Cambridge

11th July 2015

Dear NICE appraisal committee,

Re: **GID-TAG488 Idelalisib in combination with rituximab for relapsed / refractory CLL**

I am writing in my capacity as a [redacted], [redacted] and [redacted]. My conflicts and the conflicts of the CLL Forum are listed at the end of this letter.

With the licensing of ibrutinib and idelalisib / rituximab for relapsed / refractory CLL, the whole treatment landscape for this disease has changed. It is actually difficult to discuss one of these new medications in isolation from the other, but I have read the proposed decision by NICE to reject idelalisib / rituximab for relapsed / refractory CLL with some significant concerns. I also have concerns with regards to first line management of patients with 17p deletion / TP53 mutation (broadly grouped as TP53 disrupted. My concerns are broadly:

1. There appears to be a misunderstanding as to how relapsed / refractory CLL can be managed in a frail, multiply-treated patient cohort.
2. There appears to be a sense that while refractory patients (i.e. relapsed within 6 months of most recent chemotherapy) might benefit from idelalisib / rituximab, patients with relapse beyond 6 months will not derive benefit compared with alternative treatment options. I cannot accept this assumption based on the available data.
3. First line treatment of TP53 disrupted CLL

<u>The management of multiply relapsed frail patients</u>

This patient cohort is very challenging to treat. The patients in the idelalisib 116 trial were elderly (median age 71), multiply treated (median 3 prior lines of therapy), poor performance status, poor marrow function and genetically resistant to chemotherapy (over 40% had TP53 disruption). Prior to the presentation of the idelalisib 116 trial (the main evidence for TAG488) and the ibrutinib Resonate trial, there were no randomised trials in CLL beyond first relapse. Although inclusion criteria were different between the 116 and Resonate trials, they both recruited heavily pre-treated patients who were relapsed and refractory (i.e. progressed within 6 months) with little in the way of standard chemotherapy options available. With both trials, the novel therapy has proven vastly superior in terms of progression free and overall survival.

It appears that a key aspect of the difficulty NICE have with approving the use of idela / rituximab is deciding whether rituximab monotherapy, in the phase 3 Gilead 116 trial, was an appropriate control arm for both relapsed *and* refractory patients. I accept that rituximab monotherapy has little use in UK CLL practice, but I would argue that prior to access to ibrutinib or idelalisib, standard management of 4th line CLL in frail patients was palliative care. The GID-TAG488 document discusses a number of apparent alternative therapies for relapsed CLL that were proposed by the NICE scoping meeting, such as FCR / Bendamustine-R / Chlorambucil-R / high dose steroid-R. However, I would argue strongly that none of these treatment options have either an evidence base, or would be appropriate for this group of frail, heavily pre-treated patients. A single phase 3 randomised trial

with FCR as second line therapy for very lightly pre-treated patients has been published, but otherwise, all other trials in relapsed CLL with the drug combinations discussed were small phase 2 very heterogeneous, poor quality trials. All alternative therapies (with the exception of ibrutinib) lack any randomised quality trial data applicable to the type of patient studied in the Gilead 116 idelalisib trial. If idelalisib and / or ibrutinib are not available to UK CLL patients there will simply be no alternative treatment except palliation, for this type of patient.

Possible differential benefit for 'refractory' patients compared with 'relapsed' patients

The 116 trial included both refractory and relapsed patients, and the data from the trial were clear. Use of idelalisib provided a marked progression free survival and indeed a true overall survival compared with the control arm. So despite the provision for cross-over to get the active drug rather than placebo if patients progressed, there was still excess mortality in patients who were not randomised to idelalisib at the start of the trial. I am unable to see how NICE can separate the refractory patients (i.e. progression within 6 months of last therapy) from the relapsed patients in their analysis based on the data from this trial. It is clear that 'delayed' start of idelalisib in the trial (i.e. in patients randomised to placebo rather than idelalisib) had a direct impact on overall survival. If NICE approve idelalisib for refractory patients but not relapsed patients there is a very good chance this will re-create the early excess mortality seen in the trial, by denying relapsed patients early treatment with idelalisib. This will be even more striking for the TP53 disrupted patients who will have a very high chance of early death if denied either ibrutinib or idelalisib at relapse. Inevitably, a restriction of idelalisib to 'refractory' patients will push clinicians to give 2 cycles of ineffective therapy to patients who progress beyond 6 months to then make them eligible for idelalisib as 'refractory' patients. For some patients this will simply not work and early death will be the result. I am sure NICE would agree that this would not represent best practice.

First Line treatment of TP53 disrupted CLL

This group of patients represents around 5-8% of all first line patients who need therapy for active CLL. We know from multiple trials that these patients have poor response rates, early relapse and higher early mortality when treated with chemotherapy compared with non-TP53 disrupted patients. With the removal of the license for alemtuzumab, the only licensed drugs to treat first line CLL with TP53 disruption are ibrutinib or idelalisib / rituximab. Although there is no prospective randomised data in first line for these drugs with these particularly poor-risk patients, the data from the relapsed trials and the small non-randomised datasets from the first line trials were so striking that this indication was approved by the EMEA. It is simply not ethical to run a trial of 'novel agent' vs chemotherapy in the first line setting for TP53 disrupted patients and these trials will not be done. It is imperative these drugs are approved for use in first line, or again clinicians will inevitably have to give 2 cycles of ineffective therapy to patients just to move them rapidly to appropriate therapy when they are resistant to treatment. Again, this is simply 'bad medicine' and goes completely against the ethos of personalised medicine with precision-targeted therapies.

Conclusions

It is essential that UK CLL patients have access to novel CLL therapies at the time of relapse of their CLL **in line with the inclusion criteria for the respective clinic trials,** or as first line therapy if they are TP53 disrupted. Access to ibrutinib and idelalisib through clinical trials and the Cancer Drugs Fund has resulted in a complete shift in how relapsed CLL can be managed. The routine clinical experience with these drugs continues to increase rapidly across the UK. On a personal level, I now have over 30 patients on 'novel therapies' in my CLL clinic and I have many examples of patients who without doubt would have died by now without these drugs, but are instead enjoying an excellent quality of life taking daily tablet medication, and for the most part, staying out of hospital. I appreciate that this will represent a significant new cost pressure for the NHS, but managing CLL without access to these novel drugs will create huge difficulties for our patients and will undoubtedly lead to higher mortality rates for UK CLL patients.

[redacted]

[redacted], UK CLL Forum

Conflicts

Personal: [redacted] five companies with licensed drugs for CLL (Gilead / Roche / Janssen / Napp / GSK).

UK CLL Forum: The majority of the Forum income is sponsorship from the pharmaceutical industry (please see the website www.CLLForum.org for details).