

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer

## 1 Recommendations

1.1 Atezolizumab is recommended, within its anticipated marketing authorisation, as an option for untreated metastatic non-small-cell lung cancer (NSCLC) in adults if:

- their tumours have PD-L1 expression on at least 50% of tumour cells or 10% of tumour-infiltrating immune cells
- their tumours do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations and
- the company provides atezolizumab according to the commercial arrangement (see section 2).

### Why the committee made these recommendations

Standard care for untreated metastatic NSCLC tumours with no EGFR or ALK mutations depends on PD-L1 status. If tumours are PD-L1 positive with a score of at least 50%, pembrolizumab monotherapy is offered as standard. Pembrolizumab in combination with chemotherapy may also be offered.

Results from an indirect comparison suggests that atezolizumab is as effective as pembrolizumab in delaying disease progression and in extending life. However, this is uncertain because there is no direct evidence comparing them. Despite the uncertainty in the indirect comparison, the most likely cost-effectiveness estimates for atezolizumab are within what NICE considers an acceptable use of NHS resources. So atezolizumab is recommended.

## 2 Information about atezolizumab

### Anticipated marketing authorisation indication

- 2.1 On 26<sup>th</sup> March 2021, 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 (Tecentriq, Roche). The CHMP adopted a new indication as follows: first-line treatment of adult patients with metastatic non-small-cell lung cancer (NSCLC) whose tumours have a PD-L1 expression  $\geq$  50% tumour cells (TC) or at least 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

### Dosage in the marketing authorisation

- 2.2 The dosage schedule will be available in the summary of product characteristics.

### Price

- 2.3 The list price of atezolizumab is £3,807.69 per 20-ml vial (excluding VAT; BNF online accessed March 2021).

The company has a commercial arrangement (simple discount patient access scheme). This makes atezolizumab 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](#) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

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- it is appropriate for the recommendations to cover both the immune cell 3 (IC3) and tumour cell 3 (TC3) subpopulations
- GP and occupational therapist annual home visits were overestimated in the original company submission and should be reduced to align with clinical expert opinion
- the company approaches to pembrolizumab time on treatment submitted after technical engagement and using KEYNOTE-042 extrapolations are plausible and suitable for decision making.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see executive summary of ERG report tables 3, 4 and 5), and took these into account in its decision making. It discussed the following issues (issues 2, 3 and 4), which were outstanding after the technical engagement stage.

## **Clinical management**

### **A new treatment option would benefit people with untreated high PD-L1-expression metastatic non-small-cell lung cancer**

- 3.1 People with untreated metastatic non-small-cell lung cancer (NSCLC) whose tumours have high (50% or more) PD-L1 expression and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations have limited treatment options. Although survival is improving for people with metastatic NSCLC, pembrolizumab is the only immunotherapy medicine available in this indication and so there is still unmet need. Clinical expert input suggested atezolizumab is very similar to pembrolizumab, with no robust differences in toxicity or efficacy. It was also recognised that unlike pembrolizumab, atezolizumab is not subject to a stopping rule and that this could be valuable to people with untreated high PD-L1-expression metastatic NSCLC. The committee concluded that atezolizumab is an important treatment option for people with this condition.

## The main comparator is pembrolizumab monotherapy

3.2 The clinical expert explained that most people with untreated high PD-L1-expression metastatic NSCLC receive pembrolizumab monotherapy ([NICE technology appraisal on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer](#)). A vastly smaller proportion of people are treated with pembrolizumab combination therapy (pembrolizumab with pemetrexed and platinum chemotherapy; [NICE technology appraisal on pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer](#)). The Cancer Drugs Fund clinical lead indicated that real-world evidence from the NHS supported the clinical expert's opinion that pembrolizumab monotherapy is strongly preferred to combination therapy in this population, with the latter typically being reserved for clinical circumstances where a rapid response is needed. Pembrolizumab with carboplatin and paclitaxel is also available for people with squamous NSCLC as part of the Cancer Drugs Fund ([NICE technology appraisal on pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer](#)). However, in line with [NICE's position statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators](#), pembrolizumab with carboplatin and paclitaxel is not considered to be a comparator in this appraisal. The committee concluded that pembrolizumab monotherapy is the main comparator for atezolizumab.

## Clinical effectiveness

### Only TC3 and IC3 subpopulations of the IMpower110 trial are within scope of this appraisal

3.3 The clinical effectiveness evidence for atezolizumab came from IMpower110. This was an open-label phase 3 randomised controlled trial, comparing atezolizumab with chemotherapy. At screening, people eligible for the study were tested for PD-L1 expression using the SP142 immunohistochemistry assay. Only people whose tumours were PD-L1

positive were enrolled. Tumours were considered PD-L1 positive if they had at least 1% of PD-L1-expressing tumour cells or at least 1% of the tumour area occupied by PD-L1-expressing immune cells. High PD-L1 expression was defined within the IMPower110 study as tumours with PD-L1 expression on at least 50% of their cells (TC3 population) or PD-L1 expressing immune cells being at least 10% of the tumour area (IC3 population). The committee recalled that the marketing authorisation for atezolizumab and the scope of this appraisal was limited to people whose tumours have a PD-L1 expression of at least 50% tumour cells or at least 10% tumour-infiltrating immune cells. Because of this, only data for the TC3 and IC3 subpopulations were considered relevant for this appraisal.

**An indirect comparison is appropriate because there are no head-to-head trials with pembrolizumab**

3.4 The IMpower110 study demonstrated that atezolizumab improves overall survival (20.2 months compared with 13.1 months) and progression-free survival (8.1 months compared with 5.0 months) compared with chemotherapy. However, there is no evidence directly comparing atezolizumab with pembrolizumab. Therefore, the company did an indirect treatment comparison in the form of a network meta-analysis. This included data from IMpower110 (see section 3.3) and 2 studies comparing pembrolizumab with chemotherapy (KEYNOTE-024 and KEYNOTE-042). Because of an assumption that non-proportional hazards may apply, a fractional polynomial model was also applied using overall survival and progression-free survival data from an exploratory analysis from IMpower110 with longer follow-up duration. This allowed for time-varying hazard ratios to be generated from the network meta-analysis. The committee considered this approach to be acceptable for use in decision making.

## Results from the network meta-analysis show no significant differences between atezolizumab and pembrolizumab

3.5 The indirect comparisons from both the standard and the fractional polynomial network meta-analyses imply no significant differences between atezolizumab and pembrolizumab for overall survival, progression-free survival, duration of response and overall-response rate. Results from an exploratory analysis demonstrate a trend in relative hazards moving in favour of pembrolizumab over time (results are considered confidential by the company and cannot be reported here). The trend continues beyond 2 years but with widening credible limits and small sample sizes. In its response to technical engagement, the company explained that these trends are likely to be a result of bias. The company noted that the larger pembrolizumab trial only has follow-up data in line with the earlier IMpower110 data cut. Analyses done during technical engagement demonstrated that using the smaller pembrolizumab study that has longer duration of follow up, within the network meta-analyses improves the hazard ratios slightly for atezolizumab. It was also noted that longer follow-up periods of the IMpower110 study show plateauing in the chemotherapy arm, resulting in hazard ratios for atezolizumab becoming less favourable. It was considered that this is likely because of more people switching from chemotherapy to subsequent lines of cancer therapies. The company explained that these points indicate that differences in follow-up durations between pembrolizumab and atezolizumab studies leads to results being biased in favour of pembrolizumab. The ERG agreed that the points raised by the company may have biased results in favour of pembrolizumab and considered the company base case to reflect the most conservative approach to the analyses. The committee recalled that the clinical expert had considered both products to be comparable. Overall, the committee agreed with the ERG and concluded that the results from the network meta-analysis suggested no significant differences between atezolizumab and pembrolizumab.

## **Atezolizumab potentially dominates pembrolizumab in scenario analyses using the 22C3 selected high PD-L1-expression population**

3.6 People were selected for inclusion in the IMpower110 study using the SP142 assay to measure PD-L1 expression (section 3.3). However, the most frequently used immunohistochemistry assay to assess PD-L1 status in NHS clinical practice is the 22C3 assay, which measures PD-L1 expression based on tumour proportion scores. People included within the pembrolizumab KEYNOTE trials were selected using the 22C3 assay to identify those with tumour proportion scores of at least 50%. The ERG noted that network meta-analyses should be done using populations that are comparable across studies. Because of this, it had concerns about how the different use of assays between the IMpower110 and KEYNOTE studies may impact the network meta-analyses estimates. During the IMpower110 study, the company had done additional analyses of subgroups defined by the 22C3 assay to assess assay comparability. In response to technical engagement, the company submitted a sensitivity analysis using the 22C3 subgroup with a tumour proportion score of at least 50%. The additional analysis showed an improved hazard ratio for atezolizumab compared with the company base case (exact results are considered academic in confidence by the company and cannot be reported here). It was also demonstrated that overall-survival results at the 12- and 24-month landmarks were comparable using the 22C3 or SP142 assays. The company developed several cost-effectiveness scenarios based on the 22C3 assay results. In each of these, atezolizumab was associated with greater quality adjusted life year (QALY) gains than pembrolizumab. The ERG noted that the 22C3 subgroup represented a double selected population because people had first been selected by the SP142 assay (for inclusion in the IMpower110 trial). This could have biased the 22C3 subgroup analyses in favour of atezolizumab. It was recognised that the data uncertainties could not be fully resolved without long-term comparative data on people selected on the same assay. However, the company was considered to have provided

a fair account of the available data. In addition, the clinical expert had indicated that there was overlap between the available assays and NHS England had confirmed that with the approval of atezolizumab there would be no need for changes in their use in clinical practice. Overall, the committee concluded that the 22C3 scenario analysis demonstrating that atezolizumab potentially dominates pembrolizumab provides further indication that the company may have taken a conservative approach in its base case.

### **The duration of treatment effect is uncertain, so various scenarios should be considered**

3.7 The company base case applied a treatment stopping rule for pembrolizumab at 2 years (in line with the NICE technology appraisal on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) and assumed that this leads to loss of efficacy relative to chemotherapy 3 years after stopping treatment. For atezolizumab, no stopping rule was relevant, and no loss of efficacy was assumed over the time horizon of the model (that is, a lifetime treatment effect was assumed). The ERG considered the loss of effect for pembrolizumab to be pessimistic. It noted that 5-year data from the KEYNOTE-024 study reported a hazard ratio of 0.62 for pembrolizumab compared with chemotherapy. However, the ERG was also aware that these data included people who received pembrolizumab again after stopping treatment at 2 years. Clinical experts and NHS England confirmed that this would not be allowed within NHS clinical practice and therefore the applicability of the results is questionable. In response to technical engagement, the company submitted further details on its base-case assumptions. For the pembrolizumab assumptions, the company suggested that previous cancer technology appraisals demonstrate a precedent for use of a 5-year duration of treatment effect (from treatment initiation) with a 2-year stopping rule. The ERG considered it appropriate to only review previous NSCLC appraisals and found that various durations of treatment effects (including 3-, 5- and 10-year effects) have



been explored in previous NSCLC appraisals. The ERG base case maintained a lifetime duration of treatment effect for atezolizumab and a 5-year treatment cap for pembrolizumab, consistent with the company base case. However, given the lack of certainty around the duration of treatment effect for pembrolizumab and atezolizumab, the ERG also developed a range of scenarios to demonstrate the impact of alternative durations of treatment effects. The committee noted that previous pembrolizumab appraisals within NSCLC considered treatment effect durations of 3-years and 5-years and that there would need to be strong justification for longer durations of treatment effect for pembrolizumab. Regarding atezolizumab, it was acknowledged that the issue could not be fully resolved in the absence of long-term follow-up data. However, because of the lack of a stopping rule, atezolizumab could potentially be expected to have a longer treatment effect duration than pembrolizumab, although the extent of this is uncertain. Because of this, the committee agreed it would consider various duration of treatment effect scenario analyses done by the ERG for atezolizumab during its decision making.

## **Cost effectiveness**

### **The company's model structure is suitable for decision making**

3.8 The company used a partition survival model with 3 mutually exclusive health states: progression-free survival, progressed disease and death. The company explained that the health states reflect the 2 key objectives of treatment for NSCLC: delaying disease progression and prolonging life. In addition, the company noted that this structure directly corresponded with the key endpoints of the IMpower110 study (overall survival and progression-free survival) and therefore allowed full use of the available data. The committee agreed that the model structure is suitable for decision making.

## **The company and ERG base cases show atezolizumab is cost saving compared with pembrolizumab**

3.9 The committee considered both the company's cost-effectiveness and cost-comparison results. Using the confidential discount for atezolizumab and the list price for pembrolizumab, the cost-comparison results showed atezolizumab was associated with an overall lower cost of treatment than pembrolizumab. The company's cost-effectiveness base case estimated atezolizumab was associated with a small loss in QALYs compared with pembrolizumab. It was noted that in situations in which an incremental cost-effectiveness ratio (ICER) is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment becomes. The company's base-case cost-effectiveness analysis demonstrated atezolizumab was associated with cost savings per QALY lost. The ERG replicated the company analyses using the confidential discount for pembrolizumab and found that atezolizumab remained cost saving (exact ICERs are confidential and cannot be reported here). The ERG's base case and duration of treatment effect scenarios were also considered. This included consideration of atezolizumab duration of treatment effect capped at 5, 6, 7 and 8 years with treatment stopped from point of efficacy loss. Atezolizumab remained associated with cost savings per QALY lost in the ERG's base case and relevant scenarios described above. Overall, the committee concluded that atezolizumab was a cost-saving treatment option compared with pembrolizumab.

## **Considering incremental net health benefit analyses to compare atezolizumab and pembrolizumab is appropriate for decision making**

3.10 The company also provided cost-effectiveness results in a net health benefit framework. The incremental net health benefit of atezolizumab was compared with pembrolizumab at threshold values of £20,000 and £30,000 per QALY gained using the confidential discount for atezolizumab

and the list price for pembrolizumab. This resulted in positive incremental net health benefit, indicating that the overall population health is likely to be increased with the availability of atezolizumab. The ERG considered the net health benefit analyses had been done correctly. It repeated the analyses and included the confidential discount for pembrolizumab. Net health benefit results were found to remain positive at both the thresholds of £20,000 and £30,000 per QALY gained for the:

- Company base case
- ERG base case
- ERG scenarios for atezolizumab treatment effect duration capped at 5, 6, 7 and 8 years with treatment stopped from point of efficacy loss.

This confirmed that atezolizumab is cost effective compared with pembrolizumab at the range NICE considers an acceptable use of NHS resources. Given that any differences in QALYs between atezolizumab and pembrolizumab are small, the committee concluded that net health benefit was a useful supplementary analysis to inform cost effectiveness of atezolizumab compared with pembrolizumab.

## **Other factors**

3.11 No equality or social value judgement issues were identified.

## **Conclusion**

### **Atezolizumab is recommended for routine use in the NHS**

3.12 Evidence suggests that there is no statistically significant difference in the clinical effectiveness of atezolizumab and pembrolizumab. In addition, it was considered that the company may have taken a conservative approach in modelling its cost-effectiveness base case. Each of the plausible analyses resulted in ICERs showing that atezolizumab was associated with cost savings per QALY lost in the range normally considered a cost-effective use of NHS resources. In addition, all

plausible net health benefit results were positive, indicating that the overall population health is likely to be increased with the availability of atezolizumab. Overall, the committee agreed that the likelihood of atezolizumab being cost effective was high. So, it recommended atezolizumab for people with untreated high PD-L1-expression metastatic NSCLC.

## 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.
- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 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 medicine 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.

- 4.4 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 untreated metastatic NSCLC and the doctor responsible for their care thinks that atezolizumab is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 4.5 The guidance on this technology will be considered for review 3 years after publication. 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  
April 2021

## **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.

### **Fatima Chunara**

Technical lead

### **Caron Jones**

Technical adviser

### **Gavin Kenny and Kate Moore**

Project managers

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