




## ORIGINAL PAPER

# Obinutuzumab as consolidation after chemo-immunotherapy: Results of the UK National Cancer Research Institute phase II/III GALACTIC trial

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## Summary

The GA101 (obinutuzumab) monoclonal Antibody as Consolidation Therapy In chronic lymphocytic leukaemia (CLL) (GALACTIC) was a seamless phase II/III trial designed to test whether consolidation with obinutuzumab is safe and eradicates minimal residual disease (MRD) and, subsequently, whether this leads to prolonged progression-free survival (PFS) in patients with CLL who have recently responded to chemo-immunotherapy. Patients with a response 3–24 months after chemotherapy were assessed for MRD. MRD-positive patients were randomised to receive consolidation therapy with obinutuzumab or no consolidation. The trial closed after the phase II part due to slow recruitment. In all, 48 patients enrolled of whom 19 were MRD negative and were monitored. Of the 29 MRD-positive patients, 14 were randomised to receive consolidation and 15 to no consolidation. At 6 months after randomisation, 10 and 13 consolidated patients achieved MRD negativity by flow cytometry (sensitivity  $10^{-4}$ ) in bone marrow and peripheral blood respectively. PFS was significantly better in consolidated patients compared to non-consolidated patients ( $p = 0.001$ ). No difference was observed in PFS, overall survival or duration of MRD negativity when comparing the 10 MRD-negative patients after consolidation with the 19 MRD-negative patients in the monitoring group. Common adverse events in the consolidation arm were thrombocytopenia, infection, and cough. Only 1% of events were infusion-related reactions. This observation provides further evidence that consolidation to achieve MRD negativity improves outcomes in CLL and that obinutuzumab is well tolerated in patients with low levels of disease.

## KEY WORDS

chronic lymphocytic leukaemia (CLL), International Workshop on Chronic Lymphocytic Leukemia (iwCLL), minimal residual disease, obinutuzumab, phase III

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## INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia, affecting 7.1 per 100 000 population.<sup>1,2</sup> CLL is still an incurable disease, and most patients will eventually become resistant to treatment. For physically fit patients, combined chemo-immunotherapy in the form of fludarabine, cyclophosphamide and rituximab (FCR) has been the standard of care based on evidence from large randomised controlled and non-randomised trials;<sup>3,4</sup> however, the therapies are evolving rapidly with introduction of targeted drugs in a variety of front-line trials and the standards are changing based on the availability of drugs in different countries.

Attainment of minimal residual disease (MRD) negativity has been demonstrated as an independent predictor of overall survival (OS) and progression-free survival (PFS).<sup>5</sup> Multivariable analysis showed that achieving MRD negativity in CLL is an independent predictor of survival even with a variety of different treatment approaches and regardless of the line of therapy. The German CLL Study Group (GCLLSG) CLL8 trial demonstrated that although almost double the number of patients receiving FCR achieved MRD negativity compared with those receiving FC, once low-level MRD was achieved, both arms had a similar outcome.<sup>3</sup> This indirectly implies that the depth of the remission may be more important than the type of treatment given to attain that remission. MRD data analysis from FCR arms in the UK ADMIRE (International Standard Randomised Controlled Trial Number [ISRCTN]42165735) and ARCTIC (ISRCTN16544962) trials showed that there was sequential risk reduction (33%) for disease progression per log reduction in MRD level.<sup>6-8</sup>

The UK National Cancer Research Institute (NCRI) CLL207 phase II trial tested consolidation with alemtuzumab in a similar patient population to the GA101 (obinutuzumab) monoclonal Antibody as Consolidation Therapy In CLL (GALACTIC) trial in order to assess the strategy of consolidation therapy in patients with low levels of detectable residual disease. Of the consolidated patients, 39/47 (83%) attained MRD negativity and 18/47 (38%) remained MRD negative in the peripheral blood (PB) 6 months after therapy. The 5-year PFS and OS of the patients who were MRD negative at 6 months was significantly better than MRD-positive patients (PFS: 78% vs. 39% [ $p = 0.010$ ], OS: 89% vs. 64% [ $p = 0.029$ ]).<sup>9</sup> Alemtuzumab had a significant toxicity profile. The GCLLSG CLL4B trial using alemtuzumab consolidation was stopped prematurely due to patients experiencing severe infections despite demonstrating an improved outcome for patients randomised to consolidation.<sup>10</sup>

Obinutuzumab is a type II anti-CD20 monoclonal antibody (mAb) that exhibits reduced complement-dependent cytotoxicity, strong direct cell death, strong antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.<sup>11-13</sup> The efficacy and safety of obinutuzumab in an elderly, frail population with active

CLL requiring therapy was recently demonstrated in the German CLL11 trial. Patients receiving obinutuzumab with chlorambucil achieved higher overall response rates (ORRs) and MRD-negative rates as compared to patients receiving chlorambucil and rituximab, which resulted in PFS improvement but not OS benefit.<sup>14</sup> As obinutuzumab appears to induce deeper remissions and is tolerated well, this was chosen as the consolidation mAb of choice in GALACTIC study.

## METHODS

### Trial design

The GALACTIC was a seamless phase II/III, multicentre trial to assess the efficacy of obinutuzumab consolidation in patients with low levels of MRD, defined as more than one CLL cell in 10 000 leucocytes, following chemo-immunotherapy. Eligible patients assessed as MRD positive were randomised to receive either consolidation with obinutuzumab or no consolidation therapy. This design incorporated a short-term phase II primary efficacy objective to determine the rate of achieving MRD negativity following obinutuzumab consolidation, and a long-term phase III primary efficacy objective to compare consolidation therapy with obinutuzumab against no consolidation therapy with respect to PFS. The phase II primary objective was split into two stages with stopping rules at each stage based on attainment of MRD negativity in the bone marrow (BM) in patients who received at least 4 weeks of consolidation therapy with obinutuzumab. In the first stage, at least two of nine patients were required to achieve MRD negativity for the trial to continue to the second stage, and in the second stage, at least six of 23 patients were required to achieve MRD negativity for the trial to continue to evaluate the long-term phase III objectives. This was based on Simon's two-stage optimal design, where a MRD eradication rate of <15% would deem obinutuzumab inactive, and a rate >35% would deem obinutuzumab truly active, based on an 80% confidence interval (CI) with a one-sided 10% significance level.<sup>15</sup> The phase III design incorporated a calculated sample size of 188 patients to assess the primary end-point of PFS between the consolidation therapy with obinutuzumab and no consolidation therapy arms.

The trial also incorporated a monitoring group, where patients who were eligible but confirmed as MRD negative at registration were followed-up annually for MRD assessment, progression, and survival.

Secondary objectives of the trial included PFS, OS, treatment-free survival (TFS) for both the consolidation therapy with obinutuzumab and no consolidation therapy arms. The ORR as per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria following consolidation with obinutuzumab was assessed as was PFS, OS and duration of MRD negativity in patients who are and who become MRD negative with consolidation. Safety was

assessed by reported and observed adverse events (AEs), laboratory measurements, and clinical evaluation across the treatment-emergent period. AEs were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Quality-of-life assessment using the European Organisation for the Research and Treatment of Cancer quality of life questionnaire, 30-item core (EORTC QLQ-C30) and CLL Specific Module, EORTC QLQ-CLL16.

Minimal residual disease negativity was assessed in the BM at 6 months after randomisation and PB MRD analysis at 6, 12 and 24 months by highly sensitive multiparameter flow cytometry with a level of detection of less than one CLL cell in 10 000 leucocytes.<sup>16,17</sup>

An independent Data Monitoring and Ethics Committee (DMEC) reviewed the safety and ethics of the study. The trial was approved by all relevant institutional ethical committees and regulatory review bodies and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial was registered as an International Standard Randomised Controlled Trial (ISRCTN42165735); and on the European Clinical Trials Database (EudraCT: 2008-006342-25).

## Patients

Eligible patients required achievement of a complete or partial response (CR/PR) 3–24 months after chemotherapy and with a World Health Organization (WHO) performance status of 0 or 1. Patients with a lymph node of >1.5 cm were excluded. Eligible MRD-positive patients were randomised to receive either consolidation therapy with obinutuzumab or no consolidation therapy. Patients were not eligible if they had Hepatitis B or C; an active secondary malignancy; an active infection or past history of anaphylaxis following exposure to rat- or mouse-derived complementarity determining region-grafted humanised mAb. All patients provided written informed consent prior to trial enrolment and patients were able to withdraw from the trial at any time.

## Treatment and assessments

Obinutuzumab was given 1000 mg weekly for the first four doses (split over 2 days for first dose) and then four further doses fortnightly. Prophylaxis was given to reduce the risk of infusion-related reactions. Anti-viral and *Pneumocystis* pneumonia prophylaxis was not mandated. Granulocyte colony-stimulating factor (G-CSF) were mandated in patients experiencing CTCAE criteria Grade 3/4 neutropenia.

Patients were assessed for MRD response in the BM and PB at 6 months after randomisation. Long-term annual follow-up for survival is being performed until 4 years after randomisation (or 4 years after registration for MRD-negative pre-randomisation patients).

## Statistical methods

All analyses were conducted on the intention-to-treat (ITT) population, in which patients were included according to their randomised treatment. A two-sided 5% significance level was used for all formal phase III efficacy end-point comparisons. The MRD results were summarised with 80% and 95% CIs for the phase II and III objectives respectively. Kaplan–Meier curves were presented for the PFS and OS end-points. Patients without evidence of an event at the time of analysis were censored at the last date they were known to be alive and event free. Safety analyses summarised the number of safety events occurring after randomisation including treatment-related mortalities (within 3 months after treatment) and incidence of secondary cancers.

All statistical analyses were carried out using Statistical Analysis System (SAS) software 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical analysis programs were validated but are not available publicly.

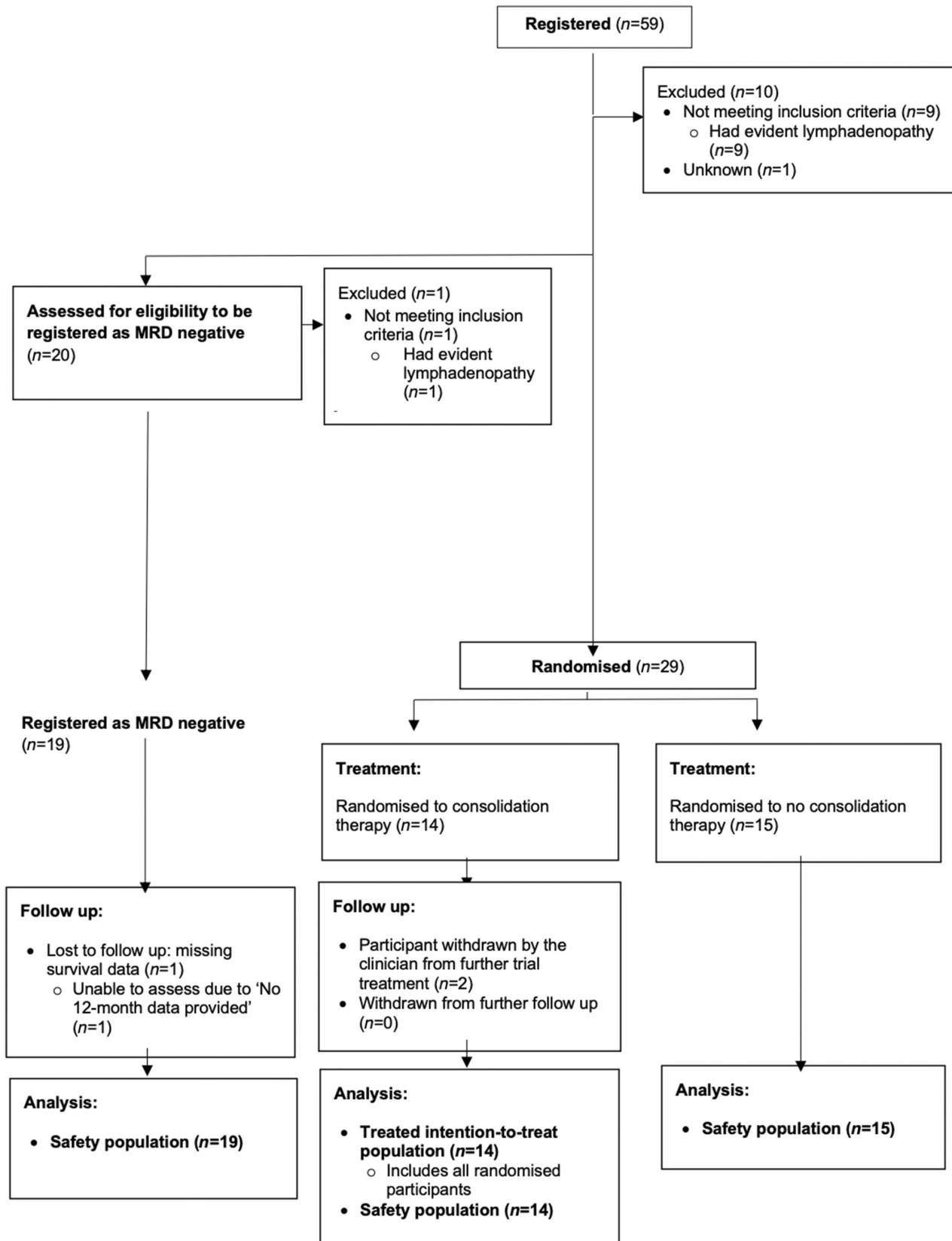
## RESULTS

### Trial timelines

The first participant was recruited to stage I of the phase II randomisation in April 2015. The DMEC approved the continuation to stage II in April 2016, after three of three consolidated patients achieved MRD negativity. In November 2016, the Trial Steering Committee (TSC), on advice from the DMEC and Trial Management Group (TMG), agreed that the trial should close due to poor recruitment. The decision was based on the fact that treatment paradigm for management of CLL was changing and it was unlikely to achieve recruitment in a reasonable time frame. The DMEC confirmed there were no safety concerns associated with the trial treatment and that it was important to continue to treat patients randomised to the consolidation therapy arm and follow-up all patients as per the protocol. The final patient was recruited into the trial on 24 February 2017. At that time, a total of 29 patients had been confirmed as MRD positive and randomised, and 19 further patients were confirmed as MRD negative and recruited into the monitoring arm.

### Patient characteristics

A total of 48 patients with written informed consent were registered between April 2015 and February 2017 from 20 UK institutions with local ethical and management approval, of which 29 patients were randomised in the MRD-positive arm and 19 patients were monitored in the MRD-negative arm. In all, 14 patients were randomised to receive obinutuzumab consolidation (seven CR, seven PR); 15 patients received no consolidation (five CR, nine PR, one N/K). The



**FIGURE 1** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. MRD, minimal residual disease.

Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1) shows the flow of patients throughout the trial.<sup>18</sup>

Baseline characteristics of the patients in the Main Study are listed in Table 1. The median (range) age was 69 (46–82) years and 72.4% were male. Overall, all patients in the

**TABLE 1** Patient characteristics

	Consolidation therapy, n (%)	No consolidation therapy, n (%)	Total, N (%)
MRD level at entry			
≤0.3%	6 (42.9)	7 (46.7)	13 (44.8)
>0.3%	8 (57.1)	8 (53.3)	16 (55.2)
Total	14 (100)	15 (100)	29 (100)
Lines of previous therapy			
1	10 (71.4)	7 (46.7)	17 (58.6)
2 or 3	4 (28.6)	8 (53.3)	12 (41.4)
Total	14 (100)	15 (100)	29 (100)
Age group			
≤65 years	6 (42.9)	7 (46.7)	13 (44.8)
>65 years	8 (57.1)	8 (53.3)	16 (55.2)
Total	14 (100)	15 (100)	29 (100)
Gender			
Male	9 (64.3)	12 (80.0)	21 (72.4)
Female	5 (35.7)	3 (20.0)	8 (27.6)
Total	14 (100)	15 (100)	29 (100)
Previous rituximab?			
Yes	14 (100.0)	13 (86.7)	27 (93.1)
No	0 (0.0)	2 (13.3)	2 (6.9)
Total	14 (100)	15 (100)	29 (100)

Abbreviation: MRD, minimal residual disease.

consolidation group and 13/15 patients in no consolidation group received prior rituximab. In all, 41.4% had received two or more lines of prior therapy and 55.2% had an MRD level of >0.3% at the time of trial entry. Of the 14 patients who were randomised to receive consolidation therapy with obinutuzumab, 12 received all eight cycles of treatment, with the other two patients receiving seven cycles before being withdrawn by the clinician. These patients were withdrawn due to treatment toxicity including neutropenia and thrombocytopenia. None of the patients withdrew consent for further follow-up.

Originally, it was planned that PFS would be the primary end-point for the phase III trial, with OS and TFS also being analysed as secondary end-points. However, due to lack of recruitment and the resulting change in trial design, it was decided that these would all become secondary end-points for the phase II trial. In addition to this, it was also decided that a Cox proportional hazards regression analysis would not be appropriate, given the small number of patients available to analyse.

### Primary end-point

The primary end-point analysis was carried out on the phase II population. As per the protocol, this included the first 23 patients randomised to consolidation therapy with obinutuzumab who received ≥4 weeks of treatment and had a known

**TABLE 2** Proportion of patients randomised to obinutuzumab consolidation with undetectable minimal residual disease at 6 months after randomisation—bone marrow and peripheral blood

Participant MRD response	Total, N (%)	Exact 80% CI of the proportion MRD negative, %	Exact 95% CI of the proportion MRD negative, %
Undetectable MRD at month 6—BM			
MRD positive	4 (28.6)		
MRD negative	10 (71.4)	50.8–86.9	41.9–91.6
Total	14 (100)		
Undetectable MRD at month 6—PB			
MRD negative	13 (92.9)		
Sample not sent	1 (7.1)	74.9–99.3	66.1–99.8
Total	14 (100)		

Abbreviations: BM, bone marrow; CI, confidence interval; MRD, minimal residual disease; PB, peripheral blood.

MRD response at 6 months after randomisation. Due to not meeting the recruitment target, the phase II population included all patients randomised to consolidation therapy with obinutuzumab prior to closing of the trial in January 2017 who received ≥4 weeks of treatment and had a known MRD response (in the BM) at 6 months after randomisation.

Although recruiting only 14 patients to the consolidation therapy arm, results in Table 2 demonstrate that 10 patients (71.4%) achieved MRD negativity in the BM (80% CI 51%–87%), exceeding the six MRD-negative responses required for the trial to continue to evaluate the long-term phase III objectives. In all, 13 patients (92.9%; 80% CI 74.9%–99.3%) achieved MRD negativity in PB; one patient was MRD positive in BM but had a missing PB MRD sample (Table 2). The PB MRD responses at month 12 and 24 in the 10 patients achieving MRD negativity with consolidation are summarised in Table 3, four of 10 and three of 10 patients remained MRD negative in PB at 12 and 24 months respectively.

### Secondary end-points

At a median follow-up of 24.9 months for consolidated patients and 27.3 months for non-consolidated patients since randomisation, the 2-year PFS rates were 92.9% for patients consolidated with obinutuzumab and 26.7% for the non-consolidated arm. Despite the smaller than required sample size, PFS was significantly better in the consolidated arm ( $p = 0.001$ ; hazard ratio [HR] 0.21, 95% CI 0.07–0.67) (Figure 2).

There has been no significant OS difference observed between the two arms ( $p = 0.308$ ; HR 0.34, 95% CI 0.04–3.32) (Figure 3). There have been four events in the consolidated arm including one death and 11 events including three deaths in the no consolidation arm.

There was no significant difference in the TFS in the two groups ( $p = 0.313$ ; HR 0.31, 95% CI 0.04–2.76) (Figure 4),



**TABLE 3** Proportion of patients randomised to obinutuzumab consolidation with undetectable minimal residual disease at 12 and 24 months after randomisation – peripheral blood

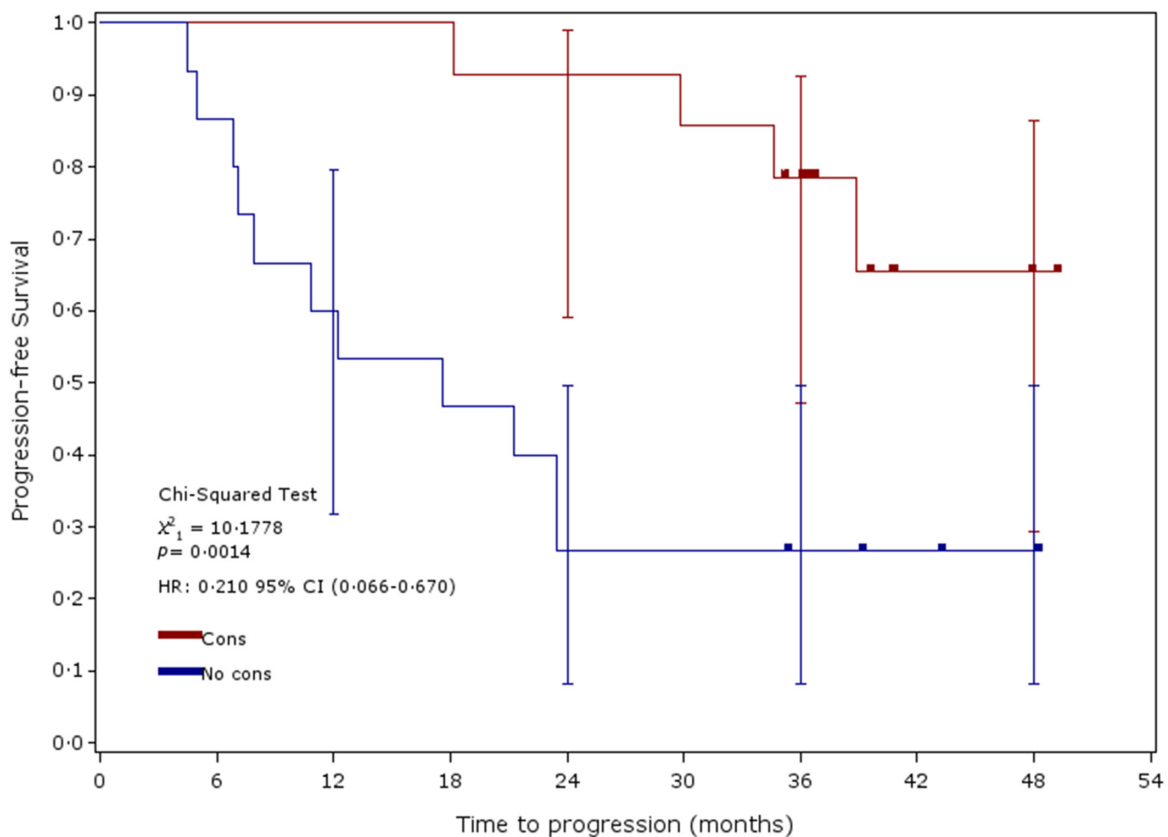
	Total, N (%)	Exact 80% CI of the proportion MRD negative, %	Exact 95% CI of the proportion MRD negative, %
<b>MRD response month 12</b>			
MRD positive	1 (10.0)	1.7–51.0	0.4–64.1
MRD negative	4 (40.0)		
Analysis not done	1 (10.0)		
Missing	4 (40.0)		
Total	10 (100)		
<b>MRD response month 24</b>			
MRD Positive	3 (30.0)		
MRD Negative	3 (30.0)	20.1–79.9	11.8–88.2
Missing	4 (40.0)		
Total	10 (100)		

Abbreviations: CI, confidence interval; MRD, minimal residual disease.

although only one participant returned to treatment in the consolidation arm in comparison to seven in the no consolidation arm.

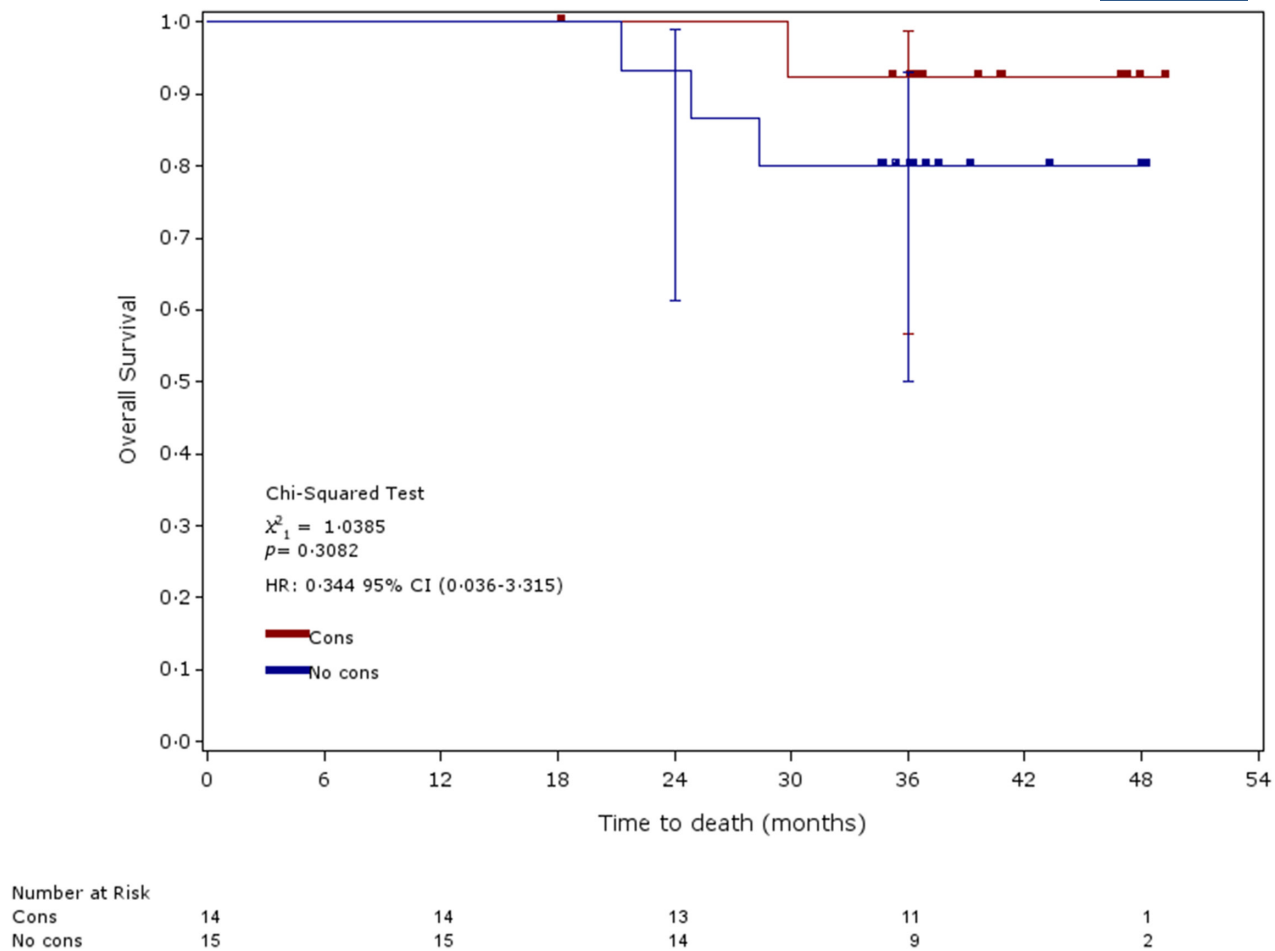
Out of the 14 patients receiving consolidation therapy, 13 (92.9%) achieved CR, whilst one (7.1%) achieved PR. Five out of the six patients who were in PR at entry improved their response to CR (Table 4).

We next compared the patients that became MRD negative in the consolidated arm with obinutuzumab (10 patients) to the MRD-negative group pre-randomisation (19). Survival time was taken from the final date of the most recently received CLL therapy for both groups. There was no difference observed in the PFS ( $p = 0.91$ ; HR 0.99, 95% CI 0.19–5.31) and OS ( $p = 0.92$ ; HR 1.07, 95% CI 0.10–12.12) respectively (Figures 5 and 6). Despite the small numbers, the curves for both arms appear similar and overlapping. The median time to MRD positivity in the pre-randomisation group was 35.0 months as compared to 23.2 months in the obinutuzumab-consolidated group. All patients in the obinutuzumab-consolidated arm had significant log reduction in MRD in PB and BM (Figure 7).



Number at Risk						
Cons	14	14	13	10	1	
No cons	15	9	4	3	1	

**FIGURE 2** Comparison of progression-free survival between trial arms. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 3** Comparison of overall survival between trial arms. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

## Safety and toxicity

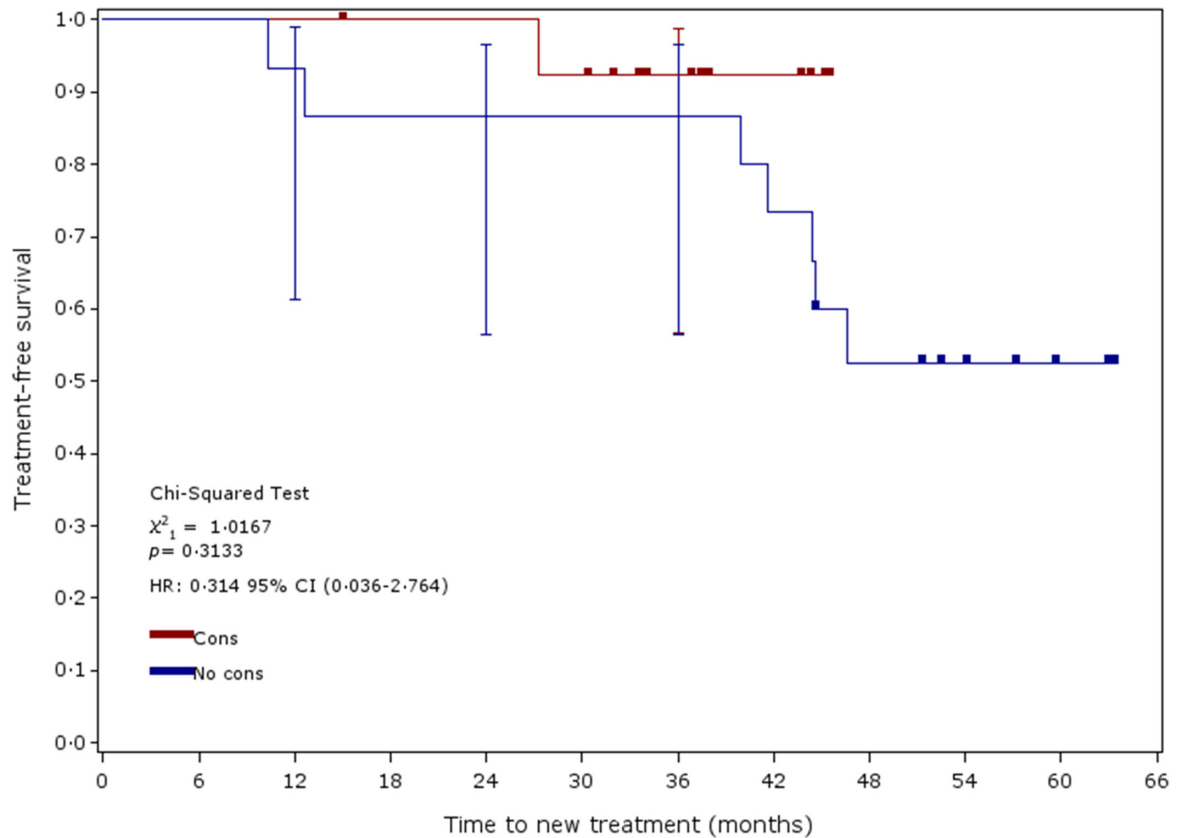
Six patients have died in the trial: one patient from the obinutuzumab-consolidated arm due to pneumonia secondary to myelodysplastic syndrome (this patient previously had treatment with FCR followed by ofatumumab in combination with FC at relapse, hence this event was not considered related to trial treatment); three patients from the non-consolidated group due to infections; and two patients from the MRD-negative pre-randomisation group due to causes unrelated to CLL (one infection and one prostate cancer).

As of 14 January 2019, five serious AEs (SAEs) have been reported from three patients, all receiving consolidation therapy with obinutuzumab. Of the five SAEs, three met the definition of an AE of special interest: two were reported from the same participant and classed as 'serious infection'; and one was reported from the second participant and classed as 'serious neutropenia'. All three were suspected to be related to obinutuzumab, classed as CTCAE Grade 3 and have now been recovered from. Two SAEs not suspected to be related to trial treatment have been reported from one participant receiving consolidation therapy. There were no reported participant deaths that occurred within 30 days post-treatment. There were 212 AEs reported from 17

patients; 203 reported from 12 patients receiving consolidation therapy with obinutuzumab and nine AEs from five patients receiving no consolidation therapy (Table 5). The five most common AEs for the consolidation therapy arm were thrombocytopenia (22.2% of AEs), infection (8.9% of AEs), cough (8.4% of AEs), non-specific pain (5.4% of AEs) and abdominal pain/bloating (5.4% of AEs). The mean serum immunoglobulin (Ig)G, IgA and IgM levels were 5.8 g/l, 0.6 g/l and 0.3 g/l respectively, not requiring any intervention.

## DISCUSSION

Attainment of MRD negativity has been demonstrated as an independent predictor of OS and PFS.<sup>5</sup> Long-term follow-up data from the GCLLSG CLL8 trial has also shown that low ( $<10^{-4}$ ) level MRD was associated with significantly better PFS and OS compared to intermediate ( $\geq 10^{-4}$  to  $<10^{-2}$ ) and high ( $\geq 10^{-2}$ ) level MRD.<sup>3,19</sup> Moreover, patients who achieve MRD negativity have a survival advantage in comparison to MRD-positive patients regardless of the approach used to achieve MRD negativity. For these reasons, the primary end-point of the phase II part of the GALACTIC trial was to determine the rate of



Number at Risk	
Cons	14      14      13      7      0
No cons	15      14      13      13      7      2

**FIGURE 4** Comparison of treatment-free survival between trial arms. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 4** International Workshop on Chronic Lymphocytic Leukemia (iwCLL) assessment of response for the consolidated patients at baseline and at 6 months after randomisation

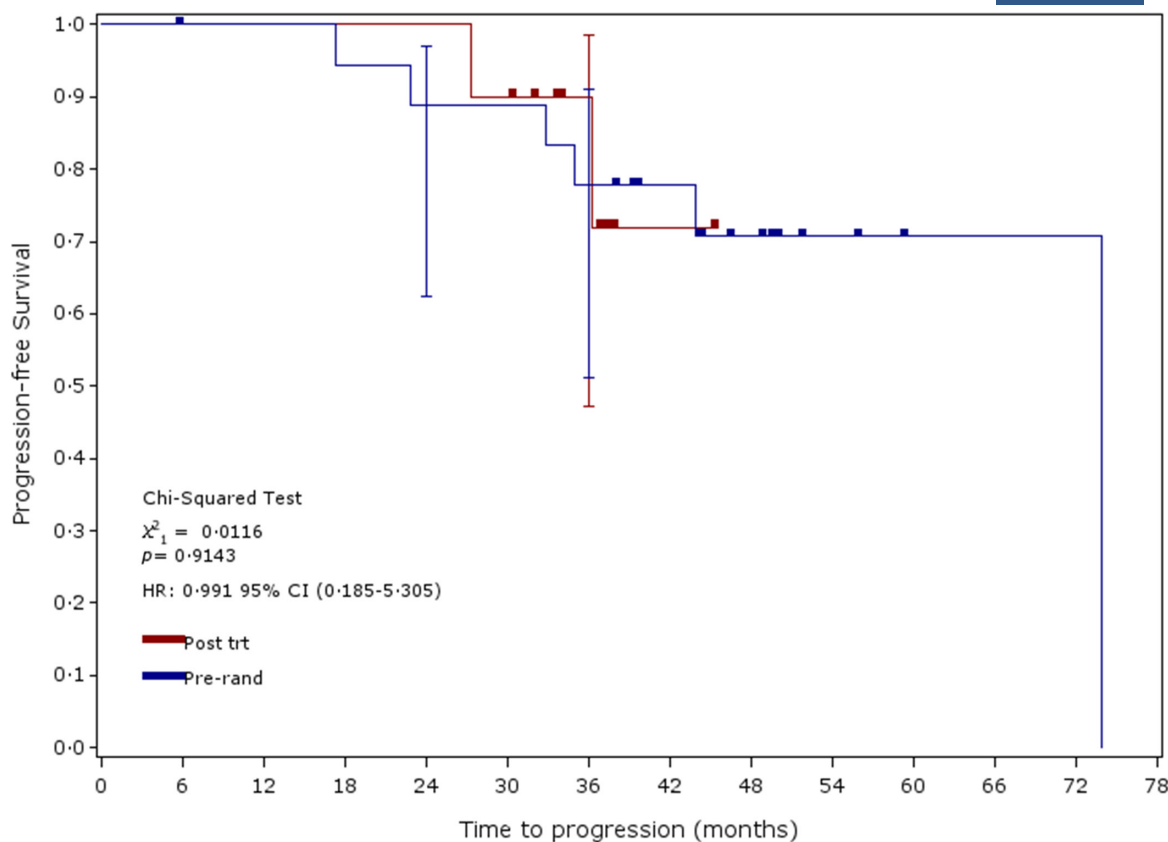
	Response to most recent previous CLL treatment, n (%)	6 months after randomisation, n (%)
iwCLL response		
Complete remission (CR)	6 (42.9)	13 (92.9)
Complete remission with incomplete marrow recovery (CRi)	2 (14.3)	0 (0.0)
Partial remission (PR)	6 (42.9)	1 (7.1)
Progressive disease (PD)	0 (0.0)	0 (0.0)
Stable disease (SD)	0 (0.0)	0 (0.0)
Unable to assess	0 (0.0)	0 (0.0)
<b>Total</b>	<b>14 (100)</b>	<b>14 (100)</b>

MRD negativity and to assess the safety of obinutuzumab in a consolidation setting. The primary focus was the rate of achievement of MRD negativity at 6 months after

randomisation in the BM. This time point was selected based on the UK CLL207 study, where it was observed that alemtuzumab efficiently cleared the disease at 3 months in the PB and BM compartment resulting in re-distribution of disease at 6 months, resulting in early MRD relapses.<sup>9</sup> We hypothesised that obinutuzumab may have a similar compartment effect; hence the assessments were performed at 6 months after randomisation.

The concept of consolidation in CLL has been studied before. The Cancer and Leukemia Group B (CALGB) 10101, an alemtuzumab consolidation trial, showed no statistically significant difference in 2-year PFS and OS between the consolidated and non-consolidated groups (PFS 76% vs. 68%,  $p = 0.35$ ; OS 84% vs. 88%,  $p = 1.0$ ), but here the consolidation treatment was given only to patients in PR or with stable disease, but not MRD-positive CRs.<sup>20</sup> The German CLL4B trial, however, randomised just 21 patients but showed a significant difference between patients who were consolidated versus not consolidated, with a 3-year PFS of 81.8% vs. 30.0% ( $p = 0.004$ ),<sup>10</sup> with patients receiving alemtuzumab having pronounced reductions in MRD levels. The UK National Cancer Research Network (NCRN) CLL207 study showed that consolidation with alemtuzumab resulted in a statistically significant





## Number at Risk

Post trt	10	10	10	5	0		
Pre-rand	19	18	16	14	7	1	1

**FIGURE 5** Comparison of progression-free survival in minimal residual disease (MRD)-negative consolidated patients versus MRD-negative monitoring group. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/bjh.18427)]

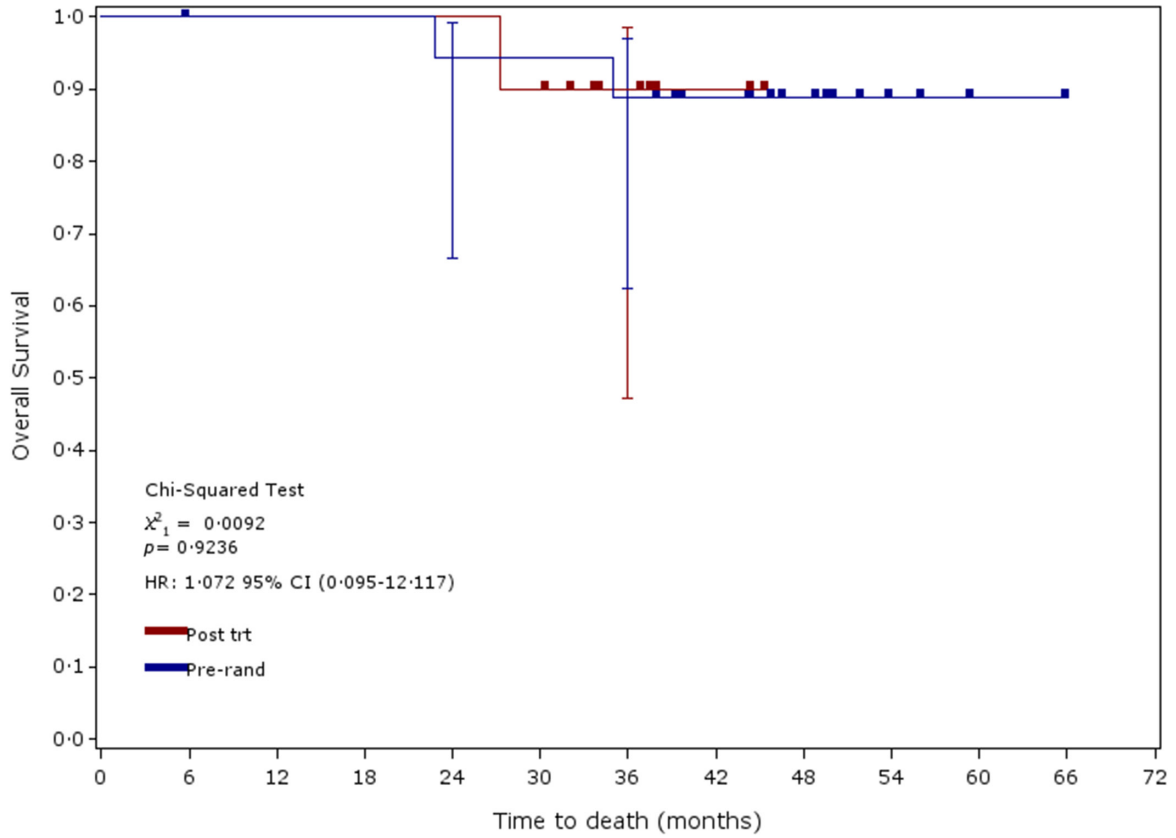
improvement in the 5-year PFS and OS of MRD-negative patients compared to patients who remained MRD positive.<sup>9</sup> Two maintenance trials using anti-CD20 antibodies, rituximab in CLL 2007 SA (ClinicalTrials.gov identifier: NCT00645606) and ofatumumab in PROLONG (ClinicalTrials.gov identifier: NCT01039376) have observed an improvement in PFS but not OS in front-line and relapsed refractory CLL.<sup>21,22</sup> However, MRD was not analysed as an end-point in these trials.

This trial showed that obinutuzumab consolidation after chemo-immunotherapy is efficient in achieving MRD negativity, in 92% and 71% of patients in PB and BM respectively. The high level of MRD clearance in both compartments resulted in an improved PFS in patients consolidated with obinutuzumab compared to those who received no consolidation. This difference was substantial despite the small numbers of events. With the relatively short follow-up and small participant numbers, no significant OS or TFS difference was observed between the two arms of the study. There were more progressions in no consolidation arm but not all progression events needed treatment hence no difference in TFS. Obinutuzumab consolidation resulted in an improvement of overall responses with all but one patient improving

their depth of response from PR to CR or CR with incomplete count recovery as per iwCLL criteria. We also observed log reductions in MRD levels in BM and PB in all patients receiving consolidation.

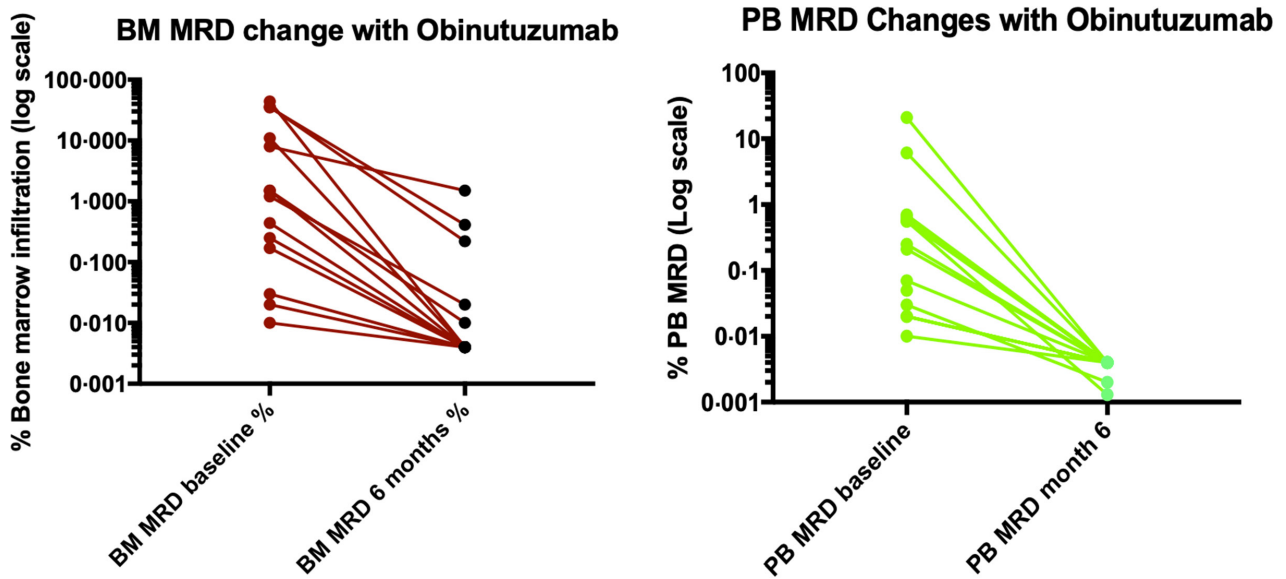
This study also demonstrates that the type 2 anti-CD20 antibody, obinutuzumab, is highly efficient in inducing deeper responses at MRD level when the disease bulk is low, as has been observed in other studies.<sup>23-26</sup> All the consolidated patients had low disease bulk as per entry criteria into the trial and were within 3–24 months of finishing chemo-immunotherapy. The selection of these patients allowed the hypothesis that obinutuzumab in this setting will be highly effective in improving the depth of response with an acceptable toxicity profile. The long-term OS data will continue to be collected, but it is likely that relapsing patients can be effectively treated with B-cell receptor inhibitors (BCRi) or B-cell lymphoma 2 (BCL-2) receptor antagonists (BCL-2i).

The GALACTIC trial also included an observation arm of 19 patients who achieved MRD-negative remission after chemo-immunotherapy at the point of entry to the trial. It was interesting that patients achieving MRD negativity after obinutuzumab consolidation had no sign of a PFS difference



Number at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Post trt	10	10	10	10	5	0	0	0	0	0	0	0	0
Pre-rand	19	18	17	16	8	1	0	0	0	0	0	0	0

**FIGURE 6** Comparison of overall survival in minimal residual disease (MRD)-negative consolidated patients versus MRD-negative monitoring group. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 7** Peripheral blood (PB) and bone marrow (BM) minimal residual disease (MRD) changes with obinutuzumab. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 5** Summary of adverse event descriptions, by trial arm

Adverse event description	Consolidation therapy, <i>n</i> (%)	No consolidation therapy, <i>n</i> (%)	Total, <i>N</i> (%)
Neutropenia	10 (4.9)	0 (0.0)	10 (4.7)
Thrombocytopenia	<b>45 (22.2)</b>	0 (0.0)	45 (20.9)
Anaemia (haemoglobin)	9 (4.4)	0 (0.0)	9 (4.2)
Neuropathy (sensory)	3 (1.5)	0 (0.0)	3 (1.4)
Diarrhoea	7 (3.4)	1 (8.3)	8 (3.7)
Nausea	1 (0.5)	0 (0.0)	1 (0.5)
Vomiting	2 (1.0)	0 (0.0)	2 (0.9)
Fever	2 (1.0)	0 (0.0)	2 (0.9)
Fatigue	9 (4.4)	0 (0.0)	9 (4.2)
Cough	<b>17 (8.4)</b>	1 (8.3)	18 (8.4)
Upper respiratory tract infection	7 (3.4)	2 (16.7)	9 (4.2)
Infusion-related reaction	2 (1.0)	0 (0.0)	2 (0.9)
Taste alteration	1 (0.5)	0 (0.0)	1 (0.5)
Abdominal pain/bloating	<b>11 (5.4)</b>	0 (0.0)	11 (5.1)
Constipation	2 (1.0)	0 (0.0)	2 (0.9)
Dyspnoea	2 (1.0)	0 (0.0)	2 (0.9)
Rash	1 (0.5)	1 (8.3)	2 (0.9)
Arthralgia	5 (2.5)	0 (0.0)	5 (2.3)
Bruising	0 (0.0)	1 (8.3)	1 (0.5)
Atrial fibrillation	1 (0.5)	0 (0.0)	1 (0.5)
Non-specific pain	<b>11 (5.4)</b>	1 (8.3)	12 (5.6)
Infection	<b>18 (8.9)</b>	1 (8.3)	19 (8.8)
Bleeding	3 (1.5)	0 (0.0)	3 (1.4)
Lymphopenia	9 (4.4)	0 (0.0)	9 (4.2)
Insomnia	7 (3.4)	0 (0.0)	7 (3.3)
Hyperglycaemia	7 (3.4)	0 (0.0)	7 (3.3)
Headache	4 (2.0)	0 (0.0)	4 (1.9)
Itching	2 (1.0)	0 (0.0)	2 (0.9)
Depression	1 (0.5)	1 (8.3)	2 (0.9)
Dry mouth	2 (1.0)	0 (0.0)	2 (0.9)
Other	2 (1.0)	3 (25.0)	5 (2.3)
<b>Total</b>	<b>203 (100)</b>	<b>12 (100)</b>	<b>215 (100)</b>

The bold values indicate significant difference between the two arms of the trial.

to the MRD-negative group in the monitoring arm of the trial ( $p = 0.91$ ; HR 0.99, 95% CI 0.19–5.31). This suggests that achievement of MRD negativity with consolidation translates into improvement of PFS that is comparable to MRD negativity following initial therapy.

Another benefit of obinutuzumab used in a consolidation setting is the toxicity profile of the drug. In similar settings where alemtuzumab treatment has been used, it has been associated with substantial toxicity. There were no deaths of trial patients related to obinutuzumab, all SAEs were resolved with no sequelae and the predominant toxicities were haematological, mainly thrombocytopenia. Neutropenia (4.7%) in the consolidated arm was managed by drug interruptions or use of G-CSF. The infusion-related reactions

were mild and predominantly with first infusion (two patients). The Ig levels, albeit slightly low, were satisfactory and did not require any intervention. This suggests that obinutuzumab consolidation after chemo-immunotherapy is safe to deliver.

The GALACTIC study findings have limitations because of early closure due to poor accrual. Recruitment was slower than anticipated due to the increasing use of BCRi and BCL-2i. This had an impact on the assessment of primary end-point of the phase III design of the trial. Although recruiting only 14 patients to the consolidation therapy arm, results demonstrated the efficacy of this approach to achieve MRD negativity in the BM at 6 months after randomisation and improving the PFS in this group. The study also recruited in the era

when chemo-immunotherapy was standard of therapy and the application of consolidation with obinutuzumab in era of targeted agent is being explored in various combinations to assess the depth of response.<sup>27,28</sup> This approach of consolidation with obinutuzumab needs to be explored in larger phase III trials in the era of targeted agents, as it is sensible to evaluate this approach in selected patients rather than use of triplet combination of mAb, BCRi and BCL-2i for all patients with CLL, thus reducing toxicity and cost.

In summary, the GALACTIC trial is strongly suggestive that consolidation of MRD-positive to MRD-negative remissions after completing conventional chemotherapy leads to improvement in PFS in CLL. Although MRD negativity is not necessary to improve outcomes with certain therapies, such as BCRi, achieving MRD negativity is associated with a better outcome in all scenarios that have been studied. As one goal of future therapy is to move to a defined shorter duration of therapy, MRD eradication will be an end-point that can be used to decide when to stop novel therapies, such as ibrutinib or venetoclax. In this setting, as far as we know, the remission will be sustained only if the treatment is continued, but it will be useful to know whether a combination or consolidation with mAbs will shorten the duration of therapy. This may have implications both in terms of toxicity of long-term use as well as the cost of treatment, but this trial even with its limitations substantiates our understanding that attaining MRD negativity, even with consolidation therapy, can improve the outcome in patients with CLL.

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#### CONFLICT OF INTEREST

Prof. Hillmen received research funding and speakers' fees from Roche Pharmaceuticals. Dr Rawstron reports personal fees from Roche Pharmaceuticals. Dr Munir reports personal fees from Roche Pharmaceuticals. Since completing work on this study, Dr Howard has become an employee of Roche Pharmaceuticals. There are no other conflicts of interest to declare in relation to the work described.

#### DATA AVAILABILITY STATEMENT

The authors would encourage data sharing. De-identified participant data is available. Any requests for trial data and

supporting material (data dictionary, protocol, and statistical analysis plan) will be reviewed by the TMG in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent TSC will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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