Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia:

Critique of cost-effectiveness of obinutuzumab from Roche given:

- Patient Access Scheme for obinutuzumab,
- Appraisal Committee / PenTAG base case,
- Roche alternatives to some utilities and costs

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Here, we comment on the results in the report submitted by Roche to NICE: “Obinutuzumab in combination with Chlorambucil for untreated chronic lymphocytic leukaemia; ACD Response” and “Appendix to ACD Response”, 23rd October 2014.

In this document, in addition to the PAS, Roche incorporate all the NICE Appraisal Committee preferred parameter values which were identified at the first committee meeting on 3rd September 2014.

We agree with Roche that the changes requested by the NICE Appraisal Committee were the following:

- Item 1 PenTAG base case: Utility whilst on obinutuzumab after first cycle of therapy.
- PenTAG sensitivity analysis: Utility PFS off treatment decreased from 0.82 to 0.71.
- Item 3 PenTAG base case: Mean dose of bendamustine and rituximab in bendamustine + rituximab arm.
- Item 4 PenTAG base case: PFS hazard ratio between obinutuzumab + chlorambucil and bendamustine + rituximab increased from 0.68 to 0.76.
- Item 5 PenTAG base case: PFS hazard ratio obinutuzumab Clb vs. Benda from 0.40 to 0.55.

We agree with Roche that it is appropriate to consider two patient sub-groups in this HTA:

- Patients suited to bendamustine: all comparators in this HTA are relevant.
- Patients unsuited to bendamustine: only chlorambucil and rituximab+chlorambucil are relevant comparators.

We note that Roche suggest that the NICE Committee consider issuing a restrictive positive recommendation supporting use of obinutuzumab+chlorambucil in patients unsuitable for bendamustine-based therapy.

1. Utility in PFS off treatment

Roche state that following release of the ACD, new evidence relevant to this appraisal has been made public which is likely to have a material impact on the Appraisal Committee’s

preferred assumptions. As part of the ongoing NICE appraisal of ofatumumab in combination with chlorambucil, EQ-5D data collected from patients directly relevant to the scope has been presented. Roche claim that this data suggests that a PFS utility value off treatment of 0.71, which is the NICE committee's preferred value, is likely to be an underestimate, and that as a result the cost-effectiveness values presented are likely to be conservative. Therefore, Roche use an alternative PFS utility value of 0.76 in a sensitivity analysis.

First, we understand that the EQ-5D data collected in the COMPLEMENT 1 RCT of ofatumumab+chlorambucil vs. chlorambucil is not publicly available at the time of writing. But it will be publicly available soon.

We find below that, under the PAS, and assuming the committee's preferred base case, the increase in the utility from 0.71 to 0.76 reduces the ICERs of obinutuzumab+chlorambucil vs. chlorambucil and vs. rituximab+chlorambucil by [redacted] per QALY. Therefore, this issue is of moderate importance.

We agree that the utility estimates recorded in the COMPLEMENT 1 RCT are very relevant to the current HTA given that the patients in the COMPLEMENT 1 trial are representative of the patients in the current HTA. The utility estimates should therefore be considered carefully. As far as we are aware, this constitutes the best source of utility data for first-line CLL in general, not just for the current decision problem.

We agree with Roche that the mean utilities in PFS measured by the EQ-5D in COMPLEMENT 1 were:

- 0.78 complete responders.
- 0.79 partial responders.
- 0.76 stable disease.

These values are to be compared to the following utilities:

- 0.71 Appraisal Committee's preferred value for PFS off treatment,
- 0.82 Roche's original base case for PFS off treatment,
- 0.76 for the UK general public at the appropriate age.

We note that in CLL11, 31% of patients responded on chlorambucil, 77% responded on obinutuzumab+chlorambucil and 66% responded on rituximab+chlorambucil. Taking a weighted average of the utilities from COMPLEMENT 1, this gives a utility in PFS of approx. 0.77 – 0.78 depending on the treatment.

On balance, we prefer the utility value of 0.71 for PFS off treatment for the following four reasons.

1. Roche are now seeking a recommendation for obinutuzumab+chlorambucil only for patients unsuited to bendamustine. Therefore, we are interested in the utility in PFS off treatment only for patients unsuited to bendamustine. However, COMPLEMENT 1 included both patients suited and unsuited to bendamustine. By definition, patients unsuited to bendamustine have a lower health-related quality of life than patients suited to bendamustine. As ERG in the ofatumumab STA, we agreed with GSK that the patients in COMPLEMENT 1 were representative of the UK general practice. GSK estimate that of patients unsuited to fludarabine, 56% are ineligible for bendamustine (p226 GSK submission). Therefore, we estimate that in COMPLEMENT 1, approx. 56% of patients were ineligible for bendamustine. It is therefore likely that the utilities in COMPLEMENT 1 for these patients would have been lower than for the patients suited to bendamustine.

2. For the purposes of the current HTA, we are interested only in the utilities in the chlorambucil arm of COMPLEMENT 1, as chlorambucil, but not ofatumumab+chlorambucil is being assessed in the current HTA. For complete and partial responders, there was a significantly greater increase in the utility compared to baseline in COMPLEMENT 1 in the ofatumumab+chlorambucil arm compared to the chlorambucil arm (p=0.03) (Appendix GSK submission). This means that the mean utility in the chlorambucil arm of COMPLEMENT 1 for responders was lower than 0.77-0.78. Of course, the COMPLEMENT 1 utilities data does not inform the utility in the obinutuzumab+chlorambucil arm.

3. As stated in our Assessment Report for the ofatumumab STA, we calculated that the mean time of completion of EQ-5D questionnaires in COMPLEMENT 1 in PFS was approximately 55% of the mean time in PFS (e.g. mean time of completion of EQ-5D for complete responders in ofatumumab + chlorambucil arm = 1.5 years, versus mean PFS complete responders in ofatumumab + chlorambucil arm = 2.7 years, ratio of 56%). This

means that the data from COMPLEMENT 1 is informing typically only the first half of the time in PFS.

By contrast, we are interested in the mean utility 6 months from the start of PFS (end of treatment) until the end of PFS. Therefore, the utility data from COMPLEMENT cited by Roche is only partially representative of the time period of interest.

4. We believe that more trust should be placed in the utility of 0.76 for the general population, estimated by Ara & Brazier (2010), than in the utilities from COMPLEMENT 1 cited by Roche. The utility value for the general population was estimated using the EQ-5D in a very large sample of several thousand people, using data from the annual Health Survey for England, which uses random samples of the population living in private households in England (Ara & Brazier 2010).

By contrast, the COMPLEMENT 1 study involved a smaller patient population, and may have been subject to biases such as non-random drop out of patients completing the EQ-5D, whereby the less healthy patients are less likely to complete the EQ-5D. For information, in COMPLEMENT 1, the EQ-5D was administered at baseline, at clinic visits every three months and at post-treatment follow-up visits for up 60 months. A total of 428 patients completed at least one outcome assessment, over a median of six treatment cycles

Given that we place more trust in the utility of 0.76 for the general population than in the utilities from COMPLEMENT 1 cited by Roche, we believe that it is logical that the utility appropriate for frail patients with multiple co-morbidities with CLL will be < 0.76.

Roche state that the general population of this age are likely to have multiple morbidities (simple by virtue of their age) and so it may be the case that (as suggested by the COMPLEMENT 1 data) the quality of life of comorbid patients with CLL may be comparable, or potentially slightly higher, than that of the general population. We do not believe that the health-related quality of life of patients in CLL11 may be slightly higher than people in the general population, because patients in CLL11 have CLL, with all the related physical symptoms that are well documented.

2. Cost of treating neutropenia

Roche state that during the course of ACD consultation period, they have identified a factual accuracy in their economic model. They say that they originally assumed that the cost of treating neutropenia was equal to the cost of treating febrile neutropenia, £3,894 (2012-13 DH HRG tariffs PA45Z). They now say that the cost of treating neutropenia should be £867, as estimated by LRiG in NICE ID620.

We agree that they did originally assume that the cost of treating neutropenia was equal to the cost of treating febrile neutropenia, £3,894.

We do not investigate this matter in detail for two reasons:

- We find below that, under the PAS, and assuming the committee's preferred base case, the decrease in the cost of treating neutropenia reduces the ICERs of obinutuzumab+chlorambucil vs. chlorambucil and vs. rituximab+chlorambucil by only about [redacted] per QALY. Therefore, this issue is of minor importance.

- At this late stage, we believe that the burden of proof should lie with Roche to demonstrate that the £867 is more appropriate than the £3,894. Their only justification for the value of £867 is that this was used by LRiG in NICE ID620. We believe that this evidence is inadequate to justify changing this parameter value. Roche ought to have investigated the source underlying the value used by LRiG.

We find that NICE ID620 concerns erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175). LRiG's estimate of the cost of treating neutropenia is discussed on p104 of their assessment report:

"*It is assumed that 10% of patients will require hospital treatment, each requiring two episodes during second-line treatment. The cost per episode is £866.61 and is estimated from the weighted average of mean costs for HRG codes WA02W (Disorders of immunity without HIV/AIDS with complicating condition) and PA48A (Blood cell disorders with complicating condition) across non-elective long and short-stay episodes and day-case admissions*."

We notice further that Roche do not mention that LRiG's estimate of the cost of treating febrile neutropenia, £7,067, is substantially greater than Roche's estimate of £3,894.

3. ICERs

3.1. ICERs without PAS

In Figures 1 and 2 of the Appendix to their response document, Roche provide ICERs assuming their original base case, without the PAS, according to variation in the utility in PFS off treatment and the cost of treating neutropenia.

Roche Figure 1. Roche original base-case ICERs given variation in utility in PFS off treatment

Utility Values	R-Benda	R-Clb	Benda	Clb
0.82	£19,898	£21,275	£26,463	£24,256
0.76	£23,167	£24,191	£29,965	£27,168
0.71	£26,843	£27,311	£33,680	£30,188

Roche Figure 2. Roche original base-case ICERs with neutropenia cost correction

Cost of Neutropenia	R-Benda	R-Clb	Benda	Clb
Incorrect	£19,898	£21,275	£26,463	£24,256
Correct	£18,652	£20,588	£25,169	£23,289

We agree with all these ICERs.

3.2. ICERs with PAS

3.2.1. Cost of treating neutropenia changed

In Table 2 of their response document, Roche present the ICERs under the PAS, given the amended cost of treating neutropenia and the Appraisal Committee preferred base case (see table below). They also present the ICERs under these conditions and assuming a utility of 0.76 in PFS off treatment (cf 0.71 Appraisal Committee value). Although the first column in Table 2 states that the population is "Patients suitable for bendamustine", the ICERs vs. chlorambucil and vs. rituximab+chlorambucil apply equally to the population unsuited to bendamustine.

Table 2 Roche response document

Population	Comparator	(1) ICER with Committee preferred ACD assumptions + Neutropenia cost	2) As per (1) with utility value based upon EQ-5D rather than ACD assumed value of 0.71
Patients suitable for bendamustine based therapy	Chlorambucil	[redacted]	[redacted]
	Rituximab + Chlorambucil	[redacted]	[redacted]
	Bendamustine	[redacted]	[redacted]
	Rituximab + Bendamustine	[redacted]	[redacted]

We agree with all these ICERs (to the nearest £thousand).

In the first case, Roche calculate the probability of obinutuzumab+chlorambucil being considered cost-effective **in patients unsuitable for treatment with bendamustine** as 74.4% at a willingness to pay of £30,000/QALY. This appears reasonable.

In the second case, they calculate the same probability as 87.9% at a willingness to pay of £30,000/QALY. This also appears reasonable. But we note that in neither case do they provide the corresponding value at a willingness to pay of £20,000/QALY.

Note that all other tables in Roche's response document are either the same as their Table 2 (Table 4), or a subset of Table 2 (Tables 1 and 3).

3.2.2. Cost of treating neutropenia unchanged

We have calculated the corresponding ICERs, excluding Roche's change in the cost of treating neutropenia.

Comparator	(1) ICER with Committee preferred ACD assumptions	(2) As per (1) with utility value based upon EQ-5D (0.76) rather than ACD assumed value of 0.71
Chlorambucil	[redacted]	[redacted]
Rituximab+chlorambucil	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]
Rituximab+bendamustine	[redacted]	[redacted]

Notice that the ICERs vs. chlorambucil and vs. rituximab+chlorambucil increase by only about [redacted] per QALY compared to the scenario of changing the cost of treating neutropenia. Therefore, Roche's proposed change to the cost of treating neutropenia has little impact on the ICERs.

Notice also from the table above that the increase in the utility from 0.71 to 0.76 reduces the same ICERs by [redacted] - [redacted] per QALY. Therefore, this change is of moderate importance.

Given that we prefer the utility of 0.71 for PFS off treatment and Roche's original cost of treating neutropenia, we believe that the most accurate ICERs are given in column (1) of the table above.

4. PenTAG factual inaccuracy

We agree with Roche when they say the following. Apologies for our error.

"*Roche sent a pro-forma response to the ERG report which included factual inaccuracies to which the ERG responded in 'Errata 22nd August' which listed the changes to be made to*

the original ERG report. There was one error highlighted by Roche that was wrongly amended in the 'Errata' publication and remains incorrect. On page 21 of the original ERG report the cost of rituximab plus bendamustine is shown as £12,000. It was pointed out that as rituximab + chlorambucil is listed as £10,000, chlorambucil as £300 and bendamustine as £7,000 the rituximab plus bendamustine figure therefore cannot be correct.

In the 'Errata' document on page 24 the cost of bendamustine has been changed to £16,000 and the cost of rituximab plus bendamustine remains as £12,000 which is incorrect. We believe that the figure for rituximab plus bendamustine should be £16,000 and the figure for bendamustine monotherapy should revert to £7,000."

To clarify then, the approximate cost of a course of:

- obinutuzumab + chlorambucil is £27,000 (no PAS),
- rituximab + chlorambucil is £10,000,
- bendamustine is £7,000,
- rituximab + bendamustine is £16,000,
- chlorambucil is £300.