Single Technology Appraisal (STA)

Idelalisib for previously treated chronic lymphocytic leukaemia [ID764]

Appraisal consultation document

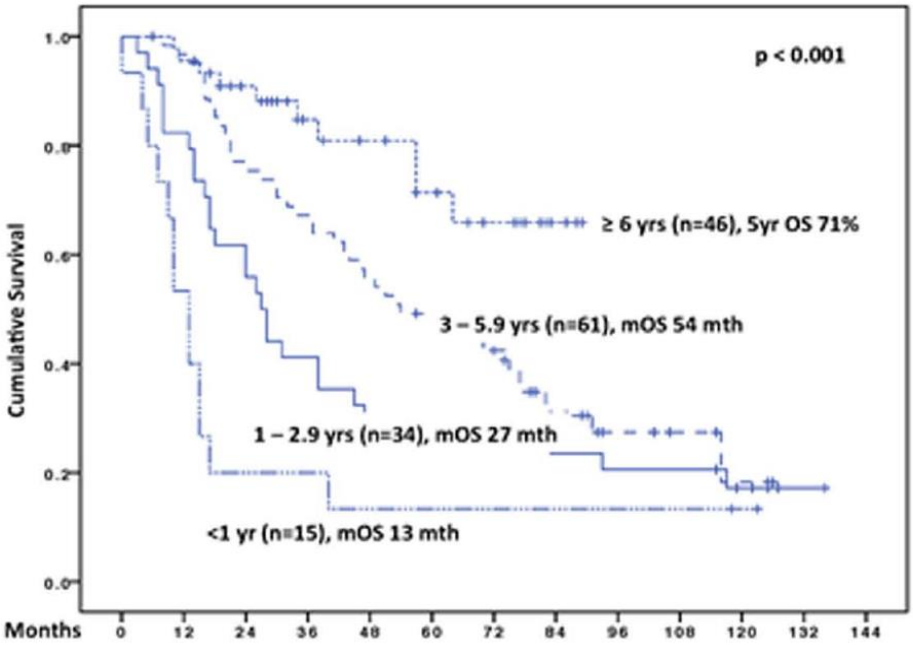
Christopher Fegan – Nominate Expert

Thank you for giving me the opportunity to comment on the NICE Appraisal document for Idelalisib for treating chronic lymphocytic leukaemia.

Overall I think the Appraisal Committee have to date discharged their duties with the utmost professionalism and honesty. However, I do have some concerns and as a result have a few comments/questions:

1) Page 3 1.1. It appears NICE plan to reject the use of idelalisib in patients with 17p deletions/mutations. The data for recommending the use of idelalisib in patients with 17p deletion/mutation was based on a relatively small number of patients. However, as the Appraisal Committee know idelalisib was very effective in this patient group and that there are no licensed NICE approved alternatives for this particular patient sub-group. Thus what would the Appraisal Committee recommend to clinicians when treating 17p deleted/mutated patients. Also in 1.2 (page 3) it appears the Appraisal Committee may recommend idelalisib to be used in refractory CLL patients. Firstly the reason why patients with 17p deletion/mutation do so poorly is exactly because they are refractory to standard chemo-immunotherapy. So assuming the Appraisal Committee do ultimately approve idelalisib for use in refractory CLL patients are they asking clinicians to use what we know will be ineffective chemo-immunotherapy until they fulfil the criteria to be classified as refractory (no response or relapse within 6 months of last therapy)? To me it seems unethical for clinicians to knowingly use ineffective therapy with a high chance of patient's side effects. Furthermore we know that the p53 deleted/mutated clone will grow when using ineffective treatment as the non p53 deleted/mutated clone will still be killed by the chemo-immunotherapy. So by denying the patient access to upfront idelalisib but then allowing it to be used once the patient is refractory is likely to lead to an overall worse outcome than if the patient had been allowed upfront idelalisib as the p53 deleted/mutated clone will have grown during the period of chemo-immunotherapy.

2) Page 3 1.1. It appears the Appraisal Committee plan to reject the use of idelalisib in patients with relapsed CLL. As the Appraisal Committee are aware the standard recommendation for patients who relapse from CLL is to potentially treat with the same agent/regimen if their response to their previous therapy lasted longer than 24 months. This is stated in the British Committee for Standards in Haematology (BCSH) Guidelines and is standard practice across the world and is based on several studies including that of Tam et al – November 2014. This study clearly shows that the effectiveness of retreating patients with fludarabine/cyclophosphamide/rituximab (FCR) who have previously received FCR is very much predicted by the duration of response to their first course of FCR. As can be seen from the survival curves there is only a limited time duration of survival in those whose first response duration following FCR lasted < 2 years. Also according to previous NICE appraisals a patient who previously received FCR should only receive FC at relapse as NICE has stated that rituximab should not be used at relapse in patients who have previously received rituximab – this would make survival even worse than that seen in the Tam paper. So given the evidence shown in the what would the Appraisal Committee be recommending a clinician should use in patients who received frontline FCR but who relapses within 2 years? Also this patient may have the opportunity of a potentially CLL curing/ life-saving allogeneic transplant – so denying the patient the opportunity to receive idelalisib is effectively condemning them to almost certain death when the patient would have had a very real chance of surviving with a reasonable quality of life.



Tam CS et al Blood, 2014 Nov 13;124(20):3059-64

3) Page 3 1.2. It appears that the Appraisal Committee is not minded to recommend idelalisib in patients with refractory CLL. I found this rather surprising as the data showing idelalisib is effective in refractory CLL patients is very good and again I'm really not sure what the Appraisal Committee would expect a clinician who is treating a patient who for example is refractory to FCR? There are no other licensed/NICE approved agents for this patient group. Is the Appraisal Committee saying that the clinician should use treatment which everyone knows will not be effective- is that ethical? Obviously the outcome for this patient will be to succumb to their CLL when idelalisib would have prolonged survival with a good quality of life in the overwhelming majority of patients. Also if the refractory CLL patient had a potentially CLL curing/ life-saving allogeneic transplant option is it really acceptable simply to allow these patients to succumb to their disease by denying this patient group access to idelalisib?

4) Page 11 3.2. The ERG noted that there was a high number of 17p deleted patients in the 116 study compared to what one would expect in "UK clinical practice". I questioned this comment at the Appraisal meeting as the 116 study included patients who had at least 1 prior therapy (3 on average) and had to have relapsed within 2 years of last therapy. Several studies have shown that in end stage CLL the often quoted figure is 40% of such patients will have p53 deletion/mutation. Also many of the patients in the 116 study were in fact UK patients. So how can the ERG say that the study was not representative of the UK patient population when it is this same UK population who took part in the 116 study?

5) Page 23 4.1. As outlined above the standard approach to refractory CLL patients is either supportive care, rituximab monotherapy or clinical trials of a novel new agent.
The text says "The clinical expert advised that re-treatment is offered to people for whom fludarabine-based regimen were suitable, and whose disease has not relapsed at least 6 months after, but within 24 months of treatment". I think the Advisory Committee have mis-understood what the experts were saying as this statement is only correct for patients who for whatever reason had not received a purine based regimen as upfront therapy but at relapse are deemed suitable for a purine based regimen- in reality this is very few patients. For patients whose disease relapses after 24 months one of the treatment options is to offer the same treatment again. However that is not the case for those patients who relapse within 6-24 months - as stated in the BCSH Guidelines – see Tam above. To those who had previously received FCR who by definition of the fact they were previously fit enough

to receive FCR other treatments will be attempted included clinical trials or off licensed drugs eg alemtuzumab, lenalidomide or ofatumumab with for those with a suitable donor these therapies acting as a bridge to allograft. For those patients who were not fit for upfront FCR or a similar bendamustine regimen then if they relapse between 6-24 months the treatment options are very limited. The only reason why for this patient group "the same treatment if offered" is simply the lack of any other licensed effective agent- they will not be eligible for the alemtuzumab compassionate use programme as they do not have 17p deletion/mutation and they will not be eligible for ofatumumab because they are not double refractory to fludarabine/alemtuzumab. The 116 study had a median population age of 71 so idelalisib will be of great value to this patient group and without doubt prolong life. Thus I would respectfully request the review their interpretation of section 4.1.

6) Pages 23/24 – 4.2. The Advisory Committee rightly refer to the BCSH guidelines which state refractory disease is defines as inadequate response or relapse within 6 months. This definition is really not of much clinical value for as stated above the same BCSH Guideline also say that patients who relapse within 24 months should not be offered the same therapy they have just received. So the term refractory is semi-meaningless in this context and there has been some discussion about whether refractoriness should be re-defined within the BCSH Guidelines as being relapse within 24 months. However, the term refractory and its definition as relapse within 6 months is still applied to national and international clinical trials and hence it was felt inappropriate to have a unique UK definition of refractoriness.
One other consideration is it will be easy to make a relapsed patient become eligible for idelalisib as a refractory patient simply by giving the patient a therapy which they – the clinician and patient - know will be ineffective. So if we take a patient who relapsed from say FCR between 6 and 24 months and give him chlorambucil monotherapy and one could be really cynical and give 2mg orally on alternate days – then clearly this will not do anything and the disease will progress. The clinician can now say the patient is refractory to chemotherapy and hence eligible for Idelalisib after 2 months of chlorambucil therapy! I understand this sort of practice is already taking place in England to access drugs – idelalisib and similar agents - from the CDF.

7) Page 30 4.13 and Page 36 4.23. I stated at the Advisory Committee meeting that overall 10-20% of all CLL patients are hypogammaglobulinaemic. However when considering heavily pre-treated patients – such as those in the 116 study - and those who had received prior rituximab the number of patients requiring IVIG would in my opinion be ~25%.

8) Page 33 4.17. I do find it surprising that given the lack of a licensed therapy for 17p deleted/mutated patients that the Advisory Committee have ruled out the use of idelalisib in this patient group. I appreciate that the 17p deleted/mutated subgroup may have been small but I would respectfully request that the Advisory Committee reconsider this as there will never be a phase 3 study to address this patient group which is a real area of unmet clinical need.

9) Page 34 4.20/4.21/4.23 I would take issue with the interpretation of the end of life criteria. As one can see from the Tam survival curve in patients who initially received FCR who then get retreated with FCR at relapse. Clearly for those who relapsed within 1 year and possibly 2 years of receiving their initial FCR the end of life criteria apply. I would therefore respectfully ask the Advisory Committee to re-consider its interpretation of the end of life criteria and access to idelalisib. To me the end of life criteria apply to many patients who relapse within 2 years of initially receiving FCR.

10) Page 37 As outlined above I would respectfully request/urge the Advisory Committee to reconsider its present recommendation in 17p deleted/mutated patients but also in relapsed patients who have received a purine based regimen as initial therapy such as FCR but who relapse within 24 months. Firstly there are really no suitable licensed alternative therapies and the end of life criteria should be applied.

11) Page 38 I welcome the acknowledgement for the Advisory Committee that more treatments are required for 17p deleted/mutated patients and hence would respectfully request they consider asking Gilead to provide more evidence for this patient group.

12) Page 38/39 I concur with the Advisory Committee that to split refractory from relapsed CLL patients but have concerns that it has cherry picked the definition of refractory from the BCSH

Guidelines which is really out of date and chosen to ignore the clinical evidence and other statement in the BCSH Guidelines which does not recommend re-treating patients with the same regimen who have relapsed within 24 months of initial therapy.

13) Page 41. The average age of diagnosis of CLL in the UK is 72 years. Clearly therefore the average age of first treatment in the UK must be higher than 72 years. I do not therefore concur with the Advisory Committee's view that the patient group in the 116 study is not representative of the UK CLL population and as stated above the UK provided many patient for this study. Likewise I disagree that the 42% p53 deleted/mutated patients is not typical of heavily pre-treated patients as the figure widely quoted is 40% of "end stage" patients and I'm sorry to say that without the likes of idelalisib these patients can be classified as "end stage".

14) Page 47 Please refer to my comments above re-relapsed patients and the applicability of the small population end of life criteria.

Christopher Fegan 1/7/15