The Appraisal Committee Decision is not to recommend that Idelalisib+Rituximab in:

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

However, this clinical expert has some major concerns on some of their own interpretations and would like the Committee to reconsider their decision based on the following:

- there is 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 is an ethical problem on where NICE is not supporting novel strategies that are likely to be effective and wants to rely on evidences from clinical trials that will be unlikely produced in any near future. This specific clinical expert stated that the claims raised by patients' representatives had to be listened.

However, this clinical expert realises that there are other ethical issues related to the costs of this compounds that should be massively reduced.

Specifically:

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The clinical experts have NOT advised that FCR is re-offered, I have said 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 demanded in this type of patients.

Page 23 section 4.1

The committee are confusing the distinction of relapsed and refractory patients. According to the IWCLL criteria REFRACTRY 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).

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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 requires a strategy. Idelalisib plus rituximab is obviously an effective strategy.

Page 26 section 4.6

The committee argues against the lack of comparative evidence in study 101-08. To my knowledge, there have not ever been randomised trials nationally or internationally in 17p- CLL. How could we ever expect such a trial for a rare but unmet clinical need for this cohort in the near future?