NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia

1 Recommendations

1.1 Ibrutinib plus venetoclax is recommended, within its marketing authorisation, as an option for untreated chronic lymphocytic leukaemia (CLL) in adults. This is only if the companies provide both drugs according to the commercial arrangements (see section 2).

Why the committee made these recommendations

Treatments for untreated CLL include acalabrutinib, fludarabine plus cyclophosphamide and rituximab (FCR), ibrutinib alone, obinutuzumab plus chlorambucil, and venetoclax plus obinutuzumab. FCR is rarely used in clinical practice.

Clinical evidence shows that CLL takes longer to get worse, and people live longer when they have ibrutinib plus venetoclax compared with obinutuzumab plus chlorambucil. An indirect comparison with acalabrutinib, FCR, ibrutinib alone, and venetoclax plus obinutuzumab suggests that CLL takes longer to get worse when treated with ibrutinib plus venetoclax.

The cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources, so ibrutinib plus venetoclax is recommended.

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2 Information about ibrutinib with venetoclax

Marketing authorisation indication

2.1 Ibrutinib (Imbruvica, Janssen-Cilag) with venetoclax (Venclyxto, AbbVie) 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 for ibrutinib.

Price

2.3 A 28-pack of 140-mg ibrutinib tablets costs £1,430.80 (excluding VAT; BNF online accessed February 2022). The company has a commercial arrangement (simple discount patient access scheme). This makes ibrutinib 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 A 112-pack of 100-mg venetoclax tablets costs £4,789.47 (excluding VAT; BNF online accessed February 2022). AbbVie has a commercial arrangement (simple discount patient access scheme). This makes venetoclax available to the NHS with a discount. The size of the discount is commercial in confidence. It is AbbVie's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Janssen-Cilag, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells and is the most common type of leukaemia in England. The patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The risk of CLL increases with age. CLL progression and poor prognosis is commonly caused by a deletion of chromosome 17p (17p deletion) or mutation of the tumour protein p53 (TP53). The committee concluded that CLL substantially affects physical and psychological quality of life.

Clinical management and comparators

3.2 The clinical and patient experts said that the population of people with untreated CLL is heterogeneous. They have different mutation statuses and comorbidities, and this affects their treatment options. The patient experts also highlighted that current treatments for CLL, such as intensive chemotherapy, have short and long-term side effects.

FCR or BR suitable population

3.3 The company said that, if people do not have a 17p deletion or TP53 mutation and can take chemo-immunotherapies, they may be offered fludarabine plus cyclophosphamide and rituximab (FCR). It said that bendamustine plus rituximab (BR) is rarely used. People with CLL who can have FCR or BR are referred to as 'FCR or BR suitable' from here onwards. The company did not present evidence comparing ibrutinib plus venetoclax with BR. The clinical experts and the NHS England representative noted that FCR is sometimes used by smaller centres that are unable to offer other treatment options. They confirmed that BR is rarely used in clinical practice in England. They highlighted that it is challenging to split diagnosis and treatment options by FCR or BR suitability because they are hardly used. The NHS England representative explained that venetoclax plus obinutuzumab is the most common treatment for this population, but it is only available through the Cancer

Drugs Fund. So it is not in scope as a comparator according to section 2.2.15 of the NICE health technology evaluation manual. The committee concluded that the FCR or BR suitable population cannot be accurately defined in clinical practice in England, and that implementing this criterion is challenging for clinicians.

FCR or BR unsuitable and the high-risk population

3.4 The company said that people without a 17p deletion or TP53 mutation, who have comorbidities that make FCR and BR unsuitable (this population is referred to as 'FCR or BR unsuitable' from here onwards), are offered:

- acalabrutinib monotherapy
- obinutuzumab plus chlorambucil or
- venetoclax plus obinutuzumab.

People with a 17p deletion or TP53 mutation (this population is referred to as the 'high-risk group' from here onwards) are offered:

- acalabrutinib monotherapy
- ibrutinib monotherapy
- idelalisib plus rituximab or
- venetoclax plus obinutuzumab.

The company did not present evidence comparing ibrutinib plus venetoclax with idelalisib plus rituximab. The clinical experts explained that idelalisib plus rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with an increased infection risk. The NHS England representative said that acalabrutinib monotherapy is the main treatment used for the high-risk group. They reiterated that FCR or BR suitability is not assessed in clinical practice (see section 3.3). Instead, for people without a 17p deletion or TP53 mutation (this population is referred to as the 'non-high-risk group' from here onwards), acalabrutinib monotherapy or venetoclax plus

obinutuzumab are the main treatment options. The committee concluded that all relevant comparators were included by the company and restated that FCR or BR suitability is not typically assessed in clinical practice. The patient and clinical experts explained that ibrutinib plus venetoclax generally causes fewer side effects than current treatments and that people with CLL value the fixed treatment duration. The committee concluded that ibrutinib plus venetoclax would be welcomed as a new treatment option for people with untreated CLL for both the high-risk and non-high-risk groups.

Clinical effectiveness

Data sources

3.5 For the company's FCR or BR suitable group, the main evidence came from the fixed duration cohort of the CAPTIVATE study. CAPTIVATE was a phase 2 open-label study with a single arm (ibrutinib plus venetoclax, n=159). The study enrolled people with untreated CLL aged between 18 and 70. Of the 159 enrolled participants, 136 did not have a 17p deletion. For the FCR or BR unsuitable group, the company submitted results from the GLOW trial. GLOW was an open label, phase 3 randomised clinical trial comparing ibrutinib plus venetoclax (n=106) with obinutuzumab plus chlorambucil (n=105). It enrolled people with untreated CLL without a 17p deletion or known TP53 mutation. They had to be either 65 or older, or between 18 and 64 with a Cumulative Illness Rating Scale score over 6 or a creatinine clearance of less than 70 ml/min, or both. Low creatinine clearance levels indicate serious kidney damage. The EAG considered that the fixed duration cohort of the CAPTIVATE study and the GLOW trial were high-quality studies. This is despite open-label study limitations applying to both studies and non-randomised study limitations applying to the CAPTIVATE study. The committee was satisfied that the clinical effectiveness evidence was largely relevant to the decision problem and the studies recruited participants that are reflective of people who would be offered ibrutinib plus venetoclax in NHS clinical practice.

Clinical study results

3.6 In the CAPTIVATE fixed duration group, median progression-free survival and overall survival were not reached for ibrutinib plus venetoclax at 38.7 months or with longer follow-up data from the updated data cut. After a median follow up of 46 months in the GLOW trial, there was a statistically significant improvement in progression-free survival and overall survival (hazard ratio 0.487, 95% confidence interval 0.262 to 0.907, p=0.0205) for ibrutinib plus venetoclax compared with obinutuzumab plus chlorambucil. The progression-free survival hazard ratio was available but is considered confidential by the company and cannot be reported here. Median progression-free survival in the GLOW trial was not reached for ibrutinib plus venetoclax but was reached for obinutuzumab plus chlorambucil. Median overall survival was not reached in either treatment arm. The committee concluded that updated data cuts for the CAPTIVATE and GLOW studies showed clinically meaningful and consistent results for ibrutinib plus venetoclax. However, it noted that there was no evidence directly comparing ibrutinib plus venetoclax with commonly used NHS treatments such as acalabrutinib monotherapy and venetoclax plus obinutuzumab (see section 3.3 and 3.4).

Clinical data immaturity

3.7 The EAG said the clinical study results for ibrutinib plus venetoclax were immature because median progression-free survival was not reached in either study (see section 3.6). The company said that not reaching median survival times shows a lack of events during follow up, which indicates that treatment with ibrutinib plus venetoclax is efficacious. It also noted that median progression-free survival was not reached in the venetoclax plus obinutuzumab or acalabrutinib arms in their pivotal trials. Nonetheless this uncertainty was accepted and both treatments were recommended in NICE's technology appraisal guidance on venetoclax with obinutuzumab for untreated CLL and on acalabrutinib for treating CLL. The EAG said that lack of events can be because of small sample

sizes in the analyses, and the duration of follow up from the direct evidence for this appraisal cannot be considered long term for first-line treatments for CLL. The clinical experts explained that long-term outcomes and adverse events for ibrutinib plus venetoclax were needed but additional trial data was not available. The committee concluded that, in the absence of more mature data at the time of evaluation, the CAPTIVATE and GLOW studies were the most relevant clinical evidence for ibrutinib plus venetoclax.

Indirect treatment comparison methods and results

3.8 Direct evidence was only available for the comparison of ibrutinib plus venetoclax with obinutuzumab plus chlorambucil from the GLOW trial. Indirect treatment comparisons were needed for the other comparators. Only the progression-free survival hazard ratio was used from this comparison in the model. Mortality rates were instead taken from clinical trials with longer follow-up data (see section 3.12 and the company submission in the committee papers). The following indirect treatment comparison methods were applied:

- **For the FCR or BR suitable group:** the company applied inverse probability for treatment weighting to adjust for prognostic factors and baseline characteristics for ibrutinib plus venetoclax from CAPTIVATE and FCR from the E1912 trial. The clinical experts said that all the important prognostic factors were considered by the company in its indirect comparisons. For the base case, the company applied the probability weighting to the FCR control arm using the average treatment effect in the control arm (ATC) approach. It also explored other methods, including estimation of the average treatment effect in the ibrutinib plus venetoclax arm (ATT). It considered the ATC approach most appropriate because the FCR arm was the reference curve estimating CLL progression in the model. The ATC approach suggested a statistically significant improvement in progression-free survival for ibrutinib plus venetoclax compared with FCR. The exact

hazard ratios and statistical values are considered confidential by the company and cannot be reported here.

- **For the FCR or BR unsuitable group:** the company did an anchored matching adjusted indirect comparison (MAIC) and used data from the acalabrutinib arm of the ELEVATE-TN trial and the venetoclax plus obinutuzumab arm of the CLL14 trial. First, the participants who would have been excluded from CLL14 were identified from GLOW and excluded from the analysis. Because of data limitations this step was not done with ELEVATE-TN and participants with a 17p deletion could not be removed from the analysis. Next, to adjust for treatment effect modifiers, 4 characteristics were matched (age, European Cooperative Oncology Group [ECOG] status, Cumulative Illness Rating Scale score, and TP53 status). Proportional hazards were assumed to estimate a constant hazard ratio for inclusion in the economic model. The progression-free survival hazard ratios favoured ibrutinib plus venetoclax but were not statistically significant. The exact hazard ratios and statistical values are considered confidential by the company and cannot be reported here.

Indirect treatment comparison limitations

3.9 The EAG had several concerns with the company's indirect comparisons:

- **For the FCR or BR suitable group:** the EAG questioned the use of the ATC hazard ratios over the ATT approach (see section 3.8) because the ATT progression-free survival hazard ratio was not statistically significant. The company explained that the FCR trial (E1912) had longer follow up and more events than ibrutinib plus venetoclax in CAPTIVATE, providing a clear justification for using the FCR reference curve and therefore the ATC hazard ratios (see the clarification responses in the committee papers). On the EAG's request, the company provided a scenario in which ibrutinib plus venetoclax from CAPTIVATE was the reference curve and the ATT hazard ratio was applied. This did not make a substantial difference to

the overall outcomes. The committee concluded that the ATC approach was suitable for decision making. But it noted that the indirect treatment comparison was associated with uncertainty because of the inconsistency between the ATT and ATC results.

- **For the FCR or BR unsuitable group:** the EAG said that the rate at which progression-free survival events (hazards) occurred was not proportional between ibrutinib plus venetoclax and the comparator arms. It remained cautious about applying the estimated hazard ratios from the GLOW trial follow-up duration to the entire model time horizon of 30 to 40 years. The company presented a scenario analysis using hazard ratios that varied over time and explained that this did not substantially affect the final outcomes. The committee acknowledged that substantial uncertainties were associated with the anchored MAICs. But it concluded that, in the absence of direct evidence and more mature data, the company's anchored MAICs with acalabrutinib and venetoclax plus obinutuzumab were acceptable for decision making.

High-risk CLL group

3.10 The company assumed that the results from the FCR or BR unsuitable indirect comparisons (see section 3.8) could apply to the high-risk CLL population, and that acalabrutinib was clinically equivalent to ibrutinib. The company said that there was no additional evidence for the high-risk group. It pointed out that the ibrutinib efficacy assumption was previously accepted in NICE's technology appraisal guidance on acalabrutinib. The committee remained cautious about this assumption and noted that ELEVATE-TN (the acalabrutinib trial) included the high-risk group but it was excluded from the GLOW trial. The clinical experts explained that poorer clinical outcomes are expected for high-risk CLL compared with non-high-risk CLL. The clinical efficacy outcomes for high-risk CLL were therefore optimistic, but there was no alternative clinical evidence for this population. The committee noted that there was no direct evidence presented for this population. Although there was uncertainty, it concluded

that clinical equivalence between acalabrutinib and ibrutinib was plausible in the high-risk CLL population, and this was acceptable for decision making.

Long-term treatment effects

3.11 The company assumed in its model that the treatment effect of ibrutinib plus venetoclax compared with obinutuzumab plus chlorambucil and the other comparators is maintained for a lifetime horizon (30 to 40 years) in the model (see section 3.8 and 3.9). The EAG said that assuming a continued treatment effect was an issue because it considered the ibrutinib plus venetoclax clinical study data to be immature (see section 3.7). The proportional hazards and comparative efficacy assumptions as discussed in section 3.9 also relied on this immature clinical data, further increasing uncertainty in the model outcomes. At the clarification stage and on the EAG's request, the company provided treatment effect waning scenarios in which ibrutinib plus venetoclax's treatment effect declined after 5 or 10 years. The committee acknowledged these scenarios and considered that assuming treatment effect waning after 5 years of stopping treatment was a conservative assumption, but considered all treatment effect waning scenarios in its decision making.

Economic model

The company's modelling approach

3.12 The company submitted a semi-Markov model with 4 health states: progression-free on first-line treatment, progression-free on second-line treatment, disease progression and death. For the FCR or BR suitable group, the company informed the transitions from the progression-free first-line state to second-line and progressed states using E1912, and the efficacy of FCR compared with ibrutinib plus venetoclax. For the FCR or BR unsuitable group the equivalent transitions were informed by GLOW and the efficacy estimates of ibrutinib plus venetoclax compared with acalabrutinib and venetoclax plus obinutuzumab (see section 3.8). The

ibrutinib arm of the RESONATE trial was used to inform the transitions from the second-line progression-free state to the progressed and death health states for both groups because it had a longer follow up (65 months) than other CLL trials. The EAG considered the model structure appropriate for modelling untreated CLL. The committee noted that the company's model structure can only apply exponential distributions with a constant rate for transitions out of the second-line progression-free and post-progression states. The company described the model as a semi-Markov model and included tunnel states in its structure. But these were used only to track costs rather than to determine health state occupancy over time. The company noted that the exponential distribution gave a good fit to the data from the RESONATE trial, but the committee remained concerned that the limitations of the model structure meant that no other survival distributions could be explored. Despite these concerns, the committee considered the model structure to be adequate for decision making.

Model outcomes

3.13 The company estimated the rate of transition from the progression-free first-line state to progression-free second-line or progressed health states by subtracting the hazards (rate at which events occur) of general population mortality from the hazards of progression. The EAG said that this method led to inconsistencies in model outcomes. The risk of progression was 0% in the FCR or BR unsuitable group after a number of years, implying that a proportion of the ibrutinib plus venetoclax and acalabrutinib arm were cured of CLL. This same estimation was not made for the FCR or BR suitable group, for whom the risk of CLL progression in the model reached 0% much later. This is because background mortality was lower for the FCR or BR suitable group compared with the FCR or BR unsuitable group. The company said that the age at which progression-free survival was capped by general population mortality was consistent (around 85 years) and the risk of progression reached zero at a similar time in both groups. Clinical experts noted that the data did not

suggest a different risk of progression between these 2 groups. They also pointed out that CLL is not usually considered to be curable, and treatments aim to maintain deep remissions instead. At technical engagement the company provided a scenario in which the transition probability of progression in the FCR or BR unsuitable group did not fall below the FCR or BR suitable group. This scenario did not substantially change the final outcomes. The EAG said that the scenario helped reduce uncertainties but the model's limitations remained. The committee concluded that the model structure and its outcomes remained appropriate for decision making despite the limitations of the data used to inform its parameters.

Utility values

Progression-free utility

3.14 The company mapped the EQ-5D-5L values from the GLOW trial to EQ-5D-3L to estimate the progression-free first-line utility value. It applied the same utility value to both the FCR or BR suitable and unsuitable groups. The EAG noted that the progression-free first-line utility value was higher than UK population age-sex matched utility and therefore an overestimate. The company said the value was consistent with the CLL14 and ELEVATE-TN trials but ran a scenario capping the value by UK population utilities. The final outcomes did not substantially change as a result of this scenario. The clinical experts explained that the quality of life of people after CLL treatment is lower than UK general population and even lower for people having chemo-immunotherapy. The committee agreed with the clinical experts and preferred the capped UK utility values.

Quality of life in second-line treatment

3.15 The company used a utility value of 0.6 from Holzner et al. 2004 for the progression-free second-line and progressed states. The paper collected quality of life data from people with CLL over 1 year. The company age-adjusted the Holzner utility value to the E1912 trial population for the FCR

or BR suitable group and to the GLOW trial population for the FCR or BR unsuitable group. The EAG only agreed with using 0.6 for the progressed state and not for the progression-free second-line state. Because Holzner was an older source, the quality of life benefits of second-line treatments are not captured and therefore underestimated. The EAG preferred to apply a utility multiplier to the age-adjusted progression-free first-line value (see section 3.14) to estimate the second-line value. The utility multiplier was calculated by dividing the EQ-5D values for progressed disease by the progression-free first-line values from the GLOW trial. The clinical experts said it was reasonable to assume a lower utility value for people in the progressed state because of their more advanced disease compared with people on second-line treatment. The committee agreed that 0.6 was an underestimate but highlighted that the EAG's utility multiplier may be an overestimate. It also acknowledged that these utility values had limited impact on the final outcomes. The committee agreed with the clinical experts and concluded that the EAG's approach was appropriate to use in the model.

Adverse effects

Tolerability profile

3.16 The CAPTIVATE and GLOW study results showed that ibrutinib plus venetoclax had an acceptable tolerability profile. The patient experts highlighted that ibrutinib plus venetoclax was associated with fewer adverse effects, which were generally well tolerated. The fixed treatment duration also meant the adverse effects were for a limited time. The clinical experts said the common adverse effects of treatments like ibrutinib include hypertension and heart problems. In rare cases continuous use may increase the risk of skin cancer. They said that people with CLL have a high burden of tumour cells. Venetoclax breaks down these tumour cells and the breakdown (lysis) of these cells leads to adverse effects called 'tumour lysis syndrome'. Venetoclax's gradual ramp up dose is therefore essential to minimise tumour lysis syndrome. For the

ibrutinib plus venetoclax combination, the clinical experts noted that the lead-in ibrutinib treatment reduces the tumour burden upfront, which reduces the risk of tumour lysis syndrome once venetoclax is introduced after the third cycle of treatment. The patient and clinical experts said that the fixed duration reduces the cumulative risk of adverse effects, and that the associated quality of life benefits should be considered by the committee. The committee agreed that ibrutinib plus venetoclax was likely to be generally well tolerated and that its fixed duration was an additional advantage compared with current treatments.

Risk of drug resistance

3.17 The committee noted that ibrutinib and venetoclax are recommended treatment options for previously treated CLL. The committee questioned whether using these 2 efficacious second-line CLL treatments together as a first-line treatment might limit the remaining treatment options for relapsed or refractory CLL. The clinical experts explained that the fixed duration of ibrutinib plus venetoclax reduces the chances of CLL becoming resistant to them, unlike what might happen for 'treat to progression' monotherapies like ibrutinib and acalabrutinib. The NHS England representative said that retreatment with ibrutinib, venetoclax or other first-line options should be allowed if the CLL has responded well to these first-line treatments, subject to marketing authorisations in Great Britain. The committee acknowledged this and agreed that ibrutinib plus venetoclax as a first-line option was unlikely to significantly limit treatment options for relapsed or refractory CLL.

Cost-effectiveness estimates

FCR or BR suitable group

3.18 The company's probabilistic base-case incremental cost-effectiveness ratio (ICER) for ibrutinib plus venetoclax compared with FCR for untreated CLL when FCR or BR is suitable was below £20,000 per quality-adjusted life year (QALY) gained. Incorporating the EAG's preferred assumptions

on applying cost and utility decrement from cycle zero in the model, including oral treatment wastage costs and updated utility values (see section 3.14 to 3.15), increased the ICER but it remained below £20,000 per QALY gained. The committee used the EAG's base case for decision making. It also considered the following scenarios:

- ibrutinib plus venetoclax's treatment effect declining over 5 and 10 years
- efficacy of ibrutinib plus venetoclax compared with FCR using the ATT indirect treatment comparison approach.

In all the scenarios the committee considered, the ICER remained below £30,000 per QALY gained.

FCR or BR unsuitable and high-risk population

3.19 In the company's and EAG's probabilistic base case, ibrutinib plus venetoclax was more effective and less costly and therefore the dominant treatment option compared with obinutuzumab plus chlorambucil and venetoclax plus obinutuzumab. Ibrutinib plus venetoclax resulted in cost savings and a small QALY loss compared with acalabrutinib and ibrutinib, producing 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 typical decision rule of accepting ICERs below a given threshold is reversed. So the higher the ICER, the more cost effective a treatment becomes. The committee used the EAG's base case for decision making. It also considered the following scenarios:

- ibrutinib plus venetoclax's treatment effect declining over 5 and 10 years
- the probability of CLL progression in the FCR or BR unsuitable group capped by the FCR or BR suitable group
- equal efficacy (a progression-free survival hazard ratio of 1) assumed for acalabrutinib and ibrutinib plus venetoclax.

In all the scenarios the committee considered, the direction of the ICERs remained consistent with the EAG's probabilistic base case. The ICERs were either dominant or significantly above £30,000 savings per QALY lost.

High-risk and non-high-risk groups

3.20 In sections 3.3 and 3.4 the committee previously concluded that implementing the 'FCR or BR suitability' criterion would be challenging for clinicians in the NHS in England. The committee therefore considered the totality of the cost-effectiveness results across all 3 groups in sections 3.18 to 3.19 to make its recommendations. The committee placed greater weight on the FCR or BR unsuitable and high-risk group results because the comparators were more relevant for the NHS in England than FCR (see section 3.4). The committee recalled that there was substantial uncertainty in the company's indirect treatment comparison and long-term treatment effect assumptions (see section 3.9 and 3.11) and said ICERs closer to £20,000 per QALY gained would be more appropriate. The decision-making ICERs used by the committee took account of all available confidential discounts, including those for comparators and follow-up treatments, so exact ICERs cannot be reported here. The ICERs remained an acceptable use of NHS resources. So the committee concluded that ibrutinib plus venetoclax is cost effective for anyone with untreated chronic lymphocytic leukaemia.

Other factors

Equality issues

3.21 No equality or social value judgement issues were identified.

3.22 NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.23 The committee considered if ibrutinib plus venetoclax was innovative. It did not identify additional benefits of ibrutinib plus venetoclax not captured in the economic modelling. So the committee concluded that all benefits of ibrutinib plus venetoclax had already been taken into account.

Conclusion

Recommendation

3.24 The committee considered inputs from clinical and patient experts which suggested there were limited treatment options for both the high-risk and non-high-risk groups. Also, ibrutinib plus venetoclax's fixed treatment duration and better toxicity profile than current treatments made it a highly valued treatment option. The committee concluded that ibrutinib plus venetoclax gives clinicians an additional valuable treatment option. It also considered ibrutinib plus venetoclax to represent a cost-effective use of NHS resources. So ibrutinib plus venetoclax is recommended for routine commissioning for anyone with untreated chronic lymphocytic leukaemia.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 guidance 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 draft guidance.

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 someone has untreated chronic lymphocytic leukaemia and the doctor responsible for their care thinks that ibrutinib plus venetoclax is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 health technology analyst (who act as a technical lead for the evaluation), a technical adviser and a project manager.

Anuja Chatterjee

Technical lead

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