NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance

Published: 5 June 2019
www.nice.org.uk/guidance/ta584

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended as an option for metastatic non-squamous non-small-cell lung cancer (NSCLC) in adults:

- who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% or
- when targeted therapy for epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC has failed.

It is recommended only if:

- atezolizumab and bevacizumab are stopped at 2 years of uninterrupted treatment, or earlier if there is loss of clinical benefit (for atezolizumab) or if the disease progresses (for bevacizumab) and
- the company provides atezolizumab and bevacizumab according to the commercial arrangements.

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

Pemetrexed plus carboplatin or cisplatin, with or without pemetrexed maintenance, is the current treatment for:

- untreated metastatic non-squamous NSCLC (with no EGFR- or ALK-positive mutations) with a PD-L1 tumour proportion score between 0% and 49% and
- metastatic non-squamous EGFR- or ALK-positive NSCLC when targeted therapy is either not an option or has failed.

Pembrolizumab monotherapy is the current treatment for untreated metastatic non-squamous

NSCLC with a PD-L1 tumour proportion score of at least 50%.

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 comparison also suggests that they live for longer before their condition worsens.

Atezolizumab plus bevacizumab, carboplatin and paclitaxel meets NICE's criteria to be considered a life-extending treatment at the end of life. There is uncertainty about the company's long-term survival estimates, especially for people with EGFR- or ALK-positive NSCLC. But including the most plausible assumptions and the commercial arrangements, the cost-effectiveness estimates are within what NICE normally considers acceptable for an end-of-life treatment. Therefore, atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended for metastatic non-squamous NSCLC that is untreated (with no EGFR- or ALK-positive mutations) and when the PD-L1 tumour proportion score is between 0% and 49%, or that is EGFR- or ALK-positive and for which targeted therapy has failed.

Atezolizumab and bevacizumab are stopped at 2 years of uninterrupted treatment, or earlier if there is loss of clinical benefit (for atezolizumab) or if the disease progresses (for bevacizumab). This is because the cost-effectiveness evidence was primarily based on 2 years of treatment and the best duration of treatment is unknown.

No recommendation can be made for atezolizumab plus bevacizumab, carboplatin and paclitaxel for treating untreated PD-L1-positive metastatic NSCLC in people whose PD-L1 tumour proportion score is at least 50% because no cost-effectiveness analyses comparing atezolizumab plus bevacizumab, carboplatin and paclitaxel with pembrolizumab monotherapy were provided.

2 Information about atezolizumab plus bevacizumab, carboplatin and paclitaxel

Marketing authorisation indication	Atezolizumab (Tecentriq, Roche) plus bevacizumab (Avastin, Roche), 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 epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies'. Atezolizumab plus bevacizumab, paclitaxel and carboplatin has been available in the UK for treating metastatic non-squamous EGFR- or ALK-positive NSCLC after failure of appropriate targeted therapies through the early access to medicines scheme.
Dosage in the marketing authorisation	In the induction phase, the recommended dose of atezolizumab is 1,200 mg administered by intravenous infusion, followed by bevacizumab (15 mg/kg), paclitaxel (200 mg/m^2)*, and then carboplatin (area under the curve 6) every 3 weeks for 4 or 6 cycles. The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg atezolizumab followed by bevacizumab (15 mg/kg) is administered by intravenous infusion every 3 weeks. * In the pivotal clinical trial (IMpower150), the paclitaxel starting dose for patients of Asian family origin was 175 mg/m^2 because of a higher overall level of haematological toxicities in these patients compared with those of non-Asian family origin. It is recommended that patients have treatment with atezolizumab until loss of clinical benefit or unmanageable toxicity, and bevacizumab until disease progression or unacceptable toxicity, whichever occurs first. Dose reductions of atezolizumab are not recommended. Paclitaxel and carboplatin were administered in the IMpower150 trial until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity, whichever occurs first.

Price	Atezolizumab: £3,807.69 per 1,200-mg vial (excluding VAT; British national formulary [BNF] online, accessed March 2019). Bevacizumab: £242.66 per 100-mg vial (excluding VAT; BNF online, accessed March 2019). Costs of carboplatin and paclitaxel may vary in different settings because of negotiated procurement discounts. The company has commercial arrangements. This makes atezolizumab and bevacizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 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, after targeted therapy. After pemetrexed combination treatment, people may be offered immunotherapy if they are well enough. The clinical experts welcomed the option to use immunotherapy at an earlier point in the treatment pathway for EGFR- or ALK-positive NSCLC because some people may not be well enough to go on to have further therapy. Immunotherapy is already an option for untreated metastatic non-squamous NSCLC in adults whose tumours have no EGFR- or ALK-positive mutations. These are pembrolizumab with pemetrexed and platinum chemotherapy, which is recommended for use in the Cancer Drugs Fund, and pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% tumour proportion score. Atezolizumab plus bevacizumab, carboplatin and paclitaxel would be a further immunotherapy option for the untreated group whose PD-L1 tumour proportion score is between 0% and 49%. The company's submission did not include a comparison with pembrolizumab monotherapy for PD-L1 in people with a tumour proportion score of at least 50%. Therefore, the committee could not make a recommendation for this group. It 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 original guideline on lung cancer: diagnosis and management (April 2011; docetaxel, paclitaxel, gemcitabine, vinorelbine with carboplatin or cisplatin with or without pemetrexed maintenance) were not relevant comparators because these were rarely used to treat non-squamous metastatic NSCLC in clinical practice. The committee was aware that the company submission was not focusing on using atezolizumab plus bevacizumab, carboplatin and paclitaxel for people whose tumours express PD-L1 with at least a 50% tumour proportion score. Therefore pembrolizumab monotherapy, which is recommended for this population, 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 for EGFR- or ALK-positive NSCLC, the marketing authorisation is for treating metastatic non-squamous NSCLC only after failure of appropriate targeted therapies. It understood that EGFR-positive NSCLC is first treated with EGFR tyrosine kinase inhibitors, such as afatinib, gefitinib or erlotinib, in line with 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, in line with NICE guidance. Ceritinib is also 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 the marketing authorisation permitted atezolizumab plus bevacizumab, carboplatin and paclitaxel to be used as a treatment option after all targeted therapies and not just those currently available. 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 a treatment option for people who are well enough

3.4 The patient expert highlighted the importance of careful selection of people who would be offered atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice. 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 6) than usually used in clinical practice. The number of people with EGFR- or ALK-positive disease who would be 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 patient expert 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 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 therapy

3.5 The Cancer Drugs Fund clinical lead and the clinical experts confirmed that in NHS clinical practice, people who are well enough to have further therapy would take docetaxel after atezolizumab plus bevacizumab, carboplatin and paclitaxel. The committee concluded that docetaxel would be offered after atezolizumab plus bevacizumab, carboplatin and paclitaxel for people who are well enough to have further 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 III 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 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 intention-to-treat 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. The committee noted that the results show a statistically significant difference in overall and progression-free survival between the groups (see table 1). 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.

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); p=0.0060	
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); p<0.0001	
Abbreviation: CI, confidence interval.		

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. 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 together. 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 (see table 2). The committee was aware that the final data from IMpower150 should help to

reduce uncertainty in the overall survival estimates. But it 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 added to the uncertainty about survival. At consultation, the company agreed that the EGFR- or ALK-positive subgroup in IMpower150 was small but this reflects the mutation rates seen in NHS clinical practice. The company further justified grouping people with EGFR- and ALK-positive NSCLC together. The committee did not agree that this justification resolved the uncertainty about this combined subgroup.

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	
Abbreviation: CI, confidence interval.		

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

3.10 The comparator in IMpower150 was bevacizumab plus carboplatin and paclitaxel (see section 3.7). 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. It estimated time-varying fractional polynomial hazards for overall and progression-free survival using a fixed effects Weibull model. To do subgroup analyses for the PD-L1 tumour proportion score 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 its 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 heterogeneity in the network because it had a different study design to the other included studies. The committee heard that the PARAMOUNT protocol included induction chemotherapy (pemetrexed-based), and this may have caused selection bias because only people whose disease 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 one for decision making (see section 3.2). The committee agreed that including PARAMOUNT in the network increased the heterogeneity in the network. At consultation, the company agreed that excluding PARAMOUNT from the network meta-analysis was reasonable and excluded it in an updated analysis. The committee agreed that the company's revised analysis was appropriate.

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 IMpower150 results 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 tumour proportion score less than 50% subgroup and the EGFR- or ALK-positive NSCLC subgroup. 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, the PD-L1 tumour proportion score less than 50% subgroup and the EGFR- or ALK-positive NSCLC subgroup to estimate relative effects for pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance in the economic model. The ERG preferred to use the hazard ratios from the ITT population for each subgroup, 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 heterogeneity (see section 3.12). At consultation, the company provided updated analyses (using the hazard ratios from the ITT network meta-analysis excluding PARAMOUNT for each subgroup, as well as for the overall ITT population) to estimate relative effects in the economic model for pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance. The committee agreed that the company's revised analyses were more appropriate than analyses using the hazard ratios from the network meta-analysis specific to the ITT population, the PD-L1 tumour proportion score less than 50% subgroup and the EGFR- or ALK-positive NSCLC subgroup.

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 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 who had treatment with standard care chemotherapy was reasonable for decision making for the pembrolizumab with pemetrexed and platinum chemotherapy appraisal. 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. At consultation, the company submitted revised analyses using the Weibull function to extrapolate overall survival. 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 For EGFR- or ALK-positive NSCLC, the company's model estimated that 27% (if the exponential function was used) or 26% (if the Weibull function was used) 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 much higher estimates of long-term overall survival for the EGFR- or ALK-positive NSCLC subgroup compared with the ITT population (see section 3.15). 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. They estimated this to be between 5% and 10%, that is, more in line with the expected estimates for the ITT population. But they explained that the EGFR- or

ALK-positive NSCLC subgroup is distinct from the ITT population and that, for this group, 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. 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. It 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. At consultation, the company highlighted that the most conservative approach was taken when extrapolating the overall survival data for the EGFR- or ALK-positive subgroup. It noted that the ERG's and NICE's preferred approach to use the relative effect from the ITT network meta-analysis to model long-term survival for the subgroups represented a more conservative way to model survival for the EGFR- or ALK-positive subgroup (see section 3.14). The ERG explained that the IMpower150 data for the EGFR- or ALK-positive subgroup were limited by the small population and low number of events. The committee understood that the analysis of the ITT population (including the EGFR- or ALK-positive subgroup) was more robust for decision making. The committee accepted that there were limitations with the overall survival data for the EGFR- or ALK-positive subgroup and concluded that the ITT population was more appropriate for decision making.

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 in IMpower150, people had treatment until loss of clinical benefit for atezolizumab and until disease progression for bevacizumab, or unacceptable toxicity. It noted that a 2-year stopping rule had been implemented in other technology appraisal guidance on NSCLC (see the NICE Pathway on lung cancer). The patient expert explained that stopping treatment is a worry for people with NSCLC, but they 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 have 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. It 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 the ERG's base case was appropriate for decision making.

Subsequent therapy

The assumption that everyone has subsequent therapy is not appropriate

3.19 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 than after 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 larger centres but noted this estimate would be much lower in smaller centres. At consultation, the company submitted updated analyses including 2 scenarios for people having subsequent therapy. The proportions were equal after treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance:

- Scenario 1: 46.6% of people had subsequent therapy (based on the proportion having subsequent therapy in the standard care arm in the KEYNOTE-189 trial).
- Scenario 2: 60% of people had subsequent therapy (based on the upper estimate given in the appraisal consultation document).

The Cancer Drugs Fund clinical lead reminded the committee that his estimate was that no more than 50% of people would have subsequent therapy in clinical practice. He noted that an estimate of between 40% and 50% was reasonable. The committee agreed that the company's revised analysis including 46.6% of people having

- subsequent therapy after treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was appropriate for decision making.

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

3.20 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 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. At consultation, the company provided updated analyses that included only atezolizumab and pembrolizumab as subsequent therapies after pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee agreed that the company's revised analyses were more appropriate than analyses including treatment options that are not immunotherapies or not routinely commissioned in the NHS in England.

Health-related quality of life

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

3.21 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.

At consultation, the company provided updated analyses that included a disutility for treatment-related adverse events that were grade 3 or higher in IMpower150. The committee agreed that the company's revised analyses were more appropriate for decision making.

Cost-effectiveness results

The company's base case is appropriate for decision making

3.22 The company revised its base-case cost-effectiveness analysis at consultation. In line with the ERG's preferred assumptions, it:

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

The company also included a new discount to the price of bevacizumab and included only immunotherapies as subsequent therapies after pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's revised base case for the ITT population. The revised base case included 46.6% of people having subsequent therapy and the discounts from the commercial access agreements and patient access schemes for atezolizumab, bevacizumab, pemetrexed maintenance and pembrolizumab (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. The committee concluded that the company's base case was appropriate for decision making.

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

3.23 The committee agreed with the company's revised base case in which 46.6% of people had subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. Although it was aware of the uncertainties about overall survival benefit for the EGFR- or ALK-positive subgroup, the committee 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 below £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

3.24 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 tumour proportion score 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. At consultation, the company updated its base-case cost-effectiveness analysis in line with the ERG's preferred assumptions (see section 3.22). The company's updated model predicted mean overall survival of less than 24 months after pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance. The committee concluded that the life expectancy of people with metastatic non-squamous NSCLC was less than 24 months.

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

3.25 The company estimated a mean life extension of 5 months for the ITT population, 3.5 months for the PD-L1 tumour proportion score less than 50% subgroup and 24 months for the EGFR- or ALK-positive NSCLC subgroup with

atezolizumab plus bevacizumab, carboplatin and paclitaxel, compared with pemetrexed plus carboplatin or cisplatin and pemetrexed maintenance. These estimates 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

3.26 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

3.27 The company stated that atezolizumab plus bevacizumab, carboplatin and paclitaxel was innovative because it was the first checkpoint inhibitor with a phase III 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-positive 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.

Other factors

3.28 No equality or social value judgement issues were identified.

Conclusion

Atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended for people with metastatic non-squamous NSCLC

3.29 The committee agreed that atezolizumab plus bevacizumab, carboplatin and paclitaxel, with the discounts agreed in the commercial arrangements, is a cost-effective use of NHS resources, and can be recommended as an option for metastatic non-squamous NSCLC in adults:

- who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% or
- when targeted therapy for EGFR-positive or ALK-positive NSCLC has failed
- only if atezolizumab and bevacizumab are stopped at 2 years of uninterrupted treatment, or earlier if there is loss of clinical benefit (for atezolizumab) or if the disease progresses (for bevacizumab).

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication for people with metastatic non-squamous non-small-cell lung cancer (NSCLC) that is untreated (with no epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive mutations). Because atezolizumab plus bevacizumab, carboplatin and paclitaxel has been available through the early access to medicines scheme for people with EGFR- or ALK-positive NSCLC, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication for this group.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic non-squamous NSCLC and the doctor responsible for their care thinks that atezolizumab plus bevacizumab, carboplatin and paclitaxel is the right treatment, it should be available for use, in line with NICE's recommendations.

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

James Maskrey
Project manager

ISBN: 978-1-4731-3423-2

Accreditation