Rituximab in combination with corticosteroids for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis: ERG comments on manufacturer's updated analyses

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Date completed 21st August 2013

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/37/01.

Declared competing interests of the authors

NL undertook one day of consultancy for Pfizer in 2012, providing advice on the analysis of an unrelated drug in an unrelated disease area. Pfizer manufacture cyclophosphamide and methotrexate (both of which are available on a non-proprietary basis).

Acknowledgements

The authors wish to thank Dr Mike Venning and Professor Raashid Luqmani for providing expert clinical advice that has contributed to this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Latimer N. Rituximab in combination with corticosteroids for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis: ERG comments on manufacturer's updated analyses. School of Health and Related Research (ScHARR), The University of Sheffield, 2013.

Contributions of authors

NL critically appraised the manufacturer's updated analyses, scrutinised the manufacturer's model, wrote the model description, conducted the additional ERG analyses and wrote the report. PT reviewed the manufacturer's updated analyses and contributed to the writing of the report.

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List of abbreviations

AAV	ANCA-Associated Vasculitis
ACD	Appraisal Consultation Document
AEs	Adverse Events
ANCAs	Anti-neutrophil Cytoplasmic Antibodies
AUC	Area Under the Curve
BSA	Body Surface Area
BSC	Best Supportive Care
BSR	British Society for Rheumatology
BVAS	Birmingham Vasculitis Activity Score
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener's Granulomatosis
CEAC	Cost Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CYC	Cyclophosphamide
DVT	Deep Vein Thrombosis
ERG	Evidence Review Group
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study Group
EQ-5D	EuroQol-5D
GC	Glucocorticoids
GPA	Granulomatosis with Polyangiitis
HRQoL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
IV	Intravenous
LFT	Liver Function Test
MMF	Mycophenolate Mofetil
MPA	Microscopic Polyangiitis
MR	Manufacturer's response
MS	Manufacturer's submission
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
PD	Prednisone / Prednisolone
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RTX	Rituximab
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio
UK	United Kingdom
VDI	Vasculitis Damage Index
WG	Wegener's Granulomatosis

1. SUMMARY

1.1 Structure of this report

In this report we review and comment upon the manufacturer's response to the National Institute for Health and Care Excellence (NICE) appraisal consultation document (ACD) on rituximab for anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis. First the new evidence submitted by the manufacturer is summarised, and then this is critiqued. We then present results of updated analyses which correct errors found in the manufacturer's newly submitted economic model. Finally we summarise the cost effectiveness evidence.

1.2 Summary of the manufacturer's updated analyses

The ERG accepts that the manufacturer has made several useful amendments to their economic model. However errors found in the amended model mean that it is not useful to interpret the manufacturer's updated results. The costs associated with the "uncontrolled disease" health state have been incorrectly calculated and are over-estimated, the costs of comparator drugs (mycophenolate mofetil (MMF) and methotrexate (MTX)) are incorrect, and the model coding for the sensitivity analysis on rituximab (RTX) retreatment is incorrect. The "uncontrolled disease" health state costs have a substantial impact on the lifetime costs accrued in the model and the manufacturer's error in calculating this cost biases the ICER in favour of RTX – in the base case analysis the manufacturer's ICER is approximately £3,000 too low because of this error. The errors in the drug costs have a smaller impact, but the coding errors have a very large impact on the sensitivity analysis ICERs – particularly for the scenario that assumes no RTX retreatment (this ICER is approximately doubled in the manufacturer's analysis). The ERG has rectified the manufacturer's errors and run probabilistic sensitivity analysis (PSA) in order to provide estimates of cost-effectiveness which better reflect the requests of the Appraisal Committee. The ERG acknowledges the new clinical data submitted by the manufacturer, but believes that questions around the most appropriate treatment sequences remain.

1.3 Summary of the ERG's critique of the manufacturer's updated analyses

The ERG estimates that the incremental cost effectiveness ratio (ICER) associated with RTX treatment is approximately **£20,879 per QALY gained** in the cyclophosphamide (CYC) eligible patient population, given the treatment sequences defined by the manufacturer, except the ERG assumes that only patients who initially respond to RTX would receive a second course. In the CYC-ineligible patient population the ERG estimates that the ICER associated with RTX treatment is approximately **£60,569 per QALY gained**, given the treatment sequences defined by the manufacturer (except the ERG assumes that only patients who initially respond to RTX would receive a second course). The ERG remains unconvinced of the validity of these estimates, given the remaining uncertainty surrounding possible treatment sequences – particularly because it appears likely that RTX maintenance therapy may be given in reality. Such usage of RTX is off-license and

has not been considered in any analyses submitted by the manufacturer, but reflects current practice (at least to some extent) in the United Kingdom (UK).

The ERG notes that adding the cost of azathioprine (AZA) maintenance therapy to the RTX arm of the economic model has a relatively minor impact upon the ICER, and evidence is generally supportive of assuming similar relapse rates for CYC (followed by AZA) and RTX even if AZA maintenance is not given in the RTX group. Hence, although clinically important, this issue is relatively less important for the economic evaluation. Assumptions around RTX retreatment are more important, although in the CYC-eligible subgroup base case, assuming no retreatment has a minor impact upon the ICER because quality adjusted life year (QALY) losses are offset by cost savings. However, the ERG notes that the assumed effectiveness of RTX retreatment is based upon very low patient numbers.

The ERG believes that the CYC-ineligible analysis presented in the manufacturer's ACD response represents an inadequate attempt at estimating the cost-effectiveness of RTX in this subgroup.

2. MANUFACTURER'S UPDATED ANALYSES

2.1 Description of the manufacturer's updated analyses

2.1.1 Revised model assumptions

The manufacturer states that they have incorporated all the changes suggested by the ERG that were specified in Section 3.42 of the ACD report.[1;2] These included:

- Using costs for prednisolone instead of prednisone in line with UK clinical practice
- Cost changes for CYC, trimethoprim and blood tests
- Utility value for pneumonia
- Relapse rate numbers at risk
- Cost parameter distributions
- Standardised mortality rate distributions
- Outpatient appointment distributions
- Mortality risk for patients aged over 91 years in the uncontrolled disease health state.

In addition, the manufacturer states that they have incorporated other changes proposed by the ERG that were specified in Section 3.4.3 of the ACD report.[1;2] These included:

- Increasing the assumed body surface area (BSA) and mean weight to 1.90m^2 and 78.89kg respectively, based upon a cohort of 30 vasculitis patients treated at the Manchester Royal Infirmary
- Including costs associated with drug wastage
- Increasing the utility value in the "uncontrolled disease" health state from 0.67 to 0.71.
- Including the cost of administering methylprednisolone
- Updating X-ray and CT scan costs using national cost sources, and assuming that 80% of scans received would be X-rays, with 20% being CT scans.
- Assuming that only severe flares would lead to renewed induction treatment, and assuming the same relapse rate for patients in the RTX group and patients in the CYC group.

The manufacturer noted that two assumptions proposed by the ERG were not endorsed by the Appraisal Committee and therefore were not included in the revised version of the economic model. These were:[1]

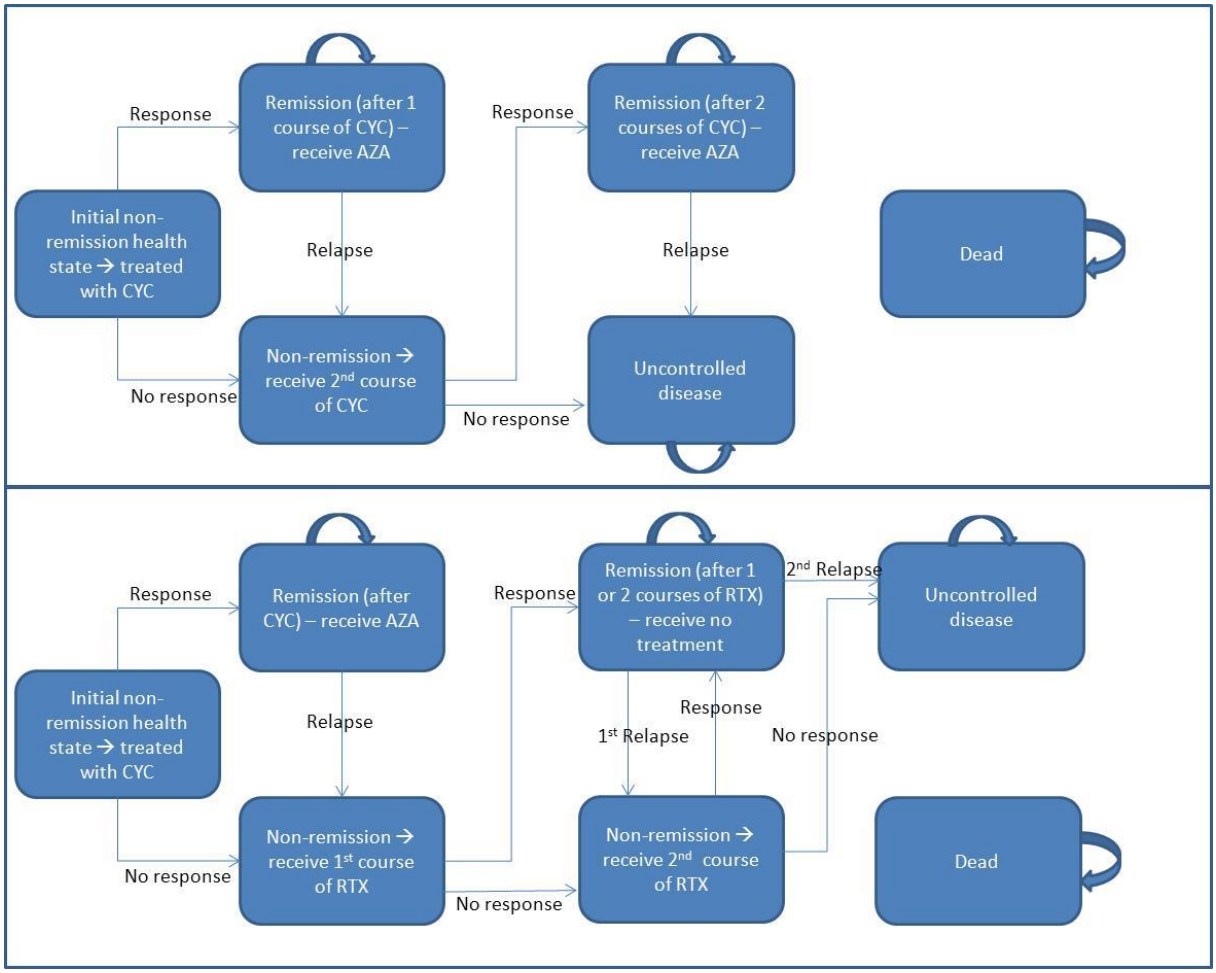
- The use of azathioprine (AZA) as maintenance therapy following RTX. The manufacturer states that such therapy is not supported by clinical evidence and is not part of current UK clinical practice. They note that recently published long-term evidence from the RAVE trial

demonstrates a similar relapse rate in RTX and CYC groups, despite patients in the RTX group receiving no maintenance therapy.[3]

- Frequency of outpatient visits in the uncontrolled disease state. The manufacturer assumes that 4 outpatient attendances would occur each 6 months for the duration of time spent in the uncontrolled disease health state. In the ERG's previous additional analysis of the manufacturer's model, it was assumed that 3 outpatient attendances would occur each 6 months in this health state.

In addition to the amendments to the model that were made based upon the ERG's suggestions and the Appraisal Committee's endorsement, the manufacturer has altered the treatment sequence assessed in the economic model. The manufacturer states that their revised treatment pathway is based upon the opinion of "a number of experts",(see manufacturer's response (MR),[1] p.6) but offer no more details upon how many experts were consulted, or how their views were elicited. They state that a patient in the UK would not be exposed to a cumulative CYC dose of greater than 25 grams, or no more than two courses of CYC IV pulse therapy. Hence, the manufacturer assumes that in the standard care group in their economic model patients receive two courses of CYC IV pulse therapy, which the manufacturer states is equivalent to approximately 23 grams of CYC. In the RTX group in the economic model, the manufacturer assumes that patients will initially receive one course of IV CYC, followed by RTX. All patients are then assumed to be retreated with a second course of RTX. The manufacturer states that the clinical experts that they contacted explained that all patients who relapsed following RTX would go on to receive an additional course of RTX. For a relapse to occur the ERG assumes that first a response must be achieved – but it should be noted that in their economic model the manufacturer assumes that *all* patients initially treated with RTX receive a second course, not only those who initially respond and subsequently relapse. It is important to note that this does not satisfy the request for further analysis made by the Appraisal Committee in the ACD, as the Committee specifically stated that they did not accept that patients who had not responded to a first course of RTX would receive a second course.[2] The manufacturer bases the effectiveness of this second course of RTX on 16 patients from the RAVE trial who received retreatment with RTX, of whom 7 (44%) achieved complete remission. Figure 1 illustrates the treatment pathways modelled by the manufacturer in their CYC-eligible analysis (note that in Figure 1 death can occur from any health state).

Figure 1: Treatment pathway assumed by manufacturer, drawn by ERG



The manufacturer has also amended their economic model such that patients in the "uncontrolled disease" health state receive either mycophenolate mofetil (MMF) (2g/day), methotrexate (MTX) (20mg/week) or azathioprine (AZA) (2mg/kg/day), with doses based upon recommendations made by the European League Against Rheumatism (EULAR).[4] This was to address the ERG's and Appraisal Committee's concerns that the resource use assumed in the "uncontrolled disease" health state was not plausible. No difference in efficacy between these treatments, or between treatment arms, is assumed once patients enter the uncontrolled disease health state.

2.1.2 Comparators

The manufacturer notes that the ACD suggests that the manufacturer has omitted relevant comparators from the economic analysis. However, the manufacturer reiterates that alternative therapies, such as MTX and MMF are generally reserved for milder disease, and cites the 2013 draft British Society for Rheumatology (BSR) guidelines to demonstrate that CYC represents the relevant comparator. The manufacturer states that remission rates for MTX and MMF for *de novo* patients are

"the same" as for CYC at six months, but that relapse rates are higher and that glucocorticoid requirements are higher in the long term.(see MR[1] p.8)

2.1.3 Modelled populations

In their original submission, the manufacturer presented cost-effectiveness estimates for four subgroups: "all patients"; "treatment naïve" "recurrent disease" and "CYC intolerant". Given the new clinical advice received by the manufacturer that RTX would not be given before CYC, this range of subgroups was not deemed to be helpful. Instead, in their updated analyses, the manufacturer presents cost-effectiveness estimates for two groups: (1) patients for whom CYC is an appropriate induction therapy – for whom RTX may be given at second-line; and, (2) patients for whom CYC is not an appropriate treatment – for whom RTX may be given at first-line. Results for the previously modelled subgroups were provided by the manufacturer in an appendix.

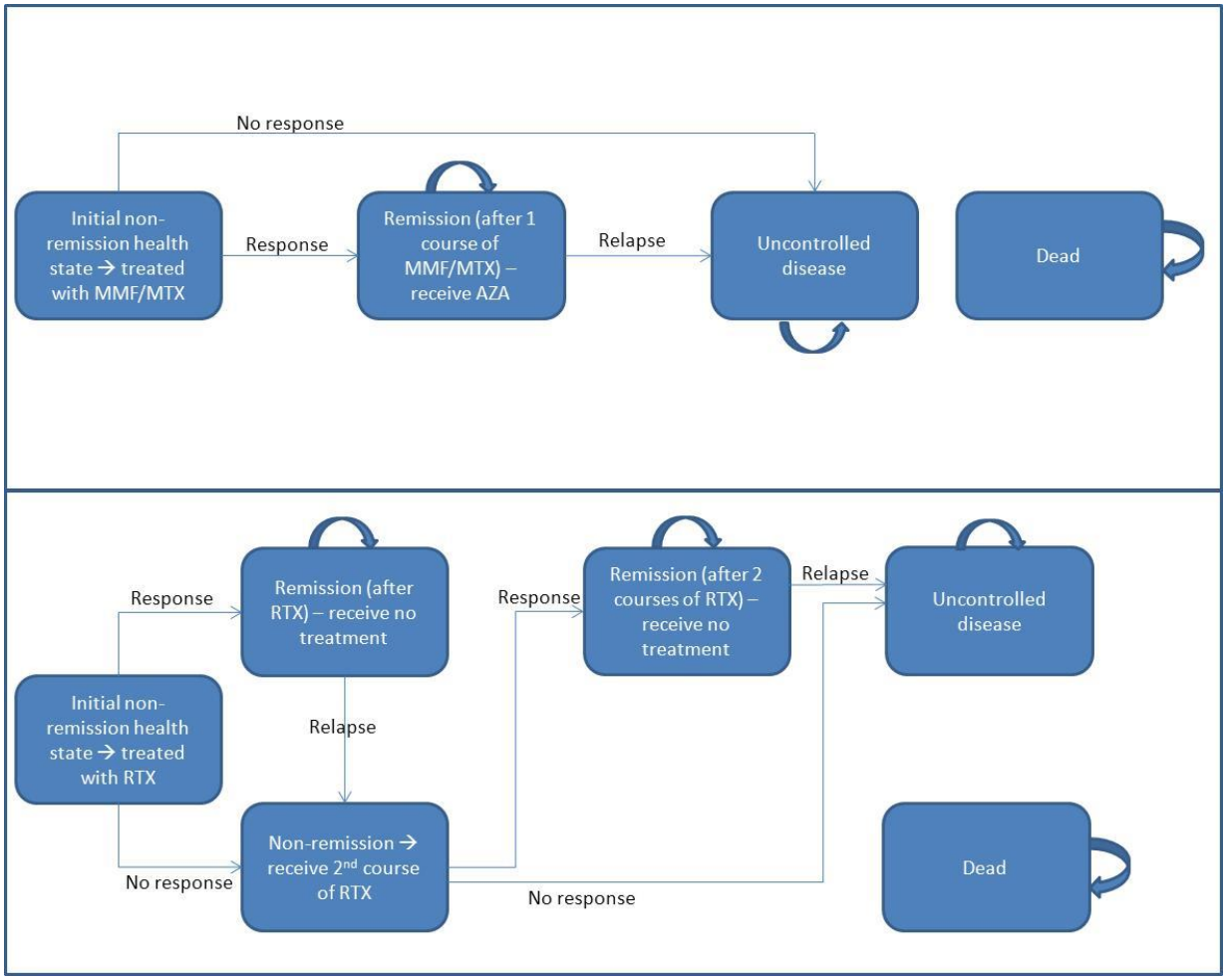
For the population for whom CYC is a relevant therapy the treatment pathways modelled are those presented in Figure 1, above. Modelling this pathway alone does not adequately address the requests made by the Appraisal Committee for two key reasons: (1) the Committee specifically stated that they did not accept the manufacturer's assumption that patients who had not responded to a first course of RTX would then receive a second course because this did not reflect UK clinical practice; and, (2) the Committee requested additional analyses for all possible treatment sequences for the different subgroup populations.[2] The ERG's comments on the treatment sequence modelled by the manufacturer are in Section 2.2.4 of this report.

For patients for whom CYC is not an appropriate treatment, the treatment pathways modelled within the post-ACD manufacturer's analysis are those presented in Figure 2 (note that death can occur from any of the health states included in the diagram). The patients included in this analysis are representative of those for whom it is desirable to avoid CYC, those who are intolerant to CYC, and those for whom CYC is inappropriate. In this subgroup, patients in the standard of care arm of the model receive initial treatment with MMF or MTX. These are assumed to be of equal efficacy, and to have the same remission rate as CYC. The manufacturer assumes that patients who achieve remission following MTX or MMF treatment receive AZA maintenance therapy. They state that based upon evidence that suggests that MMF and MTX have a higher relapse rate than CYC, they arbitrarily increase the relapse rate associated with this treatment arm by 5% (see MR[1] p.14). However, in fact, the relapse rate is increased by 20% in the manufacturer's economic model – the 5% value stated is incorrect. Upon relapse, patients move into the uncontrolled disease health state – a further line of treatment is not explicitly modelled. Again, in the RTX arm of the economic model the manufacturer assumes that *all* patients receive a second course of RTX and that no maintenance therapy is given in the RTX group. Upon second relapse, patients move into the "uncontrolled disease" health state. In

the "uncontrolled disease" health state, patients are assumed to receive treatment with MMF, MTX or AZA: no difference in efficacy between these treatments, or between treatment arms, was assumed once patients entered the uncontrolled disease health state.

The analyses undertaken by the manufacturer for the CYC-ineligible population does not adequately address the analytical requests made by the Appraisal Committee because the Committee did not accept the manufacturer's assumption that patients who had not responded to a first course of RTX would then receive a second course; and because the Committee requested additional analyses for all possible treatment sequences for the different subgroup populations.[2] The ERG's comments on the treatment sequence modelled by the manufacturer are in Section 2.2.4 of this report.

Figure 2: Treatment pathway assumed by manufacturer for patients for whom CYC is inappropriate, drawn by ERG



2.1.4 Key model parameter inputs

The key effectiveness inputs used in the manufacturer's amended model for the CYC-eligible subgroup are presented in Table 1 (reproduced from the manufacturer's ACD response[1]).

Table 1: CYC-eligible patient group remission rate inputs

CYC			**RTX**		
Line of therapy	*Value*	*Source*	*Line of therapy*	*Value*	*Source*
CYC 1	0.6458	RAVE. CYC newly diagnosed subgroup	CYC 1	0.6458	RAVE. CYC newly diagnosed subgroup
CYC 2	0.420	RAVE. CYC relapsing subgroup	RTX 1	0.6667	RAVE. RTX relapsing subgroup
			RTX 2	0.4375	RAVE. RTX retreatment subgroup

The relapse rate was assumed to be 0.0859 for each treatment, at each line, as estimated previously by the ERG based upon severe flares observed in the CYC arm of the RAVE trial.

The key effectiveness inputs used in the manufacturer's amended model for the CYC-ineligible subgroup are presented in Table 2.

Table 2: CYC-ineligible patient group remission rate and relapse rate inputs

CYC			**RTX**		
Line of therapy	*Value*	*Source*	*Line of therapy*	*Value*	*Source*
MTX/MMF 1	0.6458	Assumed equal to CYC	RTX 1	0.6042	RAVE. RTX newly diagnosed subgroup
			RTX 2	0.4375	RAVE. RTX retreatment subgroup
Relapse rate	0.1031	Assumed 20% higher than CYC/RTX	Relapse rate	0.0859	Based upon severe flares in the CYC arm of RAVE.

2.1.5 Manufacturer's cost-effectiveness results

It should be noted that all the results presented in this section are subject to substantial error, due to errors identified by the ERG within the manufacturer's amended economic model.

The manufacturer presents the results shown in Table 3 for the base case analyses of the RTX treatment pathway compared to the CYC treatment pathway in the CYC-eligible subgroup. The ICER is estimated at £18,556.

Table 3: CYC eligible patient group revised manufacturer's analysis

Treatment	QALYs	Incr. QALY	Total Costs	Incr. Cost	ICER
Rituximab	8.951	0.330	£27,821	£6,117	**£18,556**
Cyclophosphamide	8.622		£21,704		

The manufacturer presents the results shown in Table 4 for the base case analyses of the RTX treatment pathway compared to the MMF/MTX treatment pathway in the CYC-ineligible subgroup.

The ICER is estimated at £35,003. The manufacturer states that this analysis is likely to represent an "upper bound" of the cost-effectiveness of RTX in this subgroup,[1] because quality of life impacts such as the preservation of fertility have not been incorporated. However, this particular argument appears counterintuitive, since in this analysis CYC is not a comparator and patients in the control group should also maintain fertility.

Table 4: CYC ineligible patient group revised manufacturer's analysis

Treatment	QALYs	Incr. QALY	Total Costs	Incr. Cost	ICER
Rituximab	8.624	0.2910	£28,667	£10,186	**£35,003**
MMF/MTX	8.333		£18,481		

2.1.6 Manufacturer's sensitivity analysis

The manufacturer presents sensitivity analysis on the following parameters for the CYC-eligible subgroup:

- Relapse rates
- Outpatient attendance frequency
- RTX retreatment
- RTX wastage

The results of these analyses are presented in Table 5. Again, it is important to note that these results are subject to error due to mistakes found in the manufacturer's amended model.

Table 5: Manufacturer's sensitivity analysis results

Parameter	Assumption	Incr. QALY	Incr. Cost	ICER
Relapse rates	Different severe relapse rates are applied (8.6% CYC; 10.8% RTX)	0.210	£7,304	£34,775
	Assume an identical severe relapse of 10.8%	0.302	£6,815	£22,559
	All relapses will require induction treatment	0.228	£7,960	£34,942
Outpatient attendance frequency	Number of attendances in the uncontrolled disease state per 6 months set to 3, as in the ERG report	Not stated	Not stated	£21,170
RTX retreatment	Only those who initially responded receive 2nd course	0.244	£4,538	£18,564
	No retreatment	0.0682	£2,825	£41,424
RTX Wastage	88mg wastage per dose	0.330	£6,117	£18,556
	40mg wastage per dose	0.330	£5,642	£17,113
	0mg wastage per dose	0.330	£5,242	£15,899

The manufacturer did not present a sensitivity analysis of the effect of maintenance therapy following RTX, despite this being requested by the Appraisal Committee.[2] The manufacturer states that such a sequence is not supported by clinical evidence and does not reflect clinical practice. In addition, the manufacturer has not presented the following sensitivity analyses, due to a lack of evidence and time:

- An analysis on the benefit of RTX for patients with severe AAV looking to start a family
- Inclusion of costs associated with treating infections caused by CYC
- Inclusion of costs and disutility associated with long-term toxicity associated with CYC.

2.1.7 Further clinical evidence presented by the manufacturer

The manufacturer summarises the results of a newly published paper that reports upon the long-term follow-up of the RAVE trial.[3] The manufacturer states that the key findings reported in the paper were (the below is reproduced from the manufacturer's ACD response):[1]

- The proportions of patients who achieved complete remission (BVAS/WG of 0 on a prednisone dose of 0) at 6 months and who maintained complete remission at 12 months and 18 months were comparable in the RTX and CYC arms at 6, 12, and 18 months
- Rates of remission (BVAS/WG of 0) on a prednisone dose of < 10 mg/day were similar across treatment groups at 6, 12, and 18 months
- The mean BVAS/WG of each treatment group was similar at all-time points during the maintenance period
- The rates of remission were similar in both treatment groups despite a numerically lower cumulative steroid dose and lack of AZA maintenance therapy in the RTX group
- The rates of severe and limited flares did not differ significantly between treatment groups at 6, 12, and 18months; however, slightly more flares occurred after 6 months in the RTX than CYC group
- Overall, the findings between treatment groups were consistent across multiple efficacy endpoints at multiple time points

In addition, the manufacturer states that there were no significant differences in adverse events between groups at 18 months.

The manufacturer also notes that an abstract was presented at the Sixteenth International Vasculitis and ANCA Workshop, April 14-17, 2013, Paris, providing details on the 16 patients retreated with RTX in the RAVE trial.[5] Further details are not presented in the manufacturer's ACD response, but it is this abstract that the RTX retreatment remission rate assumed in the manufacturer's model is based upon.

The manufacturer also comments upon the long-term safety of RTX, owing to the Appraisal Committee's consideration that the long-term safety benefits of RTX had not yet been demonstrated. The manufacturer states that there is supporting evidence for the long-term safety of RTX in other disease areas, and that there is evidence that RTX does not prevent patients from conceiving children. Finally, the manufacturer comments upon the definition of "severe disease". They clarify the definition used in the RAVE trial, and comment that different authors have referred to this level of disease as "generalised", "generalised organ-threatening", or "organ-threatening". However, the manufacturer states that all authors agree that the patients that are included within these definitions should be treated with CYC in combination with glucocorticoids for remission induction. This suggests that the patient population that would be eligible for RTX would be any patient who would otherwise be treated with CYC.

2.1.8 Additional comments made by the manufacturer

The manufacturer argues that RTX represents a step-change in the management of ANCA-associated vasculitis, due mainly to representing a safe alternative to CYC. They also disagree with the Appraisal Committee's assessment that there are no additional QALYs associated with RTX treatment that had not been incorporated within the economic model, since the model does not include the benefits associated with maintaining fertility. In addition to this, the manufacturer states that the model does not take into account the potential benefits of the avoidance of long-term malignancies associated with higher lifetime cumulative CYC doses.

2.2 Critique of the manufacturer's updated analyses

In this section we critique the manufacturer's updated analyses and comment upon the new evidence provided. First we comment upon the new clinical evidence provided, before assessing specific qualitative points made by the manufacturer and critiquing the updated economic evaluation.

2.2.1 Comments on the new clinical evidence

The manufacturer states that data have recently been published on the long-term effectiveness of RTX compared to CYC based upon the RAVE trial.[3] In summary, the manufacturer suggests that the data show that there are no important differences in remission rates, relapse rates, and adverse events between RTX and CYC groups. Broadly, the ERG agrees with this interpretation of the evidence. However, we believe that a more thorough analysis of the evidence is required.

Firstly, it is worthy of note that while RTX was superior to CYC followed by AZA in patients with relapsing disease at baseline at 6- and 12- months, at 18-months the difference was no longer statistically significant – this was attributed by the authors to the fact that by this time point most

patients in the RTX group had reconstituted B cells.[3] However, at the 18-month time point, the rate of severe relapses in patients with relapsing disease at baseline remained lower in the RTX group (0.018 per patient-month) compared to the CYC group (0.027 per patient-month). Supplementary data demonstrate that the rate of severe relapses per patient-month for all patients (treatment naïve and those with relapsing disease at baseline) was very similar between treatment groups at 18 months (0.016 for RTX, 0.017 for CYC), which suggests that for the treatment naïve patients the severe relapse rate may have been higher in the RTX group than in the CYC group. However, data on this subgroup are not presented by Specks *et al.* or in the MR. It is also informative to note that whilst the rate of severe relapses per patient-month was lower at 18 months than at 6 or 12 months in the CYC group, it was steadily increasing in the RTX group. This would seem to corroborate with the time-to-relapse Kaplan Meier curves presented by Specks *et al.* and in the manufacturer's initial submission,[6] which cross as time progresses. This suggests that CYC followed by AZA may be associated with a higher initial relapse rate following successful remission, but that over time the RTX rate of relapse increases (as B cells are reconstituted) and may become higher than that observed in the CYC/AZA group. The ERG considers that whilst it may be reasonable to assume equal relapse rates in the RTX and CYC groups, it is relevant to consider scenarios where the relapse rate is higher in the RTX group in the long-term. Unfortunately the manufacturer's model does not allow relapse rates to alter over time.

While the ERG accepts the value of the 18-month safety data available from RAVE, we believe that this time-frame does not allow an evaluation of the true long-term effects of CYC, AZA and RTX. The ERG also notes that 18-month safety data were considered at the previous Appraisal Committee meeting and therefore these data are not new. The supposed advantage associated with RTX is not demonstrated by these data. This is important, because the manufacturer's argument that RTX represents a step-change in the treatment of ANCA-associated vasculitis rests upon it representing an effective and safe alternative to CYC – thus avoiding the toxicity associated with CYC. However, these safety claims are not supported by the RAVE data and longer-term data collection may be required. However, the ERG accepts the relevance of much longer-term data from other disease areas, which suggests that RTX is well tolerated, and allows patients to maintain fertility. Importantly though, an expert response to the ACD from the BSR suggests that whilst the absence of a safety advantage associated with RTX in RAVE may have been due to the inclusion of expert treatment centres with high quality CYC management, it may also have been due to the high use of glucocorticoids in both arms of the RAVE trial. Given that use of glucocorticoids alongside RTX is recommended, this may mean that the long-term safety advantages associated with RTX may not be as large as first thought.

2.2.2 Comments on the manufacturer's assessment of the inclusion of QALYs

The manufacturer states that there exist additional QALY gains associated with RTX treatment that are not incorporated in their economic model[1] – specifically, the QALY gains associated with allowing patients to maintain fertility. The manufacturer correctly points out that this is an issue only for patients who wish to have children presently or in the future. While the ERG accepts that this is an important issue, it is important to note that in the economic analysis that includes the patient subgroup of people who wish to maintain fertility, the comparator is MMF or MTX. The evidence on fertility associated with these treatments has not been examined in this appraisal, but it is the ERG's understanding that these do not have long-term impacts on fertility. Hence the ERG believes that in this subgroup analysis there are no additional fertility-related benefits associated with receiving treatment with RTX rather than MTX or MMF.

2.2.3 Comments on the manufacturer's definition of "severe" disease

The ERG believes that the manufacturer's definition of severe disease based upon the RAVE trial inclusion criteria is useful. We note that the text included in the manufacturer's response to the ACD is similar to that included in the supplementary data provided by Specks *et al.*[1;3] Essentially, the population indicated for RTX includes patients who would otherwise receive treatment with CYC – some commentators may describe the level of disease exhibited by these patients to be "generalised" whereas others may describe it as "severe". This supports the use of CYC as the comparator in the economic analysis, apart from in the subgroup of patients who are not eligible for CYC. However, the ERG believes that other treatments may remain relevant when considering the entire disease and treatment pathway, as other alternatives will be sought after initial treatment failure.

It also remains important that the RAVE trial excluded patients with severe disease who required mechanical ventilation because of alveolar haemorrhage, and patients with a serum creatinine level of greater than 4.0mg/dL attributed to underlying AAV disease. The EUVAS and BSR guidelines categorise severe ANCA-associated vasculitis as disease including renal or other vital organ failure, with serum creatinine of greater than 500μ/mol/litre (5.6mg/dL) and these patients would have been excluded from the RAVE trial.[4;7] Whilst the RITUXVAS trial included some more severely affected patients treatment was with RTX in combination with CYC – thus the ERG maintains that the clinical evidence submitted by the manufacturer is not relevant for *all* patients with severe disease. Expert views on the use of RTX in very severe life-threatening disease appears mixed – in their response to the ACD the BSR state that RTX is effective in very severe life-threatening disease, referencing the RITUXVAS trial and noting that observational cohorts have also been studied. However, a response from an experienced NHS professional and co-author of the upcoming 2013 BSR guideline on the treatment of vasculitis stated that – whilst supporting the use of RTX – RTX should not be used in patients with life-threatening disease at the time of treatment initiation, and that these patients should instead be treated with CYC unless the contra-indication is a risk of major organ damage.

2.2.4 Comments on the manufacturer's amended economic analysis

Whilst the ERG accepts that the treatment sequence modelled by the manufacturer is more appropriate than those considered in the original submission, it is critically important to note that the manufacturer's model contains errors which invalidate the results presented in the manufacturer's ACD response for the base case analysis and sensitivity analyses. The model contains an error in the calculation of the "uncontrolled disease" health state cost – the manufacturer assumes that in this health state patients will receive four outpatient appointments in each 6-month period whilst also receiving treatment with either AZA, MTX or MMF. However, when calculating the health state cost they multiply the outpatient appointment unit cost by 4 (which is correct) *and* the AZA/MMF/MTX treatment cost by four (which is incorrect). This results in an "uncontrolled disease" health state cost per 6-month cycle of £815.94, rather than the correct cost of £581.03. Because health state costs represent the major cost category in the economic evaluation, and because patients on average spend approximately 57% of their time in this state in the CYC arm of the model, and approximately 44% of their time in this state in the RTX arm of the model, this cost difference can be expected to lead to a substantial over-estimate of the lifetime costs calculated in the model, and can be expected to bias the ICER in favour of RTX.

It is also apparent that there is an error in the RTX retreatment sensitivity analyses presented by the manufacturer in their ACD response. In the "no RTX retreatment" analyses the model is incorrectly coded and uses the response rate attributed to RTX retreatment for first-line RTX treatment. Hence the "no RTX retreatment" ICER is likely to be over-estimated. In the "RTX retreatment only for relapsers" analysis there are several coding errors, including one that means that in fact *all* patients receive RTX retreatment. Hence the ICER associated with this analysis is incorrect. In addition, it appears that the manufacturer has used incorrect unit costs for methotrexate and mycophenolate mofetil.

Due to these errors it is not useful to interpret the results presented by the manufacturer, since they are incorrect and do not adequately address the concerns of the Appraisal Committee. The ERG also notes that the manufacturer has presented only deterministic results (whereby parameter inputs reflect point estimates), rather than probabilistic analyses which reflect the expectation of the mean.

Aside from the errors in the manufacturer's model, the ERG accepts that the manufacturer has made several amendments to their original model that are in line with those proposed by the ERG. We believe that these amendments are appropriate and important. The manufacturer notes that two changes proposed by the ERG were not made, in line with discussion at the Appraisal Committee meeting: maintenance therapy in the RTX group was assumed not to occur, and; it was assumed that patients in the "uncontrolled disease" health state would have four outpatient appointments in each 6-

month period, rather than three. The ERG believes that there are two other factors that may be perceived to be important to the Appraisal Committee that have not been considered in the manufacturer's updated analysis, that were considered as additional scenario analyses in the ERG report.[8] Clinical advice received by the ERG suggests that CYC can be infused more quickly than RTX, with infusion time approximately half the RTX infusion time. Hence it may be relevant to incorporate a lower administration cost for CYC than for RTX. Also, clinical advice received by the ERG suggested that patients receiving IV CYC may often only receive 6 administrations, rather than the 10 assumed in the manufacturer's model. Typically, treatment beyond 6 administrations would only occur if evidence remained of active disease. If these two amendments were made to the manufacturer's economic model, the ICER associated with RTX would increase.

Treatment sequences

A key alteration to the manufacturer's model involves the treatment sequences modelled. The base case sequence modelled in the resubmitted model is presented in Figure 1. Three factors are of particularly importance:

- Only one course of CYC is given in the RTX arm of the model
- RTX retreatment is assumed for all patients in the RTX group
- No maintenance treatment is given in the RTX arm of the model.

Whilst the ERG accepts that a key benefit of introducing a RTX treatment regime in ANCA-associated vasculitis may be associated with reducing CYC treatment, we are not convinced that no patients would receive more than one course of CYC, even if RTX was available. Clinical advice received by the ERG also suggests that some patients may receive more than two courses of CYC, if those courses involve low cumulative doses. For instance, if a patient weighing 75kg experienced complete remission after 6 (rather than the full 10) administrations of IV CYC they may only have received 6.75g of CYC. If this led to a long-term well-controlled remission it does not seem inconceivable that this patient would receive a second (and possibly further) course(s) of CYC upon eventual relapse, irrespective of whether RTX was available. This is important because previous analyses conducted by the ERG suggest that RTX is likely to be more cost-effective if given after two courses of CYC compared to being given after one course of CYC.

The ERG also believes that the RTX retreatment assumption made by the manufacturer is controversial. The manufacturer assumes that *all* patients receive two courses of RTX, even if they do not respond to the initial course. Previous clinical advice received by the ERG suggested that it would be very unlikely that patients who do not respond to an initial course of RTX would immediately be given a second course,[8] and the Appraisal Committee agreed that this assumption was

unacceptable.[2] If RTX retreatment is to be included in the manufacturer's model, the ERG believes that it would be most appropriate to consider that this retreatment is only provided to patients who initially enter remission after treatment with RTX.

The conclusion of the Appraisal Committee was that AZA treatment would not be given following a remission induced by RTX,[2] and the manufacturer has therefore modelled this scenario. This is in contrast to the clinical advice received by the ERG and referred to in the ERG report. The ERG notes that the two clinicians who advised the ERG responded to the ACD strongly disagreeing with the assertion that no maintenance therapy would be given following RTX treatment, with one stating that such treatment would be typical, and the other stating that the chosen maintenance therapy would be associated with clinician preference: thus there may be no consensus on this. The BSR also responded to the ACD, and outline four options for maintenance treatment after remission induced by RTX (these will appear in the forthcoming BSR guidelines on the treatment of ANCA-associated vasculitis):

i) No therapy and treat further relapse with RTX
ii) An immunosuppressive agent (azathioprine or methotrexate)
iii) Fixed interval repeat dose RTX
iv) Repeat dose RTX based on biomarkers

It is noteworthy that the manufacturer has chosen to model option i) in their updated economic model, whereas the sequence previously modelled by the ERG is represented by option ii). Importantly, the fact that the ERG's previously modelled sequence appears as option ii) demonstrates that this does represent a realistic option, contrary to the views expressed at the Appraisal Committee meeting. However, alongside these options, the BSR offers further guidance on their use. The BSR states that option i) is not desirable because it requires close patient monitoring and places the patient at risk of increased tissue damage and morbidity when relapse occurs. Hence option i) appears sub-optimal. The BSR also states that option ii) has been assessed in a retrospective, multi-centre, cohort study and continued immunosuppressive had no effect on time to B cell return or to relapse compared to no therapy.[9] Hence, this option may also be sub-optimal. The BSR state that relatively large retrospective data sets exist on fixed interval repeat RTX dosing (option iii), and that this is being compared to option ii) in the ongoing RITAZAREM RCT,[10;11] whereas there is comparatively less information available on option iv). It is important to note that options iii) and iv) are not currently within the RTX license which is likely to explain why the manufacturer has not included these scenarios in their submission. Patient and clinician experiences submitted to NICE as part of the ACD consultation process suggest that RTX retreatment as maintenance therapy, rather than only upon relapse, is happening (off license) in the UK, and could represent the most realistic treatment strategy should RTX be recommended as induction therapy. The cost-effectiveness of such a strategy

is unknown – whilst there are QALY benefits and cost offsets associated with maintaining remission, there are also significant cost implications of repeated RTX treatment.

It is also relevant to note that in the previous ERG analyses, we assumed equal relapse rates in the CYC and RTX groups based partly on the assumption that both groups involved maintenance therapy with AZA.[8] The manufacturer has retained this assumption despite assuming that no AZA maintenance is given in the RTX group.[1] Whilst the longer-term data from the RAVE trial lends some support to such an assumption some questions remain over the long-term relapse rate associated with zero maintenance therapy after an RTX remission, as alluded to in Section 2.2.1 of this report. It is also noteworthy that with access to the patient-level data from the RAVE trial it may be expected that the manufacturer could calculate a more accurate estimate of the relapse rate, since the ERG had to rely upon summary data.

The manufacturer has based the remission rate associated with RTX retreatment on data from 16 patients from the RAVE trial who received two courses of RTX.[1;5] These data are obviously very limited due to the small patient numbers. Also, it is not clear to what extent these data may be affected by selection bias – patients retreated in RAVE represent those who suffered a severe disease flare between 6 and 18 months and thus it seems that these patients achieved only relatively short-term remission – it may be conceivable that patients retreated with RTX following a more successful long-term remission have a higher probability of a second successful remission. The ERG considers that the RTX retreatment remission rate assumed by the manufacturer (0.4375) is highly uncertain, and notes that the manufacturer has not placed a distribution around this model parameter and has not conducted probabilistic sensitivity analysis (PSA). It is also notable that 3 of the 16 patients who received two courses of RTX experienced severe adverse events, including one death, metastatic colon cancer, and severe sinusitis – though the ERG is unsure as to whether any of these events could be attributed in any way to RTX.

The treatment sequence assumed by the manufacturer for patients ineligible for CYC is illustrated in Figure 2. Whilst the manufacturer states that the treatment sequence assumed for CYC-eligible patients has been based upon clinical advice, it is not clear whether this is the case for the CYC-ineligible subgroup. Hence, the ERG is uncertain as to the validity of this analysis. The sequence suffers from the same limitation as the CYC-eligible sequence in that *all* RTX patients are assumed to receive two courses of RTX, rather than only those who initially respond to RTX. The ERG believe that this assumption is not appropriate. In addition, the control group sequence appears overly simplistic: one course of MMF or MTX is assumed, with patients entering the "uncontrolled disease" health state upon relapse. It is not clear to the ERG why only one course of treatment would be considered. Also, clinical advice received by the ERG suggests that cumulative glucocorticoid use is

likely to be higher with MMF or MTX treatment, which is likely to have cost and utility implications. The manufacturer has not attempted to model this. In part, this may be due to the simplistic nature of the manufacturer's economic model – for instance, separate health states do not exist for drug-controlled and drug-free remission, despite the likelihood that these states would have very different costs and utilities. The ERG remains unconvinced by the manufacturer's CYC-ineligible analysis.

Resource use assumptions

The ERG accepts that the manufacturer's new assumption regarding the number of outpatient appointments associated with the "uncontrolled disease" health state reflects the views of the Appraisal Committee. However, it is important to note that this number represents the number of appointments per 6-month period for the entire time spent in the "uncontrolled disease" health state. Given that on average patients spend several years in this health state, the ERG is unconvinced that patients would continue to have outpatient appointments at a frequency of one every 6 weeks for the duration of their time spent in this health state, particularly as this state actually represents a state of low grade "grumbling" disease. Based upon this, the ERG believes that our previous assumption of three outpatient appointments per 6-month period may be more reasonable as an average over the duration of time spent in the "uncontrolled disease" health state – and in fact this may also represent an over-estimate. It is notable that reducing the number of outpatient attendances in this health state has the impact of increasing the ICER associated with RTX.

The ERG notes that the manufacturer calculates the "uncontrolled disease" health state cost incorrectly – the six-monthly costs of MTX/MMF treatment are erroneously multiplied by four. In addition, according to the latest version of the BNF,[12] costs for both MTX and MMF are incorrect in the manufacturer's model. The manufacturer uses a cost of £7.25 for a 50 tablet pack of 500mg mycophenolate mofetil whereas the cost should be £10.41. Taking the average cost associated with 500mg and 250mg packs, this increases the cost associated with 6-months of MMF from £105.85 (calculated by the manufacturer) to £146.88. For MTX, the manufacturer attributes a cost of £3.18 to a 28 pack of 2.5mg tablets, whereas this cost is actually £3.88. Taking the average cost associated with 24 pack and 28 packets, this increases the cost associated with 6 months of MTX treatment from £23.62 (calculated by the manufacturer) to £28.58. These errors further invalidate the manufacturer's CYC-ineligible analysis.

Results

Given the errors in the manufacturer's economic model, the ERG believes that it is not useful to comment upon the results. Instead, the ERG has rectified the key errors and re-run the manufacturer's model. The results of these analyses are presented in the following section.

3. IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE ERG

In this Section, we present the results of a set of analyses undertaken by the ERG that amend parameters within the manufacturer's updated economic model. Some of the amendments made by the ERG correct factual inaccuracies, whereas others reflect the view of the ERG and requests for further analyses made by the Appraisal Committee in the ACD. Factual inaccuracies that have been corrected include:

- Amending the "uncontrolled disease" health state cost so that MTX and MMF treatment costs are not erroneously multiplied by four.
- Correcting the drug unit-costs associated with MMF and MTX.
- Correcting the model code so that scenarios of "no RTX retreatment" and "RTX retreatment only for relapsers" can be considered.
- Incorporated uncertainty around the remission rate associated with the second course of RTX based upon the 16 patients who received RTX retreatment in the RAVE trial, and ran PSA.

Amendments made by the ERG that reflect the view of the ERG (and the request for further analyses made by the Appraisal Committee in the ACD) include:

- Amended the model such that the "base case" involves RTX retreatment only for patients who initially respond to a first course of RTX. We do not consider a scenario whereby *all* RTX patients receive a second course of RTX because the Appraisal Committee specifically stated that they did not accept this assumption in the ACD.[2]

Due to a lack of time, the ERG has not re-run all analyses investigated by the manufacturer. Instead the following scenarios are considered for both CYC-eligible and CYC-ineligible subgroups:

- RTX retreatment only for patients who initially respond to RTX. This analysis represents option ii) for RTX treatment as defined by the BSR and discussed in Section 2.2.4 of this report.
- AZA maintenance therapy in the RTX group. Although the Appraisal Committee concluded that this sequence of treatment would be unlikely in UK practice, it represents option ii) for RTX treatment as defined by the BSR and discussed in Section 2.2.4. The manufacturer did not include this analysis in their ACD response, but the ERG has incorporated it as a scenario analysis.
- No RTX retreatment. Given the uncertainty associated with the effectiveness of a second course of RTX based upon the RAVE trial data, the ERG has run an analysis in which no RTX retreatment is assumed.

The ERG's analyses come closer than the manufacturer's analyses to that requested by the Appraisal Committee in the ACD, but deficiencies remain. For instance, the Committee requested that additional analyses should be undertaken for all possible treatment sequences. While the ERG has considered alternative scenarios with regard to RTX retreatment and AZA maintenance therapy, this has been undertaken within a setting defined by the manufacturer whereby only one course of IV CYC is received in the RTX group and that this is received before RTX, and two courses of IV CYC are received in the control group. In addition, it is assumed that CYC is *never* received after RTX (even when RTX has failed and a patient has only previously received one course of IV CYC). In the CYC-ineligible subgroup it is assumed that standard care involves one course of MMF or MTX, with a patient entering "uncontrolled disease" upon first relapse. The ERG suggests that analyses of these narrow set of treatment sequences does not adequately reflect analyses of "all possible treatment sequences", as requested by the Appraisal Committee.[2]

3.1 Additional work undertaken by the ERG

In the additional work undertaken by the ERG the following amendments have been made to the manufacturer's economic model:

- "Uncontrolled disease" health state cost does not multiply MMF/MTX/AZA cost by four. We have retained the manufacturer's assumption that there are four outpatient appointments per 6-month period in this health state.
- MMF and MTX costs are corrected.
- Model code is corrected so that scenarios of "no RTX retreatment" and "RTX retreatment only for relapsers" can be considered.
- A beta distribution has been placed around the RTX retreatment remission rate based upon the 16 patients who received RTX retreatment in the RAVE trial.
- PSA has been run.

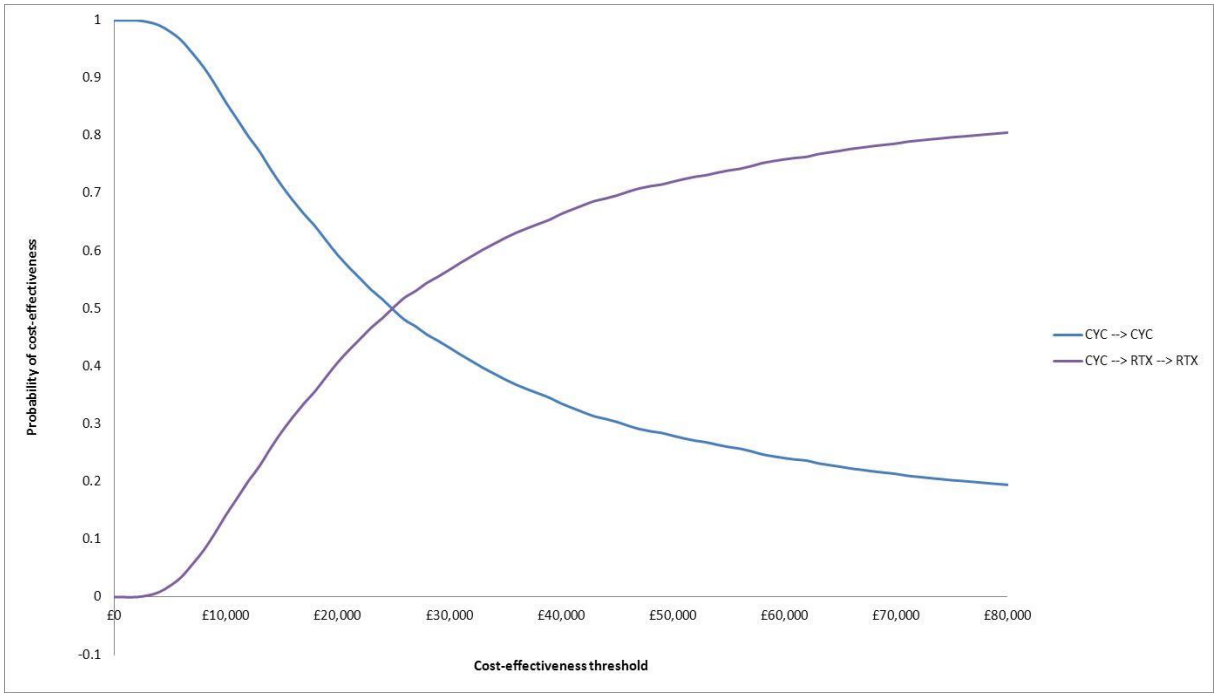
3.1.2 CYC-eligible population

Table 6: ERG preferred analyses cost-effectiveness results – CYC-eligible patients with RTX retreatment for responders

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
CYC → CYC → BSC	£18,788.82	8.58	-	-	-
CYC → RTX → RTX → BSC	£23,863.45	8.82	0.24	5,074.64	**£20,878.50**

Table 6 demonstrates that adding RTX (with retreatment for responders) to the treatment sequence after one course of CYC is associated with an ICER of £20,878.50 per QALY gained compared to a strategy of two courses of CYC with no RTX. Cost effectiveness acceptability curves (CEACs) associated with this analysis are presented in Figure 3. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders) after one course of CYC is a cost-effective strategy is approximately 56.7%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with retreatment for responders) after one course of CYC is a cost-effective strategy is approximately 40.7%.

Figure 3: Cost effectiveness acceptability curves – CYC-eligible patients with RTX retreatment for responders



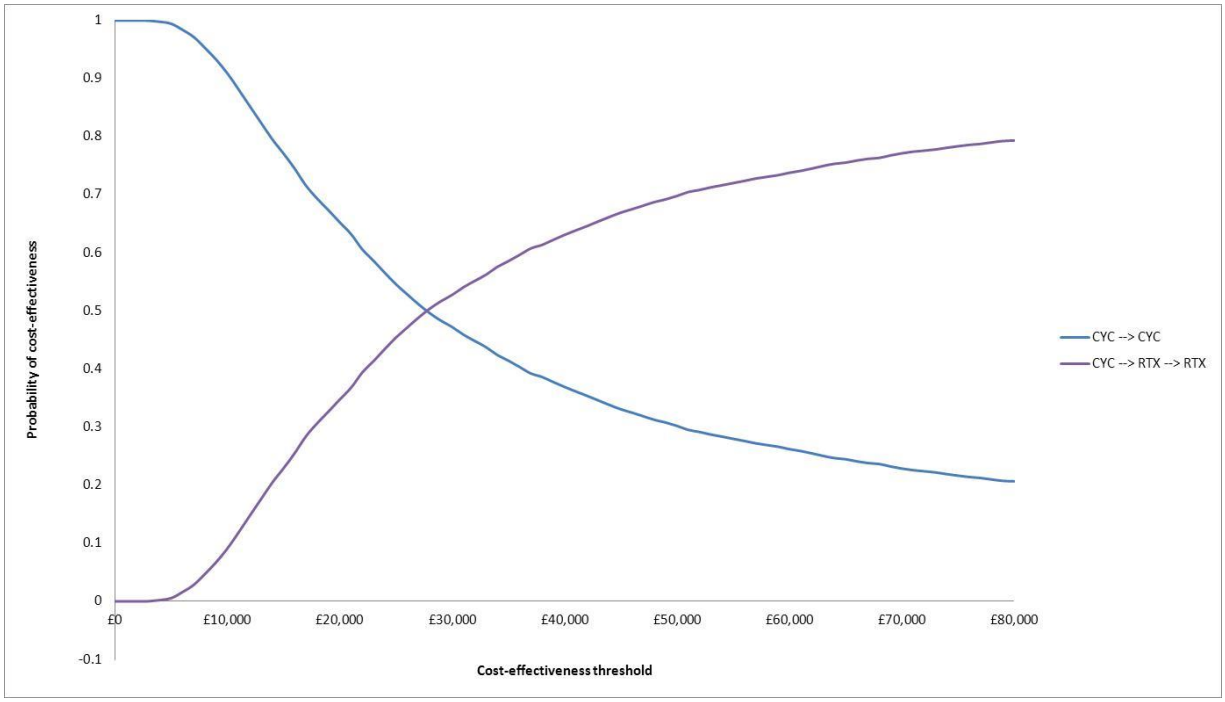
In order to demonstrate the impact on the cost-effectiveness analysis of assuming that patients in the RTX group receive maintenance therapy with AZA, the ERG has re-run the above analysis, including AZA maintenance therapy costs in the RTX group. The results of this analysis are shown in Table 7 and Figure 4.

Table 7: ERG preferred analyses cost-effectiveness results – CYC-eligible patients with RTX retreatment for responders, with AZA maintenance therapy

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
CYC → CYC → BSC	£18,788.82	8.58	-	-	-
CYC → RTX → RTX → BSC	£24,486.89	8.82	0.24	5,698.07	**£23,443.50**

Table 7 demonstrates that adding RTX (with retreatment for responders, and maintenance therapy with AZA) to the treatment sequence after one course of CYC is associated with an ICER of £23,443.50 per QALY gained compared to a strategy of two courses of CYC with no RTX. Thus, whilst adding AZA as maintenance therapy leads to an increase in the ICER, the difference is not substantial. CEACs associated with this analysis are presented in Figure 4. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders and AZA maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 52.8%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with retreatment for responders and AZA maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 34.8%.

Figure 4: Cost effectiveness acceptability curves – CYC-eligible patients with RTX retreatment for responders, with AZA maintenance therapy



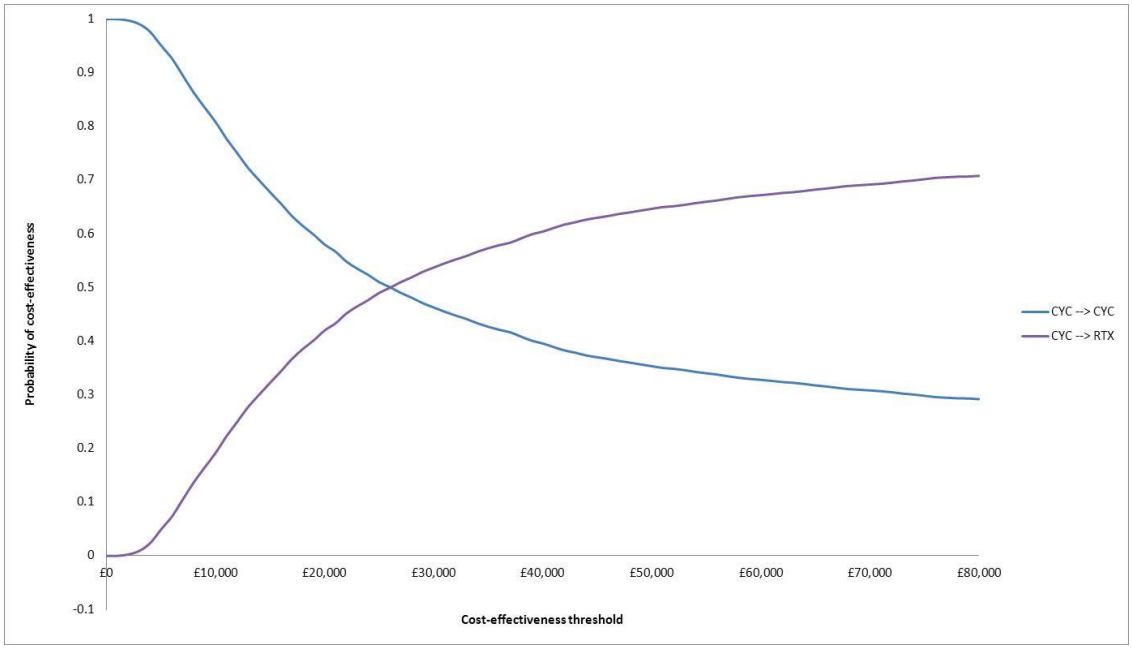
In order to demonstrate the impact on the cost-effectiveness analysis of assuming that patients who initially respond to RTX receive retreatment, the ERG has re-run the analysis presented in Table 6, excluding RTX retreatment. The results of this analysis are shown in Table 8 and Figure 5.

Table 8: ERG preferred analyses cost-effectiveness results – CYC-eligible patients with no RTX retreatment

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
CYC → CYC → BSC	£18,788.82	8.58	-	-	-
CYC → RTX → BSC	£21,578.89	8.72	0.14	2,790.07	**£20,080.23**

Table 8 demonstrates that for the "all patients" analysis, adding RTX (with no retreatment and no maintenance therapy) to the treatment sequence after one course of CYC is associated with an ICER of £20,080.23 per QALY gained compared to a strategy of two courses of CYC with no RTX. Thus, whilst excluding RTX retreatment results in fewer QALYs gained, costs are reduced to an extent such that the ICER is almost unchanged. CEACs associated with this analysis are presented in Figure 5. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders and AZA maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 53.7%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with retreatment for responders and AZA maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 42.0%.

Figure 5: Cost effectiveness acceptability curves – CYC eligible patients with no RTX retreatment



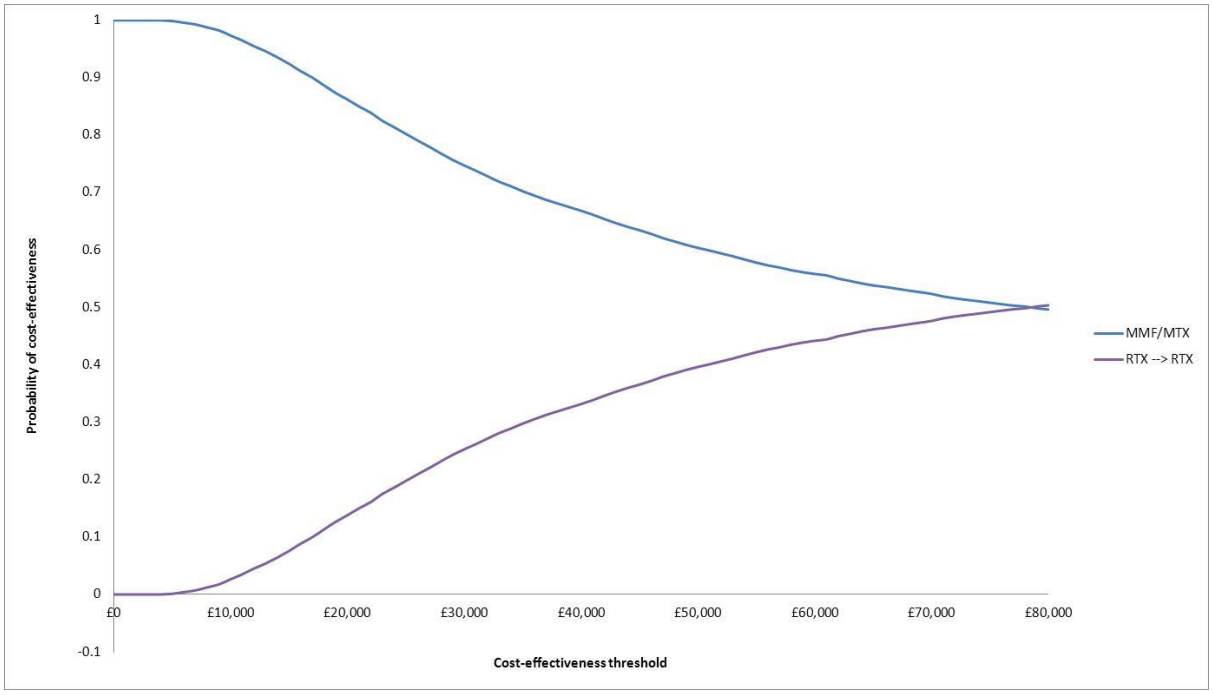
3.1.3 CYC-ineligible population

Table 9: ERG preferred analyses cost-effectiveness results – CYC-ineligible patients with RTX retreatment for responders

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,560.57	8.35	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.14	8,345.42	**£60,569.08**

Table 9 demonstrates that treating people who are ineligible for CYC treatment with RTX (with retreatment for responders) rather than MMF or MTX is associated with an ICER of £60,569.08 per QALY gained. CEACs associated with this analysis are presented in Figure 6. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders) is a cost-effective strategy is approximately 25.3%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with retreatment for responders) is a cost-effective strategy is approximately 13.8%. There are three key reasons explaining why RTX appears to be less cost-effective in this subgroup compared to the CYC eligible subgroup. Firstly, MMF and MTX treatments are much less costly than IV CYC, because they do not require infusion and because only one course of treatment is given in the model. This increases the incremental cost associated with RTX. Secondly, in the economic model RTX is assumed to be less effective when treating treatment naïve patients than when treating relapsing patients. Thirdly, the incremental QALY gain associated with the RTX arm is less than that presented in Table 6. This is because the MMF/MTX arm is assumed to have the same remission rate as first-line CYC treatment (albeit with a higher relapse rate), and so the QALY loss associated with this treatment strategy compared to a CYC treatment strategy is mainly due to the absence of a second course of treatment. However, the remission rate associated with CYC treatment at second-line is much lower than at first-line. In the RTX arm of the model the main QALY loss is associated with the absence of a first-line CYC course. Because CYC is more effective at first-line than at second-line, the relative QALY loss between the RTX treatment arm in the CYC-ineligible analysis and the CYC-eligible analysis is larger than the QALY loss between the MMF/MTX treatment arm in the CYC-ineligible analysis and the CYC arm in the CYC-eligible analysis. Together with the increased incremental costs, this results in a substantially higher ICER.

Figure 6: Cost effectiveness acceptability curves – CYC-ineligible patients with RTX retreatment for responders



In order to demonstrate the impact on the cost-effectiveness analysis of assuming that patients in the RTX group receive maintenance therapy with AZA, the ERG has re-run the above analysis, including AZA maintenance therapy costs in the RTX group. The results of this analysis are shown in Table 10 and Figure 7.

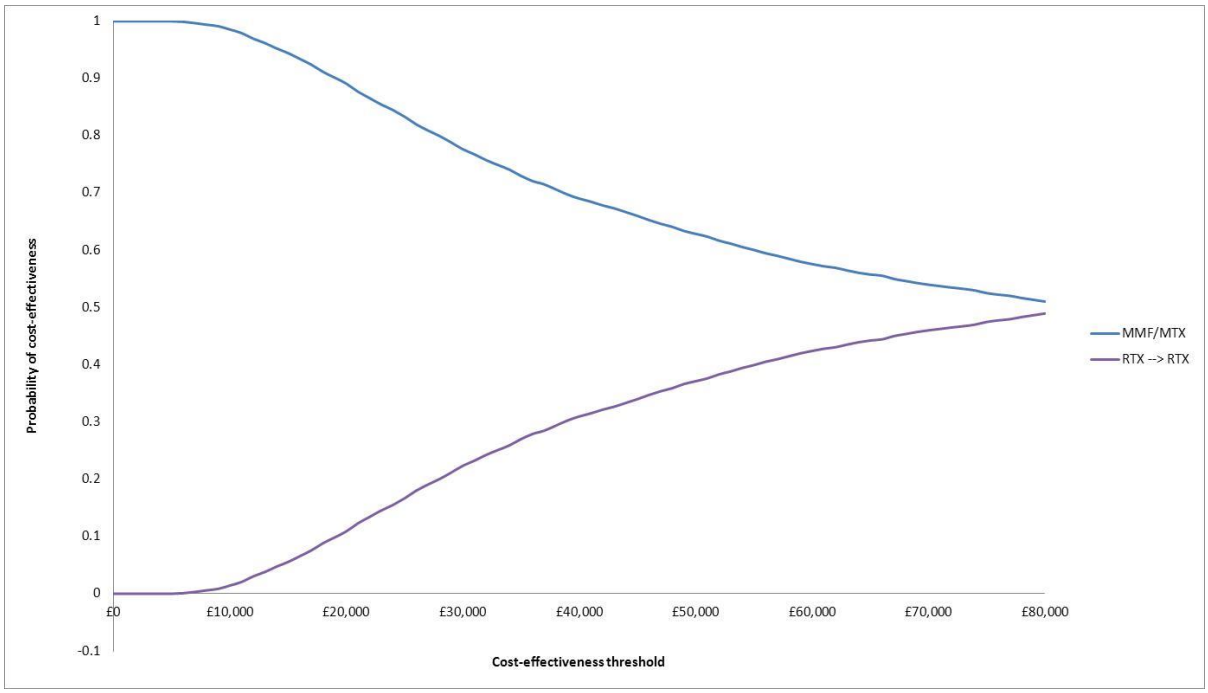
Table 10: ERG preferred analyses cost-effectiveness results – CYC-ineligible patients with RTX retreatment for responders, with AZA maintenance therapy

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,560.57	8.35	-	-	-
RTX → RTX → BSC	£23,612.96	8.49	0.14	9,052.39	**£65,700.07**

Table 10 demonstrates that treating people who are ineligible for CYC treatment with RTX (with retreatment for responders and with AZA maintenance treatment) rather than MMF or MTX is associated with an ICER of £65,700.07 per QALY gained. Thus, whilst adding AZA as maintenance therapy leads to an increase in the ICER, the difference is not substantial. CEACs associated with this analysis are presented in Figure 7. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders and AZA maintenance treatment) is a cost-effective strategy is approximately 22.4%. At a willingness-to-pay threshold of

£20,000 per QALY gained, the probability that administering RTX (with retreatment for responders and maintenance treatment) is a cost-effective strategy is approximately 10.9%.

Figure 7: Cost effectiveness acceptability curves – CYC-ineligible patients with RTX retreatment for responders, with AZA maintenance therapy



In order to demonstrate the impact on the cost-effectiveness analysis of assuming that patients who initially respond to RTX receive retreatment, the ERG has re-run the analysis presented in Table 9, excluding RTX retreatment. The results of this analysis are shown in Table 11 and Figure 8.

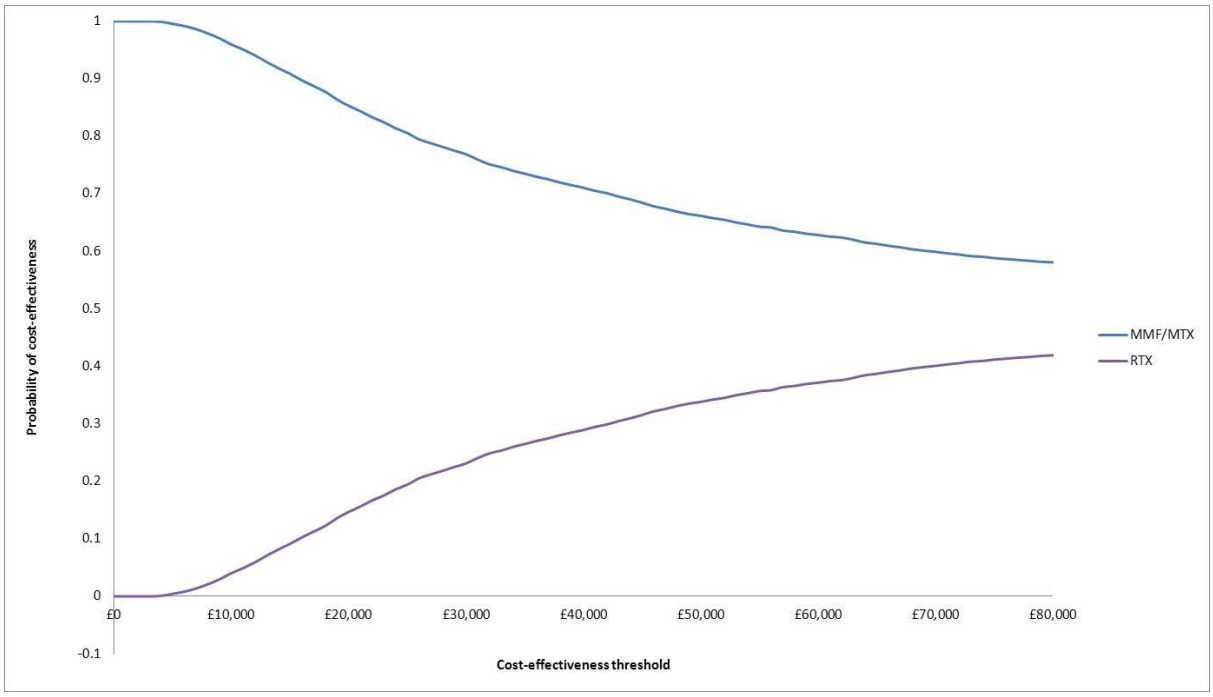
Table 11: ERG preferred analyses cost-effectiveness results – CYC-ineligible patients with no RTX retreatment

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,560.57	8.35	-	-	-
RTX → BSC	£20,023.37	8.40	0.05	5,462.80	**£118,154.07**

Table 11 demonstrates that for the "all patients" analysis, adding RTX (with no retreatment and no maintenance therapy) to the treatment sequence after one course of CYC is associated with an ICER of £118,154.07 per QALY gained compared to a strategy of two courses of CYC with no RTX. Thus, in the CYC ineligible subgroup excluding RTX retreatment results in a substantially higher ICER. CEACs associated with this analysis are presented in Figure 8. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with no retreatment for

responders and no maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 23.1%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with no retreatment for responders and no AZA maintenance therapy) after one course of CYC is a cost-effective strategy is approximately 14.7%.

Figure 8: Cost effectiveness acceptability curves – CYC-ineligible patients with no RTX retreatment



3.2 Discussion of the cost effectiveness results

The ERG undertook additional analyses to correct mistakes found in the manufacturer's model. Previous analyses undertaken by the ERG considered positioning RTX at various points in the treatment pathway, and found that RTX was likely to result in an ICER of approximately £10,699 to £12,851 per QALY gained provided it was given after CYC treatment had been exhausted. Moving RTX forward in the treatment sequence resulted in substantially higher ICERs. In the manufacturer's updated analyses in response to the ACD a new treatment sequence has been proposed – that is, RTX (with retreatment for all patients) after relapse following one course of CYC treatment. This new analysis assumes that if RTX were available no patient would receive more than one course of CYC, whereas currently two courses of CYC are commonly given. In addition, it is assumed that no maintenance therapy is given after a remission induced by RTX. The ERG continues to disagree with this assumption regarding maintenance therapy, but note that it makes little difference to the estimated ICER, particularly given that there is not currently good evidence that suggests different relapse rates with and without AZA maintenance after RTX-induced remission.

The ICERs presented in this report are higher than those presented for RTX after the exhaustion of CYC treatment in the previous ERG report, particularly in the CYC-ineligible subgroup. For treatment naïve patients the previous ERG analyses involved two key treatment sequences:

- CYC → CYC → BSC
- CYC → CYC → RTX → BSC

Where BSC represents Best Supportive Care, which in the new model submitted by the manufacturer represents treatment with MMF or MTX. The treatment sequence considered in the manufacturer's new analysis represents:

- CYC → RTX → RTX → BSC

So, essentially, RTX is moved forward in the treatment sequence and the second course of CYC is replaced by a second course of RTX. The second course of RTX has a similar remission rate as the second course of CYC, yet is substantially more expensive, and therefore the ICER is increased.

For the CYC-ineligible subgroup the estimated ICER is substantially higher than that estimated in the previous ERG report, and also that estimated by the manufacturer. The reason that the ICER is higher than that estimated in the previous ERG report is that MTX and MMF are included as the comparator, rather than no treatment. The reason that the ERG-estimated ICER is higher than that estimated by the manufacturer is due in part to the errors in the manufacturer's model, but is mainly because in the ERG analysis we have assumed RTX retreatment only for patients who respond to an initial course of RTX. This results in comparatively lower treatment costs than those estimated by the manufacturer, but substantially reduces the QALY gain associated with RTX and results in an increased ICER. The ERG believes that it is more realistic to assume that patients will only be retreated with RTX if they have previously responded favourably to it.

Based upon the ERG amendments to the manufacturer's post-ACD model, it is likely that including RTX in the treatment sequence increases health benefits compared to the current standard treatment sequence (that is, a treatment sequence that does not include RTX). In patients eligible for CYC, the ICER associated with adding RTX (with retreatment for responders) after one course of CYC is estimated to be £20,878.50 per QALY gained compared to two courses of CYC. In patients ineligible for CYC treatment, the ICER associated with initiating treatment with RTX (with retreatment for responders) is estimated to be £60,569.08 per QALY gained compared to one course of either MMF or MTX.

The ERG believes that the true cost-effectiveness of induction treatment with RTX for patients with ANCA-associated vasculitis remains uncertain. Although the CYC-eligible analyses presented in this report represent thorough analyses of the treatment sequence specified by the manufacturer (except with RTX retreatment only for previous responders, rather than all patients), it is not clear that this truly represents the most realistic treatment pathway that would be observed should RTX be recommended for use. The BSR provide four options for maintenance therapy following a RTX induced remission and appear to favour RTX maintenance therapy over AZA maintenance therapy (as previously modelled by the ERG) or RTX retreatment upon relapse (as modelled in the manufacturer's response to the ACD). However RTX is not currently licensed for maintenance therapy and this sequence has not been modelled, meaning that its associated cost-effectiveness remains unknown. It is likely that the use of RTX maintenance therapy would impact upon the cost-effectiveness of RTX induction therapy, but the direction of this impact is unknown. In addition, the ERG believes that some patients would likely receive two (or more) courses of CYC even if RTX was available, given that some remissions are achieved from a relatively low cumulative CYC course dose. In these patients it is likely to be most cost-effective to delay RTX treatment until CYC treatment has been exhausted. Given the treatment sequence modelled, the ERG believes that the estimated ICER may represent a lower bound, given that the average number of CYC administrations may be fewer than is modelled and the "uncontrolled disease" health state cost may remain overestimated – although this is subject to caveats around the utility scores associated with the "remission" health state, discussed below. It is important to reiterate that the ERG remains unconvinced that the treatment sequence defined by the manufacturer for the CYC-eligible population represents the only possible treatment sequence.

The ERG is not convinced that the CYC-ineligible analyses presented by the manufacturer and included in this report represent accurate or thorough analyses of the cost-effectiveness of RTX in this patient group. Although the efficacy assumptions applied to MMF and MTX by the manufacturer seem plausible, no attempts are made by the manufacturer to reflect the likely increase in glucocorticoid use in MMF/MTX patients, or the disutilities associated with this. Due to this rather than the fertility-related QALY arguments made by the manufacturer, the ERG believes that the estimated ICER for this subgroup is likely to be an overestimate, but acknowledges that there is a very large difference in treatment costs between RTX and MMF/MTX. It is also important to note that the manufacturer stated that they arbitrarily assumed that the relapse rate associated with MMF and MTX was 5% higher than the rate assumed for CYC: in fact an increase of 20% was incorporated within the model. If 5% rather than 20% was incorporated within the model the ICER associated with RTX would increase.

The ERG believes that the manufacturer's model is limited with respect to its ability to accurately capture all of the benefits that may be associated with RTX treatment, if it is appropriate to assume that patients would receive no ongoing maintenance treatment following RTX-induced remission. The ERG believes that if RTX were not available for maintenance therapy it is likely that AZA would be given rather than no treatment at all. However, if RTX maintenance therapy was given, perhaps, for instance, on an annual basis, there may be long periods of time during which the patient does not need to be taking any drugs. Such drug-free remission may be associated with an improved health-related quality of life and may be deserving of a separate health state in the economic model. In addition, it remains the ERG's belief that a more appropriate economic model would incorporate health states for partial responders and flares of different severity, and that the likely non-linearity of relapse rates mean that a Markov model may not represent the preferred model type for this disease area.

The ERG has not replicated all of the sensitivity analyses undertaken by the manufacturer due to a lack of time. However, based upon the manufacturer's analyses it is noted that assuming a higher relapse rate for RTX results in an increase in the ICER, as does assuming that relapses of all severities require renewed induction treatment. The pattern of these results is likely to remain the same in the ERG's amended model. It is also noted that assuming no RTX wastage will result in a reduced ICER, although the ERG believes that it is appropriate to take wastage into account. Also, in response to the manufacturer's response to the ACD, the ERG would like to clarify that their estimates of the average number of RTX and CYC vials required based upon the Manchester Royal Infirmary data set did take account of the distribution of body surface areas. We calculated that on average one 500mg vial and 2.67 100mg vials of RTX would be required per dose, and one 1000mg vial and 0.87 500mg vials of CYC would be required per dose. We acknowledge that the manufacturer has not incorporated these estimates in their analyses, and that we have not included them in our amendments to the manufacturer's model. In the CYC-eligible base case analysis we estimate that incorporating these estimates would reduce the ICER by approximately £1,000 per QALY gained, and in the CYC ineligible base case by approximately £2,000 per QALY gained.

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