Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you
Your names: Submitted by

Name of your organisation: **RCP**

Comments coordinated by **, Claire Dearden (CD)**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The first-line therapy for previously untreated CLL patients unfit for a fludarabine-based regimen has been chlorambucil monotherapy since the pivotal paper of Galton et al in 1962. Chlorambucil monotherapy in the UK CLL 4 study showed a complete response rate of 7%, an overall response rate of 72% and a median progression free survival of just under 2 years with 10% still progression free at 5 years. (Catovsky et al. Lancet 2007).

Although there have been randomised studies looking to improve on the outcome of chlorambucil monotherapy, only bendamustine and fludarabine/cyclophosphamide +/- rituximab (FC, FCR) have been consistently shown to be superior (UK CLL 4 Study – Catovsky et al Lancet 2007, German CLL 5 study – Eichhorst et al Blood 2009, Hallek et al Lancet 2009 and Knauf et al J Clin Oncol 2009). In the Knauf study, chlorambucil was given at the same dose as in the CLL 11 study and was shown to be inferior to bendamustine with a complete response rate of 2% compared to 31%, an overall response of 31% compared to 68% and a PFS of 8.3 months compared to 21.6 months. Based on this study NICE approved bendamustine for treatment-naïve CLL patients unfit for a fludarabine-based regimen. There is a study showing alemtuzumab was superior to chlorambucil in terms of overall response rate, complete response rate and time to next treatment but alemtuzumab is no longer available for treatment-naïve CLL patients unless they have p53 abnormalities (Hillmen et al JCO 2007).

Thus both FCR and bendamustine monotherapy have been approved by NICE for first-line therapy of treatment-naïve patients with CLL.

A recent single arm study of chlorambucil/rituximab combination therapy suggested this was superior to chlorambucil monotherapy based on historical data. (Hillmen et al JCO 2014) We are also awaiting publication of a randomised study showing ofatumumab/chorambucil was superior to chlorambucil monotherapy (Hillmen et al BSH Birmingham 2014) and this technology is presently undergoing NICE Technological Appraisal.

So for treatment-naïve CLL patients unfit for FC/FCR, chlorambucil monotherapy has been the overwhelming therapy of choice for this group of patients in the UK although a few previously untreated CLL patients will be treated with bendamustine +/- rituximab therapy (the latter combination is not NICE approved). Thus the two alternative therapies for this technology should be chlorambucil monotherapy or bendamustine monotherapy.

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Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

For patients unfit for FC/FCR, chlorambucil monotherapy is the treatment choice for therapy-naïve patients with the exception of those with a 17p mutation/deletion in which case an alemtuzumab and/or steroid-based regimen would be indicated as chlorambucil is typically ineffective in this group of patients.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This technology would need to be administered in hospital typically a Haematology Day Unit with both medical and nursing support and resuscitation facilities. This is in contrast to chlorambucil monotherapy which is typically administered at home with patients receiving their medication in out-patients from their specialist haematology team. Bendamustine monotherapy is also intravenously administered in a Day Unit with medical, nursing and resuscitation support.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This is a new Technology and hence only centres where this has been used in clinical trials will have experience. So there should be no UK variations in how it is used.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The British Committee for Standards in Haematology seconded the UK CLL Forum to write national guidelines for the diagnosis, management and therapeutic treatment of CLL, which were published in December 2012 (BJH). These guidelines were put together by UK experts based on internationally recognised levels of evidence following widespread research into the world literature and superseded the previous guidelines published in 2003. In these guidelines the recommended therapy for treatment-naïve patients unsuitable for FC/FCR is chlorambucil or bendamustine monotherapy.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology

be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The usual current therapy in the UK is oral chlorambucil typically given for 7 days at a dose of 10mg/m^2 for 7 days every month for up to 12 months. This is in contrast to bendamustine which is given IV (30 minute infusion) for 2 days every month typically for 4-6 months. The new technology will therefore require considerably more Day Unit input, especially nursing time, and the need for physicians to become familiar with the 15 day dosing of chlorambucil (0.5mk/kg day 1 and 15 of 28 day cycle for 6 months) used in this technology. Also there is a risk of infusion related reactions (IRR's) with the new technology, which is not a problem with chlorambucil or bendamustine monotherapy.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The criteria for starting and stopping CLL therapy are in the BCSH Guidelines and are well established in clinical practice in the UK. This new technology should not therefore result in any significant change in this respect. One of the concerns in using this technology has been the risk of IRR's, which do not occur with chlorambucil or bendamustine monotherapy. Prophylaxis with steroids, anti-histamines and paracetamol are recommended prior to the infusion although concerns have been raised about the effectiveness of prophylaxis in preventing IRR's.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

As outlined above the technology is not available in the UK outside clinical trials. However, having taken part in the licensing study CF's opinion is that this technology fits very well into UK practice and there are no major issues in its widespread introduction into UK Haematology should it be approved. If CF recalls correctly 6 UK centres took part in the licensing study and to his knowledge there were no concerns from the UK practice perspective.

As one can see from the UK CLL 4 study results the outcome in terms of length of PFS and overall survival (OS) for patients who receive single-agent chlorambucil is poor compared to what is now seen with combination chemo-immunotherapy. This has stimulated randomised clinical trials in the group of patients unable to receive current more intensive chemo-immunotherapy

regimens such as FCR in order to improve on the results for monotherapy. This is very important as < 50% of patients requiring treatment for their CLL are suitable for a fludarabine-based regimen. The licensing study clearly shows a significant difference compared to chlorambucil in the most important parameters for patients most notably:
Higher complete remission rate 22.2% versus 0%
PFS – 26.7 v 11.1 months
Prolonged OS

Several researchers have reported minimal residual disease (MRD) as a surrogate marker of depth of response and predictor of PFS and OS.
On a minor note, the licensing study reported significantly higher MRD negativity with the technology compared to chlorambucil monotherapy 31.1% versus 0% in blood and 17% versus 0% in bone marrow. The marrow data has been challenged as being misleading as one only performs bone marrow tests in patients who are thought to be in complete remission. Of the 212 patients who received the technology only 88 had a bone marrow test with 15 being MRD negative in the bone marrow. Thus some would argue that the data shows that MRD-negativity in bone marrow was proven in only 15/212 patients i.e 7%. Likewise the figure of 31.1 % for blood MRD-negativity has raised concerns as only 132 of the 212 technology treated patients (62.2%) had this analysed with 41/212 being MRD negative i.e 19.3 %. This compares with the 106 in the chlorambucil arm in whom 80 - 75.5 % had MRD analysed. It is not clear why there was a discrepancy in blood MRD testing between the 2 patient groups as it would be expected that the more potent arm would have a higher % of patients being tested for MRD-negativity. If there is a significant difference between the two arms with regard to MRD testing (62.2% versus 75.5%) then this may invalidate the MRD data.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Chlorambucil, at whatever dose, is a very well tolerated therapy. This technology shows a higher rate of grade 3 or more neutropenia compared to chlorambucil monotherapy (35% versus 16%) but no increase in infections (11% v 14%) or febrile neutropenia (25% v 4%). There was also a higher rate of grade 3 or greater thrombocytopenia with the technology compared to chlorambucil (11% v 4%).

IRR's occurred in 69% of all patients who received the technology with grade 3 or greater IRR's occurring in 21% of recipients compared to 0% of chlorambucil monotherapy treated patients. Virtually all the IRR's occurred during the first course.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be

information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The comparator arms for the licensing study included chlorambucil monotherapy and chlorambucil/rituximab combination therapy and showed the latter was superior to chlorambucil monotherapy with regard to PFS (16.3 months versus 11.1 months). However, the technology was superior to both chlorambucil monotherapy and combined chlorambucil/rituximab combination therapy. The technology was superior to chlorambucil/rituximab combination therapy in regards of improved PFS, higher CR rates and MRD-negativity. However, the Hillmen study (JCO 2014) used the British dose of chlorambucil in combination with rituximab and showed a PFS of 23.5 months, which is not too different to the 26.7 months reported with this new technology in a similarly aged group of patients – median 70 compared to 73 years. This raises the question of the dose of chlorambucil used in the UK which is much higher than that used in European studies – See Knauf et al 2009 for comparisons. Whether the higher dose of chlorambucil used in the Hillmen study is a possible explanation for the good PFS seen in that study is purely conjecture. Hence claims that this new technology may not be superior to patients treated with the British dose of chlorambucil with or without rituximab is likewise unproven. In addition, there have been some concerns raised regarding the dose of the new technology compared to rituximab, with the new technology administering 3000mg of anti-CD 20 during the first month of therapy compared to 750 mg of rituximab in a patient with a surface area of $2m^2$. Again, what effect if any the higher dose of anti-CD20 had in the apparent superiority of this technology over chlorambucil/rituximab combination therapy is uncertain.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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As mentioned above this technology involves an infusion of a drug, which especially on first infusion, may lead to reactions and the first dose may need to be split over 2 days. Thus there are at least 8 infusions – possibly 9 if the first dose is split. Each infusion will take 4-8 hours and given that IRR's are not uncommon with the first dose, close monitoring of all patients will be required. In addition, all patients receiving this technology will require prophylactic therapy with steroids, anti-histamines and paracetamol. This will put an additional burden on Day Units and their staff, which may require additional resources. Training on how to prevent/manage IRR's would probably be sensible given their frequency.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not see any equality issues with regards to the implementation of this technology.