Sent: 06 November 2006 13:12
To: Christopher Feinmann

Subject: response, fludarabine.

Importance: High

Reply to the Recommendation of NICE on Fludarabine STA.

I believe that your recommendation that Fludarabine should not be recommended for first line treatment of CLL (chronic Lymphocytic leukaemia) is in error.

I further believe that your contention that 'no recommendations can be made in respect to fludarabine plus cycloposphamide' combination is also in error.

My reasoning is, briefly, as follows:

The contention of NICE is that overall the data used to generate the study is incomplete. In the sense that the drug manufacturer has seen fit to delete some data I concur that this is, at best, unfortunate.

On a broader scale, it is inevitable that directly comparing studies will be problematic since population selection and dosages of the drugs will necessarily vary. Additionally, NICE contends with justification that the CLL 4 study is 'not complete'.

Treatment studies with drugs for CLL are essentially carried out with (thankfully) small populations since numbers of CLL patients are, compared to the general population, rare. Fewer are chemotherapy naive patients, as the disease has a long development time. Hence, whatever the theoretical end point of the study, given a disease with a 'mean' survival time of (opinions vary) 16 years, it is not feasible to 'complete' the study and the UK should take advantage of new developments.

These disease features should not be used to deny the use of fludarabine in first line cll treatment when the empirical data strongly suggests a hugely more effective result than chlorambucil, especially in combination with cycloposphamide.

The combination of fludarabine with cycloposphamide has advantages over fludarabine alone. Prof. Hamblin said words to the effect that, cycloposphamide, as an immunosuppressant, appeared to give a protective effect from AIHA instigated by fludarabine treatment in some patients.

The addition of cycloposphamide to fludarabine treatment adds pence to the total, and benefits to those patients that have to undergo treatment. I suggest that it is ethical of the manufacturer to assume/request licensing in this case.

NICE states that re-treatment rates and cost of treating patients who have suffered adverse effects from fludarabine have not been calculated correctly, or not included.

The physicians treating the patients must consider that the possible effects of treatment are still, on balance, in the patients' favour or they would not treat. There are also costs to be assumed if patients are not treated at all; hospitalisation for varying lengths of time is feasible in all cases.

The clinical experts have stated that effectively triage will take place to select patients who would benefit from fludarabine monotherapy or in combination. To some extent the costs of re treatment or treatment for adverse effects cannot be calculated.

I would add here that the contention of the clinical experts that all cll patients should be tested for the relevant markers has justification, since they directly affect the most effective type of treatment in some patients

NICE contends that progression free survival does not equate with overall survival. I cannot argue that this is untrue; however, I contend that barring evidence to the contrary, that 'progression free survival' equates with overall survival is a very reasonable assumption. Humans are long lived, and there is no comparable animal model. The disease has long progression. I submit that waiting for more data could be construed as prevaricating.

To conclude, I believe that NICE has sufficient evidence to approve fludarabine, and fludarabine in combination with cycloposphamide, as a front line treatment for CLL where the physician believes that it is appropriate.