**Single Technology Appraisal – ID764**
**Idelalisib for relapse or refractory chronic lymphocytic leukaemia**

**Clarification Questions - Gilead Responses** **19 March 2015**

**Section A: Clarification on effectiveness data**
**Literature Searches**

A1. **Priority Question.** Please clarify why the trial by Goede et al (2013) was not included as part of the evidence. This phase III trial of obinutuzumab plus chlorambucil or rituximab plus chlorambucil versus chlorambucil alone in patients with chronic lymphocytic leukaemia (CLL) does not appear to have been identified during the searching. In the absence of other evidence, the trial may provide useful data on some of the comparators which are listed in the final scope issued by NICE. Please refer to the following reference:

a. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10.

Obinutuzumab and idelalisib are licensed for different CLL populations and as such, obinutuzumab was not considered as part of the searches. Obinutuzumab was not used as a search term in the SLR for the untreated 17pDel/TP53 population, because at the time of performing the literature searches obinutuzumab was not licensed in the EMA. In addition, obinutuzumab in combination with chlorambucil (as per the NICE final scope for idelalisib December 2014) (and rituximab plus chlorambucil) were not considered to be relevant comparators as these are not routinely used in the NHS and not a part of standard of care for these first-line patients. Although obinutuzumab in combination with chlorambucil has obtained a positive final appraisal determination from NICE, the recommendation is specifically as an option for adults with previously untreated CLL who have comorbidities that make fludarabine-based therapy unsuitable (as per the licensed indication[1]), and also only where bendamustine is unsuitable and the company provides obinutuzumab with the discount agreed in the patient access scheme.[2] The recommendation does not mention high-risk patients or patients specifically with a 17p deletion/TP53 mutation so obinutuzumab with chlorambucil would not be considered an option in these patients. Furthermore, these treatments are chemo-immunotherapies and given that the licence for first-line use of idelalisib is for patients who are unsuitable for chemo-immunotherapy, obinutuzumab with chlorambucil is outside of the licensed indication for idelalisib. In addition, because they are chemo-immunotherapies, these treatments would have limited effectiveness for this untreated CLL population with 17p deletion and/or TP53 mutation. Indeed chemo-immunotherapies are not recommended as a treatment option in the BCSH guidelines for front-line patients with TP53 mutations as chemotherapy depends on functioning p53 for efficacy and efficacy. This was confirmed by data presented in the supplementary appendix to the Goede et al publication showing relatively poor hazard ratios for the antibody-containing regimens compared with chlorambucil alone in patients with 17p deletion,[3] and the lack of a benefit of the obinutuzumab over the rituximab combination is noted in the

obinutuzumab SmPC.[1] Chlorambucil alone is has little effectiveness in patients with TP53 mutations (the least effective of the three regimens used in the CLL4 study[4]). Therefore obinutuzumab with chlorambucil would not be an appropriate choice of therapy for front line patients with a 17p deletion or TP53 mutation CLL.

A2. **Priority Question.** In the company submission, the searches were undertaken on 13th January 2014 (RCTs in relapsed or refractory CLL patients), 12th February 2014 (non-RCTs in relapsed or refractory CLL patients) and 29th July 2014 (clinical studies in untreated CLL patients with 17p deletion or TP53 mutation). Please provide an update of all searches and screening. Please can you provide details of evidence which you may have excluded for the two comparator drugs - bendamustine and chlorambucil.

The systematic reviews to identify evidence for RCTs and non-RCTs in relapsed or refractory CLL patients were updated, and are presented below. The systematic review for untreated CLL patients with 17p deletion and/or TP53 mutation were performed on 29th July 2014, which is just about 6 months of the date of submission (10th February 2015). Given the time constraints for answering the ERG questions and clinical advice that no further relevant studies have been conducted since the original review, these searches were not updated. We trust this is acceptable however, if this causes major concerns, we would be able to conduct the updated SLR subsequently – please let us know.

The systematic reviews on relapsed or refractory CLL were updated using the same methods as for the main submission, and updated searches were performed on 7th January 2015. Search terms for CHOP and CVP were added to the search strategies, on the advice of global clinical experts. However, since these treatments were not relevant to this submission, any studies that were identified for these treatments were excluded.

**Systematic Review Update of RCT Evidence in Relapsed or Refractory CLL**

The systematic review of RCT evidence identified an additional 2 trials, which are summarised in Table 1 and Table 2, below. An additional secondary reference for Study 116 was also identified, however as this study has already been fully reported in the submission, no data was taken from this source.

**Table 1: Additional References Identified in SLR of RCTs**

| Primary Publication | Secondary Publication | Treatment Comparison | Relevant to Submission |
|---|---|---|---|
| Study 116 CSR[a 5] | Stilgenbauer EHA 2014[b 6] | IR vs R | Yes [No additional data to extract] |
| Byrd 2014[7] | Hillmen EHA 2014;[8] Brown ASH 2014[9] | Ibrutinib vs Ofatumumab | Yes |
| Awan 2014[10] | NA | FCR vs FCR + lumiliximab | Yes |
| **Notes:** [a] Note that this source was retrieved in the original searches; [b] An additional secondary reference for Study 116. There were no additional data reported that had not already been captured in the primary publication. | | | |

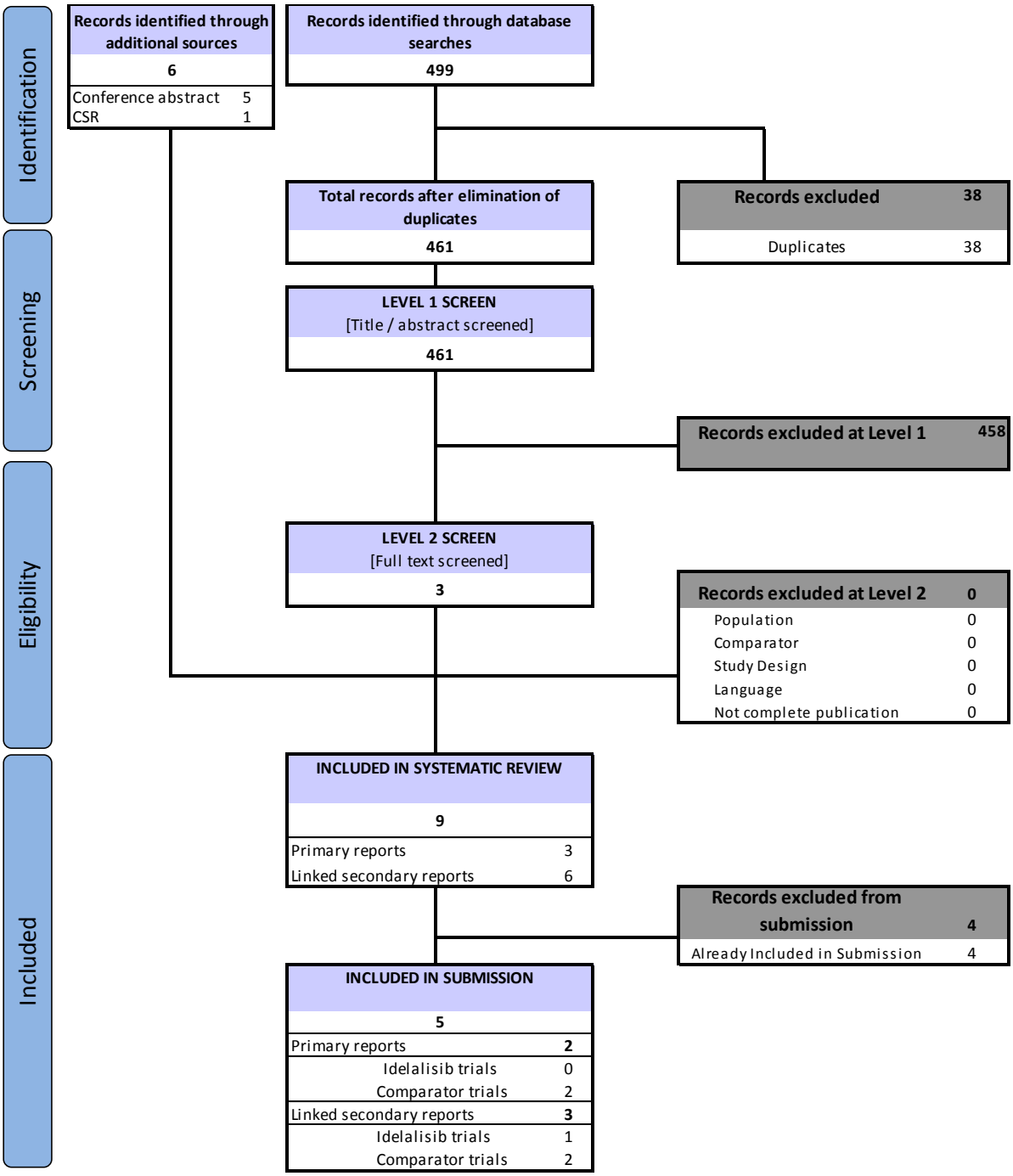
**Table 2: List of relevant RCTs**

| Trial no. (acronym) | Indication | Intervention | Comparator | Population |
|---|---|---|---|---|
| Byrd 2014[7] | Relapsed or refractory CLL or SLL | Ibrutinib 420mg/day | Ofatumumab 300mg week 1 followed by 2000mg/week for 7 weeks and then every 4 weeks for 16 weeks | Patients with CLL or SLL requiring therapy having received at least one previous therapy and were inappropriate candidates for purine analogue treatment because of a short progression-free interval after chemo-immunotherapy or because of co-existing illnesses; an age of 70 years or more or a chromosome 17p13.1 deletion; ECOG performance status of <2; an absolute neutrophil count of ≥750 cells/ml; platelet count of ≥30,000 cells/ml; and adequate liver and kidney function. |
| Awan 2014[10] | Relapsed CLL patients | FCR: F 25mg/m$^2$ IV for days 2-4 of cycle 1 and days 2-6 for cycles 2-6; C 250mg/m$^2$ IV for days 2-4 of cycle 1 and days 1-3 for cycles 2-6; R 50mg/m$^2$ IV on day 1 of cycle 1, 450mg/m$^2$ on day 3 of cycle 1, 500mg/m$^2$ on day 1 of cycles 2-6 | FCR + L: FCR using the same schedule as the other arm + L 50mg/m$^2$ IV on day 2 of cycle 1 and 450mg/m$^2$ on day 4 of cycle 1, then 500mg/m$^2$ on day 1 of cycles 2-6 | Patients with previously treated CD23+ and CD20+ relapsed CLL [11] had received 1-2 prior, single agent or combination treatments for CLL; were of Rai Stage III or IV (Binet Stage C) or Rai Stage I or II (Binet Stage A or B) if determined to have disease progression as evidenced by rapid doubling of peripheral lymphocyte count; progressive lymphadenopathy progressive splenomegaly, or B symptoms. |

**Key**: C, cyclophosphamide; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; F, fludarabine; NR, not reported; R, rituximab; SLL, small lymphocytic leukaemia.

The PRISMA diagram for the updated systematic review of RCT evidence in relapsed or refractory CLL is presented in Figure 1.

**Figure 1: PRISMA Diagram for Update to SLR of RCT evidence**




**Source:** Adapted from Moher et al., 2009.

Table 3 and

Table 4 present the methodology and the inclusion/exclusion criteria for the 2 additional RCTs that were identified by the systematic review update.

**Table 3: Methods of Included RCTs**

| Study ID | Phase | Location | Blinding | Total study duration | Median follow-up (months) | Diagnostic criteria |
|---|---|---|---|---|---|---|
| Byrd 2014[7] | 3 | US, Australia and 7 European countries | Open-label | NR | 9.4 | IWCLL (2008) |
| Awan 2014[10] | 2/3 | International | Open-label | 6 months (6 28-day cycles) | NR | NCI-WG (1996) |

**Table 4: Inclusion/exclusion criteria of included comparator trials**

| Study ID | Main inclusion criteria | Main exclusion criteria |
|---|---|---|
| Byrd 2014[7] | Patients with CLL or SLL requiring therapy were eligible for enrolment if they had received at least one previous therapy and were considered to be inappropriate candidates for purine analogue treatment because: they failed to respond (stable disease or disease progression on treatment), or they had a progression-free interval of <3 years from treatment with a purine analogue-based therapy and anti-CD20 containing chemo-immunotherapy regimen after ≥2 cycles, or because they had co-existing illnesses, an age of 70 years or more or a chromosome 17p13.1 deletion. Patients were required to have an ECOG performance status of <2, an absolute neutrophil count of ≥750 cells/ml, a platelet count of ≥30,000 cells/ml, and adequate liver and kidney function. | Patients requiring warfarin or strong CYP3A4/5 inhibitors were excluded. |
| Awan 2014[10] | Patients with previously treated CD23+ and CD20+ relapsed CLL, as defined by the National Cancer Institute (NCI) 1996 working group criteria [11] were enrolled in the trial. Additional inclusion criteria included patients who had received 1-2 prior, single agent or combination treatments for CLL; were at Rai Stage III or IV (Binet Stage C), or Rai Stage I or II (Binet Stage A or B) if determined to have disease progression as evidenced by rapid doubling of peripheral lymphocyte count, progressive lymphadenopathy, progressive splenomegaly, or B symptoms. Patients had an ECOG performance status ≤2 | NR |
| **Key:** CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; NCI | | |

Table 5 presents the baseline characteristics of the RCTs identified in the systematic review update for relapsed or refractory CLL and Table 6 presents the results.

The patient population in the Awan (2014) study is not comparable to that of Study 116; as patients were generally younger, had received fewer previous therapies, were in less severe disease stages and contained fewer patients with unmutated IgVH or 17p deletion.[10] However, despite these differences in favour of FCR +/- lumiliximab, the results from Study 116 were broadly similar, showing similar PFS, OS and ORR results for idelalisib with rituximab compared to FCR (and FCR + lumiliximab).

Although not all the characteristics are available and comparable, patients in Study 116 were older, included more patients with unmutated IgVH and more patients with TP53 abnormalities compared to the patients in Byrd 2014.[7] (i.e. these differences would likely bias any comparisons between the two studies in favour of Ibrutinib/ofatumumab). Furthermore, entry criteria for Study 116 included patients that had severe neutropenia or thrombocytopenia, patients with an early relapse and a high number of comorbidities (median cumulative illness rating scale of 8), which would be considered as a more difficult-to-treat patient population. The study designs were also different in how assessment of progression was monitored; Study 116 included CT scans every 2 months whereas the study by Byrd 2014, CT scans were conducted every 3 months allowing more time points to capture progression in Study 116 (again, such differences would favour ibrutinib/ofatumumab over Study 116). These differences in the patient population are also a likely explanation for the difference in the median PFS observed with ofatumumab between the Wierda 2010[30] and Byrd 2014 trials (5.8 versus 8.1 months for the ofatumumab arm). It should also be noted that the final analysis for the Wierda ofatumumab trial[30] reported a decrease in the median PFS (from the interim analysis of 5.8 months) to 4.6 months in the double refractory population, as reported in the summary of product characteristics for ofatumumab;[12], the median PFS reported with ofatumumab in Byrd 2014 is almost double that reported in the Wierda trial[30]. Although the populations between trials cannot be directly compared, the population of Study 116 was a more challenging population and expected to be more closely aligned to the patient population of the Wierda trial than that of Byrd 2014. Despite all these considerations, substantial improvements for patients treated with idelalisib with rituximab in Study 116 were reported when compared to the ofatumumab arm of Byrd [7].

**Table 5: Baseline characteristics of participants in the relevant RCTs**

| **Study** | **Study 116[5]** | | **Byrd 2014[7]** | | **Awan 2014[10]** | |
|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **Ib** | **O** | **FCR** | **FCR + L** |
| Patients (N) | 110 | 110 | 195 | 196 | 311 | 316 |
| ITT population | 110 | 110 | 195 | 196 | 311 | 316 |
| Age (years), mean (SD) | 71 (7.7) | 70 (8.1) | 66 (10) | 67 (9) | 61.11 | 61.2 |
| Age (years), median (range) | 71 (48-90) | 71 (47-92) | 67 (30-86) | 67 (37-88) | 61 (34-82) | 61 (34-82) |
| Gender, female, % | 30.9 | 38.2 | 34 | 30 | 30 | 31 |
| Prior therapies, median (range) | 3 (1-12) | 3 (1-9) | 3 (1-12) | 2 (1-13) | [a] | [a] |
| Binet Stage, % | | | | | NR | NR |
| A | 6.4 | 3.6 | 18 | 18 | | |
| B | 26.4 | 29.1 | 29 | 29 | | |
| C | 57.3 | 55.5 | 52 | 53 | | |
| Rai Stage, % | | | | | | |
| 0 | 0 | 0.9 | 3 | 1 | 0 | 0 |
| I/II | 30.9 | 27.3 | 41 | 41 | 65 | 63 |
| III/IV | 63.6 | 64.6 | 56 | 58 | 35 | 37 |
| Unmutated IgVH, % | 82.7 | 84.5 | 52 | 50 | 50 | 52 |
| 17p deletion and TP53 mutation % | 41.8 | 44.5 | 32[b] | 33[b] | 8 | 9 |

**Key:** C, cyclophosphamide; CLL, chronic lymphocytic leukaemia; F, fludarabine; I, idelalisib; Ib, Ibrutinib; ITT, intent to treat; L, lumiliximab; NR, not reported; O, ofatumumab; RCT, randomised controlled trial; R, rituximab; SD, standard deviation;
**Notes:** [a] Median number of prior therapies are not reported. Number of prior therapies: FCR arm: 1 = 62%, 2 = 34%, 3 = 2%, 4 <1%, 5 <1%, 6 <1%; FCR + L arm: 1 = 60%, 2 = 36%, 3 = 2%, 4 <1%, 5 <1%, 6 <1%. [b] only 17p deletion reported

**Table 6: Results of the relevant RCTs**

| **Study** | **Study 116[5]** | | **Byrd 2014[7]** | | **Awan 2014[10]** | |
|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **Ib (n=195)** | **O (n=196)** | **FCR (n=183)** | **FCR + L (n=207)** |
| **PFS** | | | | | | |
| PFS definition | From randomisation to first documentation of definitive PD (based on standard criteria) or death from any cause | | Criteria of the International Workshop on Chronic Lymphocytic Leukemia | | NR | |
| PFS assessed by | IRC | | IRC [IA][a] | | NR | |
| Median, months (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) | Not reached [not reached][a] | 8.1 [8.1][a] | 23.9 (18.6, 27.3) | 24.6 (23.6, 30.8) |
| Hazard ratio (95% CI) | 0.15 (0.09, 0.24) | | 0.22 (0.15, 0.32) [0.106 (0.073, 0.153)][a] | | NR | |
| 12-month PFS, % | 70.4 | 9.2 | 63.4 | 5.5 | 80.4 | 83.5 |
| 24-month PFS, % | NR[b] | NR[b] | NR | NR | 49.7 | 53.8 |
| **OS** | | | | | | |
| Median, months (95% CI) | Not reached [Not reached][c] | 20.8 (14.8, not reached) [redacted])][c] | Not reached | Not reached | Not reached | Not reached |
| Hazard ratio (95% CI) | 0.34 (0.19,0.60) [0.20 (0.10, 0.35)][c] | | 0.43 (0.24, 0.79) | | NR | |
| 12-month OS, % | 89.3 [89.3][c] | 66.8 [49.2][c] | 90 | 79 | 89.3 | 93.7 |
| 24-month OS, % | 71.0 [71.0][c] | 41.7 [NR[b]][c] | NR | NR | 79.5 | 85.9 |
| **Response** | | | | | | |
| Response criteria | IWCLL 2008[13] | | IWCLL 2008[13] | | NCI-WG 1996 | |
| Response assessed by | IRC | | IRC [IA][d] | | NR | |
| ORR, % | 83.6 | 15.5 | 63 [83][d] | 4 [24][d] | 72 | 71 |
| CR, % | 0 | 0 | 0 [2][d] | 0 [1][d] | NR | NR |

| Study | Study 116[5] | | Byrd 2014[7] | | Awan 2014[10] | |
|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **Ib (n=195)** | **O (n=196)** | **FCR (n=183)** | **FCR + L (n=207)** |
| PR, % | 83.6 | 15.5 | 43 [68][d] | 4 [21][d] | NR | NR |
| PR+L, % | NR | NR | 20 [15][d] | 9 [2] [d] | NR | NR |
| SD, % | 11.8 | 64.5 | 32 [11][d] | 78 [54][d] | NR | NR |
| PD, % | 0.9 | 14.5 | 3 [1][d] | 10 [14][d] | NR | NR |
| NE, % | 3.6 | 5.5 | NR | NR | NR | NR |
| Duration of response, months, median (95% CI) | 10.4 (7.1, not reached) | 6.4 (4.5, 7.4) | NR | NR | 27 (21.6, 27.8) | 24.5 (20.4, not reached) |

**Key:** C, cyclophosphamide; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CR, complete response; F, fludarabine; I, idelalisib; IA, investigator assessed; Ib, ibrutinib; IRC, independent review committee; ITT, intent to treat; L, lumiliximab; NE, not evaluable; NR, not reported; O, ofatumumab; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR+L, partial response with lymphocytosis; R, rituximab; RCT, randomised controlled trial; SD, stable disease.

**Notes:**

[a] PFS outcomes are primarily presented as assessed by an independent review committee (IRC) where this was available. Values in square brackets represent PFS assessed by investigators.

[b] The maximum observation time is <24 months.

[c] OS outcomes in square brackets are the crossover adjusted RPSFTM results from Study 116.

[d] Response outcomes are primarily presented as assessed by an IRC where this was available. Values in square brackets represent response assessed by investigators.

Table 7 presents the quality assessments for the 2 RCTs identified in the systematic review update. In general, Byrd (2014) had a low risk of bias and the risk of bias in Awan (2014) was unclear, because of the level of detail that was reported. However, there was a high risk of bias for their reporting of response, as they did not assess the outcome using an independent review committee.

**Table 7: Quality assessment results for RCTs**

| **Trial no. (acronym)** | **Byrd 2014[7]** | **Awan 2014[10]** |
|---|---|---|
| Was randomisation carried out appropriately? | Unclear risk of bias<br>Method of generating the sequence or randomisation not reported in the publication or the protocol | Unclear risk of bias<br>Method of generating the sequence or randomisation not reported |
| Was the concealment of treatment allocation adequate? | Unclear risk of bias<br>Method of allocation concealment not reported | Unclear risk of bias<br>Method of allocation concealment not reported |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Low risk of bias<br>Study groups are similar at baseline | Low risk of bias<br>Study groups are similar at baseline |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Low risk of bias for PFS and response<br>Open-label but an IRC, whose members were unaware of study-group assignment, assessed progression and response | High risk of bias for response<br>Second interim analysis was based on investigator assessed CR rates without the use of CT scans by an IRC |
| Were there any unexpected imbalances in drop-outs between groups? | Unclear risk of bias<br>Patients lost to follow-up are not reported | Low risk of bias<br>No unexpected imbalances in dropouts between groups |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | Low risk of bias<br>All pre-specified outcomes were reported | Low risk of bias<br>All pre-specified outcomes were reported |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Low risk of bias<br>ITT analysis of all randomised patients | Unclear risk of bias<br>Only those who had passed the week 33 visit or had withdrawn from the study, whichever came first were included in the primary efficacy analysis |
| **Key:** CLL, chronic lymphocytic leukaemia; CR, complete response; CT, computed tomography; ITT, intent-to-treat; IRC, independent review committee; PFS, progression-free survival. | | |

**Systematic Review Update of non-RCT Evidence in Relapsed or Refractory CLL**

The systematic review of non-RCT evidence identified an additional 4 trials, which are summarised in Table 8 and Table 9, below.

**Table 8: Additional References Identified in SLR of non-RCTs**

| Primary Publication | Secondary Publication | Treatment Comparison |
|---|---|---|
| Donnellan ASH 2014[14] | NA | Ofatumumab |
| Sanhes EHA 2014[a 15] | NA | Rituximab + bendamustine or an alkylating agent (including chlorambucil) or a purine based regimen (including FCR) |
| Zagoskina EHA 2014 [16] | NA | Rituximab + bendamustine |
| Smolej ASH 2014[b 17] | [a] | FCR |
| **Notes:** [a] Limited data is presented from this study for the treatment combinations of interest, and baseline data is only presented for the combined population, therefore this study is of limited use. [b] Smolej EHA 2013 was previously the primary publication for this study. Updated evidence from Smolej ASH 2014 is presented here and Smolej EHA 2013 will now be the secondary reference. | | |

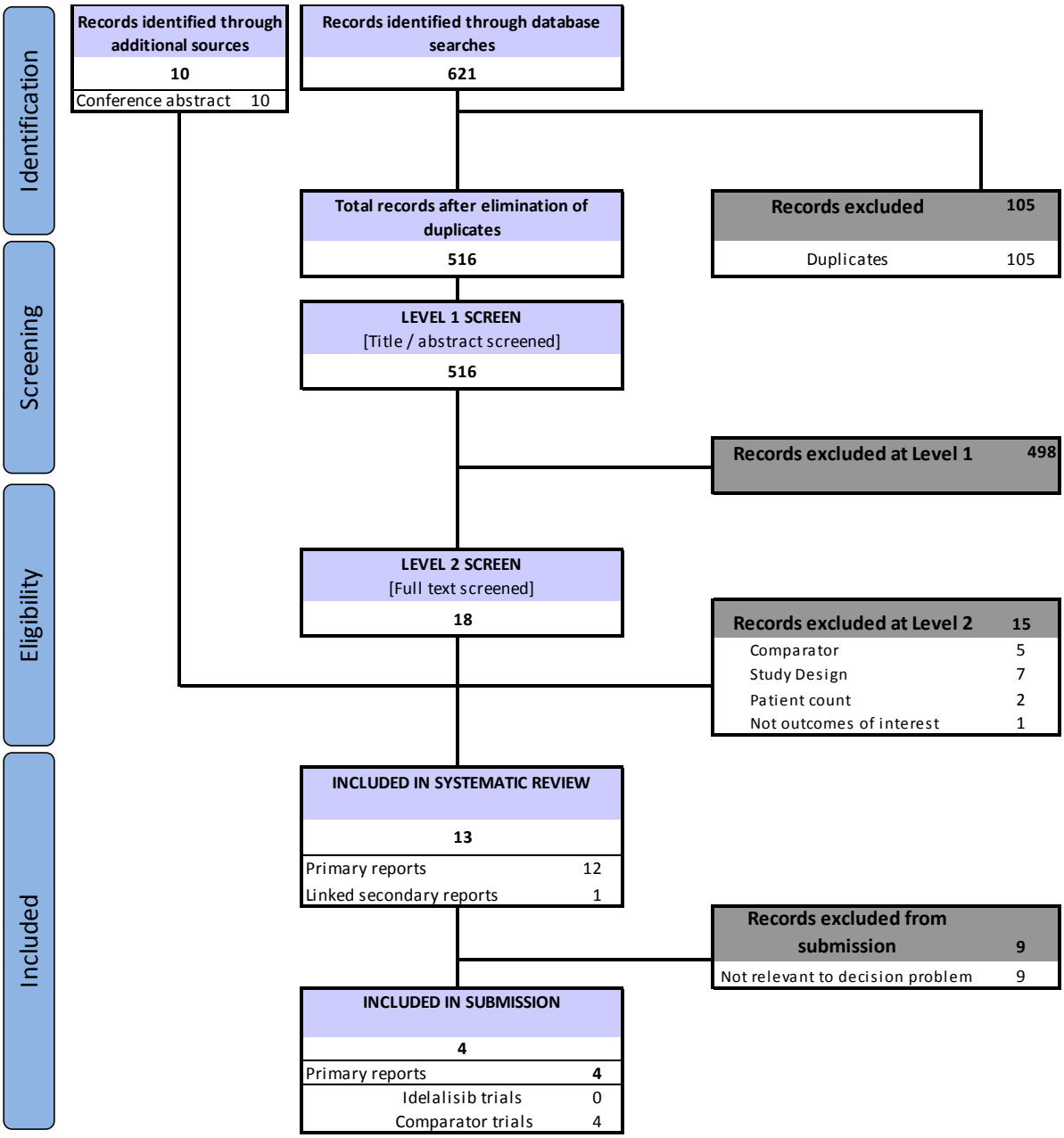
**Table 9: List of relevant non-RCTs**

| Trial no. (acronym) | Indication | Intervention | Population |
|---|---|---|---|
| Donnellan ASH 2014[14] | Relapsed CLL | O 300mg/500ml (0.6mg/mL) (dose1 – week 1, day 1), 1000mg/500mL (2mg/mL) (dose 2 – week 1, day 3), 2000mg/500mL (4mg/mL) (dose 3) | Patients with relapsed CD20+CLL, ≥1 prior therapy, no antibody therapy in the prior 3 months, ECOG PS ≤1, negative hepatitis B serology and adequate organ function. Previous treatment with ofatumumab was allowed if the patient had maintained a progressive response or better for ≥ 6 months |
| Sanhes EHA 2014[15] | Relapsed or refractory CLL | BR<br>R + alkylating agents (e.g. chlorambucil)<br>R + purine-based regimen (e.g. FCR) | Patients with relapsed or refractory CLL |
| Zagoskina EHA 2014[16] | Relapsed and refractory CLL | BR: B 90mg/m$^2$ on days 1-2; R 375mg/m$^2$ on day 1 | Relapsed and refractory CLL |
| Smolej ASH 2014[17] | First-line or previously treated patients[a] | FCR: F 12mg/m$^2$ IV or 20mg/m$^2$ orally on days 1-3; C 150mg/m$^2$ PO on days 1-3; R 375mg/m$^2$ in cycle 1 and 500mg/m$^2$ onwards on day 1 | Elderly comorbid patients, with active disease (CLL or SLL), first line or previously treated[a] |

**Notes:** [a]Results were only extracted for previously treated patients.
**Key:** ASH, American Society of Haematology, B, bendamustine; C, chlorambucil; CLL, chronic lymphocytic leukaemia; EHA, European Haematology Association, IV, intravenous; NR, not reported; SLL, small lymphocytic lymphoma ; O, ofatumumab; PO, oral; R, rituximab.

Figure 2 presents the PRISMA diagram for the systematic review update of non-RCT evidence in relapsed or refractory CLL.

**Figure 2: PRISMA Diagram for Update to SLR of non-RCT evidence**




**Source:** Adapted from Moher et al., 2009.

Table 10 and

Table 11 present the methodology and the inclusion/exclusion criteria for the 5 additional non-RCTs that were identified by the systematic review update.

**Table 10: Methods of Included non-RCTs**

| Study ID | Phase | Location | Blinding/ Study Type | Total study duration | Median follow-up (months) | Diagnostic criteria |
|---|---|---|---|---|---|---|
| Donnellan ASH 2014[14] | 2 | NR | Single-arm study | 6 months | NR | NR |
| Sanhes EHA 2014[15] | NR | France | Prospective, non-interventional study | 2 years | NR | NR |
| Zagoskina EHA 2014[16] | NR | Russia | Single-arm study | 6 months (6 28-day cycles) | 27 | IWCLL |
| Smolej ASH 2014[17] | NR | Czech Republic | Single-arm study | NR | 25 | NR |
| **Key:** ASH, American Society of Haematology; CLL, chronic lymphocytic leukaemia; EHA, European Haematology Association; IWCLL, International Working Group on CLL; NR, not reported. | | | | | | |

**Table 11: Inclusion/exclusion criteria of relevant non-RCTs**

| Study ID | Main inclusion criteria | Main exclusion criteria |
|---|---|---|
| Donnellan ASH 2014[14] | Patients with relapsed CD20+CLL, ≥1 prior therapy, no antibody therapy in the prior 3 months, ECOG PS ≤1, negative hepatitis B serology and adequate organ function. Previous treatment with ofatumumab was allowed if the patient had maintained a progressive response or better for ≥ 6 months | NR |
| Sanhes EHA 2014[15] | Patients with relapsed or refractory CLL | NR |
| Zagoskina EHA 2014[16] | Relapsed and refractory CLL | NR |
| Smolej ASH 2014 [17] | Elderly comorbid patients, with active disease (CLL or SLL), first line or previously treated[a] | NR |
| **Notes:** a. Results were only extracted for previously treated patients.<br>**Key:** ASH, American Society of Haematology; CLL, chronic lymphocytic leukaemia; EHA, European Haematology Association; NR, not reported; PR, partial response; SLL, small lymphocytic lymphoma | | |

Taking into consideration the available patient characteristics across all studies with many important ones missing (e.g. disease stage, IgVH status), the patient population in Study 116 was more heavily pretreated and had a worse prognostic outlook in terms of disease stage and genetic status (17p/TP53 and IgVH). Furthermore, It is not possible to make any

meaningful comparisons between idelalisib with rituximab (Study 116; Furman, 2013), [5, 18] and bendamustine with rituximab (Zagoskina, 2014)[16] from the identified studies in terms of PFS and OS; as these outcomes were not consistently reported, and the patient populations were not similar i.e., patients in the study of bendamustine with rituximab (Zagoskina, 2014) [16] were much younger than those in Study 116 (56 vs. 71 years), and had fewer prior therapies (2 vs. 3).

Despite the patient population differences, idelalisib with rituximab showed greater improvements in response rates (Study 116; Furman, 2013) when compared with ofatumumab, BR and FCR (Donnellan 2014, Zagoskina 2014 and Smolej 2014), [14, 16, 17] and improvements in PFS when compared with FCR (Smolej, 2014). [17]

Overall we believe that the updates to the systematic review did not provide a stronger evidence base than that which was originally presented in the submission.

**Table 12: Baseline characteristics of the relevant non-RCTs**

| | Study 116[5] | | Furman (2013)[18] | Donnellan ASH 2014[14] | Sanhes EHA 2014[a 15] | Zagoskina EHA 2014[16] | Smolej ASH 2014[17] |
|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **BR/ChlR/ FCR** | **BR** | **FCR** |
| Patients (N) | 110 | 110 | 40 | 23 | 200 | 36 | 94 |
| ITT population | 110 | 110 | | 23 | 192 | 36 | 94 |
| Age (years), mean | 71 (7.7) | 70 (8.1) | NR | NR | NR | NR | NR |
| Age (years), median (range) | 71 (48-90) | 71 (47-92) | 66 (43-87) | 69 | 72 (35-89) | 56 (35-72) | 71 (58-87) |
| Gender, female, % | 30.9 | 38.2 | 30 | 52 | 29 | NR | 39 |
| Prior therapies, median (range) | 3 (1-12) | 3 (1-9) | 2 (1-9) | NR | NR | 2 (1-4) | NR |
| Rai Stage, % | | | | | NR | NR | |
| 0 | 0 | 0.9 | | 12 | | | |
| I-II | 30.9 | 27.3 | | 40 | | | |
| III-IV | 63.6 | 64.6 | 50 | 44 | | | 64[b] |
| Binet Stage, % | | | NR | NR | NR | | NR |
| A | 6.4 | 3.6 | | | | 0 | |
| B | 26.4 | 29.1 | | | | 47 | |
| C | 57.3 | 55.5 | | | | 53 | |
| Cll genetics, % | | | | | | | |
| Unmutated IgVH, % | 82.7 | 84.5 | 75 | 60[c] | NR | NR | 73 |
| 17p deletion and/or TP53 mutation, % | 41.8 | 44.5 | 28 | 28[d] | 13[d] | 22[d] | 8[d] |

**Key**: B, bendamustine; BF-ref, fludarabine refractory with bulky (>5 cm) lymphadenopathy; C, cyclophosphamide; Chl, chlorambucil; CI. confidence interval; CLL, chronic lymphocytic leukaemia; F, fludarabine; FA-ref, fludarabine and alemtuzumab refractory; I, idelalisib; IgVH, immunoglobulin heavy chain; ITT, intention to treat; Mp, methlyprednisone; NE, not evaluable; NR, not reported; O, ofatumumab; R, rituximab.

**Notes**: [a] Sanhes (2014) only presented baseline data for the combined population, regardless of treatment assignment; [b] Reported as patients in "advanced Rai stages". [c] Calculated (40% were IgVH mutated); [d] only 17p deletion reported

**Table 13: Results of the relevant non-RCTs**

| **Study** | **Study 116[5]** | | **Furman (2013) [18]** | **Donnellan ASH 2014[14]** | **Sanhes EHA 2014[15]** | | | **Zagoskina EHA 2014[16]** | **Smolej ASH 2014[17]** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **BR** | **ChIR** | **FCR** | **BR** | **FCR** |
| **PFS** | | | | | | | | | |
| PFS definition | Randomisation to first documentation of definitive PD or death from any cause | | NR | NR | NR | NR | NR | NR | NR |
| Assessed by | IRC | | NR | NR | NR | NR | NR | NR | NR |
| Median, months (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) | 20 | NR | NR | NR | NR | 19 | 15 |
| 12-month PFS, % | 70.4 | 9.2 | NR | NR | NR | NR | NR | NR | NR |
| 24-month PFS, % | NR[a] | NR[a] | NR | NR | NR | NR | NR | NR | NR |
| **OS[b, c]** | | | | | | | | | |
| Median, months (95% CI) | Not reached [Not reached] | 20.8 (14.8, not reached) [[redacted] | Not reached | NR | NR | NR | NR | Not reached | 30 |
| 12-month OS, % | 89.3 [89.3] | 66.8 [[redacted] | NR | NR | NR | NR | NR | NR | NR |
| 24-month OS, % | 71.0 [71.0] | 41.7 [NR[e]] | NR | NR | NR | NR | NR | NR | NR |
| **Response[d]** | | | | | | | | | |
| Response criteria | IWCLL 2008 | | IWCLL (2008) | NR | NR | NR | NR | IWCLL | NR |
| Assessed by | IRC | | NR | NR | NR | NR | NR | NR | NR |
| ORR, % | 83.6 | 15.5 | 83 | 29 | 75[e] | 69[e] | 90[e] | 64 | 63 |

| Study | Study 116[5] | | Furman (2013) [18] | Donnellan ASH 2014[14] | Sanhes EHA 2014[15] | | | Zagoskina EHA 2014[16] | Smolej ASH 2014[17] |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **BR** | **ChlR** | **FCR** | **BR** | **FCR** |
| CR, % | 0 | 0 | 8 | NR | NR | NR | NR | 17 | 30 |
| PR, % | 83.6 | 15.5 | NR | NR | NR | NR | NR | 47 | NR |
| SD, % | 11.8 | 64.5 | NR | NR | 11 | | | NR | 19 |
| PD, % | 0.9 | 14.5 | NR | NR | 14 | | | NR | 9 |
| NE, % | 3.6 | 5.5 | NR | NR | NR | NR | NR | NR | 10 |
| Duration of response, months, median (95% CI) | 10.4 (7.1, not reached) | 6.4 (4.5, 7.4) | 19 | NR | NR | NR | NR | NR | NR |

**Key**: B, bendamustine; BF-ref, fludarabine refractory with bulky (>5 cm) lymphadenopathy; C, cyclophosphamide; Chl, chlorambucil; CI, confidence interval; CR, complete response; F, fludarabine; FA-ref, fludarabine and alemtuzumab refractory; IA, investigator assessed; IRC, independent review committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; Mp, methylprednisone; NCIWG, ; NE, not evaluable; NR, not reported; O, ofatumumab; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, rituximab; RCT, randomised controlled trial; SD, stable disease

Notes: [a] The maximum observation time is <24 months /

[b] Dupuis (2014) used a modified ITT analysis (n=26) to assess PFS and OS.

[c] OS outcomes presented in square brackets for Study 116 are the crossover adjusted RPSFTM results.

[d] Dupuis (2014) used both an ITT (n=30) and a modified ITT analysis (n=26) to assess response outcomes. The modified ITT results are presented in square brackets.

[e] Sanhes (2014) only presented ORR rates separately by treatments; BR, n = 101; ChlR, N = 13; FCR, n = 29. SD and PD were presented for the overall population, n = 192.

A3. **Priority Question.** It is noted that for "Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for which chemo-immunotherapy is not suitable" the search included treated CLL patients. Please provide updates of the searches to ensure that relevant evidence post 12th February 2014 concerning untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation is included.

The searches for untreated CLL patients with 17p deletion and/or TP53 mutation did not include studies of previously treated CLL patients. Although the initial searches would have identified both treated and untreated patients, articles regarding treated patients were excluded during the screening stage.

The systematic review for untreated CLL patients with 17p deletion and/or TP53 mutation were performed on 29th July 2014, which is just about 6 months from the date of submission (10th February 2015). Given the time constraints for answering the ERG questions and clinical advice that no further relevant studies have been conducted since the original review, these searches were not updated. The searches included only treatments that were deemed relevant to the submission; as such, bendamustine, chlorambucil and obinutuzumab plus chlorambucil, were excluded from the submission (despite being included in the NICE final scope) because these are chemo-immunotherapies, which are outside of the licence for first-line use of idelalisib. Further detail on this is presented in the responses to question A1 and question A7.

A4. Please provide a copy of the following report: Gilead Sciences. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS 1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia. (GS-US-312-0116). 25 November 2014.

The CSR is being sent with these responses as commercial in confidence. Please treat all information within the CSR which is not presented within either these responses or the submission document as commercial in confidence.

A5. Page 56. Please provide an update of abstracts from the other relevant conferences not already included in the submission. These should include:

a) American Society of Hematology (2010, 2011, 2014)
b) American Society of Clinical Oncology (for last 5 years)
c) European Hematology Association (2010, 2011, 2014)
d) European Society of Medical Oncology (for last 5 years)
e) International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) (2011 and 2013 [biennial meeting])
f) The International Conference on Malignant Lymphoma (ICML) (2011 & 2013 [biennial meeting]) http://www.lymphcon.ch/imcl/index.php

The updated conference abstract searches for the 2014 ASH and 2014 EHA conferences are presented in response to question A2. For the other conferences listed and pre-2012 for ASH, ASCO and EHA the searches were conducted and the outcomes are presented in appendix 1. iwCLL 2013 conference proceedings were also searched and presented in appendix 1 (i.e. iwCLL 2011 was not available).

## Clinical effectiveness data

A6. **Priority Question.** Page 12, Table 1. Please provide further rational for selecting rituximab as the main comparator for people with relapsed or refractory CLL. Rituximab monotherapy is not recommended for this population in the UK and was not included in the final scope issued by NICE.

In addition to the comparators listed in the scope, monotherapy with the anti-CD20, rituximab is also used in clinical practice in England to a limited extent.[19] In particular, rituximab monotherapy is used for the management of complications such as auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura.[20] However, clinical advisors suggested that it is more likely to be used in combination with other agents than on its own, and in district general hospitals rather than large trial/teaching hospitals and assumed that rituximab monotherapy comprises <10% of all rituximab regimen use across England.[20]

For the phase III trial in relapsed CLL patients (Study 116), on which the idelalisib licence and the subsequent NICE submission is based, rituximab monotherapy was chosen as the comparator for idelalisib with rituximab, based on the NCCN guidelines, which included dose-dense rituximab monotherapy as a treatment option for frail patients with relapsed CLL.[21] In addition, the ESMO guidelines also recommend the use of rituximab or ofatumumab with high-dose steroids as one option for patients if relapse occurs within 12–24 months after monotherapy or 24–36 months after chemo-immunotherapy.[22] Rituximab monotherapy is also a potential treatment option recommended in the recent German CLL guidelines for patients with poor performance status.[35] Some clinical use data published in 2014 also showed how rituximab monotherapy is a commonly prescribed treatment in the United States for patients with relapsed CLL and is increasingly being prescribed in Europe, particularly in Germany.[18]

Overall we suggest that rituximab monotherapy can be used to treat CLL within the UK; that rituximab monotherapy can be assumed to represent anti-CD20 efficacy in the treatment of CLL within the UK; and that both of these facts, together with the need to most appropriately utilise the Phase III data available for idelalisib, all provide rationale for use of rituximab as the main comparator for people with relapsed or refractory CLL. Although rituximab monotherapy is not a recognised comparator within the scope, it is assumed that it has a similar efficacy to ofatumumab in patients with CLL, as supported by clinical opinion from an advisory board of six UK clinicians.[20] There are no data directly comparing rituximab and ofatumumab in CLL patients; however, one study, the ORCHARRD study, found no difference in efficacy between ofatumumab compared with rituximab, when used in combination with cisplatin, cytarabine, and dexamethasone in 447 patients with relapsed or refractory diffuse large B-cell lymphoma within a phase III, randomised, controlled trial.[23]

In addition, work conducted by PenTAG ERG as part of the NICE appraisal for ofatumumab in combination with chlorambucil or bendamustine for CLL supports the conclusion of equal efficacy of rituximab and ofatumumab. A network meta-analysis was conducted that reported no significant difference between ofatumumab with chlorambucil and rituximab with chlorambucil, with the ERG recommending a PFS hazard ratio between rituximab with chlorambucil versus ofatumumab with chlorambucil of 1 and an alternative estimate

indicating rituximab with chlorambucil to be more effective than ofatumumab with chlorambucil (HR=0.7). Similar results were found for overall survival.[24]

The rationale for inclusion of rituximab monotherapy as a comparator is discussed further in Section 3.3 and Section 4.13 of the submission. This rationale is also further discussed in the response to question B5.

A7. **Priority Question.** Page 12, Table 1. Please provide further rational for excluding bendamustine (with or without rituximab) and chlorambucil (with or without rituximab) for adults with untreated CLL associated with 17p deletion or TP53 deletion, and explain the relevance to current UK standard clinical practice of rituximab as a comparator in this population?

Bendamustine (with or without rituximab) and chlorambucil (with or without rituximab) are both chemo-immunotherapy regimens, and as such they would not be suitable for patients with a 17p deletion or TP53 mutation, as was confirmed by clinical advisors[20] and highlighted at the initial NICE scoping meeting. Furthermore, these are outside of the licensed indication for first line idelalisib (given that the licence for first-line use of idelalisib is for patients who are unsuitable for chemo-immunotherapy). We have provided this rationale in Table 1.1 in Section 1.1, and again in Table 14 in Section 3.3 of the original submission.

Rituximab monotherapy is not a relevant comparator for the untreated population with a 17p deletion or TP53 mutation and has not been included as such. The relevance of rituximab monotherapy in the treated CLL population has been discussed in response to question A6.

A8. **Priority Question.** Page 67, Table 21. Please provide the number of patients who had their dose of idelalisib modified from 150 mg/day to 100 mg/day and reasons for this change in dosage.

A9. **Priority Question.** Page 67, Table 21. Please provide the mean (including standard deviation) time point, post randomisation at which the dose modification occurred?

In response to questions A8 and A9, a total of 18 patients receiving idelalisib and rituximab had their dose reduced from 150mg to 100mg, because of the occurrence of AEs.

The dose modification occurred at a mean (SD) time post-randomisation of 130.6 (89.7) days.[5]

A10. **Priority Question.** Page 84, Table 27. Please explain why there were more frequent discontinuations in the treatment arm (treatment arm 14.5 vs. placebo arm 6.4)? Please provide a table detailing reasons for discontinuation in both arms of the study (for example: progression, adverse event, patient choice).

The reasons for discontinuation in both arms were due to

- incidence of AEs (7 out of 16 for the IR arm and 2 out of 7 for the R+placebo arm),
- withdrawal by subjects (9 out of 16 for the IR arm and 4 out of 7 for R+placebo arm) or
- disease progression (0 out of 16 for the IR arm and 1 out of 7 for the R+placebo arm).

The higher frequency of discontinuations observed in patients receiving idelalisib with rituximab is most likely a consequence of the longer time spent on treatment for these patients (median [range] time on treatment of 8.1 [0.3 to 19.5] months) compared to the patients receiving rituximab plus placebo (median time on treatment of 4.6 [0.1 to 14.6] months).

A11. Page 12, Table 1 and Page 114. Please provide a more detailed rationale why on Page 114 it is stated that alemtuzumab is not considered an appropriate comparator for people previously untreated with a TP53 or 17p deletion. Alemtuzumab is included in the final scope issued by NICE and included in the company decision problem on page 12, table 1.

On page 114 of the submission, we state that “Alemtuzumab plus steroids is not a listed comparator” as this was not included in the NICE scope. However, we recognise that alemtuzumab monotherapy is a relevant comparator for these patients, as listed in the decision problem table (Table 1). As such, alemtuzumab was included in the systematic review searches and all identified evidence was presented. Only one study, a randomised controlled trial, was identified that reported data for alemtuzumab (versus chlorambucil) in untreated patients with 17p deletion or TP53 mutation (Hillmen, 2007)[25], and these data were presented in Section 4.7 of the original submission. The results of the alemtuzumab study were compared with those of the idelalisib single-arm study (Study 101-08 [18]) in this patient population in Section 4.11 of the original submission.

A12. Page 20. Please provide more information about how representative the patient population of Study 116 is to UK clinical practice considering that the results are based on a subsample of CLL patients with a worse prognosis (for example; older, with co-morbidities, intolerant to chemo immunotherapy, refractory or relapsed to previous treatment).

As detailed further in Section 4.13 of the original submission, in general, patients included in Study 116 were representative of the wider population of patients with relapsed or refractory CLL treated in the clinical setting.

- Patients in Study 116 were older than patients in the other RCT and non-RCT studies of comparator treatments (median age of 71 years vs. median age of 59 to 71 years across the studies). Given a median age at diagnosis of 71 years, this patient population is much more likely to represent actual patients seen in clinical practice.
- A similar proportion of patients were female in Study 116 (35%), compared with the other studies (25-42%).

- Patients included in Study 116 had received a median of 3 prior therapies compared with a median of 1 in all RCTs and 2-5 prior therapies across the other non-RCT studies that reported these data.
- Patients in Study 116 were of a similar disease severity compared with the other studies, according to the proportion of patients in Binet Stage C (56% vs. 12-65% across the other studies).
- In general, the proportion of patients with 17p deletion was greater in Study 116 (26%) when compared with six other studies reporting such data (9%, 10%, 7-9%, 18%, 41%, 18- 29%). This is perhaps not surprising given that the patients in Study 116 were heavily pretreated and therefore will have a higher proportion of this subgroup as they progress through treatment lines and undergo clonal selection of the chemo-immunotherapy resistant group of patients with a 17p deletion or TP53 mutation. [26]

Study 116 was a multinational, multicentre study, which included representative centres from the US, France, Germany, Italy and UK. Of the 220 patients randomised in Study 116, 32 patients (14.5% of all recruited patients) were enrolled from the UK, which represents a relatively high proportion of patients in a global study.[5]

Overall Study 116 is expected to be highly representative of the relapsed or refractory CLL population that would be found in general clinical practice. As such, the meaningful clinical effectiveness demonstrated with idelalisib with rituximab in Study 116 is expected to be replicated in clinical practice.

A13. Page 66, Table 21. Please clarify how many patients in each centre took part in Study 116? Please list these by country (US, France, UK, Italy and Germany).

Table 14 presents a breakdown of the number of patients that were recruited from each country by treatment arm and overall. The majority of the patients (74.1%) were from the US, but 14.5% were from the UK.

**Table 14: Study 116 Patient Disposition by Country -** Study 116 CSR. [5]

| **Country** | **Number of Patients, n (%)** | | |
|---|---|---|---|
| | **Idelalisib + rituximab** | **Placebo + rituximab** | **Total** |
| France | 3 (2.7) | 3 (2.7) | 6 (2.7) |
| Germany | 7 (6.4) | 5 (4.5) | 12 (5.5) |
| Italy | 2 (1.8) | 5 (4.5) | 7 (3.2) |
| UK | 18 (16.4) | 14 (12.7) | 32 (14.5) |
| US | 80 (72.7) | 83 (75.5) | 163 (74.1) |

## Section B: Clarification on cost-effectiveness data

B1. **Priority Question.** Please provide all base case results, scenario analyses, probabilistic sensitivity analyses and subgroup analyses using the list price of idelalisib. Please remove all text which references a discounted list price.

Analyses no longer required as per dialogue with the NICE Project Team on 17 March 2015.

B2. **Priority Question.** Please provide further rationale for why best supportive care was assumed to have the same clinical efficacy as rituximab monotherapy. Please clarify how the costs for best supportive care were calculated.

Best supportive care is assumed to have lower, rather than equal, clinical efficacy to rituximab monotherapy, which is an active treatment for CLL. For the purpose of providing a sensible upper bound incremental cost-effectiveness ratio (ICER) in the Study 116 patient population, where no data were available for BSC, the impact of assuming BSC has equivalent efficacy to rituximab was tested.

Conservatively, zero treatment costs were assumed for BSC; the only costs assumed for BSC were those associated with disease management and terminal care, as described in the submission. In the pre-progression health state, separate resource use estimates were applied for responders and non-responders. Zero response was assumed for the comparison to BSC, where no active treatment is received.

The estimated incremental cost-effectiveness of idelalisib with rituximab versus BSC suggests that idelalisib with rituximab is a cost-effective use of NHS resources, with a probability of being cost-effective at £20k of 46% (78% at £30k). We hope that the transparent and conservative assumptions necessary for this best available comparison allow the Institute to be confident that the most plausible ICER is actually lower than that represented, and that idelalisib with rituximab represents a highly cost-effective treatment option for patients who would otherwise receive no active treatment.

B3. **Priority Question.** Please provide further rationale for not including a cost-effectiveness analysis for the previously untreated TP53 or 17p deletion CLL group.

As described in sections 4 and 5 of the submission document, the evidence for idelalisib with rituximab is highly limited for this small patient group with high unmet need, and even more so for its comparators, and this lack of evidence precluded robust economic analysis.

To expand, the sole identified study of idelalisib with rituximab for treatment-naïve CLL patients, Study 101-08, included nine patients with 17p deletion or TP53 mutation. Progression-free survival (PFS) for these nine patients has been remarkable; at the latest cut-off, (as presented within the submission – at over 40 months) PFS remains at 100%. For the small group of patients with 17p deletion or TP53 mutation, whose disease is unresponsive to chemotherapy, an active treatment option of IR that can prolong both overall survival and time to disease progression addresses substantial unmet need.

Accurately estimating the economic value of idelalisib for this group of patients is, however, highly challenging. Extrapolating horizontal overall survival (OS) and PFS curves from the nine patients in Study 101-08 with 17p deletion or TP53 mutation would be subject to

extreme uncertainty. Comparator survival data were similarly scarce. Only one identified trial reported median PFS or OS estimates for the treatments listed as comparators in the Final Scope for patients with 17p deletion or TP53 mutation (Hillmen et al.) reported median PFS estimates for 10 patients with 17p deletion or TP53 mutation randomised to receive chlorambucil (2.2 months) and 11 patients with 17p deletion or TP53 mutation randomised to receive alemtuzumab (10.7 months)[25]. These data reinforce the impressive nature of the results observed in Study 101-08 and the likely incremental value of idelalisib for patients with 17p deletion or TP53 mutation, yet formal comparisons with the nine patients in Study 101-08 would clearly be subject to extreme assumptions.

However, in an effort to provide the most useful information possible for the Appraisal Committee, it was possible within the submission document to provide some insight into the likely cost effectiveness of idelalisib with rituximab for patients with 17p deletion or TP53 mutation. Subgroup analysis results presented in section 5.9 of the submission document replicated base case results for the subgroup of patients with 17p deletion or TP53 mutation, using survival analysis estimates of the effect of this characteristic upon OS and PFS and using ORRs specific to the subgroup of 17p deletion or TP53 mutation patients in Study 116. This analysis gave an indication of the potential economic value of idelalisib for patients with 17p deletion or TP53 mutation using information from the relapsed population who had received a median three prior active treatments, and who were not suited to receive cytotoxic-containing therapies because of either their fitness or lack of previous response to those treatments. Patients with these characteristics have a poor prognosis, and the results in section 5.9 suggested that idelalisib may be cost-effective for such patients. The difference in prognosis that an effective treatment option can promise for patients with CLL associated with 17p deletion or TP53 mutation who have not received prior treatment and who are generally fitter than Study 116 patients can be expected to be substantially greater than for patients similar to those in Study 116. Therefore these results may be viewed as highly conservative as a proxy for results for treatment-naïve patients, and further evidence that idelalisib with rituximab is a cost-effectiveness treatment alternative for previously untreated patients with CLL associated with 17p deletion or TP53 mutation.

B4. **Priority Question.** Please provide further details of the parameters that were determined through clinical validation (e.g. resource use, page 196 table 82). Specific information might include; how many clinicians, and of what specialities were involved, were they asked open ended questions, or asked to comment on the plausibility of numbers they were given, were their views elicited through a formal process (e.g. a Delphi panel) or more informally, were they asked to provide only point estimates, or measures of their uncertainty as well? The reference for this is to a clinical validation meeting, and says the data is on file. Would it be possible to have access to these data?

Following review of the cost-effectiveness literature and review of previous UK HTAs a list of health care resources linked with clinical management of CLL was created. When available the frequency reported in previous HTAs was used (NICE TA216 [27] , NICE TA202 [28]). For instance when frequencies of utilisation was not reported the list of clinical input was elicited. At a Gilead advisory board held in September 2014, the list of items was presented, in an empty table similar to table-82 in the submission, to 6 Scottish haematologist consultants who were asked individually to fill-in the grid. These values were presented to 5 English

haematologist consultants at a later advisory board (December 2014) for validation. The parameters used are the average of the reported validated inputs.

B5. **Priority Question.** Pages 156 and 211. Please provide further rationale for assuming ofatumumab has identical clinical effectiveness to rituximab, and for assuming equal efficacy for rituximab and best supportive care.

As described on Page 156 of the submission document, in the absence of information equal efficacy was assumed for the anti-CD20s rituximab and ofatumumab on the basis of results of the ORCHARRD study [23], the use of the two interchangeably within clinical trials as a class of therapies [29], conclusions from the network meta-analysis conducted as part of ongoing appraisal for ofatumumab in combination with bendamustine or chlorambucil [24] and clinical expert advice [20].

To expand on these evidence sources, the ORCHARRD study comprised an RCT that directly compared ofatumumab with rituximab as salvage therapies in combination with cisplatin, cytarabine, and dexamethasone for 447 patients with diffuse large B-cell lymphoma who had either relapsed from, or were failing to respond to, first-line “R-CHOP-like” treatment [23]. No differences in PFS or OS were found between the rituximab and ofatumumab arms of this large international study [23]. Elsewhere, approval of a Phase I study of idelalisib with either ofatumumab or rituximab for heavily pre-treated CLL suggests that the mechanisms and outcomes of these anti-CD20 antibodies are considered similar in CLL patients by regulatory authorities [29]. Expert clinical advice from an advisory board meeting held in anticipation of this technology appraisal reinforced this conclusion [20]. Lastly, an indirect comparison of rituximab with chlorambucil versus ofatumumab with chlorambucil, performed and reported by the ERG in the ongoing appraisal of ofatumumab in combination with chlorambucil or bendamustine for untreated CLL (ID642) [24], suggested that PFS outcomes for rituximab with chlorambucil and ofatumumab with chlorambucil in untreated CLL patients are similar, and in fact numerically worse for ofatumumab with chlorambucil (see Table 34, Section 4.5.3.1.3 of the ERG critique of the manufacturer’s submission for ID642 [24]).

In addition, similarities in modelled survival outcomes from the rituximab arm of Study 116 and those reported in the literature further support the assumption of equivalence between ofatumumab and rituximab in the base case analysis. The single-arm study of ofatumumab from Wierda et al [30] reported a median OS of 15.4 months for fludarabine-refractory patients who are less suited to alemtuzumab due to bulky lymph nodes, with a life expectancy of 6 months or more. The median predicted OS of 13.6 months for rituximab, adjusting for patient cross-over as reported in of the submission document, again suggests that survival outcomes for rituximab and ofatumumab in these patients are similar.

Assuming a common shape parameter with estimated Study 116 survival curves to model OS and PFS for ofatumumab using medium survival data from Weirda et al [30], and attempting to adjust for study-level differences using results from a published Cox proportional hazards model, as described in section 5.3 of the submission document, it was possible to provide an alternative estimate of the relative cost effectiveness of idelalisib with rituximab versus ofatumumab, which did not impose the assumption of equivalent clinical effectiveness across ofatumumab and rituximab. As shown in section 5.8 of the submission document, the results were reasonably similar to those under base case assumptions; both

suggest idelalisib with rituximab is a highly cost-effective treatment alternative to ofatumumab monotherapy for relapsed/refractory CLL patients.

The rationale for providing a scenario assuming equal efficacy for rituximab and best supportive care is presented within detailed in the response to question B2.

B6. **Priority Question**. Section 5.3 (from page 156 onwards). Please provide a rational for assuming a common shape parameter for assessing overall survival and progression free survival for treatments other than those in Study 116. Digitised Kaplan–Meier curves were used to validate the fits, so standard model fitting could have been done on these digitised curves, in particular for FCR where it is stated that the assumed common distribution did not fit well to the data. Please provide the digitised Kaplan–Meier curves.

Assuming a common shape parameter to estimate OS and PFS in exploratory comparisons to treatments outside of Study 116 was in the absence of network of evidence a practical approach that allowed some insight and commonality into the relative cost-effectiveness of idelalisib with rituximab versus chemotherapy regimens. As highlighted, however, it was possible to test this assumption with a comparison of estimated curve fits to digitised Kaplan–Meier (KM) curves, and the common shape assumption appear fairly robust for each comparison, except for the comparison to fludarabine, cyclophosphamide and rituximab (FCR), as demonstrated in Appendix 16 of the submission document.

Figure 3 and Figure 4 reiterate the poor visual fit of the estimated OS and PFS curves for FCR to digitised KM data from Badoux et al. These Figures also show selected alternative parametric curve fits to these KM data. As for Study 116 survival data, curves fitted to standard parametric model forms were estimated (exponential, Weibull, log-logistic and log-normal), and the fit of each parametric model was compared with the observed data. The most appropriate model function assessed using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) statistics, was the log-logistic model for OS and the log-normal model for PFS. AIC and BIC statistics for each modelled curve are shown in Table 15 and Table 16. The parametric curve fits to the KM data from Badoux et al shown in Figure 3 and Figure 4 are these, plus Weibull model curve fits to the KM data, reflecting the curve assumptions in the submission document. The visual fit of these parametric curves to the digitised KM data from Badoux et al. are good and clearly better to the fit of curves estimated using the common shape assumption.

**Figure 3: Parameter curve fits to digitised FCR OS KM data from Badoux et al**

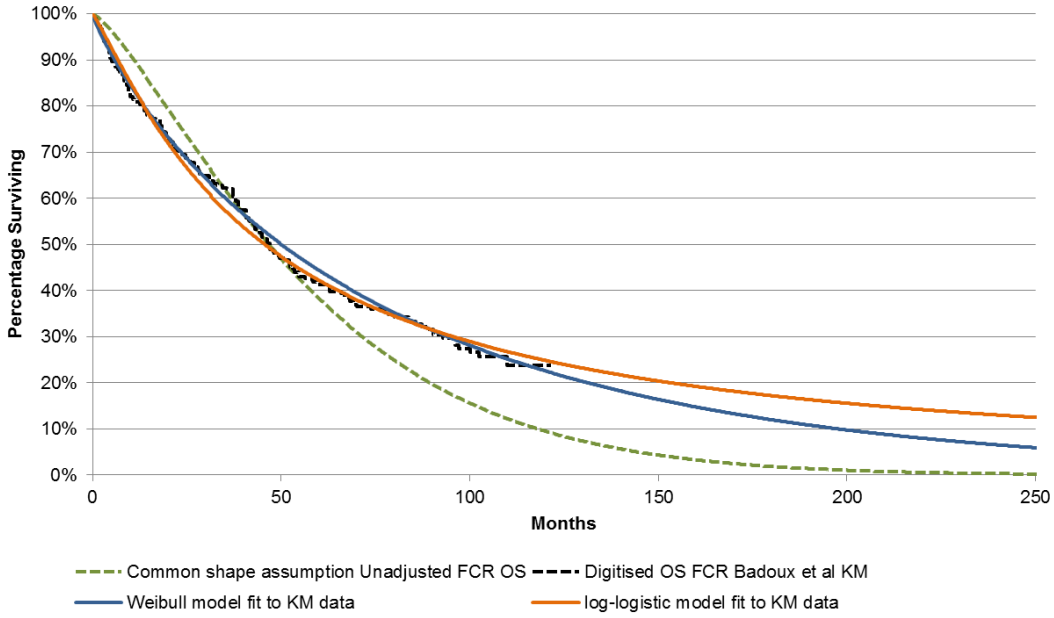



**Figure 4: Parameter curve fits to digitised FCR PFS KM data from Badoux et al**

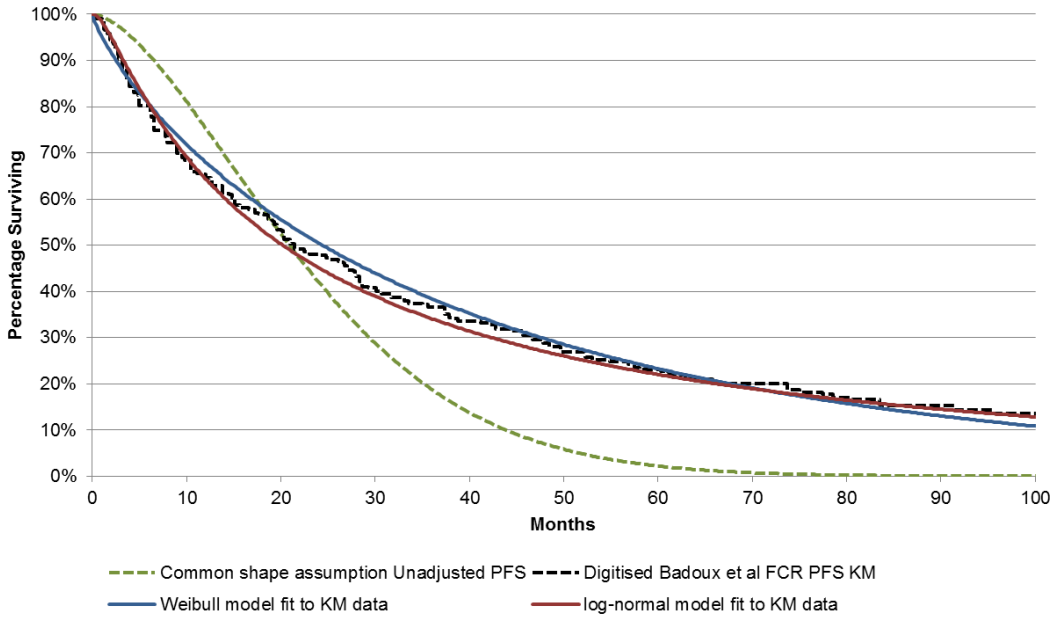



**Table 15: AIC and BIC statistics, parametric curve fits to digitised OS KM data from Badoux et al.**

| Model | AIC | BIC |
|---|---|---|
| Log-logistic | 2314.359 | 2324.499 |
| Log-normal | 2315.744 | 2325.884 |
| Weibull | 2316.144 | 2326.284 |
| Exponential | 2319.738 | 2326.498 |
| **Key:** AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan–Meier; OS, overall survival | | |

**Table 16: AIC and BIC statistics, parametric curve fits to digitised PFS KM data from Badoux et al.**

| Model | AIC | BIC |
|---|---|---|
| Log-normal | 2400.153 | 2410.812 |
| Log-logistic | 2409.555 | 2420.214 |
| Weibull | 2418.943 | 2429.602 |
| Exponential | 2432.704 | 2439.809 |
| **Key:** AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan–Meier; PFS, progression-free survival | | |

Table 17 shows estimated total cost and health outcomes for FCR and incremental results for idelalisib with rituximab versus FCR using three alternative approaches:

(i) using the common shape assumption, as presented in Table 118 of the submission document;

(ii) using the best statistical curve fits to digitised KM data from Badoux et al to model OS and PFS for FCR, after adjustment for study-level patient characteristics;

(iii) using Weibull model curve fits to digitised KM data from Badoux et al. to model OS and PFS for FCR, after adjustment for study-level patient characteristics.

Total estimated costs, life years (LYs) and quality-adjusted life years (QALYs) associated with FCR are lower using approaches (ii) and (iii) in comparison to approach (i). This reflects the higher OS and PFS estimated for initial years using the common shape assumption (see Figure 3 and 4); the important outcomes period after adjustment for patient differences across Badoux et al. and Study 116. Incremental results, however, are reasonably similar across the alternative approaches. The estimated ICER for idelalisib with rituximab versus FCR, as presented in the submission, of just over £26,200, increases to £28,242 using approach (ii) and £29,350 using approach (iii).

These results show that the choice between using the common shape assumption and estimating parametric curves from digitised KM data was not important for the estimated ICER versus FCR. Therefore, these results suggest that comparisons to other treatments outside of Study 116, for which common shape assumptions appear to be robust, would be even less sensitive to this choice. As emphasised in the submission document, and reiterated in Table 17, these comparisons are subject to further assumptions, including that study-level differences in patient characteristics across studies can be accounted for using the adjustment factors described within section 5.3 of the submission.

**Table 17: Different approaches to exploratory comparison to FCR using external clinical data (Badoux et al)**

| | | | Incremental (IR versus FCR) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Survival curve estimation method** | **Costs** | **Life Years** | **QALYs** | **Costs** | **Life Years** | **QALYs** | **ICER (IR versus comparator)** | **N patients informing comparator survival** | **Similarity of patients to Study 116** | **Ability to adjust for patient characteristics** |
| Common shape to Study 116 IR survival assumed | [redacted] | 0.53 | 0.40 | [redacted] | 4.10 | 2.41 | £26,215 | 284 | Low | High |
| Best statistical model fit to KM data from Badoux et al | [redacted] | 0.32 | 0.24 | [redacted] | 4.31 | 2.57 | £28,242 | 284 | Low | High |
| Weibull model fit to KM data from Badoux et al | [redacted] | 0.27 | 0.19 | [redacted] | 4.36 | 2.61 | £29,350 | 284 | Low | High |

**Key:** FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib and rituximab; KM, Kaplan–Meier; QALYs, quality-adjusted life years

B7. **Priority Question.** Section 5.3 (from page 156 onwards). Please explain why the treatment benefit of idelalisib with rituximab has been assumed to continue both beyond the length of the trial and after treatment discontinuation. With many other cancer drugs, rates return to those of the placebo arm after treatment discontinuation. An alternative approach would be to fit models to the length of the trial data, but then to use the same parameters for each treatment when extrapolating forward from this point. Please provide a justification, (statistical or biological), for not considering this approach here?

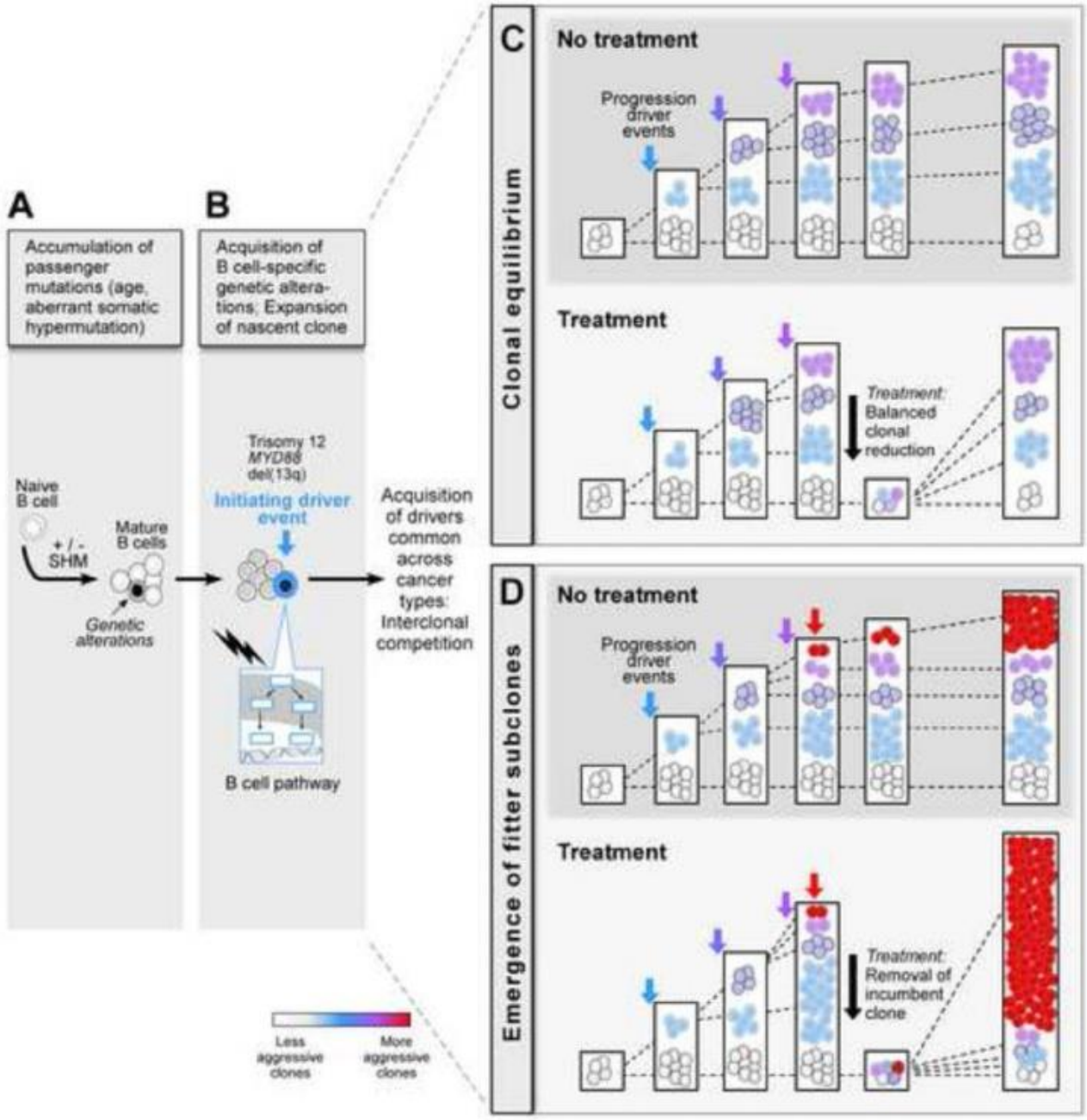
Biologically there are plausible explanations for why the treatment benefit of idelalisib with rituximab will continue beyond treatment with idelalisib: its impact on clonal evolution and on regulatory immune mechanisms.

Clonal heterogeneity and evolution during treatment are key features of CLL. A number of driver mutations including, but not restricted to, TP53 mutation are recognised. TP53 mutation conveys resistance to chemotherapy. Thus treatment with chemotherapy will reduce/eliminate subclones sensitive to chemotherapy, allowing emergence of “fitter” and more aggressive subclones resistant to chemotherapy (as depicted in Box D of Figure 5). This is reflected in the increasing incidence of 17pdel/TP53 mutation with each line of therapy in CLL. On the other hand, treatment with an agent such as idelalisib with broad efficacy across subclones, including those with TP53 mutations, will maintain clonal equilibrium and not allow chemotherapy resistant subclones to emerge and become dominant. Thus after use of idelalisib and rituximab, chemotherapy will have a greater efficacy [31].

Immune dysfunction is also a feature of CLL. Inhibition of PI3Kδ has potential immune and anticancer effects through inhibition of T regulatory cells [32]. Enhanced immune function could, for example, play a role in CLL reducing disease progression and contrasts with the immune suppression seen with fludarabine and bendamustine [33].

In addition, the side effect profile of idelalisib is different to that of conventional chemotherapy. Chemotherapy leads to cumulative effects on bone marrow, whereas idelalisib does not. An alternative approach other than chemotherapy could lead to better bone marrow function later in the course of the disease, allowing other options and further lines of treatment, and thus better outcomes.

**Figure 5: Clonal heterogeneity and evolution during treatment for CLL from Landau et al.**[31]




B8. Pages 79-80, Table 25. Please provide in a table (use a similar format to table 25 page 79), the observed baseline characteristics of patients in the UK and German sample combined in Study 116 trial for the 17p deletion or TP53 mutation subgroup.

Table 18 shows observed baseline characteristics of patients in the UK and German samples combined in Study 116 for the 17p deletion or TP53 mutation subgroup.

**Table 18: Baseline characteristics of UK and German patients with 17p deletion or TP53 mutation in Study 116**

| Baseline characteristic | IR | Placebo + R |
|---|---|---|
| Patients | n=12 | n=12 |
| ITT population | n=12 | n=12 |
| ITT definition | All randomised patients regardless of whether they received study drug or a different regimen to the one to which they were randomised | |
| Age (years), mean (SD) | 70 (7.7) | 71 (6.8) |
| Age (years), median (range) | 69 (59-90) | 71.5 (53-81) |
| Gender, female (%) | 25 | 50 |
| Rai Stage, %… 0 | 0 | 0 |
| I | 8.33 | 8.33 |
| II | 8.33 | 16.67 |
| III | 16.67 | 16.67 |
| IV | 58.33 | 50 |
| Missing | 8.33 | 8.33 |
| Binet Stage, %… A | 8.33 | 0 |
| B | 25 | 41.67 |
| C | 66.67 | 58.33 |
| Missing | 0 | 0 |
| Time since diagnosis, median (range), months | 131.2 (93.4, 279.4) | 106.4 (29.4, 173.8) |
| Time since diagnosis, mean (SD) months | 150.7 (55.55) | 101.3 (51.66) |
| Karnofsky score, % | | |
| 40 | 0 | 0 |
| 50 | 0 | 16.67 |
| 60 | 8.33 | 8.33 |
| 70 | 33.33 | 25 |
| 80 | 16.67 | 16.67 |
| 90 | 16.67 | 25 |
| 100 | 25 | 8.33 |
| ≤80 | 58.33 | 66.67 |
| CIRS Score | | |
| Median (Q1, Q3) | 8 (7, 9.5) | 7 (6, 7) |
| Total CIRS score >6, % | 75 | 75 |
| CLL genetics | | |
| IgVH unmutated, % | 75 | 75 |
| 17p deletion and/or TP53 mutation, % | 100 | 100 |
| 17p deletion, % | 41.67 | 75 |

**Key:** B, bendamustine; C, cyclophosphamide; Chl, chlorambucil; CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukaemia; F, fludarabine; FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib and rituximab; IgVH, immunoglobulin variable region heavy chain; ITT, intent to treat; n, number; NR, not reported; R, rituximab; SD, standard deviation; WHO, World Health Organisation

B9. Page 84, Table 27 & Pages 86-88, Figures 8-10. Please provide a table (using a similar format to table 27) the breakdown of progression free and overall survival (for the UK sample of patients for both groups (untreated and treated) in Study 116. In addition, please provide the 3 Kaplan-Meir curves (as in Figures 8-10 for PFS, OS [ITT] and OS [RPSFT]) for the UK sample for the two populations in study 116.

Table 19 describes the breakdown of progression free and overall survival (for the UK sample of patients for both groups (untreated and treated) in Study 116. **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.** show the Kaplan-Meir curves for these three samples.

**Table 19: Progression-free and overall survival, UK patients in Study 116**

| | **IR (n=18)** | **Placebo + R (n=14)** |
|---|---|---|
| **Progression-Free Survival[a]** | | |
| % of Subjects with Events | 5.56 | 64.29 |
| Disease Progression | 0 | 42.86 |
| Death | 5.56 | 21.43 |
| % of Subjects Censored | 94.44 | 35.71 |
| Completed Study/Crossed over to Open-Label IDELA | 94.44 | 35.71 |
| Discontinued Study | 0 | 0 |
| Received Another Antitumor Treatment | 0 | 0 |
| Missed ≥ 2 Consecutive Tumour Measurements | 0 | 0 |
| KM Estimate of PFS[b] (Months) | | |
| Q1 (95% CI) | NR (4.1, NR) | 1.5 (0.2, 3.7) |
| Median (95% CI) | NR (4.1, NR) | 3.7 (1.4, NR) |
| Q3 (95% CI) | NR (NR, NR) | NR (3.7, NR) |
| Adjusted Hazard Ratio (95% CI)[c] | 0.06 (0.01, 0.48) | |
| P-value[d] | | |
| 12-month PFS | 90 (47.3, 98.5) | 28.6 (7.3, 54.8) |
| 24-month PFS | NR (NR, NR) | NR (NR, NR) |
| **Overall Survival[e] [ITT analysis]** | | |
| % of Subjects Who Died | 11.11 | 50 |
| % of Subjects Censored | 88.89 | 50 |
| KM Estimate of OS (Months)[f] | | |
| Q1 (95% CI) | 19.0 (4.1, not reached) | 4.5 (0.2, 9.2) |

| | IR (n=18) | Placebo + R (n=14) |
|---|---|---|
| Median (95% CI) | 19.0 (19.0, not reached) | Not reached (1.9, not reached) |
| Q3 (95% CI) | not reached (19.0, not reached) | Not reached (9.2, not reached) |
| Adjusted Hazard Ratio (95% CI) | 0.15 (0.03, 0.77) | |
| P-value from Stratified Log-Rank Test[g] | | |
| P-value from Unstratified Log-Rank Test | 0.0030 | |
| 12-month OS | 94.4% | 50% |
| 24-month OS | Not reached | Not reached |
| **Overall Survival [Crossover Adjusted RPSFT analysis]** | | |
| Median (95% CI) | 19.0 (19.0, not reached) | 5.7 (1.9, not reached) |
| Adjusted Hazard Ratio (95% CI) | 0.08 (0.02, 0.41) | |
| 12-month OS | 94.4% | 47.6% |
| 24-month OS | Not reached | Not reached |
| **Key:** CI, confidence interval; IDELA, idelalisib; IR, idelalisib and rituximab; ITT, intent to treat; KM, Kaplan-Meier; NR, not reported; n, number; OS, overall survival; PFS, progression-free survival; R, rituximab; RPSFT, rank preserving structural failure time<br>**Notes:**<br>a) For subjects in Placebo + R, summary includes data up to the first dosing of open-label IDELA<br>b) PFS (months) = (minimum [date of PD, date of death] – date of randomization + 1)/30.4375<br>c) Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation)<br>d) P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation)<br>e) Analysis is based on data from Study GS-US-312-0116 and its extension study, GS-US-312-0117<br>f) OS (months) = (date of death – date of randomization + 1)/ 30.4375<br>g) P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/*TP53* mutation and *IgVH* mutation) | | |

**Figure 6: ITT Overall Survival (UK subset).**

Figure redacted

**Figure 7: RPSFT Model (UK subset)**

Figure redacted

**Figure 8: KM PFS UK sample (IRC assessment)**

Figure redacted

B10. Page 185, Table 76. Please clarify why there are higher utility values in patients who have discontinued treatment compared to those taking rituximab alone (0.8 vs 0.75)? These data are from different sources (Dretzke et al. 2010 paper [Reference 88 in the submission] vs Study 116) so are not obviously directly comparable. The difference appears to be more than the expected impact of adverse events that was calculated.

EQ-5D data were not collected post treatment in either arm of Study 116. While robust health-related quality of life (HRQL) estimates were available from the gold-standard source for patients in the 'PFS, on treatment' health state, it was necessary to rely on the literature for other model health states. For the 'PFS, off treatment' health state, it seemed most reasonable to use the best available utility estimate for pre-progressive patients: 0.80, as reported by Dretzke et al [34]. That this approach implies that patients who receive anti-CD20 monotherapy experience an improvement in HRQL after treatment withdrawal above that explained by the absence of key adverse events appears illogical, but these data are from different sources, and such differences can be expected.

This base case approach assumes that the higher HRQL observed in the intervention arm of Study 116 versus the comparator arm while patients received treatments disappears following treatment withdrawal. In reality, the HRQL of patients who receive idelalisib with rituximab may continue to outperform that of patients receiving anti-CD20 monotherapy after treatment withdrawal; therefore, the base case approach can be viewed as conservative.

Regardless, model results are robust to assumptions regarding HRQL in the 'PFS, off treatment' health state, as demonstrated in Table 20 and Table 21. Table 20 shows model results for the comparison to rituximab, assuming utility in this health state is 0.6, the best available estimate from the literature for post-progressive disease, which is also from Dretzke et al [34]. Table 21 shows base case results versus rituximab, for comparison.

**Table 20: Alternative PFS off-treatment utility estimate, IR versus R**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Costs** | **Life Years** | **QALYs** | **Costs** | **Life Years** | **QALYs** | **ICER** |
| Rituximab | [redacted] | 1.39 | 0.88 | | | | |
| Idelalisib with rituximab | [redacted] | 4.63 | 2.76 | £26,128 | 3.24 | 1.88 | £13,865 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; PFS, progression-free survival; QALYs, quality adjusted life year; R, rituximab

**Table 21: Base case results, IR versus R**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Costs** | **Life Years** | **QALYs** | **Costs** | **Life Years** | **QALYs** | **ICER** |
| Rituximab | [redacted] | 1.39 | 0.89 | | | | |
| Idelalisib with rituximab | [redacted] | 4.63 | 2.81 | £26,128 | 3.24 | 1.92 | £13,634 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; QALYs, quality adjusted life year; R, rituximab

B11. Page 200, Tables 86-87. Please provide further information on how the costs associated with diarrhoea and colitis have been estimated? Please clarify why the costs associated with the possibility of hospitalisation/more extreme adverse outcomes in relation to diarrhoea and colitis are not included and also clarify whether it is assumed that patients will require only a single outpatient visit, and if so please include the data on which this assumption is based?

The cost associated with Grade III/IV diarrhoea/colitis was assumed to be equal to the unit cost of a consultant-led gastroenterology outpatient attendance and was validated at clinical review with an NHS England clinical haematologist, as described in the submission document. This may have underestimated the costs associated with these adverse events as highlighted, although as demonstrated in the deterministic sensitivity analysis results in section 5.8, the assumptions associated with these costs are not key model drivers. To further examine the sensitivity of model results to cost assumptions for diarrhoea and colitis, Table 22 shows model results for the comparison to rituximab, assuming the cost for diarrhoea/colitis is equal to the highest adverse event (AE) cost in the model, £5,993 for febrile neutropenia. In comparison to base case results for this comparison (reproduced in Table 21), the ICER differs by only £21.

**Table 22: Base case results, IR versus R, diarrhoea/colitis cost assumed equal to highest AE cost**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Costs** | **Life Years** | **QALYs** | **Costs** | **Life Years** | **QALYs** | **ICER** |
| Rituximab | [redacted] | 1.39 | 0.89 | | | | |
| Idelalisib with rituximab | [redacted] | 4.63 | 2.81 | £26,150 | 3.24 | 1.92 | £13,645 |
| **Key:** AE, adverse event; ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; PFS, progression-free survival; QALYs, quality adjusted life year | | | | | | | |

## Section C: Textual clarifications and additional points

C1. **Priority Question.** Please ensure all commercial in confidence and academic in confidence information is both highlighted and underlined. Throughout the document there is confidential information which has been highlighted but not underlined.

Done

C2. **Priority Question.** Appendix 2, Pages 2-9. Please remove appendix 2 from the submission and submit it as part of a patient access scheme submission template. The patient access scheme submission template should also include the impact of the anticipated discounted price on clinical and cost-effectiveness analyses.

Update no longer required as per dialogue with NICE Project Team on 17 March 2015.

C3. Page 88, Figure 10. Please clarify if the figure on this page is commercial in confidence.

Many thanks for highlighting - this figure should be marked academic in confidence.
Apologies for the omission.

## References


1. Roche Products Limited. Summary of Product Characteristics (SPC). Obinutuzumab. 30 July 2014. Available at: http://www.medicines.org.uk/emc/medicine/29057 Accessed: 30 January 2015.
2. National Institute for Health and Care Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia: Final appraisal determination. 2015. Available at: http://www.nice.org.uk/guidance/gid-tag451/documents/leukaemia-chronic-lymphocytic-obinutuzumab-with-chlorambucil-1st-line-id650-final-appraisal-determination-document2 Accessed: 17 March 2015.
3. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *New England Journal of Medicine*. 2014; 370(12):1101-10.
4. Gonzalez D, Martinez P, Wade R, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *Journal of Clinical Oncology*. 2011; 29(16):2223-9.
5. Gilead Sciences. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS 1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia. (GS-US-312-0116). 25 November 2014.
6. Stilgenbauer S CS, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al.,. Efficacy of idelalisib in CLL subpopulations harboring DEL(17P) and other adverse prognostic factors: Results from a phase 3, randomized, double-blind, placebo-controlled trial. *Haematologica Conference: 19th Congress of the European Hematology Association*. Milan, Italy2014, p. 521.
7. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *The New England journal of medicine*. 2014; 371(3):213-23.
8. Hillmen P BJ, O'Brien S, Barrientos J, Kay NE, Reddy NM et al.,. Randomized comparison of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma: Results from the phase III PCYC-1112 resonate(TM) trial. *Haematologica Conference: 19th Congress of the European Hematology Association*. Milan, Itlay2014, p. 244.
9. Brown JR HP, O'Brien SM, Barrientos JC, Reddy NM, Coutre S et al.,. Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATE(TM) Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Haematologica Conference: 56th American Society of Hematology Meeting*. San Francisco, USA2014, p. Abstract 3331.
10. Awan FT, Hillmen P, Hellmann A, et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. *British journal of haematology*. 2014; 167(4):466-77.
11. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood*. 1996; 87(12):4990-7.
12. GlaxoSmithKline UK. Summary of Product Characteristics (SPC). Ofatumumab. 08/01/2015. Available at: http://www.medicines.org.uk/emc/medicine/23022 Accessed: 30 January 2015.
13. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; 111(12):5446-56.
14. Donnellan W BJ, Shipley D, Arrowsmith E, Wright D, Lunin S et al.,. Phase II Trial Evaluating the Safety of Rapid Infusion Ofatumumab (OFA) in Patients (pts) with Previously

Treated Chronic Lymphocytic Leukemia (CLL). *Haematologica Conference: 56th American Society of Hematology Meeting*. San Francisco, USA2014, p. Abstract 3336.
15. Sanhes L MB, Hacini M, Fitoussi O, Arkam Y, Orfeuvre H et al.,. Management of relapsed or refractory chronic lymphocytic leukemia patients previously treated and retreated with rituximab in daily practice: Interim results of the perle study (ML 25664). *Haematologica Conference: 19th Congress of the European Hematology Association*. Milan, Italy2014, p. 325.
16. Zagoskina T ZE, Ovsepyan V, Shardakov V.,. Efficacy of the combination of bendamustine and rituximab in patients with relapsed and refractory chronic lymphocytic leukemia. *Haematologica Conference: 19th Congress of the European Hematology Association*. Milan, Italy2014, p. 591.
17. Smolej L BY, Doubek M, Cmunt E, Spacek M, Belada D et al.,. Low-Dose FCR Is a Safe and Effective Treatment Option for Elderly/Comorbid Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Updated Results of Project Q-Lite By Czech CLL Study Group. *Haematologica Conference: 56th American Society of Hematology Meeting*. San Francisco, USA2014, p. Abstract 4670.
18. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2014; 370(11):997-1007.
19. Systemic Anti-Cancer Therapy Dataset. Top Regimens by Diagnostic Group. 2014. Available at: http://www.chemodataset.nhs.uk/view?rid=64 Accessed: 1 February 2015.
20. Gilead Sciences Ltd. NICE CLL Advisory Board Meeting Report. 2014. Data on File.
21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma 2014. 2014.
22. Eichhorst B, Dreyling M, Robak T, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011; 22 Suppl 6:vi50-4.
23. van Imhoff G, McMillan A, Matasar M, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The Orcharrd Study (OMB110928). American Society of Hematology. San Francisco, US. 6-9 December 2014. Abstract.
24. Hoyle M, Huxley N, Coelho H, et al. Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia: a critique of the submission from GSK, . 2015. Available at: https://www.nice.org.uk/guidance/gid-tag443/documents/leukaemia-chronic-lymphocytic-ofatumumab-previously-untreated-evaluation-report-and-supporting-information Accessed: 22 January 2015.
25. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(35):5616-23.
26. Pileckyte R, Jurgutis M, Valceckiene V, et al. Dose-dense high-dose methylprednisolone and rituximab in the treatment of relapsed or refractory high-risk chronic lymphocytic leukemia. *Leukemia & lymphoma*. 2011; 52(6):1055-65.
27. Napp pharmaceuticals. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. *Single technology appraisal National Institute for Health and Care Excellence*. 2010.
28. GlaxoSmithKline. Ofatumumab (Arzerra) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. 2010. Available at: http://www.nice.org.uk/guidance/TA202 Accessed: 30 January 2015.
29. Furman R, Barrientos J, Wagne-Johnston N, et al. A phase 1 study of the selective PI3K inhibitor idelalisib (GS-1101) in combination with therapeutic anti-CD20 antibodies (rituximab or ofatumumab) in patients with relapsed or refractory chronic lymphocytic leukemia. American Society of Hematology. San Francisco, US. 6-9 December 2014. Abstract.

30. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010; 28(10):1749-55.
31. Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell*. 2013; 152(4):714-26.
32. Ali K, Soond DR, Piñeiro R, et al. Inactivation of PI (3) K p110 [dgr] breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature*. 2014; 510(7505):407-11.
33. Byrd JC, Jones JJ, Woyach JA, et al. Entering the era of targeted therapy for chronic lymphocytic leukemia: impact on the practicing clinician. *Journal of Clinical Oncology*. 2014; 32(27):3039-47.
34. Dretzke J, Barton P, Kaambwa B, et al. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia. *Health Technol Assess*. 2010; 14(Suppl. 2):19-26.
35. DGHO 2014, CLL Leitlinien Wendtner

**Appendix-1: Further response to question A5**

A5. Page 56. Please provide an update of abstracts from the other relevant conferences not already included in the submission. These should include:

g) American Society of Hematology (2010, 2011, 2014)
h) American Society of Clinical Oncology (for last 5 years)
i) European Hematology Association (2010, 2011, 2014)
j) European Society of Medical Oncology (for last 5 years)
k) International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) (2011 and 2013 [biennial meeting])
l) The International Conference on Malignant Lymphoma (ICML) (2011 & 2013 [biennial meeting]) http://www.lymphcon.ch/imcl/index.php

We were unable to search iwCLL 2011 and 2013 as well as the European Society of Medical Oncology 2011 conference abstracts completely, as we found only limited information for these conferences. We took the following approach during our search for these two conferences.

We searched online for abstracts for iwCLL 2011, but did not find them published online or in a journal. We contacted the chair of the upcoming iwCLL, Dr. Stephen Mulligan to ask about abstract availability, and he advised us that he was "Not sure if they are still available. Those from Cologne were on a USB." And he recommended we: "Check Leukaemia and Lymphoma as they may have published them." We checked the Leukaemia and Lymphoma journal webpage, but did not find the abstracts there. In the absence of an abstract book, we reviewed the articles published in *New Evidence* that summarize presentations of major findings however it did not publish on iwCLL 2011.

For the European Society of Medical Oncology (ESMO) 2011 conference we searched the 2011 European Multidisciplinary Cancer Congress (ECC) website (http://2011.europeancancercongress.org/). On the website the link for the programme did not work and we were unable to obtain an abstract booklet this way. The link for posters from this conference worked so we searched for appropriate posters from this conference. We also checked the Annals of Oncology Journal's (official journal of ESMO) website for conference material from this conference but could not find any. Congress programme manager Rebekka Mattyasovszky was also contacted to see if she might be able to provide further information about where to find 2011 congress material and she has referred us to contacts at Elsevier whom we have not heard back from yet. Therefore, for the 2011 ESMO conference material available through the online posters on the website was only searched. Overall 16 abstracts were identified; 10 non-RCT studies and 6 RCT studies (see PRISMA diagram below). More details are listed in the tables below alongside the reason for including the data or not in the current submission.

**PRISMA diagram**

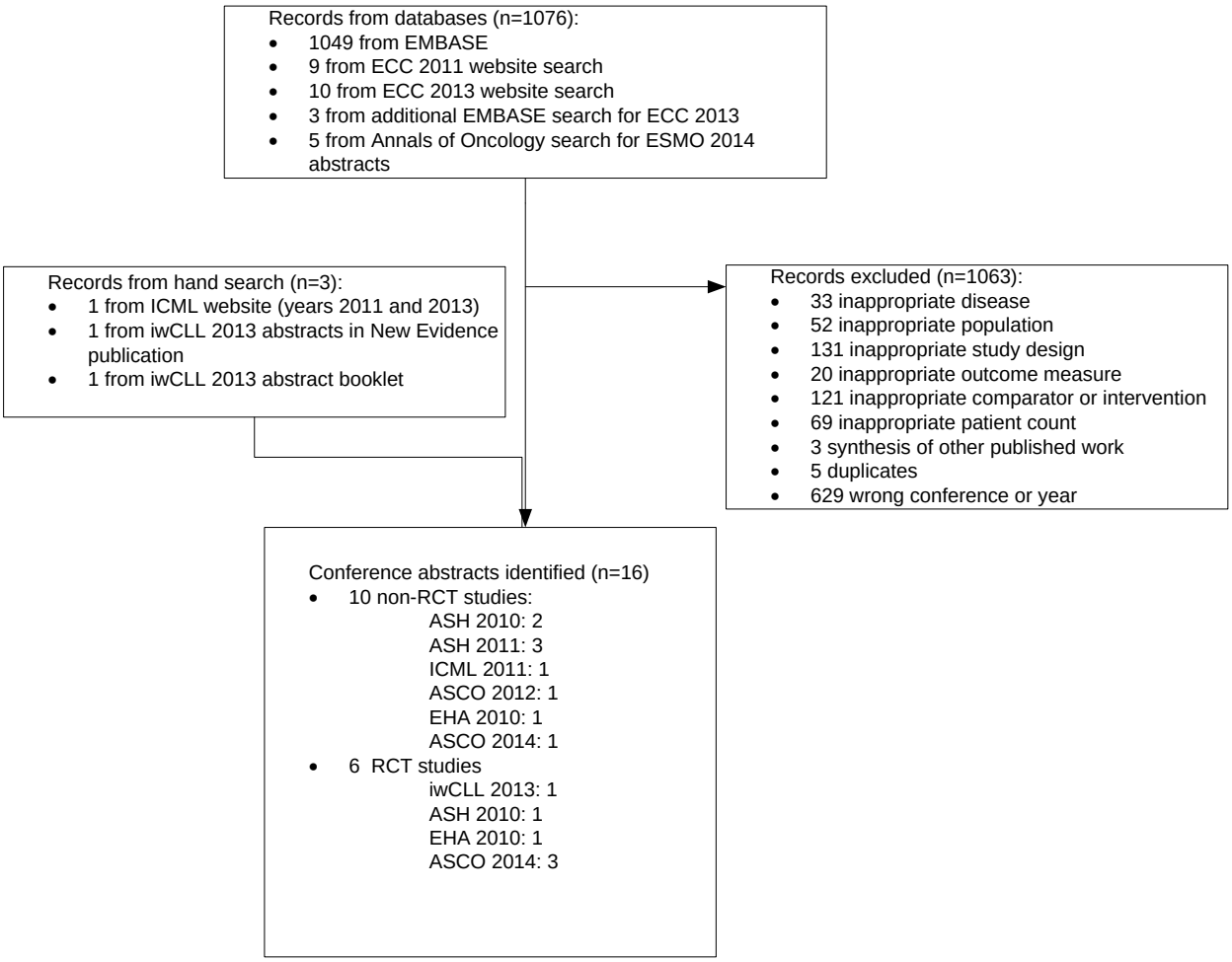



**Table -1: CLL conference abstracts from non-RCT studies (N=10)**

| Intervention/ reference | Treatment arm | N | ORR (%) | |
|---|---|---|---|---|
| **Ofatumumab** | | | | |
| Wierda ICML 2011/ ASH2010 | O (for FA-refractory patients) | 95 | 51 | Relate to the primary publication by Wierda et al (JCO 2010) already discussed and included in current submission. |
| | O (for BF-refractory patients) | 111 | 44 | |
| Osterborg ASCO 2012 | O (for FA-refractory patients) | 17 | | Follow-on from Wierda et al. study to investigate ofatumumab maintenance in responders.<br>Data not relevant to current submission. |
| | O (for BF-refractory patients) | 11 | | |

| | | | | |
|---|---|---|---|---|
| **Alemtuzumab** | | | | |
| Varghese ASH 2010 | A | 50 | 49 | Alemtuzumab not listed as a comparator for relapsed refractory CLL |
| Gritti ASH 2011 | A | 39 | 44 | |
| **Idelalisib Combinations** | | | | |
| Sharman ASH 2011 | I + R<br>I + B | 14<br>10 | NR<br>NR | Phase I data on idelalisib in combination with other CLL agents. Data not included because superseded by randomized study 116 |
| | I + BR | 3 | NR | |
| **CHOP-R** | | | | |
| Jenke ASH 2011 | CHOP-R | 15 | NR | CHOP-R not a relevant comparator, data not considered |
| | CHOP-R | 11 | NR | |
| | CHOP-R | 60 | NR | |
| **Fludabrine Combinations** | | | | |
| Milosevic EHA 2010 | FC | 34 | 22 | FC not a listed comparator, data not included |
| | FC | 11 | 12 | |
| | FC | 6 | 83 | |
| **Ibrutinib** | | | | |
| O,Brien 2014 ASCO | Ibrutinib | 101 | NR | Ibrutinib not listed as a comparator, data not included |
| Furman iwCLL 2013 | Ibrutinib | 85 | 75 | |

Abbrev: A- Alemtuzumab; B-Bendamustine; CHOP-R- Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Rituximab; F- Fludabrine; FC- Fludabrine Cyclophosphamide; Ib- Ibrutinib; I-Idelalisib; NR-not reported; O-Ofatumumab; ORR-Overall Response Rate; R- Rituximab;

**Table 2: CLL conference abstracts from RCT studies (N=6)**

| **Study - Conference** | **Treatment arm** | **N** | **ORR (%)** | |
|---|---|---|---|---|
| **Idelalisib** | | | | |
| Barrientos iwCLL 2013 | I + R | 19 | 89 | Phase I data on idelalisib in combination with other CLL agents. Data not included because superseded by randomized study 116 |
| | I + B | 18 | 78 | |
| | I + BR | 15 | 87 | |
| | all patients | 52 | 83 | |
| Sharman ASCO 2014 | I+ R | 88 | 80.7 | Data from Study 116, not included because more recent analysis used in submission. |
| | placebo + R | 88 | 12.5 | |

| | | | | |
|---|---|---|---|---|
| **Fludarabine combinations** | | | | |
| Engert ASH 2010 and EHA 2010 | F | NR | 74.3 | Fludarabine and Fludarabine-Alemtuzumab combination are not listed as comparators, data not included |
| | F + A | NR | 80.4 | |
| | all patients | 335 | NR | |
| | all patients with Rai stage III or 4 | 123 | NR | |
| | F | NR | 56 | |
| | F + A | NR | 77 | |
| **Bendamustine combinations** | | | | |
| Gladstone ASCO 2014 | R + B | 47 | NR | Relevant comparator but no efficacy data reported for the B+R arm of the study. Data not included |
| | 2mg/kg Medi-551 + B | 33 | 48 | |
| | 4mg/kg Medi-551 + B | 44 | 64 | |
| **Ibrutinib** | | | | |
| Byrd ASCO 2014 | Ibrutinib | 195 | 42.6 | Relevant to submission, but data from ASH 2014 already included in response to A2 |
| | Ofatumumab | 196 | 4.1 | |

Abbrev: A- Alemtuzumab; B-Bendamustine; F- Fludabrine; I-Idelalisib; NR-not reported; ORR-Overall Response Rate; R- Rituximab;