NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

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

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

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

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

Issue date: October 2018

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: 16 November 2018

Second appraisal committee meeting: 27 November 2018

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

1 Recommendations

1.1 Venetoclax with rituximab is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults.

1.2 This recommendation is not intended to affect treatment with venetoclax with rituximab 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

Relapsed or refractory chronic lymphocytic leukaemia is currently usually treated with ibrutinib. Clinical trial evidence suggests that venetoclax plus rituximab increases how long people live for before their disease gets worse compared with bendamustine plus rituximab (a combination that is rarely used now). Indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, so no firm conclusions can be drawn about the size of the benefit for venetoclax plus rituximab.

There are problems with the economic model inputs. For example, there are inconsistencies between the clinical- and cost-effectiveness data used because the costs of venetoclax treatment last for 2 years but the benefits continue for more than 2 years. Because of the implausible inputs in the economic model there is no 1 most plausible cost-effectiveness estimate. Estimates ranged widely from venetoclax plus rituximab being less costly and more effective to venetoclax plus rituximab being less costly and less effective when compared with ibrutinib plus rituximab. Therefore, venetoclax with rituximab cannot be recommended for routine use in the NHS. Also, the treatment cannot be recommend for inclusion in the Cancer Drugs Fund.

2 Information about venetoclax with rituximab

Anticipated marketing authorisation indication	On 21 September 2018, the Committee for Medicinal Products for Human Use adopted a positive opinion recommending a variation to the marketing authorisation for venetoclax with rituximab (Venclyxto, AbbVie). It adopted a new indication: venetoclax with rituximab is indicated 'for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy'.
Dosage in the anticipated marketing authorisation	Based on the company's submission, the anticipated recommended dose of venetoclax is: • in the titration phase, 20 mg orally once daily for 7 days, increasing by gradual weekly increments over 5 weeks to 400 mg once daily • in the post-titration phase, 400 mg orally once daily. Rituximab 375 mg/m^2 is given intravenously on day 1 of cycle 1 (a cycle is 28 days), followed by 500 mg/m^2 on day 1 of cycles 2 to 6. Rituximab is stopped after cycle 6. Venetoclax can be taken for a maximum of 2 years from day 1 of cycle 1 of rituximab, or until disease progression or unacceptable toxicity.
Price	A 112-pack of 100 mg tablets costs £4,789.47 (excluding VAT; British national formulary online, accessed September 2018). The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

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

New treatment option

People with chronic lymphocytic leukaemia would welcome a new treatment option

3.1 The clinical and patient experts noted that people with relapsed or refractory chronic lymphocytic leukaemia have limited treatment options. The committee also heard that some people spend a long time in the 'watch and wait' stage of the treatment pathway, which can have a negative psychological effect on them because of worrying about relapse. The patient experts highlighted that some people have cardiovascular comorbidities, which means that they have limited treatment options so would welcome a range of treatments. The committee understood that, although venetoclax plus rituximab can cause serious side effects (tumour lysis syndrome), it is generally well tolerated. It concluded that venetoclax plus rituximab could be an important treatment option for people with relapsed or refractory chronic lymphocytic leukaemia.

Clinical management

Current treatment for chronic lymphocytic leukaemia is ibrutinib and this is the most appropriate comparator

3.2 The clinical experts stated that people with chronic lymphocytic leukaemia whose disease has relapsed after 1 previous chemo-immunotherapy would be eligible for B-cell receptor pathway inhibitor therapy. They confirmed that most people with relapsed or refractory chronic lymphocytic leukaemia have ibrutinib rather than idelalisib plus rituximab. This is because idelalisib plus rituximab has an intensive dosing regimen, and is associated with an increased risk of infection. The committee understood that venetoclax plus rituximab would be used to treat relapsed or refractory chronic lymphocytic leukaemia in people who have had at least 1 previous therapy. The clinical experts confirmed that, within the clinical pathway, both ibrutinib and venetoclax plus rituximab can be used

for chronic lymphocytic leukaemia with or without 17p deletion or TP53 mutation. The committee concluded that established clinical management is ibrutinib, making it a relevant comparator for this appraisal.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice in England

3.3 The main clinical evidence came from MURANO (n=389), a phase III multicentre open-label parallel-arm randomised controlled trial. It included patients aged 18 years or over with relapsed or refractory chronic lymphocytic leukaemia, and compared venetoclax plus rituximab (n=194) with bendamustine plus rituximab (n=195). When the trial was started, bendamustine plus rituximab was considered the most effective treatment for managing relapsed or refractory chronic lymphocytic leukaemia. The data presented were from a May 2017 data cut; the committee stated that a more recent data cut would be informative. Venetoclax was given for a maximum of 2 years, or until disease progression or unacceptable toxic effects, whichever occurred sooner. The clinical experts explained that this was a reasonable approach because about 60% of patients in the trial had negative minimal residual disease status, which is a strong predictor of lasting remission in patients with chronic lymphocytic leukaemia. The patient experts stated that they would welcome the fixed treatment duration, especially if this was explained to them when treatment was started. The committee concluded that the clinical-effectiveness evidence was relevant to NHS clinical practice in England.

Clinical effectiveness

Venetoclax plus rituximab is clinically effective compared with bendamustine plus rituximab

3.4 The primary outcome measure in MURANO was investigator-assessed median progression-free survival. It was statistically significantly longer

with venetoclax plus rituximab compared with bendamustine plus rituximab (median not reached versus 17 months respectively; hazard ratio [HR] 0.17, 95% confidence interval [CI] 0.11 to 0.25; p<0.0001). Independent review committee-assessed median progression-free survival (a secondary outcome measure) was also statistically significantly longer with venetoclax plus rituximab compared with bendamustine plus rituximab (median not reached versus 18.1 months; HR 0.19, 95% CI 0.13 to 0.28; p<0.0001). The committee noted that follow-up for these data was a median of 23.8 months, and recalled that a later data cut was available. It concluded that, although venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab, the immaturity of the data raised uncertainty, and that more recent data from the trial would be welcomed.

The company's unanchored matched-adjusted indirect comparison (MAIC) analysis is not clinically plausible

3.5 The company did an MAIC to allow an indirect comparison of venetoclax plus rituximab with the comparators ibrutinib and idelalisib plus rituximab. The committee discussed the appropriateness of this approach. It noted the ERG concerns that the results from the unanchored analysis for venetoclax plus rituximab compared with ibrutinib were clinically implausible. This was because the hazard ratio estimate for progression-free survival was higher than the estimate for overall survival, which was not the case in the comparator trials. The clinical experts stated that the overall survival hazard ratio estimate was not plausible whereas the progression-free survival estimate was. They explained that they believed venetoclax plus rituximab to have similar, or better, efficacy to ibrutinib and that it is unlikely that it is inferior to ibrutinib. The ERG also noted that patients had not been matched correctly, making the population in the RESONATE trial (ibrutinib) appear healthier than the population in the MURANO trial (venetoclax plus rituximab). This meant that the benefit of ibrutinib may have been underestimated. The committee noted that the

MAIC had not been adjusted to account for the fixed treatment duration of venetoclax, which may have resulted in a greater treatment benefit for venetoclax plus rituximab. The committee agreed that the MAIC was flawed. It stated that it would have liked to have seen an analysis reflecting the fixed treatment duration of venetoclax and allowing for a change in the treatment effect after 2 years.

No conclusions could be drawn from the ERG's network meta-analysis

3.6 The ERG carried out an alternative indirect comparison using a fixed-effect network meta-analysis to estimate the relative benefits of venetoclax plus rituximab compared with ibrutinib. The committee acknowledged this analysis had a similar limitation to the company's MAIC because it had not accounted for the fixed duration of venetoclax treatment. It also highlighted that the network meta-analysis was based on Hillmen et al 2015, which relied on a simple adjustment that may have biased the results in either direction. The committee would have liked to have seen analyses with scenarios reflecting a change in the treatment effect after 2 years. It concluded that it could not draw conclusions from the ERG's network meta-analysis.

Adverse effects

Venetoclax plus rituximab is well tolerated

3.7 The clinical experts explained that venetoclax plus rituximab is occasionally associated with tumour lysis syndrome. This can cause a rapid breakdown of cancer cells, and can lead to complications such as kidney failure. The clinical experts explained that the 5-week dose escalation schedule helps to prevent tumour lysis syndrome. They noted that there had been few cases of tumour lysis syndrome since this dosing schedule had been implemented. The committee noted the risks associated with venetoclax plus rituximab, but agreed that the treatment had an acceptable safety profile.

The company's economic model

The model structure is appropriate for decision-making

3.8 The company's model consisted of a de novo partitioned survival model, with 3 states for progression-free and progressed disease, and death. The main effectiveness data came from the MURANO trial. It was used to estimate progression-free and overall survival using parametric curves fitted to Kaplan−Meier data. In the model, venetoclax was administered for a maximum of 2 years or until disease progression or unacceptable toxic effects, whichever occurred sooner (see section 3.3). The committee concluded that the model structure was appropriate for decision-making.

The extrapolation of survival data is not appropriate

3.9 The company explored various approaches for extrapolating survival data. It chose a Weibull distribution as the preferred parametric model for both overall and progression-free survival. The committee noted that, because the extrapolation was based on the original trial population instead of the matched population, the extrapolation did not represent the correct population. The committee also noted that the matching had not been conducted correctly, and that the hazard ratios used in the company's MAIC did not reflect the fixed duration of venetoclax treatment (see section 3.5). The committee concluded that the company's approach to extrapolating survival data was not appropriate.

Potential loss of treatment effect after 2 years with venetoclax plus rituximab is not reflected in the analysis

3.10 The committee recalled that a 2-year stopping rule was incorporated into MURANO. It noted that there were no data from MURANO on the effect of implementing the stopping rule because the data cut was based on a median follow-up of 23.8 months. The company assumed that venetoclax remained effective throughout the model's time horizon of 20 years, irrespective of time off treatment or whether the stopping rule was

implemented. The committee stated that it would be more appropriate to allow for a diminishing treatment effect after 2 years. It agreed that potential loss of treatment effect was not reflected in the analysis. It therefore concluded that it would have liked to have seen a scenario analysis in which the treatment benefit in the extrapolated phase diminishes over time.

Utility values in the model

The utility values in the company's economic model need to be further explored by additional analysis based on MURANO data

3.11 The company stated that the utility values from the MURANO trial were too high and implausible to use in the economic model. It used utility values from previous NICE technology appraisal guidance for chronic lymphocytic leukaemia, including venetoclax monotherapy (TA487) and idelalisib with rituximab (TA359). The committee noted that there was a difference of 0.14 between pre-progression and post-progression utilities used in the economic model. It agreed that it would like to see an analysis including the utility values from the MURANO trial to gain a better understanding of the difference between the pre- and post-progression-free survival states and its impact on the cost-effectiveness analysis. The committee concluded that the utility values used in the company's economic model need to be further explored using the MURANO data.

Costs and resource use in the economic model

The costs of treatment and treatment effect duration with venetoclax plus rituximab are not correctly matched in the economic model

3.12 The company limited the cost of venetoclax treatment to 2 years, similar to the treatment duration of venetoclax in MURANO. The committee recalled that the company's extrapolation of survival data did not account for any diminishing treatment effect after venetoclax treatment was stopped at 2 years (see section 3.9). It agreed that the assumptions for

the efficacy and cost data in the model should have been consistent, and that benefit and cost should not be uncoupled. The committee concluded that costs of treatment and treatment effect duration with venetoclax plus rituximab were not correctly matched in the economic model.

Cost-effectiveness results

Venetoclax plus rituximab is not recommended for routine commissioning

3.13 The committee noted that MURANO showed that progression-free survival increased with venetoclax plus rituximab, but that the data were immature (see section 3.4). The committee agreed that a more recent data cut from MURANO would be informative. It acknowledged that there were no direct data comparing venetoclax plus rituximab with ibrutinib. It also noted that the results of both the company's MAIC and the ERG's network meta-analysis produced implausible hazard ratios that did not reflect the potential loss of treatment effect at 2 years when treatment with venetoclax plus rituximab stops (see sections 3.5 and 3.6). The committee was concerned about the extrapolation of the treatment effect over 20 years and lack of scenarios in which treatment effect diminished after 2 years (see section 3.9). It also agreed that such a scenario would be consistent with the costs of venetoclax treatment being applied for only 2 years in the economic model (see section 3.10). The committee acknowledged that, because of implausible inputs in the economic model (see section 3.12), it had not been presented with 1 most plausible incremental cost-effectiveness ratio (ICER). It agreed that the ICERs had a wide range; from venetoclax plus rituximab being less costly and more effective than ibrutinib plus rituximab to venetoclax plus rituximab being less costly and less effective than ibrutinib plus rituximab. It concluded that some of the uncertainty in the modelling could be addressed by additional analyses based on a recent data cut from MURANO and by scenario analyses accounting for loss of treatment effect after 2 years. The committee noted comments from the clinical experts that venetoclax

plus rituximab has similar, or better, efficacy to ibrutinib (see section 3.5). It agreed that, because of uncertainties in the company's modelling, a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties. The committee concluded that it could not recommend venetoclax plus rituximab for routine NHS use.

Innovation

There are no additional benefits that are not captured in the cost-effectiveness analysis

3.14 The company considered venetoclax plus rituximab to be an innovative treatment for 2 reasons. It increases the chance of enduring remission and negative minimal residual disease status without the associated risks of repeated lines of chemotherapy or other agents that offer no chance of negative minimal residual disease status. It also offers very good and comparable treatment options to people with relapsed or refractory chronic lymphocytic leukaemia, so should be available as a choice of therapy for this group. The committee concluded that venetoclax plus rituximab would be beneficial. However, it noted that it had not been presented with evidence of any additional benefits that were not captured in the measurement of quality-adjusted life years.

End of life

Venetoclax plus rituximab does not meet the criteria to be considered a life-extending treatment at the end of life

3.15 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. This states that a treatment can be considered as a 'life-extending treatment at the end of life' if: it is indicated for patients with a short life expectancy, normally less than 24 months; and it offers an extension to life, normally of a mean value of at least an additional

3 months compared with current NHS treatment. The committee noted that the results of MURANO suggested that venetoclax plus rituximab could increase life expectancy by more than 3 months compared with standard care. However, the short life-expectancy criterion of less than 24 months was not met because people with chronic lymphocytic leukaemia have a life expectancy of more than 2 years. Overall, the committee concluded that venetoclax did not meet the criteria to be considered a life-extending treatment at the end of life.

Cancer Drugs Fund

Venetoclax plus rituximab is not suitable for the Cancer Drugs Fund

3.16 Having concluded that venetoclax plus rituximab could not be recommended for routine use, the committee then considered whether it could be recommended for treating relapsed or refractory chronic lymphocytic leukaemia within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee noted that the company did not make a case for venetoclax plus rituximab to be included in the Cancer Drugs Fund. It also noted that it had not been presented with a robust ICER on which it could decide whether there was plausible potential for venetoclax plus rituximab to be cost effective. The committee concluded that venetoclax plus rituximab did not meet the criteria to be included in the Cancer Drugs Fund.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

on information gathered by NICE, and in consultation with consultees and commentators.

Professor Stephen O'Brien
Chair, Appraisal Committee
October 2018

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.

Julia Sus
Technical Lead

Sally Doss
Technical Adviser

Stephanie Callaghan

Project Manager

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