# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Idelalisib for previously treated chronic lymphocytic leukaemia

Thank you for agreeing to give us a statement on your 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 name:** Christopher Fegan

**Name of your organisation** School of Medicine, Cardiff University

**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?

CLL is currently treated to agreed national guidelines and locally agreed clinical care pathways. The national guidelines are based on an extensive literature of phase 3 collaborative trials and overwhelmingly – although not quite 100% - adhering to NICE recommendations from previous technology appraisals. The present therapies recommended for CLL are chemo- immunotherapy therapy (monotherapies chlorambucil and bendamustine and combination therapy notably fludarabine/cyclophosphamide/rituximab) but an alternative to the proposed technology would include bendamustine/rituximab combination therapy and ofatumumab monotherapy. An exception to this is CLL patients with 17p deletions/mutations where chemotherapy is ineffective and a combination of steroids/alemtuzumab is presently recommended from phase 2 data. However alemtuzumab has been withdrawn fro oncological use although one can still just about access it through a compassionate use programme.

At present CLL is incurable with the exception of a few patients who are fit enough and have a suitable donor for allogeneic stem cell transplantation. So typically a CLL patient will undergo up to 5 or more differing therapies from diagnosis to ultimate demise. One of the major benefits of this new technology is that it has a very favourable efficacy and safety profile even in patients who have received multiple courses of chemo-immunotherapy or who have co-morbidities.

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?

There are innumerable prognostic markers presently available for CLL. The most important is p53 deletion/mutation as this identifies a group with very poor survival (typically 8-18 months) to conventional therapies and it is widely agreed that this is the only routinely available prognostic marker which should influence upfront therapy.

As outlined above there are really 3 areas of unmet clinical need for consideration of use of this technology:

1) Patients with p53 deletion/mutation – conventional chemo-immunotherapy requires an intact p53 apoptotic pathway to kill CLL cells so CLL patients with these abnormalities. However this technology does not require an intact p53 apoptotic pathway and so is often effective in this patient group even when chemo-immunotherapy has failed.
2) Patients with multiple relapsed/refractory CLL. The incidence of p53 deletion/mutation rises from 5-10% in treatment naïve patients up to 40-50% in heavily pre-treated patients. So there is a reasonable number of patients

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with chemo-immunotherapy resistance who do not have a demonstrable p53 abnormality – clearly there are unknown mechanisms of drug resistance waiting to be discovered. However the data from this technology shows that patients with relapsed/refractory CLL may respond to this new technology.

3) Patients with co-morbidities/heavily pre-treated – CLL is a disease of the more mature in life who often have many other co-morbidities rendering standard recommended therapies unsuitable as they cannot be delivered safely eg renal impairment for FCR, post allogeneic stem cell transplantation. In addition multiple courses of differing chemo-immunotherapies often leads to long term toxicity eg marrow damage, infections – again rendering conventional therapeutic options unsuitable. Given the mode of action and safety profile of this technology the data indicates that many of this group of patients can safely receive and benefit from this technology.

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)?

The actual technology is an oral medication but initial use involves 6 months of rituximab so this will need to start in the secondary sector. However once the initial 6 month period of rituximab therapy has give, the patient could be seen in the primary sector with initial supervision from the secondary sector. This is a very simple technology requiring specialist overview but not operational delivery.

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?

The technology has been used in clinical trials in the UK, through the CDF in England and there is an Early Access Programme in Wales and Ireland so many clinicians are gaining experience in its use. Obviously the studies were the licensing studies but the CDF and EAP use is to my knowledge within the licensed indications.

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 Society of Haematology guidelines are widely used throughout the UK (and much wider within the world) as the template for CLL patient care. They are presently being revised in the light of this – and other - newly licensed technologies. I am on the CLL guidelines committee and this technology is expected be recommended in the revised version. It is expected to be included in the updated ESMO CLL guidelines.

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**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?

This new technology is a non immunotherapy/chemotherapy oral agent which improves outcomes in CLL patients when other therapeutic options have failed including allogeneic transplantation. It is less toxic and in very many instances easier to deliver than conventional therapeutic options. Also given its ability to be effective when other agents fail it may well act as either a bring to allogeneic transplantation – where the outcome is largely determined by the performance status of the patient entering transplant - but in some clinicians and patients mind may even be a substitute for allogeneic transplantation.

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 use of this agent should be restricted to its licensed indications. As a continuous therapy there is no data available at present saying it is a cure or that it can be safely stopped.

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?

The delivery of this technology is very straight forward by the standards of therapies presently administered in UK haematology departments on a daily basis and all units would be able to offer this. I think the trial was well conducted and has convincing data with regards to efficacy in terms of progression free survival and safety profile. The comparator arm was rituximab monotherapy which is not a standard treatment recommended in the UK- although it is in the US. However given the very heavily pre-treated group in this study the UK comparator arm would have been “no therapy” or “clinicians choice” as there is simply no available data or guideline guidance for this group of patients. For me the real impressive things was the effectiveness of the technology in p53 deleted/mutated patients and those refractory or multi – relapsed following chemo-immunotherapy. One of the most impressive factors which isn’t really identified within the study data is that the general rule of thumb for any CLL patient receiving chemo-immunotherapy is that the duration of response gets progressively shorter with each course of treatment. This is really unsurprising given that virtually all chemo-immunotherapy use the same p53 apoptotic pathway. However this new technology turns that very old dogma which

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applies to very many tumours on its head as it is capable of inducing responses far, far longer than that achieved in an individual patient from their previous therapies.

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?

The side effect profile is excellent. The only real one of concerns is colitis which occurs in a minority of patients but can lead to the need to stop therapy. It may be possible to re-introduce the technology once the colitis has settled albeit often commencing at a lower dose.

**Equality and Diversity**

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; No
- 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; No
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities: No

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

I don't think this is relevant to the present technology.

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**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.

I am unaware of any such data at present. There is a lot of anecdotal data being collected from individual clinician's experience of clinical trials which should in due course become available when trials are published.

**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)?

I think there will be minimal impact in terms of staff requirements etc to enable effective and safe delivery of this technology within the NHS.

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