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Dear Steve

Thank you for asking the NHS England Chemotherapy Clinical Reference Group (CRG) to re-examine the commissioning treatment criteria for the use of ibrutinib in previously treated patients with chronic lymphocytic leukaemia (CLL).

The CRG reviewed evidence submitted from three patient groups (the CLL Support Association, Bloodwise and Leukaemia Care), one clinical group (the CLL Forum), the company (Janssen) and two individual patient submissions. The main focus of the CRG in this process was on previously treated CLL patients without 17p deletions or TP53 mutations and with previous remission durations of 3 or more years.

Our detailed considerations and conclusions are set out in a full report at Appendix A. However, the key points can be summarised as follows:

- Firstly, the CRG had been correct in its interpretation of the evidence base for the use of ibrutinib in 2015 (entry into the Cancer Drugs Fund) and 2017 (publication of NICE final guidance) as being in patients considered unsuitable for treatment or re-treatment with chemoimmunotherapy (CIT). The CRG noted that NICE endorsed this interpretation in July 2018. The CRG also considered that it had been correct to set the treatment criteria that it did, as these were based on the available published evidence in 2015 and 2017.
- Secondly, having reviewed the latest available data, much of which has only become available in 2018, the CRG concluded that the evidence now supports ibrutinib, on clinical effectiveness grounds, as a treatment option in patients who have previous remission durations of 3 or more years. Newly available data shows that ibrutinib is more effective than previously thought in patients unsuitable for CIT and points to the likelihood of ibrutinib being more effective in patients suitable for treatment or re-treatment with CIT than in patients deemed unsuitable. Furthermore, the CRG reviewed the changes in clinical trials and practice as to the choice of CIT regimens in patients with previously treated CLL as well as the 2016 and 2018 trial data and this revealed less activity for treatment or re-treatment with CIT than previously

thought. The CRG has also concluded that the recent additions to the evidence base for using a remission duration of 3 or more years with the preceding line of therapy as a way of defining suitability for CIT mean that it is now not one that is robust enough in 2018 for NHS England to use in setting treatment criteria for access to ibrutinib.

- Thirdly, the CRG was unable to conclude whether expanded access to ibrutinib in patients considered suitable for retreatment with CIT would represent a cost effective use of NHS resources. The available evidence simply does not allow for a judgment on cost effectiveness to be formed. Given the inevitable budget impact of expanding access, this should be noted.
- Fourthly, the CRG noted that it would welcome Janssen's input in assisting NHS England to mitigate the financial risk of commissioning of ibrutinib in a broader population of patients. I am pleased to confirm that Janssen has agreed a commercial arrangement which will enable NHS England to recommend its use in the wider population. The CRG recognises Janssen's flexibility and partnership approach to working with NHS England which has allowed a solution to be developed which is a win-win for all parties involved and ensures that ibrutinib is available to patients, while securing fair value for taxpayers.

Having considered all of the above, the CRG was unanimous in its view that, on clinical grounds, the ibrutinib clinical commissioning treatment criteria in this indication should be amended such that it can be made available as a treatment option for those patients who have had remission durations of 3 years or more with their preceding line of therapy. The other considerations and changes are set out in the full report.

The arrangements to commission ibrutinib in those patients who have had previous remission durations of 3 years or more with their preceding line of therapy now require a short period of time for NHS England and Janssen to work together to implement. We would therefore expect access to ibrutinib for this population to commence within the next 2 weeks.

I would like to express my thanks to all those in the CRG who participated in this review and particularly to the patient and clinical groups for their constructive engagement with the process and their submissions of evidence.

Yours sincerely



Professor Peter Clark
Chair, Chemotherapy Clinical Reference Group

Appendix A

Summary and conclusions of the issues considered by the NHS England Chemotherapy Clinical Reference Group in its July 2018 re-assessment of the NHS England commissioning criteria for the use of ibrutinib in patients with previously treated chronic lymphocytic leukaemia

1. Ibrutinib entered the previous Cancer Drugs Fund in January 2015 for the treatment of previously treated chronic lymphocytic leukaemia (CLL) in patients in whom treatment or re-treatment with purine analogue-based therapy was unsuitable. At that time the NHS England Chemotherapy Clinical Reference Group (CRG) set treatment criteria which had to be fulfilled for access to ibrutinib to be funded. These treatment criteria reflected both the evidence base available and the CLL treatment pathway at the time and also incorporated advice from the senior CLL clinicians who led the application for this indication of ibrutinib to enter the CDF.
2. For CLL patients with 17p deletion or TP53 mutations, the CDF approved access for use of ibrutinib as 1st or 2nd line therapy.
3. For the treatment of relapsed/refractory CLL which did not have a 17p deletion or a TP53 mutation, the CRG set treatment criteria in January 2015 which all had to be fulfilled, of which the most important were:
 - i) Criterion 3: the patient has received at least 1 prior anti-CD20-containing chemoimmunotherapy (CIT)
 - ii) Criterion 4: the clinician considered it was not appropriate for treatment or re-treatment with purine analogue-based therapy due to a) a failure to respond to CIT or b) a progression-free interval of <3 years with the prior treatment or c) the patient was aged ≥70 years or d) the patient was aged ≥65 years and had comorbidities. One or more of these 4 measures had to apply for criterion 4 to be fulfilled.
 - iii) Criterion 9: the patient has had no prior treatment with idelalisib unless idelalisib has had to be stopped within 6 months of its start and solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.
4. In 2016, NICE appraised ibrutinib monotherapy in CLL and as part of this appraisal, NHS England made a submission to NICE which stated that the marketing authorisation for use of ibrutinib in patients with previously treated CLL was much wider than the robust ibrutinib evidence base which was confined to patients unsuitable for CIT.
5. In January 2017, NICE issued guidance on the use of ibrutinib in previously treated CLL and recommended ibrutinib monotherapy within its marketing authorisation which for one group was for patients who have had at least 1 prior therapy and for a second group was for patients who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable. This guidance made no reference to the use of ibrutinib in patients who do not have a 17 p deletion or TP53 mutation and are also suitable for CIT. The clinical and cost effectiveness of ibrutinib in this latter group of CLL patients was therefore unknown.

6. In January 2017, NHS England examined both the evidence base submitted to NICE for the ibrutinib CLL appraisal and the content of the NICE ibrutinib guidance. NHS England concluded that these contained a clinical evidence base which remained founded on relapsed CLL patients unsuitable for CIT. NHS England therefore made no planned changes to its treatment criteria for access to ibrutinib when ibrutinib transitioned from funding in the CDF to that of routine commissioning in April 2017.
7. The CLL Forum wrote to NHS England in March 2017 challenging this retention of the same ibrutinib treatment criteria in the light of the NICE guidance recommending use of ibrutinib within its marketing authorisation. A detailed reply was sent to the CLL Forum in March 2017 justifying NHS England's position including a stated willingness by NHS England to re-examine the ibrutinib treatment criteria consequent to further dialogue with CLL clinicians. No further approach to NHS England was made from the CLL Forum.
8. NHS England did not receive any comment on the ibrutinib treatment criteria from Janssen even though there was much dialogue between Janssen and NHS England in 2017 as regards the transition from the CDF of ibrutinib for its CLL and mantle cell lymphoma indications.
9. Following publicity in May/June 2018 as to the continued use of the NHS England ibrutinib CLL treatment criteria, NICE issued a statement on 5 July 2018 which recorded that the marketing authorisation for ibrutinib in this indication is not comprehensive in its description of the eligible population and neither is NICE's guidance. Given the evidence that was considered by the NICE technology appraisal committee, NICE considered it reasonable for the guidance to be read as referring to those patients considered unsuitable for re-treatment. Because unsuitability for re-treatment was not defined in NICE's guidance, NICE considered it appropriate for NHS England, as the commissioner, to take clinical advice in order to do so.
10. As described above, NHS England had taken clinical advice in January 2015 from its Chemotherapy CRG and this advice was reviewed again in the light of the positive NICE guidance in January 2017. NHS England had also stated that it was open to dialogue with CLL clinicians in March 2017. On 19 June 2018, NHS England offered the opportunity for patient groups, the CLL Forum and the manufacturer of ibrutinib to submit new evidence that might have a bearing on the appropriateness of the current treatment criteria for ibrutinib in previously treated CLL without 17p deletion or TP53 mutation and also evidence relating as to how to define the population of patients considered unsuitable for treatment or re-treatment with CIT. NHS England committed to reviewing any evidence submissions by the end of July 2018.
11. The NHS England Chemotherapy Clinical Reference Group met on 17 July 2018 having considered submissions from the CLL Support Association, Bloodwise, Leukaemia Care, the CLL Forum and Janssen. Two individual patient submissions were also received and considered by the CRG.

12. The Chemotherapy CRG came to the following conclusions:

- a) Cross trial indirect comparisons of historical data are very difficult (particularly in CLL) as trials had a wide variety of designs: differing inclusion and exclusion criteria (such as the number of previous lines of therapy, the duration of remission with last treatment, adverse genetic abnormalities); differing lengths of follow-up; some were single centre series and others international randomised trials; some reflected practice in the pre-rituximab era; and some were recent whereas others were older at times when favourable and adverse genetic abnormalities were not known or routinely tested.
- b) Data with a median duration of follow up of 52 months of patients treated with ibrutinib in the Resonate study showed that in patients unsuitable for CIT, ibrutinib resulted in a median progression free survival (PFS) of 44 months (2018, Janssen). This data clearly shows the very considerable efficacy of ibrutinib in patients unsuitable for CIT. This benefit comes at the cost of side effects such that 12% discontinue treatment (Byrd et al abstract 2017, due for submission as paper 2018). The CRG noted that disease-related cytopenias improved with ibrutinib and that there does not appear to be any increased risk of myeloid malignancy with ibrutinib treatment. The CRG observed that, within the limits set by indirect comparisons, there appeared to be a cumulative serious infection rate of 24% with longer-term ibrutinib therapy (Byrd et al, 2014, Byrd et al 2017) which was similar to the serious infection rate seen with shorter-term CIT.
- c) A multivariate analysis of the Resonate trial ibrutinib data (Byrd et al 2017 abstract, due for submission for publication in 2018) at a time when the median duration of follow up was 44 months found that the influence of the number of previous lines of treatment was an important predictor of benefit with ibrutinib: the fewer the lines of previous treatment, the greater the degree of benefit.
- d) Although the CRG was not presented with the analyses that it would have wished for in terms of ibrutinib efficacy in patients specifically with progression-free intervals of ≥ 3 years on the directly preceding line of treatment in patients before ibrutinib, the CRG considered it likely that in such patients, the ibrutinib PFS would exceed the PFS observed in patients unsuitable for CIT i.e. the PFS duration would be greater than 44 months.
- e) The CRG examined publications from 2010 (Robak et al), 2011 (Badoux et al) and 2014 (Tam et al, Awan et al) which demonstrated the efficacy of treatment or re-treatment with purine-based analogue CITs in previously treated CLL. It observed that the 2010 paper by Tam was a 12 year analysis from a single centre series which had pointed to the greater efficacy of such treatment in patients with previous remission durations of ≥ 3 years. This series had also demonstrated a very striking benefit with further CIT in those patients with previous remission durations of ≥ 6 years. In the more contemporaneous clinical trials of purine analogue-based trials in previously treated CLL (2011, 2014), the CRG noted considerable efficacy with PFS durations of 24-30 months but also very substantial toxicity, the need for bone marrow colony-stimulating factors, a high rate of treatment discontinuations, a 6-7%

mortality rate, persistent cytopenias and an increased risk (5%) of myelodysplasia and acute myeloid leukaemia.

- f) The CRG examined the publications of efficacy of bendamustine plus rituximab (BR), the preferred CIT option of NHS clinicians for previously treated CLL. Although an audit published in 2015 (Fornecker et al) suggested particular efficacy of BR in patients with previous remission durations of ≥ 3 years (there was no analysis of remission durations exceeding 6 years), results from two recent large randomised control trials (reported in Chanan-Khan et al, 2016 and Seymour et al, 2018) which used BR as the control arm have demonstrated more modest efficacy of BR with median PFS durations of 13-17 months. There was also evidence based on substantial numbers that patients treated with BR do not have substantially longer PFS durations if the previous remission durations were ≥ 3 years (2016). Both randomised studies recorded high rates of serious infections (22-25%) and treatment-related deaths in 5-6%.
- g) The CRG therefore understood that, whilst there was some evidence relating to the usefulness of a 3 year previous remission duration being a clinically useful pointer as to the suitability of further CIT, it recognised that the most recent BR data cast doubt on the value of this 3 year rule. The CRG recalled the British Society for Haematology CLL guidelines (2018) which had concluded that re-treatment with CIT may be more effective in those patients with long initial remissions from previous therapy. The CRG considered that whilst previous remission durations considerably in excess of 3 years probably did lead to further durable responses with CIT (as evidenced in the Tam et al data, 2014), it concluded that there now remained doubt as to the robustness of the use of a 3 year previous remission duration in clinical practice to determine suitability of further CIT.
- h) The advantages of CIT with BR are that it is treatment with a fixed duration (maximum of 24 weeks) and retains ibrutinib as a treatment option for the future. The disadvantages of BR are the toxicities of chemotherapy and especially the myelosuppression, the serious infection rate, the high discontinuation rate and the mortality rate of 5-6%. The advantages of ibrutinib in those patients with previous remission durations of ≥ 3 years are that it is very probably better than CIT, is generally well tolerated by most but not all patients and it allows existing cytopenias to improve. So far, ibrutinib does not seem to increase the risk of myeloid malignancy. The disadvantages of ibrutinib are that it is taken daily for very long periods and can thus be burdensome, 12% stop treatment on account of side-effects and the most recent data suggests it has the equivalent long term serious infection rates as seen in the short term with CIT. It is not known whether treatment with ibrutinib earlier in the treatment pathway prejudices CIT options later in the treatment pathway.
- i) The CRG also examined emerging therapies in previously treated CLL and concluded that in 2018 the treatment landscape has changed to make 2nd or further line CIT a less relevant option for most patients with CLL. The 2018 trial data of fixed duration venetoclax plus rituximab (Seymour et al, 2018) offers another systemic therapy option which does not include any cytotoxic chemotherapy agent. Venetoclax plus rituximab has been shown to be superior in patients able to receive CIT with BR. There are thus non-cytotoxic chemotherapy

options in the CLL treatment pathway with ibrutinib/idelalisib plus rituximab and potentially also venetoclax plus rituximab. The CRG was aware that all new future options in CLL will be targeted therapies or monoclonal antibodies or combinations of these two types of agents.

- j) The CRG concluded that i) the 2018 evidence of the efficacy of ibrutinib, ii) the 2016 and 2018 data on the efficacy and toxicity of BR, iii) the recent analyses of the usefulness of a 3 year previous remission duration as a marker of benefit with further CIT and iv) the evolving changes in the CLL treatment landscape have combined together for the CRG to recommend changes in the current 4th NHS England treatment criterion for ibrutinib. This would be to allow the option of treatment with ibrutinib in patients whose remission durations were ≥ 3 years in the directly preceding line of therapy. The CRG also concluded that there remained some patients who after a fully informed consenting process would opt for further CIT (such as those that were attracted to a fixed and relatively short duration of therapy, those that wanted to keep their known treatment options open for the future, those with remission durations with previous CIT of considerably in excess of 3 years). The CRG also concluded that there would be other patients who would opt for ibrutinib who did not want further CIT.
- k) The CRG noted that, whilst the cost effectiveness of ibrutinib for those unsuitable for purine analogue-based CIT was assured, the cost effectiveness of ibrutinib in patients with a previous remission duration of ≥ 3 years was not known. The CRG could not draw any appropriate parallels from the NICE ibrutinib appraisal as to the cost effectiveness of ibrutinib in those patients with previous remission durations of ≥ 3 years. This was because the comparator used in the Resonate study was relatively ineffective and costly as opposed to CIT which would likely be of greater efficacy but cost significantly less as bendamustine is generic and rituximab has biosimilar preparations. The CRG noted the potential advantage of engaging with the company to explore mitigation of the increased expenditure for this group of patients in which the cost effectiveness is unknown.
- l) The CRG was aware that the availability of BR in NHS England is an issue in CLL and this is currently being addressed by the NHS England Specialised Commissioning policy prioritisation process.
- m) The CRG also considered the issue of age in the current 4th NHS England ibrutinib treatment criterion. Although age is an important prognostic factor in CLL and that an age of ≥ 70 years is frequently used in clinical practice as a contra-indication to further CIT (and the Resonate trial used this ≥ 70 year rule as one criterion to define unsuitability for further CIT), the CRG considered that it was now appropriate to recommend removing this criterion even though there had been no criticism of this age stipulation. The Resonate trial also defined another reason for patient unsuitability for further CIT as being patients of age ≥ 65 years plus having significant comorbidities. Although no criticism of this criterion had been received, the CRG considered it also appropriate to recommend removing any reference to age in this comorbidity criterion.
- n) The CRG also considered other potential significant changes to the current NHS England treatment criteria for the use of ibrutinib in previously treated CLL:

- i) Criterion 3. Whilst the CRG was aware that 6% of patients in the Resonate study had not previously received treatment with rituximab, it recognised the clinical efficacy and cost effectiveness in CLL of anti-CD20 antibodies in combination with chemotherapy. The CRG concluded that it was appropriate in 2018 to maintain the criterion of requiring patients to have previously received treatment with an anti-CD20-containing CIT regimen before any consideration of access to ibrutinib.
 - ii) Criterion 9. The CRG recognised that although most patients commencing a B cell receptor pathway inhibitor were treated with ibrutinib, some patients receive therapy with idelalisib plus rituximab. The current NHS England treatment criteria for ibrutinib allows the sequencing of these two therapies but ibrutinib can only be given to patients previously treated with idelalisib if they experience dose-limiting toxicity within 6 months of commencing idelalisib and do not have progressive disease. The converse also applies to patients commencing ibrutinib, suffering similar toxicity and then being able to switch access to idelalisib plus rituximab. The CRG agreed that there is now evidence of idelalisib dose-limiting toxicity occurring beyond 6 months and hence agreed to recommend removing this time restriction from criterion 9. In addition, the CRG reviewed the 2016 paper (Mato et al) on sequential treatment of ibrutinib/idelalisib plus rituximab and agreed that toxicity in the absence of disease progression should be the sole reason for the commissioning of sequential treatment. The CRG noted that NICE in its appraisals of ibrutinib and idelalisib had not been presented with any evidence of the cost effectiveness of sequential therapy. The CRG also observed that the 2018 British Society for Haematology CLL guideline on the basis of present evidence had also suggested the brevity of remission durations with sequential therapy in patients who had progressed on the first B cell receptor pathway inhibitor.
- o) In conclusion, the CRG considered that it had made the correct evidence-based decision in 2015 as regards the ibrutinib treatment criteria which had to be fulfilled for ibrutinib access to be funded. It also agreed that it was correct in 2017 for these to be maintained. It noted the development in the evidence base since then, particularly in 2016-2018 and especially so in 2018. It now concluded that whilst it was appropriate for it to recommend to NHS England to make changes to the ibrutinib treatment criteria on clinical grounds, there is currently no evidence available to know that by so doing, ibrutinib remains cost effective within the broad wording of its marketing authorisation in previously treated CLL.
- p) The CRG considered the potential budget impact of its recommendations. It noted the likely ibrutinib treatment duration to be in excess of 44 months in most patients and thus considered the additional expenditure to be significant at a time when the NHS is under very great financial pressure. In view of the confidential nature of the Patient Access Scheme in use, the estimated budget impact of the recommended changes to the NHS England treatment criteria are commercial in confidence and thus cannot be set out in this document.

Summary of the key evidence and issues considered by the NHS England Chemotherapy Clinical Reference Group in its re-assessment of the NHS England commissioning criteria for the use of ibrutinib in patients with previously treated chronic lymphocytic leukaemia

Current guidelines

13. In June 2017, the European Society of Medical Oncology updated its CLL treatment recommendations as follows:

“First-line treatment may be repeated if the relapse or progression occurs at least 24-36 months after chemoimmunotherapy and if TP53 deletion/mutation was excluded (III,B). If relapse occurs within 24-36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed. Treatment options include (III,B): Bruton’s tyrosine kinase inhibitor ibrutinib; PI3K inhibitor idelalisib in combination with rituximab; BCL2 antagonist venetoclax (if patient failed BCR inhibitor therapy).; Other chemoimmunotherapy combinations should only be administered if TP53 deletion/mutation was excluded.”

<http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia>

14. BSH 2018 guidelines for CLL were published in July 2018 (Schuh et al) and the CRG noted the following relevant statements:

- i) Chemoimmunotherapy (CIT) is not advised in patients who have not responded to previous CIT, relapsed within 24-36 months of intensive CIT with FCR or BR or have acquired TP53 disruption
- ii) The consideration to treat relapse with CIT depends on (1) the time to relapse, (2) the type of frontline therapy and (3) the absence of TP53 disruption
- iii) Re-treatment with CIT may be more effective in those patients with long initial remissions from previous therapy
- iv) Patients who were less heavily pre-treated or who had experienced a prolonged first remission with CIT were excluded from the respective randomised trials of ibrutinib and idelalisib plus rituximab [versus the chosen comparators in those trials]. Furthermore, neither ibrutinib nor idelalisib plus rituximab have been evaluated prospectively against CIT in the relapsed CLL setting
- v) Idelalisib plus rituximab, or ibrutinib monotherapy, are the treatments of choice for patients with CLL who are refractory to CIT, have relapsed after CIT or for whom re-treatment with CIT is inappropriate [existing co-morbidities, presence of TP53 disruption]
- vi) Re-treatment with CIT may be considered as an option for fit patients with CLL who relapse after a prolonged remission
- vii) Real-world case studies of patients who progressed on one B cell receptor pathway inhibitor (ibrutinib/idelalisib plus rituximab) and were switched to an alternative targeted agent [i.e. another B cell receptor pathway inhibitor{BCRi}] suggest a short progression-free interval
- viii) Venetoclax in combination with rituximab might also become an option for BCRi-naïve patients.

15. The CRG notes that any guideline can potentially be out of date by the time it is published.

Efficacy and toxicity of ibrutinib in patients with previously treated CLL

16. Ibrutinib monotherapy has only been formally tested in a directly comparable trial in patients with previously treated CLL who were unsuitable for CIT (the Resonate study).
17. The current NHS England commissioning treatment criteria for ibrutinib incorporated a definition of patients unsuitable for CIT that was widely held in 2015. These criteria were set at a time when the median duration of follow up in the Resonate study was 9.4 months and thus the longer term benefit of ibrutinib was still unclear (Byrd et al, 2014). Only in 2018 was Resonate trial data published with a median duration of follow up of 19 months (Brown et al, 2018). A further follow up study with a median duration of follow up of 44 months was described in a 2017 conference abstract (Byrd et al, 2017) and this data is shortly to be submitted for publication.
18. The latest intention to treat (ITT) analysis of the ibrutinib arm of the Resonate trial with a median duration of follow-up of 52 months demonstrates a PFS of 44.1 months (provided in Janssen's submission to NHS England).
19. There were 73 patients in the Resonate study that had a progression-free interval of ≥ 3 years in any previous line of treatment and these patients had a PFS on ibrutinib of 49.7 months (Janssen's submission). However, Janssen's submission does not compare these 73 patients with the intention to treat number of 195 patients minus the 73 patients (i.e. no comparison is made with the remaining 122 patients). Nor does the Janssen analysis identify from the Resonate trial patients who had a progression-free interval of ≥ 3 years in the directly preceding line of treatment. Nevertheless, the CRG considered that it is biologically plausible that patients with remission durations of ≥ 3 years in the directly preceding line of therapy would have a median progression free duration with ibrutinib which exceeded 49.7 months.
20. A multivariate analysis of the Resonate ibrutinib data (Byrd et al, 2017 in abstract and shortly to be submitted for publication) at a time when the median duration of follow up was 44 months found that the influence of the number of previous lines of treatment was an important predictor of benefit with ibrutinib. In the ≤ 2 prior lines group (n=92), the median PFS was not reached whereas it was 35.1 months in the >2 prior group (n=103) [HR 0.53, 95% CI 0.33-0.80] {Figure 3D in the 2017 conference abstract}.
21. An analysis of the Resonate ibrutinib data (Brown et al, 2018) at a time when the median duration of follow up was 19 months also examined the influence of number of lines of treatment on PFS (see figure 1c in this publication). The PFS rates at 18 months were over 90% in the 1-prior group (n=35), about 76% in the 2-prior group (n=57), about 76% in the 3-prior group (n=32) and about 64% in the ≥ 4 -prior group (n=71). When the 1-prior treatment group was compared for PFS with the >1 prior therapy group the HR was 3.3 (95% CI 1.02-10.65, p=0.035).

22. Of these two analyses as to the benefit of ibrutinib according to the number of prior lines of therapy, the CRG considered that the multivariate analysis with the much longer follow up had greater statistical weight (i.e. the results described in paragraph 20 are preferred to those in paragraph 21), especially as the numbers in the 4 subgroups in paragraph 21 are individually relatively small.
23. In terms of efficacy of ibrutinib in the Resonate trial, the CRG concluded that it seems likely that ibrutinib has a longer PFS in those with i) a progression-free interval of ≥ 3 years with the immediately preceding line of treatment and ii) in those with fewer prior therapies.
24. The CRG noted that those patients with baseline cytopenias generally improve their blood counts as treatment with ibrutinib continues.
25. The CRG observed that 12% of patients discontinued treatment with ibrutinib on account of toxicity, the rate of discontinuation diminishing in successive years on therapy. The main toxicities of ibrutinib are diarrhoea, fatigue, nausea, infections and hypertension. Using the data from the report with a median duration of follow up of 44 months in the Resonate trial, the CRG concluded that although a direct comparison cannot be made with CIT, the long term experience with ibrutinib appears to show that the grade 3 infection risk is similar to that observed in CIT trials performed in the relapsed CLL setting where that same infection risk is over a much shorter period with CIT. The CRG concluded that toxicity with ibrutinib was clinically significant, particularly infection.
26. The CRG noted that there does not appear to be any signal so far that treatment with ibrutinib raises the existing risk of CLL patients developing myelodysplastic syndrome or acute myeloid leukaemia.

Efficacy and toxicity of CIT in patients with previously treated CLL and considered suitable for further chemoimmunotherapy

27. The CRG concluded that cross trial indirect comparisons of historical data are very difficult (particularly in CLL) as trials had a wide variety of designs: differing inclusion and exclusion criteria (such as the number of previous lines of therapy, the duration of remission with last treatment, adverse genetic abnormalities); differing lengths of follow up; some were single centre series and others international randomised trials; some reflected practice in the pre-rituximab era; and some were recent whereas others were older at times when favourable and adverse genetic abnormalities were not known or routinely tested.

Relapsed patients treated with fludarabine, cyclophosphamide and rituximab

28. One of the more important papers submitted for consideration by the CLL Forum concerns the subsequent treatment of patients initially treated with the 1st line CIT regimen of fludarabine, cyclophosphamide and rituximab (FCR) [Tam et al, 2014]. The patients in this single centre study were generally treated with intensive 2nd line CIT regimens (some of which were/are not available in England) and achieved outcomes which largely depended on the

progression free interval following 1st line therapy. The best statistical divider of poor versus good risk patients in terms of the benefits of 2nd line therapy was a 1st line remission of <3 years versus ≥3 years (highly significant at p=0.000045).

29. The CRG further considered the robustness of the 3 year PFS divider and noted that in the Tam publication there was a median duration of follow up of 77 months after disease progression had occurred following 1st line chemotherapy. In patients with a 1st remission of 6 years, there was a 71% rate of overall survival (OS) at 5 years after disease progression (n=46); in patients with a 1st remission of 3-5.9 years, the median duration of OS was 54 months (n=61); in patients with a 1st remission of 1-2.9 years, the median OS was 27 months (n=34); and in those with a 1st remission of <1 year, the median OS was 13 months (n=15) [these groups are shown in Figure 2C in the Tam et al publication]. A further and more detailed analysis also examined OS after disease progression according to 1st line remission duration and this is shown in Supplementary Figure 2B in the Tam et al publication. The rate of 6 year survival was about 65% in those with a 1st remission of ≥6 years (n=46), about 46% in those with a 1st remission of 5-5.9 years, about 37% in those with a 1st remission of 4-4.9 years, about 43% in those with a 1st remission of 3-3.9 years, about 23% in those with a 1st remission of 2-2.9 years, about 32% in those with a 1st remission of 1-1.9 years and about 15% in those with a 1st remission of <1 year. Survival after disease progression was clearly related to the duration of 1st remission after FCR (p<0.001) but the CRG considered that by far the most impressively separated data was in the patient group with a 1st remission of 6 or more years.
30. In this Tam et al paper (2014), toxicity of further CIT was considerable although the authors concluded that re-challenge with FCR after 1st line FCR represented a reasonable standard of care in those patients relapsing after 1st line FCR with remission durations of 3 or more years. This was a single centre paper from the MD Anderson Cancer Centre with a worldwide reputation for treatment and thus the role of selection bias was considered to be relevant. The CRG noted these results and observed that by far the widest separation of the OS Kaplan Meier plot was in patients with previous remission durations of ≥6 years.
30. Other trials using FCR (Badoux et al, 2011, Robak et al 2014, Awan et al 2014) as a treatment of relapsed CLL have found clear evidence of efficacy of FCR (median PFS values of 21-30 months) but with substantial grade 3 and 4 infection rates and treatment-related death rates of 6-7%.
31. UK clinicians have not wished to and do not wish to treat patients with FCR as 2nd line therapy in view of the high infection rate, the prolonged cytopenias that can occur during and after treatment, the treatment-related fatality rate and the expected higher incidence of myelodysplastic syndrome and acute myeloid leukaemia (5%) which would occur following re-treatment with FCR.

Relapsed patients treated with bendamustine and rituximab (BR)

32. As a 2nd line CIT, UK clinicians have preferred to use the combination of bendamustine plus rituximab (BR) as this has been shown to be active in this setting. From the point of view of the use of 2nd line BR, interpretation of historical studies is hindered by patients having a greater number of previous lines of therapy and also not having previously received treatment with rituximab.
33. Bendamustine was removed from the old CDF in 2015 (at the same time that ibrutinib entered the CDF) using the then CDF scoring system for prioritisation based on the only available data of BR at that time which was on phase II data. There was no phase III data available and had there been so, BR would have then been retained in the CDF. In 2015, the CDF suggested to the CLL community that an application to the NHS England prioritisation process should commence for the commissioning of 2nd line BR.
34. A French study (Fornecker et al 2015) examined outcomes of patients relapsing after 1st line therapy with FCR. Half of these 132 patients received BR as 2nd line treatment and the observed PFS was 18 months. The 3 year overall survival in these relapsed patients was 95% if the 1st remission was 3 years or more, 57% if the remission was 24-35 months and 45% if <24 months (see figure 2A in Fornecker et al). The authors proposed that a 1st remission of <36 months is a crucial threshold for identifying high risk patients with shortened survival. The authors also concluded that CIT is a reasonable standard of treatment in patients whose first remission is 36 months or more.
35. There have been two much more contemporaneous randomised controlled trials which have used BR as the control arm. Their constituent populations are heterogeneous in the manner described above in paragraph 27. The Helios trial (Chanan-Khan et al 2016) and the Murano trial (Seymour et al 2018) used BR as the control arm in these studies and recorded median PFS durations of 13-17 months. Both trials recorded high rates of infections (22-25%) and treatment related deaths in 5-6%.
36. The Helios trial (Chanan-Khan et al, 2016) analysed progression free interval according to previous treatment-free interval (see page 18 and Fig 1e of the Helios trial supplementary appendix). In the BR arm, median PFS was about 12 months in those with a treatment-free interval of <36 months (n=207) and was about 14.5 months in those that had a treatment-free interval of ≥36 months (n=82). The CRG noted the rather greater number of patients in this analysis than in those described above.

Key issues considered by the CRG

37. The key NHS England commissioning treatment criterion for ibrutinib that patients and clinicians wish to change is the one that stipulates that remission durations has to be less than 3 years for ibrutinib to be used. The data in paragraphs 28 and 34 support this criterion although it is fair to state that the data used to delineate this remission duration of 3 or more years is based on relatively small numbers. The Helios 2016 data significantly undermines the

value of ≥ 3 year previous remission duration as being a clinically useful marker of significant benefit with further CIT. The 6 year previous remission duration as a marker of greater benefit with further CIT is both striking in a single centre series and biologically plausible but does not appear to have been repeated in other analyses and thus cannot be used in current setting of NHS England treatment criteria with sufficient surety.

38. The other NHS England ibrutinib treatment criteria mean that access is already granted to patients over 70 years of age and those with deleted 17p disease: these two factors are known key adverse prognostic indicators in CLL. A third prognostic factor for benefit with further therapy may be that of longer remission durations of ≥ 3 yrs achieved with a directly preceding line of treatment. It is very difficult to know how much better treatment outcomes with FCR re-challenge or 2nd line treatment with BR would be in the population of previously treated CLL patients who fall outside the current NHS England treatment criteria with one prior therapy and a previous remission duration of 3 or more years. This is because of the heterogeneities of the clinical trial populations, the outcomes of which are described above. It is likely that median PFS durations with BR in a group with only 1 prior treatment and with a previous remission duration of ≥ 3 years would be better than many of the publications suggest. The Helios 2016 data does however point to relatively poor outcomes with BR in those with a treatment-free interval of ≥ 36 months but it is not known how many of these patients had only 1 previous line of therapy. As a consequence, there is therefore no clear cut and unanimous evidence from indirect comparisons of how much more efficacious ibrutinib monotherapy might be versus CIT in the population of patients not included in the NHS England treatment criteria. Nevertheless the CRG concluded that ibrutinib was likely to be more efficacious than CIT in the ≥ 3 year previous remission duration group. The CRG was unsure as to whether ibrutinib would be better if patients had a previous remission duration which was much longer than 3 years e.g. ≥ 6 years as in this case the necessary comparison would be ibrutinib versus the sequence of further CIT and then ibrutinib.
39. The CRG concluded that the advantages of CIT with BR are that it is treatment with a fixed duration (maximum of 24 weeks) and retains the ibrutinib treatment option for the future. The disadvantages of BR are the toxicities of chemotherapy and especially the myelosuppression, the serious infection rate, the high discontinuation rate and the mortality rate of 5-6%.
40. The CRG concluded that the advantages of ibrutinib in those patients with previous remission durations of ≥ 3 years are that it is very probably better than CIT, is generally well tolerated by most but not all patients and it allows existing cytopenias to improve. So far, it does not seem to increase the risk of myeloid malignancy. The disadvantages of ibrutinib are that it is taken daily for very long periods and can thus be burdensome, 12% stop treatment on account of side-effects and the most recent data suggests it has the same long term serious infection rates as seen in the short term with CIT. It is not known whether treatment with ibrutinib earlier in the treatment pathway prejudices CIT options later in the treatment pathway although it is known that fitter patients can tolerate venetoclax after ibrutinib (venetoclax monotherapy post ibrutinib is currently in the CDF).

41. The CRG also examined emerging therapies in previously treated CLL and concluded that in 2018 the treatment landscape has changed to make 2nd or further line CIT a less relevant option for most patients with CLL. The 2018 Murano trial data of fixed duration venetoclax plus rituximab offers another systemic therapy option which does not include any cytotoxic chemotherapy agent. Venetoclax plus rituximab has been shown to be superior in patients able to receive CIT with BR (Seymour et al, 2018). There are thus options in the CLL treatment pathway with ibrutinib/idelalisib plus rituximab and potentially also venetoclax plus rituximab. The CRG was aware that all new future options in CLL will be targeted therapies or monoclonal antibodies or combinations of these agents.
42. The CRG noted that ibrutinib monotherapy was cost effective in those patients who are unsuitable for CIT and this conclusion by NICE was based on a comparator (single agent ofatumumab) which was relatively ineffective yet moderately costly, had never been routinely commissioned by NHS England and had been removed from the CDF in January 2015. The CRG also observed that the mean duration of ibrutinib modelled in the NICE appraisal was 32 months yet the latest PFS results showed a median of 44 months: even with 12% discontinuations, it is likely that the mean treatment duration of ibrutinib in the Resonate population is significantly in excess of 44 months. The CRG observed that whilst this data would increase the incremental benefit with ibrutinib, it would also substantially raise the incremental cost. The CRG noted that the comparator for ibrutinib monotherapy in those with previous remission durations of ≥ 3 years would be BR which would have greater efficacy than single agent ofatumumab and cost much less as bendamustine is generic and rituximab is biosimilar. The CRG therefore did not know whether ibrutinib would be cost effective in a comparison with BR and could not draw any meaningful inferences from the clinical trial data and the NICE appraisal of ibrutinib in order to come to any clearer conclusion as to the cost effectiveness of ibrutinib in patients with previous remission durations which were ≥ 3 years.
43. The availability of BR in NHS England is an issue in CLL which is currently being addressed by the NHS England Specialised Commissioning policy prioritisation process. The CRG was aware that a NHS England decision on the routine commissioning of BR for relapsed CLL is currently due late 2018/early 2019.
44. The CRG noted in the Janssen submission that there is real world data indicating that in France and Belgium, 26-28% of patients starting ibrutinib had a remission duration of at least 3 years with the previous treatment. It is not known how many of these would currently fit into the current NHS England ibrutinib treatment criteria by being over 70 years old or having significant comorbidities. The CRG considered that at least over half of these 26-28% of patients were likely to be already having access to ibrutinib in England. This would mean an extra 10% or so patients accessing ibrutinib in England if there was no need for remission durations to be less than 3 years. The expected treatment duration would be substantial and thus the CRG considered it likely that such expanded access would result in a significant additional expenditure.
45. The CRG noted that CLL patients and clinicians wished to have the option of ibrutinib or BR available if the patient is under 70 years old, without any comorbidities and with a previous

remission duration with CIT of 3 years or more. The CRG noted the need for a fully informed consenting process for patients to decide as to the best option for them with short and long terms consequences of both options being discussed in detail.

46. The CRG considered the issue of age in the current 4th NHS England ibrutinib treatment criterion. Although age is an important prognostic factor in CLL and that an age of ≥ 70 years is frequently used in clinical practice as a contra-indication to further CIT (and the Resonate trial used this patient being ≥ 70 year rule as one criterion to define unsuitability for further CIT), the CRG considered that it was now appropriate to recommend removing this criterion even though there had been no criticism of this age stipulation.
47. The Resonate trial also defined another reason for patient unsuitability for further CIT as being patients aged ≥ 65 years plus having significant comorbidities. Although no criticism of this criterion had been received, the CRG considered it also appropriate to recommend removing any reference to age in the comorbidity criterion.
48. The CRG also considered whether it was right to retain the NHS England commissioning treatment criterion (criterion 3) which stipulated the need for previous treatment to have included an anti-CD20 monoclonal antibody. Whilst the CRG was aware that 6% of patients in the Resonate study had not previously received treatment with rituximab, it recognised the clinical efficacy and cost effectiveness in CLL of anti-CD20 antibodies in combination with chemotherapy (routine commissioning offers access to rituximab, obinutuzumab and ofatumumab). The CRG concluded that it was appropriate in 2018 to maintain the criterion of requiring patients to have previously received treatment with an anti-CD20-containing chemotherapy regimen given the efficacy of such treatment and its proven cost effectiveness.
49. The CRG also recognised that although most patients commencing a B cell receptor pathway inhibitor are treated with ibrutinib, some patients receive therapy with idelalisib plus rituximab. The current NHS England treatment criteria for ibrutinib allows the sequencing of these two therapies but ibrutinib can only be given to patients previously treated with idelalisib if they experience dose-limiting toxicity within 6 months of commencing idelalisib and do not have progressive disease (criterion 9). The converse also applies to patients commencing ibrutinib and suffering similar toxicity. The CRG agreed that there is now evidence of dose-limiting idelalisib toxicity occurring beyond 6 months and hence agreed to recommend removing this time restriction. In addition, the CRG reviewed the 2016 paper on sequential treatment and agreed that toxicity in the absence of progression should be the sole reason for the commissioning of sequential treatment. The CRG noted that NICE in its appraisals of ibrutinib and idelalisib had not been presented with any evidence of cost effectiveness of sequential therapy and also observed that the 2018 British Society of Haematology CLL guideline on the basis of present evidence had also suggested a short remission duration with sequential therapy in patients who had progressed on the first B cell receptor pathway inhibitor.
50. The CRG also wished to make minor changes to 3 other criteria. Criterion 6 and 7 currently require patients commencing ibrutinib to have a neutrophil count which is $\geq 0.75 \times 10^9/L$ and

a platelet count which is $\geq 30 \times 10^9/L$, respectively. The CRG agreed to add 'unless due to disease' to both these criteria. Criterion 8 specifies that patients accessing ibrutinib should not be taking warfarin or CYP3A4/5 inhibitors. The CRG agreed to precede CYP3A4/5 inhibitors with the word 'strong' as this phrasing is in the Summary of Product Characteristics.

51. The CRG welcomed plans discussed by NICE and NHS England as to the earlier incorporation into the NICE technology appraisal process of input from NHS England as regards cancer drugs. It was aware of steps being taken by NICE for NHS England to provide submissions at the scoping stage, once the company had made its submission, after the Evidence Review Group and both clinical and patient group submissions had been made and to be part of the technical engagement process. The CRG considered that such steps would help the appraisal of all cancer drugs, particularly those involved in the increasingly complex treatment pathways that are now commonplace.

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References

- Schuh, A. *et al.* Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *British J Haematol* 2018 July 15. doi:10.1111/bjh.15460 Epub ahead of print
- Brown, J. R. *et al.* Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. *Leukemia* **32**, 83–91 (2018)
- Byrd, J. C. *et al.* Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. *N. Engl. J. Med.* **369**, 32–42 (2013)
- Byrd, J. C. *et al.* Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *N. Engl. J. Med.* (2014). doi:10.1056/NEJMoa1400376
- Byrd, J. C. *et al.* Long-term efficacy and safety with ibrutinib in previously treated chronic lymphocytic leukaemia: up to 4 years follow-up of the Resonate study. *Abstract 7510 ASCO 2017 in J Clin Oncol* 2017
- Chanan-Khan, A. *et al.* Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): A randomised, double-blind, phase 3 study. *Lancet Oncol.* (2016). doi:10.1016/S1470-2045(15)00465-9
- Fischer, K. *et al.* Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A Multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J. Clin. Oncol.* **29**, 3559–3566 (2011)
- Seymour, J. F. *et al.* Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N. Engl. J. Med.* **378**, 1107–1120 (2018)
- Awan, F. T. *et al.* A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed ch. *Br. J. Haematol.* **167**, 466–477 (2014)
- Robak, T. *et al.* Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J. Clin. Oncol.* **28**, 1756–1765 (2010)
- Niederle, N. *et al.* Bendamustine compared to fludarabine as second-line treatment in chronic lymphocytic leukemia. *Ann. Hematol.* **92**, 653–660 (2013)
- Tam, C. S. *et al.* Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). *Blood* **124**, 3059–3064 (2014)
- Fornecker, L. M. *et al.* Salvage outcomes in patients with first relapse after fludarabine, cyclophosphamide, and rituximab for chronic lymphocytic leukemia: The French intergroup experience. *Am. J. Hematol.* (2015). doi:10.1002/ajh.23999
- Badoux, X. C. *et al.* Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly

effective treatment for relapsed patients with CLL. *Blood* (2011). doi:10.1182/blood-2010-08-304683

Benjamini, O. *et al.* Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk. Lymphoma* (2015). doi:10.3109/10428194.2014.957203

Mato, A. R. *et al.* Outcomes of CLL patients treated with sequential kinase inhibitor therapy: A real world experience. *Blood* (2016). doi:10.1182/blood-2016-05-716977