

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Technology Appraisal Review Proposal paper

**Review of TA192; Gefitinib for the first-line treatment of non-small cell lung cancer.**

**Review of TA258; Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer**

**Review of TA310; Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer**

	TA192	TA258	TA310
Original publication date	July 2010	June 2012	April 2014
Review date	April 2013	April 2013	April 2017
Existing recommendations	recommended	recommended	recommended

#### 1. Proposal

We propose that TA258 and TA192 should remain on the static list and TA310 should be transferred to the 'static guidance list'. All three topics can then be incorporated into the forthcoming clinical guideline for the diagnosis and management of lung cancer.

#### 2. Rationale

There are currently 3 related technology appraisals (TA192, TA258 and TA310) that assess first line treatment for epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC). There had been no direct evidence from head to head trials for erlotinib, gefitinib and afatinib so far. In the most recent appraisal (TA310) the committee acknowledged the importance of results from the on-going LUX-LUNG 7 trial that directly compares afatinib with gefitinib. The older appraisals (TA192 and TA258) did not include results from any of the relevant LUX-LUNG trials and assumed erlotinib and gefitinib had similar clinical benefit.

The companies have confirmed that no changes are anticipated in marketing authorisations or costs. The results from the LUX-LUNG 7 trial are now available

comparing the clinical effectiveness of afatinib with gefitinib which would allow a differentiation between 2 of the currently recommended drugs. However, an MTA review of these 3 drugs is not warranted because erlotinib can still not be directly compared with the other 2 drugs, and because we expect that clinicians will be able to base their treatment decisions on the latest available clinical evidence.

### 3. Summary of new evidence and implications for review

The most recent technology appraisal (TA310) included a mixed treatment comparison with initial results from the LUX-LUNG 3 (comparing afatinib with pemetrexed plus cisplatin) and LUX-LUNG 6 trials (comparing afatinib with gemcitabine plus cisplatin). There is new evidence available that compares afatinib with gefitinib (LUX-LUNG 7). The mixed treatment comparison could now be updated with evidence from the head-to-head trial LUX-LUNG 7, leading potentially to more robust results compared with previous appraisals. The results from LUX-LUNG 7 indicates that afatinib may provide improved progression-free survival compared with gefitinib (Park et al 2016).

The search strategy from the original ERG Reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References were reviewed from May 2009 for TA192, September 2011 for TA258 and March 2012 for TA310. 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 above. See Appendix C for further details of ongoing and unpublished studies.

<b>Has there been any change to the price of the technologies since the guidance was published?</b>
The companies have confirmed that no changes to the prices are anticipated.
<b>Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?</b>
The companies have confirmed that no changes are anticipated in the marketing authorisations that would affect the existing guidance for first line treatment.
<b>Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?</b>
In the most recent appraisal (TA310), overall survival results from the LUX-LUNG trials were immature so there was uncertainty about whether treatment with afatinib resulted in an overall survival benefit compared with chemotherapy. The mixed treatment comparison was also not sufficiently robust, was based on a predominantly Asian population, who were not considered generalisable to the UK and did not include any head-to-head evidence. The addition of results from LUX-LUNG 7 and more mature overall survival data from the previous LUX-LUNG trials would allow a more robust comparison between erlotinib, gefitinib and afatinib. Results from the LUX-LUNG 7 trial suggest that afatinib may

improve progression-free survival compared with gefitinib (Park et al 2016) and there was a similar trend for overall survival (Paz-Arez 2016).

The older appraisals (used for TA192 and TA258) did not include results from any of the relevant LUX-LUNG trials and assumed erlotinib and gefitinib had similar clinical benefit.

**Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?**

It is intended that the update to CG121 (Lung cancer: diagnosis and management) will develop a treatment algorithm for the management of stage III and IV lung cancer. This will incorporate all of the relevant technology appraisals including TAs 192, 258 and 310.

**Additional comments**

None

#### **4. Equality issues**

No specific equalities issues were raised during the development of TA192, TA258 and TA310.

**GE paper sign off: Meindert Boysen, 17 January 2018**

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### Appendix A – Information from existing guidance

#### 5. Original remit

##### 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.

##### 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.

##### TA310

To appraise the clinical and cost-effectiveness of afatinib within its licensed indication for the treatment of epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer.

#### 6. Current guidance

##### 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.

##### 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).

##### TA310

1.1 Afatinib is recommended as an option, within its marketing authorisation, for treating adults with locally advanced or metastatic non-small-cell lung cancer only if:

- the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and
- the person has not previously had an EGFR-TK inhibitor and
- the manufacturer provides afatinib with the discount agreed in the patient access scheme.

### 7. Research recommendations from original guidance

#### TA310

6.1 The Committee recognised the importance of further clinical trials comparing the effectiveness of the tyrosine kinase inhibitors (afatinib, erlotinib and gefitinib) in EGFR mutation-positive locally advanced or metastatic NSCLC. It acknowledged the relevance of the ongoing study (LUX-Lung 7) which directly compares afatinib and gefitinib in people with EGFR mutation-positive advanced NSCLC and is due to report in 2015.

### 8. Cost information from original guidance

#### TA192

2.4 The cost for a pack of 250-mg tablets (30 tablets per pack) is £2167.71 (excluding VAT, 'British national formulary' [BNF] edition 59). The manufacturer has agreed with the Department of Health a patient access scheme in which gefitinib for first-line treatment of NSCLC will be available at a single fixed cost of £12,200 per patient irrespective of the duration of treatment. The manufacturer will not invoice the NHS until the third monthly pack of gefitinib is supplied. This means that patients who need less than 3 months of treatment will not incur a charge. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

#### TA258

2.3 Erlotinib is given orally at a recommended dosage of 150 mg/day. The cost of a pack of 30 (150-mg) tablets is £1631.53 (excluding VAT; 'British national formulary' [BNF] edition 63). Dosage reductions (typically to 100 or 50 mg/day) are possible if the clinician considers it appropriate, and erlotinib is also available in tablet strengths of 100 mg and 25 mg. The manufacturer of erlotinib has agreed a patient access scheme (revised in 2012) with the Department of Health in which a confidential discount from the list price is applied to original invoices. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

#### TA310

2.3 Afatinib is given orally at a recommended dosage of 40 mg once daily. The dosage may be increased to a maximum of 50 mg/day in the first 3 weeks in patients who are able to tolerate 40 mg/day without adverse reactions of greater than grade 1 severity. For patients who have more severe adverse reactions, the dose may be reduced (usually by 10 mg decrements) or treatment interrupted or discontinued. For full details see the summary of product characteristics. The NHS list price, provided by the manufacturer, is £2023.28 per pack of 28 tablets (20 mg, 30 mg, 40 mg or 50 mg). The manufacturer stated that the NHS list price per course of treatment is expected to be around £22,000 per patient, based on a progression-free survival of 11 months. The manufacturer of afatinib has agreed a patient access scheme with the Department of Health in which a confidential discount is applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

## Appendix B – 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. The review will be conducted through the STA or MTA process.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred.	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. The review will be conducted through the MTA process.	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. The review will be conducted through the MTA process.	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>	Yes

## Appendix B

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline <sup>1</sup> .	<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.	No
The guidance should be withdrawn	<p>The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS.</p> <p>The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.</p>	No

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<sup>1</sup> Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the [guide to the processes of technology appraisal](#).

## Appendix C – other relevant information

### 1. Relevant Institute work

#### Published

Bevacizumab for treating EGFR mutation-positive non-small-cell lung cancer (terminated appraisal) (2017) NICE technology appraisal guidance 436.

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (2016) NICE technology appraisal guidance 416.

EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (2013) NICE diagnostics guidance 9.

Lung cancer: diagnosis and management (2011) NICE guideline CG121  
Review date: 2016; Review decision available here. Status: partial update in progress.

Lung cancer in adults (2012) NICE quality standard 17.

Lung cancer NICE pathway.

#### In progress

Osimertinib for untreated EGFR-positive non-small-cell lung cancer NICE technology appraisal guidance [ID1302] Publication date to be confirmed

Durvalumab with tremelimumab for untreated EGFR-positive, ALK-negative non-small-cell lung cancer NICE technology appraisal guidance [ID1143] Publication expected January 2019

Lung cancer: diagnosis and management [update] NICE guideline. Publication expected January 2019

### 2. Details of new products

Drug (company)	Details (phase of development, expected launch date)
Dacomitinib (Pfizer)	Phase 3 clinical trials
Epidermal growth factor cancer vaccine (Bioven)	Phase 3 clinical trials
Nivolumab, Opdivo (Bristol-Myers Squibb)	Phase 3 clinical trials



### 3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
<p>Gefitinib (Iressa, AstraZeneca) has a UK marketing authorisation for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations of EGFR-TK.</p> <p>The cost for a pack of 250-mg tablets (30 tablets per pack) is £2167.71 (excluding VAT, 'British national formulary' [BNF] edition 59). The manufacturer has agreed gefitinib will be available at a single fixed cost of £12,200 per patient.</p>	<p>No change.</p> <p>Source: SPC (March 2017)</p> <p>No change to the list price.</p> <p>Source: BNF (5 October 2017)</p>
<p>Erlotinib (Tarceva, Roche Products) has a UK marketing authorisation 'for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with EGFR activating mutations'.</p> <p>The cost of a pack of 30 (150-mg) tablets is £1631.53 (excluding VAT; 'British national formulary' [BNF] edition 63). The manufacturer has agreed a patient access scheme in which a confidential discount from the list price is applied</p>	<p>No change.</p> <p>Source: SPC (November 2016)</p> <p>No change to the list price.</p> <p>Source: BNF (5 October 2017)</p>
<p>Afatinib (Giotrif, Boehringer Ingelheim) has a marketing authorisation as a monotherapy 'for the treatment of EGFR TKI-naive adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating EGFR mutation(s)'.</p> <p>The NHS list price, provided by the manufacturer, is £2023.28 per pack of 28 tablets (20 mg, 30 mg, 40 mg or 50 mg). The manufacturer has agreed a patient access scheme in which a confidential discount is applied.</p>	<p>No change.</p> <p>Source: SPC (July 2017)</p> <p>No change to the list price.</p> <p>Source: BNF (5 October 2017)</p>

### 4. Registered and unpublished trials

Gefitinib

<p>Multicentre, Open Label, Extension Study of Treatment With Gefitinib (IRESSA) for Patients Completing Other Gefitinib Clinical Studies Who May Benefit From Gefitinib Treatment</p> <p>NCT00683306 D791AC00008</p>	<p>Status: ongoing, not recruiting</p> <p>Estimated enrolment: 94</p> <p>Start date: January 2005</p> <p>Expected completion date: December 2017</p>
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Erlotinib

<p>Phase 3 Study of Erlotinib 100mg or 150mg in Treating EGFR Mutated Patients With Non-small Cell Lung Cancer</p> <p>NCT02140333</p> <p>FAHG20130819, GZMC201301</p>	<p>Status: currently recruiting</p> <p>Estimated enrolment: 220</p> <p>Start date: August 2013</p> <p>Expected completion date: December 2018</p>
<p>Randomized Study of Erlotinib vs Observation in Patients With Completely Resected Epidermal Growth Factor Receptor (EGFR) Mutant Non-small Cell Lung Cancer (NSCLC)</p> <p>NCT02193282</p> <p>NCI-2014-01508, CALGB A081105</p>	<p>Status: currently recruiting</p> <p>Estimated enrolment: 450</p> <p>Start date: August 2014</p> <p>Expected completion date: November 2017</p>

Afatinib

## Appendix D

A Single Arm Phase IV Study of Afatinib in Elderly Patients With Stage IV or Recurrent Non-Small Cell Lung Cancer Whose Tumors Have Epidermal Growth Factor Receptor (EGFR) Exon 19 Deletions or Exon 21(L858R) Substitution Mutations  NCT02514174	Status: currently recruiting  Estimated enrolment: 50  Start date: August 2015  Expected completion date: December 2018
An Open Label, Multicentre, Single Arm Trial to Assess the Safety of Afatinib for Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation(s)  NCT01953913	Status: currently recruiting  Estimated enrolment: 550  Start date: September 2013  Expected completion date: July 2018
An Open Label Trial of Afatinib (Giotrif) in Treatment-naive (1st Line) or Chemotherapy Pre-treated Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation(s)  NCT01853826	Status: ongoing, not recruiting  Estimated enrolment: 481  Start date: July 2013  Expected completion date: March 2018

### 5. Relevant services covered by NHS England specialised commissioning

NHS England (2013) NHS standard contract for cancer: chemotherapy (adult)

### 6. Additional information

American College of Pathologists (2013) Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Cancer Care Ontario (2014) Use of the epidermal growth factor receptor inhibitors, gefitinib (Iressa) erlotinib (Tarceva), afatinib, dacomitinib or icotinib in the treatment of non-small cell lung cancer: a clinical practice guideline

European Society for Medical Oncology (2016) Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Greenhalgh, J et al. (2016) First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database of Systematic Reviews, Issue 5. Art. No.: CD010383.

## Appendix D – References

Paz-Ares, L. et al. (2016). Afatinib (A) vs gefitinib (G) in patients (pts) with EGFR mutation-positive (EGFRm+) non-small-cell lung cancer (NSCLC): overall survival

## Appendix D

(OS) data from the phase IIb trial LUX-Lung 7 (LL7). *Annals of Oncology*, 27(suppl\_6).

Park, K., et al. (2016). Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *The Lancet Oncology*, 17(5), 577-589.

Park et al (2017). First-Line Afatinib versus Gefitinib in EGFRm+ Advanced NSCLC: Updated Overall Survival Analysis of LUX-Lung 7. *Journal of Thoracic Oncology*, 12 (1 supplement) S335-S336.