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Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
c/o Lori Farrar and NICE docs

9 July 2015

Dear Mr Boysen

Re: Idelalisib for previously treated chronic lymphocytic leukaemia [ID764] – Appraisal Consultation Document (ACD)

I write on behalf of the NCRI/RCP/ACP with regard to the above ACD consultation. We are grateful for the opportunity to comment and would like to make the following joint response.

We note the Committee's decision not to recommend idelalisib + rituximab in:

- untreated CLL with 17p- in first line
- relapsed CLL

Our experts have major concerns regarding some of the interpretations made by the Committee and would ask that the decision is reconsidered for the following reasons:

- confusion in the definition of refractory and most importantly of relapsed patients categories.
- CLL with 17p- identifies ~ 5-10% of all CLLs prior to first treatment. Frequency makes this category of patients rare and difficult to investigate in large clinical trials - while they are an unmet clinical need.
- there are ethical issues in not supporting novel strategies that are likely to be effective. Relying on evidences from clinical trials that are unlikely to be produced in the near future is not in the best interests of patients.

There are other ethical issues related to the costs which our experts believe could be greatly reduced. Specifically:

Page 23 section 4.1
The clinical experts have not advised that FCR is re-offered. Instead, they outlined that in the current setting FCR has been an effective solution for FIT patients in the pre-BCR-inhibitors era (MD Anderson data) and can be re-considered as per current NICE guidelines. Clearly new solutions are requested because PFS will become shorter after first line with the same treatment. New treatment solutions are therefore necessary in this type of patients.

Page 23 section 4.1
The Committee have confused the distinction of relapsed and refractory patients. According to the IWCLL criteria refractory patients relapse within 6 months. However, the BSH guidelines recommend that patients who have relapsed within 24 months from first treatment should be considered high-risk and recommended

not treating with the same option but treating 'ideally' within clinical trials. This guideline was written when data on BCR-associated inhibitors were not available (2012).

Page 26 section 4.6
The Committee reasons against the lack of comparative evidence in study 101-08. To our knowledge, randomised trials in 17p- CLL have not taken place either nationally or internationally. Furthermore, our experts do not expect a trial for such a rare but unmet clinical need in this cohort in the near future.

Page 36 section 4.24
It is true that data from only 9 patients with CLL 17p- treated with idelalisib front-line is currently available from the literature (Hillmen). The limited number is not dissimilar from that of other trials or clinical studies presented over the years on this rare but aggressive form of CLL. However, even in this limited number idelalisib appears highly effective for a population of patients who:

i) are very likely to be refractory to conventional (immuno)chemotherapy and
ii) will very likely acquire complex genetic lesions.

The occurrence of a complex caryotype will make the patients even more likely to be refractory to old and novel genetic strategies in second or subsequent lines (Jain P, Blood. 2015 Mar 26;125(13):2062-7). This biological observation provides scientific evidence for the use of drugs alternative to chemotherapy in first line. Idelalisib is one of these alternative drugs. Also, CLL with 17p- is a clinically unmet need and does require a strategy. Idelalisib plus rituximab is an effective strategy.

In conclusion, we believe that the ACD includes serious misinterpretations with relation to:

- Clinical demand
- Rarity of disease subset
- Definition of relapsed patients

We would further highlight that in front line CLL there is a trial of 64 patients treated with idelalusib plus rituximab which shows excellent results. These include nine 17p deleted patients with the same outcome as those without 17p del. This indicates that these patients should be treated with idelalisib + rituximab in front line as their outcome is better than those treated in relapse - this is always the case with CLL. The current ACD means that clinicians have to give patients with 17p del - an ineffective, expensive and toxic therapy - before moving to an effective therapy.

We would also stress that there is a significant overall survival benefit for idelalisib + rituximab in refractory CLL. The current ACD denies refractory patients this life prolonging therapy.

Yours sincerely