Phase II trial of ofatumumab, dexamethasone and lenalidomide for high-risk CLL (NCRI CLL210)

CLINICAL TRIAL REPORT

Chief Investigator	Professor Andrew Pettitt *Clatterbridge Cancer Centre NHS Foundation Trust*
Sponsors	Royal Liverpool Broadgreen University Hospital NHS Trust and the University of Liverpool
EudraCT Number	2010-019575-29
ISRCTN Number	ISRCTN40303610

Sample and data collection performed in compliance with ICH GCP guidelines

CONFIDENTIAL

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Contents

1. INTRODUCTION

This document details the rules followed, as closely as possible to the Statistical Analysis Plan, when analysing and reporting the main results from the phase II clinical trial of ofatumumab, dexamethasone and lenalidomide in patients with high-risk CLL (CLL210), funded by Celgene.

Amendments to the statistical analysis are described and justified in this document.

Particular issues - instructions for the reader

A series of substantial amendments in the study design occurred since study initiation:

- Initially the induction treatment regimen included Alemtuzumab instead of Ofatumumab and a subsequent randomisation to lenalidomide maintenance or no further treatment for eligible patients (2 years follow-up). The study was planned to recruit 85 patients but only 16 were recruited before Alemtuzumab was withdrawn. All 16 patients received treatment and were followed-up as per protocol.
- Alemtuzumab was replaced by Ofatumumab; the study was re-initiated with the same design, statistical considerations and recruitment target; 85 more patients were planned to be recruited.
- Recruitment target was reduced to 50 patients resulting in new statistical considerations (increased type I error rate).
- Randomised part of the study was dropped due to very few patients being eligible and follow-up reduced to one instead of two years. This affected only the last two patients recruited in the study.

Please keep in mind the above clarifications when reading this document.

2. TRIAL DESIGN

Title of Study:	Phase II trial of ofatumumab, dexamethasone and lenalidomide *(followed by randomisation to lenalidomide maintenance versus no further treatment*)* for high risk CLL (NCRI CLL210)
Current Version of Protocol:	
ISRCTN:	40303610
Chief Investigator:	Professor Andrew Pettitt
Sponsor(s):	University of Liverpool and Royal Liverpool and Broadgreen University Hospitals NHS Trust
Number of Study Centres:	21 throughout the United Kingdom
Study Period:	2 years recruitment, minimum 1.5 years follow up of all patients, 3.5 years total*. February 2012 – August 2016 (initial design) September 2013 – March 2017 (revised design)
Main Objective:	The CLL210 trial will investigate the safety and efficacy of combination induction therapy with ofatumumab, dexamethasone and lenalidomide in patients with high-risk CLL.
Patient population:	50 high-risk CLL patients will be recruited; high risk CLL defined by at least one of the following criteria: • TP53 deletion or mutation affecting at least 20% of CLL cells • Resistant (SD/PD) to fludarabine-containing combination therapy • Relapse within 12 months of responding to fludarabine-containing combination therapy.
Methodology:	Suitable patients are screened and then enrolled on the study by trial sites sending a copy of the eligibility, registration and screening forms to LCTU. All patients receive 24 weeks of induction therapy. *At the end of induction therapy, patients who are locally determined to have responded to induction treatment (i.e., have a CR or PR) and who have not elected to receive an allogeneic transplant are randomised equally between receiving no further treatment or lenalidomide maintenance*.*
Duration of Treatment:	24 weeks induction treatment. *Maintenance treatment until disease progression for patients randomised to lenalidomide maintenance*.*

Outcomes:	<u>Primary outcomes:</u> • Proportion of patients with CR/CRi after 6 months of induction therapy. • Proportion of patients able to tolerate treatment after 6 months of induction therapy. <u>Secondary outcomes:</u> • Proportion of patients with overall, complete and partial response following induction therapy. • Proportion of patients with minimal residual disease (MRD) negativity following induction therapy. • Overall survival *(time from initiation of study treatment to death).* • Progression-free survival *(time from initiation of study treatment to progression or death).* • Time to treatment failure *(time from initiation of study treatment to treatment failure defined as progression, death or initiation of alternative treatment due to failure to achieve CR or PR)** • Duration of response *(time from first achievement of CR or PR to progression or death)* • Toxicity • Quality of life • Descriptive summary of progression-free and overall survival among transplant eligible patients

*see clarifications in section "1. Introduction"

2.1 Randomisation procedure

2.1.1 Generation of sequence

The randomisation code list has been generated by the LCTU trial statistician using the Stata user-written package "*ralloc*", employing block randomisation with variable block length, and equal allocation to the two treatment arms, stratified on Prior treatment/No Prior treatment and TP53 defect or not.

2.1.2 Concealment & implementation of sequence

The allocation sequence has been held centrally at the LCTU. Once the sequence was generated in the form of treatment codes the IS developer assigned the codes to actual treatments. Access to the sequence has been confined to the IS developer assigned to the study.

2.2 Blinding

This is an open-label study, and thus no blinding procedures are in place.

2.4 Sample size

A single evaluation of tolerability and induction success was to be performed after all 50 patients have completed up to 6 months induction therapy. The main risk of the induction treatment was considered to be infection and a patient would be considered able to tolerate treatment if there was an absence of any grade 3-4 infection and no treatment-related death at 6 months. Most such events were expected to occur earlier rather than later in this interval. In the previous CLL206 trial, the reported percentage of patients experiencing at least one grade 3-4 infection of any type was 54%, giving a tolerability rate of 46%.

For the current trial, a tolerability rate of 30% or less would not be of interest, while a tolerability rate of 50% or more would be of interest. With a sample size of 45 the null hypothesis would be rejected if there were 17 or more who were able to tolerate the regime, with Type I error = 0.1642 and Power = 0.9638. Allowing for 10% attrition rate we would need to recruit at least 50 patients.

The primary efficacy outcome for induction is presence of complete response (CR\CRi) after 6 months of receiving induction therapy. The CR rate in the CLL206 trial was 24%. For the current trial we have taken the lowest response rate that would be of definite clinical interest to be 20% and the highest response rate that would be of no interest to be 10%. With a sample size of 45 (50 patients recruited to allow for 10% attrition rate) the null hypothesis would be rejected if there are 7 or more responders with a Type I error = 0.1585 and Power =0.8232.

The Type I error and Power estimates above (both for tolerability & efficacy) are based on single-arm A'Hern tests.

Tolerability and efficacy outcomes for the induction treatment are treated as a co-primary outcome; a success is declared only if both null hypotheses are rejected. The overall Power would then be 0.9368 x 0.8232 = 0.7934. Assuming that tolerability and efficacy are independent the overall Type I error would be 0.1642 x 0.1585 = 0.026 but since this assumption is unlikely to hold, we report the most conservative overall Type I error which in this case is 0.1642.

2.5 Interim Monitoring, Interim Analyses and Stopping Guidelines

The trial was monitored by an ISDMC which assessed the trial data and took into account the current world-wide evidence. An initial review by the ISDMC of trial toxicity data for the induction phase was performed once 25 patients had completed or withdrawn from the revised (dexamethasone, lenalidomide and ofatumumab) induction phase.

Once all patients had completed or withdrawn from or failed induction (unless there was a "for cause" trigger for an earlier review such as 30 or more withdrawals due to toxicity during induction), there would be a second timetabled DMC meeting to assess tolerability and efficacy. The ISDMC could convene additional meetings as it required.

The frequency of subsequent reviews, in order to assess toxicity, recruitment rates, losses to follow up and extent of missing data, were set according to the ISDMC Charter.

All ISDMC Reports were confidential to the ISDMC members and were not for review by the trial management group (except the trial statistician preparing the ISDMC report), TSC, investigators or collaborators.

2.6 Trial Oversight Committees

2.6.1 Trial Management Group (TMG)

A TMG was formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTU. The TMG was responsible for the day-to-day running and management of the trial and met at least 3 times a year.

2.6.2 Trial Steering Committee (TSC)

The TSC will consist of the following members:

Dr Isabel Syndikus	-	Independent Chairman (Consultant Oncologist)
Prof Dr Clemens Wendtner	-	Independent Haematologist
Dr Zoltan Matra	-	Independent Clinician
Dr Lukas Smolej	-	Independent Clinician
Miss Dena Cohen	-	Independent Statistician
Mr Paul Flight	-	Independent Layman
Ms Alexandra Smith	-	Independent Advisor (Senior Trial Manager, Leeds CTRU)
Prof Andrew Pettitt	-	Chief Investigator
Dr Nagesh Kalakonda	-	Deputy Chief Investigator
Prof Peter Hillmen	-	Co-Investigator
Prof Don Milligan	-	Co-Investigator
Prof Sarah Coupland	-	Pathologist
Dr Ke Lin	-	Clinical Scientist
Mr Fotis Polydoros	-	Main Trial Statistician
Dr Christina Yap	-	Original Trial Statistician
Mr James Dodd	-	Trial Coordinator
Dr Seema Chauhan	-	Operational Director, LCTU
Dr Melanie Oates	-	CLL Biobank Manager

The role of the TSC was to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lay with the TSC.

2.6.3 Independent Safety and data Monitoring Committee (ISDMC)

The ISDMC consisted of the following members:

- Dr Steve Johnson – Chairman and expert clinician
- Prof. Marius van Oers – Expert clinician
- Dr. Wendi Qian - Statistician

The ISDMC provided a recommendation to the Trial Steering Committee concerning the continuation of the study.

2.6.4 Endpoint Review Committee (ERC)

The Independent Endpoint Review Committee (ERC) consisted of the following members, all of whom are clinical experts:

- Dr Christopher Fox
- DrScott Marshall
- Dr Renata Walewska

The role of the ERC is to assess treatment responses for all trial patients and in particular those where CT scan and/or bone marrow data necessary for response assessment according to the revised (2008) NCI/IWCLL response criteria is incomplete. If all results are available, assessing response is entirely objective. However, if data are missing for whatever reason assessment of response requires potentially subjective interpretation of available results.

Members of the Endpoint Review Committee individually reviewed all cases including those where there were missing CT scan and/or bone marrow data and gave their opinion of response. In cases where all members were in agreement as to the response, their decision was accepted and no further action was necessary.

3. TRIAL HISTORY

This section provides a short summary of substantial amendments in the study design and statistical considerations since the initiation of the study.

3.1 Trial Publicity

Information regarding CLL210 can be found in the following websites:

- Liverpool Cancer Trials Unit:
  https://www.lctu.org.uk/LCTU_NET/frontend/core/Features/trialinfo.aspx?Data=W1tWSEpwWVd4SGNtOTFjQT09XV1bTlE9PV1bW1ZISnBZV3hKUkE9PV1dW05qaz1dW1tiRzlqWVd4bF1dW01RPT1d
- Cancer Research UK:
  http://www.cancerresearchuk.org/about-cancer/trials/trial-looking-at-treatment-for-high-risk-chronic-lymphocytic-leukaemia-CLL-210
- UK Clinical Trials Gateway
  https://www.ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialId=3962

CLL210 is included in the NCRI Haematological Oncology Clinical Study Group (CSG) annual trials review. The latest newsletter was circulated in June 2015. An abstract including the final results from the initial cohort (Alemtuzumab) was included in the Abstract Book of the 21st Congress of the European Haematology Association.

3.2 Protocol amendments

A summary of all protocol version for the duration of the study is given below.

Version 1 (11/01/2011)

Original version submitted to MREC and the MHRA.

Version 2 (29/03/2011)

Changes made following ethical and regulatory review of version 1:

- Justification for the use of subcutaneous alemtuzumab added to section 3.2. Alteration to maintenance phase: trial medication (and pharmacovigilance and follow-up) will continue until disease progression or death for any patients that have not progressed by the time of the primary analysis (2.5 years after the last patient has been recruited). It was intended that Revlimid would continue to be made available to those patients off-trial but they will now remain on-trial until they progress. Changes made to sections 2, 8.4 and 10.1.
- Correction of the randomisation method described in section 7.3 to match the method described in section 10.2.
- Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.

Version 3 (30/06/2011)

Changes made to contact details and list of TSC members:

- Dr Sarah Coupland and Dr Ke Lin added to list of contacts
  Dr Lucas Smolej and Dr Zoltán Mátrai added to list of independent TSC members
- Changes made to translational research to bring it in line with RiAltO CLL trial:
  Section 7.4 updated to include details of collection of and tests to be performed on translational samples collected at baseline
  Section 9.2.4 updated with details of how bone marrow trephine biopsies are to be processed centrally
- Section 9.5 updated to emphasise that patients can consent to having baseline
- and sequential samples taken, or baseline samples only
- Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.

Version 4 (26/09/2011)

Changes made to contact details and list of TSC members:

- James Dodd added as Trial Coordinator (replacing Karl Harvey)
- Dr Wendy Qian and Dr Steve Johnson's addresses updated
- LCTU fax and contact number (for randomisations and pharmacovigilance reporting) updated.
- References to minimisation removed in section 7.3 and 14.4.5
- Details of specific tests to be performed at study visits added to section 7.1 and section 9
- Added details regarding retention of bone marrow trephine samples for future research to section 7.4.
- Updated section 9 to state the screening and baseline assessments must be performed within 42 days of study treatment starting (changed from 28 days).
- Explicitly stated AEs should be reported from consent until 28 days post treatment in section 9.1
- Added reference to CMV PCR in table B, section 9.1.
- Removed reference to samples for biobanking during follow-up in Table D, section 9.1.
- Removed reference to response assessment at 39 weeks in section 9.2.1
- Section 10.4 updated by Trial Statistician
- Updated links and references to CTCAE v4 (rather than v3 as previously)
- Section 11 (Pharmacovigilance) updated to reflect move to on-line reporting of SAEs and AEs, and annual submission of Development Safety Update Report.
- Section 14.4.11 (Statistical Monitoring) Deleted)
- Sections 14.4.5 updated to be emphasise that patients are registered onto the study, and only randomised to lenalidomide maintenance or no further treatment at the end of induction treatment.
- Replace QLQ C30 Questionnaire (Appendix E) with CLL210 Health & Quality of Life Questionnaire, and updated references in protocol.

- Miscellaneous spelling, punctuation and grammar corrections and other minor admin
- changes.

Version 5 (09/02/2012)

- Section 2 (and 6.2) Extra qualification on exclusion criterion "Seropositivity for HIV, HCV or HBV (surface antigen and core antibody)" added.
- Updated Section 5 as previous sections 5.1 and 5.2 are redundant since they are expressed more clearly in section 10.3 and in any case did not state the trial design
- Section 7.4 Blood sample requested for flow cytometry and IGHV/FISH/TP53 mutation testing changed to 6ml from 5ml.
- Section 8.2.2.3 Additional advice on storage and administration of subcutaneously administered alemtuzumab added
- Section 8.2.4 (and 8.4.4 and 8.5) Allow sites to give alternative equivalent co-trimoxazole regimens according to local practice
- Section 8.4.2 Changed references to lenalidomide IB from lenalidomide SPC.
- Section 8.4.7 Sites should allow 10 days for delivery of lenalidomide (instead of 5 as previously)
- Section 8.6.2 Clarified pregnancy tests can be either blood or urine
- Section 9.1 Updated tables A, B and C to bring frequency of pregnancy tests for WCBP in line with section 8.6 of study protocol.
- Section 9.1 updated table C of assessments during induction treatment to make it clearer that patients should receiving lenalidomide maintenance past week 129 should continue to be assessed every 8 weeks
- Section 9.1 (and 9.1.3) Updated table of assessments with details of when to perform monitoring for PCR for HBcAb+ patients who are eligible for the study.
- Section 9.2.4 details of reporting of central pathological review results to study sites added
- Section 10.1 & 10.6 Amended sections to avoid repetition of text
- Section 10.1 Amended section so that survival analysis and final publication of trial results will be carried out when all patients have completed a minimum of 21⁄2 years follow-up after randomisation (instead of 2 years as previously).
- Section 10.6.1 & 10.6.2 Moved IWCLL Guidelines Table 4 because response following induction is a Primary outcome for the induction phase of the trial
- Section 11.7.1 & 11.7.2 Added instructions on period for which AEs and SAEs should be reported.
- Section 11.7.2 Added details relating to reporting of Second Primary Malignancies (SPMs) as SAEs. Also added instructions to sites regarding conformation of receipt of SAEs sent by LCTU
- Section 17.3 clarified dates ISDMC will meet
- Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes.

Version 6 (25/11/2012)

- Changed study title to reflect substitution of ofatumumab for alemtuzumab
- Updated contact details for Professor Andrew Pettitt and Dr Melanie Oates
- Section 2. Clarified that an estimated 58 patients will be randomised to lenalidomide maintenance versus no further treatment (changed from 54)
- Section 2, 6.1 Changed inclusion criterion from “no prior treatment with alemtuzumab” to “no prior treatment with ofatumumab”
- Section 2, 6.1 Qualified inclusion criterion relating to previous treatment episodes for CLL by adding “excluding chlorambucil-based regimens”
- Section 2, 6.2 Added exclusion criterion “Total bilirubin >1.5 times upper normal limit (unless due to involvement of liver or a known history of Gilbert’s disease) or ALT >2.5 times upper normal limit (unless due to disease involvement of liver)”
- Section 2, Changed renal impairment exclusion criterion to allow eGFr to be calculated from serum creatinine
- Section 2, 6.2 Removed exclusion criterion “allergy to rat proteins” as alemtuzumab no longer administered
- Section 2, 6.2 Changed minimum remission for previous cancers from 5 years to “Concomitant malignancies except adequately treated localised non-melanoma skin cancers and other in-situ cancers, or invasive cancers that have been in remission for a period of time considered by the local investigator to pose a negligible risk of relapse during the period of the trial.”
- Section 2, 6.2 Updated text of exclusion criterion relating to pregnancy prevention
- Section 2, 6.2 Added exclusion criterion relating to women of childbearing potential
- Section 2, 8 Replaced alemtuzumab regimen with that for ofatumumab
- Section 2, 8.2.4 Added qualification that allopurinol, alendronic acid and lansoprazole can be omitted at discretion of local investigator if sound clinical reasons to do so.
- Section 2, 8.2.4, 8.4.5, 8.5 Allow alternative equivalent regimen to be given for aciclovir, according to local practice.
- Section 2,8.2.4, 8.4.5, 8.5 Itraconazole removed from list of concomitant medication
- Section 2, 8.2.3.1, 8.2.4 Clarified that G-CSF could be tapered or suspended at the discretion of the local investigator if neutrophil counts normal during weeks 5-8
- Section 3.1, 3.2. Rewritten study objectives and rationale and combined into new section. Moved list of references to section 19.
- Section 3.3.1 Added text relating to risk of hepatic adverse reactions
- Section 7.1 Provided link for calculator for MDRD formula for calculating eGFR
- Section 8. Major updates to this section to reflect replacement of alemtuzumab with ofatumumab in induction treatment regimen, including:
- Section 8.2.1.3, 8.2.2.3, 8.2.7 Details on formulation, packaging, labelling, storage, stability, preparation, dosage, administration and ordering of
- ofatumumab added Section 8.2.2.1 qualified timing of dexamethasone dose on days ofatumumab administered
- Sections 8.2.3.4, 8.4.3.2 (treatment interruption) added
  Section 8.2.4, 8.4.4, 8.5 Updated list of supportive medication

Section 8.2.4, 8.4.4 Added that patient need not take aspirin if taking dalteparin
Section 8.2.6, 8.4.6 (Medication not permitted) added advice for treatment of patients taking oral anticoagulants
Section 8.4.3.1 added to provide guidance on dose modification because of infection in maintenance treatment
Section 8.7.4 added section on risk of Progressive Multifocal Leukocephalopathy (PML)

- Section 8.11 Clarified time points until which concomitant medications are recorded
- Section 9 Added comprehensive list of results required from each assessment.
- Section 9, 9.5 Removed requirement to take Biobank samples at week 5
- Section 9, 9.13 Assessments no longer required day 5 weeks 3, 5 and 7, and on day 1 weeks 10,12,14,16,18,20 and 22
- Section 9.1.2. Stated that CT Scans and Bone Marrow Samples for central pathological review need not be repeated (at the CI's discretion) if previously taken more than 42 days before study treatment starting, or before otherwise scheduled in protocol.
- Section 9.1.3 Added section advising sites on what to do if biobanking samples due on a Friday or Bank Holiday
- Section 9.4.1 Removed reference to CLL210 Health & Quality of Life Questionnaire (to be no longer completed by patients), and removed questionnaire from Appendices.
- Section 10.1 re-phrased
- Section 10.3.1 Primary outcome measures for induction treatment separated into tolerance and CR rate.
- Sections 10.4, 10.5, 10.6 and 17.3 Extensive changes made to text covering sample size, analysis, and timing of ISDMC meetings
- Section 10.5.1 Added futility analysis to stopping guidelines
- Section 10.6.1.6 re-phrased
- Section 10.6.1.8 relating to analysis of Quality of Life forms re-written
- Section 11.1, 11.2.3 Added text relating to reporting of AEs and pregnancy to GSK
- Section 11.9 added for reference safety information
- Section 14.4.2 Updated section to clarify site staff who (as a minimum) should attend site initiation, and that it is the responsibility of the PI to ensure staff not attending site initiation are suitable trained on the study.
- Section 14.4.5 Removed reference to automated e-mail reminders for screening logs, as screening forms are now completed on-line
- Section 14.4.8 removed reference to forwarding details of all deviations to co-sponsor
- Section 16 added that ofatumumab is to be provided free of charge by GlaxoSmithKline
- Section 17.2 added Zoltan Matrai, Lukas Smolej, Peter Hillmen, Don Milligan, Sarah Coupland, Ke Lin and Melanie Oates to list of TSC members.
- Section 19 Included references in their own section
- Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes

Version 7 (19/09/2013)

- Update to contact details for Professor Andrew Pettitt and Dr Lukas Smolej
- Dr Arvind Arumainathan added as co-investigator
- Serum biochemistry assessments chloride, bicarbonate, γGT no longer required. Uric Acid required at baseline only.
- Section 8.2.4, 8.4.4 LMW heparin can be given as an alternative to aspirin if patients at high risk of thrombosis.

Version 8 (27/11/2013)

- Section 2 Removed exclusion criterion "Hepatic impairment (serum bilirubin more than twice the upper limit of normal unless due to Gilbert's syndrome)" as it duplicates exclusion criterion "Total bilirubin >1.5 times upper normal limit (unless due to involvement of liver or a known history of Gilbert's disease) or ALT >2.5 times upper normal limit (unless due to disease involvement of liver)"
- Section 7.4 Added paragraph that allows use of historic bone marrow trephine samples (taken more than 42 days before start of treatment) for baseline Central Pathology Review
- Section 8.2 Allow local investigators the discretion to extend tapering dexamethasone dose for patients who have steroid withdrawal symptoms, and to allow a tapering dose if patient had grade 3/4 steroid related toxicities prior to starting on study treatment
- Section 8.2.2.3 Updated instructions for ofatumumab if patients have an infusion related reaction to the first dose, including guidance on pre-treatment steroids for future infusions and allowing a repeat of the 300mg dose if not tolerated at week 7
- Section 8.2.3.1 Allow lenalidomide to be started and dose increased if low platelet and neutrophil counts are due to underlying CLL
- Section 8.2.3.3 Clarification of when an attenuated dose of dexamethasone can be given
- Section 8.2.4, 8.4.4 Allows an alternative anti-platelet drug to be given in place of aspirin

Version 9 (04/08/2014)

- Contacts, Section 17.2 Updated details for Trial Statistician in contacts section. Mr Fotis Polydoros replaces Dr Paul Silcocks.
- Section 2, 6.1 Removed the inclusion criterion "No more than 3 previous treatment episodes for CLL (excluding chlorambucil-based regiments".
- Section 7.3 and 10.2 Randomisation blocks corrected to being fixed length size, not varying
- Section 8.2.3.4 Section added advising about risk of hyperglycaemia. Previous section 8.2.3.4 now 8.2.3.5
- Miscellaneous spelling, punctuation and grammar corrections and other minor admin changes
- Section 8.3. Recommended washout period for patients receiving transplant amended from 4 months to 2 months.

- Section 9 Added that CMV monitoring may be omitted in patients who have not received prior therapy with alemtuzumab and who do not have a prior history of CMV reactivation. Patients with progressive CMV viraemia should receive pre-emptive valganciclovir or equivalent in accordance with local practice.
- Section 9, 9.5 Update to details of bone marrow and blood samples sent to Biobank at disease progression
- Section 9.6 Added details of Genomics England 10,000 Genomes Project to sub-studies section

Version 10 (27/10/2014)

- Removed references to maintenance part of study from all parts of protocol (including in study title).
- Change to protocol to reduce target recruitment from 85 to 50 and remove maintenance part of study. Affects sections 2, 5, 7.3, 8, 10, 12, 14.4.5
- Section 2, 6.2. Changes to the wording of the exclusion criterion relating to women of childbearing potential.
- Section 8.5 Updates to the pregnancy prevention plan text.
- Update to primary endpoints and major changes to section 10 (statistical considerations), as a result of the above changes.
- Section 17.3 Change to timing of ISDMC meetings
- Section 2, 6.2. Reverted final exclusion criterion to state that women of children bearing potential who do are “unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol” are excluded from the study, instead of “study start to 28 days after the last dose of protocol” as in version 10.

3.3 Trial milestones

Table 1. Trial Milestones

	Revised design (Ofatumumab)	Initial design (Alemtuzumab)
First patient was recruited on:	**13th September 2013**	**6th February 2012**
Last patient was recruited on:	**8th October 2015**	**4th September 2012**
Cut-off date (data freeze) for this report:	**30th September 2016**	
Date of final data extraction for this report:	**12th June 2018**	
Total number screened to data freeze:	**67**	**25**
Total number recruited to data freeze:	**48**	**16**

* The Trial Coordinator and/or Chief Investigator have completed the initiation visit at site. Research staff including research nurses has been fully initiated and have signed the delegation log and initiation log. All staff have been fully trained by the Chief Investigator and/or Trial Coordinator; All regulatory and ethical approvals are in place; All signatures are complete and all documentation is in place; The Research Site Agreement is signed by all parties; The CRFs are at site; The drug has been released to site.

3.4 Interim Analyses

The trial was monitored by an ISDMC which assessed the accumulating trial data and take into account the current world-wide evidence. An initial review by the ISDMC of trial toxicity data for the induction phase was performed once 22 patients have completed the revised (dexamethasone, lenalidomide and ofatumumab) induction phase.

The IDMC met on the 8th October 2014 to assess this specific interim analyses. The IDSMC did not recommend stopping on the grounds of excess toxicity and the study continued to recruit patients.

4. RECRUITMENT

Section 4 gives the details the regarding the recruitment of patients into the study.

Table 2. Recruitment By Site

Table 2 details the patients recruited by each site into the study. Please note that site was included as a stratification factor in the study.

Site Name	Date of Greenlight	Date of first recruitment	Date of last recruitment	No. Screened	No. Ineligible	No. Declined	Patients recruited (Alemtuzumab)	Patients recruited (Ofatumumab)
Aberdeen Royal Infirmary	03/06/2014	08/10/2015	08/10/2015	2	1	0	0	1
Castle Hill Hospital (Cottingham)	27/11/2013	16/12/2013	15/05/2014	6	2	1	0	3
Churchill Hospital (Oxford)	15/03/2012	13/04/2012	24/10/2013	8	1	0	4	3
Derriford Hospital (Plymouth)	26/04/2012	13/09/2013	13/09/2013	2	1	0	0	1
Eastbourne District General Hospital	05/02/2014	-	-	4	4	0	0	0
Glan Clwyd Hospital (Rhyl)	16/09/2013	27/09/2013	16/03/2015	2	0	0	0	2
Heartlands Hospital (Birmingham)	09/12/2013	18/02/2014	28/10/2014	4	0	0	0	4
King's College Hospital (London)	05/02/2014	13/06/2014	19/08/2014	2	0	0	0	2
Leicester Royal Infirmary	13/07/2012	31/08/2012	04/09/2012	4	2	0	2	0
Nottingham City Hospital	05/11/2013	11/11/2013	19/02/2015	7	0	0	0	7
Queen Elizabeth Hospital (Gateshead)	18/05/2012	26/01/2015	13/02/2015	7	4	1	0	2
Royal Liverpool University Hospital	03/02/2012	15/06/2012	15/06/2015	10	0	0	1	9
Royal Marsden Hospital (Sutton)	18/05/2012	25/05/2012	26/06/2012	3	1	0	2	0
Southampton General Hospital	22/03/2012	23/04/2012	25/04/2012	2	0	0	2	0
St. James's University Hospital (Leeds)	11/05/2012	03/12/2013	10/03/2015	3	1	0	0	2
The Beatson West of Scotland Cancer Centre (Glasgow)	17/09/2014	11/11/2014	11/11/2014	2	1	0	0	1

Site Name	Date of Greenlight	Date of first recruitment	Date of last recruitment	No. Screened	No. Ineligible	No. Declined	Patients recruited (Alemtuzumab)	Patients recruited (Ofatumumab)
The Christie (Manchester)	23/01/2012	24/02/2012	01/08/2014	9	2	0	2	5
The Royal Bournemouth Hospital	27/01/2012	06/02/2012	02/02/2015	3	0	0	2	1
University College Hospital (London)	27/02/2012	15/09/2014	07/09/2015	6	4	0	0	2
University Hospital of Wales	06/03/2012	31/07/2012	31/07/2012	2	1	0	1	0
Ysbyty Gwynedd (Bangor)	13/09/2013	07/11/2013	06/10/2014	4	0	1	0	3
			Total	**92**	**25**	**3**	**16**	**48**

Figure 1.Cumulative Recruitment

Figure 1 shows the cumulative recruitment of patients against the anticipated recruitment rate at the onset.

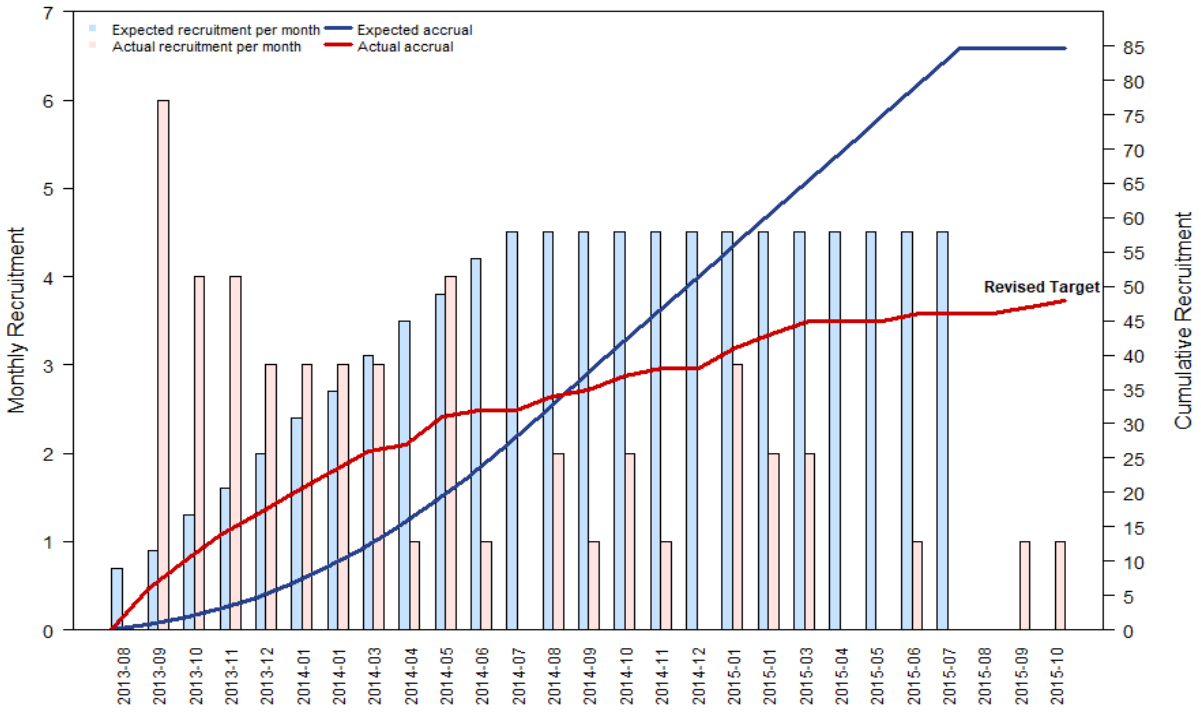


Table 3. Recruitment and Completion of Induction of Treatment

Table 3 shows the number of patients to complete induction and to enter the maintenance phase of the study.

Cohort	Patients Recruited	Did not complete Induction, N (%)	Completed Induction		
			Randomised, N (%)	Transplant, N (%)	Not Randomised, N (%)
Ofatumumab	48	23 (48%)	15 (31%)	3 (6%)	7 (15%)
Alemtuzumab	16	7 (44%)	5 (31%)	4 (25%)	0 (0%)

5. ASSESSMENT OF STUDY QUALITY

Section 5 contains details regarding measures undertaken to ensure the quality of the collected data.

5.1 Quality Control and data validation procedures

5.1.1 Randomisation checks

Generation of the randomisation list was reviewed (*ST002_CHK1.1*) to ensure provision of adequate randomisation numbers, appropriate block sizes and treatment allocations, and balanced allocation of treatments for various cumulative totals.

During the course of the trial periodic (normally at each ISDMC meeting) checks were made for omitted or out of sequence allocations and balance in treatment allocations, and informativeness of baseline variables on treatment allocation.

Table 4. Randomisation Checks

Table 4 details the randomisation checks undertaken at the point of the final analysis.

	Result
Are randomisation numbers in MACRO database in correct date order?	Yes
Are there missing randomisation trial numbers?	Yes
Are Stratification factors & baseline covariates uninformative for treatment allocation, overall and for sections of randomisation schedule (applies ONLY if minimisation/stratified randomisation is being implemented)	Yes

Randomisation Errors: No randomisation errors were reported during the study.

5.1.2 Automated checks

The MACRO database includes validation features which alerts the user to certain inconsistent or missing data on data entry and automatically raises a query which is emailed to site. Automated email reminders are also generated by the database if follow up data from a scheduled patient visit is overdue.

5.1.3 Other checks

Eligibility criteria, informed consent and randomisation dates/numbers were checked by the trial team at the time of registration/randomisation. All captured data points are subject to standard LCTU QC processes.

5.2 Data Completion

This is measured via the number of CRF pages completed and returned to the LCTU and the number of outstanding queries.

Table 5. Missing CRF pages by Site

Table 5 details the number of missing CRF pages at each site and the number of outstanding queries. Please note that none of the outstanding queries related to key data items relating to evaluation of the primary endpoint.

Site Name	Date of green light	No. of expected CRF pages	No. of CRF pages received	% missing CRF pages	No. of outstanding Queries
The Royal Bournemouth Hospital	27/01/12	77	55	29	17
Glan Clwyd Hospital	16/09/13	30	17	43	25
Aberdeen Royal Infirmary	03/06/14	33	21	36	0
Heartlands Hospital (Birmingham)	09/12/13	66	54	18	2
The Beatson (Glasgow)	17/09/14	30	21	30	17
Royal Liverpool University Hospital	03/02/12	150	144	4	0
Nottingham City Hospital	05/11/13	114	111	3	1
Churchill Hospital (Oxford)	15/03/12	148	145	3	40
University College Hospital (London)	27/02/12	25	24	1	6
The Christie (Manchester)	23/01/12	129	128	1	0
Royal Marsden Hospital (Sutton)	18/05/12	38	38	0	0
Southampton General Hospital	22/03/12	34	34	0	1
Leicester Royal Infirmary	13/07/12	33	33	0	0
Ysbyty Gwynedd (Bangor)	13/09/13	26	26	0	1
University Hospital of Wales	06/03/12	10	10	0	1
St. James's University Hospital (Leeds)	11/05/12	16	16	0	14
Queen Elizabeth Hospital (Gateshead)	18/05/12	51	51	0	1
Derriford Hospital (Plymouth)	26/04/12	11	11	0	0

Site Name	Date of green light	No. of expected CRF pages	No. of CRF pages received	% missing CRF pages	No. of outstanding Queries
Castle Hill Hospital (Cottingham)	27/11/13	59	59	0	0
King's College Hospital (London)	05/02/14	40	40	0	4
	Total	1120	1038	7	130

5.3 Protocol Completion

A total of 250 protocol deviations have been reported during the course of the study of which 25 were major. Please note that any patient with a major protocol deviation is included in the final analysis but is removed from the per protocol sensitivity analysis.

Table 6. Summary of Protocol Deviations

Table 6 details all reported protocol deviations broken down by the specified categories.

Category	Deviation Type	Total No.
Major	Major protocol deviation in patient management and/or assessment	16
	Other major protocol deviation	9
Minor	Blood results	7
	Patient examination/test	1
	Other protocol deviations (not expected to have an impact on defined endpoints of the trial)	214

A total of 9 'Other' major protocol deviations have been reported and for clarity these are highlighted in Table 7.

Table 7. Major Deviations by Treatment Site

Table 7 includes all major protocol deviations broken down by Site.

Site	Date of Deviation	Category	Description
Castle Hill Hospital (Cottingham)	19/05/2014	5: Major: Major protocol deviation in patient management and/or assessment	Patient 0140044 week 1 neutrophils 0.79 and platelets 37. Per protocol G-CSF should be given and aspirin omitted, however neither of these actions were taken.
	24/02/2014	6: Major: Other major protocol deviation	Castle Hill Hospital (Hull) started patient screening no 014003 on treatment 24-Feb-2014 without going through the formal registration procedure or even informing the LCTU. The LCTU discovered this because the Biobank received a week 1 day 1 sample which was partially missing, and asked if there was a reason for this. Patient had consented to the trial and was eligible, registration forms received at LCTU 25-Feb-2014 and patient registered as 014-0039.
	02/01/2014	6: Major: Other major protocol deviation	Patient 0140032 JW. Per CRF cumulative dose of lenalidomide 1300mg. Per pharmacy accountability logs, looking at doses dispensed and returned maximum cumulative dose (assuming patient returned all unused drug) would be 1200mg. Site study team were unable to reconcile this difference and confirm cumulative lenalidomide dose.
Churchill Hospital (Oxford)	07/06/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1530004 BM had grade 3/4 skin infection onset 7 June 2013. Immunoglobulin replacement therapy not given as required by study protocol.
	21/09/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1530005 RS had Lung Infection onset 11 June 2012. Immunoglobulin given 21-27 August 2012 but not continued after that.
	17/12/2013	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1530025 GP. 17 December 2013 had neutrophil count of 0.09x10^9/L and ofatumumab was given. 31 December 2013 had neutrophil count of 0.22x10^9/L and ofatumumab was given. Per protocol, ofatumumab should be omitted if neutrophils < 0.5x10^9/L. Also G-CSF missed 31/12/2013 and also 22/04/2014 when neutrophils <1x10^9/L.
	19/01/2013	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1530025 GP. Day 1 week 5 19 November 2013 neutrophil count 0.38x10^9/L. Per protocol lenalidomide should be reduced to reduced to 0mg, however per CRF increased to 10mg. Not clear if this was due to underlying CLL. Per query response signed by local PI (Dr Anna Scuh) neutrophil count was overlooked when prescribing lenalidomide.

Site	Date of Deviation	Category	Description
	05/09/2013	6: Major: Other major protocol deviation	Churchill consented a patient to the CLL210 study, prior to being given green-light to re-start treatment after change to treatment regimen. Site did have local R&D approval for updated protocol, but addendum to Research Site Agreement (dealing with GSK drug supply) was not yet signed off.
	01/05/2012	6: Major: Other major protocol deviation	Patient 1530007 TB experienced grade 3/4 infection 30 April 2012. Immunoglobulin replacement therapy given 1 and 21 May 2012 but not subsequently. Per protocol should be continued for 6-12 motnhs.
King's College Hospital (London)	28/08/2015	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1610048 Disease Progression. Bone Marrow (trephine and aspirate) and Blood Samples for CPR reporting, and CT scan not taken at disease progression. Per site CPR samples missed because they mistakenly thought that they were not needed, and CT scan not performed as progression was shown by physical examination and blood results In addition the Quality of Life forms were not completed by patient at disease progression.
Leicester Royal Infirmary	28/08/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 0310015 RNK Bone Marrow trephine sample not available for central review. Pateint 0310016 week 23 Bone Marrow trephine sample not available for central review.
Queen Elizabeth Hospital (Gateshead)	24/03/2015	5: Major: Major protocol deviation in patient management and/or assessment	Patient 0710058 lenalidomide dose increased to 10mg at week 5 despite neutrophil count being 0.1x10^9/L. Per protocol neutrophil count should have been decreased from 5mg to 0 if neutrophil count fell below 0.5x10^9/L.
	01/05/2015	5: Major: Major protocol deviation in patient management and/or assessment	Patient 0710055 ARK and 0710058 RAS were dispensed with lenalidomide expiry date 30 April 2015 which the patients took from 1-18 May 2015. On 18 May 2015 site pharmacy informed LCTU that expired stock had been issued. LCTU advised site to immediately contact patients and ask them to stop taking drug. There was a then a delay to patient treatment whilst an emergency supply of lenalidomide was ordered and delivered.
Royal Liverpool University Hospital	28/09/2013	6: Major: Other major protocol deviation	Patient 0460018 MB received tapering dexamethasone dose day 5 onwards week 1,3,5,7,9,11,13,15. Drug accountability records kept for dexamethasone given days 1-4 these weeks, but not from day 5 onwards.
	20/08/2012	5: Major: Major protocol deviation in	Patient experienced grade 3 lung infection onset 20 August 2012. Immunolglobulins not given following infection.

Site	Date of Deviation	Category	Description
		patient management and/or assessment	
	14/12/2012	6: Major: Other major protocol deviation	The following discrepancies between the CRF and pharmacy drug accountability logs could not be resolved: Dexamethasone, 12-Sep-12 160 x 2mg tablets dispensed weeks 13/15, 40mg per day taken 17-18 September, 20mg 19-20 September and 8-11 October. Expected to be 60 tablets returned, per drug accountability log 80 returned. Lenalidomide, 19 October 2012 28x10mg capsules dispensed, 10mg 22-Oct - 1-Nov before dose reduction to 5mg, expect 17 returns, 21 per drug accountability log. Alemtuzumab no dispense record for : week 11 d1, 3(3 & 5 September 2012), week 18 d1, 3 (29 & 31 October), week 21 (3,5, 7 December). Also 6x30mg dispensed 31 October 2012 for weeks 19-20, no drug taken day 3, 5 week 20, only one unused vial returned (expected to be 2).
Southampton General Hospital	18/07/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1140008 JN experienced grade 3/4 infection 18 July 2012. Study protocol requires that patients receive immunoglobulin replacement therapy if grade 3/4 infection is experienced during induction treatment. Per site, no immunoglobulins given.
	20/08/2012	6: Major: Other major protocol deviation	Patient 1140006 AS. The following discrepancies between the CRF and pharmacy drug accountability logs could not be resolved. 23 May 2012 80 2mg dexamethasone tablets dispensed, per CRF 40 tablets taken week 5, 10 tablets taken week 7 day 4. Per drug accountability log 40 tablets returned, 10 more than expected. Alemtuzumab dispensed 30mg on 13, 16 July and 20 August 2012 with nor record of being taken per CRF and no returns on log.
	13/06/2012	6: Major: Other major protocol deviation	Patient 1140008 JN. Numerous discrepancies between CRF and pharmacy drug accountability logs which could not be resolved: Dexamethasone week 9-11 per CRF 4x40mg given 25-28 June 2012 and 9-12 July 2012. No record of dispense on pharmacy log. Lenalidomide: Week 12 18-22 July 2012 5 doses omitted. No returns noted on pharmacy log; Per CRF from 20 August 2012 15 5mg doses given but only 14 capsules dispensed per log 20 August 2012 Alemtuzumab: Following dates alemtuzumab taken per CRF but no record on log: 13, 15, 18, 20 June, 27 August 2012. Per log doses dispensed 18 July, 28 August 2012 but no record on CRF.

Site	Date of Deviation	Category	Description
The Christie (Manchester)	29/05/2015	5: Major: Major protocol deviation in patient management and/or assessment	Patient 0180024 AG was diagnosed with progressive disease 29 May 2015. As per protocol, site were required to submit bone marrow trephine and aspirate biospies for central anaylsis to confirm PD. However these were not taken. According to the site, because the patient had shown signs of impending progression across a number of trial visits prior to meeting the criteria for PD, the requirement to send bone marrow samples was overlloked. A clinical decision was made not to take a bone marrow sample locally to confirm PD.
The Royal Bournemouth Hospital	19/06/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1120001 RC experienced grade 3/4 UTI 19 June 2012. Immunoglobulin replacement therapy not commenced until 24 September 2012 (and given monthly thereafer).
	17/07/2012	5: Major: Major protocol deviation in patient management and/or assessment	Patient 1120003 CH had grade 3 sepsis onset date 17 July 2012. Immunoglobulin replacement therapy not given subsequently, despite being required by study protocol.
	31/01/2015	6: Major: Other major protocol deviation	Patient 1120057 MG originally recruited to RIAltO study. Local investigator concerned patient's CLL was agressive and not suitable for RIAltO treatment, so went off that study without receiving treatment. Local investigator contacted CI and asked if patient could be entered into CLL210, that the patient had been consented to the study and that because of urgent clinical need the patient started week 1 dexamethasone as per protocol 31 January 2015 (i.e. after consent but before formal registration). The CI agreed that in such an expceptional circumstance it was reasonable to start treatment prior to formal registration. The patient met the eligibility criteria and was registered for CLL210 2 February 2015.
University Hospital of Wales	14/09/2012	5: Major: Major protocol deviation in patient management and/or assessment	For patient 3520013 TRV Site did not give immunoglobulin therapy cycle 7 following grade 3 sepsis onset date 14/09/2012.
	13/03/2013	5: Major: Major protocol deviation in patient management and/or assessment	Bone marrow trephine sample not taken at week 23 assessment, making it potentially impossible to determine a CR from a PR and hence the primary endpoint.

6. STATISTICAL ANALYSES – METHODOLOGY

Unless terminated early for efficacy/futility the final statistical analysis will be triggered when the last patient still on follow-up has completed 12 months in follow-up. Statistical analyses were performed using a suitable recognised statistical software such as STATA v15, R version 3.3.0 and SAS version 9.3 or above.

6.1 Patient Groups for Analysis

Full Analysis set: In order to follow the Intention to Treat (ITT) principle this consists of all registered patients excepting for a) patients withdrawing consent or experiencing an event (death/ progression) between registration and starting therapy b) patients withdrawn from the study after registration because of irregularities with the consent process and c) patients whose information determining ineligibility existed before registration but was not read until after registration.

Per protocol (PP) set: This consists of those patients in the Full Analysis set without any major protocol deviations; these includes mis-randomised patients.

Safety set: All patients who received any trial treatment.

Major deviations from protocol that lead to exclusion of a subject from the per-protocol set will be assessed by blind review before data lock.

6.2 Handling of dropouts and mis-randomised patients

For efficacy analyses, in order to follow the ITT principle mis-randomised patients were analysed as randomised. For safety analyses patients were analysed as treated. Dropouts, that are unevaluable patients, were censored at last visit date in time-to-event analyses or treated as non-responders for the purpose of estimating event rates.

6.2 Identification and handling of Outliers

For continuous variables potential outliers are defined as follows (Tukey, 1977) after testing for symmetry and if non-symmetric, transforming to approximate symmetry using a "ladder of powers" approach (e.g., using the Stata command *ladder)*:

- "Mild" outliers: UQ+1.5×IQR to UQ+3×IQR or LQ-1.5×IQR to LQ-3×IQR
- Severe outliers: values more extreme than the above

(Note: UQ=Upper Quartile, LQ=Lower Quartile, IQR=Inter Quartile Range)

If after transformation no outliers are apparent then no action is taken even if values appear as outliers on the original scale, apart from use of the transformation if normality is required for a particular statistical procedure, or to remove the leverage effect of the outlying values. Outliers that are still present on the transformed scale are "winsorised" before analysis.

6.3 Study Centre effects

There is limited capacity to investigate these formally and such centre effects are to be expected by chance.

6.4 Adjustment for multiple testing

Formal adjustment for multiple significance testing is not applied.

6.5 Missing data

This problem is not expected to arise for the primary analysis, as the primary outcome will be assessed by the Endpoint Review Committee. If >20% of patients have unacceptable scores on any other variable of interest, then multiple imputation should be attempted, performing at least 10 separate sets of multiple imputations by treatment arm using chained equations.

The multiply-imputed data sets can then be recombined for formal analysis, either using *mim* command prefix (Stata) or if necessary a bespoke routine to estimate parameter values and combine them using Rubin's rules.

6.6 Levels of significance

For the tolerability primary outcome statistical tests is performed at 16.4% significance level (one-sided) and parameter estimates presented with 67.2% Clopper-Pearson exact confidence intervals. For the efficacy primary outcome statistical tests are performed at 15.8% significance level (one-sided) and parameter estimates presented with 68.4% Clopper-Pearson exact confidence intervals. The overall type I error reported for the co-primary outcome is 16.4% one-sided. For all secondary outcome parameter estimates are presented with 67.2% Clopper-Pearson exact confidence intervals.

6.7 Sensitivity analyses

These consist of:

- Per protocol analysis for both primary outcomes.
- Complete cases only\Weighted analysis for the efficacy primary outcome in case the Endpoint Review Committee cannot provide an entirely conclusive assessment.

6.8 Derived variables, definitions and analysis plan

6.8.1 Induction Phase primary outcomes

- **Tolerability:** tolerability is defined as absence of any grade 3-4 **infection** and no treatment-related death during induction treatment. Apart from events captured as "Infections and Infestations" based on CTCAE v4, infections include events of "febrile neutropenia", "progressive multifocal encephalopathy" and "hepatic failure due to hepatitis". Events captured as "Blood & Lymphatic System disorders - Other" based on CTCAE v4 are also examined individually. The key tolerability parameter is the proportion of patients being able to tolerate the treatment.
- **Efficacy**: the primary outcome is presence of complete response (CR\CRi) after 6 months of receiving induction (response assessment according to Endpoint Review Committee). The key efficacy parameter is the proportion of patients with CR\CRi at the end of induction treatment

6.8.2 Secondary outcomes

- **Overall, complete and partial response**: the key efficacy parameter is the proportion of patients with overall, complete and partial response at the end of induction treatment as assessed by the Endpoint Review Committee.
- **MRD negativity**: the key efficacy parameter is the proportion of patients with MRD negativity at the end of induction treatment as assessed by lab results.
- **Overall survival:** survival time defined as Survival (months) = (min (censoring date, date of death) – date of treatment initiation)/30.4; estimated separately for the induction and post-induction phases of the study using the Kaplan-Meier method.
- The final - administrative - censoring date for the post-induction phase (at which the trial terminates) is the date of most recent randomisation + one year. The final censoring date for the induction phase is the date of assessment for response to the induction treatment. Patients assumed alive at the final censoring date except for cases withdrawn/lost to follow-up who will be censored at the date last known alive.
- Induction phase observation period: from start of study treatment to death/ censoring date. Post-induction phase observation period: from randomisation to death/ censoring date (by arm).
- **Progression-free survival:** survival time defined as time to progression (months) = (min (censoring date, date of progression/death) – date of treatment initiation)/30.4; estimated separately for the induction and post-induction phases of the study using the Kaplan-Meier method.
- Similar rules as in **Overall Survival** apply for final censoring dates and observation periods.
- **Time to treatment failure:** time defined as time to failure (months) = (min (censoring date, date of progression/death/initiation of alternative treatment due to failure to achieve CR/CRi) – date of treatment initiation)/30.4; estimated using the Kaplan-Meier method.
- Similar rules as in **Overall Survival** apply for final censoring dates and observation periods.
- **Duration of response:** time defined as time to progression/death (months) = (min (censoring date, date of progression/death) – date of first achievement of CR/PR)/30.4; estimated using the Kaplan-Meier method.
- Similar rules as in **Overall Survival** apply for final censoring dates and observation periods.
- **Toxicity:** tabulation of Adverse and Serious Adverse Events separately for the induction and post-induction phases.
- **Quality of Life:** tabulation and graphical representation of longitudinally captured Quality of Life scores by QoL questionnaires.

7. PATIENTS POPULATION

Categorical variables are summarised as N (%), continuous variables by mean (SD) or median (Q1-Q3).

Table 8. Baseline Demographics

Table 8 details the demographics of patients at the point of recruitment.

	Ofatumumab (N=48)	**Alemtuzumab (N=16)**	**Total (N=64)**
Demographic Characteristics			
Age, *[median (IQR)]*	66 (59, 70)	68 (57, 74)	66 (59, 70)
Gender *[n (%)]*			
Female	15 (31%)	3 (19%)	18 (28%)
Male	33 (69%)	13 (81%)	46 (72%)
Physical findings			
WHO performance status *[n, (%)]*			
0	25 (52%)	9 (56%)	34 (53%)
1	17 (35%)	7 (44%)	24 (38%)
2	6 (12%)	0 (0%)	6 (9%)
CIRS Total Score,* *[median (IQR)]*	2 (0, 4)	2 (1, 4)	2 (1, 4)
CIRS Severity Index, *[median (IQR)]*	1 (0, 1.5)	1.4 (1, 2)	1 (1, 1.6)
Previous Treatment *[n (%)]*			
No	21 (44%)	8 (50%)	29 (45%)
Yes	27 (56%)	8 (50%)	35 (55%)
TP53 defect *[n (%)]*			
No	8 (17%)	3 (19%)	11 (17%)
Yes	40 (83%)	13 (81%)	53 (83%)

**CIRS score calculated omitting the 4 points allocated for having a diagnosis of CLL.*

7.1 End of Study Treatment/End of Study

This sections details the patients who have ended treatment for reasons other than the planned end of treatment as well as patients who have ended the study altogether.

Table 9. End of Trial Treatment

Table 9 details the patients who have ended treatment prior to their planned end of treatment date.

	Reason	Ended Treatment During Induction	Ended Treatment during Maintenance
Ofatumumab: N = 48	Clinican decision (not adverse event)	0	1
	Death	1	0
	Disease Progression	1	1
	Elected to receive allogeneic transplant after induction treatment	0	3
	Not randomised to lenalidomide maintenance after induction treatment	0	2
	Other (please specify reason)	1	1
	Toxicity	4	1
	Unknown	0	0
	median (IQR) (Range)	1.5 (0.9, 3.1) (0.4, 4.2)	6.5 (6.0, 7.5) (5.0, 34.1)
Alemtuzumab: N = 16	Death	5	0
	Disease Progression	5	4
	Elected to receive allogeneic transplant after induction treatment	0	4
	Inadequate response (SD or PD) to induction treatment	0	5
	Not randomised to lenalidomide maintenance after induction treatment	0	7

	Reason	Ended Treatment During Induction	Ended Treatment during Maintenance
	Other (please specify reason)	7	1
	Patient decision (not Adverse Event)	1	0
	Toxicity	3	1
	Withdrawal of consent	2	0
	Unknown	0	3
	median (IQR) (Range)	1.9 (1.0, 3.9) (0.2, 5.7)	5.6 (5.5, 6.0) (5.1, 24.0)

7.1.1 Ending treatment for 'Other' reasons:

Further detail on the patients who have ended study for 'Other' reasons are detailed below.

1) Patients on Ofatumumab who ended treatment during induction:
   a) SAE Infective Intracranial Process
   b) Patient did not start treatment, developed acute ITP
   c) clinician's decision due to deterioration in conduction
   d) Patient underwent septic shock and pneumonia, did not recover enough to continue trial when discharged from hospital
   e) Richter's Transformation (PD)
   f) patient's general condition
   g) SAE requiring lengthy hospitalisation and treatment
2) Patients on Ofatumumab who ended treatment during maintenance:
   a) diagnosis of new malignancy - acute myeloid leukaemia
3) Patients on Alemtuzumab who ended treatment during induction:
   a) Change of diagnosis therefore ineligible
4) Patients on Alemtuzumab who ended treatment during maintenance:
   a) patient randomised to maintenance lenalidomide, then later elected to have transplant

Table 10. End of Study

Table 10 summarises the end of study reasons by study stage.

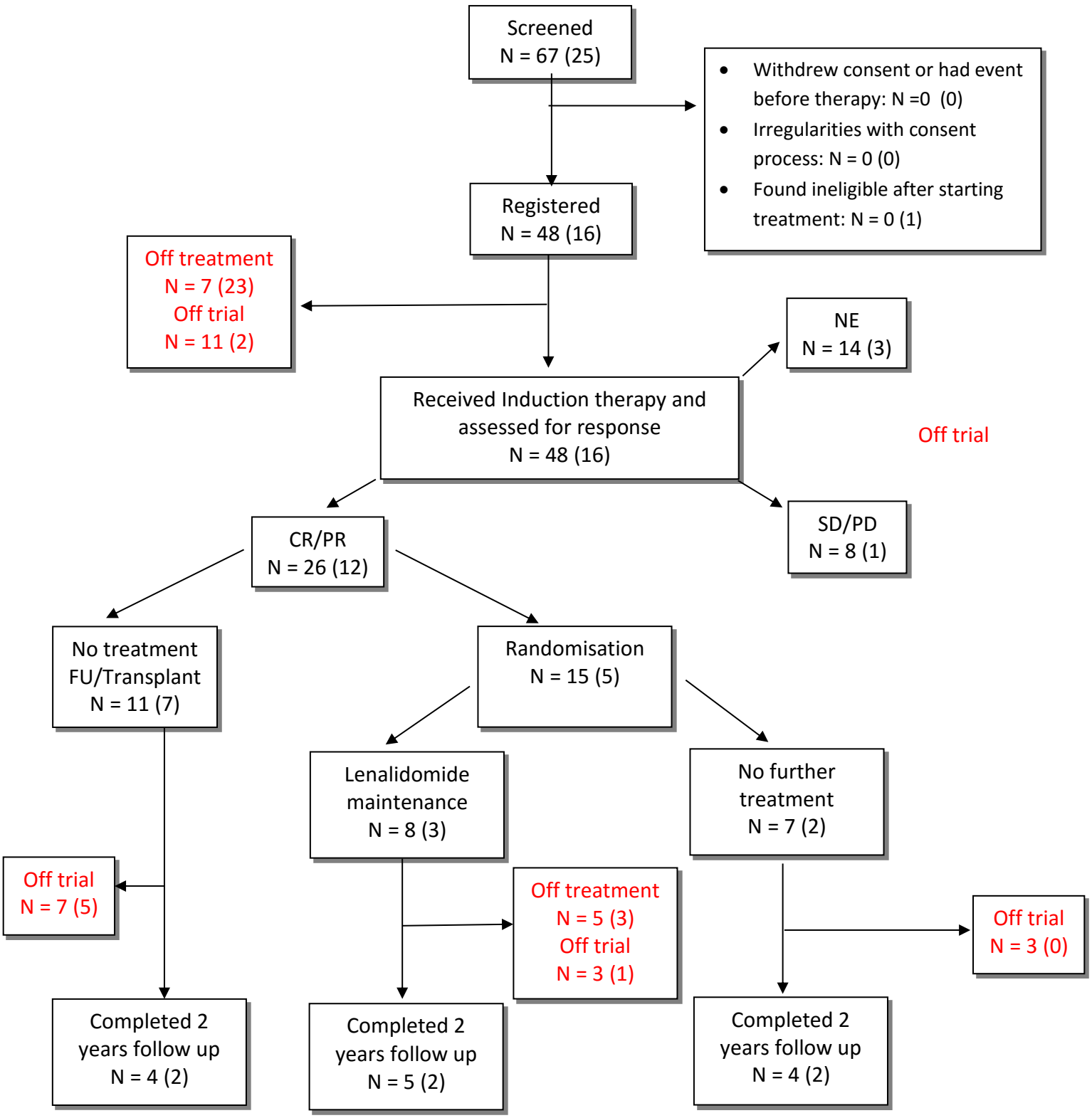
	End of Study Reason	End of Study Stage		
		During Induction Chemotherapy	**Follow up**	**Pre-treatment**
Ofatumumab: N = 48	Clinician decision (not adverse event)	2	0	0
	Death	9	8	1
	Disease Progression	0	1	0
	median (IQR) (Range)	1.5 (0.6, 2.1) (0.3, 4.0)	11.5 (5.1, 17.9) (3.5, 22.1)	
Alemtuzumab: N = 16	Consent withdrawn	0	2	
	Death	1	3	
	Other	1	0	
	median (IQR) (Range)	1.9 (1.0, 3.9) (0.2, 5.7)	5.6 (5.5, 6.0) (5.1, 24.0)	

Ending study for 'Other' reasons:

A single patient ended study during induction therapy whilst on Alemtuzumab.

7.1.2 Patient Disposition

Figure 2.Patient disposition – Ofatumumab (Alemtuzumab)



8. ANALYSIS OF PRIMARY OUTCOMES

As the trial contains co-primary endpoints, results are presented in terms of 'Tolerability' and 'Complete Response Rate' separately.

For all analyses, results are presented initially for the full cohort of patients and then following that, broken down by whether patients were recruited under the initial protocol (Alemtuzumab) or under the revised cohort (Ofatumumab). Patients are further stratified by their TP53 status and whether or not they had received prior treatment. Note that for one patient, their TP53 information is unknown. This patient was also unevaluable for response data and so are not included in the table below.

8.1 Tolerability

Tolerability is defined as patients experiencing either a treatment related death or a grade 3+ Infection over the induction phase of the study.

Table 11. Tolerability to induction treatment (All patients)

Table 11 details the results of patients' tolerability to induction treatment. Please note that 3 patients are deemed unevaluable due to insufficient therapy (≤ treatment weeks of induction therapy). The overall results shows that 45% (38% - 52%) of patients experienced either a grade 3+ infection or a treatment related death. Please note that in line with the conditions of the sample size calculations, all estimates of tolerability are presented alongside 67.2% confidence intervals.

	Total no. of patients	No. of unevaluable patients	Effective sample	No. with at least one event[1]	Rate of intolerability D/C	Confidence Interval	No. of Grade 3+ infections	Grade 3+ infections/ patient
Stratum	**A**	**B**	**C = A – B**	**D**				
Stratum undefined	1	1	0	0	-	-	-	-
Stratum 1: prior treatment & TP53 defect	18	2	16	9	**0.562**	(0.411, 0.705)	24	1.5
Stratum 2: prior treatment & no TP53 defect	17	0	17	8	**0.471**	(0.33, 0.615)	16	0.94
Stratum 3: no prior treatment & TP53 defect	21	1	20	10	**0.5**	(0.37, 0.63)	17	0.85
Stratum 4: no prior treatment & no TP53 defect	7	0	7	0	**0**	(0, 0.228)	0	0
Total	63	3	60	27	**0.45**	(0.38, 0.521)	57	0.95

Table 12. Tolerability to induction treatment (Alemtuzumab Patients)

	Total no. of patients	No. of unevaluable patients	Effective sample	No. with at least one event[1]	Rate of intolerability D/C	Confidence Interval	No. of Grade 3+ infections	Grade 3+ infections/ patient
Stratum	**A**	**B**	**C = A – B**	**D**				
Stratum 1: prior treatment & TP53 defect	4	0	4	4	**1**	(0.636, 1)	12	3
Stratum 2: prior treatment & no TP53 defect	4	0	4	1	**0.25**	(0.044, 0.613)	6	1.5
Stratum 3: no prior treatment & TP53 defect	6	1	5	5	**1**	(0.697, 1)	10	2
Stratum 4: no prior treatment & no TP53 defect	2	0	2	0	**0**	(0, 0.595)	0	0
Total	16	1	15	10	**0.667**	(0.507, 0.8)	28	1.87

Table 13. Tolerability to induction treatment (Ofatumumab Patients)

	Total no. of patients	No. of unevaluable patients	Effective sample	No. with at least one event[1]	Rate of intolerability D/C	Confidence Interval	No. of Grade 3+ infections	Grade 3+ infections/ patient
Stratum	**A**	**B**	**C = A – B**	**D**				
Stratum undefined	1	1	0	0	**-**	-	-	-
Stratum 1: prior treatment & TP53 defect	14	2	12	5	**0.417**	(0.253, 0.597)	12	1
Stratum 2: prior treatment & no TP53 defect	13	0	13	7	**0.538**	(0.369, 0.701)	10	0.77
Stratum 3: no prior treatment & TP53 defect	15	0	15	5	**0.333**	(0.2, 0.493)	7	0.47
Stratum 4: no prior treatment & no TP53 defect	5	0	5	0	**0**	(0, 0.303)	0	0
Total	47	2	45	17	**0.378**	(0.3, 0.462)	29	0.64

8.1.1 Efficacy (Complete Response Rate)

Study efficacy for the primary endpoint is evaluated on the complete response rate defined as the number of patients to achieve a complete response (CR or CRi), based on the IWCLL/NCI 2008 criteria as a proportion of all patients deemed eligible. It should be noted that for the efficacy response data, all outcome data was subject to independent review and clarification.

Table 14. Summary of IWCLL/NCI 2008 Criteria

Table 14 gives a summary of patient response to induction therapy.

Induction Cohort	CRi	PR	SD	PD	NE	Total
Ofatumumab	1 (2%)	24 (50%)	4 (8%)	5 (10%)	14 (29%)	48
Alemtuzumab	1 (6%)	11 (69%)	0 (0%)	1 (6%)	3 (19%)	16
Total	**2 (3%)**	**36 (56%)**	**4 (6%)**	**5 (8%)**	**17 (27%)**	**64**

Table 15. Complete Response Rate during induction (All patients)

Table 15 gives the summary of the complete response rate during the induction phase of the study. There were two patients who achieved CRi and zero patients who achieved a CR rate. Please note that in line with the conditions of the sample size calculations, all estimates of tolerability are presented alongside 68.4% confidence intervals. The overall complete response rate was 4.3% (1.5% - 9.6%).

	Total no. of patients	No. of Evaluable patients	No. of patients with CR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum undefined	1	1	0	**0**	(0, 0.842)
Stratum 1: prior treatment & TP53 defect	18	11	0	**0**	(0, 0.154)
Stratum 2: prior treatment & no TP53 defect	17	13	2	**0.154**	(0.055, 0.322)
Stratum 3: no prior treatment & TP53 defect	21	18	0	**0**	(0, 0.097)
Stratum 4: no prior treatment & no TP53 defect	7	4	0	**0**	(0, 0.37)
Total	64	47	2	**0.043**	(0.015, 0.096)

Note that a sensitivity analysis was carried out on the per protocol patient population. Here 45 patients were included of which 30 were evaluable. The overall complete response rate was **0.033 (0.006, 0.106).** No other sensitivity analyses were performed as the review committee provided unanimous agreement on the study outcome.

Table 16. Complete Response Rate during induction (Alemtuzumab Patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with CR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	4	4	0	**0**	(0, 0.37)
Stratum 2: prior treatment & no TP53 defect	4	3	1	**0.333**	(0.056, 0.748)
Stratum 3: no prior treatment & TP53 defect	6	5	0	**0**	(0, 0.309)
Stratum 4: no prior treatment & no TP53 defect	2	1	0	**0**	(0, 0.842)
Total	16	13	1	**0.077**	(0.013, 0.233)

Table 17. Complete Response Rate during induction (Ofatumumab Patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with CR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum Undefined	1	1	0	**0**	(0, 0.842)
Stratum 1: prior treatment & TP53 defect	14	7	0	**0**	(0, 0.232)
Stratum 2: prior treatment & no TP53 defect	13	10	1	**0.1**	(0.017, 0.295)
Stratum 3: no prior treatment & TP53 defect	15	13	0	**0**	(0, 0.132)
Stratum 4: no prior treatment & no TP53 defect	5	3	0	**0**	(0, 0.459)
Total	48	34	1	**0.029**	(0.005, 0.094)

Overview of Primary Endpoints

The rate of intolerability (67.2% CI) is 0.45 (0.38,0.52). The upper limit of the confidence interval of 0.52 is lower than the 0.7 specified by the study design and so the rate of tolerability **satisfies** the conditions to reject the null hypothesis.

The complete response rate 0.045 (68.4% CI) (0.015, 0.096). The upper limit of the confidence interval is less than 10% specified by the samples size calculations and so the rate of complete response **does not satisfy** the conditions to reject the null hypothesis.

9. Analysis of Secondary Outcomes

Section 9 includes details on the secondary endpoints in the study, namely:

- Partial Response Rate
- Overall Response Rate
- MRD Negativity Rate
- Overall Survival
- Progression Free Survival
- Quality of Life
- Toxicity

9.1 Partial Response Rate

The partial response rate is defined as the number of patients to achieve a partial response (PR) over the course of induction treatment.

Table 18. Partial Response Rate during induction (All patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with PR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	18	11	8	**0.727**	(0.531, 0.872)
Stratum 2: prior treatment & no TP53 defect	17	13	7	**0.538**	(0.366, 0.704)
Stratum 3: no prior treatment & TP53 defect	21	19	17	**0.895**	(0.772, 0.963)
Stratum 4: no prior treatment & no TP53 defect	7	4	4	**1**	(0.63, 1)

Total	63	47	36	**0.766**	(0.688, 0.831)

Table 19. Partial Response Rate during induction (Alemtuzumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with PR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	4	4	4	**1**	(0.63, 1)
Stratum 2: prior treatment & no TP53 defect	4	3	2	**0.667**	(0.252, 0.944)
Stratum 3: no prior treatment & TP53 defect	6	5	4	**0.8**	(0.475, 0.966)
Stratum 4: no prior treatment & no TP53 defect	2	1	1	**1**	(0.158, 1)
Total	16	13	11	**0.846**	(0.678, 0.945)

Table 20. Partial Response Rate during induction (Ofatumumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with PR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	14	7	4	**0.571**	(0.323, 0.794)
Stratum 2: prior treatment & no TP53 defect	13	10	5	**0.5**	(0.304, 0.696)
Stratum 3: no prior treatment & TP53 defect	15	14	13	**0.929**	(0.783, 0.988)
Stratum 4: no prior treatment & no TP53 defect	5	3	3	**1**	(0.541, 1)
Total	47	34	25	**0.735**	(0.638, 0.816)

9.2 Overall Response Rate

Overall Response Rate (ORR) is defined as the number of patients to obtain either a complete response (CR) or a partial response (PR) over the course of induction treatment as a proportion of all evaluable patients.

Table 21. Overall Response Rate during induction (All patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with ORR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	18	11	8	**0.727**	(0.531, 0.872)
Stratum 2: prior treatment & no TP53 defect	17	13	9	**0.692**	(0.515, 0.833)
Stratum 3: no prior treatment & TP53 defect	21	19	17	**0.895**	(0.772, 0.963)
Stratum 4: no prior treatment & no TP53 defect	7	4	4	**1**	(0.63, 1)
Total	63	47	38	**0.809**	(0.733, 0.868)

Table 22. Overall Response Rate during induction (Alemtuzumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with ORR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	4	4	4	**1**	(0.63, 1)
Stratum 2: prior treatment & no TP53 defect	4	3	3	**1**	(0.541, 1)
Stratum 3: no prior treatment & TP53 defect	6	5	4	**0.8**	(0.475, 0.966)
Stratum 4: no prior treatment & no TP53 defect	2	1	1	**1**	(0.158, 1)

Total	16	13	12	**0.923**	(0.767, 0.987)

Table 23. Overall Response Rate during induction (Ofatumumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with ORR	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	14	7	4	**0.571**	(0.323, 0.794)
Stratum 2: prior treatment & no TP53 defect	13	10	6	**0.6**	(0.395, 0.78)
Stratum 3: no prior treatment & TP53 defect	15	14	13	**0.929**	(0.783, 0.988)
Stratum 4: no prior treatment & no TP53 defect	5	3	3	**1**	(0.541, 1)
Total	47	34	26	**0.765**	(0.669, 0.842)

9.3 MRD Negativity Rate

MRD negativity rate is defined as the number of patients who achieve MRD negativity over the course of induction treatment as a proportion of all patients who were assessed for MRD negativity. Please note that of the 64 patients randomised, 24 patients were associated for MRD negativity over the course of induction.

Table 24. MRD Negativity Rate during induction (All patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with MRD Negativity	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	18	7	1	**0.143**	(0.024, 0.4)
Stratum 2: prior treatment & no TP53 defect	17	6	1	**0.167**	(0.028, 0.455)
Stratum 3: no prior treatment & TP53 defect	21	9	3	**0.333**	(0.158, 0.555)
Stratum 4: no prior treatment & no TP53 defect	7	2	1	**0.5**	(0.082, 0.918)
Total	63	24	6	**0.25**	(0.155, 0.37)

Table 25. Overall Response Rate during induction (Alemtuzumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with MRD Negativity	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	4	3	1	**0.333**	(0.056, 0.748)
Stratum 2: prior treatment & no TP53 defect	4	3	1	**0.333**	(0.056, 0.748)
Stratum 3: no prior treatment & TP53 defect	6	3	3	**1**	(0.541, 1)
Stratum 4: no prior treatment & no TP53 defect	2	1	1	**1**	(0.158, 1)
Total	16	10	6	**0.6**	(0.395, 0.78)

Table 26. Overall Response Rate during induction (Ofatumumab patients)

	Total no. of patients	No. of Evaluable patients	No. of patients with MRD Negativity	B/A % -	Confidence Interval
Stratum		**A**	**B**		
Stratum 1: prior treatment & TP53 defect	14	4	0	**0**	(0, 0.37)
Stratum 2: prior treatment & no TP53 defect	13	3	0	**0**	(0, 0.459)
Stratum 3: no prior treatment & TP53 defect	15	6	0	**0**	(0, 0.265)
Stratum 4: no prior treatment & no TP53 defect	5	1	0	**0**	(0, 0.842)
Total	47	14	0	**0**	(0, 0.123)

9.4 Overall Survival

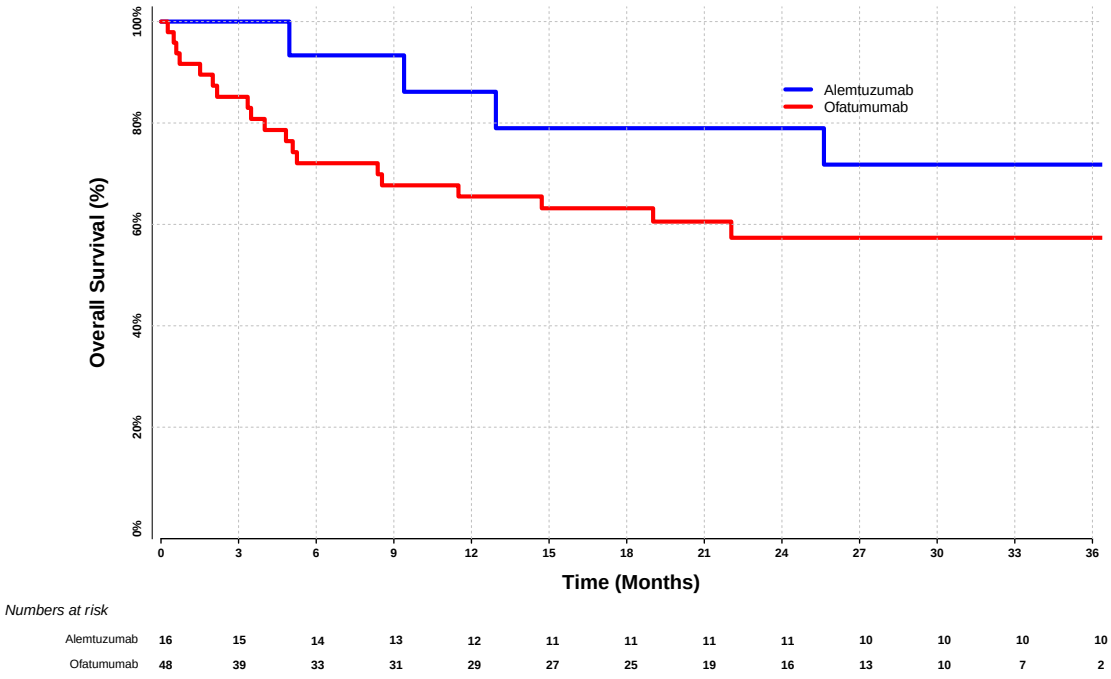
Overall Survival is defined as the time until death by any cause. At the point of analysis, 23 deaths had been reported on the study. Only Three deaths were observed whilst patients were on induction therapy.

Deaths in the study are defined based on whether they occurred whilst receiving induction therapy or after stopping induction Therapy.

9.4.1 Overall Survival from the point of registration

Please note that 23 events have been observed in the study at the point of final analysis. The 2 years OS rate was 63% (52% – 77%) for all patients [79% (60% – 100%) for Alemtuzumab and 57% (44% - 74%) for Ofatumumab patients].

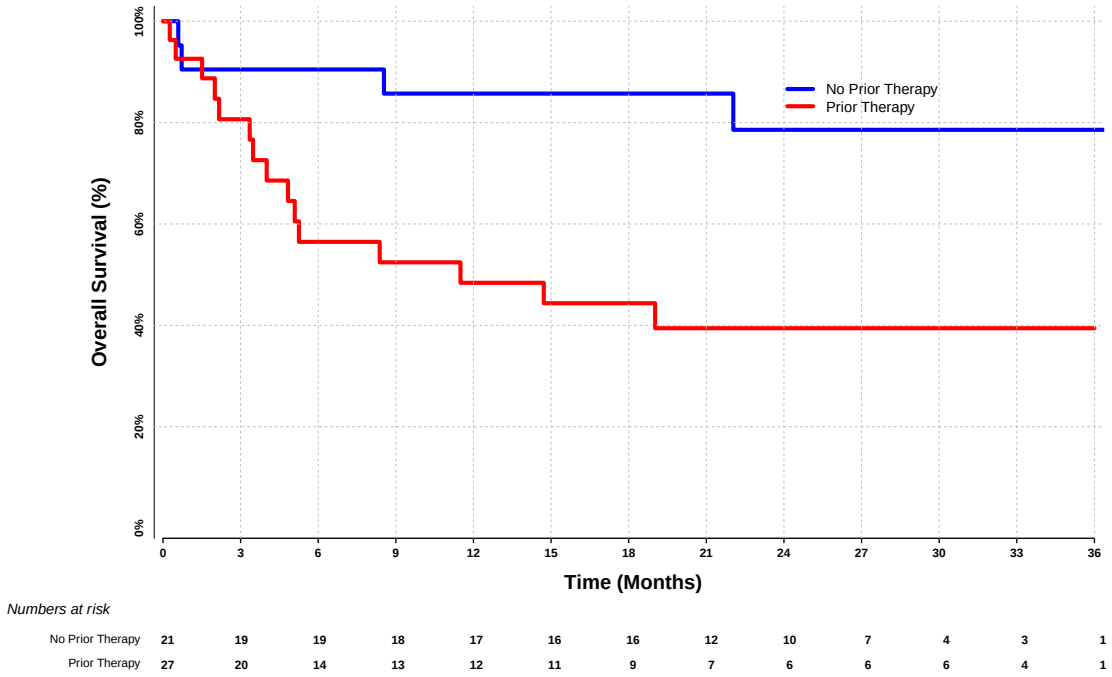
Figure 3.Kaplan-Meier plot for Overall Survival for all patients measured from the point of registration



Overall Survival from the point of registration by Prior Therapy

OS is further broken down for Ofatumumab patients by those who received prior therapy and those who did not (Figure 4). For those patients with no prior therapy the 2 year OS was 79% (62% - 100%) and for patients who did receive prior therapy the 2 year OS was 39% (24% - 65%).

Figure 4.Kaplan-Meier plot for Overall Survival for all patients measured from the point of registration for Ofatmumab patients by prior therapy



9.4.2 Death After Induction

Deaths after induction are reported as all deaths following the end of induction and secondly for the subgroup of patients who entered the randomisation phase.

Table 27. Deaths post induction for all patients

Please note here that overall survival is measured as the time from the end of induction until death by any cause. Note that 2 year OS following induction was 64 % (52% - 78%) for all patients [72% (52% - 100%) for Alemtuzumab patients and 61% (47% - 79%) for Ofatumumab patients]

	Ofatumumab N = 48	**Alemtuzumab N = 16**	**Total N = 64**
Deaths	16	4	20
Median time to death (IQR), months	2.45 (0.38 – 5.53)		2.45 (0.49 – 5.53)

Figure 5.Overall survival after induction by induction therapy cohort

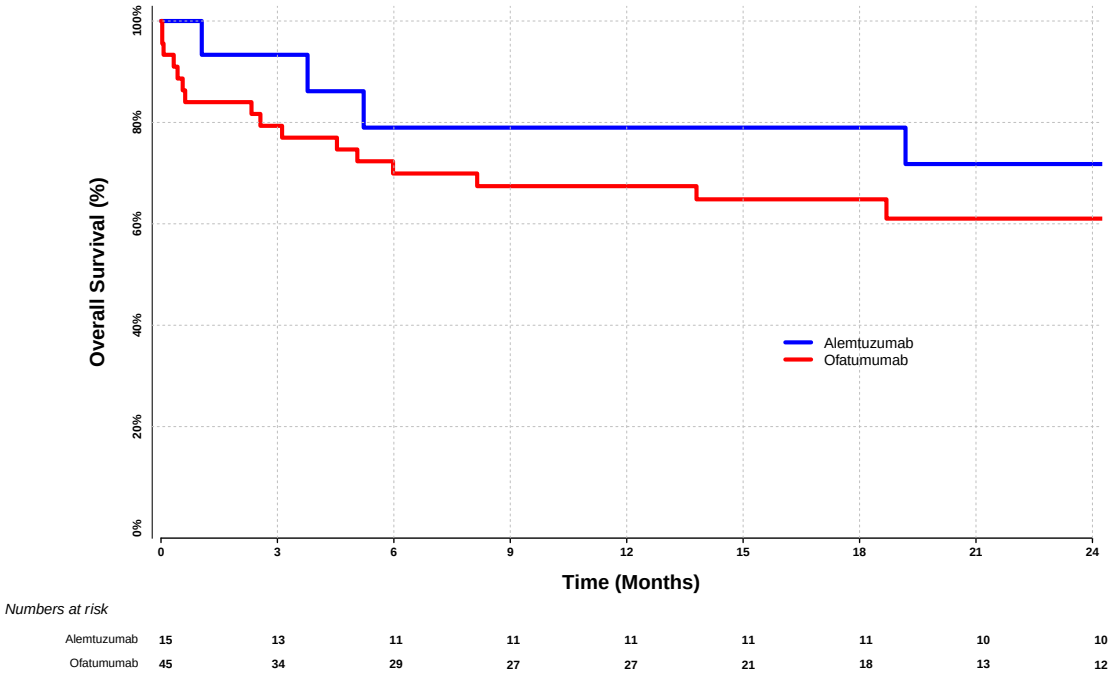
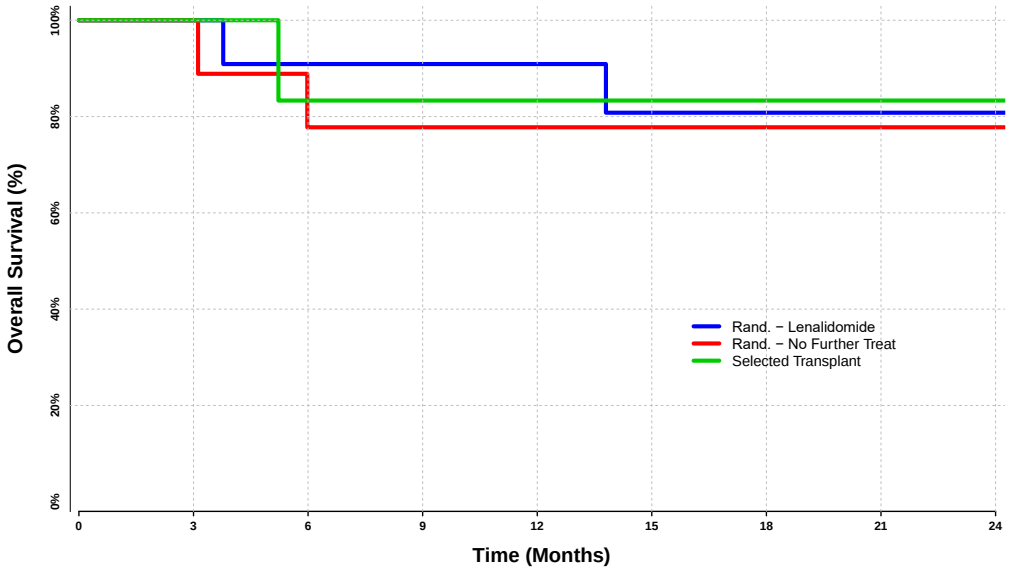


Table 28. Deaths post induction for patients who were randomised or received a transplant

Please note here that overall survival is measured as the time from randomisation until death by any cause. Note that 2 year OS following induction was 80% (66% - 97%) for all patients [81% (60% - 100%) for those randomised to Lenalidomide, 78% (55% - 100%) for those randomised to no further treatment and 83% (58% - 100%) for those who elected for transplant].

	Lenalidomide maintenance N = 11	**No further treatment N = 9**	**Transplant N = 6**	**Total N = 26**
Deaths	2	2	1	5
Median time to death (IQR)	8.57 (3.52 – 13.62)	4.28 (2.57 – 5.99)	1.48 (1.48 – 1.48)	3.52 (2.57 – 5.99)

Figure 6.Overall survival following post induction randomisation



Numbers at risk

Rand. − Lenalidomide	11	11	9	9	9	6	5	5	5
Rand. − No Further Treat	9	9	7	6	6	5	5	3	3
Selected Transplant	6	6	5	5	5	5	4	4	4

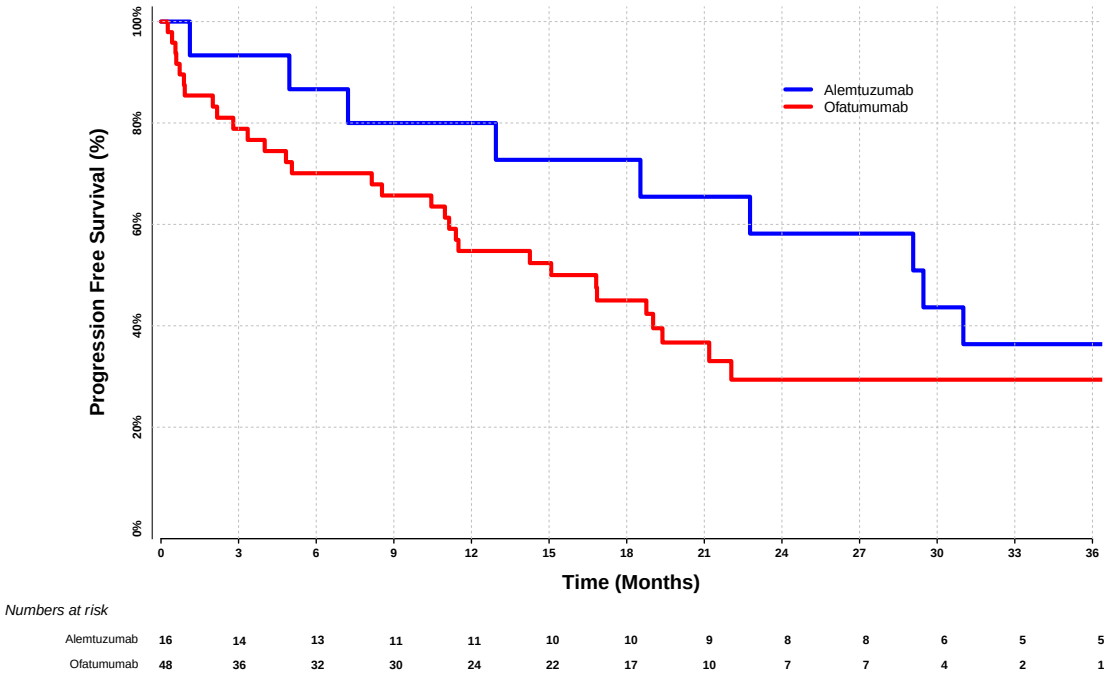
9.5 Progression Free Survival

Progression Free Survival is defined as the time until disease progression or death by any cause. At the point of the Final Analysis, 39 patients had progressed (or died) over the course of the study.

9.5.1 Progression Free Survival from the point of registration

Progression Free Survival measured from the point of registration is shown in Figure 6. Median PFS was 18.5 (11.5 -29.5) months for all patients [29.5 (18.5 – Undefined) months for Alemtuzumab patients and 15.1 (11.0 – 22) months for Ofatumumab patients). 2 year PFS was 37% (26% - 53%) for all patients [58% (27% - 91%) for Alemtuzumab patients and 30% (18% - 49%) for Ofatumumab patients].

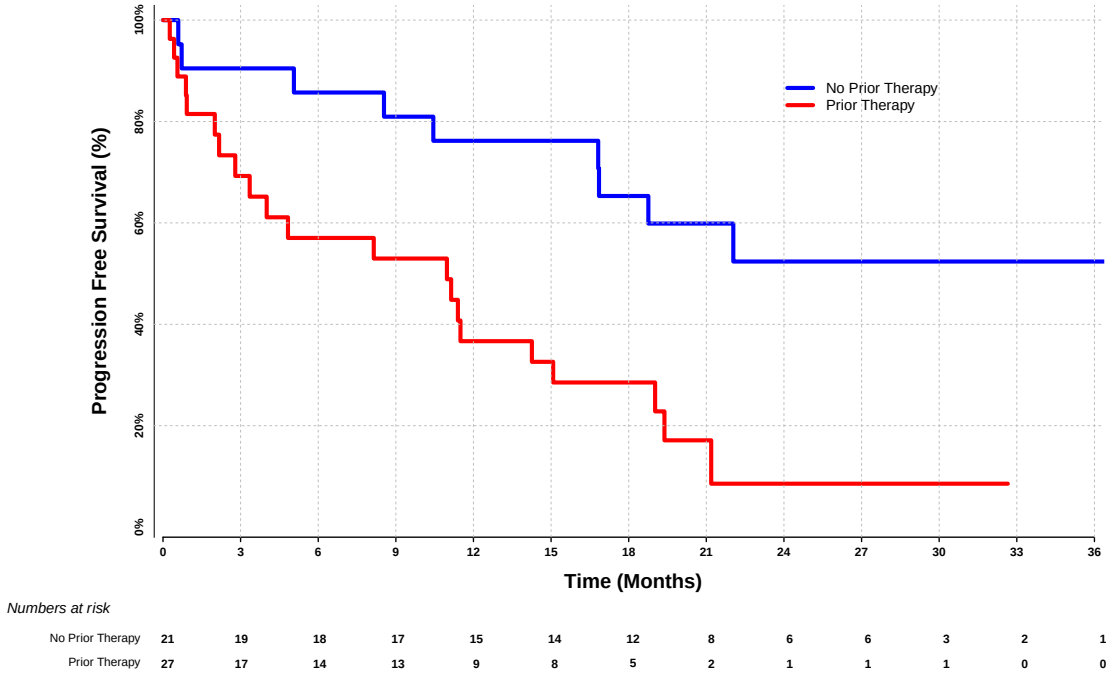
Figure 7.Kaplan-Meier plot for Progression Free Survival for all patients measured from the point of registration



Progression Free Survival from the point of registration by Prior Therapy

PFS is further broken down for Ofatumumab patients by those who received prior therapy and those who did not (Figure 4). Median survival for patients who had prior therapy was 11 (3.35 - 19) months. Median survival was undefined for those patients with no prior therapy. For those patients with no prior therapy the 2 year PFS was 52% (34% - 82%) and for patients who did receive prior therapy the 2 year PFS was 9% (2% - 46%).

Figure 8.Kaplan-Meier plot for Overall Survival for all patients measured from the point of registration for Ofatmumab patients by prior therapy



9.5.2 Progressions After Induction

Table 29. Progression post induction for all patients

Please note here that progression free survival is measured as the time from the end of induction until disease progression or death by any cause. Note that 2 year PFS following induction was 38% (25% - 56%) for all patients [46% (26% - 83%) for Alemtuzumab patients and 36% (22% - 59%) for Ofatumumab patients].

	Ofatumumab N = 48	**Alemtuzumab N = 16**	**Total N = 64**
Progressions/deaths	30	9	30
*Median time to progression or death (IQR), months**	5.46 (0.56 – 11.48)	13.72 (1.41 – 22.42)	5.92 (1.35 – 13.26)
*Median progression free survival time (95% CI)**	13.6 (8.74 – NE)	24.0 (12.58 – NE)	15.7 (11.8 – NE)

Figure 9.Progression Free survival after induction by induction therapy cohort

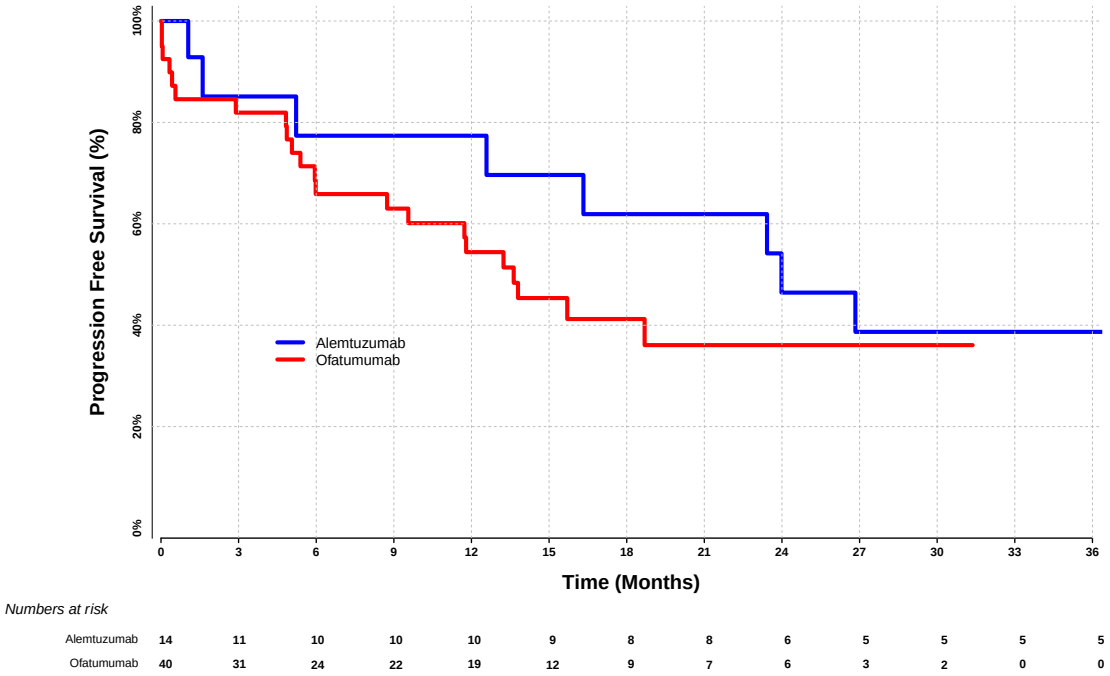
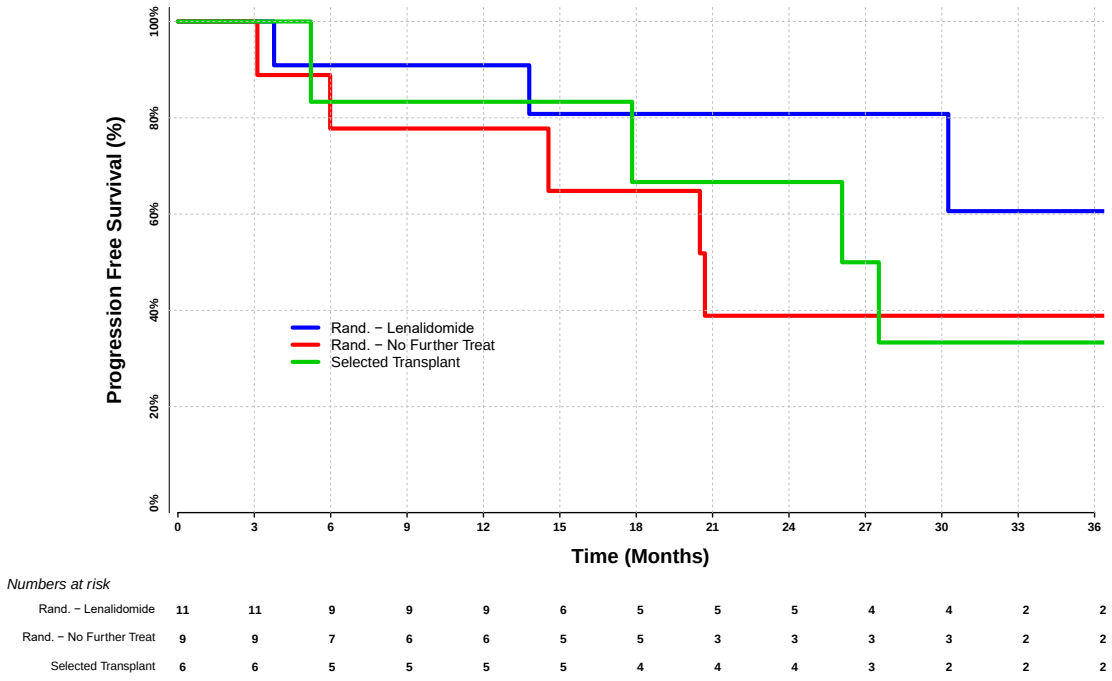


Table 30. Progression post induction for patients who were randomised or received a transplant

Please note here that progression free survival is measured as the time from randomisation until disease progression or death by any cause. Note that 2 year PFS following induction was 34% (19% - 62%) for all patients [53% (27% - 100%) for those randomised to Lenalidomide, 26% (8% - 85%) for those randomised to no further treatment and 17% (3% - 100%) for those who elected for transplant].

	Lenalidomide maintenance N = 11	**No further treatment N = 9**	**Transplant N = 6**	**Total N = 26**
Progressions/Deaths	4	6	5	15
*Median time to progression/death (IQR)**	9.74 (3.60 – 18.65)	11.45 (5.99 – 13.26)	9.28 (3.91 – 11.09)	11.09 (3.91 – 13.26)
*Median progression free survival time (95% CI)**	NE	13.2 (11.7 – Undefined)	11.1 (5.4 – Undefined)	15.7 (11.8 – NE)

Figure 10. Progression Free survival following post induction randomisation



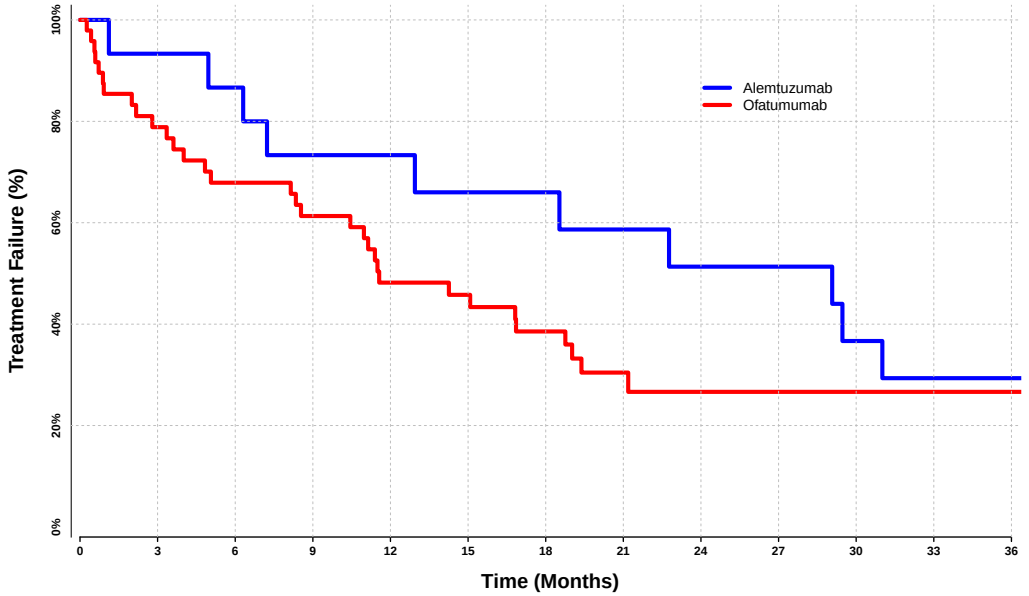
9.6 Duration of Response

Estimates of duration of response defined as the time from initial response until disease progression/death are not reported as response was defined over the initial induction period without a start date attached.

9.7 Time to Treatment Failure

Time to treatment failure (TTF) as measured from the point of registration is shown in Figure 11. Median TTF was 15.1 (11.0 - 22.8) months for all patients [29.1 (12.94 – Undefined) months for Alemtuzumab patients and 11.6 (8.5 – 19.4) months for Ofatumumab patients). 2 year PFS was 33% (22% - 48%) for all patients [51% (31% - 85%) for Alemtuzumab patients and 27% (16% - 45%) for Ofatumumab patients].

Figure 11. Kaplan-Meier plot for Time to Treatment Failure for all patients measured from the point of registration



Numbers at risk

Alemtuzumab	16	14	13	10	10	9	9	8	7	7	5	4	4
Ofatumumab	48	36	31	28	21	19	15	8	6	6	4	2	1

9.6 Quality of Life

Quality of Life was measured using the EQ5D-3L quality of life form. Results are presented in terms of summarising the results of each EQ5D-3L domain at each time-point and in terms of the reported Visual Analogue Scale (VAS).

9.8.1 Summary of Quality of Life EQ5D-3L results

Table 31. EQ-5D proportions of reported problems by dimension and visit.

In Table 33 EQ-DD levels are dichotomised as "no problems" (i.e. level 1) and "problems" (i.e. level 2 and 3) and reported as frequencies and percentages for each visit and each dimension.

EQ-5D DIMENSION		Baseline	Week23	Week33	Week57	Week81	Week105	Week129
		No. available: 55	No. available: 22	No. available: 22	No. available: 12	No. available:16	No. available: 5	No. available:7
MOBILITY n (%)	No problems	37 (67)	12 (55)	17 (77)	8 (67)	9 (56)	4 (80)	6 (86)
	Problems	18 (33)	10 (45)	5 (23)	4 (33)	7 (44)	1 (20)	1 (14)
		No. available: 58	No. available: 23	No. available: 22	No. available: 12	No. available: 15	No. available: 5	No. available:7
SELF-CARE n (%)	No problems	52 (90)	19 (83)	21 (95)	9 (75)	13 (87)	5 (100)	5 (71)
	Problems	6 (10)	4 (17)	1 (5)	3 (25)	2 (13)	0 (0)	2 (29)
		No. available: 56	No. available: 22	No. available: 22	No. available: 12	No. available: 16	No. available: 5	No. available:7
USUAL ACTIVITIES n (%)	No problems	29 (52)	9 (41)	17 (77)	9 (75)	8 (50)	4 (80)	4 (57)
	Problems	27 (48)	13 (59)	5 (23)	3 (25)	8 (50)	1 (20)	3 (43)
		No. available: 58	No. available: 23	No. available: 22	No. available: 12	No. available: 16	No. available: 5	No. available:7
PAIN-DISCOMFORT n (%)	No problems	32 (55)	11 (48)	15 (68)	7 (58)	7 (44)	4 (80)	5 (71)
	Problems	26 (45)	12 (52)	7 (32)	5 (42)	9 (56)	1 (20)	2 (29)
		No. available: 58	No. available: 22	No. available: 22	No. available: 12	No. available: 16	No. available: 5	No. available:7

EQ-5D DIMENSION		Baseline	Week23	Week33	Week57	Week81	Week105	Week129
ANXIETY n (%)	No problems Problems	36 (62) 22 (38)	16 (73) 6 (27)	15 (68) 7 (32)	9 (75) 3 (25)	11 (69) 5 (31)	5 (100) 0 (0)	4 (57) 3 (43)

Table 32. EQ VAS score by dimension and visit.

EQ VAS	Baseline	Week23	Week33	Week57	Week81	Week105	Week129
No. available	52	21	21	12	16	4	7
Mean (sd)	0.71 (0.20)	0.73 (0.19)	0.73 (0.24)	0.69 (0.31)	0.69 (0.27)	0.65 (0.40)	0.76 (0.34)
Median (IQR)	0.75 (0.58 -0.88)	0.75 (0.70 -0.80)	0.80 (0.70 -0.89)	0.82 (0.65 - 0.89)	0.78 (0.66 - 0.85)	0.80 (0.58 -0.87)	0.89 (0.70 -0.97)

9.8.2 Graphical summaries of Quality of Life EQ5D-3L results

Figures 11 -16 give a graphical summary of the number of patients to report problems over each of the 5 EQ5D dimensions. Figure 16 gives a graphical summary of the reported VAS over the course of the study.

Figure 12. Percentage of reported problems by visit for mobility dimension.

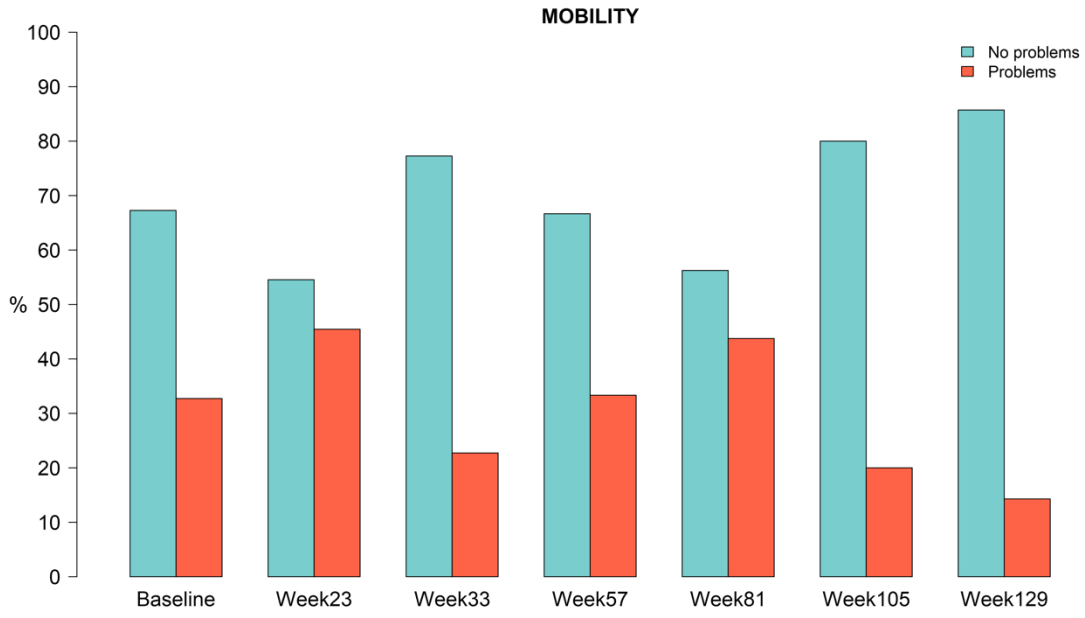


Figure 13. Percentage of reported problems by visit for self-care dimension.

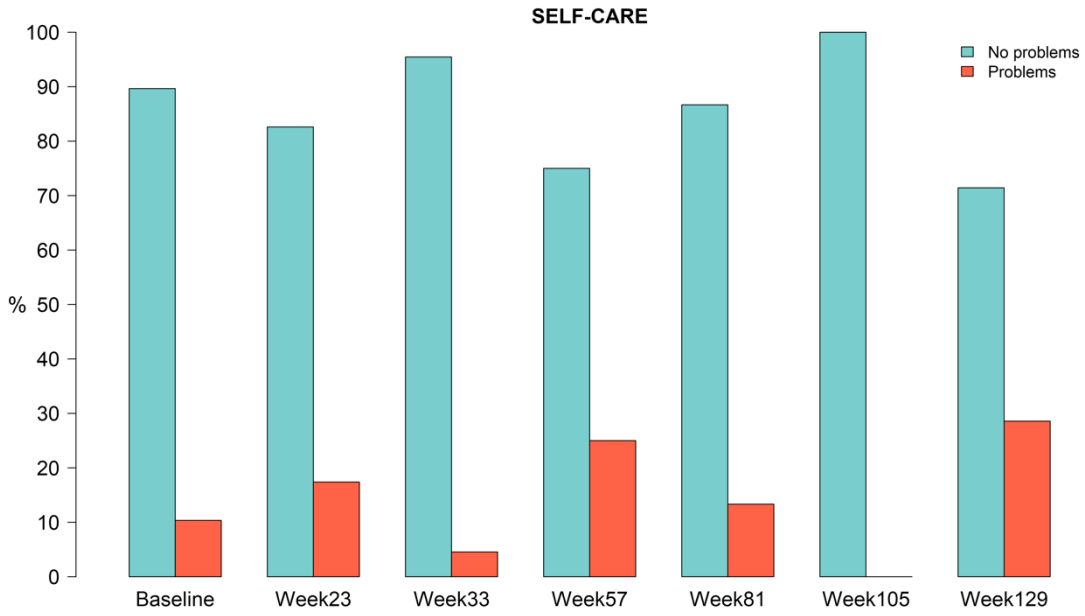


Figure 14. Percentage of reported problems by visit for usual activities dimension.

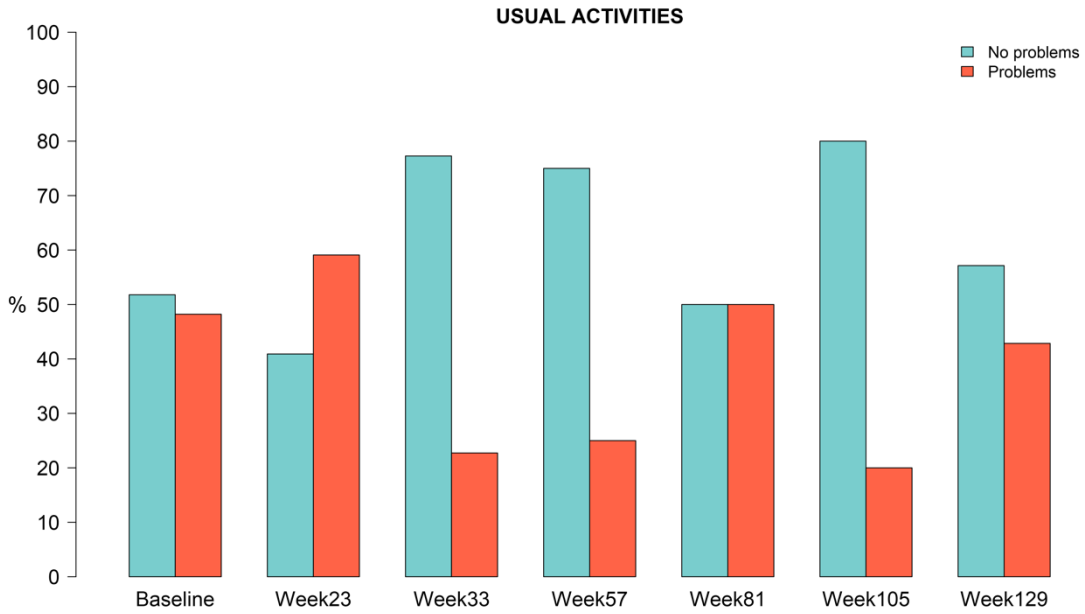


Figure 15. Percentage of reported problems by visit for pain/discomfort dimension.

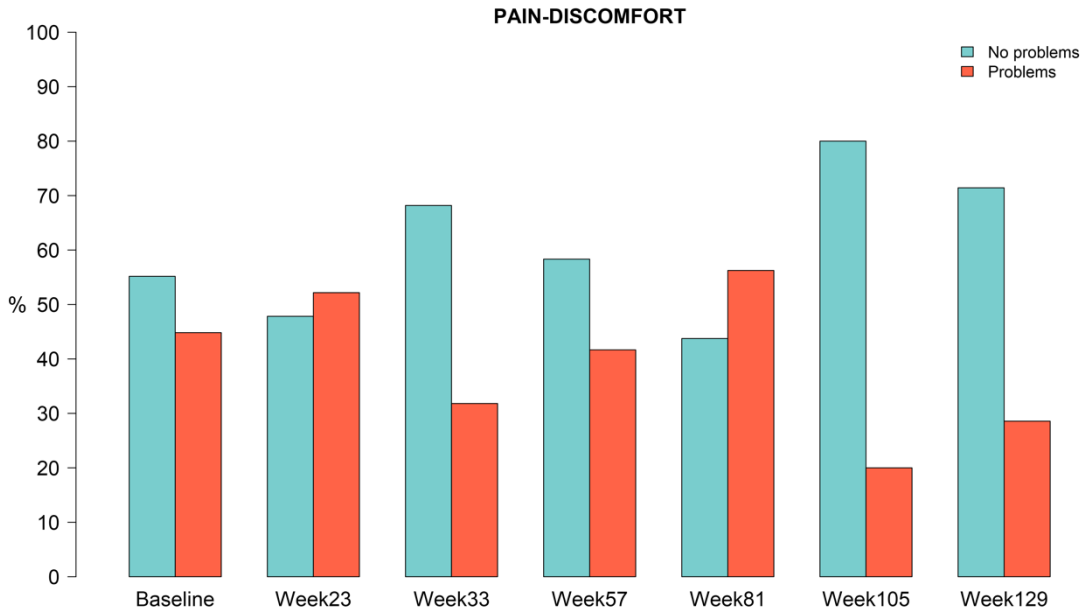


Figure 16. Percentage of reported problems by visit for anxiety dimension.

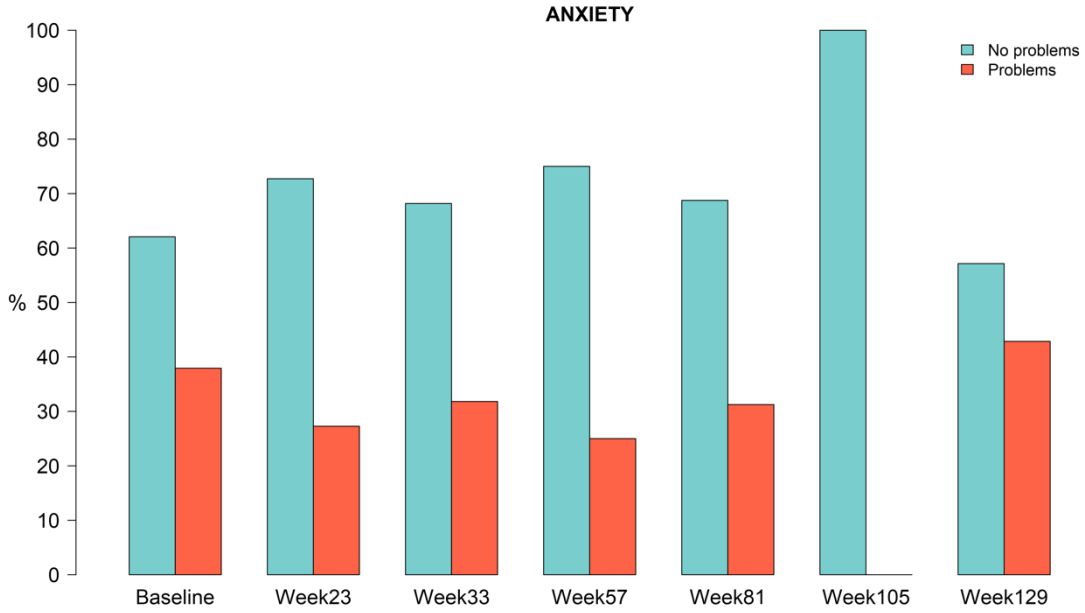
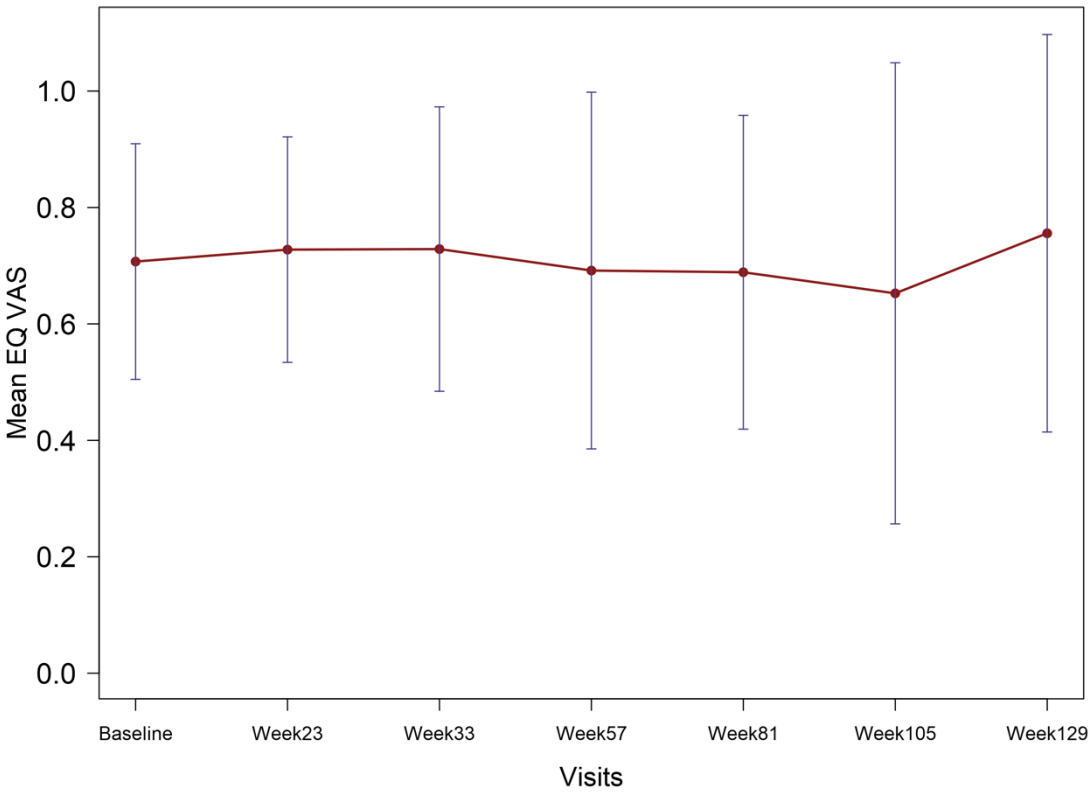


Figure 17. Profile plot of mean and standard error bars of EQ VAS across visits.



9.9 Toxicity

Non serious adverse events were assessed at each visit and scored according to CTCAE Version 4. The number of patients reporting a non-serious adverse event is summarised by treatment group, body system, preferred term and severity.

Haematological toxicities are graded according to the 2008 IWCLL Guidelines as follows:

Grade*	Decrease in platelets† or Hb‡ (nadir) from pre-treatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥2000
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-74%	≥500 and <1000
4	≥75%	<500

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pre-treatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is $<20x10^9$/L (20 000/µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $20x10^9$/L [20 000/µL]) was present pre-treatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches $<1x10^9$/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $<1x10^9$/L (1000/µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

9.9.1 AEs tables for Revised design (Ofatumumab)

Table 33. Non Serious Adverse Events by severity during induction

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
Blood and lymphatic system disorders	Anemia	4	5	2	0	0
	Blood and lymphatic system disorders - Other	1	0	0	0	0
	Febrile neutropenia	0	0	1	0	0
	Leukocytosis	0	0	1	0	0
	Lymph node pain	2	0	0	0	0
Cardiac disorders	Acute coronary syndrome	0	0	1	0	0
	Palpitations	2	0	0	0	0
	Ventricular fibrillation	0	0	0	0	1
Ear and labyrinth disorders	Tinnitus	1	0	0	0	0
	Vertigo	1	0	0	0	0
Endocrine disorders	Cushingoid	1	0	0	0	0
Eye disorders	Blurred vision	2	0	0	0	0
	Eye disorders - Other, specify	0	1	0	0	0
Gastrointestinal disorders	Abdominal pain	1	0	1	0	0
	Bloating	1	0	0	0	0
	Constipation	7	2	0	0	0
	Diarrhea	7	4	0	0	0
	Dry mouth	1	0	0	0	0
	Dyspepsia	2	1	0	0	0
	Flatulence	2	0	0	0	0
	Gastroesophageal reflux disease	1	0	0	0	0
	Gastrointestinal disorders - Other	2	0	0	0	1
	Mucositis oral	2	0	0	0	0
	Nausea	5	2	0	0	0
	Oral dysesthesia	1	0	0	0	0
	Oral pain	2	0	0	0	0
	Vomiting	2	0	2	0	0
General disorders and administration site conditions	Edema face	1	0	0	0	0
	Edema limbs	4	1	0	0	0
	Facial pain	1	1	0	0	0
	Fatigue	4	3	0	0	0
	Fever	3	0	0	0	0
	Flu like symptoms	3	0	0	0	0
	Gait disturbance	1	0	0	0	0
	General disorders, admin. site conditions - Other	1	0	1	0	0

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
	Infusion related reaction	0	1	2	0	0
	Localized edema	3	0	0	0	0
	Malaise	1	0	0	0	0
	Non-cardiac chest pain	1	0	0	0	0
	Pain	2	2	0	0	0
Immune system disorders	Allergic reaction	0	3	0	0	0
Infections and infestations	Infections and infestations - Other	3	4	4	0	0
	Lung infection	0	1	3	0	0
	Mucosal infection	0	1	0	0	0
	Rash pustular	0	0	1	0	0
	Sepsis	0	0	0	1	0
	Skin infection	0	1	0	0	0
	Upper respiratory infection	0	6	3	1	0
	Urinary tract infection	0	1	0	0	0
Injury, poisoning and procedural complications	Bruising	3	0	0	0	0
	Fall	2	0	0	0	0
	Injury, poisoning, procedural complications - Other	0	1	0	0	0
Investigations	Alanine aminotransferase increased	3	1	0	0	0
	Alkaline phosphatase increased	2	0	0	0	0
	Aspartate aminotransferase increased	2	2	0	0	0
	Blood bilirubin increased	3	0	0	0	0
	Creatinine increased	3	2	0	0	0
	Investigations - Other, specify	3	0	0	0	0
	Lymphocyte count increased	0	0	1	0	0
	Weight loss	5	0	0	0	0
Metabolism and nutrition disorders	Anorexia	2	1	0	0	0
	Dehydration	0	1	0	0	0
	Glucose intolerance	0	0	2	0	0
	Hypercalcemia	0	1	1	1	0
	Hyperglycemia	0	0	2	1	0
	Hyperuricemia	1	0	0	0	0
	Hypoalbuminemia	0	1	0	0	0
	Hypocalcemia	7	3	0	0	0
	Hypoglycemia	0	1	0	0	0
	Hypokalemia	3	1	1	0	0
	Hypomagnesemia	1	0	0	0	0
	Hyponatremia	1	0	0	0	0

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
	Hypophosphatemia	0	2	4	0	0
	Metabolism and nutrition disorders - Other	2	0	0	0	0
	Tumor lysis syndrome	1	0	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	0	0	0	0
	Arthritis	1	0	0	0	0
	Back pain	3	0	1	0	0
	Bone pain	1	0	0	0	0
	Joint range of motion decreased	1	0	0	0	0
	Muscle weakness lower limb	1	1	1	0	0
	Musculoskeletal, connective tissue disorder - Other	3	1	0	0	0
	Myalgia	1	0	0	0	0
	Neck pain	0	1	0	0	0
	Pain in extremity	4	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	0	0	0	0	1
Nervous system disorders	Concentration impairment	2	0	0	0	0
	Dizziness	5	1	0	0	0
	Dysarthria	0	0	1	0	0
	Dysesthesia	1	0	0	0	0
	Dysgeusia	3	0	0	0	0
	Headache	2	0	0	0	0
	Lethargy	2	4	1	0	0
	Neuralgia	1	0	1	0	0
	Paresthesia	4	0	0	0	0
	Peripheral sensory neuropathy	2	0	1	0	0
	Sinus pain	0	1	0	0	0
Psychiatric disorders	Anxiety	1	0	0	1	0
	Depression	3	1	0	0	0
	Euphoria	1	0	0	0	0
	Insomnia	6	4	0	0	0
	Mania	3	0	0	0	0
	Psychiatric disorders - Other, specify	1	0	0	0	0
	Psychosis	0	0	0	1	0
Renal and urinary disorders	Cystitis noninfective	1	0	0	0	0
	Urinary retention	0	1	0	0	0
	Urinary tract pain	1	0	0	0	0
Reproductive system and breast disorders	Prostatic obstruction	0	0	1	0	0

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
Respiratory, thoracic and mediastinal disorders	Atelectasis	0	1	0	0	0
	Cough	6	3	0	0	0
	Dyspnea	5	2	0	0	0
	Epistaxis	5	0	0	0	0
	Hiccups	2	0	0	0	0
	Hoarseness	1	0	0	0	0
	Hypoxia	0	1	0	0	0
	Laryngeal inflammation	0	0	1	0	0
	Pleural effusion	0	0	1	0	0
	Postnasal drip	1	0	0	0	0
	Productive cough	0	1	0	0	0
	Sore throat	1	0	0	0	0
Skin and subcutaneous tissue disorders	Alopecia	1	0	0	0	0
	Dry skin	3	0	0	0	0
	Hyperhidrosis	2	0	0	0	0
	Pain of skin	1	0	0	0	0
	Rash maculo-papular	0	0	1	0	0
	Rash Papular	1	0	0	0	0
	Skin and subcutaneous tissue disorders - Other	6	1	0	0	0
	Skin ulceration	1	0	0	0	0
	Urticaria	0	1	1	0	0
Vascular disorders	Flushing	1	0	0	0	0
	Hot flashes	2	0	0	0	0
	Hypertension	0	1	0	0	0
	Hypotension	0	1	0	0	0
	Thromboembolic event	1	0	2	0	0

Table 34. Non Serious Adverse Events by severity during induction

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
Lenalidoide maintenance	Blood and lymphatic system disorders	Anemia	0	1	0	0	0
	Blood and lymphatic system disorders	Lymph node pain	1	0	0	0	0
	Ear and labyrinth disorders	Ear and labyrinth disorders - Other	1	0	0	0	0
	Endocrine disorders	Hyperthyroidism	0	1	0	0	0
	Eye disorders	Retinal vascular disorder	0	1	0	0	0
	Gastrointestinal disorders	Anal pain	1	1	0	0	0
		Constipation	1	0	0	0	0
		Diarrhea	1	2	0	0	0
		Gastritis	1	0	0	0	0
		Haemorrhoidal haemorrhage	1	0	0	0	0
		Haemorrhoids	0	1	0	0	0
		Nausea	1	0	0	0	0
		Vomiting	1	0	0	0	0
	General disorders and administration site conditions	Chills	1	0	0	0	0
		Fever	1	0	0	0	0
		Infusion related reaction	0	1	0	0	0
		Pain	1	0	0	0	0
	Infections and infestations	Anorectal infection	0	0	1	0	0
		Infections and infestations - Other	1	1	0	0	0
		Lung infection	0	0	1	0	0
		Upper respiratory infection	1	1	0	0	0
	Investigations	Alanine aminotransferase increased	1	0	0	0	0
		Alkaline phosphatase increased	2	0	0	0	0
		Blood bilirubin increased	0	0	1	0	0
		Creatinine increased	1	0	0	0	0
		GGT increased	0	0	1	0	0
		Investigations - Other, specify	0	1	0	0	0
	Metabolism and nutrition disorders	Anorexia	0	1	0	0	0
		Hypoalbuminemia	0	1	0	0	0
		Hypocalcemia	0	1	0	0	0
		Hypokalemia	0	0	1	0	0
		Hypomagnesemia	1	0	0	0	0
		Hyponatremia	0	0	1	0	0
		Hypophosphatemia	0	0	1	0	0

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
	Musculoskeletal and connective tissue disorders	Musculoskeletal, connective tissue disorder - Other	1	0	0	0	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	0	0	0	1	0
	Nervous system disorders	Tremor	1	0	0	0	0
	Renal and urinary disorders	Renal and urinary disorders - Other, specify	1	0	0	0	0
	Reproductive system and breast disorders	Pelvic pain	1	0	0	0	0
	Vascular disorders	Hypotension	0	1	0	0	0
No Further study treatment	Gastrointestinal disorders	Diarrhea	1	0	0	0	0
	Hepatobiliary disorders	Cholecystitis	0	0	1	0	0
	Infections and infestations	Skin infection	1	0	0	0	0
		Upper respiratory infection	1	2	0	0	0
		Urinary tract infection	0	1	0	0	0
	Respiratory, thoracic and mediastinal disorders	Cough	1	1	0	0	0
Not randomised	Blood and lymphatic system disorders	Anemia	1	1	2	0	0
		Febrile neutropenia	0	0	0	1	0
		Haemolysis	0	0	1	0	0
	Ear and labyrinth disorders	Hearing impaired	1	0	0	0	0
	Eye disorders	Eye disorders - Other, specify	0	0	0	1	0
		Optic nerve disorder	0	1	0	0	0
	Gastrointestinal disorders	Diarrhea	1	1	0	0	0
		Gastrointestinal disorders - Other	1	0	0	0	0
		Mucositis oral	1	0	0	0	0
		Nausea	2	1	0	0	0
		Toothache	1	0	0	0	0
		Vomiting	1	1	0	0	0
	General disorders and administration site conditions	Edema limbs	0	1	0	0	0
		Facial pain	0	0	1	0	0
		Fatigue	1	0	0	0	0
		Fever	2	2	0	0	0
		Flu like symptoms	0	0	1	0	0
		Multi-organ failure	0	0	0	1	0
		Non-cardiac chest pain	1	0	0	0	0
	Immune system disorders	Allergic reaction	0	1	0	0	0
	Infections and infestations	Enterocolitis infectious	0	0	1	0	0
		Infections and infestations - Other	0	1	1	0	1
		Lung infection	0	0	1	0	0

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
		Sepsis	0	0	0	3	0
		Sinusitis	0	1	0	0	0
		Upper respiratory infection	0	3	0	0	1
	Injury, poisoning and procedural complications	Fall	1	1	0	0	0
	Investigations	Creatinine increased	0	0	1	0	0
		Investigations - Other, specify	1	0	0	0	0
		Urine output decreased	0	0	1	0	0
	Metabolism and nutrition disorders	Anorexia	0	1	0	0	0
		Dehydration	0	1	0	0	0
		Hyperglycemia	0	0	1	0	0
		Hyperkalemia	0	1	0	0	0
		Hypermagnesemia	1	0	0	0	0
		Hypoalbuminemia	1	0	1	0	0
		Hypocalcemia	1	0	0	0	0
		Hypoglycemia	1	0	0	0	0
		Hypokalemia	1	1	1	0	0
		Hyponatremia	1	0	1	0	0
		Metabolism and nutrition disorders - Other	1	0	0	0	0
	Musculoskeletal and connective tissue disorders	Arthralgia	1	0	0	0	0
		Arthritis	1	0	0	0	0
		Back pain	1	0	0	0	0
	Nervous system disorders	Depressed level of consciousness	0	0	0	1	0
		Dizziness	0	2	0	0	0
		Headache	2	0	0	0	0
		Peripheral sensory neuropathy	0	1	0	0	0
		Presyncope	0	1	0	0	0
		Sinus pain	1	0	0	0	0
		Stroke	0	1	0	0	0
	Psychiatric disorders	Agitation	0	1	0	0	0
		Anxiety	1	0	0	0	0
		Confusion	0	1	0	0	0
	Renal and urinary disorders	Acute kidney injury	0	0	0	1	0
	Respiratory, thoracic and mediastinal disorders	Cough	0	2	0	0	0
		Dyspnea	0	0	0	1	0
		Hypoxia	0	0	0	1	0
		Respiratory failure	0	0	0	1	0
	Skin and subcutaneous tissue disorders	Alopecia	1	0	0	0	0
		Hyperhidrosis	1	0	0	0	0
		Rash maculo-papular	1	1	0	0	0
	Vascular disorders	Haematoma	0	0	0	0	1

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
		Hypertension	0	0	1	0	0

9.9.2 AEs tables for Initial design (Alemtuzumab)

Table 35. Non Serious Adverse Events by severity during induction

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
Blood and lymphatic system disorders	Anemia	2	1	0	1	0
	Disseminated intravascular coagulation	0	0	1	0	0
	Febrile neutropenia	0	0	1	0	0
Gastrointestinal disorders	Abdominal pain	1	1	0	0	0
	Constipation	3	0	0	0	0
	Diarrhea	5	6	1	0	0
	Gastrointestinal disorders - Other	1	0	0	0	0
	Mucositis oral	2	2	0	0	0
	Nausea	4	0	0	0	0
	Vomiting	2	0	1	0	0
General disorders and administration site conditions	Chills	1	0	1	0	0
	Edema limbs	3	3	0	0	0
	Fatigue	1	4	0	0	0
	Fever	0	1	2	0	0
	Flu like symptoms	1	1	0	0	0
	General disorders, admin. site conditions - Other	1	0	1	0	0
	Localized edema	0	1	1	0	0
	Malaise	1	0	0	0	0
	Pain	1	0	0	0	0
Infections and infestations	Bronchial infection	0	0	1	0	0
	Encephalitis infection	0	1	0	0	0
	Infections and infestations - Other	3	1	1	0	0
	Lung infection	0	0	2	1	0
	Mucosal infection	0	3	0	0	0
	Pharyngitis	0	1	0	0	0
	Sepsis	0	0	4	3	0
	Skin infection	0	1	0	1	0
	Upper respiratory infection	1	2	0	0	0
Injury, poisoning and procedural complications	Bruising	3	0	0	0	0
Investigations	Blood bilirubin increased	0	1	0	0	0

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
	GGT increased	0	1	0	0	0
	Weight loss	2	0	0	0	0
	White blood cell decreased	0	1	1	0	0
Metabolism and nutrition disorders	Dehydration	0	0	1	0	0
	Hyperglycemia	0	1	2	1	0
	Hypermagnesemia	1	0	0	0	0
	Hypoalbuminemia	0	0	1	0	0
	Hypocalcemia	0	1	0	0	0
	Hypoglycemia	1	0	0	0	0
	Hypomagnesemia	0	1	0	0	0
	Hyponatremia	0	0	1	0	0
	Metabolism and nutrition disorders - Other	2	0	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	0	0	0	0
	Arthritis	0	1	0	0	0
	Back pain	1	1	0	0	0
	Chest wall pain	1	0	0	0	0
	Generalized muscle weakness	0	1	0	0	0
	Muscle weakness lower limb	1	1	1	0	0
	Musculoskeletal, connective tissue disorder - Other	0	3	0	0	0
	Myalgia	2	1	0	0	0
	Neck pain	1	0	0	0	0
	Pain in extremity	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	1	0	0	0	0
Nervous system disorders	Dizziness	2	0	0	0	0
	Dysgeusia	3	1	0	0	0
	Headache	2	0	0	0	0
	Lethargy	2	1	0	0	0
	Paresthesia	2	0	0	0	0
	Peripheral sensory neuropathy	2	0	0	0	0
	Somnolence	0	0	1	0	0
	Spasticity	1	0	0	0	0
	Tremor	3	1	0	0	0
	Vasovagal reaction	0	0	1	0	0
Psychiatric disorders	Confusion	1	0	0	0	0
	Insomnia	2	1	0	0	0
Renal and urinary disorders	Urinary frequency	0	2	0	0	0
	Urinary retention	0	1	0	0	0
Reproductive system and breast disorders	Reproductive system and breast disorders - Other	1	0	0	0	0

CTCAEC Category	CTCAE short name	Grade				
		1	2	3	4	5
Respiratory, thoracic and mediastinal disorders	Cough	4	2	0	0	0
	Dyspnea	3	2	1	0	0
	Epistaxis	2	0	0	0	0
	Hiccups	1	1	0	0	0
	Hoarseness	1	0	0	0	0
	Laryngeal inflammation	1	0	1	0	0
	Nasal congestion	1	0	0	0	0
	Sore throat	1	0	0	0	0
Skin and subcutaneous tissue disorders	Alopecia	1	0	0	0	0
	Dry skin	0	1	0	0	0
	Hyperhidrosis	3	2	0	0	0
	Rash maculo-papular	1	2	1	0	0
	Skin and subcutaneous tissue disorders - Other	3	1	2	0	0
	Skin ulceration	0	1	0	0	0
	Urticaria	0	1	0	0	0
Vascular disorders	Hot flashes	1	0	0	0	0
	Thromboembolic event	0	1	0	0	0

Table 36. Non Serious Adverse Events by severity post induction

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
Lenalidomide maintenance	Blood and lymphatic system disorders	Anemia	0	1	0	0	0
	Gastrointestinal disorders	Diarrhea	1	0	0	0	0
		Gastrointestinal disorders - Other	1	0	0	0	0
		Nausea	1	0	0	0	0
	Immune system disorders	Autoimmune disorder	0	0	1	0	0
	Infections and infestations	Infections and infestations - Other	0	0	1	0	0
	Injury, poisoning and procedural complications	Bruising	0	0	1	0	0
	Investigations	White blood cell decreased	0	0	0	1	0
	Musculoskeletal and connective tissue disorders	Musculoskeletal, connective tissue disorder - Other	1	0	0	0	0
	Nervous system disorders	Headache	1	0	0	0	0
		Oculomotor nerve disorder	0	0	1	0	0
	Respiratory, thoracic and mediastinal disorders	Cough	1	0	0	0	0
		Epistaxis	1	0	0	0	0

Treatment Arm	CTCAEC Category	CTCAE short name	Grade				
			1	2	3	4	5
		Sore throat	1	0	0	0	0
No Further study treatment	Blood and lymphatic system disorders	Anemia	0	0	1	0	0
	Gastrointestinal disorders	Diarrhea	0	1	0	0	0
		Lower Gastrointestinal hemorrhage	1	0	0	0	0
	General disorders and administration site conditions	Edema limbs	0	0	1	0	0
		Fever	1	0	0	0	0
	Immune system disorders	Autoimmune disorder	0	0	1	0	0
	Infections and infestations	Bronchial infection	0	0	1	0	0
		Infections and infestations - Other	0	0	1	0	0
		Lung infection	0	0	1	0	0
		Mucosal infection	1	0	0	0	0
		Sinusitis	1	0	0	0	0
		Tooth infection	1	0	0	0	0
		Upper respiratory infection	1	0	0	0	0
	Respiratory, thoracic and mediastinal disorders	Cough	2	0	0	0	0
		Productive cough	1	0	0	0	0
Not randomised	Gastrointestinal disorders	Vomiting	1	0	0	0	0
	General disorders and administration site conditions	Edema limbs	0	1	1	0	0
	Infections and infestations	Infections and infestations - Other	1	1	0	1	0
		Lung infection	0	1	0	0	0
		Rash pustular	0	1	0	0	0
		Upper respiratory infection	1	0	0	0	0
	Metabolism and nutrition disorders	Anorexia	1	0	0	0	0
	Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other	1	0	0	0	0
	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders - Other	0	1	0	0	0
		Urticaria	1	0	0	0	0

9.9.3 Haematological toxicity

Table 37. Non Serious Adverse Events by severity post induction

Table 39 details the number of haematological toxicities by design, phase and grade.

	Neutrophil count decreased						Platelet count decreased				
	Grade						Grade				
	1	2	3	4	5		1	2	3	4	5
Ofatumumab											
Induction	0	2	7	8	0		1	4	2	1	0
Post-induction	0	0	2	2	0		2	0	0	3	0
Alemtuzumab											
Induction	1	1	1	4	0		1	2	1	1	0
Post-induction	0	0	1	0	0		0	1	1	0	0

** Please note no haemoglobin decreased was recorded as non-serious adverse event.*

10. ANALYSIS OF SAFETY

10.1 Definitions

Serious Adverse Events (SAE)

Serious adverse events were followed-up until resolution or death. A Serious Adverse Event was defined as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (i.e. the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect.

Medical and scientific judgement should have been exercised in deciding whether expedited reporting was appropriate in other situations, such as important medical events that may have not been immediately life-threatening or result in death or hospitalisation but may have jeopardised the patient or may have required intervention to prevent one of the other outcomes listed above. These should have also usually been considered serious. Examples of such events are intensive treatment in an emergency room or at home for infections, neuropathy, thrombocytopenia; or development of drug dependency or drug abuse.

The following classifications was used when evaluating the relationship of serious adverse events to investigational drug:

Severity of SAE

Definition of Severity of Adverse Events	Description
(1) Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
(2) Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
(3) Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])
(4) Life Threatening	Grade 4 - Results in risk of death, organ damage, or permanent disability (unacceptable)
(5) Death	Grade 5 – Results in death (unacceptable)

Causality of SAE

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the SAE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The number of patients reporting a serious adverse event is summarised by treatment group, body system, preferred term, severity, and relationship to treatment arm using the worst severity for each patient and each event and worst causality for that severity. If severity is missing, grade 1 will be assumed if relationship is missing "None" will be assumed.

10.2 Serious Adverse Events

10.2.1 SAE tables for Revised design (Ofatumumab)

Table 19: Aggregated Serious Adverse Events during induction

Severity			Causality				
CTCAEC Category	**CTCAE short name**	**Maximum Grade**	**Not related**	**Unlikely**	**Possible**	**Probable**	**Highly Probable**
Blood and lymphatic system disorders	Anemia	3	0	0	1	0	0
	Febrile neutropenia	3	0	0	1	1	1
Cardiac disorders	Acute coronary syndrome	3	0	0	1	0	0
	Cardiac arrest	5	1	0	0	0	0
Gastrointestinal disorders	Vomiting	3	0	0	1	0	0
General disorders and administration site conditions	Infusion related reaction	3	0	0	0	0	2
Infections and infestations	Bronchial infection	3	0	0	1	0	0
	Enterocolitis infectious	3	0	0	1	0	0
	Infections and infestations - Other	3	0	0	1	0	0
	Lung infection	3	0	0	7	0	0
		5	0	0	1	0	0
	Pharyngitis	3	1	0	0	0	0
	Soft tissue infection	5	0	0	1	0	0
	Urinary tract infection	3	0	0	1	0	0
Metabolism and nutrition disorders	Hypercalcemia	3	0	1	0	0	0
		4	0	1	0	0	0

Severity			Causality				
CTCAEC Category	**CTCAE short name**	**Maximum Grade**	**Not related**	**Unlikely**	**Possible**	**Probable**	**Highly Probable**
Musculoskeletal and connective tissue disorders	Myalgia	3	0	0	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	1	0	0	0	0
Psychiatric disorders	Anxiety	4	0	0	1	0	0
	Depression	2	0	0	0	0	1
	Psychosis	4	0	0	1	0	0
Respiratory, thoracic and mediastinal disorders	Pleural effusion	3	0	0	1	0	0
Vascular disorders	Thromboembolic event	3	1	0	0	1	0
	Visceral arterial ischemia	5	0	0	1	0	0

Table 20: Aggregated Serious Adverse Events during post-induction

	Severity			Causality				
Treatment Arm	**CTCAEC Category**	**CTCAE short name**	**Maximum Grade**	**Not related**	**Unlikely**	**Possible**	**Probable**	**Highly Probable**
Lenalidomide maintenance	Infections and infestations	Anorectal infection	3	0	1	0	0	0
		Bronchial infection	3	0	0	1	0	0
		Lung infection	3	0	0	0	1	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	4	0	0	1	0	0
No Further study treatment	Hepatobiliary disorders	Cholecystitis	3	1	0	0	0	0
Not specified	Infections and infestations	Encephalitis infection	5	0	0	1	0	0
		Enterocolitis infectious	3	0	1	0	0	0
		Lung infection	4	0	0	1	0	0
			5	0	0	1	0	0
	Investigations	Creatinine increased	2	0	0	1	0	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	2	0	1	0	0	0
	Vascular disorders	Haematoma	5	0	0	1	0	0

10.3 SAE tables for Initial design (Alemtuzumab)

Table 21: Aggregated Serious Adverse Events during induction

Severity			Causality				
CTCAEC Category	**CTCAE short name**	**Maximum Grade**	**Not related**	**Unlikely**	**Possible**	**Probable**	**Highly Probable**
Blood and lymphatic system disorders	Anemia	4	0	0	0	1	0
Gastrointestinal disorders	Diarrhea	3	0	1	0	0	0
General disorders and administration site conditions	General disorders, admin. site conditions - Other	3	0	0	0	0	1
Infections and infestations	Enterocolitis infectious	1	0	1	0	0	0
	Infections and infestations - Other	3	0	0	3	0	0
	Laryngitis	3	0	0	1	0	0
	Lung infection	3	0	0	3	0	0
		4	0	0	1	0	0
	Sepsis	3	0	0	1	1	0
		4	0	0	1	1	0
		5	0	0	1	0	0
	Skin infection	4	0	0	1	0	0
	Upper respiratory infection	1	0	0	1	0	0
	Urinary tract infection	2	0	0	1	0	0
		3	0	0	1	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	3	0	0	1	0	0
Skin and subcutaneous tissue disorders	Rash maculo-papular	3	0	0	1	0	0

Table 22: Aggregated Serious Adverse Events during post-induction

	Severity			Causality				
Treatment Arm	**CTCAEC Category**	**CTCAE short name**	**Maximum Grade**	**Not related**	**Unlikely**	**Possible**	**Probable**	**Highly Probable**
Lenalidomide maintenance	Blood and lymphatic system disorders	Blood and lymphatic system disorders - Other	3	0	0	1	0	0
		Febrile neutropenia	3	0	0	1	0	0
	Infections and infestations	Lung infection	3	0	0	1	0	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	0	1	0	0	0
		Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	5	0	0	1	0	0
No Further study treatment	Blood and lymphatic system disorders	Blood and lymphatic system disorders - Other	3	0	0	1	0	0
	Infections and infestations	Lung infection	3	0	0	2	0	0
Not specified	Blood and lymphatic system disorders	Febrile neutropenia	4	0	0	1	0	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	0	1	0	0	0
	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	0	0	1	0	0

APPENDIX

APPENDIX 1: By-PATIENT listings shells

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
10009	62	Male	25/05/2012	Alemtuzumab, Induction, Not specified	14/06/2012	02/07/2012	Infections and infestations	Enterocolitis infectious	1	Resolved with sequelae	Unlikely	Yes	Involved or prolonged hospitalisation	
10009	62	Male	25/05/2012	Alemtuzumab, Induction,Not specified	19/12/2012	23/12/2012	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
10011	46	Male	26/06/2012	Alemtuzumab,Induction,Not specified	20/08/2012	25/08/2012	Infections and infestations	Lung infection	3	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
10011	46	Male	26/06/2012	Alemtuzumab,Induction,Not specified	17/09/2012	18/09/2012	Infections and infestations	Urinary tract infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
10011	46	Male	26/06/2012	Alemtuzumab,Induction,Not specified	23/09/2012	22/10/2012	Infections and infestations	Sepsis	4	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
10011	46	Male	26/06/2012	Alemtuzumab,Induction,Not specified	19/10/2012	24/10/2012	Infections and infestations	Sepsis	4	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
140044	61	Male	15/05/2014	Ofatumumab,Induction,Not specified	22/05/2014	23/05/2014	Vascular disorders	Visceral arterial ischemia	5	Fatal	Possible	Yes	Subject died, Involved or prolonged hospitalisation, Life threatening	Drug withdrawn
180002	57	Male	24/02/2012	Alemtuzumab,Induction,Not specified	28/05/2012	31/05/2012	Infections and infestations	Upper respiratory infection	1	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
180033	60	Male	20/12/2013	Ofatumumab,Induction,Not specified	26/02/2014	08/03/2014	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
180033	60	Male	20/12/2013	Ofatumumab,Induction,Not specified	31/03/2014	NA	Infections and infestations	Lung infection	5	Fatal	Possible	Yes	Subject died, Involved or prolonged hospitalisation	Drug withdrawn
180037	60	Female	07/02/2014	Ofatumumab,Induction,Not specified	24/02/2014	28/02/2014	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
180046	73	Male	19/05/2014	Ofatumumab,Induction,Not specified	10/07/2014	14/07/2014	Musculoskeletal and connective tissue disorders	Myalgia	3	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	
180046	73	Male	19/05/2014	Ofatumumab,Post-Induction,Not specified	22/09/2014	03/12/2014	Investigations	Creatinine increased	2	Resolved with sequelae	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn
180046	73	Male	19/05/2014	Ofatumumab,Post-Induction,Not specified	12/10/2014	20/10/2014	Infections and infestations	Enterocolitis infectious	3	Resolved	Unlikely	No	Involved or prolonged hospitalisation	
180049	63	Female	01/08/2014	Ofatumumab,Induction,No Further study treatment	27/10/2014	29/10/2014	Gastrointestinal disorders	Vomiting	3	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
180049	63	Female	01/08/2014	Ofatumumab,Post-Induction,No Further study treatment	05/02/2015	13/02/2015	Hepatobiliary disorders	Cholecystitis	3	Resolved	Not related	No	Involved or prolonged hospitalisation	
310015	73	Female	31/08/2012	Alemtuzumab,Induction,Not specified	19/09/2012	27/09/2012	General disorders and administration site conditions	General disorders, admin. site conditions - Other	3	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	Dose reduced,

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
310016	55	Male	04/09/2012	Alemtuzumab,Induction,Lenalidomide maintenance	29/01/2013	08/02/2013	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
390029	50	Female	11/11/2013	Ofatumumab,Post-Induction,Not specified	30/12/2013	NA	Infections and infestations	Lung infection	5	Fatal	Possible	No	Subject died, Involved or prolonged hospitalisation, Life threatening	Drug withdrawn
390030	66	Male	28/11/2013	Ofatumumab,Post-Induction,Lenalidomide maintenance	03/07/2014	16/07/2014	Infections and infestations	Bronchial infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
390030	66	Male	28/11/2013	Ofatumumab,Post-Induction,Lenalidomide maintenance	12/11/2014	13/11/2014	Infections and infestations	Anorectal infection	3	Resolved	Unlikely	Yes	Involved or prolonged hospitalisation	
390030	66	Male	28/11/2013	Ofatumumab,Post-Induction,Lenalidomide maintenance	23/12/2014	11/06/2015	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	4	Resolved	Possible	No	Life threatening	Drug withdrawn
390034	42	Female	03/01/2014	Ofatumumab,Induction,Not specified	28/01/2014	17/02/2014	Metabolism and nutrition disorders	Hypercalcemia	3	Resolved	Unlikely	Yes	Involved or prolonged hospitalisation	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
390042	69	Male	17/03/2014	Ofatumumab,Post-Induction,Not specified	07/04/2014	NA	Vascular disorders	Haematoma	5	Fatal	Possible	No	Subject died, Involved or prolonged hospitalisation, Life threatening	Drug withdrawn
460010	78	Male	15/06/2012	Alemtuzumab,Induction,Not specified	25/06/2012	05/07/2012	Gastrointestinal disorders	Diarrhea	3	Resolved	Unlikely	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460010	78	Male	15/06/2012	Alemtuzumab,Induction,Not specified	12/07/2012	14/08/2012	Infections and infestations	Sepsis	4	Resolved	Probable	Yes	Involved or prolonged hospitalisation	
460020	69	Female	27/09/2013	Ofatumumab,Induction,Not specified	17/09/2013	NA	Vascular disorders	Thromboembolic event	3	Ongoing at death	Not related	Yes	Involved or prolonged hospitalisation	
460020	69	Female	27/09/2013	Ofatumumab,Induction,Not specified	18/10/2013	28/10/2013	Infections and infestations	Lung infection	3	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460020	69	Female	27/09/2013	Ofatumumab,Induction,Not specified	18/10/2013	28/10/2013	Metabolism and nutrition disorders	Hypercalcemia	4	Resolved	Unlikely	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460021	70	Male	27/09/2013	Ofatumumab,Induction,Not specified	12/11/2013	13/11/2013	General disorders and administration site conditions	Infusion related reaction	3	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460021	70	Male	27/09/2013	Ofatumumab,Induction,Not specified	03/03/2014	21/03/2014	Infections and infestations	Urinary tract infection	3	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
460023	67	Male	07/10/2013	Ofatumumab,Induction,Not specified	08/02/2014	11/03/2014	Vascular disorders	Thromboembolic event	3	Resolved with sequelae	Probable	Yes	Involved or prolonged hospitalisation	
460027	54	Male	01/11/2013	Ofatumumab,Induction,Not specified	07/01/2014	12/01/2014	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
460027	54	Male	01/11/2013	Ofatumumab,Induction,Not specified	20/01/2014	23/01/2014	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460036	65	Male	05/02/2014	Ofatumumab,Induction,No Further study treatment	20/05/2014	23/05/2014	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460043	50	Male	28/04/2014	Ofatumumab,Induction,Not specified	10/06/2014	11/06/2014	General disorders and administration site conditions	Infusion related reaction	3	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460045	69	Male	15/05/2014	Ofatumumab,Induction,Not specified	16/06/2014	20/06/2014	Cardiac disorders	Acute coronary syndrome	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
460045	69	Male	15/05/2014	Ofatumumab,Induction,Not specified	24/06/2014	01/07/2014	Infections and infestations	Enterocolitis infectious	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
460045	69	Male	15/05/2014	Ofatumumab,Induction,Not specified	18/08/2014	14/09/2014	Infections and infestations	Lung infection	3	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	
460045	69	Male	15/05/2014	Ofatumumab,Induction,Not specified	13/09/2014	NA	Infections and infestations	Bronchial infection	3	Ongoing at death	Possible	Yes	Involved or prolonged hospitalisation	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
460045	69	Male	15/05/2014	Ofatumumab,Induction,Not specified	14/09/2014	NA	Cardiac disorders	Cardiac arrest	5	Fatal	Not related	Yes	Subject died	
460062	63	Male	15/06/2015	Ofatumumab,Induction,Not specified	19/07/2015	04/09/2015	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
500031	59	Female	03/12/2013	Ofatumumab,Post-Induction,Not specified	06/01/2014	17/01/2014	Infections and infestations	Lung infection	4	Resolved with sequelae	Possible	No	Involved or prolonged hospitalisation, Life threatening	Drug withdrawn
560051	42	Male	15/09/2014	Ofatumumab,Induction,Not specified	17/11/2014	23/03/2015	Respiratory, thoracic and mediastinal disorders	Pleural effusion	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
710058	72	Female	13/02/2015	Ofatumumab,Induction,Lenalidomide maintenance	24/03/2015	26/03/2015	Blood and lymphatic system disorders	Febrile neutropenia	3	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	
710058	73	Female	13/02/2015	Ofatumumab,Post-Induction,Lenalidomide maintenance	10/05/2016	16/05/2016	Infections and infestations	Lung infection	3	Resolved	Probable	Yes	Involved or prolonged hospitalisation	
1120001	69	Male	06/02/2012	Alemtuzumab,Induction,Lenalidomide maintenance	19/06/2012	21/06/2012	Infections and infestations	Urinary tract infection	2	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
1120001	69	Male	06/02/2012	Alemtuzumab,Induction,Lenalidomide maintenance	10/08/2012	18/08/2012	Infections and infestations	Infections and infestations - Other	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
1120001	69	Male	06/02/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	23/08/2012	01/09/2012	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Dose reduced
1120001	69	Male	06/02/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	01/11/2012	21/11/2012	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	Resolved	Unlikely	Yes	Important Medical Event	
1120001	73	Male	06/02/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	10/11/2016	NA	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	5	Fatal	Possible	No	Subject died	
1120003	52	Male	19/03/2012	Alemtuzumab,Induction,Not specified	16/07/2012	21/07/2012	Infections and infestations	Sepsis	3	Resolved	Probable	Yes	Involved or prolonged hospitalisation	Dose reduced, Drug withdrawn
1120003	53	Male	19/03/2012	Alemtuzumab,Post-Induction,Not specified	07/10/2013	24/10/2013	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	Resolved	Unlikely	No	Secondary non-malignant tumour - informed by trial to report.	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
1140006	79	Female	23/04/2012	Alemtuzumab,Induction,Not specified	04/06/2012	13/06/2012	Blood and lymphatic system disorders	Anemia	4	Resolved	Probable	Yes	Involved or prolonged hospitalisation	Drug withdrawn
1140006	80	Female	23/04/2012	Alemtuzumab,Induction,Not specified	20/08/2012	NA	Infections and infestations	Sepsis	5	Ongoing at death	Possible	Yes	Subject died, Involved or prolonged hospitalisation, Life threatening	Drug withdrawn
1140008	64	Male	25/04/2012	Alemtuzumab,Induction,Not specified	18/07/2012	23/07/2012	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Dose reduced
1140008	65	Male	25/04/2012	Alemtuzumab,Post-Induction,Not specified	16/10/2013	24/10/2013	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	Resolved	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn
1180017	66	Male	13/09/2013	Ofatumumab,Post-Induction,Not specified	22/01/2014	NA	Infections and infestations	Encephalitis infection	5	Fatal	Possible	No	Subject died, Involved or prolonged hospitalisation	Drug withdrawn
1530004	48	Male	13/04/2012	Alemtuzumab,Induction,No Further study treatment	24/05/2012	31/05/2012	Respiratory, thoracic and mediastinal disorders	Dyspnea	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Dose reduced, Drug withdrawn
1530004	48	Male	13/04/2012	Alemtuzumab,Induction,No Further study treatment	07/06/2012	08/06/2012	Infections and infestations	Skin infection	4	Resolved with sequelae	Possible	Yes	Involved or prolonged hospitalisation	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
1530004	48	Male	13/04/2012	Alemtuzumab,Induction,No Further study treatment	20/08/2012	03/09/2012	Infections and infestations	Infections and infestations - Other	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
1530004	48	Male	13/04/2012	Alemtuzumab,Post-Induction,No Further study treatment	14/10/2012	22/10/2012	Infections and infestations	Lung infection	3	Resolved	Possible	No	Involved or prolonged hospitalisation	
1530005	74	Male	13/04/2012	Alemtuzumab,Induction,Lenalidomide maintenance	11/06/2012	14/06/2012	Infections and infestations	Lung infection	4	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
1530005	74	Male	13/04/2012	Alemtuzumab,Induction,Lenalidomide maintenance	28/07/2012	06/08/2012	Infections and infestations	Laryngitis	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
1530005	74	Male	13/04/2012	Alemtuzumab,Induction,Lenalidomide maintenance	17/08/2012	24/08/2012	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
1530005	75	Male	13/04/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	03/12/2012	07/12/2012	Blood and lymphatic system disorders	Febrile neutropenia	3	Resolved	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn
1530005	75	Male	13/04/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	03/12/2012	NA	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	Ongoing at death	Unlikely	No	Involved or prolonged hospitalisation	Drug withdrawn
1530005	75	Male	13/04/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	03/12/2012	03/01/2013	Blood and lymphatic system disorders	Blood and lymphatic system	3	Resolved	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
								disorders - Other						
1530005	75	Male	13/04/2012	Alemtuzumab,Post-Induction,Lenalidomide maintenance	29/12/2012	NA	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	Ongoing at death	Unlikely	No	Involved or prolonged hospitalisation, Risk of loss of vision	Drug withdrawn
1530007	67	Male	24/04/2012	Alemtuzumab,Induction,No Further study treatment	30/04/2012	05/05/2012	Infections and infestations	Infections and infestations - Other	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
1530007	67	Male	24/04/2012	Alemtuzumab,Induction,No Further study treatment	14/05/2012	17/05/2012	Infections and infestations	Infections and infestations - Other	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
1530007	68	Male	24/04/2012	Alemtuzumab,Post-Induction,No Further study treatment	06/12/2012	17/12/2012	Blood and lymphatic system disorders	Blood and lymphatic system disorders - Other	3	Resolved	Possible	No	Involved or prolonged hospitalisation	
1530007	68	Male	24/04/2012	Alemtuzumab,Post-Induction,No Further study treatment	08/01/2013	04/03/2013	Infections and infestations	Lung infection	3	Resolved	Possible	No	Involved or prolonged hospitalisation	
1530025	73	Female	21/10/2013	Ofatumumab,Induction,No Further study treatment	25/11/2013	03/12/2013	Infections and infestations	Lung infection	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
1530025	73	Female	21/10/2013	Ofatumumab,Induction,No Further study treatment	24/03/2014	05/04/2014	Blood and lymphatic system disorders	Febrile neutropenia	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	
1610048	60	Male	13/06/2014	Ofatumumab,Induction,Not specified	14/06/2014	16/06/2014	Infections and infestations	Pharyngitis	3	Resolved	Not related	Yes	Involved or prolonged hospitalisation	
1610048	60	Male	13/06/2014	Ofatumumab,Induction,Not specified	21/07/2014	26/07/2014	Blood and lymphatic system disorders	Febrile neutropenia	3	Resolved	Probable	Yes	Involved or prolonged hospitalisation	
3490028	71	Male	07/11/2013	Ofatumumab,Induction,Not specified	29/12/2013	02/01/2014	Psychiatric disorders	Depression	2	Resolved	Highly Probable	Yes	Involved or prolonged hospitalisation	Dose reduced
3490028	71	Male	07/11/2013	Ofatumumab,Induction,Not specified	05/01/2014	10/01/2014	Psychiatric disorders	Psychosis	4	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
3490028	71	Male	07/11/2013	Ofatumumab,Induction,Not specified	13/01/2014	21/01/2014	Psychiatric disorders	Anxiety	1	Resolved	Unlikely	Yes	Involved or prolonged hospitalisation	Drug withdrawn
3490028	71	Male	07/11/2013	Ofatumumab,Induction,Not specified	23/01/2014	02/04/2014	Psychiatric disorders	Anxiety	4	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Dose reduced, Drug withdrawn
3490035	74	Male	17/01/2014	Ofatumumab,Post-Induction,Not specified	07/06/2016	07/06/2016	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc	2	Resolved	Unlikely	No	malignancy	

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
								cysts, polyps) - Other						
3490052	68	Male	06/10/2014	Ofatumumab,Induction,Not specified	03/11/2014	10/11/2014	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant, unspec (inc cysts, polyps) - Other	3	Resolved	Not related	Yes	Involved or prolonged hospitalisation	Drug withdrawn
3520013	74	Male	31/07/2012	Alemtuzumab,Induction,Not specified	14/09/2012	24/09/2012	Infections and infestations	Sepsis	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn
3520013	74	Male	31/07/2012	Alemtuzumab,Post-Induction,Not specified	10/10/2012	24/10/2012	Blood and lymphatic system disorders	Febrile neutropenia	3	Resolved	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn
3520013	74	Male	31/07/2012	Alemtuzumab,Post-Induction,Not specified	03/11/2012	09/11/2012	Blood and lymphatic system disorders	Febrile neutropenia	4	Resolved	Possible	No	Involved or prolonged hospitalisation	Drug withdrawn
3530022	58	Male	27/09/2013	Ofatumumab,Induction,Not specified	29/11/2013	NA	Infections and infestations	Soft tissue infection	5	Fatal	Possible	Yes	Subject died	Drug withdrawn
3530061	69	Female	16/03/2015	Ofatumumab,Induction,Not specified	19/06/2015	26/06/2015	Infections and infestations	Infections and infestations - Other	3	Resolved	Possible	Yes	Involved or prolonged hospitalisation	Drug withdrawn

Trial Number	Age	Gender	Recruitment Date	Design, Phase, Arm	SAE Onset Date	SAE Offset Date	CTCAE Grouping	CTCAE Subgroup	CTCAE Grade/Severity	Outcome	Relationship to Study Treatment	Taking Study Treatment when SAE recorded?	Serious Criteria	Event Action
3640054	70	Male	11/11/2014	Ofatumumab,Induction,Not specified	13/01/2015	NA	Blood and lymphatic system disorders	Anemia	3	Not resolved/ongoing	Possible	Yes	anaemia and bonw marrow features may be a permanent possible myelodysplasia	Drug withdrawn

11. DISCUSSION and CONCLUSION

General considerations. This study was conducted in an attempt to improve on the results of the phase II NCRI CLL206 trial in which patients with ultra-high-risk CLL (defined as deletion of TP53 on chromosome 17p) received alemtuzumab (anti-CD52 monoclonal antibody) in combination with high-dose methylprednisolone (HMDP). These drugs were selected as they had established activity in CLL but, in contrast to chemotherapy-based treatments, do not depend on p53 for their action. The CLL206 trial showed that alemtuzumab plus HDMP provided good cytoreduction. However, response duration was disappointing and there was a high rate of infection and glucocorticoid-related toxicity.

In an attempt to improve the efficacy and reduce the toxicity of the alemtuzumab/ glucocorticoid combination , the CLL210 trial investigated a novel drug combination consisting of alemtuzumab, dexamethasone (lower glucocorticoid activity than HDMP) and lenalidomide. Lenalidomide has established activity in CLL, does not require p53 for its action and has largely non-overlapping toxicities with HDMP and alemtuzumab. The trial included a randomisation to lenalidomide maintenance versus no further treatment for patients responding to induction. When alemtuzumab became unavailable owing to withdrawal of its marketing authorisation, it was replaced by ofatumumab, a CD20 antibody with a similar mechanism of action, less toxicity and similar clinical efficacy in relapsed/refractory CLL. The alemtuzumab and ofatumumab cohorts consisted of 16 and 48 patients, respectively.

To reflect the evolving definition of ultra-high-risk CLL, entry criteria for CLL210 included not only 17p deletion but also TP53 mutation or resistance to FCR chemoimmunotherapy irrespective of TP53/17p aberrations. Owing to the importance of achieving an appropriate balance between treatment efficacy and toxicity, a co-primary endpoint was employed comprising CR rate and grade 3 or higher infection (the most significant toxicity anticipated in this setting).

Trial recruitment. Recruitment was higher than expected initially but the study had to be paused when marketing authorisation for alemtuzumab was withdrawn. Recruitment then slowed owing to competing commercial studies and the availability of novel agents. The study was terminated when it became clear that the target accrual would not be reached.

Patient demographics. Baseline characteristics were as expected, with a median age of 66, a preponderance of males, impaired performance status in 47% and prior therapy in 55%. 83% of patients had a TP53 mutation. Although the median comorbidity score (CIRS) was only 2, the scoring system used in CLL210 did not include 4 points for having CLL. When this is taken into account, the burden of comorbidity is as expected and not insignificant. Patient characteristics were very similar in the alemtuzumab and ofatumumab cohorts.

Patient disposition. 16 patients in the alemtuzumab cohort commenced trial treatment. Treatment was terminated prematurely during the induction phase in 7 patients. Reasons included toxicity (4), disease progression (1), death (1) and incorrect

diagnosis (1). Among the 12 responders, 5 patients were randomised, 3 to lenalidomide maintenance versus 2 to no further treatment. Maintenance treatment was discontinued prematurely in 3/3 patients. Reasons included disease progression (1), clinician decision (1) and elective stem-cell transplantation (1). Follow-up was discontinued prematurely in 7/16 patients due to death (4), withdrawal of consent (2) and clinician decision (1).

48 patients in the ofatumumab cohort commenced treatment. Treatment was terminated prematurely during the induction phase in 23/48 patients. Reasons included toxicity (3), SAEs (2), septic shock/pneumonia (1), general deterioration (2), disease progression (5), Richter transformation (1), death (5) withdrawal of consent (2), patient decision (1), clinician decision (1) and acute ITP prior to commencing treatment. Among the 26 responders, 15 patients were randomised to lenalidomide maintenance (8) versus no further treatment (7). Maintenance treatment was discontinued prematurely in 8/8 patients due to disease progression (3), unknown reasons (3), acute myeloid leukaemia (1) and toxicity (1). Follow-up was discontinued prematurely in 21/48 patients due to death (18), clinician decision (2) and disease progression (1).

These treatment and follow-up completion rates are as expected in this complex and challenging clinical setting characterised by failure of normal haematopoietic and immune function.

Tolerability. 10/16 (67%) patients in the alemtuzumab cohort and 17/47 (38%) patients in the ofatumumab cohort experienced at least one grade 3 or higher infection. This compares with 56% in the CLL206 trial of alemtuzumab and HDMP. The design parameters for CLL210 stipulate that a tolerability rate of 30% or less would not be of interest, while a tolerability rate of 50% or more would be of definite interest. Consequently, the ofatumumab-based regimen (tolerability 62%) is of definite interest while the alemtuzumab-based regimen (tolerability 33%) is of intermediate interest. As expected, grade 3 or higher infection was more frequent in previously treated patients (17/34, 50%) compared with treatment-naïve patients (10/26, 38%).

Efficacy endpoints. Among the 16 patients within the alemtuzumab cohort, 1, 11, 0 and 1 achieved a CR/CRi, PR, SD and PD, respectively while 3 (19%) were non-evaluable. This equates to CR/CRi, PR, SD and PD rates of 6%, 69%, 0 and 6%, respectively, for the entire cohort and 8%, 85%, 0 and 8% for the 13 evaluable patients.

Among the 48 patients within the ofatumumab cohort, 1, 25, 4 and 4 achieved a CR/CRi, PR, SD and PD, respectively while 14 (29%) were non-evaluable. This equates to CR/CRi, PR, SD and PD rates of 2%, 52%, 8% and 8%, respectively, for the entire cohort and 3%, 74%, 0 and 12% for the 34 evaluable patients.

For comparison, the CR/CRi and OR rates following alemtuzumab plus HDMP in the CLL206 trial were 36% and 85%.

The design parameters for CLL210 stipulate that the lowest CR/CRi rate of definite clinical interest is 20% and that the highest response rate of no interest is 10%. The observed CR/CRi rates of 6-8% (alemtuzumab cohort) and 2-3% (ofatumumab cohort)

are therefore both below the threshold for considering either regimen to be of any interest.

In the alemtuzumab cohort, 7/8 (87%) versus 5/8 (62%), respectively, or 7/7 (100%) versus 5/6 (83%) in evaluable patients. In the ofatumumab cohort, the OR (CR/CRi plus PR) rate for treatment-naïve and previously treated patients was 16/20 (80%) versus 10/27 (37%), and 16/17 (94%) versus 10/17 (59%). This suggests that the ofatumumab-based regimen may be less effective than the alemtuzumab-containing one at inducing remissions in previously treated patients.

In the alemtuzumab cohort, the OR rate for patients with or without TP53 mutations was 8/10 (80%) versus 5/8 (62%), respectively, or 7/7 (100%) versus 5/6 (83%) in evaluable patients. In the ofatumumab cohort, the corresponding figures were 17/29 (59%) versus 9/18 (50%), and 17/21 (81%) versus 9/13 (69%). This suggests that the cytoreductive effect of both regimens is unaffected by TP53 status.

Blood MRD negativity (less than 1 CLL cell in 10,000 leukocytes) was documented in 6/10 patients in the alemtuzumab cohort and 0/14 patients in the ofatumumab cohort. This equates to MRD negativity rates of 60% and 0, respectively, in the subset of patients tested, and 6/47 (12.8%) and 0, respectively, in the overall cohorts. The higher rate of blood MRD negativity observed in the alemtuzumab cohort suggest that this regimen is more effective than the ofatumumab-containing one at clearing CLL cells from the blood.

The median (95% confidence interval) PFS was 29.5 (18.5 - undefined) months for the alemtuzumab cohort and 15.1 (11.0 - 22.0) months for the ofatumumab cohort. Within the ofatumumab cohort, PFS was better for treatment-naïve patients compared to those who had received prior therapy [2-year PFS rate 52% (34% - 82%) versus 9% (2% - 46%)]. These results compare favourably with the PFS observed with alemtuzumab plus HDMP in the CLL206 trial (median PFS 11.8 months overall and 18.3 months for treatment-naïve patients) and suggest a beneficial effect of adding lenalidomide to the antibody/glucorticoid backbone.

The OS rate at 2 years was 79% (60% - 100%) for the alemtuzumab cohort and 57% (44% - 74%) for the ofatumumab cohort. Within the ofatumumab cohort, OS was better for treatment-naïve patients compared to those who had received prior therapy [2-year OS rate 79% (62% - 100%) versus 39% (24% - 65%)]. These results compare favourably with OS in the CLL206 trial (median OS 23.5 months overall and 38.9 months in treatment-naïve patients) and are in keeping with a beneficial effect of lenalidomide and/or the availability of novel agents such as ibrutinib and idelalisib for patients who progress.

Effect of lenalidomide maintenance. Comparison of patients randomised to lenalidomide maintenance (11) or no further treatment (9) showed no difference in PFS or OS, with an outcome similar to that of patients who opted to have a stem-cell transplant (6). However, these results should be interpreted with caution owing to the small number of patients in each group.

Toxicity and safety. The number, profile and severity of AEs and SAEs were in keeping with the known toxicity profiles of the individual trial drugs in this challenging clinical setting. No new safety signals were observed.

Summary. Neither of the two regimens investigated in CLL210 met their primary efficacy endpoint (CR/CRi). This may be explained by the lower glucocorticoid dose used compared to that used in CLL206 and, in the ofatumumab cohort, the use of a less potent antibody. Despite the disappointing CR/CRi rates, alemtuzumab, dexamethasone and lenalidomide appeared to have better long-term efficacy than alemtuzumab plus HDMP, while ofatumumab, dexamethasone and lenalidomide had comparable long-term efficacy and a better safety profile. This apparent uncoupling of CR/CRi rates and long-term efficacy might be explained by the known immunomodulatory effects of lenalidomide.

End of Study Clinical Trial Report Approval

This confirms approval of the End of Study Clinical Trial Report for the CLL210 Trial

Trial Co-ordinator

Name: ……MATTHEW BICKERSTAFF……

Signature: …….

Date: __ __/__ __ __ /__ __ __ __

Trial Statistician

Name: ……RICHARD JACKSON……

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Date: __ __/__ __ __ /__ __ __ __

Chief Investigator

Name: ……ANDREW PETTITT……

Signature: …….

Date: __ __/__ __ __ /__ __ __ __