NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using atezolizumab plus bevacizumab, carboplatin and paclitaxel in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: February 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using atezolizumab plus bevacizumab, carboplatin and paclitaxel in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 4 March 2019

Second appraisal committee meeting: 20 March 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Atezolizumab plus bevacizumab, carboplatin and paclitaxel is not recommended, within its anticipated marketing authorisation, for untreated metastatic non-squamous non-small-cell lung cancer (NSCLC) or for previously treated (with targeted therapy) epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC in adults.

1.2 This recommendation is not intended to affect treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with untreated metastatic non-squamous NSCLC (with no EGFR- or ALK-positive mutations) are currently offered pemetrexed plus carboplatin or cisplatin, with or without pemetrexed maintenance. People with EGFR- or ALK-positive NSCLC that has not responded to targeted therapy are also offered the same drugs as their next treatment.

Evidence from an indirect comparison of studies suggests that people having atezolizumab plus bevacizumab, carboplatin and paclitaxel live longer than those having pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. This evidence also suggests that they live for longer before their condition worsens.

But the company's assumption about the proportion of people who have subsequent therapy is too high. Also, the long-term survival estimates from the company's model for people with EGFR- or ALK-positive NSCLC are not credible.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel meets NICE's criteria to be considered a life-extending treatment at the end of life. But the most plausible cost-effectiveness estimates, compared with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance, are above what NICE normally considers acceptable for an end-of-life treatment. Therefore, atezolizumab plus bevacizumab, carboplatin and paclitaxel is not recommended for use in the NHS for metastatic non-squamous NSCLC. Also, it does not meet NICE's criteria to be included in the Cancer Drugs Fund.

2 Information about atezolizumab plus bevacizumab, carboplatin and paclitaxel

Anticipated marketing authorisation indication	Atezolizumab (Tecentriq, Roche) has an anticipated marketing authorisation with bevacizumab (Avastin, Roche), paclitaxel and carboplatin for 'the first-line treatment of adult patients with metastatic non-squamous non‑small cell lung cancer (NSCLC). Patients with epidermal growth factor receptor (EGFR) activating mutant or anaplastic lymphoma kinase (ALK)-positive tumour mutations NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab.' On 31 January 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product atezolizumab. The CHMP adopted a new indication as follows: 'Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.'
Dosage in the marketing authorisation	The proposed recommended dosages are: Atezolizumab: 1,200 mg every 3 weeks by intravenous infusion (based on company submission). Bevacizumab: 15 mg/kg every 3 weeks by intravenous infusion (based on company submission). Carboplatin: 6 mg/ml/min (AUC) every 3 weeks for 4 or 6 cycles by intravenous infusion. Paclitaxel: 15 mg/kg every 3 weeks for 4 or 6 cycles by intravenous infusion. In the Impower150 study, atezolizumab was given until disease progression or unacceptable toxicity. The summary of product characteristics recommends treatment with bevacizumab until disease progression or unacceptable toxicity.
Price	Atezolizumab: £3,807.69 per 1,200 mg vial (excluding VAT; British national formulary [BNF] online [accessed January 2019]). Bevacizumab: £242.66 per 100 mg vial (excluding VAT; BNF online [accessed January 2019]).

	Costs of carboplatin and paclitaxel may vary in different settings because of negotiated procurement discounts. The company has a commercial arrangement for atezolizumab and for bevacizumab, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical need

A new treatment option would benefit people with EGFR- or ALK-positive metastatic non-squamous NSCLC

3.1 People with epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive metastatic non-squamous non-small-cell lung cancer (NSCLC) are offered pemetrexed plus carboplatin or cisplatin, with or without pemetrexed maintenance, if the disease has not responded to targeted therapy. After pemetrexed plus carboplatin or cisplatin, with or without pemetrexed maintenance, people may be offered immunotherapy if they are well enough. People can only have immunotherapy if they have already had multiple lines of previous treatment. The clinical experts welcomed the option to use immunotherapy at an earlier point in the treatment pathway for EGFR- or ALK-positive NSCLC and explained that some people may not be well enough to go on to have further lines of therapy. An immunotherapy option is available for untreated metastatic non-squamous NSCLC in adults whose tumours have no EGFR- or ALK-positive mutations. This is pembrolizumab with pemetrexed and platinum chemotherapy, which is recommended for use in the Cancer Drugs Fund as a treatment option for people whose tumours express PD-L1 with a 0% to 100% tumour proportion score. The committee agreed that more treatment options at an

earlier point in the treatment pathway would benefit people with EGFR- or ALK-positive NSCLC who have already had targeted therapy.

Clinical management

Pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance is the relevant comparator for this appraisal

3.2 The clinical experts explained that current standard care for people with untreated non-squamous NSCLC, and for people with EGFR- or ALK-positive NSCLC who have had targeted therapy, is pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. They noted that not all people can have pemetrexed maintenance. The Cancer Drugs Fund clinical lead confirmed that pemetrexed plus carboplatin or cisplatin, with pemetrexed maintenance, was the relevant comparator for this appraisal. His statement included that other induction chemotherapies recommended in NICE's guideline on lung cancer: diagnosis and management (docetaxel, paclitaxel, gemcitabine, vinorelbine with carboplatin or cisplatin with or without pemetrexed maintenance therapy) were not relevant comparators because these were rarely used to treat non-squamous locally advanced or metastatic NSCLC in clinical practice. The committee was aware that the company was not focusing its submission on the use of atezolizumab plus bevacizumab, carboplatin and paclitaxel in the subgroup of people whose tumours express PD-L1 with at least 50% tumour proportion score. Therefore, pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% tumour proportion score was not a relevant comparator. The committee concluded that pemetrexed plus carboplatin or cisplatin, with pemetrexed maintenance, was the relevant comparator for this appraisal.

For EGFR- or ALK-positive NSCLC, atezolizumab plus bevacizumab, carboplatin and paclitaxel would be an option after all targeted therapies

3.3 The committee noted that the anticipated marketing authorisation is for treating metastatic non-squamous NSCLC only after failure of appropriate

targeted therapies for EGFR- or ALK-positive NSCLC. It understood that EGFR-positive NSCLC is first treated with EGFR tyrosine kinase inhibitors, such as afatinib, gefitinib or erlotinib, according to NICE guidance. Osimertinib is available in the Cancer Drugs Fund as a treatment option for NSCLC with the T790M mutation after afatinib, gefitinib or erlotinib. ALK-positive NSCLC is first treated with alectinib, crizotinib or ceritinib, according to NICE guidance. Ceritinib is a treatment option after crizotinib. The committee understood that the number of treatment options for NSCLC is increasing rapidly and that the treatment pathway is constantly changing. The company confirmed that atezolizumab plus bevacizumab, carboplatin and paclitaxel would be a treatment option after all targeted therapies and not limited to the targeted treatments that are available currently. The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel would be a treatment option after all targeted therapies.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel would only be considered as a treatment option for people who are well enough

3.4 The Cancer Drugs Fund clinical lead confirmed that only people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 would have atezolizumab plus bevacizumab, carboplatin and paclitaxel. This is because atezolizumab and bevacizumab are being added to chemotherapy and the dose of carboplatin would be higher (area under the curve [AUC] 6) than usually used in clinical practice. The patient expert highlighted the importance of careful selection of people who would have atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice. They noted that side effects of treatment are an important consideration for patients. The Cancer Drugs Fund clinical lead explained that carboplatin plus paclitaxel results in hair loss whereas pemetrexed plus carboplatin or cisplatin does not. The number of people with EGFR- or ALK-positive disease who are well enough (ECOG score of 0 or 1) to have atezolizumab plus bevacizumab, carboplatin and paclitaxel was

considered to be small by the patient expert. The clinical experts noted that atezolizumab plus bevacizumab, carboplatin and paclitaxel would not be a treatment option for people with brain metastases. The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel would only be a treatment option for people who are well enough.

Docetaxel would be offered as a subsequent therapy if people are well enough to have further lines of therapy

3.5 After treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel, people have subsequent therapies if they are well enough. The Cancer Drugs Fund clinical lead and the clinical experts confirmed that in NHS clinical practice, people who are well enough to have further lines of therapy would take docetaxel after atezolizumab plus bevacizumab, carboplatin and paclitaxel. The committee concluded that docetaxel would be offered as a subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel for people who are well enough to have further lines of therapy.

After pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance people would have an immunotherapy if they are well enough

3.6 The Cancer Drugs Fund clinical lead and the clinical experts confirmed that after pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance people would have an immunotherapy monotherapy if they are well enough for subsequent treatment. The committee was aware that the immunotherapy options that are available through routine commissioning are pembrolizumab for people with a PD-L1 tumour proportion score of 1% to 100% and atezolizumab for people with a PD-L1 tumour proportion score of 0% to 100%. Nivolumab is also available through the Cancer Drugs Fund as an option for people with a PD-L1 tumour proportion score of 1% to 100%. The committee concluded that the next line of treatment after pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance is an immunotherapy monotherapy.

Clinical evidence

The main evidence for atezolizumab plus bevacizumab, carboplatin and paclitaxel is generalisable to UK clinical practice

3.7 The clinical effectiveness evidence for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with bevacizumab plus carboplatin and paclitaxel came from IMpower150. This is an ongoing randomised, open-label, phase 3 study. IMpower150 included adults with untreated NSCLC (with tumours expressing no EGFR- or ALK-positive mutations) and adults with EGFR-positive or ALK-positive NSCLC who had already had a targeted therapy, and with an ECOG performance status of 0 or 1. The study included patients regardless of PD-L1 status. IMpower150 did not include any UK study centres or comparators that are used in UK clinical practice. The committee was not made aware of any reason why the IMpower150 results for the atezolizumab plus bevacizumab, carboplatin and paclitaxel treatment arm were not generalisable to the UK. It accepted that the IMpower150 population broadly reflected people with non-squamous metastatic NSCLC in England. It acknowledged that, because there was no head-to-head evidence with the relevant comparator (pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance), an indirect treatment comparison would be the only way to judge the relative effectiveness of atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee concluded that IMpower150 provided evidence that was generalisable enough to clinical practice for decision making.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel improves overall and progression-free survival in the ITT population

3.8 At the most recent data cut (January 2018), median overall survival for atezolizumab plus bevacizumab, carboplatin and paclitaxel was reached in the intention to treat (ITT) population. The median follow-up was around 20 months.

Table 1 Clinical data from IMpower150 ITT population

	Atezolizumab plus bevacizumab, carboplatin and paclitaxel	**Bevacizumab plus carboplatin and paclitaxel**
Number of people	400	400
Overall survival		
Overall survival, median months (95% CI)	19.8 (17.4 to 24.2)	14.9 (13.4 to 17.1)
Hazard ratio (95% CI)	0.76 (0.63 to 0.93)	
Progression-free survival		
Progression-free survival, median months (95% CI)	8.3 (7.7 to 9.8)	6.8 (6.0 to 7.1)
Hazard ratio (95% CI)	0.59 (0.50 to 0.69)	
Abbreviation: CI, confidence interval		

The committee noted that the results show a statistically significant difference in overall and progression-free survival between the groups. The committee would welcome further data from IMpower150 when it becomes available. It concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel improved overall and progression-free survival compared with bevacizumab plus carboplatin and paclitaxel in the ITT population.

The EGFR- or ALK-positive subgroup in IMpower150 is small, with no biological reason for combining the groups and survival data are immature

3.9 At the most recent data cut (January 2018), median overall survival for atezolizumab plus bevacizumab, carboplatin and paclitaxel was not reached for the EGFR- or ALK-positive NSCLC subgroup. The median follow-up was around 18 months.

Table 2 Clinical data from IMpower150 EGFR- or ALK-positive NSCLC subgroup

	Atezolizumab plus bevacizumab, carboplatin and paclitaxel	Bevacizumab plus carboplatin and paclitaxel
Number of people	41	63
Overall survival		
People with event, n (%)	13 (31.7)	33 (52.4)
Overall survival, median months (95% CI)	Not estimated (17.0 to not estimated)	17.5 (10.4 to not estimated)
Hazard ratio (95% CI)	0.54 (0.29 to 1.03); p=0.0578	
Progression-free survival		
People with event, n (%)	28 (68.3)	57 (90.5)
Progression-free survival, median months (95% CI)	10.0 (7.9 to 15.2)	6.1 (5.6 to 8.4)
Hazard ratio (95% CI)	0.55 (0.35 to 0.87); p=0.0101	
Abbreviations: CI, confidence interval		

The EGFR- or ALK-positive NSCLC subgroup in IMpower150 included 104 people (41 in the atezolizumab plus bevacizumab, carboplatin and paclitaxel treatment arm). The ERG highlighted that caution was needed when interpreting the results for this subgroup because the study was not stratified by EGFR or ALK status. The clinical experts explained that there was no biological reason to group people with EGFR- and ALK-positive NSCLC into 1 subgroup. The committee accepted this, and that this grouping was not part of the study design. At the time of the last data cut, only 13 events had been recorded in the atezolizumab plus bevacizumab, carboplatin and paclitaxel treatment arm. The committee was aware that the final data from IMpower150 should help to reduce uncertainty in the overall survival estimates. But the committee noted that although more data are welcome, the number of events will still be low. The committee concluded that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 was small, there was no biological reason for combining the

groups and the survival data were immature. These factors substantially add to the uncertainty about survival.

IMpower150 does not include any of the comparator treatments used in NHS clinical practice

3.10 The clinical effectiveness evidence for atezolizumab plus bevacizumab, carboplatin and paclitaxel came from IMpower150 and the comparator in this study was bevacizumab plus carboplatin and paclitaxel (see section 3.9). The main overall and progression-free survival evidence for pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance came from 5 studies:

- ERACLE
- PRONOUNCE
- KEYNOTE-021
- KEYNOTE-189
- PARAMOUNT.

PARAMOUNT was the only study that reported results for pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance. ERACLE and PRONOUNCE reported results for pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. KEYNOTE-021 and KEYNOTE-189 reported results for pembrolizumab with pemetrexed-based chemotherapy. The committee accepted that IMpower150 did not include any of the relevant comparator treatments used in NHS clinical practice. It concluded that data from other studies were needed for the comparator in this appraisal.

Indirect treatment comparison

An indirect comparison is appropriate because there are no head-to-head trials with the relevant comparators

3.11 Because there were no head-to-head trials comparing atezolizumab plus bevacizumab, carboplatin and paclitaxel with pemetrexed plus carboplatin

or cisplatin with or without pemetrexed maintenance, the company did a network meta-analysis. The company estimated fractional polynomial time-varying hazards for overall and progression-free survival using a fixed effects Weibull model. To do subgroup analyses for the PD-L1 less than 50% and EGFR- or ALK-positive populations, it was assumed that the level of PD-L1 expression and presence of EGFR or ALK mutations were not effect modifiers. The ERG's clinical expert did not agree with this assumption but the committee was aware that this limitation in the analysis was necessary for a connected network to be established and to be able to compare atezolizumab plus bevacizumab, carboplatin and paclitaxel with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. The ERG noted that the company's approach to the indirect treatment comparison using a time-varying fractional polynomial model was appropriate given the different mechanisms and speeds of action for immunotherapies and chemotherapies and it agreed with the choice of the Weibull model. The committee concluded that the company's approach was appropriate.

PARAMOUNT should not be included in the network meta-analysis

3.12 The company included PARAMOUNT in their network meta-analysis. PARAMOUNT was the only trial that had pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance as a comparator. The ERG highlighted that including PARAMOUNT in the network meta-analysis greatly increased clinical heterogeneity in the network because PARAMOUNT had a different study design to the other included studies. The committee heard that the protocol for PARAMOUNT included induction pemetrexed-based chemotherapy and this may have caused selection bias because only people who had responded to induction therapy would continue in the study. The committee understood that if PARAMOUNT was not included in the network then no comparison could be made with pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance. But it recalled that the with-maintenance comparator was considered the relevant comparator for decision making (see section 3.2).

The committee agreed that including PARAMOUNT in the network increased the clinical heterogeneity in the network. It concluded that PARAMOUNT should not be included in the network meta-analysis.

The company's economic model

The company's model structure is acceptable for decision making

3.13 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. People were able to move to different health states; from pre-progression to post-progression and death and from post-progression to death. The ERG agreed with the company's model structure. The company used the results from IMpower150 to model overall and progression-free survival for people who had atezolizumab plus bevacizumab, carboplatin and paclitaxel. Specific survival curves were modelled for the ITT population and for the PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups. Hazard ratios from the indirect treatment comparison were then applied to the atezolizumab plus bevacizumab, carboplatin and paclitaxel data to estimate overall and progression-free survival for pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. The committee concluded that the model structure and approach to modelling survival for the atezolizumab plus bevacizumab, carboplatin and paclitaxel treatment arm was acceptable and appropriate for decision making.

Clinical evidence in the economic model

The results for the ITT network meta-analysis that excludes PARAMOUNT are appropriate to include in the model

3.14 The company used the hazard ratios from the network meta-analysis specific to the ITT population, PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups to estimate relative effects for the pemetrexed

plus carboplatin or cisplatin with or without pemetrexed maintenance in the economic model. The ERG preferred to use the results from the network meta-analysis for the ITT population for the PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups, as well as for the overall ITT population. This was because IMpower150 did not show that PD-L1, EGFR or ALK status modified the effect of the treatment so the ITT network meta-analysis results were considered more robust given the larger population. The committee recalled that including PARAMOUNT in the network increased clinical heterogeneity (see section 3.12). The committee concluded that the results for the ITT network meta-analysis that excludes PARAMOUNT were appropriate to include in the model.

Extrapolating overall survival data in the economic model

The exponential and Weibull functions are both acceptable for extrapolating overall survival for the intervention and comparator

3.15 The company extrapolated overall survival in its model using the exponential function. The ERG's preferred choice was the Weibull function, based on it being a plausible alternative to the exponential function and giving long-term overall survival estimates for non-squamous NSCLC closer to those previously considered reasonable by the committee. The committee considered both of these functions to be suitable because they fitted the observed period of data well (based on statistical fit). The committee recalled its conclusion that a 5-year survival rate of 5% to 11% for people with non-squamous NSCLC was reasonable for decision making for the appraisal of pembrolizumab with pemetrexed and platinum chemotherapy. For the ITT population, the Weibull function gave 5-year survival estimates at the top end of this range; 10% for atezolizumab plus bevacizumab, carboplatin and paclitaxel and 9% for pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The exponential function gave values slightly above the 5% to 11% range, with 5-year survival estimates of 13% for people who had atezolizumab plus bevacizumab, carboplatin and paclitaxel and 12% for people who had

pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee agreed that the exponential and Weibull functions were acceptable for extrapolating overall survival.

The company's model gives 5-year overall survival estimates for the EGFR- or ALK-positive NSCLC subgroup that are not credible

3.16 The company's model estimated that 27% (if the exponential function was used for extrapolation) or 26% (if the Weibull function was used for extrapolation) of people who had atezolizumab plus bevacizumab, carboplatin and paclitaxel would be alive after 5 years and 18% of people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance would be alive after 5 years. The committee discussed the large difference in the estimates of long-term overall survival between the ITT population (see section 3.15) and the EGFR- or ALK-positive NSCLC subgroup, with the estimates for the EGFR- or ALK-positive NSCLC subgroup being substantially higher. The clinical experts confirmed that the estimate of 18% overall survival at 5 years for people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was too high and estimated this to be between 5% and 10%, that is, more in line with the expected estimates for the ITT population. They explained that the EGFR- or ALK-positive NSCLC subgroup is distinct from the ITT population and that it was biologically plausible that treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel would give 5-year overall survival estimates that are substantially higher than treatment with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance for people with EGFR- or ALK-positive NSCLC. This biological rationale was said to be particularly strong for EGFR-positive NSCLC because of the vascular nature of these tumours and their response to vascular endothelial growth factor inhibitors such as bevacizumab. The committee accepted that the EGFR- or ALK-positive NSCLC subgroup is distinct and acknowledged that the 5-year overall survival estimates that had been accepted in previous appraisals in this disease area were likely not valid for this subgroup (see section 3.15).

The committee was concerned that it had not heard a biological explanation why the long-term overall survival estimates were plausible for people with ALK-positive NSCLC. The committee recalled that the EGFR- or ALK-positive NSCLC subgroup in IMpower150 was small, there was no biological rationale for combining these groups and that median overall survival had not been reached at the last data cut, in January 2018 (see section 3.9). It was aware that there had only been 13 events in the atezolizumab plus bevacizumab, carboplatin and paclitaxel treatment arm of the study and this made extrapolation of long-term survival more uncertain. The committee agreed that the long-term overall survival estimates from the company's model were too high and not credible. But, a difference of around 8% to 10% between the long-term overall survival estimates for people who had atezolizumab with bevacizumab, carboplatin and paclitaxel and people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance was plausible. The committee concluded that the company's estimates of long-term overall survival for people with EGFR- or ALK-positive NSCLC were too high and not credible. It accepted that atezolizumab plus bevacizumab, carboplatin and paclitaxel increased overall survival but by how much was uncertain.

Stopping rule

Including a 2-year stopping rule is acceptable

3.17 The company included a 2-year treatment stopping rule for atezolizumab and bevacizumab in the model. The committee was aware that people had treatment in IMpower150 until disease progression or unacceptable toxicity. It noted that implementing a 2-year stopping rule was consistent with NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic NSCLC, pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC and atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy and others in the disease area. The patient expert explained that stopping treatment is a worry for people

having treatment for NSCLC but people generally understood that treatment would be stopped at some point. The Cancer Drugs Fund clinical lead's statement included that a 2-year stopping rule would be implemented in clinical practice. The committee agreed that the best treatment duration with atezolizumab plus bevacizumab, carboplatin and paclitaxel was unknown but accepted that a 2-year stopping rule would be used in clinical practice. It therefore concluded that it was appropriate for the company to include a 2-year treatment stopping rule in its economic model.

Duration of treatment benefit after progression

A long-term treatment effect of atezolizumab and bevacizumab after stopping treatment is plausible

3.18 The company's base case included a 3-year treatment effect after stopping treatment with atezolizumab and bevacizumab. The committee was aware that the duration of treatment effect is an area of uncertainty for new immunotherapies. In previous technology appraisals in this disease area, scenarios of a treatment effect lasting between 3 and 5 years had been considered. The committee was also aware that there was no evidence to inform the long-term treatment effect of atezolizumab and bevacizumab from IMpower150 or any other sources. The committee agreed that, although it was biologically plausible for the treatment effect to continue after stopping atezolizumab and bevacizumab, its duration was uncertain. It concluded that the 3-year treatment effect from when treatment was stopped in the company's and ERG's base case was appropriate for decision making.

A lifetime continued treatment effect for pemetrexed maintenance, even after treatment is stopped, is not supported by any evidence

3.19 The company included a persistent survival advantage with pemetrexed maintenance over the full time horizon of the economic model in its base case. The ERG highlighted in its critique of the company's submission that

this was not realistic but did not provide an alternative approach in its base case. The committee was aware that in previous technology appraisals in this disease area (including pemetrexed maintenance treatment for non-squamous NSCLC after pemetrexed and cisplatin), the committee concluded that there was no evidence to support a post-progression survival benefit for pemetrexed maintenance compared with placebo. The committee heard that including a lifetime continued effect of pemetrexed maintenance in the economic model was likely to overestimate the long-term survival gain for atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. The committee was aware that this led to the incremental cost-effectiveness ratio (ICER) for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin without pemetrexed maintenance being underestimated. The committee concluded that there was no evidence to support a lifetime of continued benefit after stopping treatment with pemetrexed maintenance and the company's modelling of a lifetime continued treatment effect was not realistic.

Subsequent therapy

The assumption that 100% of people have subsequent therapy is not appropriate

3.20 In their base cases, the company and ERG assumed that 100% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. The clinical experts explained that no more than 60% of people would be well enough to have subsequent therapy. However, the Cancer Drugs Fund clinical lead estimated this to be no more than 50%. The committee was aware that in previous technology appraisals for ALK-positive NSCLC, clinical experts estimated that 50% of people whose disease had progressed while taking alectinib would have subsequent therapy. The committee heard that some

people with non-squamous NSCLC can have poor performance status and their disease can progress quickly. People with brain metastases would not have any further treatment with a cytotoxic chemotherapy or immunotherapy. The clinical experts noted that fewer people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance given that there would be fewer therapeutic options available. They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres. The committee concluded that the assumption that 100% of people would have subsequent therapy did not reflect clinical practice and accepted that the appropriate proportion of people was much lower.

The distribution of subsequent therapies in the company's model after pemetrexed combination treatment is not appropriate for decision making

3.21 The subsequent therapies offered in IMpower150 did not reflect the treatment options available in NHS clinical practice in England. The company included docetaxel, nivolumab, pembrolizumab and atezolizumab as subsequent treatment options in its economic model and estimated the distributions from UK market share data. The committee heard that because nivolumab is recommended in the Cancer Drugs Fund and not routinely commissioned in the NHS in England, it should not be considered in decision making. The Cancer Drugs Fund clinical lead and the clinical experts explained that after treatment with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance people would have an immunotherapy (see section 3.6). Therefore, nivolumab and docetaxel were not considered to be appropriate subsequent therapies to be included in the analysis. The committee concluded that including nivolumab and docetaxel as options for subsequent therapy after treatment with pemetrexed plus carboplatin or cisplatin with or

without pemetrexed maintenance was not appropriate for decision making.

Health-related quality of life

It is reasonable to include a disutility for treatment-related adverse events

3.22 The company included utility values using the proximity to death approach. The utility values were the same for atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. It did not include a disutility for adverse events. The ERG included a disutility for treatment-related adverse events that were grade 3 or higher in IMpower150. Disutility values were sourced from Nafees et al. 2008. The clinical experts explained that atezolizumab plus bevacizumab, carboplatin and paclitaxel has similar toxicity to pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. The main toxicity concern is hypertension with atezolizumab plus bevacizumab, carboplatin and paclitaxel. The Cancer Drugs Fund clinical lead also highlighted that it can cause hair loss. The patient expert explained that the number of people who have had previous treatment and would be well enough to have atezolizumab plus bevacizumab, carboplatin and paclitaxel and who would have treatment-related adverse events would be small. The committee concluded that it was reasonable to include a disutility for treatment-related adverse events that were grade 3 or higher in IMpower150.

Cost-effectiveness results

The company's base case is not appropriate for decision making

3.23 The committee considered the ICERs from the company's base case, recalculated by the ERG to include the commercial access agreements and patient access scheme discounts for atezolizumab, bevacizumab, pemetrexed maintenance, pembrolizumab, nintedanib and nivolumab (which are confidential so the ICERs cannot be reported here). The

company's base-case ICER comparing atezolizumab plus bevacizumab, carboplatin and paclitaxel with pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was below £50,000 per quality-adjusted life year (QALY) gained for the ITT population, PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups. The committee concluded that the company's base case was not appropriate for decision making because of concerns about the following inputs and assumptions in the model:

- including PARAMOUNT in the network meta-analysis (see section 3.12)
- including the hazard ratios from the PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroup network meta-analyses for overall and progression-free survival for the subgroup analyses (see section 3.14)
- the extrapolation used to estimate overall survival (see section 3.15)
- the proportion of people having subsequent therapy (see section 3.20)
- the treatment options included as subsequent therapies (see section 3.21).

The ERG's preferred base case increases the ICER

3.24 The ERG's preferred base case included the following changes:

- correcting discrepancies in the company model
- using a Weibull distribution to extrapolate overall survival
- using the hazard ratios from the meta-analysis that excluded PARAMOUNT from the network
- using the hazard ratios from the ITT network meta-analysis for overall and progression-free survival for the PD-L1 less than 50% and EGFR- or ALK-positive NSCLC subgroups
- including disutility for treatment-related adverse events of grade 3 or higher.

The committee noted that combining the ERG's preferred assumptions increased all the ICERs, with a substantial increase in the ICERs for the EGFR- or ALK-positive NSCLC subgroup, compared with the company's base case. However, the ERG's base case with its preferred assumptions still gave an ICER for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance that was lower than £50,000 per QALY gained.

The committee's most plausible ICER is higher than £50,000 per QALY gained

3.25 Having considered the ICERs using the ERG's preferred assumptions, the committee accepted the ERG's corrections for discrepancies in the company's model, excluding PARAMOUNT from the network meta-analysis, using the hazard ratio from the ITT network meta-analysis for all groups and including a disutility for treatment-related adverse events of grade 3 or higher. The committee took into account its preferred assumptions that differed from the ERG's base case:

- assuming between 30% and 60% of people have subsequent therapy
- only immunotherapies are subsequent therapies after treatment with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance.

The committee recalled that the clinical experts confirmed that not everyone who had atezolizumab plus bevacizumab, carboplatin and paclitaxel or pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance would go on to have subsequent therapy (see section 3.20). The committee considered the ERG's scenario analysis of modelling fewer people having subsequent therapy. It understood that decreasing the proportion of people who would have subsequent therapy would increase the ICER substantially in the ITT population. The committee also recalled that the company's model did not provide clinically plausible estimates of long-term survival for the EGFR- or ALK-positive NSCLC subgroup. It concluded that the most plausible ICER for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus

carboplatin or cisplatin and pemetrexed maintenance in people with metastatic non-squamous NSCLC was above £50,000 per QALY gained.

End of life

Life expectancy for people with metastatic non-squamous NSCLC is considered to be less than 24 months

3.26 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company's model predicted a mean overall survival for people with metastatic non-squamous NSCLC of more than 24 months after pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance (26 months for the ITT population, 27 months for the PD-L1 less than 50% subgroup and 38 months for the EGFR- or ALK-positive NSCLC subgroup). The ERG's model predicted a mean overall survival of 21 months for the ITT population. The committee was aware that if it considered the mean estimates predicted by the company's model for overall survival for people who had pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance only, then the short life expectancy criteria would not apply. However, the committee heard from the clinical experts that the life expectancy of people with metastatic non-squamous NSCLC was less than 24 months. The committee concluded that the life expectancy of people with metastatic NSCLC was less than 24 months.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel extends life by at least 3 months

3.27 The company estimated a mean life extension of 5 months in the ITT population, 3.5 months in the PD-L1 less than 50% population and 24 months in the EGFR- or ALK-positive NSCLC subgroup with atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. This met the second criterion for an end-of-life treatment. The committee acknowledged that the data used to estimate the extension to life in the

EGFR- or ALK-positive NSCLC subgroup were not robust, but extension to life in the ITT population and all subgroups was likely to be at least 3 months. The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel for metastatic non-squamous NSCLC would extend life by at least 3 months.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel meets the criteria for end-of-life treatments

3.28 The committee concluded that it was satisfied that atezolizumab plus bevacizumab, carboplatin and paclitaxel met the criteria for end-of-life treatments.

Innovation

The benefits of atezolizumab plus bevacizumab, carboplatin and paclitaxel are captured in the measurement of the QALY

3.29 The company stated that atezolizumab plus bevacizumab, carboplatin and paclitaxel was innovative because it was the first checkpoint inhibitor with a phase 3 combination study showing a statistically significant and clinically meaningful overall and progression-free survival benefit. The company highlighted in its submission that atezolizumab plus bevacizumab, carboplatin and paclitaxel improved survival in all key subgroups including people with EGFR- or ALK-positive NSCLC and people with liver metastases. The committee was aware that the Medicines and Healthcare products Regulatory Agency had granted atezolizumab plus bevacizumab, carboplatin and paclitaxel Early Access to Medicines Scheme status for treating metastatic non-squamous EGFR- or ALK-positive NSCLC after failure of appropriate targeted therapies. However, the committee concluded that there were no relevant additional benefits that had not been captured in the QALY calculations.

Routine NHS use

Atezolizumab plus bevacizumab, carboplatin and paclitaxel is not routinely recommended for people with metastatic non-squamous NSCLC

3.30 The committee considered all of the available evidence for atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. It concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel was not a cost-effective use of NHS resources for metastatic non-squamous NSCLC, so it was not recommended.

Cancer Drugs Fund

Atezolizumab plus bevacizumab, carboplatin and paclitaxel is not recommended for use in the Cancer Drugs Fund

3.31 Having concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel could not be recommended for routine use, the committee then considered if it could be recommended for treating metastatic non-squamous NSCLC within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company did not express an interest in it being considered for funding through the Cancer Drugs Fund. The committee did not acknowledge any possibility that the clinical uncertainty could be addressed through collecting data from patients having atezolizumab plus bevacizumab, carboplatin and paclitaxel through the Cancer Drugs Fund. The final data from IMpower150 will be available soon. The committee concluded that atezolizumab plus bevacizumab, carboplatin and paclitaxel did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund. It did not recommend atezolizumab plus bevacizumab, carboplatin and paclitaxel for use within the Cancer Drugs Fund as an option for people with metastatic non-squamous NSCLC.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
February 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Emily Eaton Turner

Technical lead

Caron Jones

Technical adviser

Stephanie Callaghan

Project manager

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