Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Member UK Vasculitis RDG
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I believe that the delay in NICE recommendation for patients with contraindication to cyclophosphamide therapy (such as women with child-bearing age) may lead to some patients being denied this appropriate treatment. Such denial may carry with it increased risk from later (although short-term) development of disease acceleration which can carry major morbidity,even mortality. I do not include those patients with life-threatening disease at the time of treatment initiation, who should be treated with cyclophosphamide unless the contra-indication is of risk of major organ damage. AS co-author of the BSR 2013 Guidelines (submitted for publication to Rheumatology MSS No RHE- 13- 096(lead author [redacted])I can inform the Committee that it is stated "Recommendation Rituximab is as effective as CYC for remission induction of previously untreated patients (1b/A) and may be preferable, when CYC avoidance is desirable (infertility, infection) (1b/B). Final consensus 100%."
Section 4 (Consideration of the evidence)	many if not most expert centres continue maintenance therapy for longer than 2 years,A) to allow steroid reduction and withdrawal and B) because late relapse is not uncommon. I have grave concerns about the conclusion "Based on ...clinical specialists ..., the Committee concluded that maintenance treatments such as azathioprine would not be routinely given in UK clinical practice after induction of remission with rituximab". Current UK practice is dependent on local funding and Dr preference: many centres continue rituximab as maintenance treatment. it is acknowledged that following rituximab therapy relapse is likely if there is no maintenance treatment. The BSR Guidelines 2013 as submitted for publication state: "Once remission has been achieved with induction therapy, long term maintenance treatment is required";it is added that after induction treatment with rituximab "There is no clear consensus regarding the timing or dose of RTX retreatment, but there are four possible options: 1. Wait for clinical relapse and retreat 2. Fixed interval retreatment 3 Switch to alternative maintenance therapy 4. Biomarker relapse (ANCA) and retreatment. This is key to the NICE decision
Section 7 (Related NICE guidance)	I propose a review date of October 2014 if the recommendation 1.1 is not modified to recommend RTX use in specific settings. Witholding recommendation for RTX Rx for those such as women of childbearing age would be unfortunate and would carry risk as many such women refuse cyclophosphamide Rx. If NICE were to not recommend RTX Rx in this sort of

	setting,delay to reappraisal would lead to a prolonged period of such women or other patients with cyclophosphamide contra-indications being exposed to this risk with many Drs following NICE guidance rather than the BSR Guidelines which will appear soon,likely in e-form in 2013.
Date	8/12/2013 4:53:00 PM

Name	[redacted]
Role	NHS Professional
Other role	Co-author of report by Latimer et al
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I disagree with the main conclusion, but would make a case for limited use of RTX for patients in whom cyclophosphamide therapy would normally be recommended for efficacy, but where potential or actual toxicity would prevent its use, either for treatment of newly presenting disease or relapsing disease. Â A follow up study of RAVE patients has just been published (Specks et al NEJM 2013 369:417-427) giving 18 month follow up data. Â It showed superiority of a single course of rituximab compared to conventional cyclophosphamide followed by azathioprine, at 12 months, but not at 18 months, in relapsing patients Â Nevertheless there was no inferiority of RTX vs conventional therapy for all patients. In practice, we do not use induction therapy in isolation. Â Usual practice is to commence maintenance therapyafter induction therapy. Â Most centres in the UK would use RTX followed buy maintenance azathioprine, rather than no therapy. Â The evidence base for this type of regimen has not yet been available, but there is a new study, (RITAZAREM) which will compare the effect of maintenance RTX vs maintenance standard of care, in patients who have had induction therapy with either RTX or cyclo
Section 2 (The technology)	No comments
Section 3 (The manufacturer's submission)	I agree that the manufacturer's assumptions about how cyclophosphamide is used vary from practice in the UK, where there is much greater use of high dose pulse IV therapy. Hoowever, rituximab remains an important, effective option, out of the relatively limited therapeutic choices available, to treat these patients with.
Section 4 (Consideration of the evidence)	I strongly disagree with the suggestion that it's unlikely that maintenance treatment would be given after induction with RTX. Â Azathioprine is typically given as maintenance when RTX course are completed. Â For persistent relapses there may be a case for maintenance RTX, but in most cases this is not the case. Â In addition, other maintenance drugs such as methotrexate, mycophenolate mofetil and leflunomide may be used would be given as maintenance after induction. In ANCA vasculitis we have a clear evidence base for immunosuppression; we can measure clinical response, and

	deterioration and adjust therapy accordingly. Â Rituximab has an important, measureable role (amongst other agents) in the induction of remission in some patients with ANCA vasculitis.
Section 5 (Implementation)	No comment
Section 6 (Proposed recommendations for further research)	No comment
Section 7 (Related NICE guidance)	We urge urgent review of this decision now.
Section 8 (Proposed date of review of guidance)	No comment
Date	8/12/2013 12:28:00 PM

Name	[redacted]
Role	NHS Professional
Location	England
Conflict	no
Notes	I am a Consultant Nephrologist with a subspecialty interest, and research interest in ANCA vascultis. I contribute to a multi-specialty clinic for patients with refractory or multi-organ ANCA-vasculitis. I am preparing to recruit patients to the forthcoming RITAZEREM study on the treatement of relapsing ANCA-vasculitis with Rituximab, as well as to the UKVAS registry. However I will receive no personal payment in relation to either.
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	The ERG appear to conclude that IV Cyclophosphamide (CYC) is clearly preferable to oral. Relapse rates are higher with IV (Harper et al Ann Rheum Dis 2012:71:955?960). Where silent, but profound, relapse is possible (recurrent renal disease) this shouldn?t be underplayed. Despite higher doses, oral CYC, is thus justifiable with implications for the comparative risk/benefit and cost/ benefit of RTX. Regarding long term safety of RTX. Please see Jones et al Arthritis & Rheumatism 2009; 60:7, pp 2156?2168, and van Vollenhoven et al, Ann Rheum Dis 2012. Long term data is also published from lymphoma studies comparing Rituximab+CHOP (chemo) to CHOP (chemo) alone. The ERG also express doubt about expected responses to retreatment with Rituximab. Please see Jones et al Jones et al Arthritis & Rheumatism 2009; 60:7, pp 2156?2168, Â Smith et al (Arthritis Rheum. 2012 Nov;64(11):3760-9. doi: 10.1002/art.34583.) which are reassuring. We have a number of patients, with previous life threatening disease, who are kept well by repeat Rituximab dosing. Cambridge, Birmingham and other places do too. Â Further case series are not being published as this is not in dispute nor ?newsworthy? now.
Date	7/31/2013 5:00:00 PM