NICE National Institute for Health and Care Excellence

NICE guidance

# Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma

Technology appraisal guidance
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# 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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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 is recommended as an option for treating advanced or unresectable hepatocellular carcinoma (HCC) in adults who have not had previous systemic treatment, only if:

- they have Child-Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with atezolizumab plus bevacizumab 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**

Standard care for advanced or unresectable HCC is either sorafenib or lenvatinib for people who have not had previous systemic treatment. Atezolizumab plus bevacizumab is a potential new treatment option.

Clinical trial evidence shows that people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 who have atezolizumab plus bevacizumab live longer and have longer before their disease progresses than people who have sorafenib. Results of an indirect comparison suggest that atezolizumab plus bevacizumab is more effective than lenvatinib. But 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 plus bevacizumab compared with sorafenib and with lenvatinib are within what NICE considers an acceptable use of NHS resources. Therefore, atezolizumab plus bevacizumab is recommended.

# 2 Information about atezolizumab plus bevacizumab

## Marketing authorisation

2.1 Atezolizumab (Tecentriq, Roche) is indicated 'for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

## Price

2.3 The NHS list price of atezolizumab (60 mg/ml) is £3,807.69 per 20-ml vial. The NHS list price of bevacizumab (25 mg/ml) is £242.66 per 4-ml vial and £924.40 per 16-ml vial (excluding VAT; BNF online, accessed October 2020).

2.4 The company has commercial arrangements for atezolizumab and bevacizumab. These make atezolizumab plus 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 considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), NICE's technical report, 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:

- It is appropriate to cap the utility values for people with unresectable hepatocellular carcinoma (HCC) so that they do not exceed the age- and sex-matched level of the general population (issue 4, see technical report page 4).
- Of the approaches to estimate drug dosing, the most plausible is expected to be between the company's scenario 2 and the ERG's scenario 2b (issue 5, see technical report page 4).
- It is appropriate to include the costs of oral chemotherapy wastage in the analysis (issue 6, see technical report page 5).
- It is acceptable to use overall-survival data from the IMbrave150 trial that have not been adjusted for the effect of subsequent treatments not recommended in England, as long as the cost of those treatments is included (issues 3 and 7, see technical report pages 3 and 6).

  It recognised that there were remaining areas of uncertainty associated with the analyses presented, and took these into account in its decision making. It discussed the following issues (issues 1 and 2, see technical report pages 2 and 3) in further detail, which were outstanding after the technical engagement stage.

## Treatment pathway and comparator

### People would welcome a new treatment option

3.1 People with advanced or unresectable HCC have few approved systemic treatment options. Prognosis remains poor with rapid progression and short overall survival. The clinical experts explained that there has been

little progress in this disease area since the targeted systemic treatments sorafenib and lenvatinib were introduced, and there is a considerable unmet need for people with advanced HCC. They also explained that atezolizumab plus bevacizumab is an intravenous treatment. But people with advanced HCC would prefer it to oral treatments such as sorafenib and lenvatinib if it is more clinically effective. The committee concluded that atezolizumab plus bevacizumab would be welcomed as a new treatment option for people with advanced or unresectable HCC.

### Sorafenib and lenvatinib are relevant comparators for people with Child-Pugh grade A liver impairment and an ECOG status of 0 or 1

3.2 The clinical evidence for atezolizumab plus bevacizumab comes from IMbrave150, a randomised controlled trial of 501 people with locally advanced, metastatic or unresectable HCC who had not had systemic treatment. Participants in the trial had Child-Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In the company's evidence submission atezolizumab plus bevacizumab was compared with sorafenib and with lenvatinib. The committee noted that NICE guidance recommends sorafenib and lenvatinib for people with Child-Pugh grade A liver impairment. Lenvatinib is also recommended for people with an ECOG performance status of 0 or 1. The clinical experts advised that both drugs are first-line treatment options in NHS practice, although there is some regional variation across England in which is preferred. They advised that deciding which treatment to use is usually done with the person with HCC, after discussing potential side effects with them. The Cancer Drugs Fund clinical lead advised that about 60% of people have sorafenib and about 40% have lenvatinib. The committee concluded that the company's proposed positioning in the treatment pathway is appropriate, and sorafenib and lenvatinib are both relevant comparators.

## Clinical effectiveness evidence

### Atezolizumab plus bevacizumab is more clinically effective than

## sorafenib

3.3 The IMbrave150 trial excluded people with Child-Pugh grade B or above liver impairment and people with an ECOG performance status of 2 or more. The committee understood the results may not be generalisable to these groups, but noted that the positioning of atezolizumab plus bevacizumab in people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 was in line with the trial population and with NICE's guidance for sorafenib and lenvatinib. In IMbrave150 atezolizumab plus bevacizumab (n=336) was compared with sorafenib (n=165). The ERG noted that IMbrave150 had a higher proportion of people from Asian regions excluding Japan (40%), and more people with hepatitis B compared with the population that would be eligible for treatment with atezolizumab plus bevacizumab in NHS clinical practice. But otherwise, based on clinical expert advice, it considered the trial population to be representative of people who would be eligible for treatment. The median duration of follow up for survival was 8.6 months for all patients and the results were as follows:

- Progression-free survival was statistically significantly longer with atezolizumab plus bevacizumab compared with sorafenib (stratified hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.47 to 0.76).
- Median progression-free survival was 6.8 months (95% CI 5.7 to 8.3) with atezolizumab plus bevacizumab, and 4.3 months (95% CI 4.0 to 5.6) with sorafenib.
- Overall survival was statistically significantly longer with atezolizumab plus bevacizumab compared with sorafenib (stratified HR 0.58, 95% CI 0.42 to 0.79).

- Median overall survival for atezolizumab plus bevacizumab was not reached, but the median for sorafenib was reached (13.2 months, 95% CI 10.4 to not reached).

  The committee agreed that IMbrave150 was generalisable enough to the population expected to be treated in clinical practice for decision making. It concluded that atezolizumab plus bevacizumab is clinically effective compared with sorafenib in people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

# Indirect treatment comparison

## The company's network meta-analysis is uncertain but acceptable for decision making

3.4 Because there was no direct evidence comparing atezolizumab plus bevacizumab with lenvatinib, the company did an indirect treatment comparison to estimate the relative treatment effect. A random effects base-case network meta-analysis (NMA) of log-hazard ratios was done using 3 studies identified from a systematic literature review:

- IMbrave150 (atezolizumab plus bevacizumab compared with sorafenib)
- REFLECT (lenvatinib compared with sorafenib)

- CheckMate 459 (nivolumab compared with sorafenib).

  Responding to a clarification request from the ERG, the company did a fractional polynomial random effects NMA. The ERG advised that the company's approach was inconsistent because it used direct trial evidence from IMbrave150 to compare with sorafenib and indirect NMA evidence to compare with lenvatinib. The first approach (equivalent to a fixed effects model) allowed for less uncertainty than the NMA approach. The ERG explained that it would have preferred to have seen relative effects for all 3 treatments estimated using a single, coherent random effects model allowing for time-varying treatment effects. The committee noted that at technical engagement, a stakeholder advised that the company's NMA underestimated lenvatinib's effectiveness. The ERG advised that it did not believe this was a credible criticism, and that taking this into account would not address its other methodological concerns. The committee agreed that these methodological concerns increased the uncertainty of the NMA results. But it concluded that it would consider the company's NMA, including its potential limitations, in its decision making.

## Atezolizumab plus bevacizumab is likely to be more clinically effective than lenvatinib

3.5 The company's base-case NMA produced the following results for atezolizumab plus bevacizumab:

- increased progression-free survival compared with lenvatinib (HR 0.91, 95% credible interval [CrI] 0.23 to 3.65)

- increased overall survival compared with lenvatinib (HR 0.63, 95% CrI 0.32 to 1.25).

The ERG advised that the fractional polynomial NMA produced similar results, but with greater uncertainty. The committee noted that the wide credible intervals showed uncertainty in the point estimate of the hazard ratio. It also recalled the ERG's methodological concerns about the company's approach (see section 3.4). The clinical experts advised that sorafenib and lenvatinib are broadly considered to be equally effective in clinical practice. Deciding which to use depends on the individual patient. They advised that they would have expected to see similar results from IMbrave150 if the comparator had been lenvatinib, rather than sorafenib. The committee agreed that the NMA results suggested atezolizumab plus bevacizumab was more effective than lenvatinib. This would be consistent with sorafenib and lenvatinib having similar effectiveness (shown in the non-inferiority REFLECT trial). It concluded that lenvatinib and sorafenib are likely to have similar clinical effectiveness, so atezolizumab plus bevacizumab is likely to be more effective than lenvatinib.

# Modelling overall survival

## The log-normal function is suitable for modelling overall survival, but the log-logistic and generalised gamma functions should also be considered

3.6 The company investigated a range of parametric survival distributions fitted independently to each treatment arm to model overall survival. In its base-case analysis the company used the exponential function to predict overall survival. This was informed by a panel of 6 clinical experts, who advised that the survival projections from the exponential function most closely matched survival in NHS practice for sorafenib and lenvatinib. The panel suggested the generalised gamma function may also be plausible. The ERG noted that the exponential function did not provide a good statistical fit to the observed trial data and imposed an unsupported assumption of a constant mortality hazard over time. It explained that comparing survival projections from a closely controlled clinical trial, subject to strict patient selection criteria, with survival in NHS clinical practice is a flawed approach. This is because the trial was

likely to achieve better outcomes than in NHS practice. It advised that the log-normal function was the best-fitting model, although the log-logistic and generalised gamma functions also fitted the data well. It explained that there was no strong clinical rationale to favour any of these 3 functions over the other. Therefore, its preferred choice would be the best-fitting log-normal function. After technical engagement, the company agreed that the log-normal distribution was clinically plausible. The clinical experts advised that a constant mortality hazard over time was not plausible for people with advanced HCC. The committee agreed with the ERG and clinical experts that the exponential function should not be used to model overall survival. It noted that lenvatinib was predicted to have higher or lower life expectancy than sorafenib, depending on the choice of overall-survival function. The committee understood that this was an artefact of the company's modelling approach. The choice of survival function for atezolizumab plus bevacizumab and sorafenib was informed directly by IMbrave150 data. Survival for lenvatinib was informed by applying a hazard ratio from the NMA to the function for atezolizumab plus bevacizumab. The committee agreed that it would have been preferable to apply the hazard ratio from the NMA for lenvatinib compared with sorafenib to the sorafenib survival function, because the drugs have a similar mechanism of action. However, it would not expect this to have much effect on cost effectiveness. The committee concluded that it would consider cost-effectiveness results using the log-normal function to model survival, because this was the best-fitting function. But the log-logistic and generalised gamma functions were plausible and should also be considered.

# Exploratory analysis

## The ERG's exploratory analyses for bodyweight and region should be considered as a way of exploring uncertainty

3.7 The company included a large number of sensitivity analyses in its submission. The ERG did exploratory analyses to test the effect on cost effectiveness of bodyweight (less than 60 kg compared with 60 kg or more) and region (all regions compared with excluding Asian regions, except Japan). The ERG explained that it was important to explore the

potential effect of bodyweight because the dosing of lenvatinib and bevacizumab depend on bodyweight, so it affects associated drug costs. It explained that region was also potentially important because the underlying cause of HCC varies by region. Hepatitis C is more common in Europe, North America and Japan, and hepatitis B is more common in Asia (excluding Japan) and Africa. In Europe and North America, HCC is increasingly associated with metabolic dysfunction-associated fatty liver disease, obesity and exposure to toxic substances. The committee noted that IMbrave150 was done in 17 countries, with 40% of patients from Asia (excluding Japan). The ERG advised that considering the results for all combinations of the 2 bodyweight and 2 region categories allowed the committee to consider possible upper and lower bounds of the cost-effectiveness estimate for a given preferred analysis. The committee noted that the hazard ratio for overall survival was only marginally affected by bodyweight and region. It agreed that it would not be appropriate to make different recommendations for atezolizumab plus bevacizumab based on bodyweight or region. However, it felt that the ERG's exploratory analyses would be useful in considering the uncertainty around the cost-effectiveness estimates. So, it concluded that it would consider the exploratory analyses in its decision making.

# End of life

## Atezolizumab plus bevacizumab meets the criteria to be considered an end of life treatment

3.8 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. It reviewed the mean overall-survival estimates from the model. Life expectancy with sorafenib and lenvatinib was less than 24 months. Also, the undiscounted life-years gained for atezolizumab plus bevacizumab were much higher than 3 months, regardless of which overall-survival function was used. The committee therefore concluded that the end of life criteria were met.

# Cost-effectiveness analysis

## The most plausible ICERs are within the range normally considered a cost-effective use of NHS resources

3.9 All the ERG's base-case incremental cost-effectiveness ratios (ICERs) for atezolizumab plus bevacizumab, compared with sorafenib and with lenvatinib, were below £50,000 per quality-adjusted life year (QALY) gained. The exact ICERs cannot be reported because of confidential commercial arrangements for the drugs. The ERG's base-case analysis used the log-normal function to model survival and considered all 4 combinations of the bodyweight and region categories. The ICERs were below £50,000 per QALY gained in most of the ERG's exploratory analyses. There was only 1 plausible analysis in which the ICERs exceeded £50,000 per QALY gained. This was in comparison with sorafenib, using the log-logistic distribution to model survival and the least favourable bodyweight and region categories for atezolizumab plus bevacizumab (bodyweight of 60 kg or more and excluding Asian regions, except Japan). The committee recalled that the cost-effectiveness model used indirect NMA evidence to inform the relative effectiveness of lenvatinib, and this evidence was uncertain (see section 3.4). However, it noted that the clinical experts considered lenvatinib and sorafenib to have similar effectiveness (see section 3.5). It agreed that it was reasonable to conclude that atezolizumab plus bevacizumab would be cost effective compared with both lenvatinib and sorafenib. The committee concluded that the most plausible ICER was highly likely to be less than £50,000 per QALY gained for atezolizumab plus bevacizumab compared with sorafenib and with lenvatinib.

# Innovation

## The model adequately captures the benefits of atezolizumab plus bevacizumab

3.10 The company considered atezolizumab plus bevacizumab to be innovative because it is a targeted immunotherapy with efficacy in the

first-line treatment of advanced and unresectable HCC. The clinical experts noted that it is expected to replace sorafenib and lenvatinib because it improves progression-free survival and overall survival for this population. The committee recognised these benefits for people with advanced or unresectable HCC. However, it concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.

# Conclusion

## Atezolizumab plus bevacizumab is recommended for routine commissioning

3.11 The committee acknowledged the need for a better treatment option for adults with advanced or unresectable HCC. The most plausible estimates of cost effectiveness for atezolizumab plus bevacizumab compared with sorafenib and with lenvatinib were within what NICE considers an acceptable use of NHS resources. Therefore, atezolizumab plus bevacizumab is recommended as an option for advanced or unresectable HCC in adults with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1, who have not had previous systemic treatment.

# 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 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.

4.4 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 advanced or unresectable hepatocellular carcinoma and the doctor responsible for their care thinks that atezolizumab with bevacizumab 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 C.

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.

**Luke Cowie**
Technical lead

**Jamie Elvidge**
Technical adviser

**Gavin Kenny**
Project manager

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# Accreditation