NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA124; Pemetrexed for the treatment of non-small-cell lung cancer, TA162; Erlotinib for the second-line treatment of non-small-cell lung cancer and TA175; Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal)

TA124 was issued in August 2007. The review date for this guidance was January 2010.

TA162 was issued in November 2008. The review date for this guidance was June 2010.

TA175 was issued in July 2009. A review date for this guidance has not been defined.

1. Recommendation

A review of the guidance should be planned into the appraisal work programme, including TA124, TA162 and TA 175. That we consult on this proposal.

2. Original remit(s)

TA124: *"To appraise the clinical and cost effectiveness of pemetrexed (within the context of the licensed indication) for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen".*

TA162: *"To produce an appraisal on the clinical and cost-effectiveness of erlotinib for the second-line treatment of patients with locally advanced or metastatic (stage III/IV) non-small-cell lung cancer".*

TA175: *"To appraise the clinical and cost effectiveness of gefitinib, within its licensed indication, for the treatment of locally advanced or metastatic non-small-cell lung cancer".*

3. Current guidance

TA124

1.1. Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer.

1.2. People currently receiving pemetrexed should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

TA162

1.1. Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel.

1.2. The decision to use erlotinib or docetaxel (as outlined in section 1.1) should be made after a discussion between the responsible clinician and the individual about the potential benefits and adverse effects of each treatment.

1.3. Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.

1.4. People currently receiving treatment with erlotinib, but for whom treatment would not be recommended according to section 1.3, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

TA175

NICE is unable to recommend the use in the NHS of gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer because no evidence submission was received from the manufacturer or sponsor of the technology.

4. Rationale[1]

A review of the TA 124 (pemetrexed) should be planned into the appraisal work programme because there are three trials comparing pemetrexed with erlotinib and erlotinib is considered a standard comparator (in addition to docetaxel), following the publication of TA162 (erlotinib)

A review of TA 162 (erlotinib) should be planned into the appraisal work programme because there are two trials that address the difference in effectiveness between erlotinib and docetaxel and the targeting of specific subgroups for erlotinib. In addition, section 4.1 (Therapeutic indications) of the erlotinib SPC has been updated since the publication of TA 162. Finally, the main comparator for the erlotinib guidance (docetaxel) has gone off-patent.

A review of TA 175 (gefitinib) should be planned into the appraisal work programme because there is a trial that compares gefitinib with pemetrexed and a second non-

[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

submission by the manufacturer would not prevent the MTA from progressing as an evidence submission would be received from the Assessment Group.

It is therefore recommended that the three reviews are combined into one MTA and that the timing be based on when new data for erlotinib will become available in or around Q2 2012.

5. Implications for other guidance producing programmes

CG121 (April 2011) includes the following recommendation: 'Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. [2005]'. The technology appraisal review of erlotinib, gefitinib or pemetrexed may have implications for this guideline recommendation which, depending on the outcome of the technology appraisal, may need to be updated.

CG 121 also cross references the individual technology appraisal guidance documents for erlotinib, gefitinib and pemetrexed. A review which brings these pieces of guidance together will mean that the cross reference(s) in the guideline will need to be updated.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. For TA124 references from January 2006 onwards were reviewed. For TA162 references from April 2006 onwards were reviewed. There were no date limits on the searches for TA175. Additional searches of 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 ongoing and unpublished studies.

7. Summary of evidence and implications for review

<u>TA124</u>

The original guidance (TA124) compared the use of pemetrexed with docetaxel and with best supportive care. The updated literature search identified two phase III studies comparing pemetrexed with docetaxel which have completed since the publication of TA124. Both studies were identified as on-going during the review of TA 124 in March 2010. Neither study has been published to date. It is not possible to determine from the information available in the public domain whether these studies prospectively identified any subgroups that correspond to the population in the updated marketing authorisation of pemetrexed.

There has been no change to the acquisition cost of pemetrexed since the publication of TA124. However, according to Sanofi Aventis (the manufacturer of docetaxel, the comparator in TA162) docetaxel was going off-patent in November 2010. Any reduction in the acquisition cost of docetaxel resulting from it going off-patent would result in an increase in the ICER for pemetrexed and therefore no change to the recommendation in TA 124.

TA 162

The original guidance compared the use of erlotinib with docetaxel and best supportive care. At the time TA 162 was undertaken there was no evidence available regarding a direct comparison of erlotinib with docetaxel or on subgroups towards whom erlotinib treatment could be targeted, At the time the guidance was issued (November 2008) the Committee noted that there were on-going trials comparing erlotinib with docetaxel and that EGFR status and other tumour biochemical markers were being explored in research that would advance the understanding of the mechanism of action of erlotinib. The Committee considered that a review of this guidance should take into account the results of the on-going trails comparing erlotinib with docetaxel.

Since the original appraisal the SPC for erlotinib has been updated. Section 4.1 (Therapeutic indications) of the SPC states that 'No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR) negative tumours'. This appears to address the Committee's research question regarding the effectiveness of erlotinib in subgroups defined by EGFR status.

The updated literature search identified two on-going studies (TITAN and TAILOR) that compared erlotinib with docetaxel (or pemetrexed) and erlotinib with docetaxel. The studies address both the uncertainty identified by the Committee regarding the difference in effectiveness between erlotinib and docetaxel and the targeting of specific subgroups for erlotinib treatment. Both studies were identified during the review of TA 162 in July 2010. Information provided by the manufacturer at the time of the review in July 2010 indicated that the estimated completion dates of the TITAN and TAILOR studies are August 2014 and May 2012 respectively.

Interim data from the TITAN study (erlotinib compared with docetaxel or pemetrexed) was published in Q1 2011.[1]The results indicate that there was no difference in overall survival between the arms: HR = 0.96 (95% CI 0.78 1.19; log-rank p = 0.73; median 5.3 months with erlotinib versus 5.5 months with chemotherapy (docetaxel or pemetrexed). Similarly, no significant difference was seen in progression-free survival. More treatment related adverse events (AE) were seen with erlotinib (AEs; 58.2% versus 40.8% with chemotherapy [docetaxel or pemetrexed]), mostly grade 1/2 rash or diarrhoea. Grade 5 AEs were rare with erlotinib (1.5% versus 5.2% of patients receiving chemotherapy [docetaxel or pemetrexed]) Serious treatment-related AEs were seen in 1% of patients in the erlotinib arm versus 6.6% of those in the chemotherapy (docetaxel or pemetrexed) arm; withdrawal due to AEs was required in 1% and 3.8% of patients, respectively.

TA 162 recommends the use of erlotinib for this indication only 'on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events, and monitoring costs) equal to that of docetaxel'. This patient access scheme was implemented as a discount of the list price for erlotinib, the size of which was predominantly based on the list price of docetaxel at the time of publication of the guidance. Since publication of the guidance generic formulations of docetaxel, indicated for the treatment of lung cancer, have received marketing

authorisation and are available in the NHS. Although list prices of the generic preparations are the same/similar to the branded formulation, it is known that generic medicines are provided with significant discounts and hence it would be expected that when following the guidance of TA 162 the manufacturer of erlotinib would be adjusting the discount provided on erlotinib to match the new aquisition cost of docetaxel. Anecdotal feedback from the NHS suggests that this not always happens; although this is in itself would not be a reason to review the guidance as it is clear in its recommendation concerning this issue. A possible complicating factor that might have an influence on the implementation of TA 162 for what concerns the PAS, is the fact that the company has now agreed a simple discount PAS for all erlotinib indications that sets the level of discount to what was originally the basis of TA 162. And although the company is not restricted to offer further discounts, it might not actively be doing so and hence there could be a consequential impact in the cost effectiveness of erlotinib versus docetaxel. The opportunity to review the guidance of TA 162 will allow these uncertainties concerning the PAS to be addressed.

TA175

Gefitinib received its marketing authorisation in June 2009 for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK. The summary of product characteristics (SPC) states that gefitinib was examined in two studies as a second line treatment; the INTEREST and the ISEL. The INTEREST study was conducted in patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. In the overall population, no statistically significant difference between gefitinib and docetaxel (75 mg/m^2) was observed for overall survival, progression free survival and objective response rates. The ISEL study was conducted in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen. Gefitinib plus best supportive care was compared to placebo plus best supportive care. Gefitinib did not prolong survival in the overall population. Survival outcomes differed by smoking status and ethnicity.

The up-dated literature search identified two completed and one on-going trial examining the efficacy and safety of gefitinib that do not appear in the SPC for gefitinib. However it is not possible to determine from the information available in the public domain whether these studies add significantly to the data available from the pivotal regulatory trials (ISEL and INTEREST) referred to in the SPC.

Comparison of pemetrexed, erlotinib and gefitinib

The updated literature search identified a number of ongoing trails that compared erlotinib with pemetrexed or pemetrexed with gefitinib. There are two on-going studies (including the TITAN study) comparing erlotinib and pemetrexed (estimated completion dates May 2011 and August 2014) and one on-going study comparing pemetrexed with gefitinib (final data collection date for primary outcome measure October 2010). These studies may enable the relative effectiveness of the three technologies to be determined.

Clinical guideline CG121 ‘Lung cancer: diagnosis and treatment’ was published in April 2011 and replaces CG 24 which was published in 2005. Clinical guideline 121 incorporates TA124, TA162 and TA175. The clinical guideline states that ‘The NHS has commissioned a review of first-line therapy for NSCLC through the NIHR Health Technology Assessment Programme. This review is due to be published in 2011. The clinical guideline does not specify that a review of second-line therapy for NSCLC has been commissioned.

In Summary

A review of the TA 124 should be planned into the appraisal work programme because:

- There are three trials (two ongoing [one of which is the TITAN study] and one completed) comparing pemetrexed with erlotinib. Following the publication of TA162, erlotinib can be considered a standard comparator in addition to docetaxel (which along with best supportive care were the only two comparators considered in TA124).

A review of TA 162 should be planned into the appraisal work programme because

- The SPC for erlotinib has been updated since the publication of TA 162
- The main comparator for the erlotinib guidance (docetaxel) has gone off-patent.
- There are two ongoing trials that address the uncertainties raised regarding the difference in effectiveness between erlotinib and docetaxel and the targeting of specific subgroups for erlotinib.

A review of TA 175 should be planned into the appraisal work programme because:

- It is a terminated appraisal as a result of a non-submission by the manufacturer. If the review was incorporated into an MTA, a second non-submission by the manufacturer would not prevent the appraisal from progressing as an evidence submission would be received from the Assessment Group.
- There is one on-going trial that compares gefitinib with pemetrexed (the technology appraised in TA124).

It is recommended that the three reviews are combined into one MTA: It is proposed that the timing of the MTA be based on the time that new data for erlotinib will become available. The final results of an ongoing study – TAILOR trial – will become available in or around Q2 2012.

8. Implementation

No submission was received from Implementation.

9. Equality issues

None

10. GE paper sign off: Frances Sutcliffe 10 May and 1 June 2011

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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.**	**Yes (TAs 124,162 and 175)**
The decision to review the guidance should be deferred to	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.	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. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	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. 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).	No

Options	Consequence	Selected – 'Yes/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.	No

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. The technology falls within the scope of a clinical guideline (or public health guidance)

iii. 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

iv. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

v. 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

vi. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Lung cancer: diagnosis and treatment. Clinical Guideline CG24. Issued: February 2005. Currently being reviewed. Publication expected: April 2011.

In progress

Afatinib for the treatment of locally advanced or metastatic non-small cell lung cancer after previous platinum containing chemotherapy and gefitinib or erlotinib. Technology Appraisal. Due: TBC.

Suspended/terminated

Vandetanib for the second and subsequent line treatment of non-small cell lung cancer after previous platinum containing chemotherapy. Technology Appraisal. Suspended in 2009 after the manufacturer informed NICE that they would not be seeking a license for this indication at this time.

Erlotinib, in combination with bevacizumab for the second line treatment of non-squamous advanced or metastatic non-small-cell lung cancer after previous platinum containing chemotherapy. Suspended in 2009 after the manufacturer informed NICE that regulatory approval was not being sought for this indication.

In topic selection[2]

[redacted]

[2] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

[redacted]

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Pemetrexed (TA124): Monotherapy for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy	Since the original appraisal the licence for the second-line treatment of NSCLC has been restricted to exclude patients with predominantly squamous cell histology. The current indication relevant to this appraisal is therefore: *monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology*. [redacted]
Erlotinib (TA162): The treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	Since the original appraisal the SPC for erlotinib has been updated. Section 4. 1 (Therapeutic indications) of the SPC states that 'No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR) - negative tumours '

Indication considered in original appraisal	Proposed indication (for this appraisal)
Gefitinib (TA175): TA175 was scheduled to look at the second-line treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of EGFR-TK.	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK Note that TA192 recommends gefitinib for first-line use. Any review of TA175 would cover use following relapse after first line therapy.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Aflibercept (Sanofi Aventis)	Phase III in combination with docetaxel for advanced or metastatic non-squamous NSCLC who have failed one platinum-based therapy. [redacted].
Apricoxib (Takeda)	Phase II as second or third line therapy in patients who have failed previous platinum agent therapy. UK launch not planned until 2016
ARQ 197 (Daiichi Sankyo)	Phase III as second or third line therapy in patients with non-squamous NSCLC.
Belinostat (Spectrum)	Phase II as add-on to erlotinib for patients with previously treated NSCLC. UK launch not planned before 2015
Cediranib (AstraZeneca)	Phase II. UK launch not planned before 2016.
Crizotinib (Pfizer)	Phase III as first and second line therapy in patients with alterations of the ALK gene.
Dimesna (Takeda)	Phase III. UK launch planned Q1 2012.
Entinostat (Syndax)	Phase II. Add-in to erlotinib. UK

Drug (manufacturer)	Details (phase of development, expected launch date,)
	launch not planned before 2015.
Iniparib (Sanofi Aventis)	Phase III. UK launch planned Q3 2012.
Intedanib (Boehringer Ingelheim)	Phase III as second line therapy in combination with pemetrexed or docetaxel UK launch planned Q3 2012.
Ipilimumab (Bristol Myers Squibb)	Phase III.
PF 00299804 (Pfizer)	Phase III for advanced or metastatic disease in patients who have failed standard therapy.
Pralatrexate (Allos pharmaceuticals)	Phase II in patients who have failed at least one prior platinum-based chemo regimen.
Sorafenib (Bayer)	Phase III for non-squamous NSCLC who have failed two or three previous treatments. UK launch not anticipated for >5 years
Talactoferrin alfa (Agennix)	Phase III as second line treatment for NSCLC.
Vinflunine (Pierre Fabre)	Phase III add-on to cetuximab for the second line treatment of NSCLC.

Registered and unpublished trials

Trial name and registration number	Details
Trial of Pemetrexed Versus Erlotinib in Pretreated Patients With Non Small Cell Lung Cancer (NSCLC) NCT00440414; CT/06.05.	Phase III Completed ~ April 2010 n = 320
Pharmaco-Economic Study of a Second Line Treatment in Advanced Non Small Cell Lung Cancer NCT00284778; I05026.	Phase III Completed ~ December 2009 Pemetrexed vs. docetaxel n = 150

Trial name and registration number	Details
A Study of Tarceva (Erlotinib) and Standard of Care Chemotherapy in Patients With Advanced, Recurrent, or Metastatic Non-Small Cell Lung Cancer (NSCLC) NCT00556322; BO18602; TITAN.	Phase III Estimated completion date: stated as November 2010 Erlotinib vs. Pemetrexed vs. Docetaxel Interim results published in abstract form at the European Multidisciplinary Conference in Thoracic Oncology conference, February 2011 [1]. Awaiting full publication. n = 650
Chemotherapy for Patients With Non-Small Cell Lung Cancer NCT00391274; 10717, H3E-MC-JMID.	Phase III Completed Pemetrexed vs. docetaxel n = 211 Results available at clinicaltrials.gov
Pemetrexed or Erlotinib as Second-Line Therapy in Treating Patients With Advanced Non-Small Cell Lung Cancer NCT00738881; CDR0000612010, NCCTG-N0723, CALGB-30802, CAN-NCIC-BRC4.	Phase III Ongoing Estimated completion date: May 2011 n = 1196
Tarceva Italian Lung Optimization tRial (TAILOR) NCT00637910; FARM6F5JER, EudraCT Number 2007-004786-17.	Phase III Ongoing Estimated completion date: May 2012 Erlotinib vs. docetaxel n = 1500

Trial name and registration number	Details
Pemetrexed (ALIMTA) and Gefitinib (IRESSA®) in Never-Smoker and Adenocarcinoma Patients With Non-Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy NCT01066195; 2008-04-030.	Phase IV Currently enrolling Estimated primary completion date: stated as October 2010 n = 129
Iressa as Second Line Therapy in Advanced NSCLC-Asia NCT00478049; D7913L00039.	Phase III Completed ~ February 2009 Docetaxel vs. gefitinib n = 163
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.	Phase III Currently recruiting Estimated completion date: December 2011 n = 250
Study to Assess Safety/Tolerability/Efficacy of Gefitinib Versus Docetaxel in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) NCT00536107; D7913C00046.	Phase IV Completed ~ August 2009 n = 40
Open Label Extension Study With Gefitinib (IRESSA™) for Completing Trial Patients Who May Benefit From Further Treatment NCT00683306; D791AC00008.	Phase IV Ongoing Estimated completion date: stated as December 2010. n = 533

Trial name and registration number	Details
A Study on the Long Term Survivals in an Expand Access Program (EAP) of Iressa NCT01000740; 1839IL/0052 SubStudy.	Phase IV Completed ~ April 2010 Single arm quality of life study tied to an expanded access protocol for gefitinib. n = 59

References

1. .Ciuleanu T, Stelmakh L, Cicens S et al. (February 2011) OT - chemotherapy in second-line advanced non-small-cell lung cancer (NSCLC) with poor prognosis: The phase III titan study. Lung Cancer Conference: European Multidisciplinary Conference in Thoracic Oncology, EMCTO Lugano Switzerland.

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