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1 May 2013

Dear [redacted]

Re: Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkins lymphoma [ID414] – Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 28,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to respond jointly to NICE oncological Technology Appraisals. We are grateful for the opportunity to review the above ACD and would like to make the following comments.

The Appraisal Committee's decision not to recommend pixantrone within its marketing authorisation will be a disappointment both for clinicians and for those many patients who do not respond well to, or relapse, following two lines of standard aggressive lymphoma treatment. Depending on age and fitness these patients are actively palliated with single agent or combination chemotherapy for which there is no evidence base. Few patients can access or are eligible for clinical trials and most at this stage of their disease are discharged back from cancer centres or by preference are managed locally in a District General Hospital. Although in the technology under review, the prospective randomised study is small and underpowered for PFS and OS, it provides a platform on which to rationalise care and to combine and develop new agents in this area of urgent unmet clinical need.

The reported CR rate in DLBCL rituximab failures (30%) are among the best reported in Phase 1 and 2 trials to date. The closest competitor, lenalidomide has a response rate of 19.2% and a CRR of 11.2% in the DLBCL population (Wiernik et al. JCO 2008; 26:1-6). Clinically it is important that patients who responded to the drug did so after 2 cycles so patients are not exposed to ineffective therapy both from a toxicity and cost-efficacy viewpoint. This does not seem to have been factored into the modelling but should be considered due the impact on costs.

Our experts believe that the committees decision to restrict the analysis to "the sub group with aggressive B-cell lymphoma confirmed by central independent review " does not bear rigorous analysis. Certainly considering only the HITT population very much reduces the power of an already small trial. Such trials will always be difficult to conduct due to the small population at risk, the rapidity of disease progression and that given the palliative nature of care patients wish to be treated closer to home.

To better reflect UK clinical practice, we would vigorously recommend restricting the assessment to third- and fourth-line treatment and exclude treatment at fifth and subsequent lines from the sub-group for decision-making. As reflected in the Pix301 trial these patients do not achieve meaningful responses. In addition, this would be in keeping with the marketing authorisation which excludes treatment at fifth-line. The cost efficacy of the model might be greatly improved if these additional lines were not included.

Furthermore, as regards histology, the HITT population was a retrospectively defined subset of the ITT population. The 74% - 77% consensus is consistent with the high end reported in the scientific literature (Matasar et al. Ann Oncol 2012; 23:159-166). The complete complement of diagnostic slides may not be provided for a central retrospective review. For example, 18 of the 32 patients for which consensus of aggressive histology could not be reached had no or insufficient material available for review in the study. To say these were indolent and that HITT was the appropriate population for decision-making is not scientifically supported as the HITT results were consistent with the ITT results below;

	HITT B-Cell 3rd 4th line (n=39/39)	**ITT B-cell 3rd 4th line (N=50/49)**
CR/CRu	23% v 5%	28% v 4%
ORR	43% v 13%	48% v 12 %
PFS	5.7m v 2.8m	5.8m v 2.8m
OS	11.9 v 7.0 (+4.9m)	13.9 v 7.8 (+6.1m)

This data instead substantiates that the missing patients from the HITT population are behaving as the histologically confirmed aggressive NHL patients and so should not be excluded from the analyses, further reducing the power of the study.

Prior Rituximab use also shows the same directional magnitude of benefit in the ITT as the HITT population so to restrict decision making to the rituximab only pretreated histologically confirmed group may be misleading, as shown in the following data set;

	HITT B-Cell 3rd 4th line + Rituximab (n=20/18)	**ITT B-Cell 3rd 4th line + Rituximab(n=25/25)**
CR/CRu	30% v 5.6%	24% v 4%
ORR	45% v 11%	44% v 12%
PFS	5.4m v 2.8m	4.3m v 2.8m
OS	7.5m v 5.4 (+2.1m)	10.2 v 6.1 (+4.1m)

We believe that the data demonstrates a similar benefit in the ITT population as the HITT population in patients previously exposed to rituximab, inferring concordance of histology again, justifying analysis of the larger ITT population.

It is difficult to conclude that 'the range of comparators may well not be representative of current clinical practice in England and Wales', given that there is no evidence base for standard of care. Choice of agent, now as in 2004, is based on the personal experience of the physician, patient choice and access to novel agents. The lack of evidence is reflected is the change in frequency with which some of the comparators available within the trial (eg gemcitabine, rituximab, etoposide, orally bioavailable platinum) are being used today and that any novel agent that can be accessed is being given to these patients. No individual cytotoxic agent has shown superiority over another, so in our view, the only important difference in practice is that in 2013 all patients will have received prior rituximab.

Clearly, it is important to complete the current prospective trial to confirm benefit for Pixantrone in patients previously treated with rituximab as soon as possible. The relevance of the trial to current UK clinical practice is reflected in the NCRN adoption of the study. However, for those patients ineligible for or unable to access the trial, we urge the manufacturer and NICE to revise their current decision such that the only licensed treatment currently available for this difficult to treat and badly served patient population are able to gain access to an evidence based and active drug.

Yours sincerely

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