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Eradication of minimal residual disease improves overall and progression free survival in patients with chronic lymphocytic leukaemia, evidence from NCRN CLL207: A Phase II trial assessing alemtuzumab consolidation.

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Summary

With immunochemotherapy, remission duration and survival in patients with CLL is dependent on the level of minimal residual disease after treatment. This phase II trial assessed alemtuzumab consolidation post-chemotherapy in patients who responded with persistent low levels of detectable disease. Blood was screened for MRD using multi-parameter flow cytometry, 6 to 24 months post-chemotherapy. MRD-positive participants received alemtuzumab 30mg subcutaneously 3 times weekly for 6 weeks. Following a marrow assessment, MRD-negative participants or non-responders stopped therapy and MRD-positive participants with 1+ log reduction had 6 more weeks of alemtuzumab. Alemtuzumab consolidation was received by 47 participants. One death and 19 of 22 serious adverse events reported from 17 (36%) participants were alemtuzumab related. MRD eradication from blood and bone marrow was achieved in 39 (83%) participants at the end of consolidation, with 18 (38%) remaining MRD-negative in the blood 6 months later. Of the 18 MRD-negative participants at 6 months, the median time to MRD relapse was 46 months which was similar to patients who were MRD-negative at baseline and were followed up. The 5-year PFS and OS of MRD-negative participants at 6 months was significantly better than MRD-positive participants (PFS: 78%vs39% (p=0.010), OS: 89%vs64% (p=0.029)).

Keywords: Chronic lymphocytic leukaemia, minimal residual disease, alemtuzumab

Introduction

The treatment of Chronic Lymphocytic Leukaemia (CLL) has seen several advances over the past decade including advent of combination immunochemotherapy with Fludarabine, Cyclophosphamide and Rituximab (FCR) as the standard first line treatment and development of new agents such as several monoclonal antibodies, B-cell receptor signalling pathway inhibitors and BCL-2 inhibitors. **It is well established that with immunochemotherapy patients attaining complete remission (CR) have a better survival rate than those attaining partial response or less.** This led to the concept of improving the depth of response up to the point of eradication of minimal residual disease (MRD), which is a standard practice in many other haematological malignancies(Hallek *et al*, 2008). **In CLL patients treated with different immunochemotherapy, Kwok et al has shown that attainment of MRD-negativity is an independent predictor of Overall Survival (OS) and Progression-Free Survival (PFS) in a retrospective analysis**(Kwok *et al*, 2009). In addition MRD-negativity following front-line FCR is a strong predictor of PFS and OS(Böttcher *et al*, 2012)(Strati *et al*, 2014).

At the time of trial recruitment, alemtuzumab, a humanised monoclonal antibody specific for CD52, was licensed for the treatment of refractory CLL. But from 2012 onwards alemtuzumab is available for this purpose only on patient access programs as it was withdrawn by the manufacturer due to non-medical reasons. However the trial still serves as a proof of principle for consolidation treatment, and there are several other effective monoclonal antibodies which can be used for further trials. Previous trials consistently showed that alemtuzumab is more efficacious when administered to patients with lower levels of disease, providing a rationale to use the

drug as consolidation when patients have only MRD detectable after chemoimmunotherapy and no bulk disease. The German CLL4B trial, a phase III trial to compare alemtuzumab consolidation against observation after purine analogue therapy, was prematurely stopped due to infection related toxicity(Wendtner *et al*, 2004)(Schweighofer *et al*, 2009). A long term follow up of the 21 participants has shown that PFS was significantly prolonged for the 11 treated participants vs. those in observation arm. Possible reasons for the toxicity were the proximity to initial therapy, the dose and the route of administration. In treatment for clinically progressive disease, the median duration of alemtuzumab therapy required to attain an MRD-negative CR was 9 weeks in a study of 91 participants(Moreton *et al*, 2005). The pharmacokinetics of alemtuzumab in MRD is more likely to be related to that observed in the bone marrow transplant setting than with conventional CLL treatment due to the low level of disease(Hale *et al*, 2004)(Rebello *et al*, 2001). Thus, for MRD level treatment, a reasonable dosing strategy was selected to be 30mg three times weekly subcutaneously for 6 weeks, at least 6 months after the last chemotherapy, with the treatment period extended to 12 weeks if necessary. Moreover careful surveillance for infection and pre-emptive treatment, if needed, would help to reduce the infection related toxicity in these patients.

Methods

Trial design

CLL207 was a phase II, multi-centre, single-arm study, to determine the efficacy and safety of alemtuzumab consolidation in patients with low levels of MRD, definied as >1 CLL in 10,000 leucocytes, following conventional therapy. The joint primary endpoints were the MRD-negativity rate at the end of therapy and the proportion of

participants experiencing a predefined unacceptable level of toxicity. The secondary objectives were to assess clinical response to alemtuzumab therapy as defined by NCI Criteria, time to MRD relapse, progression free survival, overall survival and the pharmacokinetic profile of alemtuzumab in the MRD setting. An unacceptable toxicity was defined as any death or grade 3 or above toxicity attributed to the study treatment or its complications, excluding lymphopenia, grade 3 neutropenia or grade 4 neutropenia responding to GCSF. A two stage design was planned to incorporate a stopping rule if the treatment was not felt to be acceptable in terms of either efficacy or toxicity. The sample size was determined using the Bryant and Day design which incorporates toxicity considerations as well as clinical responses(Bryant & Day, 1995). The calculation was based on the assumptions that an MRD rate over 40% and toxicity rate under 20% is desired, and an MRD rate below 20% and toxicity rate above 40% is unacceptable. With 10% significance and 90% power, a total of 54 participants were planned, with the stage I assessment after 24 participants. 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.

Patients

Eligible patients had completed chemotherapy for CLL between 6 to 24 months prior to registering, having attained a complete or partial remission. They did not have lymph nodes greater than 2cm in diameter by CT-scan nor a peripheral B-cell count more than 5 x 10^9/l, and had not received more than 3 prior therapies for CLL or an allogeneic transplant. Patients who previously failed alemtuzumab therapy and those with persisting severe pancytopenia due to previous therapy rather than disease

were also excluded. MRD status was assessed at entry; MRD-positive participants received consolidation therapy in the Main Study; MRD-negative participants were followed up within the study and only treated if they become MRD-positive during the eligibility period, otherwise they were followed under a Monitoring Investigation.

Treatment

Participants were treated with 30mg subcutaneous alemtuzumab three-times weekly for 6 weeks after which bone marrow and peripheral blood were assessed for MRD. Alemtuzumab was stopped if bone marrow was MRD-negative or if there was no significant improvement in the level of CLL cells. Participants who were responding but remained MRD-positive were treated with a further 6 weeks of alemtuzumab and then reassessed for MRD. Peripheral blood MRD status was reassessed every 3 months after treatment. Participants were eligible to be retreated with alemtuzumab when they become MRD-positive, if they had remained MRD-negative for at least 6 months (Figure 1). Standard antimicrobial prophylaxis for alemtuzumab were given including monitoring of CMV PCR. Participants with neutrophils below 1.0 x 10^9/l were treated with G-CSF (filgrastim 300µg three-times weekly on the days of alemtuzumab).

Treatment was interrupted in the presence of the following events: platelets <25 x 10^9/l or neutrophils<0.25 x 10^9/l, grade 4 non hematologic toxicity, and grades 3 to 4 infection. Following the recovery of platelets to >50 x 10^9/l and neutrophils >0.5 x 10^9/l, alemtuzumab was re-introduced.

Response assessments

MRD response assessments were based on the bone marrow MRD findings, and were categorised as follows:

MRD-negative response: No detectable CLL in the bone marrow and peripheral blood by 4 colour flow cytometry and absence of lymphadenopathy and organomegaly attributed to CLL(Rawstron *et al*, 2007).

Partial response: At least 1 logarithmic reduction in bone marrow CLL cells but still MRD-positive.

Progressive disease: At least 1 logarithmic increase in bone marrow CLL cells or new clinically evident lymphadenopathy or splenomegaly.

Stable disease: Not falling into any of the above categories.

Clinical response was also assessed according to the NCI response criteria 1996(Cheson *et al*, 1996)

Pharmacokinetics study

A pharmacokinetics study was planned on consenting participants from selected centres. Serum alemtuzumab concentration was analysed using indirect immunofluorescence described by Rebello and Hale(Hale *et al*, 2004) at baseline,3, 6, 9 and 12 weeks of treatment, where appropriate, and at 1, 2, 4, 6 and 12 weeks after treatment.

Statistical methods

Response rates derived based on bone marrow findings as well as NCI criteria are summarised for the Main Study population and 95% confidence intervals (CI) reported for the proportion of participants who became MRD-negative. Time to MRD relapse, PFS and OS are described using Kaplan-Meier curves. Safety is summarised by the number and proportion of participants who suffer an unacceptable toxicity, and 95% CIs reported. Details of the toxicities are also summarised using adverse event and treatment-related mortality rates. Planned

subgroup analyses summarise the primary endpoints, MRD relapse and survival data (where appropriate).

Results

Participant Characteristics

Sixty-one participants with written informed consent were registered between December 2006 and January 2010 from 11 UK institutions with local ethical and management approval. 47 participants were treated within the Main Study, of which 43 had detectable disease at registration and 4 became MRD-positive within 24 months of completing their prior therapy. 11 participants remained in the Monitoring Investigation and 3 withdrew or were found to be ineligible before receiving treatment. The CONSORT diagram(Schulz *et al*, 2010)(Figure 2) shows the flow of participants throughout the trial. The recruitment target of 54 participants to the Main Study was not met due to slower than anticipated recruitment.

Baseline characteristics of the participants in the Main Study are displayed in Table 1. The median age was 58 years (range 40-77) with 75% men. The relatively young population is expected given the concerns of additional toxicity with alemtuzumab. 49% had received just one prior therapy, and 30% had received two (range 1-4). 98% received prior fludarabine and 19% prior rituximab. 45% had responded to prior therapy with a CR and 55% with a PR. The mean neutrophil count of the participants was 2.91×10^9/l (range 0.7-5.1), lymphocyte count was 1.45×10^9/l (range 0.3-6.2), 49% had a normal or high IgG level and 28% had a low but detectable IgG.

Treatment

The duration of treatment received is summarised in Table 2. **Of the 47 participants, 6(12.8%) did not receive the full 6 cycles as protocolled.**

12(25.5%) participants were eligible to be treated for a further 6 weeks, and of these 4(33.3%) did not receive all 12 cycles. Reasons for early stopping included Adverse (AEs), CMV reactivation, cytopenia and participant choice. 20(42.6%) participants had a dose delay or modification for at least one week of treatment.

Primary Endpoint Analysis

At the analysis of stage I, reported to the DMEC in December 2008, 18/24(75.0%) participants responded to treatment with MRD-negativity, and 5(20.8%) suffered an unacceptable adverse reaction (AR), which did not pass the planned stopping boundaries. The DMEC felt that the toxicity was significant but manageable, and since the efficacy outcome was encouraging, the trial should proceed.

At the stage II analysis, summarised in Table 2, 39/47 (83%; 95%CI: 69%-92%) responded to treatment with MRD-negativity, which greatly exceeded the stopping boundary for efficacy of 13 responses. The denominator includes the participant with a missing response, to ensure the most conservative response rate by intention to treat. An unacceptable adverse reaction occurred in 10/47(21.3%), which was less than the stopping boundary of 15 participants, so the pre-defined stopping criteria were not met.

Efficacy Endpoints

The overall response rate (ORR), defined as complete or partial remission (CR/PR) by NCI Criteria, was 91.5% as summarised in Table 2. **As of August 2015, the median follow-up for survivors was 6.3 years. The five-year PFS was 53.2%, and OS was 72.2%.** Kaplan-Meier OS and PFS curves are presented in figures 3A and 3B respectively. The median time to progression was 70 months, and the median OS was not yet reached.

Of the 39 participants who became MRD-negative following treatment, the five-year survival for MRD relapse, progression or death was 11.2%. The median duration of MRD-negativity was 6.7 months (95%CI: 5.6,25.0). 21/39 MRD-negative participants (53.8%) became MRD-positive within 6 months of completing therapy, and participants who remained MRD-negative beyond 6 months appeared to have a greater chance of sustained MRD-negativity, as illustrated by the Kaplan-Meier MRD curve presented in figure 3C. If MRD-negativity is assessed in the peripheral blood 6 months after completing alemtuzumab, 18/47 participants (38%) reached this target (Table 2). PFS and OS was significantly better in the MRD-negative participants at 6 months compared to those who were MRD-positive (p-values 0.010 and 0.029 respectively) (figures 4A and 4B).

Fifteen participants were MRD-negative at registration to the trial, 4 of whom became MRD-positive and were eligible for trial treatment, and the remaining 11 were followed up for relapse within the monitoring investigation. As of August 2015, the median follow-up from previous treatment in these 11 participants was 7 years, with one clinical progression at approximately 6 years after treatment and 2 deaths, both approximately 5 years after treatment. Ten of the 15 participants who were MRD-negative at registration have relapsed to become MRD-positive or died. The median duration of MRD-negativity is 59.4 months (95%CI: 24.7,not reached), which was not significantly different to those patients who converted to MRD negativity when assessed 6 months after alemtuzumab consolidation, although the numbers for comparison are small (hazard ratio 1.57 (95%CI: 0.62,3.97)), figure 4C.

Subgroup Analyses

Nine participants went on to receive 11 or 12 weeks of therapy of which 6(67%) became MRD-negative by the end of treatment, but only 1(11%) remained MRD-

negative at 6 months post-alemtuzumab. This suggests that there is no advantage to extend the therapy beyond 6 weeks.

Nine participants had previously received rituximab; all became MRD-negative following therapy, and 2 (22%) remained MRD-negative after 6 months. None of these participants suffered an unacceptable toxicity.

The MRD responses in participants who had received one (20/23(87%)) or multiple prior therapies (19/24(79%)) were comparable. After 6 months these response rates became 10/23(44%) and 8/24(33%) respectively. **There was a trend towards more participants who had received multiple prior therapies suffering an unacceptable toxicity (7/24(29%) vs 3/23(13%)), and having a worse median PFS and OS (PFS 71 vs 45 months; OS not reached vs 60 months). Since the subgroup analyses are exploratory, it was not planned to assess significance in the differences between the subgroups, but the trends seen are expected due to the nature of the disease and treatment.**

Safety

As of August 2015, 15 participants in the main trial (31.9%) have died. One death, caused by parainfluenza pneumonitis, was considered directly related to treatment. Two other deaths were the outcome of SAEs, although not directly related to treatment: myelodysplasia related infection and EBV driven lymphoproliferative disorder. Other causes of death were: 4 CLL related infections; 3 overwhelming tumour burden; 2 transformed disease; 1 Crohn's Disease; 1 pulmonary embolism; 1 multiple myeloma. 22 SAEs were reported from 17(36.2%) participants, with 19suspected to be related to alemtuzumab, of which 2 were unexpected (SUSARs): the parainfluenza infection resulting in death and an EBV related diffuse large B-cell lymphoma (DLBCL) leading to upper gastrointestinal haemorrhage. SAEs and AEs

are summarised in Table 2.Eleven events from 10 participants were considered unacceptable as per protocol definition. Four were considered highly unacceptable:1 pneumocystis pneumonia;1 parainfluenza related death and 2 EBV related transformed diseases. Seven other events were easily manageable but considered unacceptable due to requirement of intravenous antibiotics (n=5), grade 4 thrombocytopenia (n=1) and grade 4 neutropenia not responding to G-CSF (n=1). 414 AEs were reported with 339 suspected to be alemtuzumab related, the most common being rashes(13%), cytopenia(13%), fatigue(8%), non-specific respiratory symptoms(8%) and fever(5%).Twenty-one(44.7%) of the treated participants had a positive CMV PCR during alemtuzumab;19(90.5%) occurred within the first 3 weeks of treatment. 30 participants received growth factor support, before treatment(n=3), while on treatment(n=12) or after treatment(n=15). The range of G-CSF support varied widely from pre-treatment to 27 months post treatment, with median duration11 months (range 0–67 months).

Of the 12 participants receiving more than 6 weeks of treatment, 4 SAEs related to alemtuzumab were reported from 3 (25%) participants. Of these, only 2 were reported after their 6th cycle. Of the 11 events that were deemed unacceptable, only 1 was from 1 participant who received 12 cycles (at cycle 12). The other 10 were within the first 6 cycles. This may imply that most of the toxicity happens within the first 6 weeks of treatment itself.

Pharmacokinetics study

Serum alemtuzumab concentration was analysed in 5 participants. Lympholytic level was reached within 3 weeks (when the 1st post dose sample was tested) in all participants, unlike refractory patients treated with alemtuzumab in whom it took an average of 6 weeks to reach a concentration of 1µg/mL . The mean highest

concentration in individual participants was 8.24µg/mL(range2.70µg/mL-11.97µg/mL), similar to the refractory patient group. The drug was detected in plasma up to 11 weeks after finishing treatment.

Discussion

Alemtuzumab consolidation is efficient, with 83% of participants attaining MRD-negativity at the end of treatment. This high rate of MRD-negativity was not sustained, and 54% of MRD-negative participants relapsed at the MRD level in the peripheral blood by 6 months. At this time the MRD relapse curve flattened, suggesting that the 18 participants who remained MRD-negative in their peripheral blood at 6 months had a sustained MRD-negative response. Although a number of participants relapsed quickly at the MRD level, this did not translate into a fast clinical progression or death. Of the 47 treated participants, the 5 year PFS and OS rates were 53% and 72% respectively.

Faster rate of MRD relapse within the first 6 months after treatment compared to beyond this period is probably explained by the redistribution of malignant cells between compartments. It is well described that alemtuzumab clears the disease in blood and marrow much more effectively than nodal disease. It seems likely that residual disease in lymph nodes redistributes to the blood and marrow within the first 6 months after completing alemtuzumab suggesting that this is not a true relapse, but a redistribution of resistant disease. The participants who relapse beyond this initial 6 month period represent a true progression.

This study also demonstrates that patients benefiting from alemtuzumab consolidation tend to respond within the first 6 weeks of treatment. In addition, peripheral blood MRD level at 6 months after consolidation is a truer indicator of persistent disease at MRD level than a marrow at the end of treatment, which would

be an unnecessary investigation as it is unlikely to change the future disease management.

Participants who attained MRD-negativity have a better PFS and OS compared to those who remained MRD-positive. Previously, CALGB-10101, an alemtuzumab consolidation trial, showed no statistically significant difference in 2-years PFS and OS between 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 participants in PR or SD, but not MRD-positive CRs(Lin *et al*, 2010). GermanCLL4B, however, randomised just 21 participants but showed a significant difference between participants who were consolidated vs not consolidated, with 3-year PFS 81.8% vs 30.0% (p=0.004)[5], with participants receiving alemtuzumab having pronounced reductions in MRD levels. **Long term follow up data from the German CLL8 trial has also shown that low (< 10^{-4}) level MRD was associated with significantly better PFS and OS compared to intermediate (≥ 10^{-4} to <10^{-2}) and high (≥ 10^{-2}) level MRD(Böttcher *et al*, 2012).** Although MRD negativity is not necessary to improve outcomes with certain therapies, such as B-cell receptor inhibitors, achieving MRD negativity is associated with a better outcome in all scenarios that have been studied and 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 monoclonal antibodies will shorten the duration of therapy. This may have implication both in terms of toxicity of long term use as well as the cost of treatment. Alemtuzumab is not the right choice in this situation,**

due to its toxic profile and non availability for commercial use, but this trial substantiates our understanding that attaining MRD negativity even with consolidation therapy can improve the survival outcome in CLL patients.

Further analysis has shown that the MRD status at the end of treatment is not the accurate determinant of long-term PFS and OS (p=0.602 and p=0.780 respectively), but it is the MRD status 6 months after the treatment. The 5-year PFS and OS of MRD-negative and positive participants at 6 months are 77.8% vs 39.3% (p=0.010) and 88.9% vs 63.9% (p=0.029) respectively. Their progression is similar to the participants who were MRD-negative at the entry of trial (HR=1.57 (95%CI: 0.62,3.97)). **Meaningful interpretations of subgroup analysis for various prognostic factors including genetic factors were not possible due to small numbers in each subgroup.**

Treatment is associated with substantial but manageable toxicity. Delaying the treatment to at least 6 months after the immediate prior treatment means that patients entering trial had a relative high proportion of normal haematological and other laboratory parameters. In addition, limiting the duration of treatment to 6 weeks reduces the chance of alemtuzumab being toxic to other CD52+ve targets like CD4+ T-cells. The pharmacokinetic study supports this shorter duration of treatment as the lympholytic dose is reached much earlier, as the disease burden is much smaller when compared to patients with clinical disease. Similarly patients who had more than one line of previous therapy experienced higher rate of unacceptable toxicity and had shorter PFS and OS. These suggest the need for careful patient selection and possibly consider consolidation at an earlier stage in the treatment line of CLL.

In summary, the CLL207 trial is strongly suggestive that that consolidation of MRD-positive to MRD-negative remissions after completing conventional chemotherapy

leads to a large improvement in outcome. However alemtuzumab in this setting carries a significant toxicity and it would be preferable to use a more specific monoclonal antibody that did not deplete T-cells. On the basis of the very promising sustained remissions seen in CLL207 we have commenced a randomised Phase III consolidation trial, the NCRI GALACTIC Trial, of the anti-CD20 antibody, obinutuzumab, which appears to result in MRD-negative remissions without the immune suppressive problems associated with alemtuzumab.

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Figure Legends

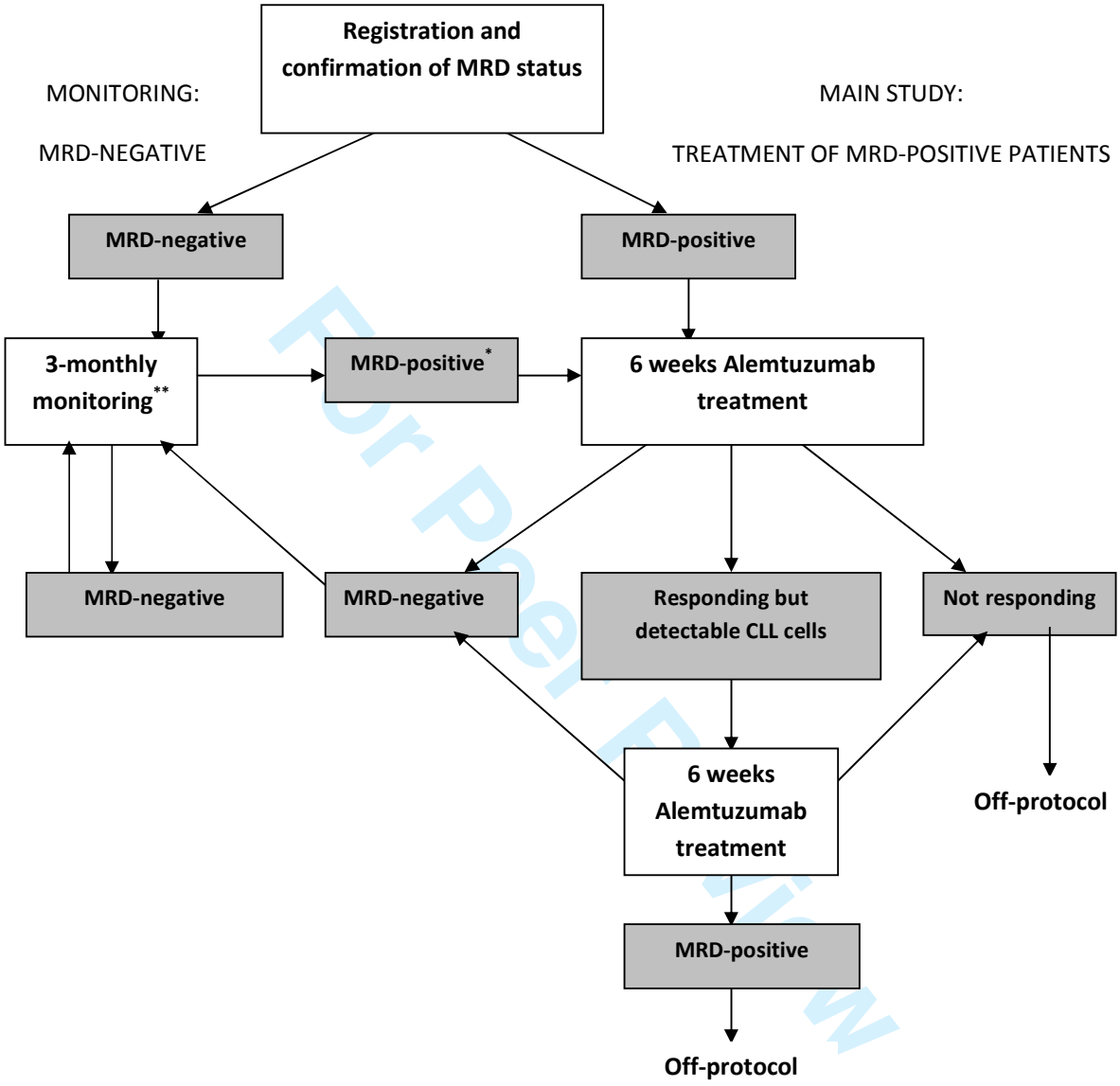
Figure 1: Study flow diagram

Figure 2: CONSORT flow diagram

Figure 3: (A) Progression-free survival and (B) overall survival of the treated population (C) MRD relapse in participants who were MRD-negative at end of therapy

Figure 4: (A) Progression-free Survival and (B) overall survival by MRD status at 6 months post treatment (C) survival outcomes for MRD relapse in participants who were MRD-negative at end of therapy compared to those who became MRD-negative 6 months after consolidation

Figure 1



* Participants previously entering the main study must have had a minimum of 6 months since treatment Alemtuzumab
** Until end of study

Figure 2

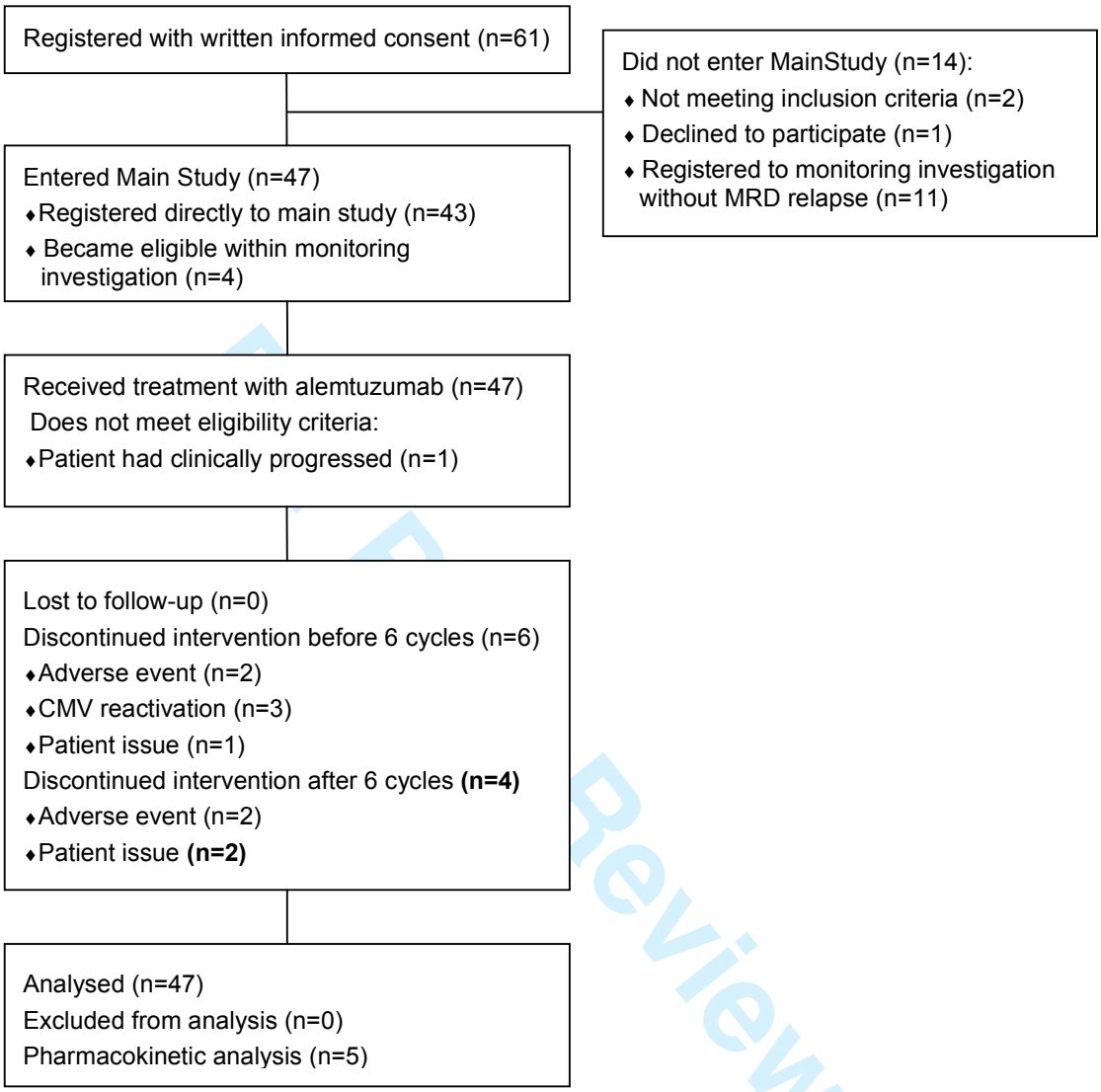
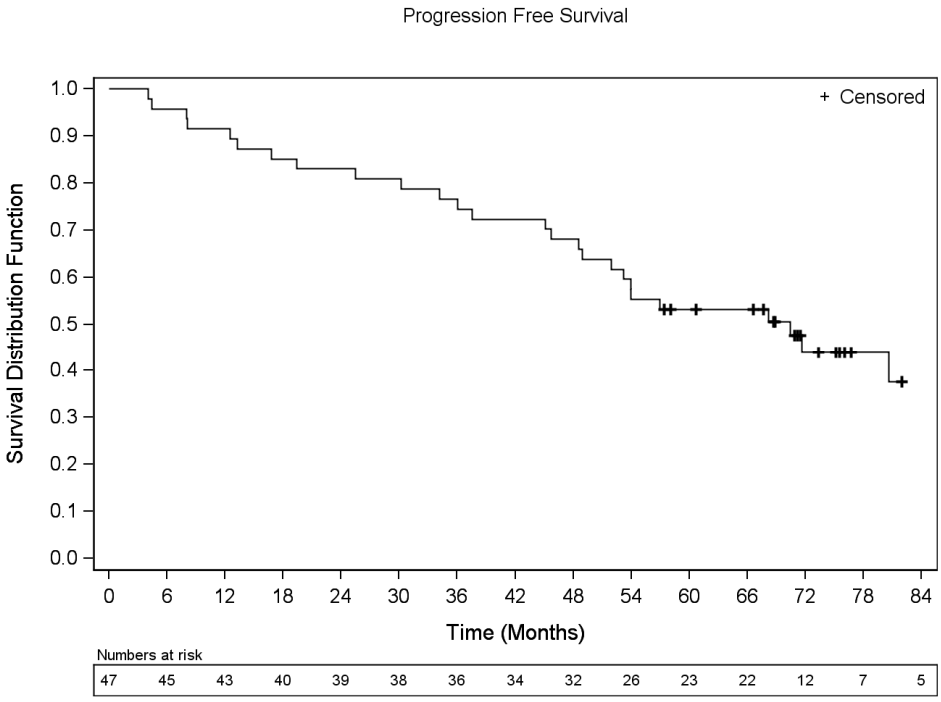
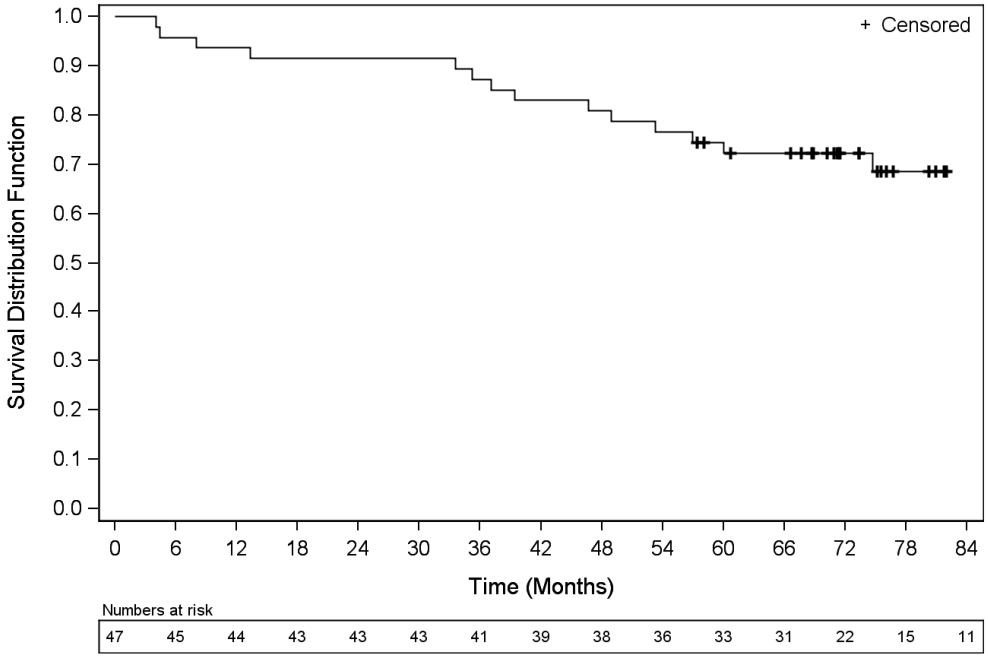


Figure 3

A


Progression Free Survival
+ Censored
Survival Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Time (Months)
Numbers at risk
47 45 43 40 39 38 36 34 32 26 23 22 12 7 5


Overall Survival
+ Censored
Survival Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Time (Months)
Numbers at risk
47 45 44 43 43 43 41 39 38 36 33 31 22 15 11

B

C

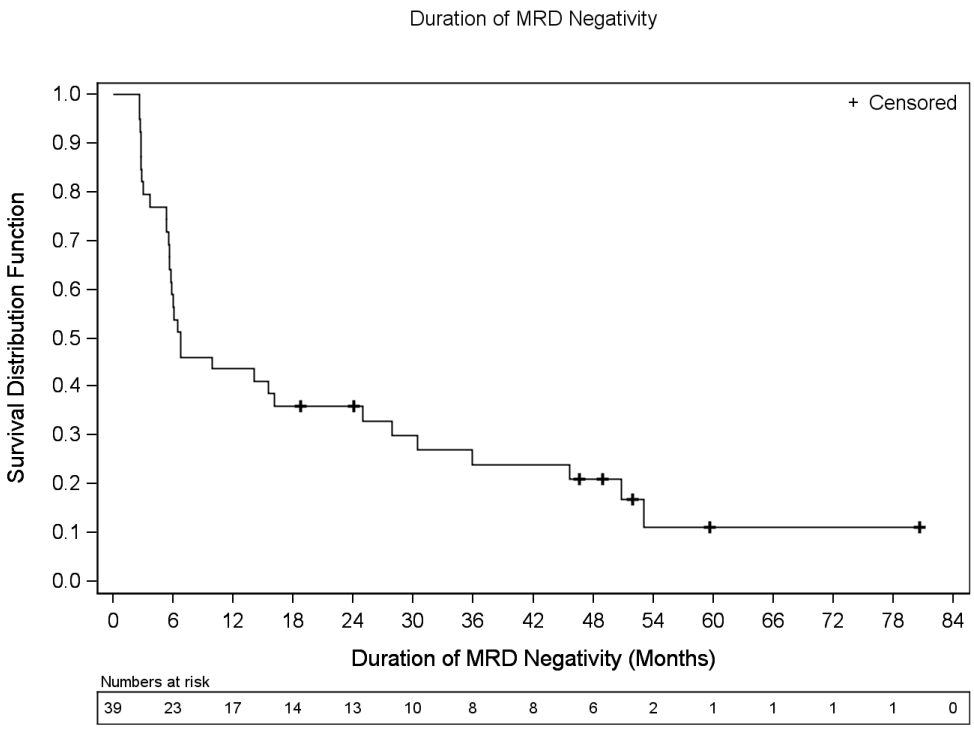
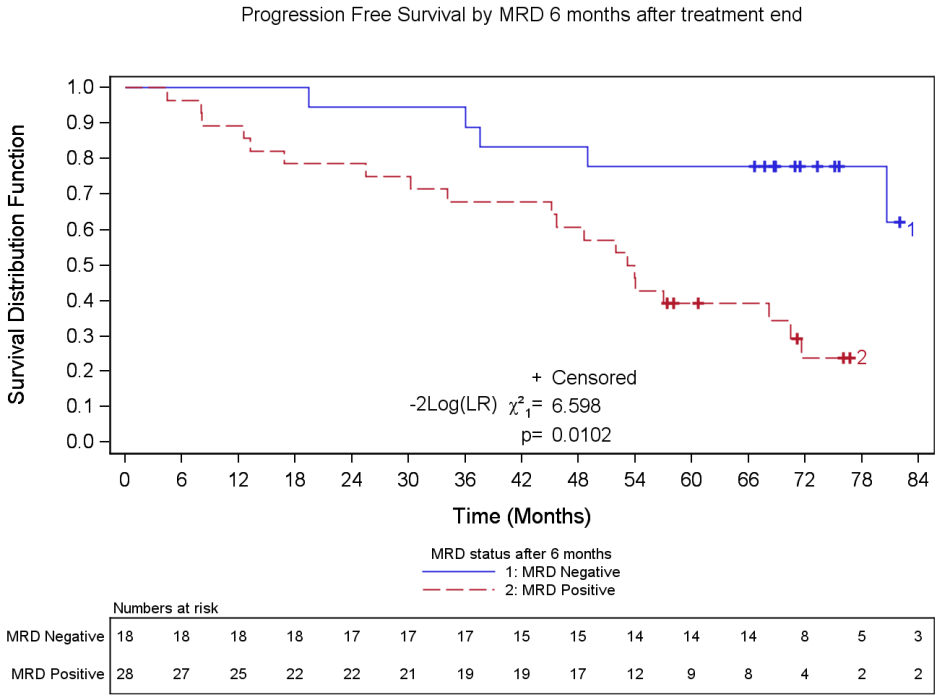
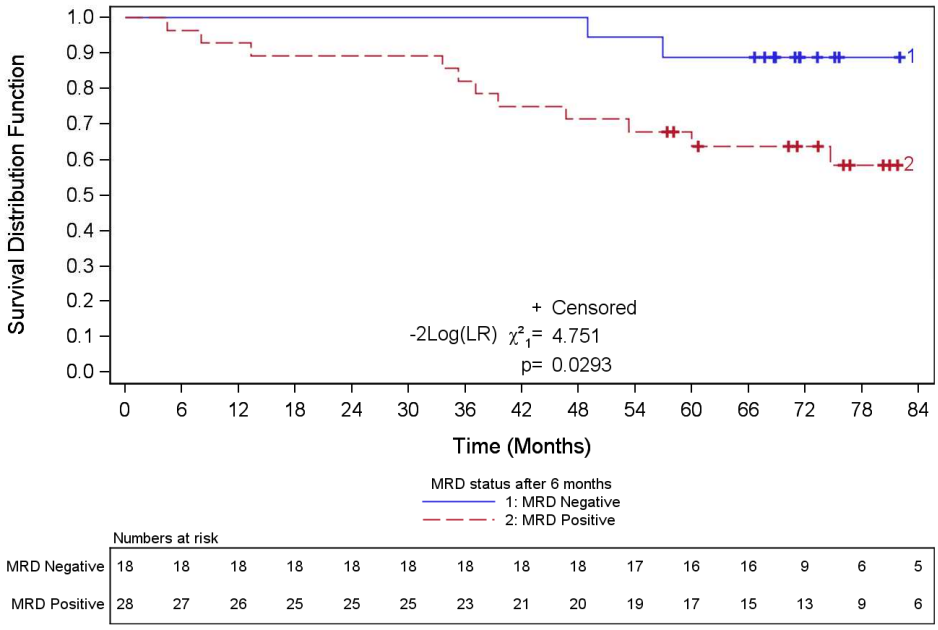

Duration of MRD Negativity
+ Censored
Survival Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Duration of MRD Negativity (Months)
Numbers at risk
39 23 17 14 13 10 8 8 6 2 1 1 1 1 0

Figure 4

A


Progression Free Survival by MRD 6 months after treatment end
Survival Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
+ Censored
-2Log(LR) χ^2_1= 6.598
p= 0.0102
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Time (Months)
MRD status after 6 months
1: MRD Negative
2: MRD Positive
Numbers at risk
MRD Negative 18 18 18 18 17 17 17 15 15 14 14 14 8 5 3
MRD Positive 28 27 25 22 22 21 19 19 17 12 9 8 4 2 2

B


Overall Survival by MRD 6 months after treatment end
Survival Distribution Function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
+ Censored
-2Log(LR) χ^2_1= 4.751
p= 0.0293
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Time (Months)
MRD status after 6 months
1: MRD Negative
2: MRD Positive
Numbers at risk
MRD Negative 18 18 18 18 18 18 18 18 18 17 16 16 9 6 5
MRD Positive 28 27 26 25 25 25 23 21 20 19 17 15 13 9 6

C

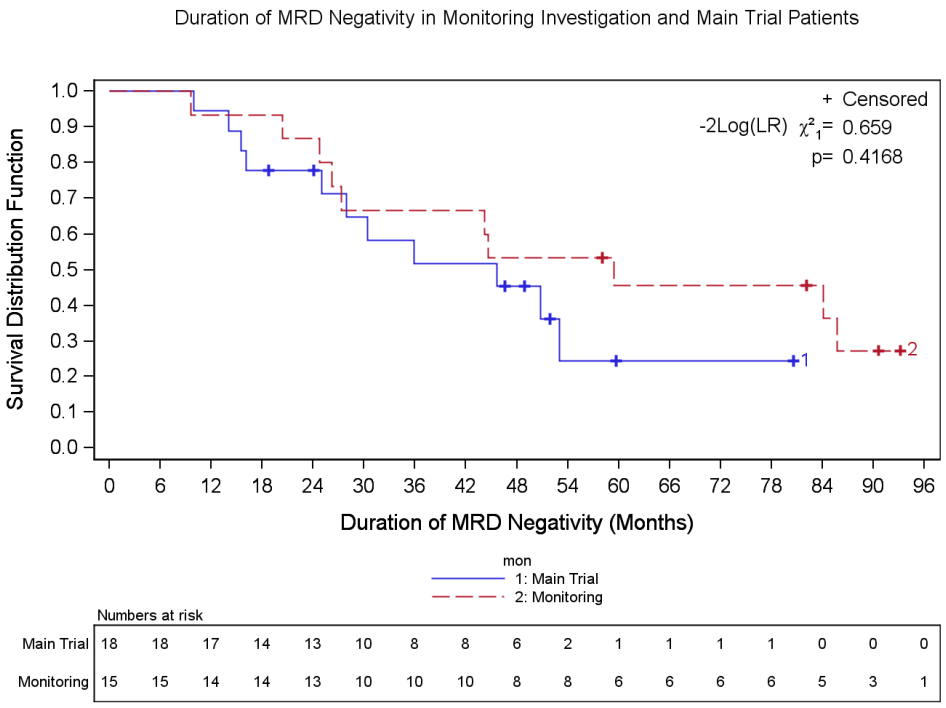


Table 1 Baseline Characteristics

	Main Study (Treated Population)	Monitoring Investigation (No Consolidation Treatment)	Total
Total	47	11	58
Male	35 (74.5%)	8 (72.7%)	43 (74.1%)
Age: median (range)	58.0 (40–77)	60.0 (44-76)	58.5 (40-77)
Disease Stage (BINETS criteria)			
Stage A	39 (83.0%)	5 (45.5%)	44 (75.9%)
Stage B	2 (4.3%)	2 (18.2%)	4 (6.9%)
Stage C	3 (6.4%)	0 (0.0%)	3 (5.2%)
Number of Previous Lines of Therapy			
1	23 (48.9%)	8 (72.7%)	31 (53.4%)
2	14 (29.8%)	3 (27.3%)	17 (29.3%)
3-4*	10 (21.3%)	0 (0.0%)	10 (17.2%)
NCI Response to Previous Treatment			
Complete Response	21 (44.7%)	8 (72.7%)	29 (50.0%)
Partial Response	26 (55.3%)	2 (18.2%)	28 (48.3%)
Prior Fludarabine Treatment	46 (97.9%)	10 (90.9%)	56 (96.6%)
Prior Rituximab Treatment	9 (19.1%)	2 (18.2%)	11 (19.0%)

* The eligibility criteria were limited to 3 previous lines of therapy after two participants had already entered with 4.

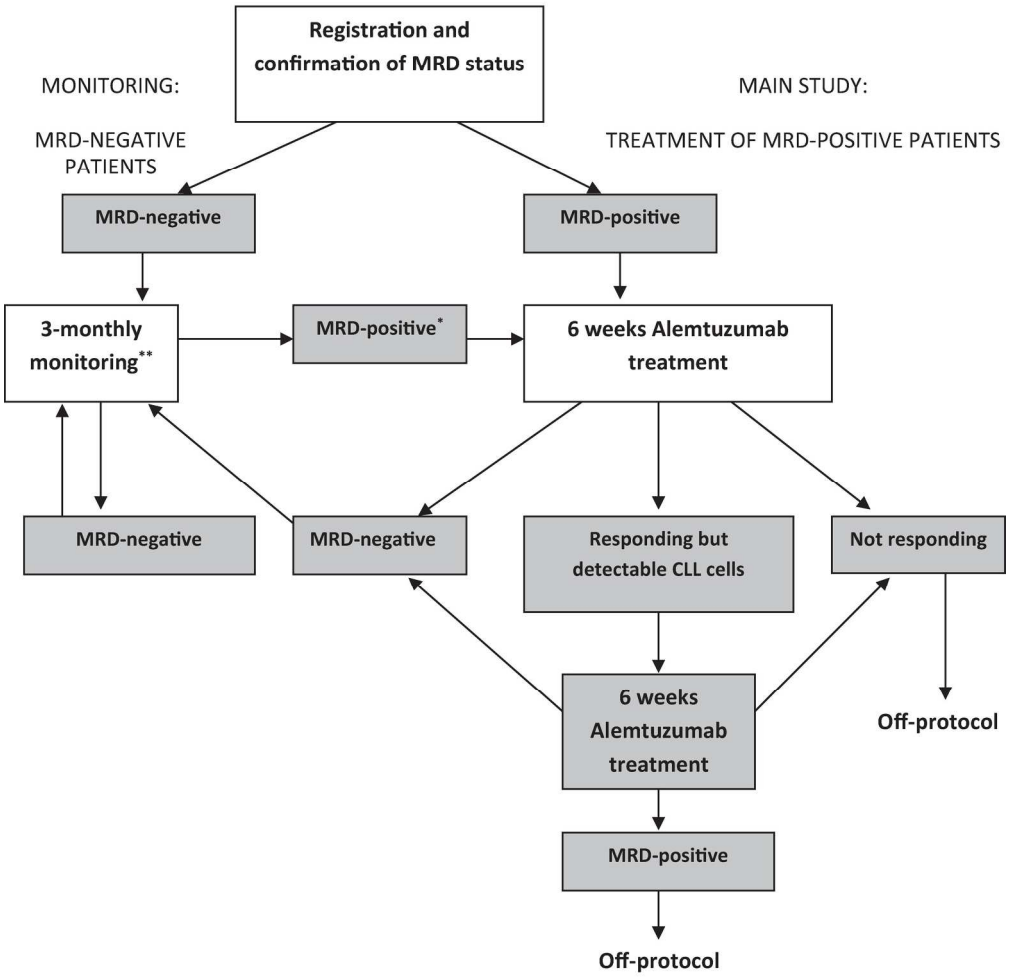
Table 2 Treatment Duration, Efficacy and Safety Summaries

	Main Study (Treated Population)
Total	47
Treatment Received	
6 weeks	41(87.2%)
3 weeks	2 (4.3%) (1 AE (non-specific), 1 CMV reactivation)
4 weeks	3 (6.4%) (1 AE (Chronic Obstructive Pulmonary Disease); 2 CMV reactivation)
5 weeks	1 (2.1%) (participant choice)
Eligible to continue beyond 6 weeks	12 (25.5%)
completed 12 weeks	8 (66.6%)
6 weeks	3 (25%) (1 cytopenia; 1 AE (non-specific); 1 participant choice)
completed 11 weeks	1 (8.3%) (participant choice)
MRD response following therapy (Efficacy Primary Endpoint)	
MRD-Negative [95% CI]	39 (83.0%) [69.2%, 92.4%]
MRD-Positive	7 (14.9%)
Missing*	1 (2.1%)
Unacceptable Treatment Related Toxicity (Safety Primary Endpoint)	
Yes [95% CI]	10 (21.3%) [10.7%, 35.7%]
No	37 (78.7%)
Overall Response	
Achieved at least PR [95% CI]	43 (91.5%) [79.6%, 97.6%]
Complete Remission (CR)	27 (57.4%)
Partial Remission (PR)	7 (14.9%)
At least PR (Undeterminable CR)	9 (19.1%)
Did not achieve PR	3 (6.4%)
Stable Disease (SD)	3 (6.4%)
Progressive Disease (PD)	0 (0.0%)
Missing*	1 (2.1%)
MRD response 6 months after treatment end	
MRD-Negative	18 (38.3%)
MRDPositive	28 (59.6%)
Missing*	1 (2.1%)
SAE Summaries	

	Main Study (Treated Population)
Any participants with SAEs reported	17 (36.2%)
Total number of SAEs reported:	22
Suspected, unexpected	2 (9.1%) (1 parainfluenza related death, 1 EBV related DLBCL)
Suspected, expected	17 (77.3%)
Not suspected	3 (13.6%)
No SAEs reported	30 (63.8%)

* The participant was too ill to have their sample taken.

Figure 1



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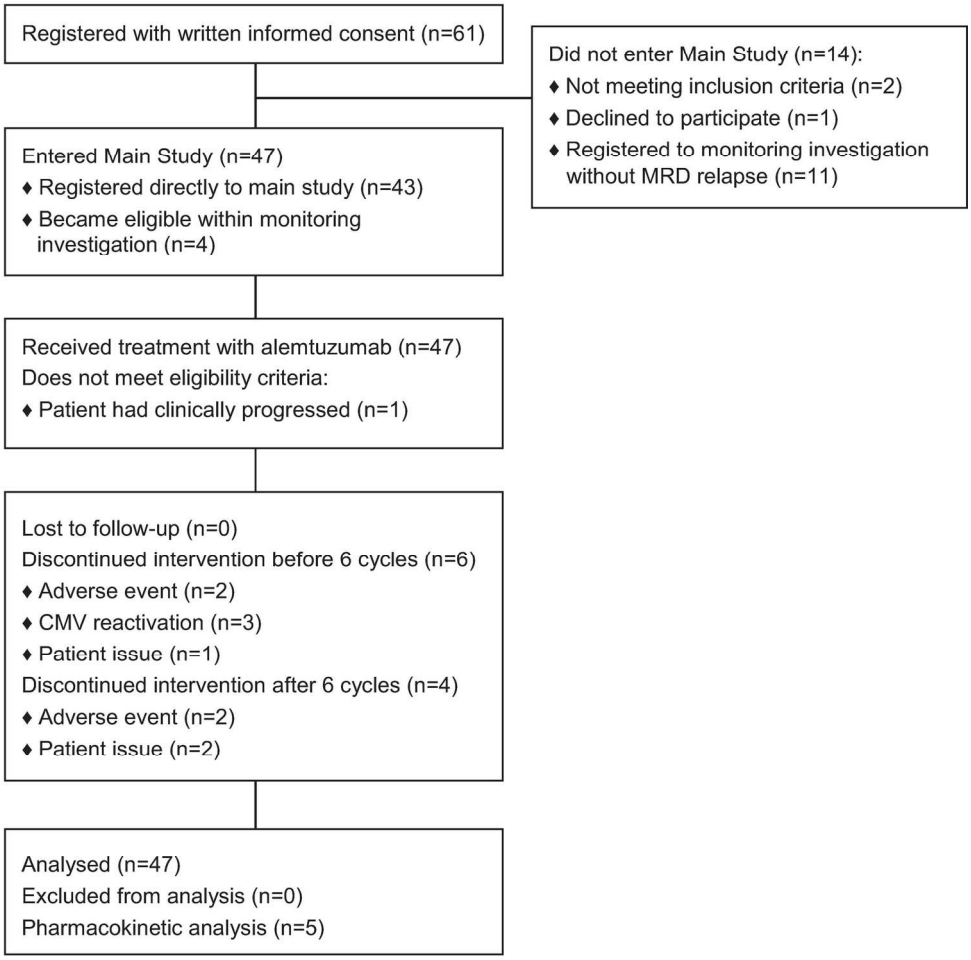
**** Until end of study**

Study flow diagram

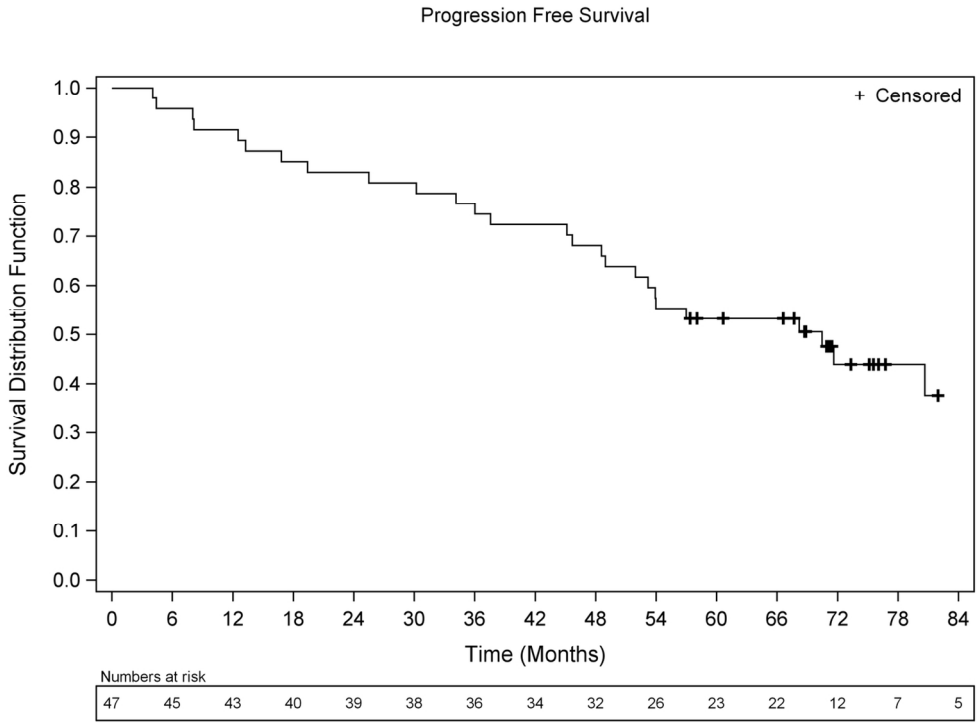
189x217mm (300 x 300 DPI)

Figure 2



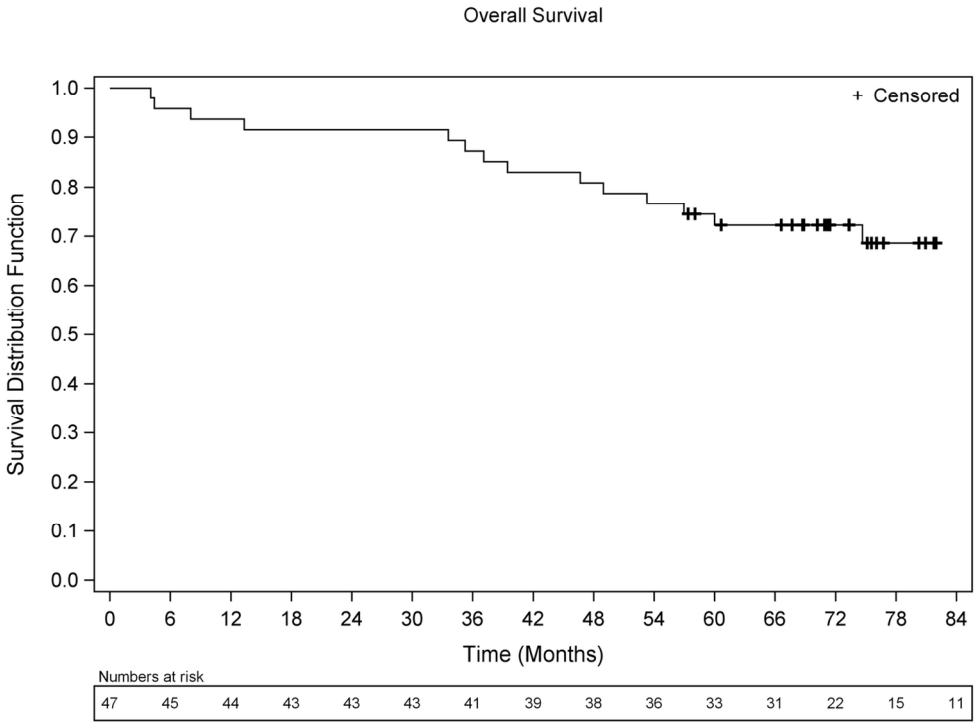
CONSORT flow diagram

162x162mm (300 x 300 DPI)



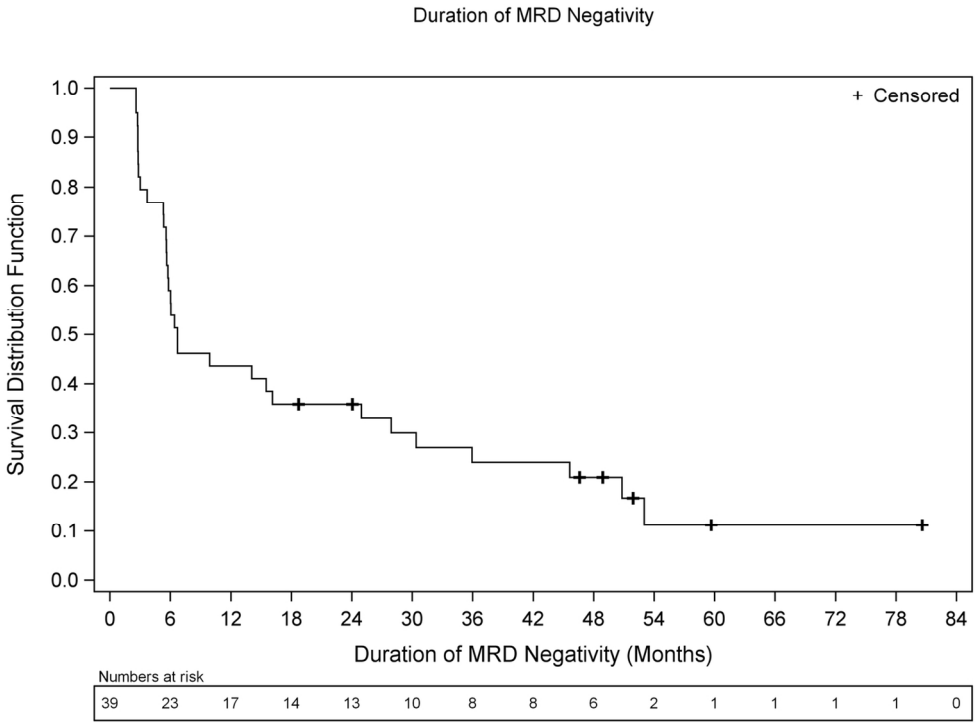
(A) Progression-free survival and (B) overall survival of the treated population (C) MRD relapse in participants who were MRD-negative at end of therapy

127x95mm (300 x 300 DPI)



(A) Progression-free survival and (B) overall survival of the treated population (C) MRD relapse in participants who were MRD-negative at end of therapy

127x95mm (300 x 300 DPI)



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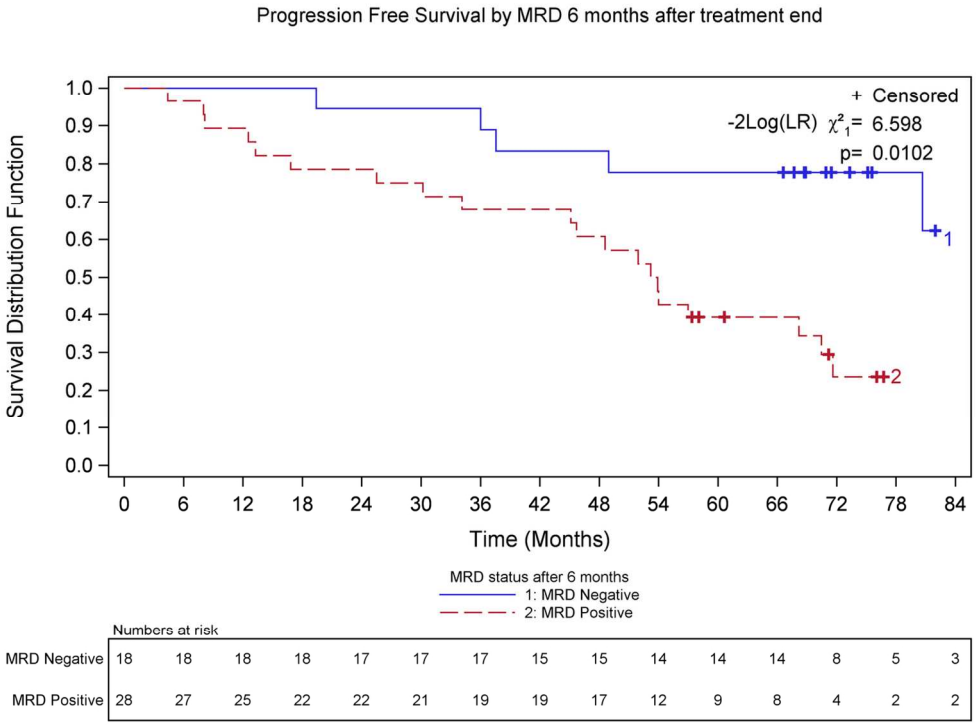
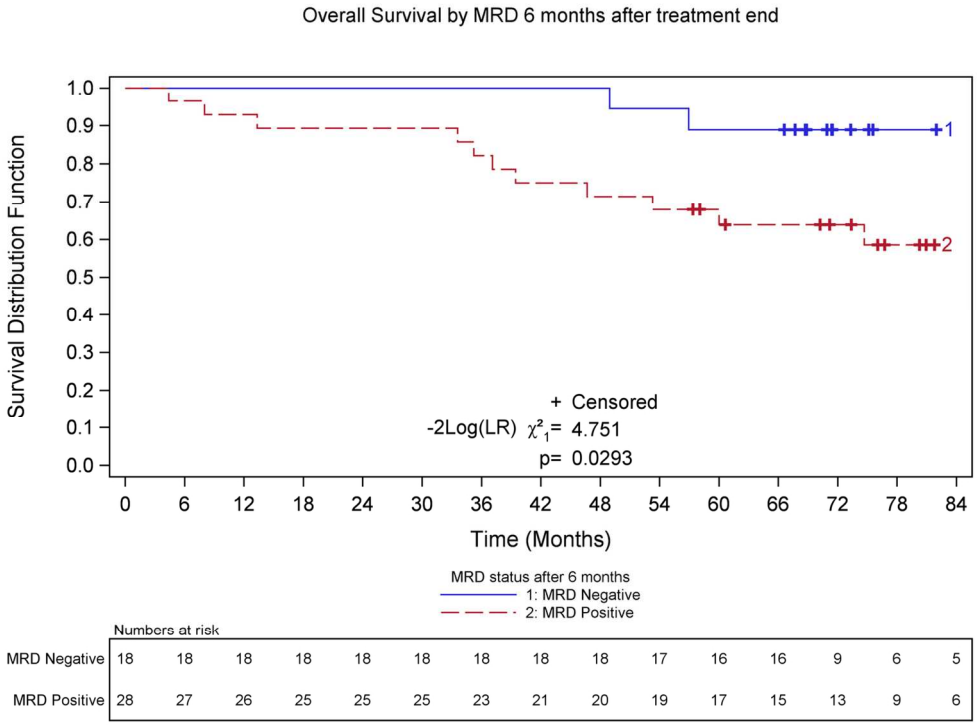
127x95mm (300 x 300 DPI)



(A) Progression-free Survival and (B) overall survival by MRD status at 6 months post treatment (C) survival outcomes for MRD relapse in participants who were MRD-negative at end of therapy compared to those who became MRD-negative 6 months after consolidation

127x95mm (300 x 300 DPI)



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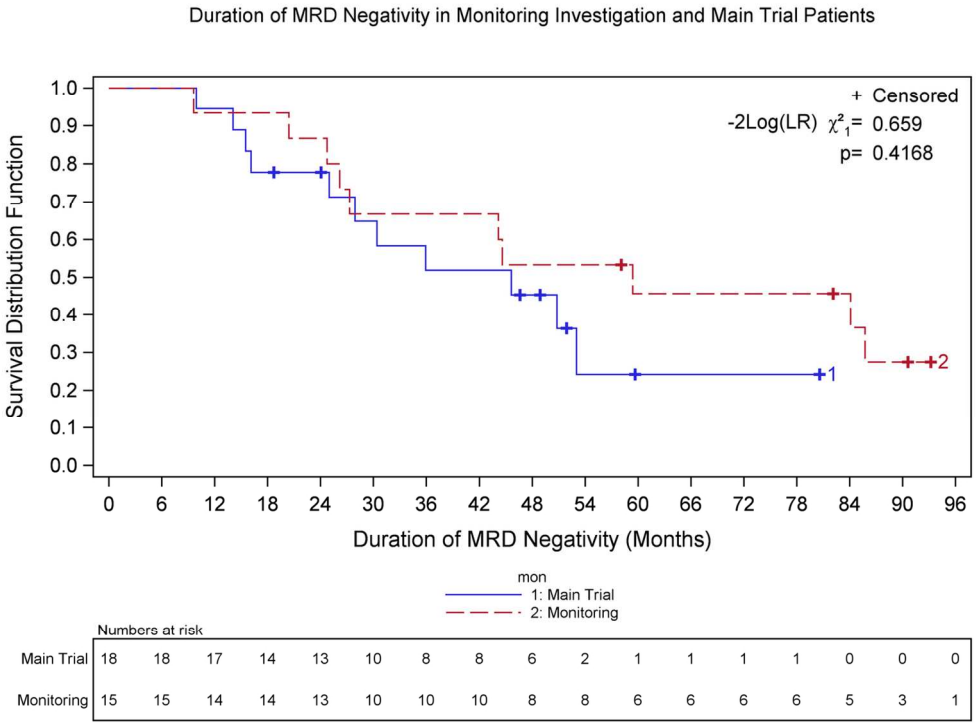

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127x95mm (300 x 300 DPI)