NICE National Institute for Health and Care Excellence

NICE guidance

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia

Technology appraisal guidance
Published: 9 December 2020

www.nice.org.uk/guidance/ta663

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 Venetoclax plus obinutuzumab is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:

- there is a 17p deletion or TP53 mutation, or
- there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable, and
- the companies provide the drugs according to the commercial arrangements.

1.2 Venetoclax plus obinutuzumab is recommended for use within the Cancer Drugs Fund as an option for untreated CLL in adults, only if:

- there is no 17p deletion or TP53 mutation, and FCR or BR is suitable, and
- the conditions in the managed access agreement for venetoclax plus obinutuzumab are followed.

1.3 These recommendations are not intended to affect treatment with venetoclax plus obinutuzumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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

People with untreated CLL are offered different treatments depending on whether they are likely to tolerate chemo-immunotherapy, and whether they have certain genetic abnormalities (such as a 17p deletion or TP53 mutation). In people with a 17p deletion or TP53 mutation, CLL does not usually respond well to standard chemo-immunotherapy, and ibrutinib is usually used. In people without a 17p deletion or TP53 mutation, FCR or BR are the most common chemo-immunotherapies used. If FCR or BR is unsuitable, obinutuzumab plus chlorambucil is used instead.

Venetoclax plus obinutuzumab has not been directly compared with ibrutinib in people with a 17p deletion or TP53 mutation, and the results of an indirect comparison are uncertain. The cost-effectiveness estimates suggest that venetoclax plus obinutuzumab is less effective but less costly than ibrutinib. These estimates are within what NICE normally considers an acceptable use of NHS resources, so it is recommended for routine use in the NHS for these people.

Clinical trial evidence shows that, in people without a 17p deletion or TP53 mutation and for whom FCR or BR is unsuitable, CLL treated with venetoclax plus obinutuzumab takes longer to progress than CLL treated with obinutuzumab plus chlorambucil. The cost-effectiveness estimates suggest that venetoclax plus obinutuzumab is more effective and less costly than obinutuzumab plus chlorambucil. Therefore, venetoclax plus obinutuzumab is recommended for routine use in the NHS for these people.

Venetoclax plus obinutuzumab has not been directly compared with FCR or BR in people without a 17p deletion or TP53 mutation and for whom these treatments are suitable. The results of an indirect comparison are uncertain. Also, some of the cost-effectiveness estimates are higher than the range NICE normally considers an acceptable use of NHS resources. Therefore, venetoclax plus obinutuzumab cannot be recommended for routine use in the NHS for these people.

An ongoing clinical trial is directly comparing venetoclax plus obinutuzumab with FCR and BR in people with untreated CLL without a 17p deletion or TP53 mutation for whom these treatments are suitable. Data from this trial could help address the uncertainty about the clinical effectiveness of venetoclax plus obinutuzumab in this population. Venetoclax plus obinutuzumab has the potential to be a cost-effective use of NHS resources. Therefore, it is recommended for use in the Cancer Drugs Fund for these people while the data from the trial are collected.

2 Information about venetoclax with obinutuzumab

Marketing authorisation indication

2.1 Venetoclax (Venclyxto, AbbVie) with obinutuzumab is indicated 'for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia'.

Dosage in the marketing authorisation

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

Price

2.3 A 112-pack of 100-mg venetoclax tablets costs £4,789.47 (excluding VAT; BNF online, accessed August 2020). The company has a commercial arrangement. This makes venetoclax 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.

2.4 The price of obinutuzumab is £3,312 per 1,000-mg vial (excluding VAT; BNF online, accessed August 2020). Roche has a commercial arrangement. This makes obinutuzumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is Roche's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by AbbVie, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 3 issues were resolved during the technical engagement stage, and agreed that:

- adults with untreated chronic lymphocytic leukaemia (CLL) for whom fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is suitable should be considered in the appraisal (issue 1, see technical report page 24)
- the most appropriate utility value for the 'pre-progression, off-treatment' health state is 0.7703 (issue 7, see technical report page 56)
- venetoclax plus obinutuzumab is likely to have a quality-of-life benefit over obinutuzumab plus chlorambucil, based on feedback from clinical and patient experts.

The committee recognised that there were remaining areas of uncertainty (see technical report table 13, page 65), and took these into account in its decision making. It discussed the issue of long-term survival estimates in people for whom FCR or BR is unsuitable (issues 2, 3 and 4b, see technical report pages 27, 33 and 41). This included uncertainty about how long people who have had venetoclax plus obinutuzumab live, how long before their disease progresses, and how long before they begin having subsequent treatment. The committee also discussed the duration of subsequent treatments (issue 4a, see technical report page 39). The committee discussed how effective venetoclax plus obinutuzumab is at prolonging survival and delaying disease progression compared with ibrutinib when there is a 17p deletion or TP53 mutation, (issues 5 and 6, see technical report pages 46 and 50). During technical engagement, NICE requested that the company provide cost-effectiveness analyses of venetoclax plus obinutuzumab compared with FCR and BR in people for whom FCR or BR is suitable. The committee discussed new issues resulting from these analyses, including how effective venetoclax plus obinutuzumab is at prolonging survival and delaying disease progression compared with FCR and BR.

Unmet need, clinical management and comparators

People with untreated CLL would welcome a new treatment option with a fixed treatment duration

3.1 The clinical and patient experts noted that people with untreated CLL are a heterogeneous population in terms of mutational status and comorbidities. They agreed that there is an unmet need for an effective, time-limited treatment with fewer side effects than existing treatments available in the NHS in England. They considered that this unmet need is particularly great in the population with a 17p deletion or TP53 mutation. This is because ibrutinib and idelalisib plus rituximab are the only available treatments, and idelalisib is poorly tolerated and not widely used. However, in the population without a 17p deletion or TP53 mutation there is also a need for a greater treatment choice. Around one-third of this population are offered FCR or BR, which are known to have considerable long-term side effects. The committee understood that people have venetoclax plus obinutuzumab for a fixed duration of 12 months, and that it is generally well tolerated. Patient experts highlighted that most current treatments for untreated CLL are taken until disease progression, and that people would value a fixed duration treatment that offers a break from side effects. They also mentioned that some people with untreated CLL have cardiovascular comorbidities, which could prevent them from taking certain treatments such as ibrutinib. The committee concluded that venetoclax plus obinutuzumab would be welcomed as a new treatment option for all people with untreated CLL.

People with untreated CLL for whom FCR or BR is suitable are a relevant population for venetoclax plus obinutuzumab

3.2 The company's original submission included 2 subgroups of people with untreated CLL: those with a 17p deletion or TP53 mutation; and those without a 17p deletion or TP53 mutation for whom FCR or BR is unsuitable. The company's original submission did not include people without a 17p deletion or TP53 mutation for whom FCR or BR is suitable, although this population was in the NICE scope and is included in the

marketing authorisation for venetoclax. This subgroup was initially omitted by the company because it did not reflect the population in its clinical trial, CLL14 (see section 3.4). The ERG noted that there is no standard assessment in the UK to determine whether FCR or BR is suitable. In addition, the ERG suggested that physicians in the UK are keen to offer venetoclax plus obinutuzumab to 'fitter' patients, who would otherwise have FCR or BR. Clinical and patient experts considered that people for whom FCR or BR is suitable are a relevant population for the reasons described in section 3.1. The committee agreed that this was an important subgroup to consider.

Treatment varies depending on mutational status and comorbidities, and the comparators selected by the company are appropriate

3.3 Clinical experts confirmed that mutational status and comorbidities affect the available treatment options for people with untreated CLL. They verified that people without a 17p deletion or TP53 mutation who also have comorbidities that make FCR and BR unsuitable for them would be offered obinutuzumab plus chlorambucil. People with a 17p deletion or TP53 mutation would usually be offered ibrutinib. Idelalisib plus rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with increased risk of infection. Finally, the clinical experts stated that people without a 17p deletion or TP53 mutation for whom FCR or BR is suitable would usually be offered either FCR or BR. However, FCR is used more commonly in clinical practice in the NHS, so is the most relevant comparator. The committee agreed that these were the relevant comparators for this appraisal and matched the analyses submitted by the company.

Clinical effectiveness

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

3.4 The company presented results from CLL14 (n=432), an open-label randomised controlled trial comparing venetoclax plus obinutuzumab

(n=216) with obinutuzumab plus chlorambucil (n=216). CLL14 included people aged 18 years or over with untreated CLL whose comorbidities made FCR or BR unsuitable treatment options. People in CLL14 had to have a Cumulative Illness Rating Scale (CIRS) score greater than 6, or a creatinine clearance of less than 70 ml/minute (low creatinine clearance levels indicate serious kidney damage). The company considered that these criteria meant that FCR or BR would be unsuitable for similar patients in NHS clinical practice in England. Of the 432 people in CLL14, 49 had a 17p deletion or TP53 mutation. The ERG considered that CLL14 was well designed with a low risk of bias within the limits of the open-label trial design. The ERG noted a discrepancy between the number of cycles of chlorambucil typically offered in NHS clinical practice in England (6 cycles) and the number had in CLL14 (12 cycles). However, it understood that the lower dosage per cycle in CLL14 meant that the overall dose was similar. The ERG also noted that only 8 people in CLL14 were from the UK. Because there is no standard assessment in England to determine the suitability of FCR or BR, the ERG considered it likely that some people included in CLL14 may have been eligible for treatment with FCR or BR in England. The committee was satisfied that CLL14 was representative of NHS clinical practice despite the low number of UK patients. It noted that people with CLL for whom FCR or BR is suitable were now being considered within the appraisal (see section 3.2).

Venetoclax plus obinutuzumab improves progression-free survival, but the overall survival benefit is likely to be similar to the comparator

3.5 After a median follow up of 39.6 months, there was a statistically significant improvement in progression-free survival for venetoclax plus obinutuzumab compared with obinutuzumab plus chlorambucil (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.22 to 0.44, p<0.001). Median progression-free survival was not reached in the venetoclax plus obinutuzumab arm and was 35.6 months in the obinutuzumab plus chlorambucil arm. The time between the date of randomisation and the date at which someone was first offered a new anti-leukemic therapy was measured in CLL14 as 'time to next treatment'. Median time to next treatment was not reached in either treatment arm, but the likelihood of starting a new treatment was reduced in the venetoclax plus

obinutuzumab arm compared with the obinutuzumab plus chlorambucil arm (HR 0.51, 95% CI 0.34 to 0.78). Median overall survival was not reached in either treatment arm, and there was no difference in overall survival between the 2 arms (HR 1.03, 95% CI 0.60 to 1.75, p=0.92). The committee concluded that the trial data showed that venetoclax plus obinutuzumab improved progression-free survival and time to next treatment compared with obinutuzumab plus chlorambucil. The committee considered that the benefit of venetoclax plus obinutuzumab on overall survival was likely to be similar to obinutuzumab plus chlorambucil, noting that the immaturity of the data meant there was considerable uncertainty.

The company's indirect treatment comparison with ibrutinib is acceptable for decision making, despite limitations

3.6 The comparator in CLL14 was obinutuzumab plus chlorambucil, a combination that is not a relevant comparator in people with a 17p deletion or TP53 mutation (see section 3.3). So, the company did an indirect treatment comparison to compare progression-free and overall survival for venetoclax plus obinutuzumab with ibrutinib. The company used a real-world evidence study published by Mato et al. (2018) for its base-case comparison. This was because it had the largest number of patients with relevant characteristics out of the ibrutinib studies identified. The company's comparison was unanchored because there was no common comparator arm between CLL14 and Mato et al. The results showed that there was no statistically significant difference between venetoclax plus obinutuzumab and ibrutinib in either progression-free survival (HR 1.515, 95% CI 0.619 to 3.703, p=0.363) or overall survival (HR 1.189, 95% CI 0.425 to 3.322, p=0.741), with wide confidence intervals. The ERG identified several areas of uncertainty in the company's indirect treatment comparison. There were 25 people in the venetoclax plus obinutuzumab arm of CLL14 with a 17p deletion or TP53 mutation, and 110 people with a 17p deletion were relevant in Mato et al. The low patient numbers meant that the comparison was underpowered to detect differences between the treatments. There was also considerable heterogeneity between the studies in terms of their design, eligibility criteria and outcomes, which was not adjusted for by the company. The company did a second unadjusted indirect treatment

comparison using data from a single-arm study published by Ahn et al. (2018). However, the ERG considered that the results of the comparison using the data from Ahn et al. were as uncertain as those based on the data from Mato et al. The clinical experts highlighted that 17p deletions or TP53 mutations are uncommon, so it is unlikely that head-to-head data will become available comparing venetoclax plus obinutuzumab with ibrutinib. The committee concluded that, despite its limitations, the company's indirect treatment comparison with ibrutinib was acceptable for decision making.

The network meta-analysis comparing venetoclax plus obinutuzumab with FCR and BR is sufficient for decision making, despite limitations

3.7 In response to technical engagement, in the absence of head-to-head trial data, the company submitted a network meta-analysis (NMA) to compare the effect of venetoclax plus obinutuzumab with FCR and BR on progression-free and overall survival in people for whom FCR or BR is suitable. The company's network included 9 trials. It used the data on all patients in the venetoclax plus obinutuzumab arm of CLL14 for the comparison. This included only people who could not have FCR or BR on the basis of their CIRS score and creatinine clearance (see section 3.4). It also included some people with a 17p deletion or TP53 mutation. As described in section 3.4, the ERG considered it likely that some of these people may have been eligible for treatment with FCR or BR in England. The other trials in the company's network had people who were either 'fit' or 'unfit', with fitness determined based on age, CIRS score and fludarabine eligibility. The results suggested a progression-free survival benefit for venetoclax plus obinutuzumab over FCR (HR 0.258, 95% CI 0.151 to 0.481) and BR (HR 0.178, 95% CI 0.109 to 0.312). Overall survival was comparable for venetoclax plus obinutuzumab compared with FCR (HR 0.622, 95% CI 0.273 to 1.789) and BR (HR 0.792, 95% CI 0.378 to 1.969). The ERG considered the company's NMA to have a high degree of uncertainty, noting the substantial heterogeneity between the study populations in the NMA in terms of age and fitness. The wide confidence intervals were of concern to the ERG, as was the sensitivity of the results to the studies included in the NMA. The ERG was unable to reproduce the company's original NMA, so did its own analysis, with similar results

to that of the company. The clinical experts explained that venetoclax plus obinutuzumab is very likely to be more efficacious than FCR in people for whom FCR or BR is suitable. They also said that there is no reason why venetoclax plus obinutuzumab would not work well in this patient population. The committee acknowledged this point and concluded that, despite the results of the NMA being highly uncertain, on balance they were sufficient for decision making.

Adverse effects

Venetoclax plus obinutuzumab is generally well tolerated compared with current treatments

3.8 The results of CLL14 showed that venetoclax plus obinutuzumab had an acceptable tolerability profile compared with obinutuzumab plus chlorambucil. Patient submissions highlighted 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. Three people had tumour lysis syndrome in the venetoclax plus obinutuzumab arm of CLL14 compared with 5 in the obinutuzumab plus chlorambucil arm. The company considered that these results showed the effectiveness of prophylaxis against tumour lysis syndrome for venetoclax plus obinutuzumab. The committee agreed that venetoclax plus obinutuzumab is likely to be generally well tolerated compared with current treatments.

Cost-effectiveness model structure

The model structure is appropriate for decision making, despite uncertainty around the duration of subsequent treatment

3.9 The company submitted a partitioned survival model with 3 states (progression-free, progressed disease and death). To compare venetoclax plus obinutuzumab with obinutuzumab plus chlorambucil in people for whom FCR or BR is unsuitable, the company used data from CLL14 to estimate progression-free survival, overall survival and time to

next treatment using parametric curves fitted to Kaplan–Meier data. Half the patients starting subsequent treatment were modelled to have ibrutinib, and the other half were modelled to have venetoclax plus rituximab. This assumption was applied to both treatment arms. Subsequent treatment costs were accrued from the start of subsequent treatment until death. To compare venetoclax plus obinutuzumab with ibrutinib in people with a 17p deletion or TP53 mutation, the company used the results of the indirect treatment comparison with ibrutinib (see section 3.6) to model the differences in efficacy. Patients having venetoclax plus obinutuzumab as their first-line treatment were modelled to have ibrutinib monotherapy as their subsequent treatment. Patients having ibrutinib as their first-line treatment were modelled to have venetoclax monotherapy as their subsequent treatment, with only new incidences of disease progression or death counting towards the associated costs. To compare venetoclax plus obinutuzumab with FCR and BR when these treatments are suitable, the company used the results of the NMA (see section 3.7) to model the differences in efficacy. The subsequent treatment mix was the same as in people for whom FCR or BR is unsuitable. However, like ibrutinib, only new incidences of disease progression or death counted towards the subsequent treatment costs for FCR and BR. The ERG considered that the company's model structure was largely appropriate. Its clinical expert confirmed that the subsequent treatment mix was consistent with that offered in NHS clinical practice in England. However, the ERG noted that patients were modelled to have subsequent treatments for much longer than the median second-line treatment durations reported in the literature. It suggested that this was likely to bias the analysis against obinutuzumab plus chlorambucil. The committee noted the uncertainty about the duration of subsequent treatment (see section 3.13), but concluded that the model structure was appropriate for decision making.

Survival extrapolations

In people for whom FCR or BR is unsuitable, both the company's and ERG's survival extrapolations are relevant for decision making

3.10 The company explored various approaches for extrapolating the progression-free survival, overall survival and time-to-next-treatment data in people for whom FCR or BR is unsuitable. It chose an independent log-logistic distribution as its preferred parametric model for progression-free survival, and a dependent exponential distribution to extrapolate overall survival. The company applied the same obinutuzumab plus chlorambucil overall survival extrapolation for both treatment arms, reflecting the immaturity of the data and lack of evidence for an overall survival benefit for venetoclax plus obinutuzumab. The company used an independent log-logistic distribution for time to next treatment, matching the company's progression-free survival distribution, an outcome closely correlated with time to next treatment. The ERG noted that the survival data from CLL14 were very immature. It considered that the company's survival extrapolations were too dependent on the constraint that the hazard rate of death, disease progression, or starting a subsequent treatment could not fall below the background mortality of the age-matched general population. The ERG also noted that the company's extrapolations were optimistic compared with the 5-year data from the CLL11 trial, an earlier trial that included an obinutuzumab plus chlorambucil treatment arm in a similar patient population to CLL14. For progression-free survival, the ERG instead favoured an independent 2-knot hazard spline distribution. For a more conservative overall survival distribution, the ERG modelled the overall survival hazard rate from CLL14 up to 3 years. It then fitted an exponential model to the hazard rate from the ERIC study after this point. ERIC was a retrospective study that evaluated the efficacy and safety of obinutuzumab with or without chlorambucil in a similar patient population to CLL14. The ERG's progression-free and overall survival extrapolations were less dependent on the background mortality constraint than those of the company. For time to next treatment, the ERG derived a hazard ratio between progression-free survival and time to next treatment,

which it applied to its progression-free survival distribution. Clinical experts considered the ERG's progression-free survival distribution more plausible than that of the company. However, they warned that the CLL11 data were inappropriate for validating the overall survival extrapolations. Clinical practice has evolved since CLL11, and overall survival is expected to be longer for people in CLL14. The clinical experts also explained that it was reasonable to expect that many people will reach the life expectancy of the general population after treatment with venetoclax plus obinutuzumab, and will be functionally cured. The committee concluded that, despite the limitations of the company's and ERG's survival extrapolations, both were relevant for decision making.

When there is a 17p deletion or TP53 mutation, both the company and ERG's survival extrapolations are relevant for decision making

3.11 The company used the same progression-free survival, overall survival and time-to-next-treatment distributions for people with a 17p deletion or TP53 mutation as used in people for whom FCR or BR is unsuitable (see section 3.10). The company applied the progression-free and overall survival hazard ratios from the indirect comparison with ibrutinib (see section 3.6) to generate extrapolations for ibrutinib. The ERG noted that the company's extrapolations resulted in patients spending little time alive after their disease had progressed. The ERG considered that a 1-knot hazard spline distribution was more plausible for progression-free survival, overall survival and time to next treatment. The committee acknowledged the uncertainty, but concluded that both the company's and ERG's survival extrapolations were relevant for decision making.

In people for whom FCR or BR is suitable, both the company and ERG's survival extrapolations are relevant for decision making

3.12 The company used the same survival extrapolations for people for whom FCR or BR is suitable as for the other 2 subgroups (see section 3.10 and section 3.11). The ERG preferred a 2-knot hazard spline distribution for the progression-free survival extrapolations. This is because it considered that the likelihood of disease progression for people for

whom FCR or BR is suitable would be similar to that of people for whom FCR or BR is unsuitable. The committee concluded that both the company's and ERG's progression-free survival extrapolations were relevant for decision making.

Costs in the cost-effectiveness model

Subsequent treatment costs are likely to lie between the company's 2 scenarios, both of which are appropriate for decision making

3.13 In the company's base-case model, subsequent treatment and its associated costs were modelled to continue from the start of subsequent treatment until death for venetoclax plus obinutuzumab and obinutuzumab plus chlorambucil. The company considered this approach fair. This was because a lack of published evidence meant that it was not possible to create a treatment sequencing model in relapsed or refractory CLL. The company acknowledged that its approach was likely to overestimate subsequent treatment costs. However, it considered that restricting these costs to 1 subsequent treatment line would not align with NHS clinical practice in England. The ERG considered that the company's approach failed to account for periods of no treatment. It was also likely to be biased against obinutuzumab plus chlorambucil because patients having this treatment began having subsequent treatment earlier. In response to technical engagement, the company presented a revised economic model in which the duration of subsequent treatment was constrained by the median durations of second-line treatment reported in the literature. Clinical expert feedback suggested that it was appropriate to model subsequent treatment costs until death because of the continuous nature of salvage treatments for CLL. The committee acknowledged the uncertainty around the duration of subsequent treatment. It concluded that the actual subsequent treatment cost was likely to lie between the company's original and revised approaches, and that both were appropriate for decision making.

Cost-effectiveness results

When FCR or BR is unsuitable, venetoclax plus obinutuzumab is more effective and less costly than obinutuzumab plus chlorambucil

3.14 The company's base case for all 3 patient subgroups incorporated the ERG's preferred utility value of 0.7703 for the 'pre-progression, off-treatment' health state. In people for whom FCR or BR is unsuitable, the company's deterministic base case showed that venetoclax plus obinutuzumab was more effective and less costly than obinutuzumab plus chlorambucil. The ERG preferred the following assumptions:

- an independent 2-knot hazard spline progression-free survival distribution (see section 3.10)
- an overall survival extrapolation derived by fitting an exponential model to the hazard rate from ERIC beyond 3 years (see section 3.10)
- time-to-next-treatment extrapolations derived by applying a hazard ratio to the ERG's preferred independent 2-knot hazard spline progression-free survival distribution (see section 3.10)
- subsequent treatment durations constrained by the median durations of second-line treatment reported in the literature (see section 3.13).

  Venetoclax plus obinutuzumab remained more effective and less costly than obinutuzumab plus chlorambucil using the ERG's preferred assumptions, and in all but 1 scenario explored by the ERG. The committee acknowledged that there was considerable uncertainty around the long-term survival estimates and the duration for which people have subsequent treatments. However, it concluded that, in all scenarios, venetoclax plus obinutuzumab could be considered an acceptable use of NHS resources.

In people with a 17p deletion or TP53 mutation, the estimates are within the range considered a cost-effective use of NHS resources

3.15 The company's deterministic base case showed that venetoclax plus obinutuzumab resulted in cost savings and a quality-adjusted life year (QALY) loss compared with ibrutinib, producing incremental cost-effectiveness ratios (ICERs) that reflected 'savings per QALY lost'. The committee noted that, in situations in which an ICER is derived from 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 ERG preferred a 1-knot hazard spline distribution for progression-free survival, overall survival and time to next treatment (see section 3.11). In the ERG's analyses, venetoclax plus obinutuzumab resulted in a cost saving of £199,622 and a QALY loss of 0.363, with an ICER of £549,699 saved per QALY lost. These analyses included the patient access scheme for venetoclax, but not for the comparators or subsequent treatments. The decision-making ICERs used by the committee took account of all available confidential discounts, including those for comparators and follow-up treatments, and were lower. However, they remained within the range NICE normally considers an acceptable use of NHS resources. The committee recalled that that there was considerable uncertainty in the company's indirect treatment comparison (see section 3.6). However, it concluded that, in all scenarios, venetoclax plus obinutuzumab could be considered an acceptable use of NHS resources based on the saving per QALY lost.

In people for whom FCR or BR is suitable, the ICERs are higher than the range NICE normally considers an acceptable use of NHS resources

3.16 The company's deterministic base case suggested that the ICER was £32,669 per QALY gained for venetoclax plus obinutuzumab compared with FCR, and £36,768 per QALY gained compared with BR. The ERG preferred to use the progression-free and overall survival hazard ratios derived from its own NMA (see section 3.7), and a 2-knot hazard spline

distribution progression-free survival (see section 3.12). The ERG's analyses suggest an ICER of £47,494 per QALY gained for venetoclax plus obinutuzumab compared with FCR, and £67,445 per QALY gained compared with BR. With the confidential discounts for obinutuzumab and ibrutinib applied, the ICERs remained above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). The committee focused on the comparison with FCR because it understood that this is more widely used than BR in clinical practice, so is the most relevant comparator (see section 3.3). The committee recalled that the company's NMA was subject to considerable uncertainty (see section 3.7). It understood that the ICERs varied widely if the upper and lower bounds of the progression-free and overall survival hazard ratio confidence intervals were applied. On balance, the committee considered the ERG's preferred analysis to represent the most plausible scenario, although it was still subject to considerable uncertainty. The committee also noted that assuming the effect of venetoclax plus obinutuzumab on overall survival was the same as FCR resulted in an ICER that was higher than the ERG's preferred analysis. The committee concluded that venetoclax plus obinutuzumab could not be recommended for routine use in the NHS in this population.

Innovation

There are no additional benefits that are not captured in the quality-adjusted life year calculations

3.17 The company considered venetoclax plus obinutuzumab to be an innovative treatment because venetoclax is a first-in-class, oral, selective inhibitor of B-cell lymphoma 2. It has a unique targeted mechanism of action that distinguishes it from other therapies. Venetoclax plus obinutuzumab also has a fixed treatment duration. This means people can have time without therapy, unlike with most other treatments, which people must have until they stop working. Venetoclax plus obinutuzumab increases the range of treatment options for people with untreated CLL, and avoids the need for chemo-immunotherapy. The committee concluded that venetoclax plus obinutuzumab would be a beneficial additional treatment option. However, it noted that it had not been

presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

Equality considerations

There are no remaining equality issues relevant to the recommendations

3.18 The company's original submission did not include people without a 17p deletion or TP53 mutation for whom FCR or BR is suitable. Patient and professional submissions highlighted that this would potentially deny these people access to a new treatment option that is well tolerated. In response to technical engagement, the company provided cost-effectiveness analyses comparing venetoclax plus obinutuzumab with FCR and BR in people without a 17p deletion or TP53 mutation for whom FCR or BR is suitable. The committee considered these analyses during the appraisal (see section 3.16). No other equality or social value judgement issues were identified by the committee.

End of life

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

3.19 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 people 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 considered that the short life expectancy criterion of less than 24 months was not met because people with CLL have a life expectancy of more than 2 years. The committee concluded that venetoclax plus obinutuzumab does not meet the criteria to be considered a life-extending treatment at end of life.

Cancer Drugs Fund

Further data collection could address uncertainties in the clinical and cost-effectiveness evidence in people for whom FCR or BR is suitable

3.20 Having concluded that venetoclax plus obinutuzumab could not be recommended for routine use in people with untreated CLL when FCR or BR is suitable (see section 3.16), the committee considered whether it could be recommended for use within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee considered whether the clinical uncertainty associated with venetoclax plus obinutuzumab in this patient population could be addressed through collecting more data. It was aware that CLL13, a randomised controlled trial directly comparing venetoclax plus obinutuzumab with FCR and BR in people with untreated CLL, is currently ongoing. CLL13 has a primary completion date of January 2023, with an interim analysis of progression-free survival planned after 49 months. The committee agreed that:

- the company has expressed an interest in venetoclax plus obinutuzumab being considered for funding through the Cancer Drugs Fund in people with untreated CLL for whom FCR or BR is suitable
- the relative benefits of venetoclax plus obinutuzumab on progression-free and overall survival compared with FCR and BR are highly uncertain
- there is plausible potential that the ICER for venetoclax plus obinutuzumab compared with FCR could fall within the range normally considered a cost-effective use of NHS resources
- data on progression-free and overall survival from CLL13 for venetoclax plus obinutuzumab compared with FCR and BR would be a valuable addition to the clinical evidence base and would likely resolve uncertainties around survival

- using venetoclax plus obinutuzumab in the NHS in patients for whom FCR or BR is suitable would allow data to be collected using the Systemic Anti-Cancer Therapy dataset, which would more accurately reflect the benefits of its use in clinical practice.

Conclusions

Venetoclax plus obinutuzumab is a cost-effective use of NHS resources and is recommended when FCR or BR is unsuitable

3.21 The committee noted that there was considerable uncertainty around the long-term survival estimates and the duration for which people for whom FCR or BR is unsuitable had subsequent treatments. However, it acknowledged that, in all scenarios, the ICERs suggested that venetoclax plus obinutuzumab was a cost-effective treatment (see section 3.14). The committee concluded that venetoclax plus obinutuzumab for untreated CLL in adults for whom FCR or BR is unsuitable is a cost-effective use of NHS resources and could be recommended as an option for this population.

Venetoclax plus obinutuzumab is a cost-effective use of NHS resources and is recommended when there is a 17p deletion or TP53 mutation

3.22 The committee noted that there was considerable uncertainty associated with the company's indirect treatment comparison with ibrutinib in people with a 17p deletion or TP53 mutation. However, it acknowledged that, in all scenarios, the ICERs suggested that venetoclax plus obinutuzumab was a cost-effective treatment (see section 3.15). In addition, the committee acknowledged that there is a high unmet need for a new treatment option in this patient population, and that venetoclax plus obinutuzumab would likely represent a tolerable alternative to ibrutinib and idelalisib. The committee concluded that venetoclax plus obinutuzumab for untreated CLL in adults with a 17p deletion or TP53 mutation is a cost-effective use of NHS resources and could be recommended as an option for this population. Given the QALY losses for venetoclax plus obinutuzumab compared with ibrutinib, treatment choice

should be a decision made between the doctor and patient. Other factors to consider in making this decision include the adverse events associated with both treatments, and the fixed duration of venetoclax plus obinutuzumab treatment compared with taking ibrutinib until disease progression. The committee also acknowledged that some people have cardiovascular comorbidities that could prevent them from taking ibrutinib (see section 3.1).

Venetoclax plus obinutuzumab meets the criteria to be included in the Cancer Drugs Fund in people for whom FCR or BR is suitable

3.23 The company's NMA suggested that venetoclax plus obinutuzumab is likely to have a progression-free survival benefit compared with FCR and BR. Input from the clinical experts also suggested that it is likely that venetoclax plus obinutuzumab has a survival benefit over FCR in clinical practice. The committee acknowledged that people with this condition strongly desire an alternative to FCR and BR even if these treatments are considered suitable. It also agreed that there is an unmet need for new treatment options, given the heterogeneity of the patient population. The committee also understood that offering venetoclax plus obinutuzumab to these people up front may be beneficial in the long term. Many people treated with FCR or BR do not go into remission (either complete remission or minimal residual disease). They also have long-term side effects that may affect the efficacy of targeted therapies used in later lines. The incidence of a 17p deletion or TP53 mutation is also higher in relapsed or refractory CLL, limiting treatment choice in this setting. The committee noted that the ICER for venetoclax plus obinutuzumab compared with FCR was uncertain. However, it concluded that venetoclax plus obinutuzumab had the plausible potential to satisfy the criteria for routine use if this uncertainty could be reduced. The committee recognised that comparative survival data compared with FCR and BR from CLL13 would allow for a more robust cost-effectiveness estimate. So, it agreed that venetoclax plus obinutuzumab met the criteria to be included in the Cancer Drugs Fund for untreated CLL in adults for whom FCR or BR is suitable.

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 untreated chronic lymphocytic leukaemia (CLL) and a 17p deletion or TP53 mutation, or has untreated CLL and no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is unsuitable,

and the doctor responsible for their care thinks that venetoclax with obinutuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

4.5 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that if a patient has untreated CLL and no 17p deletion or TP53 mutation, and FCR or BR is suitable, and the doctor responsible for their care thinks that venetoclax with obinutuzumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.6 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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. 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.

4.7 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales,

whichever is the later.

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.

Charlie Hewitt
Technical lead

Richard Diaz
Technical adviser

Louise Jafferally
Project manager

ISBN: 978-1-4731-3932-9

Accreditation