NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Venetoclax with rituximab for previously treated relapsed or refractory chronic lymphocytic leukaemia

1. Recommendations

1.1 Venetoclax with rituximab is recommended, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy. It is recommended only if the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

People with previously treated chronic lymphocytic leukaemia (relapsed or refractory chronic lymphocytic leukaemia) usually have ibrutinib. Clinical trial evidence shows that venetoclax plus rituximab increases how long people live for before their disease gets worse compared with bendamustine plus rituximab (a combination that is not frequently used). There is no trial directly comparing venetoclax plus rituximab with ibrutinib. Indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, but can be used for decision making because there is no other evidence.

Estimates from the cost-effectiveness analyses range from venetoclax plus rituximab being less costly and more effective to it being less costly and less effective, when compared with ibrutinib. Although it is uncertain how effective venetoclax is compared with ibrutinib, a cost-comparison analysis shows that venetoclax plus rituximab is considered to be a cost-effective use of NHS resources and it is recommended for routine use in the NHS.

2. Information about venetoclax with rituximab

Marketing authorisation indication	Venetoclax (Venclyxto, AbbVie) plus 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 marketing authorisation	The 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 should be administered after the patient has completed the dose-titration schedule and has had the recommended daily dose of 400 mg venetoclax for 7 days. 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 (commercial access agreement). This makes venetoclax with rituximab 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 6) 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 previously treated chronic lymphocytic leukaemia (relapsed or refractory chronic lymphocytic leukaemia) have limited treatment options. They explained that some people spend a long time in the 'watch and wait' stage of the treatment pathway, which can have a psychological effect on them because of worry about relapse. The patient experts highlighted that some people have cardiovascular comorbidities, which limits their treatment options, so they 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 would be welcomed as a new 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 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 stated that people with chronic lymphocytic leukaemia whose disease has relapsed after 1 previous chemo-immunotherapy would be eligible for a B-cell receptor pathway inhibitor, such as ibrutinib or idelalisib. They confirmed that most people have ibrutinib rather than idelalisib plus rituximab, because idelalisib plus rituximab has an intensive dosing regimen and is associated with increased risk of infection. The clinical experts confirmed that, within the clinical pathway, both ibrutinib and venetoclax plus rituximab can be used for chronic lymphocytic leukaemia. 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). In the company's original submission the data came from a May 2017 data cut, with a median follow-up of 23.8 months from starting treatment. In response to consultation the company presented data from a May 2018 data cut, with a median follow-up of 36 months from starting treatment. Venetoclax plus rituximab was given for a maximum of 2 years in MURANO, or until disease progression or unacceptable toxic effects, whichever occurred sooner (specified in the summary of product characteristics). The clinical experts explained that this was a reasonable approach because in this time about 60% of patients in the trial had undetectable minimal residual disease, which is a strong predictor of lasting remission in patients with chronic lymphocytic leukaemia. The patient experts stated that people would welcome a fixed treatment duration, especially if this was explained to them when treatment was started. The committee concluded that the clinical-effectiveness evidence is 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. The May 2018 data cut showed that progression-free survival was statistically significantly longer with venetoclax plus rituximab than with bendamustine plus rituximab (median not reached, compared with 16 months respectively; hazard ratio 0.16, 95% confidence interval [CI] 0.12 to 0.23; p<0.0001). Overall survival was longer with venetoclax plus rituximab than with bendamustine plus rituximab (median not reached in either group; hazard ratio 0.50, 95% CI 0.30 to 0.85; p=0.0093). The committee considered how many patients did not have undetectable minimal residual disease because they might need additional treatment after 2 year's therapy with venetoclax plus rituximab. The latest data cut from MURANO confirmed that at 24 months 48% of people had undetectable minimal residual disease and after an additional 9.9 months of follow-up most patients still had undetectable minimal residual disease. In the bendamustine plus rituximab arm only 2% of patients had undetectable minimal residual disease at 24 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab.

The company's unanchored matched-adjusted indirect comparison (MAIC) analysis has limitations

3.5 Because the comparator in MURANO was bendamustine plus rituximab, a combination that is no longer standard care (see section 3.2), the company did a MAIC to indirectly compare progression-free survival and overall survival for venetoclax plus rituximab with ibrutinib or idelalisib plus rituximab. The committee had previously agreed that idelalisib plus rituximab was not a relevant comparator so only considered the comparison with ibrutinib (see section 3.2). The committee discussed the

appropriateness of this approach. At the first committee meeting, it noted the ERG's concerns that the results from the unanchored analysis for venetoclax plus rituximab compared with ibrutinib were clinically implausible. This was because the estimated hazard ratio for progression-free survival (hazard ratio 0.696, 95% CI 0.412 to 1.178) was much higher than the estimate for overall survival (hazard ratio 0.297, 95% CI 0.129 to 0.684), 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 was unlikely to be inferior to ibrutinib. In response to consultation, the company presented a new MAIC based on the May 2018 data cut from MURANO. The ERG noted that the results of the analysis were still clinically implausible and the hazard-ratio estimate for progression-free survival (hazard ratio 0.797, 95% CI 0.505 to 1.258) was higher than the estimate for overall survival (hazard ratio 0.445, 95% CI 0.218 to 0.909). The ERG also highlighted that the effectiveness of ibrutinib was still underestimated in the analysis. The committee concluded that the company's updated MAIC had some limitations, but because there was no other evidence it was acceptable for decision making.

The ERG's network meta-analysis also has limitations

3.6 The ERG did an alternative indirect comparison using a fixed-effect network meta-analysis to estimate the relative benefits of venetoclax plus rituximab compared with ibrutinib. The network meta-analysis showed that progression-free survival and overall survival were shorter with venetoclax plus rituximab than with ibrutinib (progression-free survival hazard ratio 1.43, 95% CI 0.78 to 2.61; overall survival hazard ratio 1.08, 95% CI 0.42 to 2.73). The ERG also highlighted that the network meta-analysis was based on Hillmen et al. (2015), which relies on a simple adjustment that may have biased the results. In response to consultation and the

company's new evidence the ERG produced a new network meta-analysis based on the May 2018 data cut from MURANO. The revised analysis still showed that progression-free survival and overall survival were shorter with venetoclax plus rituximab than with ibrutinib (progression-free survival hazard ratio 1.20, 95% CI 0.68 to 2.12; overall survival hazard ratio 1.12, 95% CI 0.48 to 2.63). The committee noted that the new network meta-analysis was also based on the uncertain data from Hillmen et al. (2015) and therefore the limitations still applied. The committee concluded that neither the company's MAIC nor the ERG's network meta-analysis were ideal but, because there were no other analyses, it agreed that they can be used for decision making (see section 3.13).

Adverse effects

Venetoclax plus rituximab is generally well tolerated

3.7 The clinical experts explained that venetoclax is occasionally associated with tumour lysis syndrome. This is caused by 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 have been few cases of tumour lysis syndrome since this dosing schedule was implemented in clinical practice for venetoclax monotherapy. The committee noted the risks associated with venetoclax plus rituximab, but concluded that it is generally well tolerated.

The company's economic model

The model structure is appropriate for decision making

3.8 The company's model is a de novo partitioned survival model with 3 states (progression-free, progressed disease and death). Data from MURANO was used to estimate progression-free and overall survival using parametric curves fitted to Kaplan−Meier data. In the model,

venetoclax plus rituximab was taken for a maximum of 2 years or until disease progression or unacceptable toxic effects, whichever occurred sooner. This was similar to how it was used in MURANO (see section 3.3). The committee concluded that the model structure was appropriate for decision making.

The extrapolation of survival data is reasonable

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 the extrapolation did not represent the correct population because it was based on the original trial population instead of the matched population. The committee also noted that the matching had not been done correctly (see section 3.5). In response to consultation, the company presented a scenario in which the extrapolation was based on the matched population rather than on the original population from MURANO. The committee concluded that the company's new approach for extrapolating survival data was reasonable and noted that it had little effect on the incremental cost-effectiveness ratio (ICER).

Potential loss of treatment effect after 2 years with venetoclax plus rituximab is reflected in the company's revised analyses

3.10 The committee recalled that a 2-year stopping rule was incorporated into MURANO and is also specified in the summary of product characteristics. In the company's original submission, the company assumed that venetoclax plus rituximab remained effective throughout the model's time horizon of 30 years, irrespective of time off treatment or whether treatment was stopped at 2 years. In response to consultation the company presented scenario analyses with a diminishing treatment benefit from 2 years, with annual increases in hazard ratios of 5%, 10%, 20%, 30% and 40%. The ERG repeated these analyses and agreed that the diminishing treatment benefit was correctly incorporated into the

company's base-case analysis. The committee noted that there were limited data from MURANO on the effect of stopping treatment at 2 years because the latest data cut only has a median follow-up of 36 months. The committee concluded that given the lack of evidence it was not possible to know how much venetoclax plus rituximab's treatment effect continues over time after treatment has stopped. But because there were no other data it agreed that the range of estimates could be used for decision making.

Utility values in the model

The utility values in the company's economic model are reasonable

3.11 The company stated that the utility values from MURANO 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 and idelalisib with rituximab. In response to consultation, the company presented scenarios using utility values from MURANO for the pre-progression state. It explored a range of potential values for the post-progression state because these could be not obtained from the trial because of lack of available data. The committee concluded that the difference between the utility values for pre- and post-progression-free survival from MURANO was uncertain and noted that it had little effect on the ICER.

Costs and resource use in the economic model

The costs of treatment and the treatment-effect duration with venetoclax plus rituximab are captured in the company's revised analyses

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 provided a range of analyses to account for the diminishing treatment effect of venetoclax with rituximab (see section 3.10). The committee agreed that the scenario analyses captured

the loss of treatment effect of venetoclax plus rituximab well. It concluded that there was no direct evidence to define the most appropriate continued treatment benefit for venetoclax plus rituximab, and therefore it would consider the range of estimates presented.

Cost-effectiveness results

The company's and the ERG's ICERs differ greatly but are within the range considered a cost-effective use of NHS resources

3.13 The company's revised analyses submitted in response to consultation used results from the new MAIC analysis (see section 3.5) and the discounted price for venetoclax. The ERG's revised base-case analysis used results from the new network meta-analysis (see section 3.6) and the discounted prices for both venetoclax and ibrutinib. The committee noted that the company's cost-effectiveness estimates showed that venetoclax plus rituximab was cheaper and more effective than ibrutinib, but the ERG's base-case analysis showed venetoclax to be cheaper but less effective (the ICERs incorporated confidential discounts so cannot be reported here). The committee agreed that because of the lack of trial data directly comparing venetoclax plus rituximab with ibrutinib, and limitations in the MAIC and the network meta-analysis (see section 3.5 and section 3.6), it could not decide which analysis was more appropriate for decision making. It was therefore not able to determine the most plausible ICER. The committee concluded that even though the relative treatment effect of venetoclax plus rituximab compared with ibrutinib was uncertain, both sets of analyses produced ICERs within the range considered to be an acceptable use of NHS resources based on the cost per quality-adjusted life year (QALY) lost or gained.

The cost-comparison analysis provides supporting evidence that venetoclax plus rituximab is a cost-effective use of NHS resources

3.14 In response to consultation, the company presented a cost comparison for venetoclax plus rituximab with ibrutinib to address uncertainties in the modelling expressed by the committee during the first committee meeting (see section 3.5, section 3.6 and sections 3.9 to 3.12). The company based the cost-comparison analysis on the assumption of equal efficacy between venetoclax plus rituximab and ibrutinib. The committee concluded that this was appropriate based on the clinical experts' opinion (see section 3.5) and because there was no evidence of a difference in treatment effect. The company's cost-comparison analysis provided scenarios for 30%, 50% and 100% of people having subsequent ibrutinib treatment if they did not have undetectable minimal residual disease after 2 years of treatment with venetoclax plus rituximab (see section 3.4). The ERG repeated these scenario analyses but they used hazard ratios from the network meta-analysis and a generalised gamma curve for the extrapolation of treatment effect instead of hazard ratios from the MAIC and Weibull curve for the extrapolation, which was the company's preferred approach. The committee considered that based on the May 2018 data cut from MURANO the scenarios for 30% to 50% of people having ibrutinib were the most clinically plausible, and the 100% scenario was too pessimistic and not supported by the evidence. It concluded that both the company's and the ERG's analyses supported the estimates from the cost-effectiveness analyses (the analyses incorporate confidential discounts so exact values cannot be reported here).

Innovation

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

3.15 The company considered venetoclax plus rituximab to be an innovative treatment. This was because it increases the chance of enduring

remission and having undetectable minimal residual disease, without the associated risks of repeated lines of chemotherapy or other agents that offer little chance of having undetectable minimal residual disease. It also offers another very good treatment option 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 QALYs.

End of life

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

3.16 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 a mean value of at least an additional 3 months compared with current NHS treatment. The committee noted that the results of MURANO suggest that venetoclax plus rituximab could increase life expectancy by more than 3 months compared with bendamustine plus rituximab, although this is not the appropriate comparator. 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 does not meet the criteria to be considered a life-extending treatment at the end of life.

Conclusion

Venetoclax plus rituximab is a cost-effective use of NHS resources and is recommended for routine commissioning

3.17 In response to consultation the company presented additional data from MURANO showing that venetoclax plus rituximab increases progression-free survival compared with bendamustine plus rituximab, and that most patients had undetectable minimal residual disease after 2 years of treatment. Therefore the committee concluded that venetoclax plus rituximab is a clinically effective treatment compared with bendamustine plus rituximab (see section 3.4). It considered the new MAIC and network meta-analysis comparing venetoclax plus rituximab with ibrutinib (the appropriate comparator), but it could not decide which was more appropriate because of their limitations. However, because there were no other analyses it agreed to take them into account during decision making (see sections 3.5 and 3.6). It noted that the ICERs ranged from venetoclax plus rituximab being less costly and more effective than ibrutinib (company estimates) to venetoclax plus rituximab being less costly and less effective than ibrutinib (ERG estimates). However, both analyses produced ICERs showing that venetoclax was a cost-effective treatment (see section 3.13). The committee noted that the cost-comparison analysis supported the conclusions from the cost-effectiveness analysis. The committee concluded that venetoclax with rituximab was a cost-effective use of NHS resources and could be recommended as an option for treating chronic lymphocytic leukaemia in adults after at least 1 previous 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 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 chronic lymphocytic leukaemia and has had at least 1 previous therapy and the doctor responsible for their care thinks that venetoclax with rituximab is the right treatment, it should be available for use, in line with NICE's recommendations.

5. Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
November 2018

6. 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

ISBN: [to be added at publication]