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GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA347; Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer, TA374; Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175), TA395; Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer, TA403; Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer, TA422; Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (review of TA296) and TA428; Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy

Original publication dates:	2015–2017
Review dates:	2018–2019
Existing recommendations:	TA347 Nintedanib: Recommended TA374 Erlotinib: Optimised TA374 Gefitinib: Not recommended TA395 Ceritinib: Recommended TA403 Ramucirumab: Not recommended TA422 Crizotinib: Recommended TA428 Pembrolizumab: Optimised To see the complete existing recommendations and the original remits, see Appendix A.

1. Proposal

We propose that TA347 (nintedanib) and TA395 (ceritinib) should be transferred to the 'static guidance list'. These technology appraisals will be cross referenced in the update of NICE's clinical guideline [CG121](#) Lung cancer: diagnosis and management

We propose that TA403, TA374 and TA422 should also be transferred to the 'static guidance list'. The recommendations from these technology appraisals will not be cross referenced in the guideline update.

The decision for TA428 will be deferred and reviewed after the CDF reconsiderations of [TA483](#) and [TA484](#) are completed.

2. Rationale

No evidence has been identified which would lead to a change in the recommendations for technology appraisals 347 (nintedanib). and 395 (ceritinib). However, the position of these technologies in the lung cancer pathway has changed and requires context for use in clinical practice. The recommendation for ceritinib in TA395 relates to a patient population that is small and diminishing in clinical practice. Therefore, it is recommended that this guidance be transferred to the static list. TA347 will then be cross referenced in the update of NICE's clinical guideline CG121.

There has also been no evidence identified which would lead to a change in the recommendations for technology appraisals 374 (erlotinib and gefitinib), 403 (ramucirumab) and 422 (crizotinib). Therefore, it is considered appropriate to transfer the guidance to the static list. Ramucirumab and gefitinib are not recommended. The recommendations for erlotinib in TA374 and crizotinib in TA422 relate to patient populations are small or diminishing in clinical practice. In addition, the evidence for crizotinib in TA422 is based on a population that is no longer seen in clinical practice (that is, the evidence is based on people who had first line chemotherapy, but other more effective first line options are now available in clinical practice). Therefore, it is considered appropriate to transfer the guidance to the static list without being cross referenced in the update of NICE's clinical guideline CG121.

A review of the literature relating to technology appraisal 428 (pembrolizumab) has identified emerging evidence that the current recommendations may include a cost-ineffective subgroup. A meta-analysis of evidence from clinical trials suggests that checkpoint inhibitors have similar efficacy to docetaxel for treating people who have previously had an EGFR-targeted therapy for EGFR-mutation-positive NSCLC. Also, there is uncertainty about the optimum treatment duration and the long-term benefit of pembrolizumab (that is, whether pembrolizumab should be stopped after 2 years of treatment). As these factors apply to the PD-1 inhibitor class as a whole it is recommended that the decision to review TA428 is deferred until after the CDF reconsideration of the other PD-1 inhibitor, nivolumab (recommended for use in the Cancer Drugs Fund in [TA483](#) and [TA484](#)).

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?
Yes. A commercial access arrangement for pembrolizumab was agreed with NHS England after publication of TA428. The dosing regimen has changed, and this has an impact on cost (see below)

There have been no changes to the prices of the other technologies under consideration.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No. Since the publication of TA428 pembrolizumab is now licensed as a fixed 200 mg dose every 3 weeks instead of a weight based dose (2 mg/kg) every 3 weeks. This change is likely to increase the drug acquisition costs for pembrolizumab, however this increase is mostly offset by the change in price of pembrolizumab (from the commercial access arrangement) and does not affect the recommendations in the existing guidance.

There have been no changes to the marketing authorisations of the other technologies under consideration that would affect the existing guidance.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

Nintedanib and ramucirumab for previously treated non-small cell lung cancer (TA347 and TA403)

Both TA347 (nintedanib) and TA403 (ramucirumab) identified uncertainties in the extrapolation of overall survival associated with the interventions. There are no further data for either drug that would address these uncertainties.

Further evidence has been published for both nintedanib (Gottfried, 2017) and ramucirumab (Reck, 2017) in subgroups of patients considered to have progressive or aggressive disease. This evidence continues to support the current recommendations.

Erlotinib and gefitinib for previously treated EGFR-mutation-positive non-small cell lung cancer (TA374)

In TA374, the evidence for erlotinib and gefitinib was based on retrospective analyses of small patient numbers and lacked statistical power. Several publications are supportive of the conclusions on clinical effectiveness in the appraisal, including clinical trials comparing erlotinib and gefitinib (Urata Y, 2016; Yang JJ 2017), a Cochrane systematic review of gefitinib (Sim, 2018) and meta-analyses comparing tyrosine kinase inhibitors (Yang Z, 2017; Zhang, 2018).

The optimised recommendation for erlotinib reflects that erlotinib is only likely to be used as a second-line option for a small population of patients who have a delayed diagnosis or EGFR-mutation positive disease or an unknown EGFR-mutation status. There is no new evidence available which would change this recommendation.

Ceritinib and crizotinib for previously treated ALK-mutation-positive non-small cell lung cancer (TA395 and TA422)

Current treatment options for untreated ALK-mutation-positive non-small cell lung cancer are now alectinib (TA536), ceritinib and crizotinib. Due to the introduction of alectinib, the treatment pathway is evolving and the optimum treatment pathway is still to be determined. Clinical experts (in TA536) stated that alectinib is increasingly likely to be used first-line and would not be followed with either of

the current tyrosine kinase inhibitors (ceritinib or crizotinib) as there is limited evidence available to determine whether such a sequence would be clinically effective. Therefore, crizotinib treatment will likely be limited to a small number of patients who are diagnosed as ALK-mutation-positive following an alternative first-line therapy. The recommendations in TA395 and TA422 remain unaffected.

The committee noted in TA395 that there was uncertainty in the cost-effectiveness estimates of ceritinib around the overall survival extrapolation, whether ceritinib treatment continues after disease progression and the duration of treatment benefit. Results from a phase III clinical trial (Shaw, 2017) provide additional evidence for patients who have previously been treated with chemotherapy and crizotinib. These results would also only apply to the small population of patients who are not diagnosed as ALK-mutation-positive prior to their first treatment and are supportive of the current recommendation. There is no further evidence for patients who were treated with crizotinib as a first-line therapy.

Pembrolizumab for previously treated PD-L1-positive non-small cell lung cancer (TA428)

TA428 recommended pembrolizumab for people with EGFR-mutation-positive disease who have received at least one targeted therapy (in line with its marketing authorisation). A meta-analysis of checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab) suggests that overall survival with checkpoint inhibitors for patients previously treated with targeted therapies is similar to treatment with docetaxel (Lee, 2017). This analysis is limited by a lack of data on number of lines of previous therapy and EGFR-mutation subtype, and whether these characteristics were distributed evenly between treatment arms. However, it suggests that the current recommendations may be masking a cost-ineffective subgroup. There is no further published evidence available on the efficacy of checkpoint inhibitors for patients who have previously been treated with targeted therapy for ALK-positive disease.

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

See Appendix C for a list of related NICE guidance.

Additional comments

Possible generics from 2019 onwards: the EU patents for erlotinib and gefitinib are expected to expire in March 2020 and September 2019 respectively. If generic versions become available this may have an impact on the cost-effectiveness of these interventions. There is currently 1 application to the EMA for a generic version of erlotinib.

Pembrolizumab treatment duration and 2-year stopping rule: in TA428 there was uncertainty around the optimum treatment duration with pembrolizumab and whether a subgroup of patients would have a long-term treatment benefit after treatment with pembrolizumab was stopped. Therefore, a 2 year stopping rule was considered reasonable and that the evidence around optimum treatment duration and long-term benefit should be reviewed after 2 years. There is no new evidence in the published literature to support changing the recommendations. However, there have been several queries from the media, members of

parliament and the public about the appropriateness of the 2 year stopping rule when the treatment is successful. NHS England have clarified the duration of treatment if the drugs are restarted after a treatment break.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from Feb 2014 (TA347); March 2013 (TA374); March 2015 (TA395); August 2015 (TA103); August 2015 (TA422); March 2016 (TA428) onwards were reviewed. 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.

4. Equality issues

TA374

The Committee concluded that the exclusion of patients whose disease progressed after maintenance therapy did not present an equality issue as there is no evidence on whether this group would get a benefit from nintedanib plus docetaxel.

TA374

The Committee agreed that its recommendations do not constitute detrimental treatment of patients whose disease is likely to test negative for EGFR-TK mutations and therefore its recommendations were fair and did not constitute an equality issue.

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Appendix A – Information from existing guidance

5. Original remit

TA347: To appraise the clinical and cost effectiveness of nintedanib within its licensed indication for previously treated locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology.

TA374: To appraise the clinical and cost effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of non-small-cell lung cancer following prior chemotherapy (review of NICE technology appraisals 162 and 175).

TA395: To appraise the clinical and cost effectiveness of ceritinib within its marketing authorisation for previously treated anaplastic lymphoma kinase-positive non-small cell lung cancer.

TA403: To appraise the clinical and cost effectiveness of ramucirumab within its marketing authorisation for treating locally advanced or metastatic non-smallcell lung cancer that has progressed after platinum-based chemotherapy.

TA422: To appraise the clinical and cost effectiveness of crizotinib within its licensed indication for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.

TA428: To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating advanced or recurrent PD-L1 positive nonsmall-cell lung cancer after progression with platinum-based chemotherapy.

6. Current guidance

TA347

Nintedanib in combination with docetaxel is recommended, within its marketing authorisation, as an option for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy, only if the company provides nintedanib with the discount agreed in the patient access scheme.

TA374

1.1 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, only if the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 258.

1.2 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours of unknown EGFR-TK mutation status, only if:

- the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA and
- the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive and
- the person's disease responds to the first 2 cycles of treatment with erlotinib and
- the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 258.

1.3 Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-negative.

1.4 Gefitinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive.

1.5 People whose treatment with erlotinib or gefitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

TA395

Ceritinib is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase positive non-small-cell lung cancer in adults who have previously had crizotinib. The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

TA403

1.1 Ramucirumab, in combination with docetaxel, is not recommended within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer in adults whose disease has progressed after platinum-based chemotherapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with ramucirumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

TA422:

Crizotinib is recommended, within its marketing authorisation, as an option for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults. The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

TA428:

1.1 Pembrolizumab is recommended as an option for treating locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour), only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and
- the company provides pembrolizumab in line with the commercial access agreement with NHS England.

1.2 This guidance is not intended to affect the position of patients whose treatment with pembrolizumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

Nothing relevant

8. Cost information from original guidance

TA347: The recommended dose is 200 mg twice daily. This can be reduced to 150 mg or 100 mg twice daily in patients who experience adverse events. Nintedanib costs £2151.10 for a 30-day pack of 150 mg or 100 mg capsules for oral use (excluding VAT, MIMS online accessed March 2015). The company has agreed a patient access scheme with the Department of Health.

TA374: Erlotinib is given orally at a recommended dosage of 150 mg once daily. The cost for a 30-tablet pack of 150-mg tablets is £1631.53 (excluding VAT; British national formulary [BNF], accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts. Roche Products has agreed a patient access scheme with the Department of Health, with a simple discount applied at the point of purchase or invoice.

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Appendix A

Gefitinib is given orally at a recommended dosage of 250 mg once daily. The cost for a 30-tablet pack of 250-mg tablets is £2167.71 (excluding VAT; British national formulary [BNF], accessed online September 2015).

TA395: Ceritinib is taken orally, once daily. The recommended dose is 750 mg (5 × 150-mg capsules). The company submission stated that the NHS list price is £4,923.45 for a 30-day supply. The summary of product characteristics states that treatment should be continued as long as clinical benefit is seen. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ceritinib at the point of purchase or invoice.

TA403: Ramucirumab costs £500 per 10-ml vial (containing 100 mg ramucirumab) and £2,500 per 50-ml vial (containing 500 mg ramucirumab). The company estimated that the mean cost of ramucirumab was £3,733 per cycle with an average of 6 treatment cycles. The average cost of a course of treatment is estimated to be approximately £22,400.

TA422: The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; 'British national formulary' [BNF] online, accessed October 2016).

The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of crizotinib, with the discount applied at the point of purchase or invoice.

TA428: Pembrolizumab is available at a cost of £1,315.00 per 50-mg vial (excluding VAT; 'British national formulary' [BNF] online, accessed November 2016).

The pricing arrangement considered during guidance development was that Merck Sharp & Dohme had agreed a patient access scheme with the Department of Health. This scheme provided a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. After guidance publication in January 2017, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.

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 Technology Appraisals 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 to be reviewed after the CDF reconsideration of TA483 and TA484	NICE will reconsider whether a review is necessary at the specified date.	TA428
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>	No

Appendix B

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline ¹ .	<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.	TA403, TA347, TA374, TA395, TA422.
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

¹ 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

Alectinib for untreated ALK-positive advanced non-small-cell lung cancer (2018) Technology appraisal guidance [TA536]

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (2018) Technology appraisal guidance [TA520]

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (2018) Technology appraisal guidance [TA529]

Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2018) Technology appraisal guidance [TA531]

Nivolumab for previously treated squamous non-small-cell lung cancer (2017) Technology appraisal guidance [TA483]

Nivolumab for previously treated non-squamous non-small-cell lung cancer (2017) Technology appraisal guidance [TA484]

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (2016) Technology appraisal guidance [TA416]

Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (2014) Technology appraisal guidance [TA310]

Pemetrexed for the treatment of non-small-cell lung cancer (2007) Technology appraisal guidance [TA124]

Lung cancer: diagnosis and management (2011) NICE guidelines [CG121](#)

Lung cancer (2017) NICE pathway

Quality standard for lung cancer. (2012) NICE Quality Standard 17

In progress

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210] NICE technology appraisal guidance in progress. Publication expected 05 June 2019

Cimavax for treating wild-type EGFR-positive non-small-cell lung cancer [ID1259] NICE technology appraisal guidance in progress. Publication expected TBC

Dabrafenib with trametinib for treating advanced, metastatic BRAF V600E mutation-positive non-small-cell lung cancer ID929 NICE technology appraisal guidance in progress. Publication date to be confirmed.

Lorlatinib for treating ALK-positive advanced non-small-cell lung cancer [ID1338] NICE technology appraisal guidance in progress. Publication date to be confirmed.

Lung cancer (non-small cell, advanced, inoperable) - liposomal cisplatin (with chemotherapy) [ID 657] NICE technology appraisal guidance in progress. Publication date to be confirmed.

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

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [ID1328] NICE technology appraisal guidance in progress. Publication expected March 2019.

Lung cancer: diagnosis and management (update) (partial update of CG¹²¹) NICE guidance. Publication March 2019.

Suspended/terminated

Afatinib for treating squamous non-small-cell lung cancer after platinum-based chemotherapy (2017) Terminated appraisal. NICE technology appraisal guidance TA444. NICE is unable to make a recommendation about the use in the NHS of afatinib for treating locally advanced or metastatic squamous non-small-cell lung cancer after platinum-based chemotherapy because no evidence submission was received from Boehringer Ingelheim.

Alectinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer (2017) Terminated appraisal. NICE technology appraisal guidance TA438 NICE is unable to make a recommendation about the use in the NHS of alectinib for anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer previously treated with crizotinib because no evidence submission was received from Roche.

Lung cancer (non-small cell) - afatinib [ID357] NICE technology appraisal guidance. Suspended appraisal: the manufacturer was not expecting to receive a separate marketing authorisation for this indication.

Bevacizumab for treating EGFR mutation-positive non-small-cell lung cancer (terminated appraisal) (2017) NICE technology appraisal guidance 436. No evidence submission was received from the manufacturer. No evidence submission was received from the manufacturer.

Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal) (2008) NICE technology appraisal guidance 148. No evidence submission was received from the manufacturer.

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Cetuximab for the treatment of advanced non-small cell lung cancer [ID9] NICE technology appraisals guidance. The manufacturer has withdrawn their licence application..

Lung cancer (non-small-cell, advanced or metastatic second line) - erlotinib (in combination with bevacizumab) [ID43] NICE technology appraisal guidance in progress. The manufacturer has advised us that regulatory approval for this technology is not being sought.

Lung cancer (non-small-cell, EGFR T790M-positive, metastatic, treated) – rociletinib [ID883] NICE technology appraisal guidance in progress. The company that it will no longer be pursuing a licensing application.

Vandetanib for the second and subsequent line treatment of non-small cell lung cancer after previous platinum containing chemotherapy [ID46] NICE technology appraisals guidance. The manufacturer has advised us that regulatory approval for this technology is not being sought.

Nivolumab monotherapy for non-small-cell lung cancer [ID1088]. NICE technology appraisal guidance. The company have advised that the pivotal study failed to reach its primary end point and they will not be seeking regulatory approval from the European Medicines Authority for this indication at this time.

Abemaciclib for treating KRAS mutation-positive non-small-cell lung cancer after platinum-based chemotherapy [ID1147] NICE technology appraisal guidance. Suspended appraisal - the company have advised that abemaciclib in this indication will no longer be progressing at this time.

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Ramucirumab (Eli Lilly)	Phase 3 clinical trials.	[REDACTED]
Plinabulin (BeyondSpring)	Phase 3 clinical trial.	[REDACTED]
Nazartinib/capmatinib (Novartis)	Phase 2 clinical trial.	[REDACTED]

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
TA347: Nintedanib has a UK marketing authorisation for use 'in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy'	Treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel) (initiated under specialist supervision) Price: no change (source: BNF (2 August 2018))
TA374 Erlotinib has a UK marketing authorisation for the 'treatment of patients with locally advanced or metastatic non-small-cell lung cancer after the failure of at least 1 prior chemotherapy regimen'.	Indication: no change (source: BNF (2 August 2018)) Price: no change (source: BNF (2 August 2018))
TA374: Gefitinib has a UK marketing authorisation for the treatment of adults with 'locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK'.	Indication: no change (source: BNF (2 August 2018)) Price: no change (source: BNF (2 August 2018))
TA395: Ceritinib has a marketing authorisation in the UK for treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib.	Indication: no change (source: BNF (2 August 2018)) Price: no change (source: BNF (2 August 2018))
TA403: Ramucirumab in combination with docetaxel for treating locally advanced or metastatic non-small-cell lung cancer in adults with disease progression after platinum-based chemotherapy.	Indication: no change (source: BNF (2 August 2018)) Price: no change (source: BNF (2 August 2018))
TA422: Crizotinib has a marketing authorisation in the UK which includes 'adults with previously treated ALK-positive advanced non-small-cell lung cancer'.	Indication: no change (source: BNF (2 August 2018)) Price: no change (source: BNF (2 August 2018))
TA428: Pembrolizumab has a marketing authorisation for treating	Indication: no change (source: BNF (2 August 2018))

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<p>locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 (that is, with a tumour proportion score [TPS] $\geq 1\%$) and who have had at least 1 chemotherapy regimen. Patients with epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive tumour mutations should also have had approved therapy for these mutations before having pembrolizumab.</p>	<p>Price: no change (source: BNF (2 August 2018))</p>
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4. Registered and unpublished trials

Trial name and registration number	Details
<p>A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination With Ramucirumab or Placebo in Previously Untreated Patients With EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NCT02411448)</p>	<p>543 participants Study Completion Date: August 2021 Recruiting</p>
<p>JUNIPER: A Randomized Phase 3 Study of Abemaciclib Plus Best Supportive Care Versus Erlotinib Plus Best Supportive Care in Patients With Stage IV NSCLC With a Detectable KRAS Mutation Who Have Progressed After Platinum-Based Chemotherapy (NCT02152631)</p>	<p>450 participants Study Completion Date: November 2018 Active, not recruiting</p>
<p>Phase 3 Study of Erlotinib 100mg or 150mg in Treating EGFR Mutated Patients With Non-small Cell Lung Cancer (NCT02140333)</p>	<p>220 participants Study Completion Date: December 2018 Recruiting</p>

Trial name and registration number	Details
Evaluation of the Efficacy of Domestic Gefitinib Tablets in the Treatment of Locally Advanced or Metastatic Non-small Cell Lung Cancer Patients Using a Multicenter, Randomized, Positive Drug Gefitinib Pharmacodynamics and Pharmacodynamics (NCT03264794)	100 participants Study Completion Date: June 2022 Not yet recruiting
Phase 3 Randomized Study Comparing X-396 (Ensartinib) to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients (NCT02767804)	402 participants Study Completion Date: April 2020 Recruiting
A Multicenter, International, Rollover Study of Alectinib in Patients With Anaplastic Lymphoma Kinase (ALK)-Positive or Rearranged During Transfection (RET)-Positive Cancer (NCT03194893)	200 participants Study Completion Date: June 2024 Recruiting
A Multinational, Multicenter, Phase III, Randomized Open-label Trial of Pembrolizumab Versus Docetaxel in Previously Treated Subjects With Non-Small Cell Lung Cancer (NCT02864394)	740 participants Study Completion Date: January 2019 Recruiting

Relevant services covered by NHS England specialised commissioning

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

5. Additional information

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

American Society of Clinical Oncology (2017) Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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

National Comprehensive Cancer Network (2018) NCCN clinical practice guidelines in oncology: Non-small cell lung cancer version 6.2018

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Appendix D – References

TA347

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TA395

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