of afatinib (that is, non-targeted chemotherapies were not included). The latest information available to the technical team therefore suggests that the scope for a re-appraisal of gefitinib would need to be amended to reflect the treatments that would be displaced by gefitinib in current clinical practice. Instead, a more appropriate decision problem would be to compare the different targeted TKI therapies. Whilst the recent appraisal of afatinib (TA310) examined the incremental cost effectiveness of all 3 targeted therapies, as a Single Technology Appraisal was only able to issue recommendations for afatinib. The LUX Lung 7 trial (comparing afatinib with gefitinib) is anticipated to report in 2015, and this evidence would be of value for a decision to review. It is therefore suggested that TA192 is placed on the static guidance list, flagged for further consideration of a review when this head to head evidence is available.

4. TA227 – erlotinib maintenance treatment: there is no change in the evidence base for this appraisal and therefore nothing to suggest a review of TA227 is required. The technical team therefore recommends that this piece of guidance be placed on the static list.
5. TA258 – erlotinib first-line: the discussion for TA192 (see above) is directly relevant to this appraisal. Accordingly, this guidance should be placed on the static guidance list, flagged for further consideration of a review in line with that for TA192.

Summary of Recommendations

Technology appraisal guidance 181, 190, 192, 227 and 258 should be placed on the static list.

Technology appraisal guidance 192 and 258 should be flagged for further consideration of a review when the results of the LUX Lung 7 trial are available.

8. Implementation

A submission from Implementation is included in Appendix 3.

Based on this submission it is apparent that, following NICE guidance which recommends the use of pemetrexed as first-line and maintenance treatment for people with locally advanced or metastatic NSCLC, the volume and cost of prescriptions of pemetrexed in the NHS has increased substantially. Similarly, following NICE guidance recommending gefitinib for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations of EGFR-TK, the volume and cost of prescriptions of gefitinib in the NHS has increased substantially

9. Equality issues

None

GE paper sign off: Helen Knight, September 2014

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred until the results of the LUX-lung 7 trial report, currently anticipated to be in 2015.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment
 - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Quality standard for lung cancer. QS17, issued: March 2012.

Lung cancer: The diagnosis and treatment of lung cancer. Clinical Guideline CG121, issued: April 2011. Review date: April 2014.

EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. Diagnostics guidance DG9. Issued: August 2013. Review date: August 2016.

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. Technology Appraisal Guidance 309. Issued April 2014. Review date: April 2017.

Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. Technology Appraisal Guidance 310. Issued April 2014. Review date: April 2017.

Suspended/terminated

Bevacizumab for the treatment of non-small-cell lung cancer. Technology Appraisal TA148 (terminated appraisal). Terminated in 2007 after the manufacturer informed NICE that they would not be seeking a marketing authorisation for this indication.

Cetuximab for the treatment of advanced non-small cell lung cancer. Technology Appraisal (suspended). Suspended in 2012 after the manufacturer informed NICE that they had withdrawn their license application for this indication.

Erlotinib, in combination with bevacizumab for the maintenance treatment of non-squamous advanced or metastatic non-small-cell lung cancer after previous platinum-containing chemotherapy. Technology Appraisal (suspended). Suspended in 2012 after the manufacturer informed NICE that regulatory approval for this indication was no longer being sought.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Dacomitinib (Pfizer)	1 st line. Phase III.
Dimesna (Takeda)	1 st line. Phase III
Ipilimumab (Bristol-Myers Squibb)	1 st line. Phase III.

Drug (manufacturer)	Details (phase of development, expected launch date,)
Liposomal Cisplatin (Regulon)	1 st line. Phase III
Necitumumab (Eli Lilly)	1 st line. Phase III.
Paclitaxel, albumin bound (Celgene)	1 st line. Phase III. Launched in the US.
Talactoferrin alfa (Agennix)	1 st line. Phase III.
TG4010 (Transgene)	1 st line. Phase III.
LDK378 (Novartis)	1 st line, ALK positive. Phase III.

Registered and unpublished trials

First line

Trial name and registration number	Details
<p>A Study of Alimta/Cisplatin/Gefitinib for Asian Non-smoking Patients With Non Small Cell Lung Cancer</p> <p>NCT01017874; 21, H3E-CR-S131.</p>	<p>First-line pemetrexed/cisplatin followed by gefitinib vs. gefitinib alone.</p> <p>n=226</p> <p>Estimated primary completion date: April 2013</p> <p>Estimated study completion date: October 2014</p>
<p>A Study of Tarceva (Erlotinib) or Placebo in Combination With Platinum-Based Therapy as First Line Treatment in Patients With Advanced or Recurrent Non-Small Cell Lung Cancer</p> <p>NCT00883779; MO22201.</p>	<p>n=451</p> <p>Estimated study completion date: August 2014</p>
<p>A Study of Tarceva (Erlotinib) Versus Gemcitabine/Cisplatin as First-Line Treatment in Patients With Non-Small Cell Lung Cancer With EGFR Mutations</p> <p>NCT01342965; YO25121.</p>	<p>n=210</p> <p>Estimated primary completion date: December 2013</p> <p>Estimated study completion date: December 2013</p>
<p>ZD 1839 Plus Chemotherapy in Treating Patients With Non-Small Cell Lung Cancer</p> <p>NCT00006049; CDR0000068065, ZENECA-1839IL/0017, MSKCC-00100.</p>	<p>Two doses of gefitinib in combination with paclitaxel and carboplatin vs. placebo in combination with paclitaxel and carboplatin</p> <p>n=1029</p> <p>Current status unknown.</p>
<p>ZD 1839 Plus Combination Chemotherapy in Treating Patients With Non-Small Cell Lung Cancer</p> <p>NCT00006048; CDR0000068064; ZENECA-1839IL/0014</p>	<p>Two doses of gefitinib in combination with gemcitabine and cisplatin vs. placebo, gemcitabine and cisplatin</p> <p>n=1029</p> <p>Current status unknown.</p>
<p>Iressa v BSC (Best Supportive Care) in First Line NSCLC</p> <p>NCT00259064; 1839IL/0711; D7913C00711</p>	<p>n=200</p> <p>Estimated primary completion date: December 2012</p> <p>Estimated study completion date: December 2012</p>

Trial name and registration number	Details
Randomized Gefitinib Trial NCT00807066; RANGE; ONC-2008-001	Gefitinib vs. platinum-based chemotherapy n = unknown completed
Erlotinib in Treating Patients With Stage III or Stage IV Non-Small Cell Lung Cancer NCT00275132; CDR0000457755, LLCG-TOPICAL, EU-20313.	Erlotinib vs. placebo n=670 Ongoing Estimated primary completion date: March 2012 Estimated study completion date: March 2012
Influence of Prior Chemotherapy on Clinical Benefit With Erlotinib in Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer With or Without EGFR Gene Mutation NCT01204307; 99-1896C.	Docetaxel/cisplatin vs. pemetrexed cisplatin with erlotinib second line in both arms n=250 Estimated primary completion date: July 2012 Estimated study completion date: December 2012
A Study With Tarceva and Chemotherapy vs. Chemotherapy Alone in Patients With Advanced Lung Cancer NCT00047736; NCT00029016; OSI2298g	n = unspecified Completed:
First-line Gefitinib Versus Chemotherapy for Lung Adenocarcinoma in Never Smoker NCT00455936; NCCCTS-05-126, D7913L00054	n=315 Completed
Chemotherapy in Treating Patients With Non-Small Cell Lung Cancer NCT00520676; 11626, H3E-CR-S380	Pemetrexed + carboplatin vs. docetaxel + carboplatin n= 260 Completed. Results available at clinicaltrials.gov

Trial name and registration number	Details
<p>Study of Patients With Advanced Non-Small Cell Lung Cancer</p> <p>NCT00948675; 13258, H3E-US-S130</p>	<p>Pemetrexed and carboplatin followed by pemetrexed maintenance; or paclitaxel, carboplatin, and bevacizumab followed by bevacizumab maintenance</p> <p>n=360</p> <p>Estimated primary completion date: August 2012</p> <p>Estimated study completion date: June 2013</p>
<p>A Study Comparing Two Different Chemotherapy Types in Chinese Patients With Advanced Non Small Cell Lung Cancer</p> <p>NCT01005680; 12878, H3E-CR-JMIL.</p>	<p>Pemetrexed plus cisplatin vs. gemcitabine plus cisplatin</p> <p>n=256</p> <p>Estimated primary completion date: November 2012</p> <p>Estimated study completion date: November 2012</p>
<p>Quality of Life Comparison in Advanced Non-squamous Non Small Cell Lung Cancer</p> <p>NCT01303926; ERACLE; Goim 2903; 2009-015807-19</p>	<p>Induction pemetrexed and cisplatin followed by pemetrexed as maintenance vs carboplatin-paclitaxel and bevacizumab followed by bevacizumab as maintenance</p> <p>n=118</p> <p>Estimated primary completion date: June 2012</p> <p>Estimated study completion date: June 2012</p>
<p>TaxoteRe Plus Cisplatin Versus Allmta Plus Cisplatin in 1st Line Non-squamous Cell Type Lung Cancer</p> <p>NCT01282151; TRAIL; docetaxel ET_L_05478.</p>	<p>Docetaxel + cisplatin vs. pemetrexed + cisplatin.</p> <p>n=562</p> <p>Estimated primary completion date: June 2014</p> <p>Estimated study completion date: June 2014</p>
<p>BIBW 2992 (Afatinib) Versus Chemotherapy as First Line Treatment in NSCLC With EGFR Mutation</p> <p>NCT00949650; 1200.32; 2008-005615-18.</p>	<p>Afatinib vs. cisplatin + pemetrexed</p> <p>n=330</p> <p>Estimated study completion date: December 2013</p>

Maintenance therapy

Trial name and registration number	Details
<p>Intercalating and Maintenance Use of Iressa Versus Chemotherapy in Selected Advanced Non Small Cell Lung Cancer</p> <p>NCT01404260; CTONG 1102.</p>	<p>Gefitinib, gemcitabine & carboplatin vs. gemcitabine & carboplatin.</p> <p>n=218</p> <p>Estimated primary completion date: July 2013</p> <p>Estimated study completion date: April 2014</p>
<p>Erlotinib or Placebo Following Chemoradiotherapy (Chemo/RT) in Stage III Non-Small Cell Lung Cancer (NSCLC)</p> <p>NCT00153803; D-0410.</p>	<p>n=380</p> <p>Estimated primary completion date: December 2012</p> <p>Estimated study completion date: December 2012</p>
<p>A Study of First-line Maintenance Tarceva (Erlotinib) Versus Tarceva at Time of Disease Progression in Patients With Advanced Non-small Cell Lung Cancer After Chemotherapy</p> <p>NCT01328951; BO25460.</p>	<p>n=610</p> <p>Estimated primary completion date: June 2016</p> <p>Estimated study completion date: June 2016</p>
<p>IFCT-GFPC 05.02 A Randomized Phase III Trial Assessing in Patients With Advanced Non-small Cell Lung Cancer</p> <p>NCT00300586; 2005.386</p>	<p>Maintenance gemcitabine vs “sequential” erlotinib vs. observation</p> <p>n=842</p> <p>Completed (~March 2011)</p>
<p>A Randomized Phase III Trial of Chemotherapy Alone Versus Chemotherapy Followed by Gefitinib in Stage IIIB/IV Non-Small Cell Lung Cancer</p> <p>NCT00144066; WJTOG0203.</p>	<p>n=600</p> <p>Completed ~2005</p>
<p>Genius Study to Compare Efficacy and Safety of Gefitinib/ Pemetrexed With Pemetrexed Alone as Maintenance Therapy in Patients With Stage IV EGFR Mutation Negative or T790M Single Mutation Who Respond to Pemetrexed/Platinum as First-line Therapy</p> <p>NCT01579630; D7913L00077</p>	<p>n=338</p> <p>Estimated primary completion date: June 2013</p>

Trial name and registration number	Details
Strategies for Maintenance Therapies in Advanced Non Small Cell Lung Cancer NCT01631136; IFCT-GFPC-1101	Pemetrexed vs. gemcitabine n=932 Estimated primary completion date: July 2014 Estimated study completion date: July 2016
Bevacizumab or Pemetrexed Disodium Alone or In Combination After Induction Therapy in Treating Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer NCT01107626; CDR0000666482; ECOG-E5508	n=1282 Estimated primary completion date: October 2012
MODEL (Maintenance Versus Observation After inDuction Chemotherapy in Non-progressing Elderly Patients With Advanced Non-small Cell Lung Cancer) NCT01850303; IFCT-1201.	Pemetrexed or gemcitabine maintenance vs. observation. n=549 Estimated completion date: April 2020

Additional information

None.

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Liverpool Review and Implementation Group, Liverpool University. (2013) Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. *Health Technology Assessment* 17 (31).

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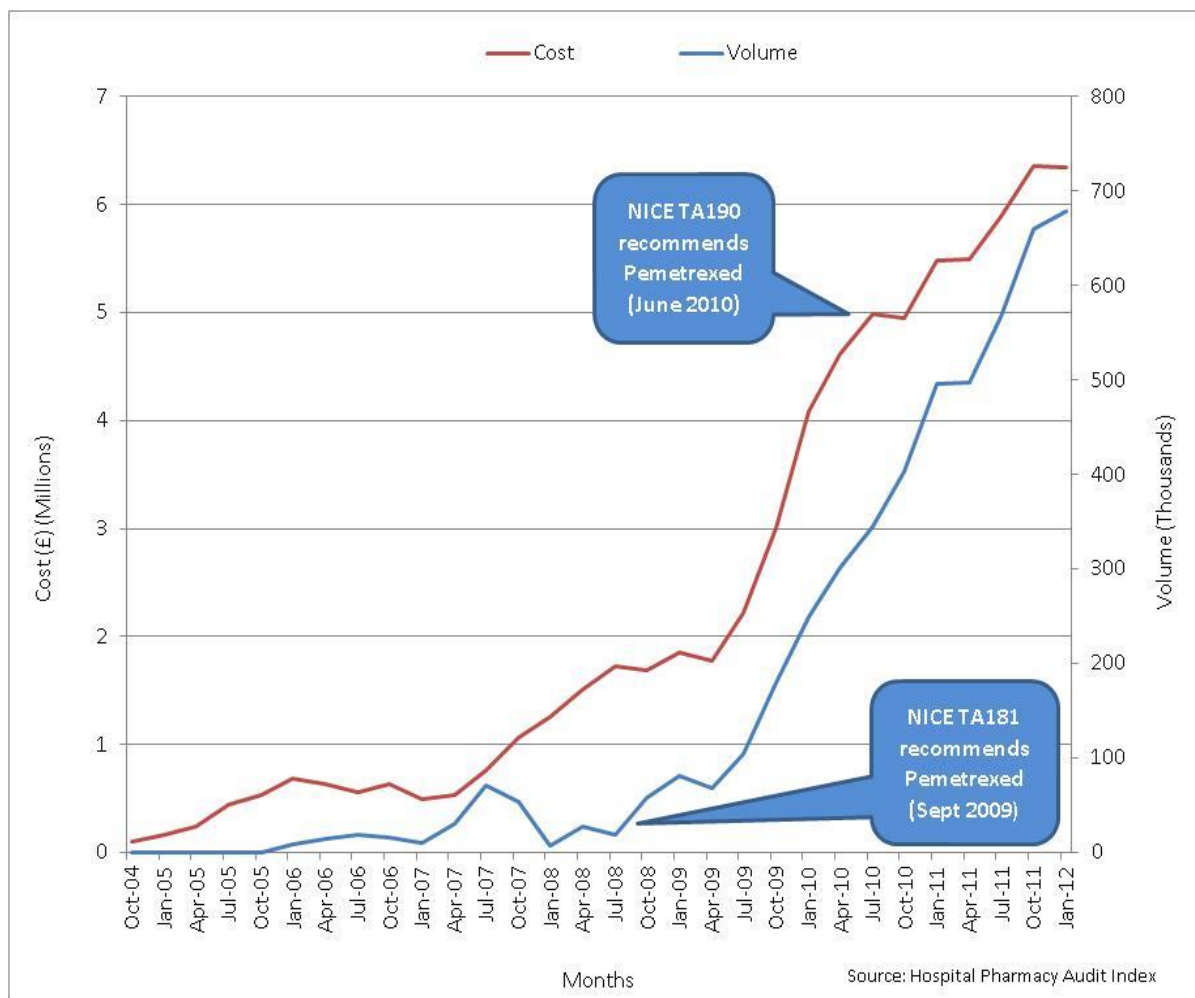
Appendix 3 – Implementation submission – TAs 181, 190, 192

Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the cost and volume of Pemetrexed prescribed and dispensed in hospitals in England between October 2004 and January 2012. These data need to be treated with caution as there is more than one indication for Pemetrexed³.

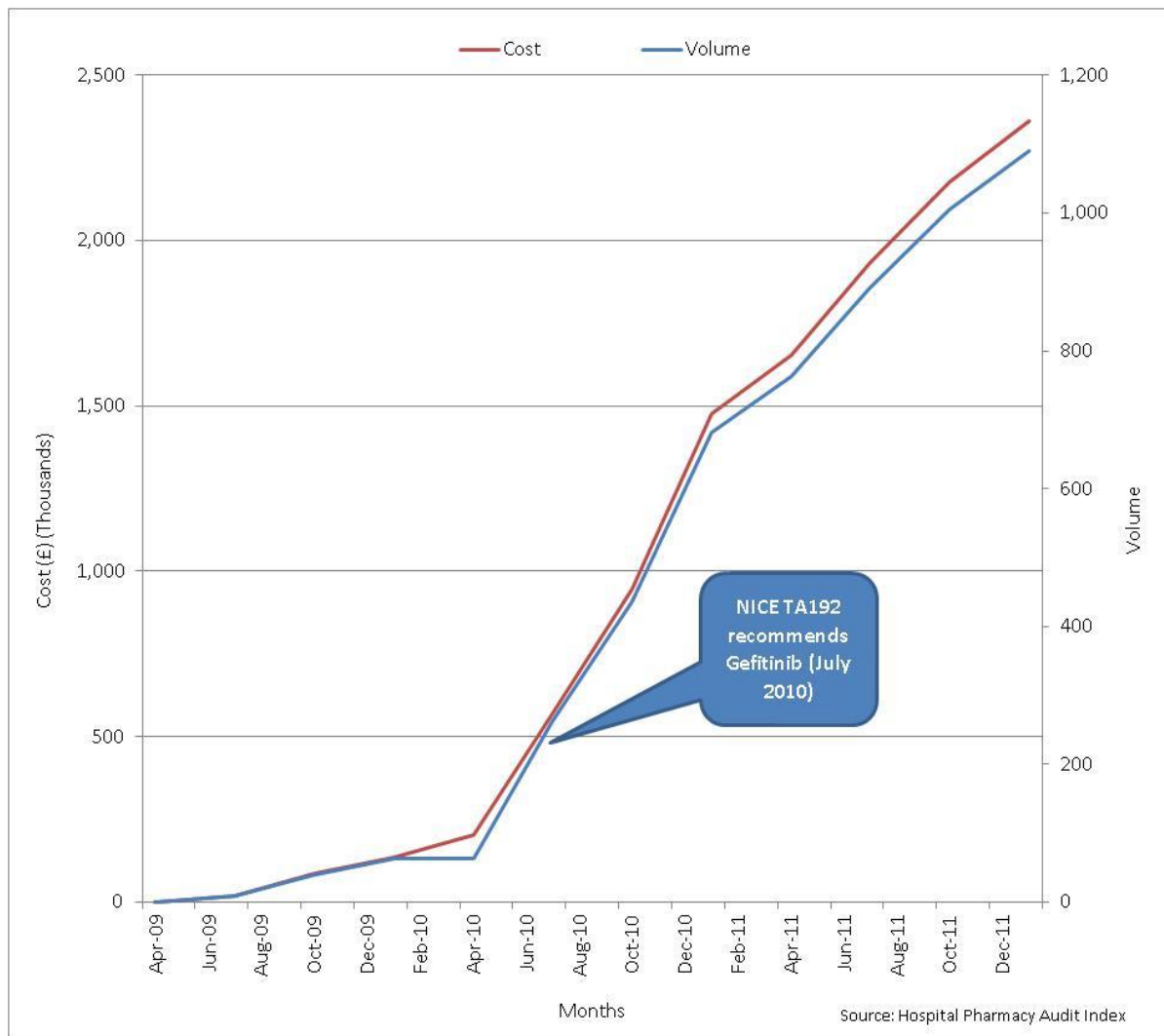
Figure 1 Cost and volume of Pemetrexed prescribed and dispensed in hospitals in England



³ NICE TA135 Pemetrexed for the treatment of malignant pleural mesothelioma (January 2008)

NICE TA124 Pemetrexed for the treatment of non-small-cell lung cancer (August 2007)

Figure 2 Cost and volume of Gefitinib prescribed and dispensed in hospitals in England



1 Implementation studies from published literature

Information is taken from the uptake database ([ERNE](#)) website.

2.1 Richards, M (2010) [Extent and causes of international variation in drug usage: A report for the Secretary of State for Health](#)

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present

calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

2 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

Notes on implementation submission: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients.

Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.