Article:
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Supplementary Appendix

MRD guided Ibrutinib and Venetoclax for Frontline Treatment of CLL

Munir T, et al.

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List of Investigators and centers according to the number of included patients

Center name	Principal Investigator	Recruited patients in this comparison
University College London Hospital	Dr Kate Cwynarksi	18 (3.44%)
Royal Liverpool Hospital	Professor Andrew Pettitt	17 (3.25%)
The Christie Hospital	Professor Adrian Bloor	17 (3.25%)
St James's University Hospital	Dr Talha Munir	16 (3.06%)
Castle Hill Hospital	Dr David Allsup	14 (2.68%)
Churchill Hospital, Oxford	Dr Toby Eyre	14 (2.68%)
Kings College Hospital	Dr Piers Patten	14 (2.68%)
Nottingham City Hospital	Dr Christopher Fox	14 (2.68%)
Southampton General Hospital	Professor Francesco Forconi	13 (2.49%)
Leicester Royal Infirmary	Dr Ben Kennedy	11 (2.1%)
University Hospital of Wales, Cardiff	Dr Nagah Elmusharaf	11 (2.1%)
Worcestershire Royal Hospital	Dr Nicholas Pemberton	11 (2.1%)
Belfast City Hospital	Dr Oonagh Sheehy	10 (1.91%)
Blackpool Victoria Hospital	Dr Marian Macheta	9 (1.72%)
St Bartholomew's Hospital	Professor John Gribben	9 (1.72%)
Aberdeen Royal Infirmary	Dr Gavin Preston	8 (1.53%)
Barnet General Hospital	Dr Parag Jasani	8 (1.53%)
Birmingham Heartlands Hospital	Dr Shankara Paneesha	8 (1.53%)
Good Hope Hospital	Dr Shankara Paneesha	8 (1.53%)
Royal Hallamshire Hospital	Dr Nick Morley	8 (1.53%)
Royal Stoke University Hospital	Dr Neil Phillips	8 (1.53%)
Royal United Hospital	Dr Christopher Knechtli	8 (1.53%)
Colchester General Hospital	Dr Mahalakshmi Mohan	7 (1.34%)
Royal Devon Exeter Hospital	Dr Anthony Todd	7 (1.34%)
Russell's Hall Hospital	Dr Jeff Neilson	7 (1.34%)
Singleton Hospital	Dr Unmesh Mohite	7 (1.34%)
Bradford Royal Infirmary	Dr Abida Naeem	6 (1.15%)
East Surrey Hospital	Dr Pawel Kaczmarek	6 (1.15%)
Ipswich Hospital	Dr Isobel Chalmers	6 (1.15%)
Milton Keynes Hospital	Dr Moez Dungarwalla	6 (1.15%)
Peterborough City Hospital	Dr Sateesh Nagumantry	6 (1.15%)
Pilgrim Hospital Boston	Dr Gamal Sidra	6 (1.15%)
Queen Alexandra Hospital Portsmouth	Dr Edward Belsham	6 (1.15%)
Royal Cornwall Hospital	Dr Michelle Furtado	6 (1.15%)
Royal Oldham Hospital	Dr Antonina Zhelyazkova	6 (1.15%)
Royal Shrewsbury Hospital	Dr Dewi Eden	6 (1.15%)
St Richard's Hospital	Dr Santosh Narat	6 (1.15%)
Worthing Hospital	Dr Santosh Narat	6 (1.15%)
Basildon Hospital	Dr Sudhakaran Makkuni	5 (0.96%)

Center name	Principal Investigator	Recruited patients in this comparison
Beatson Oncology Centre	Dr Mark Rafferty	5 (0.96%)
Bristol Haematology & Oncology	Dr Nikesh Chavda	5 (0.96%)
Harrogate District Hospital	Dr Claire Hall	5 (0.96%)
Neville Hall Hospital	Dr Nilima Parry-Jones	5 (0.96%)
New Victoria Hospital Glasgow	Dr Alison McCaig	5 (0.96%)
Raigmore Hospital	Dr Caroline Duncan	5 (0.96%)
St George's Hospital	Dr Fenella Willis	5 (0.96%)
Stoke Mandeville Hospital	Dr Helen Eagleton	5 (0.96%)
University Hospital Aintree	Dr Vikram Singh	5 (0.96%)
Western General Hospital	Dr Angus Broom	5 (0.96%)
Wrexham Maelor Hospital	Dr David Watson	5 (0.96%)
Addenbrookes Hospital	Dr George Follows	4 (0.76%)
Cheltenham General Hospital	Dr Rory McCulloch	4 (0.76%)
Croydon University Hospital	Dr Betty Cheung	4 (0.76%)
James Cook University Hospital	Dr Jamie Maddox	4 (0.76%)
Kings Mill Hospital	Dr Steve Jones	4 (0.76%)
Musgrove Park Hospital	Dr Belinda Austen	4 (0.76%)
Queens Hospital, Romford	Dr Paul Greaves	4 (0.76%)
Royal Derby Hospital	Dr Meghna Ruparellia	4 (0.76%)
Wythenshawe Hospital	Dr Simon Watt	4 (0.76%)
York Hospital	Dr Annika Whittle	4 (0.76%)
Gloucestershire Royal Hospital	Dr Rory McCulloch	3 (0.57%)
Queen Elizabeth Hospital, Birmingham	Professor Guy Pratt	3 (0.57%)
Royal Bournemouth Hospital	Dr Renata Walewska	3 (0.57%)
Royal Surrey County Hospital	Dr Elisabeth Grey-Davies	3 (0.57%)
Torbay District General Hospital	Dr Deborah Turner	3 (0.57%)
Watford General Hospital	Dr Hassen Al-Sader	3 (0.57%)
Altnagelvin Hospital	Dr Patrick Elder	2 (0.38%)
Calderdale Royal Hospital	Dr Kate Rothwell	2 (0.38%)
Countess of Chester Hospital	Dr Salaheddin Tueger	2 (0.38%)
Crosshouse Hospital	Dr Fiona Nicholson	2 (0.38%)
Derriford Hospital	Dr Claire Hutchinson	2 (0.38%)
Epsom and St Helier	Dr Corinne De Lord	2 (0.38%)
Glan Clwyd Hospital	Dr Earnest Heartin	2 (0.38%)
Hammersmith Hospital	Dr Sasha Marks	2 (0.38%)
Kettering General Hospital	Dr Mark Kwan	2 (0.38%)
Manchester Royal Infirmary	Dr Sarah Burns	2 (0.38%)
Monklands Hospital	Dr Lindsay Mitchell	2 (0.38%)
Poole Hospital	Dr Ram Jayaprakash	2 (0.38%)
Queen Elizabeth Hospital Gateshead	Dr Scott Marshall	2 (0.38%)

Center name	Principal Investigator	Recruited patients in this comparison
Royal Gwent Hospital	Dr Helen Jackson	2 (0.38%)
Royal Lancaster Hospital	Dr David Howarth	2 (0.38%)
Royal Marsden Hospital	Dr Sunil Iyengar	2 (0.38%)
Sandwell General Hospital	Dr Yasmin Hasan	2 (0.38%)
University Hospital Coventry	Dr Sarah Nicolle	2 (0.38%)
Victoria Hospital, Kirkcaldy	Dr Kerri Davidson	2 (0.38%)
West Middlesex University Hospital	Dr Anastasia Chew	2 (0.38%)
Ysbyty Gwynedd	Dr Earnest Heartin	2 (0.38%)
Doncaster Royal Infirmary	Dr Sophie Todd	1 (0.19%)
Dorset County Hospital	Dr Anna Morris	1 (0.19%)
George Elliot Hospital, Nuneaton	Dr Jhansi Muddana	1 (0.19%)
Lincoln County Hospital	Dr Gamal Sidra	1 (0.19%)
Rotherham General Hospital	Dr Kathryn Goddard	1 (0.19%)
Royal Hampshire County Hospital	Dr Jennifer Arnold	1 (0.19%)
Salford Royal Hospital	Dr Sonya Ravenscroft	1 (0.19%)
Salisbury District Hospital	Dr James Milnthorpe	1 (0.19%)
Scunthorpe General Hospital	Dr Afzal Ponnambath	1 (0.19%)

Main inclusion/exclusion criteria:

Inclusion criteria

Patients with the following characteristics are eligible for this study:

- At least 18 years old.
- Maximum age of 75 years old.
- A diagnosis of CLL or small lymphocytic lymphoma (by International Workshop on Chronic Lymphocytic Leukemia [IWCLL] criteria) with a phenotype that is acceptable for disease monitoring. The central laboratory, Leeds HMDS, will assess if the phenotype is acceptable and confirmation of this is required before randomization.
- Binet's Stages C, B or Progressive Stage A
- Requiring therapy by the IWCLL criteria in that they must have at least one of the following:
    1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia.
    2. Massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
    3. Massive nodes (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
    4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months as long as the lymphocyte count is over $30x10^9$/L
- A minimum of any one of the following disease-related symptoms must be present:
    a) Unintentional weight loss more than or equal to 10% within the previous 6 months.
    b) Significant fatigue (i.e. Eastern Cooperative Oncology Group PS 2 or worse; cannot work or unable to perform usual activities)
    c) Fevers of greater than 38.0°C for 2 or more weeks without other evidence of infection.
    d) Night sweats for more than 1 month without evidence of infection.
- Considered fit for treatment with FCR as determined by the treating clinician.
- World Health Organisation (WHO) performance status (PS) of 0, 1 or 2
- Able to provide written informed consent
- Biochemical values must be within the following limits within 14 days prior to randomization and at baseline:
    - Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤3 x ULN.
    - Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

Exclusion criteria

Patients with the following characteristics are ineligible for this pathway

- Prior therapy for CLL
- History or current evidence of Richter's transformation
- Major surgery within 4 weeks prior to randomization
- Active infection.
- TP53 abnormality
- Past history of anaphylaxis following exposure to rat or mouse derived CDR-grafted humanised monoclonal antibodies.*
- Concomitant warfarin (or equivalent vitamin K inhibitor) or other oral anticoagulant* treatment
- Concomitant ACE inhibitors
- Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception (defined in appendix J) whilst receiving treatment and for 12 months after treatment with rituximab has finished, or 30 days after treatment with ibrutinib or venetoclax has finished, whichever is latest. Women must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction.
- Men whose partners are capable of having children but who are not willing to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment with rituximab has finished, or 3 months after treatment with ibrutinib or venetoclax has finished, whichever is latest, unless they are surgically sterile. For male patients, the Investigator must discuss sperm banking prior to venetoclax treatment if they are considering preservation of fertility given the potential for decreased spermatogenesis.
- Central nervous system involvement with CLL.
- Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)
- Respiratory impairment (eg bronchiectasis or moderate COPD)
- Other severe, concurrent diseases or mental disorders that could interfere with their ability to participate in the study.
- Inability to swallow oral medication
- Disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease etc)
- Known HIV positive

- Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.**
- Positive serology for Hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a test for hepatitis C RNA (for example HCV RNA PCR). If positive the subject will be excluded
- History of prior malignancy, with the exception of the following:
  - Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
  - Adequately treated cervical carcinoma in situ without current evidence of disease.
- Persisting severe pancytopenia (neutrophils $<0.5 \times 10^9$/L or platelets $<50 \times 10^9$/L) unless due to direct marrow infiltration by CLL
- Current treatment with prednisolone of >10mg/day.
- Active haemolysis (patients with haemolysis controlled with prednisolone at a dose 10mg or less per day can be entered into the trial)
- Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula [Appendix C] or alternative locally approved formula).
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Requirement for treatment with a strong CYP3A inhibitor or inducer (see Appendix F).
- Current treatment with two or more antiplatelet drugs
- Allergy or inability to tolerate uric acid reducing agents (eg allopurinol/rasburicase).
- Unwilling or unable to take PCP prophylaxis (eg cotrimoxazole).

*Anyone requiring anticoagulation treatment for greater than 6 months is not eligible for trial entry.

**Anyone who is HBsAg-ve/HBcAb+ve/HB DNA–ve should be referred to a liver disease specialist before the start of treatment with rituximab. During treatment, they should be monitored and managed to prevent HBV reactivation.

Methods:

STUDY DESIGN AND PARTICIPANTS

Participants were initially randomized on a 1:1 basis to receive FCR or IR to assess the original objectives (to compare the effect on progression-free survival (PFS) of ibrutinib plus rituximab (IR) with that of fludarabine, cyclophosphamide and rituximab (FCR) in patients with previously untreated chronic lymphocytic leukaemia (CLL). The primary analysis of FCR vs IR has already been published.[1]

Following the addition of the I and I+V arms patients were randomized on a 1:1:1:1 basis to receive FCR, IR, I+V or I to assess the additional objectives. The additional trial arms allowed a comparison of PFS between ibrutinib plus venetoclax (I+V) and ibrutinib alone (I) with FCR, and a comparison of undetectable measurable residual disease (uMRD) rates in I+V with those in I. A successful interim analysis of I vs I+V in terms of uMRD has already been reported.[2,3]

Once 754 participants had been randomized to FCR and IR, the IR arm was closed to recruitment and participants were randomized on a 1:1:1 basis to receive FCR, I or I+V. The analysis of FCR vs ibrutinib only and ibrutinib only vs I+V will be presented later, once sufficient events are observed. A further amendment was added to include an additional population of participants with TP53 abnormalities to allow a comparison of uMRD rates between I and I+V in patients with TP53 abnormalities.

Figure S1 outlines the trial stages and when recruitment was conducted for each stage. The trial aimed to provide evidence for the future front-line treatment of CLL patients by assessing whether IR is superior to FCR in terms of PFS, whether I+V is superior to FCR in terms of PFS, whether I+V is superior to I in terms of MRD negativity, and whether toxicity and safety of I, IR and I+V are favourable compared with FCR. Other key endpoints to be assessed include: overall survival; attainment of undetectable MRD; response to therapy; health-related quality of life and cost-effectiveness; as well as an evaluation of discontinuation and re-continuation of I-containing therapy, if indicated.

This trial platform protocol allows the opportunity for both IR and I+V to be declared superior to the current standard, FCR, within a primary analysis, therefore increasing the chance of a type I error for an ibrutinib-containing combination. Whilst both give the opportunity for a therapy containing ibrutinib to be declared superior, the aim of giving the additional treatments in combination with ibrutinib (rituximab and venetoclax) is to be able to take a break from ibrutinib therapy and in fact reduce the burden of ibrutinib compared to the likely future standard of care of continuous single-agent ibrutinib. Since a type I error for these comparisons does not directly benefit the same claim of effectiveness for an experimental therapy, family-wise type I error rate (FWER) control is not necessary for this reason.[4] If the two primary hypotheses had been assessed in separate protocols, no adjustment would be required. It is feasible to assume that the questions would have otherwise been assessed in different trials. Since there is an overlap in recruitment, some of the control data is shared between the IR and I+V vs FCR hypotheses. The resulting correlation between the

hypotheses reduces the overall type I error over what it would have been if they had been assessed independently,[4] and therefore, FWER adjustment is also not necessary.

In FLAIR, the I+V group is being assessed in two primary hypotheses: against FCR for PFS and against I for MRD negativity. For I+V to be deemed a 'success', it needs to be significantly better than both of its control groups. Where both hypotheses are required to be superior, there is no inflation of the type I error rate, and therefore, no adjustment is required.[5]

This protocol was approved by the Yorkshire and the Humber Leeds West Research Ethics Committee (reference: 14/YH/0085), institutional review boards of the participating centers, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London), and was done according to the Declaration of Helsinki and the principles of Good Clinical Practice as espoused in the Medicines for Human Use (Clinical Trials) Regulations.

RANDOMIZATION AND PROCEDURES

Participants were assigned (1:1) to treatment with either FCR or I+V. A minimisation algorithm with a random element was used to avoid chance imbalances in three variables established at entry: Binet stage (stage A progressive or B *vs* C), age (≤65y *vs* >65y), sex (male *vs* female), and center (Appendix).

Randomizations were done at the Leeds Cancer Research UK Clinical Trial Unit at the University of Leeds by authorised members of staff with a centralised automated 24h telephone system according to a validated minimisation algorithm developed under the supervision of DRH. Because of the nature of the intervention, the study was open-label, and the allocated treatment was not masked from study investigators or patients. The funders remained masked to treatment results until data cut-off.

Sex and ethnicity were collected from electronic medical records where possible, and self-report otherwise. Patients were free to refuse to disclose this information.

FCR was repeated every 28 days for six cycles in the absence of disease progression or toxicity requiring cessation. Fludarabine was administered orally at a dose of 24 mg/m^2 and cyclophosphamide was administered orally at a dose of 150 mg/m^2 per day for the first 5 days of each cycle. Rituximab was administered intravenously at 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 in cycles 2-6. Ibrutinib was administered orally at a dose of 420 mg/day for 8 weeks prior to the initiation of venetoclax at which was incrementally dose escalated over 5 weeks to 400 mg/day orally. Dose reductions and delays were permitted for toxicity and renal function.

MRD was assessed in the peripheral blood (PB) and bone marrow (BM) by highly sensitive multiparameter flow cytometry (Becton Dickinson, Franklin Lanes, NJ; Miltenyi Biotec, Bergisch Gladbach, Germany; IQ Products, Groningen, Netherlands) with a detection limit of 1 CLL cell in 100 000 leukocytes (0.001%, 10^{-5}) in a central laboratory (HMDS, Leeds). MRD was deemed to be detectable if CLL-cells represented at least 0.01% of total blood or BM leukocytes and was undetectable-MRD (uMRD) if CLL cells represented less than 0.01% of

total blood or BM leukocytes. The first assessment was 9m post-randomization (PBand BM) followed by PB assessment at 12m, then every 6m thereafter in I+V and every 12m in FCR.

FISH analysis (Cytocell, Cambridge UK) and *IGHV* mutation status (Sigma-Genosys, Haverhill, UK) were done at baseline and measurable residual disease was assessed in the peripheral blood and bone marrow by highly sensitive multiparameter flow cytometry (Becton Dickinson, Franklin Lanes, NJ; Miltenyi Biotec, Bergisch Gladbach, Germany; IQ Products, Groningen, Netherlands) with a detection limit of one CLL cell in 100000 leukocytes (0.001%, 1×10^{-5}) in a central laboratory (Haematological Malignancy Diagnostic Service, Leeds, UK).

Detailed dose reduction schedules are shown in the protocol and prophylaxis with granulocyte colony-stimulating factor was recommended for patients who had neutropenia.

ASSESSMENTS AND ENDPOINTS

Secondary endpoints were overall survival, defined as the time from randomization to death from any cause or last follow-up. Additional secondary endpoints were MRD assessments including the proportion of patients with undetectable MRD at 9 months post-randomization and longitudinally (MRD response over time), pattern of MRD relapse and retreatment, response to therapy according to IWCLL criteria at 9 months post-randomization and longitudinally including proportion with complete response, partial response, and overall response, safety, and toxicity, health-related quality of life assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16 (EORTC QLQ-CLL16) and cost-effectiveness assessed by means of the Short-Form 12 and EQ-5D to produce quality adjusted life years. Health-related quality of life and cost-effectiveness are the subject of separate reports in preparation.

Response assessments according to IWCLL criteria were done at 9 months post randomization (3 months after the end of treatment with FCR or I+V) and then every 6 months from 12 months post-randomization until 7 years post-randomization or progressive disease, whichever occurred first. A CT-scan (thorax, abdomen, and pelvis) was done at trial entry, at 9 months post-randomization and at stopping and restarting treatment with ibrutinib. Response and progression were assessed by local investigators according to IWCLL criteria. All patients ended 6 monthly follow-up at progressive disease if this was sooner. Post progression follow-up is annual for survival status**.**

Adverse events (AEs) were assessed at the start of each treatment cycle and were graded according to the US National Cancer Institute Common Terminology Criteria for AEs version 5.0 except for hematological toxicity that were assessed by IWCLL criteria.[6] AEs were collected from randomization until 30 days after the last dose of treatment. Serious AEs (SAEs) were reported for all participants from the date of randomization until 30 days after the last dose of treatment except in the case of serious adverse reactions (SAEs with a suspected relationship to an investigational medicinal product), which were collected for the duration of the trial.

STATISTICAL ANALYSIS

The trial was designed to show a 2y increase in median PFS in I+V (median 6.5y) compared with the FCR group (median 4.5y, hazard ratio [HR] 0.69) when a total of 232 PFS events had been observed. This calculation assumed that the time-to-event was exponentially distributed with a 2.5y recruitment period and a further 3.5y of follow-up, a two-sided 5% significance level, and 80% power. A minimum recruitment target of 548 participants randomly assigned (1:1) to I+V or FCR was specified, allowing for 5% dropout. These assumptions and estimated outcomes with FCR were based on results from the German CLL8 trial.[7] The Trial Steering Committee recommended that recruitment cease on March 24, 2021 with 523 participants enrolled to this comparison. A formal interim analysis was prespecified in the study protocol for the primary endpoint, PFS. This was to occur when at least 50% of required PFS events had been observed (116 events) or 69 events had been observed in FCR, whichever was earlier. To ensure that an overall significance level of 5% was maintained, the O'Brien and Fleming alpha-spending function was used with prespecified bounds of 0.5% for interim and 4.8% for final analysis.[8] The interim analysis was completed and presented to the data monitoring and ethics committee on July 3, 2023 and the recommendation was made to report the interim analysis. The trial steering committee accepted the recommendation on July 12, 2023.

Efficacy analyses were done by intention to treat, including all patients randomly assigned to either I+V or FCR. The safety population included all patients who received at least one dose of study treatment.

Overall survival was analysed in the same manner at the primary endpoint, progression-free survival. The proportional hazards assumptions were assessed by plotting the hazards over time for each treatment group. Subgroup analysis for PFS and OS was prespecified for the minimisation factors (excluding center), *IGVH* mutation status, hierarchical model of chromosomal abnormalities,[9] FISH abnormalities (17p deletion, *ATM* deletion, trisomy 12, 13q14 deletion), next generation sequencing, creatinine clearance and granulocyte colony stimulating factor use. Binary logistic regression models were fitted to assess the effect of treatment on the odds of attaining undetectable MRD disease in the bone marrow and peripheral blood at any point in the trial, adjusting for the minimisation factors, excluding center. Similar analysis was done for achieving overall response and complete response at 9 months post-randomization. Time to undetectable measurable residual disease was estimated by means of the Kaplan-Meier method. Post-hoc exploratory analyses considered the effect of I+V on PFS within key subgroups.

We summarised toxicity, in terms of adverse events, descriptively. All deaths occurring on study were reviewed by the Chief Investigator and another clinical trial management group member masked to treatment allocation. Other cancers will be summarised for all participants who have had such a diagnosis after randomization. Person-years on trial were calculated as the sum of all patients receiving at least one dose of study treatment of the time in years from randomization to death or last date known to be alive. We estimated 95% CIs for incidence using approximations to the Poisson distribution.

Bone marrow MRD results can be missing at any time point, if a bone marrow sample is not taken, or if an MRD result cannot be obtained due to an insufficient sample or an analysis is not carried out. For participants randomized to FCR, if a bone marrow MRD result is missing at 3 months post-treatment, the participant's next available blood result at 12, 24, 36 etc. months post-randomization will be carried back and imputed in place of the missing result. For participants randomized to I+V, if a bone marrow MRD is missing at 9 months post-

randomization, the participant's next available blood result at 12, 18, 24 etc. months post-randomization will be carried back and imputed in place of the missing result. This is felt to be a conservative approach as participants are not thought to improve over time without treatment. The number of participants who have MRD results imputed is summarised.

All reported p values are two-sided and considered significant at an overall significance level of 5%. We used SAS (version 9.4) and R (version 4.0.1) for statistical analyses.

Supplemental Data (Tables and Figures)

Table S1: Representativeness of study participants

Category	Example
Disease under investigation	Chronic lymphocytic leukemia
Special considerations related to	
Sex and gender	CLL affects more men as compared to female. The cause is uncertain.
Age	Prevalence increases with age. It is uncommon below the age of 40 years.
Race or ethnic group	CLL is the most common leukemia in person of European descent. However, it is rare amongst Indian Asians, East Asians, Africans and native Latin Americans.
Geography	CLL is commonest leukemia reported in United Kingdom. With an annual incidence of 7.3 per 100,000 people, an estimated 4720 people are diagnosed with CLL each year in United Kingdom.
Other considerations	In the United Kingdom, the average age of diagnosis is 72 years. 5-year net survival for all age is 84.1%. The survival decreases with age due to comorbidities, but there is no difference in outcomes between sexes.
Overall representativeness of this trial	The participants in the FLAIR trial demonstrated the expected ratio of men to women. Biologic sex was reported by the participants on the case report forms. Information about the ethnic origin and race was also collected and patients chose to disclosure of information. The age distribution in the trial was younger than average age of CLL in real world. However, this is consistent with other clinical trials where FCR was chosen as standard arm of the trial due to suitability of ability of patients to receive FCR. The trial recruited entirely from United Kingdom. Overall, the trial captured the true representation of CLL population with the caveats mentioned as above.

Table S2: Number of treatment cycles received per participant for FCR

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	FCR (n=263)	I+V (n=260)
Number of participants who have received at least one dose of trial treatment	239 (90.9%)	252 (96.9%)
Number of cycles of treatment received		
Mean (s.d.)	5.1 (1.5)	31.8 (13.8)
Median (range)	6.0 (1.0, 6.0)	27.0 (2.0, 72.0)
Number of cycles of FCR received		
1	15 (6.3%)	
2	11 (4.6%)	
3	13 (5.4%)	
4	21 (8.8%)	
5	20 (8.4%)	
6	159 (66.5%)	
Summary statistics		
≤ 3 cycles of treatment	39 (16.3%)	
> 3 cycles of treatment	200 (83.7%)	

Table S3: Dose modifications by group and by IMP

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	FCR (n=263)	I+V* (n=260)
Number of participants reporting at least one modification, by IMP		
F	144 (54.8%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
C	136 (51.7%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
R	125 (47.5%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
I	0 (0.0%)	143 (55.0%)
V	0 (0.0%)	107 (41.2%)
Number of participants reporting at least one omission, by IMP		
F	6 (2.3%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
C	6 (2.3%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
R	3 (1.1%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
I	0 (0.0%)	135 (51.9%)
V	0 (0.0%)	97 (37.3%)
Median (range) number of days of ibrutinib omitted for participants reporting at least one ibrutinib omission	. (., .)	8.0 (1.0, 90.0)
Median (range) number of days of venetoclax omitted for participants reporting at least one venetoclax omission	. (., .)	7.0 (1.0, 97.0)
Number of participants reporting at least one reduction, by IMP (F, C and R only)		
F	69 (26.2%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
C	58 (22.1%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
R	7 (2.7%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
Median (range) % reduction, by IMP (F, C and R only)		
F	30.0 (15.0, 75.0)	. (., .)
Missing	2	0
C	25.0 (15.0, 80.0)	. (., .)
Missing	2	0
R	26.5 (2.0, 86.0)	. (., .)
Missing	2	0
Number of participants reporting at least one delay, by IMP (F, C and R only)		
F	117 (44.5%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)

	FCR (n=263)	I+V* (n=260)
C	118 (44.9%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
R	114 (43.3%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
Number of participants who stopped treatment early, by IMP (F, C and R only)		
F	15 (5.7%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
C	13 (4.9%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
R	9 (3.4%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
Number of participants receiving IMP through alternative route of administration (F and C)		
F	12 (4.6%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
C	12 (4.6%)	0 (0.0%)
N/A	24 (9.1%)	0 (0.0%)
Number of participants with an ibrutinib dose change	0 (0.0%)	43 (16.5%)
Median (range) dose of ibrutinib for participants reporting at least one ibrutinib dose change		280 (140, 420)
Ibrutinib modification planned?**		
Yes	0 (0.0%)	314 (73.5%)
No	0 (0.0%)	88 (20.6%)
Missing	0 (0.0%)	25 (5.9%)
Number of participants with an Venetoclax dose change	0 (0.0%)	30 (11.5%)
Median (range) dose of Venetoclax for participants reporting at least one Venetoclax dose change		200 (100, 300)
Venetoclax modification planned?**		
Yes	0 (0.0%)	194 (66.2%)
No	0 (0.0%)	92 (31.4%)
Missing	0 (0.0%)	7 (2.4%)

*ibrutinib plus venetoclax for first 12m only

**These percentages are out of those with a reported dose modification in any cycle

N/A consists of participants who have either withdrawn from trial treatment, progressed, or died.

Table S4: Summary of dose modifications, 12 monthly follow-up (ibrutinib plus venetoclax)

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	0-1 year (n=260)	1-2 years (n=260)	2-3 years (n=260)	3-4 years (n=236)	4-5 years (n=168)	5-6 years (n=86)
Number of participants reporting at least one modification	34 (13.1%)	80 (30.8%)	31 (11.9%)	18 (7.6%)	6 (3.6%)	0 (0.0%)
N/A	6 (2.3%)	24 (9.2%)	30 (11.5%)	33 (14.0%)	40 (23.8%)	41 (47.7%)
Missing	157 (60.4%)	29 (11.2%)	141 (54.2%)	149 (63.1%)	114 (67.9%)	43 (50.0%)
Number of participants reporting at least one omission	83 (31.9%)	87 (33.5%)	36 (13.8%)	24 (10.2%)	18 (10.7%)	0 (0.0%)
N/A	6 (2.3%)	24 (9.2%)	30 (11.5%)	33 (14.0%)	40 (23.8%)	41 (47.7%)
Missing	7 (2.7%)	1 (0.4%)	18 (6.9%)	49 (20.8%)	65 (38.7%)	37 (43.0%)
Median (range) number of days omitted for participants reporting at least one dose omission	7.0 (1.0, 87.0)	7.0 (1.0, 84.0)	8.5 (1.0, 90.0)	7.0 (1.0, 34.0)	7.0 (1.0, 28.0)	
Missing	154	93	31	22	7	
Number of participants reporting at least one dose change	7 (2.7%)	14 (5.4%)	6 (2.3%)	5 (2.1%)	3 (1.8%)	0 (0.0%)
N/A	6 (2.3%)	24 (9.2%)	30 (11.5%)	33 (14.0%)	40 (23.8%)	41 (47.7%)
Missing	7 (2.7%)	1 (0.4%)	18 (6.9%)	49 (20.8%)	65 (38.7%)	37 (43.0%)
Median (range) dose of ibrutinib received for participants reporting at least one dose change	280 (140, 420)	280 (140, 840)	280 (100, 420)	280 (140, 280)	280 (140, 280)	
Missing	0	2	0	0	0	
Median (range) dose of venetoclax received for participants reporting at least one dose change	200 (10.0, 400)	200 (100, 300)	200 (20.0, 300)	250 (100, 300)	100 (100, 100)	
Missing	0	1	1	0	0	
Number of participants reporting at least one planned modification of those who have had at least one dose modification	115 (41.5%)	123 (46.2%)	51 (47.2%)	23 (40.4%)	11 (55.0%)	
Missing	122 (44.0%)	108 (40.6%)	47 (43.5%)	27 (47.4%)	7 (35.0%)	

N/A consists of participants who have either withdrawn from trial treatment, progressed or died.

Table S5: Reasons for early discontinuation of FCR*

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	FCR (n=62)
Disease progression	2 (2.5%)
Toxicity	36 (45.0%)
Participant choice	11 (13.8%)
Clinician choice	27 (33.8%)
Death	1 (1.3%)
Other reason discontinued	3 (3.8%)

* Reasons for early discontinuation are not mutually exclusive.

Table S6: Reasons for early discontinuation of ibrutinib and venetoclax*

Abbreviations: MRD, measurable residual disease.

	Ibrutinib (n=182)	Venetoclax (n=173)
Unplanned		
Toxicity	21 (10.8%)	11 (6.1%)
Participant choice	12 (6.2%)	9 (5.0%)
Other reason	7 (3.6%)	5 (2.8%)
Disease progression	2 (1.0%)	2 (1.1%)
Death	2 (1.0%)	2 (1.1%)
Clinician choice	14 (7.2%)	8 (4.4%)
Per protocol		
Participant has met the MRD negative stopping criteria	136 (70.1%)	143 (79.4%)

* Reasons for early discontinuation are not mutually exclusive.

Table S7: Estimates for I+V treatment stopping for attaining MRD stopping rules up to 5 years (+ 3m) post-randomization with corresponding 95% confidence intervals

Abbreviations: CI, confidence interval

Time from starting treatment (months)	Number stopped treatment due to MRD stopping rules	Number continuing treatment	Percentage stopped treatment (95% CI)
0	0	256	0.0% (95% CI, 0.0%-0.0%)
12	0	243	0.0% (95% CI, 0.0%-0.0%)
15	0	241	0.0% (95% CI, 0.0%-0.0%)
24	65	158	28.9% (95% CI, 23.0%-34.8%)
27	111	106	49.9% (95% CI, 43.3%-56.5%)
36	126	74	58.0% (95% CI, 51.3%-64.6%)
39	135	60	63.1% (95% CI, 56.4%-69.8%)
48	144	25	71.8% (95% CI, 64.6%-79.0%)
51	145	16	72.9% (95% CI, 65.7%-80.2%)
60	146	4	78.4% (95% CI, 67.2%-89.5%)
63	146	2	78.4% (95% CI, 67.2%-89.5%)

Table S8: PFS summaries up to 5 years post-randomization with corresponding 95% confidence intervals

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

Progression-free survival (%) post-randomization (months)	FCR (n=263)	I+V (n=260)
12	92.8% (91.2%, 94.4%)	99.6% (99.2%, 100%)
24	83.3% (80.9%, 85.7%)	98.0% (97.1%, 98.9%)
36	76.8% (74.0%, 79.6%)	97.2% (96.1%, 98.2%)
48	64.8% (61.2%, 68.5%)	93.5% (91.6%, 95.4%)
60	61.3% (57.3%, 65.3%)	93.5% (91.6%, 95.4%)

Table S9: OS summaries up to 5 years post-randomization with corresponding 95% confidence intervals

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

Overall survival (%) post-randomization (months)	FCR (n=263)	I+V (n=260)
12	96.0% (94.7%, 97.2%)	100% (100%, 100%)
24	93.5% (91.9%, 95.1%)	98.4% (97.6%, 99.2%)
36	93.0% (91.3%, 94.6%)	98.0% (97.1%, 98.9%)
48	87.3% (84.7%, 89.9%)	94.9% (93.1%, 96.6%)
60	85.9% (82.9%, 88.8%)	94.9% (93.1%, 96.6%)

Table S10: Undetectable MRD summaries in the bone marrow up to 5 years post-randomization in evaluable patients estimated by Kaplan-Meier method with corresponding 95% confidence intervals

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; MRD, measurable residual disease; uMRD, undetectable MRD; BM, bone marrow.

Randomization allocation	Time from randomization (months)	Percentage uMRD (BM) (95% CI)
FCR	12	49.8% (95% CI, 43.2%-56.5%)
FCR	24	49.8% (95% CI, 43.2%-56.5%)
FCR	36	49.8% (95% CI, 43.2%-56.5%)
FCR	48	49.8% (95% CI, 43.2%-56.5%)
FCR	60	49.8% (95% CI, 43.2%-56.5%)
I+V	12	35.6% (95% CI, 29.5%-41.8%)
I+V	24	52.4% (95% CI, 45.9%-58.9%)
I+V	36	64.0% (95% CI, 57.7%-70.4%)
I+V	48	65.9% (95% CI, 59.5%-72.3%)
I+V	60	65.9% (95% CI, 59.5%-72.3%)

Table S11: Undetectable MRD summaries in the peripheral blood up to 5 years post-randomization in evaluable patients estimated by Kaplan-Meier method with corresponding 95% confidence intervals

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; MRD, measurable residual disease; uMRD, undetectable MRD; PB, peripheral blood.

Randomization allocation	Time from randomization (months)	Percentage uMRD (PB) (95% CI)
FCR	12	66.0% (95% CI, 60.0%-72.1%)
FCR	24	67.9% (95% CI, 61.9%-73.9%)
FCR	36	67.9% (95% CI, 61.9%-73.9%)
FCR	48	67.9% (95% CI, 61.9%-73.9%)
FCR	60	67.9% (95% CI, 61.9%-73.9%)
I+V	12	47.5% (95% CI, 41.2%-53.7%)
I+V	24	70.5% (95% CI, 64.7%-76.2%)
I+V	36	83.2% (95% CI, 78.4%-88.0%)
I+V	48	89.2% (95% CI, 85.0%-93.4%)
I+V	60	92.7% (95% CI, 88.1%-97.3%)

Table S12: Proportion of participants with undetectable MRD in the bone marrow at 9-months post randomization

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; N/A, not applicable- consists of participants who have either withdrawn from trial treatment, progressed or died; MRD, measurable residual disease.

	Proportion (Percentage) | Exact 95% CI			
	FCR (n=263)		I+V (n=260)	
Detectable MRD	82 of 263 (31.2%)	25.63%, 37.16%	138 of 260 (53.1%)	46.81%, 59.27%
Undetectable MRD	127 of 263 (48.3%)	42.11%, 54.51%	108 of 260 (41.5%)	35.48%, 47.79%
N/A	25 of 263 (9.5%)	6.25%, 13.71%	5 of 260 (1.9%)	0.63%, 4.43%
Missing	29 of 263 (11.0%)	7.51%, 15.45%	9 of 260 (3.5%)	1.59%, 6.47%

Table S13: Proportion of participants with undetectable MRD in the peripheral blood annually

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; N/A, not applicable- consists of participants who have either withdrawn from trial treatment, progressed or died; MRD, measurable residual disease.

	Proportion (Percentage) | Exact 95% CI			
	FCR (n=263)		I+V (n=260)	
12 months post-randomization				
Analysis not done	0 of 263 (0.0%)	0.00%, 1.39%	0 of 260 (0.0%)	0.00%, 1.41%
Blood sample not sent	0 of 263 (0.0%)	0.00%, 1.39%	0 of 260 (0.0%)	0.00%, 1.41%
Undetectable MRD	125 of 263 (47.5%)	41.36%, 53.75%	123 of 260 (47.3%)	41.11%, 53.57%
Detectable MRD	47 of 263 (17.9%)	13.44%, 23.05%	88 of 260 (33.8%)	28.12%, 39.95%
Missing	87 of 263 (33.1%)	27.42%, 39.12%	48 of 260 (18.5%)	13.94%, 23.72%

	Proportion (Percentage) | Exact 95% CI			
	FCR (n=263)		I+V (n=260)	
N/A	4 of 263 (1.5%)	0.42%, 3.85%	1 of 260 (0.4%)	0.01%, 2.12%
Not required- participant randomized to FCR and detectable MRD previously	0 of 263 (0.0%)	0.00%, 1.39%	0 of 260 (0.0%)	0.00%, 1.41%
24 months post-randomization				
Analysis not done	0 of 263 (0.0%)	0.00%, 1.39%	1 of 260 (0.4%)	0.01%, 2.12%
Blood sample not sent	0 of 263 (0.0%)	0.00%, 1.39%	0 of 260 (0.0%)	0.00%, 1.41%
Undetectable MRD	90 of 263 (34.2%)	28.50%, 40.30%	146 of 260 (56.2%)	49.89%, 62.28%
Detectable MRD	27 of 263 (10.3%)	6.88%, 14.58%	48 of 260 (18.5%)	13.94%, 23.72%
Missing	90 of 263 (34.2%)	28.50%, 40.30%	61 of 260 (23.5%)	18.45%, 29.09%
N/A	13 of 263 (4.9%)	2.66%, 8.30%	4 of 260 (1.5%)	0.42%, 3.89%
Not required- participant randomized to FCR and detectable MRD previously	43 of 263 (16.3%)	12.09%, 21.38%	0 of 260 (0.0%)	0.00%, 1.41%
36 months post-randomization				
Analysis not done	0 of 232 (0.0%)	0.00%, 1.58%	0 of 232 (0.0%)	0.00%, 1.58%
Blood sample not sent	0 of 232 (0.0%)	0.00%, 1.58%	0 of 232 (0.0%)	0.00%, 1.58%
Undetectable MRD	77 of 232 (33.2%)	27.16%, 39.65%	130 of 232 (56.0%)	49.39%, 62.52%
Detectable MRD	16 of 232 (6.9%)	3.99%, 10.96%	26 of 232 (11.2%)	7.45%, 15.99%
Missing	68 of 232 (29.3%)	23.54%, 35.62%	70 of 232 (30.2%)	24.34%, 36.52%
N/A	16 of 232 (6.9%)	3.99%, 10.96%	6 of 232 (2.6%)	0.95%, 5.54%
Not required- participant randomized to FCR and detectable MRD previously	55 of 232 (23.7%)	18.39%, 29.71%	0 of 232 (0.0%)	0.00%, 1.58%
48 months post-randomization				
Analysis not done	0 of 156 (0.0%)	0.00%, 2.34%	0 of 155 (0.0%)	0.00%, 2.35%
Blood sample not sent	0 of 156 (0.0%)	0.00%, 2.34%	0 of 155 (0.0%)	0.00%, 2.35%
Undetectable MRD	40 of 156 (25.6%)	18.99%, 33.24%	76 of 155 (49.0%)	40.93%, 57.18%
Detectable MRD	10 of 156 (6.4%)	3.12%, 11.47%	16 of 155 (10.3%)	6.02%, 16.22%
Missing	46 of 156 (29.5%)	22.47%, 37.31%	55 of 155 (35.5%)	27.97%, 43.56%
N/A	25 of 156 (16.0%)	10.65%, 22.74%	8 of 155 (5.2%)	2.25%, 9.92%
Not required- participant randomized to FCR and detectable MRD previously	0 of 156 (0.0%)	0.00%, 2.34%	0 of 155 (0.0%)	0.00%, 2.35%
60 months post-randomization				
Analysis not done	0 of 56 (0.0%)	0.00%, 6.38%	0 of 57 (0.0%)	0.00%, 6.27%
Blood sample not sent	0 of 56 (0.0%)	0.00%, 6.38%	0 of 57 (0.0%)	0.00%, 6.27%
Undetectable MRD	11 of 56 (19.6%)	10.23%, 32.43%	25 of 57 (43.9%)	30.74%, 57.64%
Detectable MRD	1 of 56 (1.8%)	0.05%, 9.55%	1 of 57 (1.8%)	0.04%, 9.39%
Missing	16 of 56 (28.6%)	17.30%, 42.21%	26 of 57 (45.6%)	32.36%, 59.34%
N/A	10 of 56 (17.9%)	8.91%, 30.40%	5 of 57 (8.8%)	2.91%, 19.30%
	18 of 56 (32.1%)	20.29%, 45.96%	0 of 57 (0.0%)	0.00%, 6.27%
Not required- participant randomized to FCR and detectable MRD previously	0 of 56 (0.0%)	0.00%, 6.38%	0 of 57 (0.0%)	0.00%, 6.27%

Table S14: Proportion of participants that achieved response at 9 months, by allocated group

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; CI, confidence interval

	Proportion (Percentage) | Exact 95% CI			
	FCR		I+V	
Complete Remission (CR)	94 of 263 (35.7%)	29.95%, 41.86%	127 of 260 (48.8%)	42.62%, 55.10%
Complete Remission with incomplete marrow recovery (CRi)	35 of 263 (13.3%)	9.45%, 18.02%	27 of 260 (10.4%)	6.96%, 14.75%
Partial Remission (PR)	72 of 263 (27.4%)	22.08%, 33.19%	70 of 260 (26.9%)	21.63%, 32.75%

	Proportion (Percentage) | Exact 95% CI			
	FCR		I+V	
Partial Remission with lymphocytosis	0 of 263 (0.0%)	0.00%, 1.39%	1 of 260 (0.4%)	0.01%, 2.12%
Stable disease	4 of 263 (1.5%)	0.42%, 3.85%	3 of 260 (1.2%)	0.24%, 3.33%
Progressive Disease (PD)	1 of 263 (0.4%)	0.01%, 2.10%	0 of 260 (0.0%)	0.00%, 1.41%
Unable to assess	13 of 263 (4.9%)	2.66%, 8.30%	9 of 260 (3.5%)	1.59%, 6.47%
Unavailable due to Progression, Death or Withdrawal from follow-up	11 of 263 (4.2%)	2.11%, 7.36%	18 of 260 (6.9%)	4.15%, 10.72%
Missing	33 of 263 (12.5%)	8.80%, 17.17%	5 of 260 (1.9%)	0.63%, 4.43%

Table S15: Most frequent AEs over time in participants treated with I+V

Abbreviations: I+V, ibrutinib plus venetoclax.

	1-2 years (n=251)			2-3 years (n=249)			3-4 years (n=224)			4-5 years (n=153)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Acute kidney injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Anemia	10 (4%)	0 (0%)	0 (0%)	8 (3.2%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Atrial fibrillation/Arrythmia	6 (2.4%)	1 (0.4%)	0 (0%)	7 (2.8%)	2 (0.8%)	0 (0%)	2 (0.9%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Constipation	2 (0.8%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cough	6 (2.4%)	0 (0%)	0 (0%)	11 (4.4%)	0 (0%)	0 (0%)	5 (2.2%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Diarrhea	43 (17.1%)	3 (1.2%)	0 (0%)	22 (8.8%)	2 (0.8%)	0 (0%)	11 (4.9%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Dyspnea	10 (4%)	0 (0%)	0 (0%)	8 (3.2%)	1 (0.4%)	0 (0%)	5 (2.2%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)
Fatigue	20 (8%)	0 (0%)	0 (0%)	11 (4.4%)	0 (0%)	0 (0%)	9 (4%)	0 (0%)	0 (0%)	5 (3.3%)	0 (0%)	0 (0%)
Febrile neutropenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	8 (3.2%)	0 (0%)	0 (0%)	6 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Haemolysis / Haemolytic anaemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	8 (3.2%)	0 (0%)	0 (0%)	3 (1.2%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Hypertension	8 (3.2%)	2 (0.8%)	0 (0%)	3 (1.2%)	3 (1.2%)	0 (0%)	4 (1.8%)	3 (1.3%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Infections and infestations - Other	0 (0%)	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Infusion related reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung infection	1 (0.4%)	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lymphocyte count decreased	5 (2%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)	0 (0%)	5 (2.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Nausea	25 (10%)	0 (0%)	0 (0%)	12 (4.8%)	0 (0%)	0 (0%)	8 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutropenia	19 (7.6%)	8 (3.2%)	0 (0%)	8 (3.2%)	2 (0.8%)	0 (0%)	3 (1.3%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Other	28 (11.2%)	2 (0.8%)	0 (0%)	39 (15.7%)	2 (0.8%)	0 (0%)	29 (12.9%)	5 (2.2%)	0 (0%)	16 (10.5%)	1 (0.7%)	0 (0%)
Platelet count decreased	17 (6.8%)	0 (0%)	0 (0%)	7 (2.8%)	0 (0%)	0 (0%)	4 (1.8%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)
Rash	19 (7.6%)	2 (0.8%)	0 (0%)	11 (4.4%)	0 (0%)	0 (0%)	3 (1.3%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)
Sepsis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin infections	4 (1.6%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Taste alteration/loss of appetite	2 (0.8%)	0 (0%)	0 (0%)	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Upper respiratory infection	9 (3.6%)	1 (0.4%)	0 (0%)	9 (3.6%)	0 (0%)	0 (0%)	5 (2.2%)	0 (0%)	0 (0%)	1 (0.7%)	2 (1.3%)	0 (0%)
Vomiting	13 (5.2%)	0 (0%)	0 (0%)	5 (2%)	1 (0.4%)	0 (0%)	3 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Grade 1-2 in ≥10% of participants and Grade 3-5 in ≥1% of participants in the safety population within first year.

Table S16: SAEs, by MedDRA System organ class

Abbreviations: SAE, serious adverse event; MedDRA, Medical Dictionary for Regulatory Activities; FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	Number of participants reporting one or more SAE		
	FCR (n=239)	I+V (n=252)	Total (n=491)
Infections and infestations	45 (18.8%)	56 (22.2%)	101 (19.3%)
Blood and lymphatic system disorders	74 (31%)	13 (5.2%)	87 (16.6%)
Cardiac disorders	1 (0.4%)	27 (10.7%)	28 (5.4%)
Gastrointestinal disorders	19 (7.9%)	9 (3.6%)	28 (5.4%)
General disorders and administration site conditions	12 (5%)	4 (1.6%)	16 (3.1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2.1%)	6 (2.4%)	11 (2.1%)
Metabolism and nutrition disorders	0 (0%)	10 (4%)	10 (1.9%)
Respiratory, thoracic and mediastinal disorders	6 (2.5%)	4 (1.6%)	10 (1.9%)
Musculoskeletal and connective tissue disorders	3 (1.3%)	6 (2.4%)	9 (1.7%)
Skin and subcutaneous tissue disorders	5 (2.1%)	4 (1.6%)	9 (1.7%)
Investigations	0 (0%)	8 (3.2%)	8 (1.5%)
Nervous system disorders	2 (0.8%)	5 (2%)	7 (1.3%)
Eye disorders	0 (0%)	6 (2.4%)	6 (1.1%)
Renal and urinary disorders	3 (1.3%)	1 (0.4%)	4 (0.8%)
Hepatobiliary disorders	0 (0%)	2 (0.8%)	2 (0.4%)
Injury, poisoning and procedural complications	0 (0%)	2 (0.8%)	2 (0.4%)
Psychiatric disorders	1 (0.4%)	1 (0.4%)	2 (0.4%)
Vascular disorders	0 (0%)	2 (0.8%)	2 (0.4%)
Ear and labyrinth disorders	0 (0%)	1 (0.4%)	1 (0.2%)
Endocrine disorders	0 (0%)	1 (0.4%)	1 (0.2%)
Immune system disorders	0 (0%)	1 (0.4%)	1 (0.2%)

Table S17: Deaths, categorised by study team

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	FCR (n=23)	I+V (n=8)	Total (n=31)
Allogeneic transplant related complication: Refractory GvHD	1 (4.3%)	0 (0.0%)	1 (3.2%)
Allogeneic transplant related complication: infection	1 (4.3%)	0 (0.0%)	1 (3.2%)
Cardiac	2 (8.7%)	3 (37.5%)	5 (16.1%)
Covid-19 infection	2 (8.7%)	2 (25.0%)	4 (12.9%)
Disease Progression	1 (4.3%)	0 (0.0%)	1 (3.2%)
Haemorrhage	1 (4.3%)	0 (0.0%)	1 (3.2%)
Infection	7 (30.4%)	1 (12.5%)	8 (25.8%)
Lymphoma	1 (4.3%)	0 (0.0%)	1 (3.2%)
Non-Haematological malignancy	2 (8.7%)	1 (12.5%)	3 (9.7%)
Richter's transformation	2 (8.7%)	1 (12.5%)	3 (9.7%)
Treatment related bone marrow failure	1 (4.3%)	0 (0.0%)	1 (3.2%)
Treatment related myeloid neoplasm	2 (8.7%)	0 (0.0%)	2 (6.4%)

Table S18: Other diagnosed cancers following randomization

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

	FCR (n=34)	I+V (n=17)	Total (n=51)
Type of cancer			
Lymphoma (Richter's)	4 (8.9%)	1 (4.2%)	2 (2.9%)
Lymphoma (Other)	1 (2.2%)	2 (8.3%)	6 (8.7%)
Myelodysplastic syndrome	6 (13.3%)	1 (4.2%)	7 (10.1%)
Acute myeloid leukaemia	2 (4.4%)	0 (0.0%)	2 (2.9%)
Basal cell carcinoma	8 (17.8%)	11 (45.8%)	19 (27.5%)
Squamous cell carcinoma	8 (17.8%)	2 (8.3%)	10 (14.5%)
Melanoma	1 (2.2%)	1 (4.2%)	2 (2.9%)
Lung	3 (6.7%)	0 (0.0%)	3 (4.3%)
Breast	1 (2.2%)	1 (4.2%)	2 (2.9%)
Upper gastrointestinal	0 (0.0%)	1 (4.2%)	1 (1.4%)
Lower gastrointestinal	1 (2.2%)	0 (0.0%)	1 (1.4%)
Urological (Prostate)	3 (6.7%)	1 (4.2%)	4 (5.8%)
Urological (Other)	2 (4.4%)	0 (0.0%)	2 (2.9%)
Endocrine	0 (0.0%)	1 (4.2%)	1 (1.4%)
Other	5 (11.1%)	2 (8.3%)	7 (10.1%)

*Other: FCR (Plasma cell myeloma * 2, rectal adenocarcinoma of the rectum, urothelial carcinoma, T Cell Lymphoma) and I+V (Type A Thymoma, Carcinoid Intrapulmonary Nodule)

Table S19: Cumulative incidence and 95% confidence interval of other diagnosed cancers, by group and overall

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

Time from randomization (months)	FCR (n=263)	I+V (n=260)	Total (n=523)
12	4.1% [1.63%, 6.65%]	2.0% [0.26%, 3.65%]	3.0% [1.51%, 4.51%]
24	9.0% [5.31%, 12.64%]	3.2% [1.00%, 5.32%]	5.9% [3.85%, 8.05%]
36	11.5% [7.34%, 15.74%]	5.4% [2.52%, 8.23%]	8.3% [5.81%, 10.83%]
48	17.2% [11.52%, 22.90%]	6.9% [3.38%, 10.34%]	11.7% [8.44%, 14.96%]
60	18.5% [12.35%, 24.58%]	13.0% [3.21%, 22.72%]	15.6% [9.55%, 21.60%]

Figure S1: Major amendments to the FLAIR trial

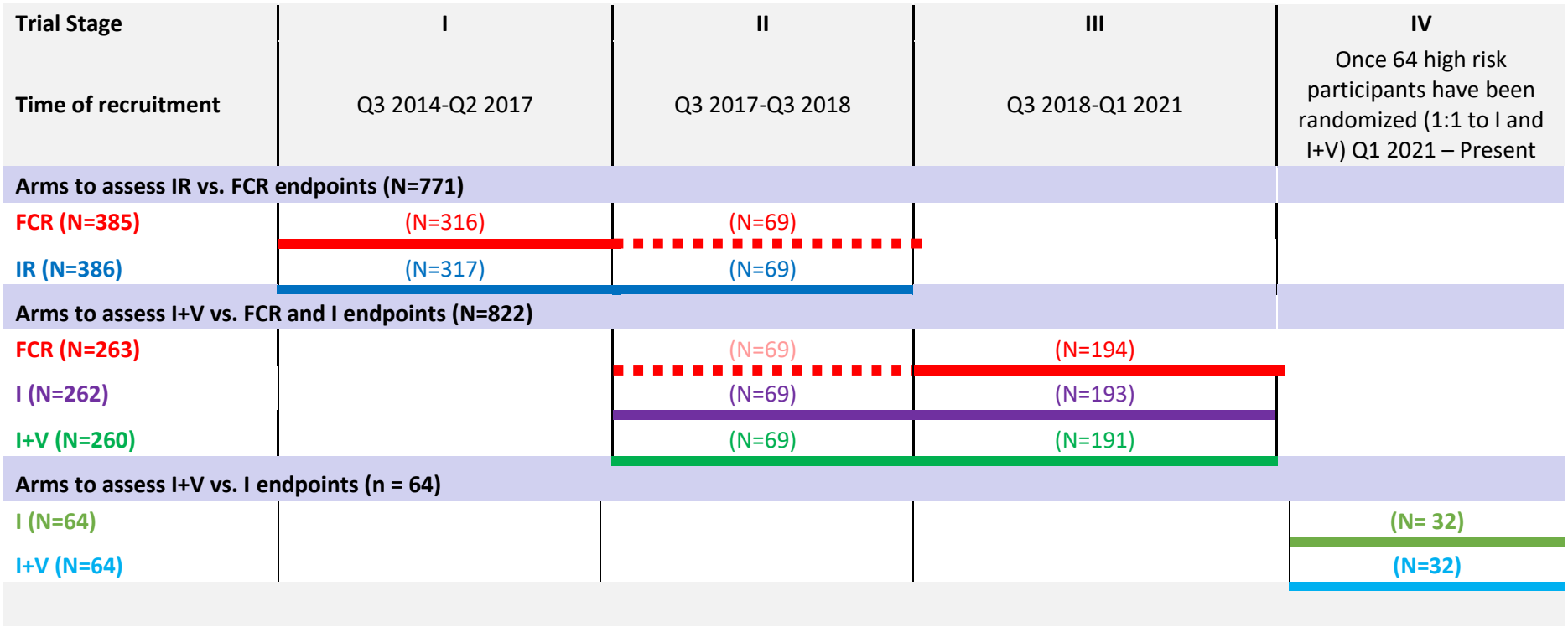


Figure S2: Measurable Residual Disease Stopping Algorithm

Starting at the 12m assessment, once an uMRD result was obtained, the time from starting treatment to this first uMRD result was calculated, and treatment continued for that same duration before being stopped. Sustained uMRD to confirm stopping was checked with a PB test 3m following the first instance of uMRD and a BM aspirate and PB test 6m later. If participants randomized to I+V stopped treatment due to MRD stopping rules and then had MRD relapse (before 6y post randomization), their randomized treatment was recommenced until a total of 6y of treatment had been administered.

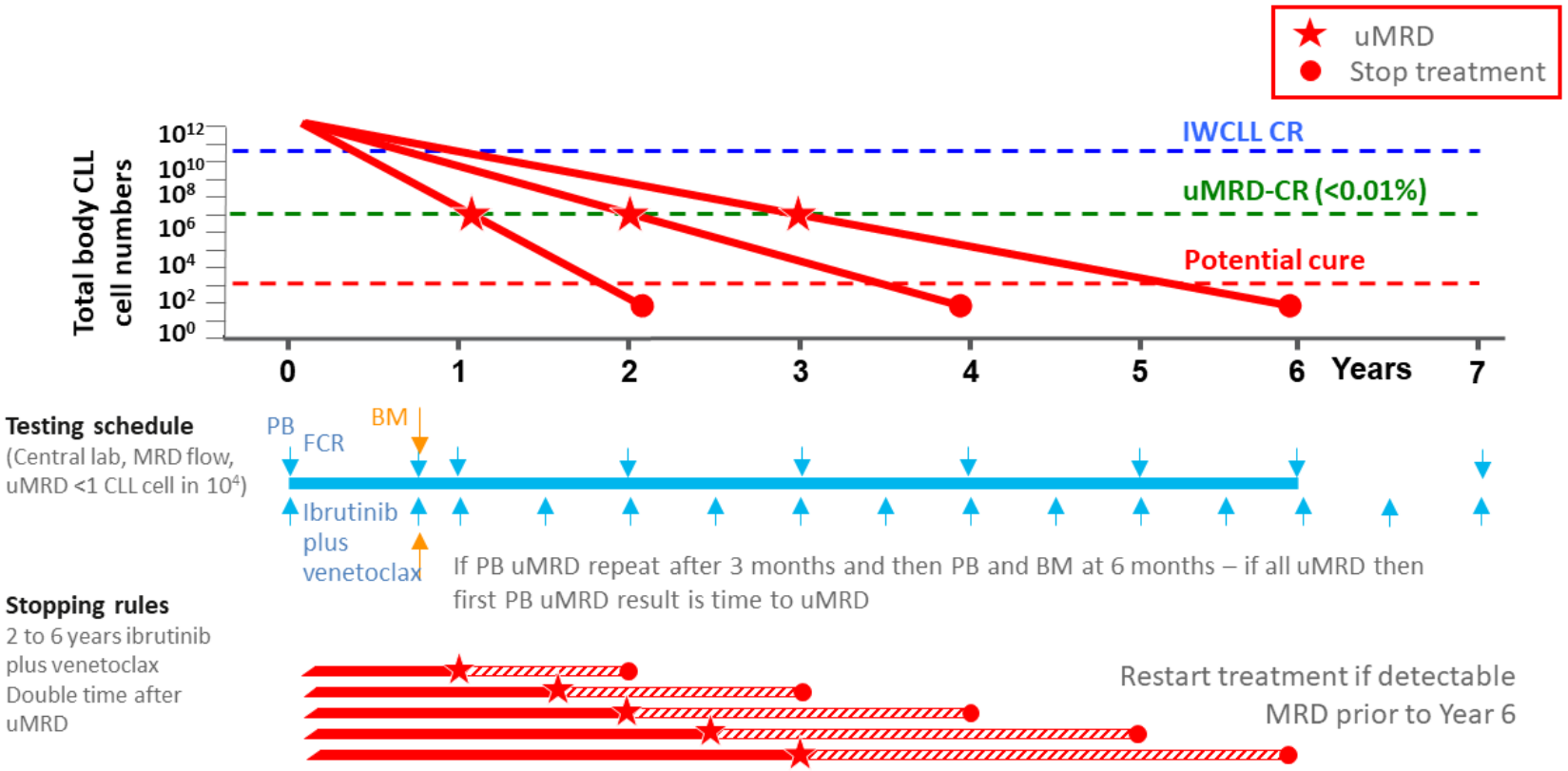


Figure S3: Screening, Randomization, and Follow-up (CONSORT diagram)

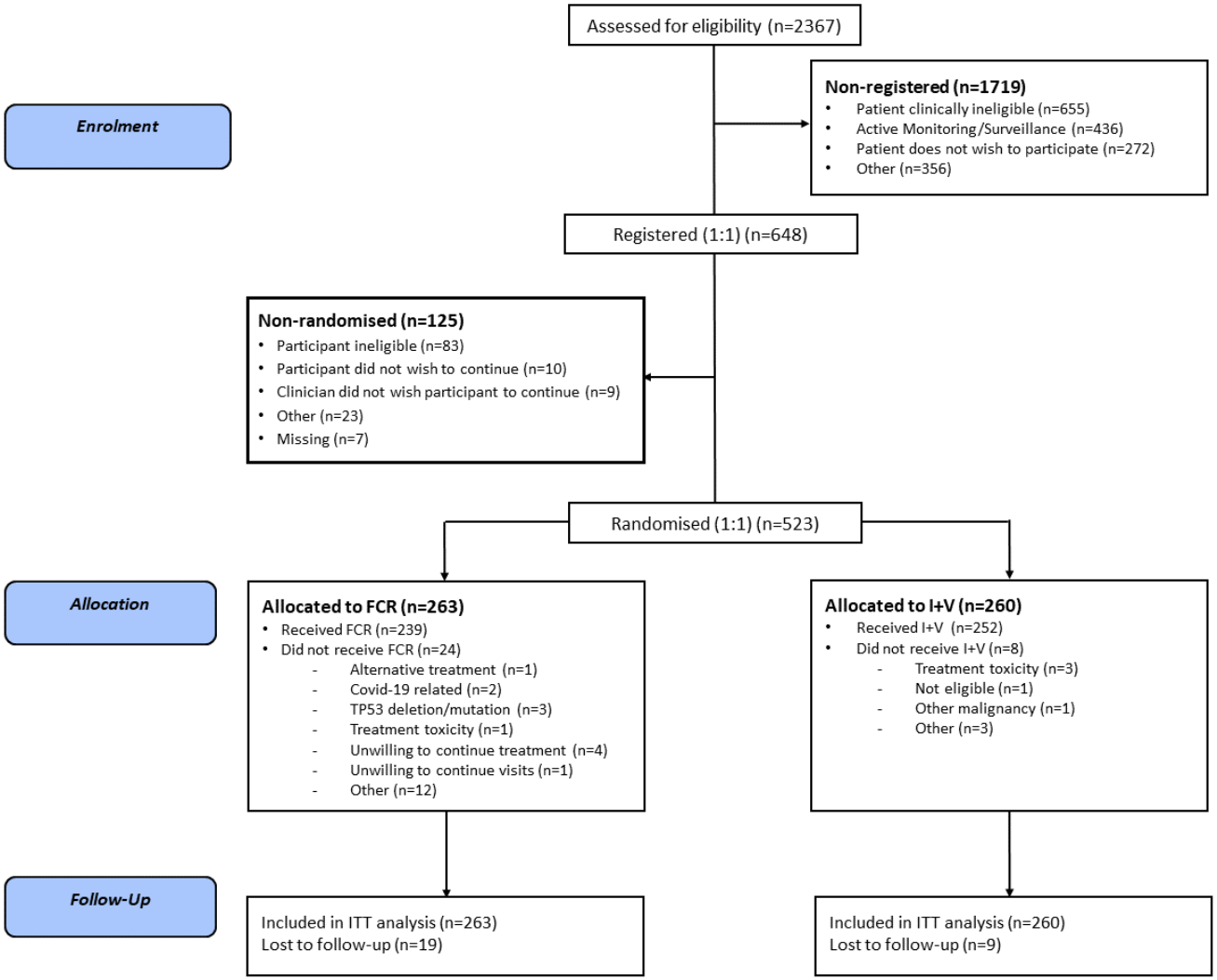
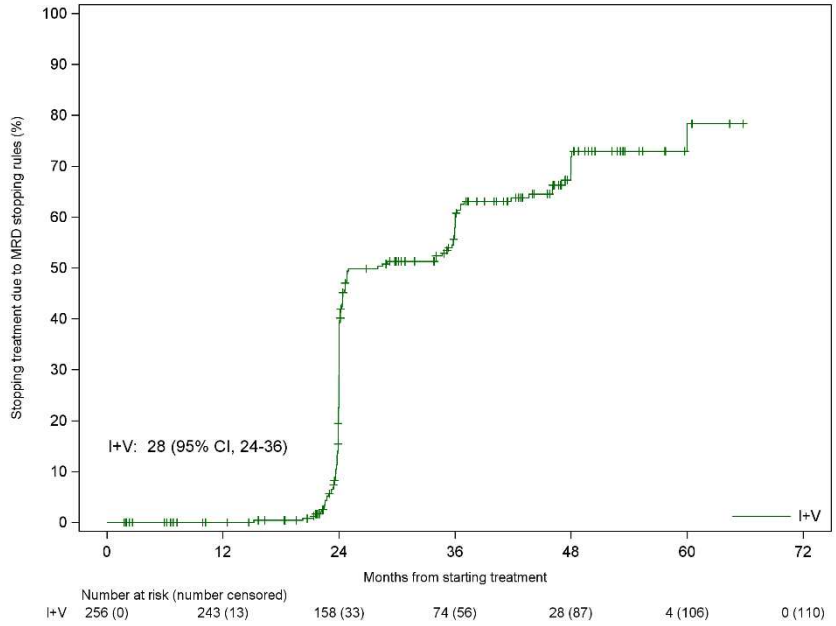


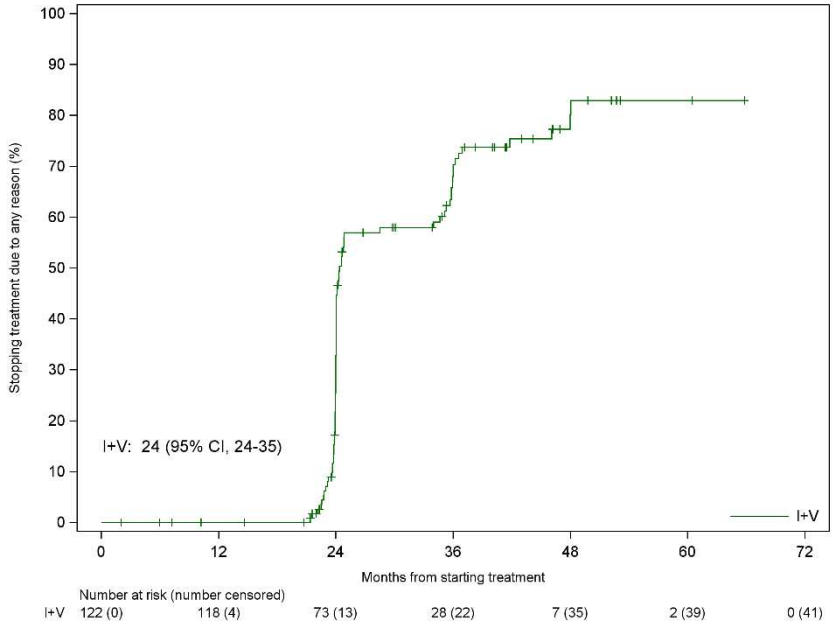
Figure S4: Time to stopping treatment for attaining MRD stopping rules in I+V group (A) in all participants, (B) in participants with unmutated IGHV, (C) in participants with mutated IGHV

Abbreviations: I+V, ibrutinib plus venetoclax.

A



B


Stopping treatment due to any reason (%)
100
90
80
70
60
50
40
30
20
10
0
I+V: 24 (95% CI, 24-35)
I+V
0
12
24
36
48
60
72
Months from starting treatment
Number at risk (number censored)
I+V 122 (0) 118 (4) 73 (13) 28 (22) 7 (35) 2 (39) 0 (41)

C

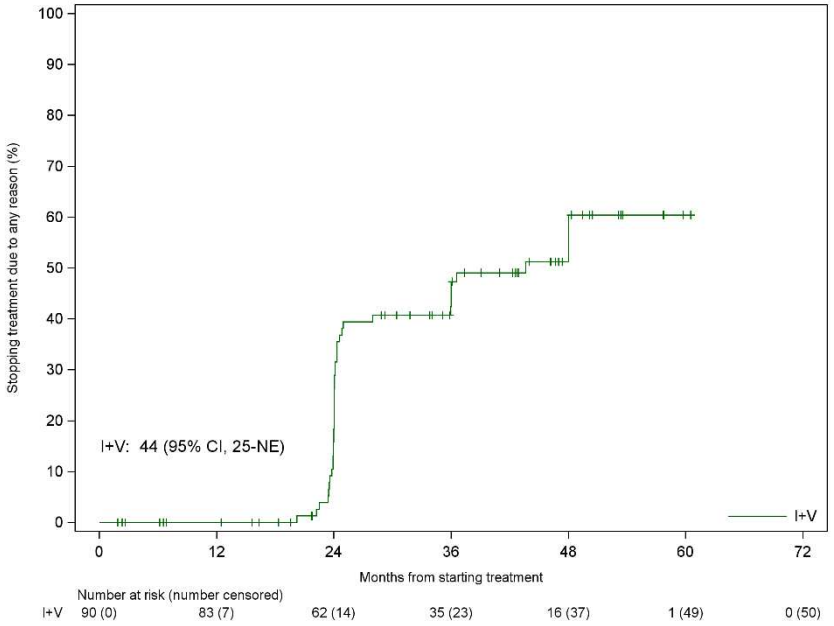
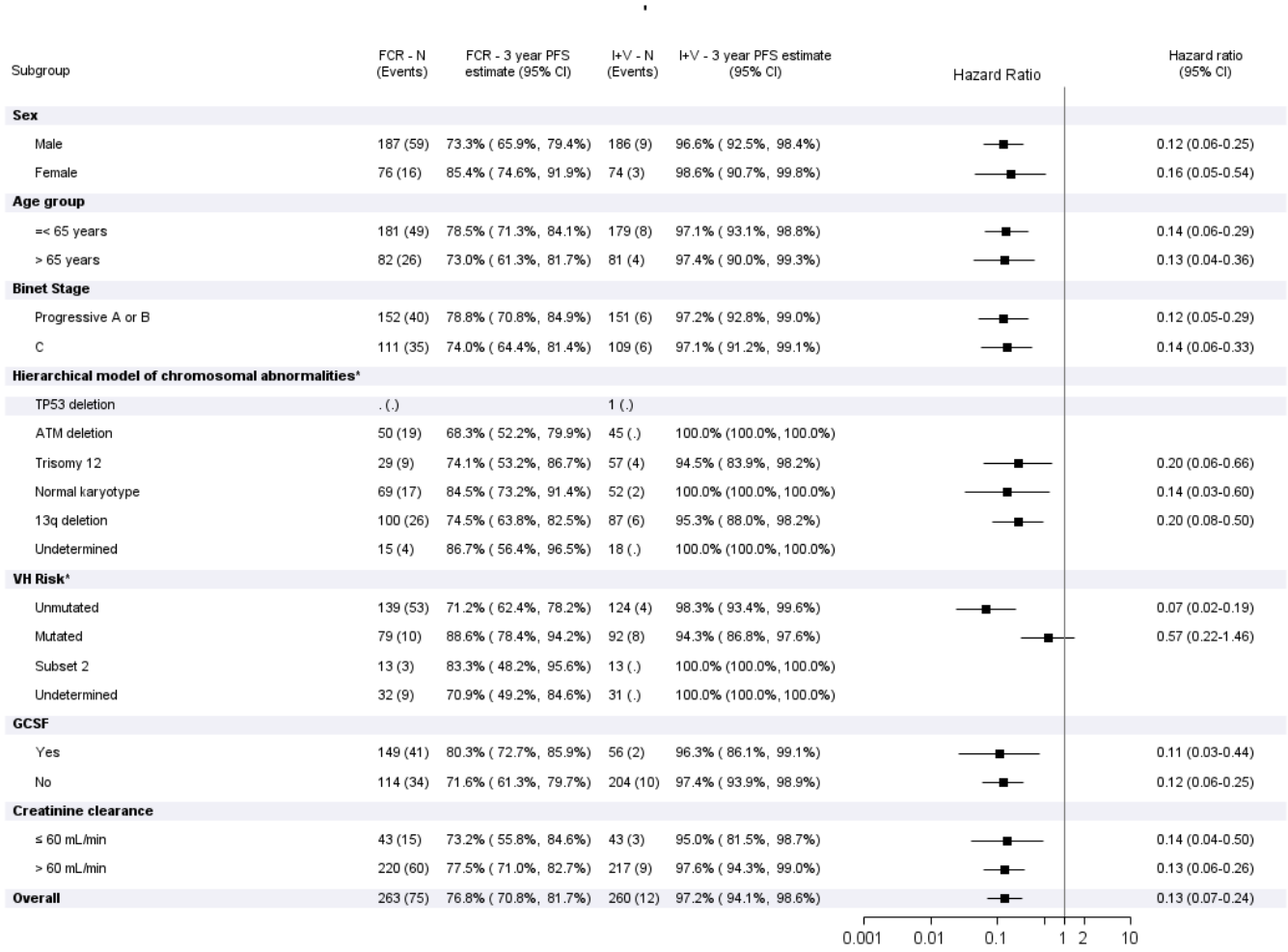

Stopping treatment due to any reason (%)
100
90
80
70
60
50
40
30
20
10
0
I+V: 44 (95% CI, 25-NE)
I+V
0
12
24
36
48
60
72
Months from starting treatment
Number at risk (number censored)
I+V 90 (0) 83 (7) 62 (14) 35 (23) 16 (37) 1 (49) 0 (50)

Figure S5: Subgroup analysis for PFS

Abbreviations: PFS, progression-free survival; CI, confidence interval, FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; G-CSF, granulocyte-colony stimulating factor.

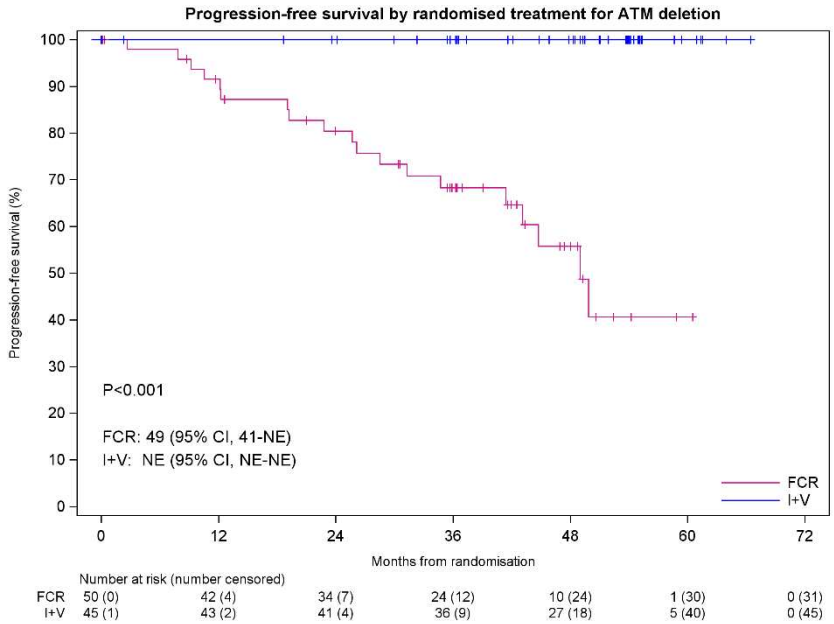


*Note that for subgroups without events, hazard ratios are inestimable and Kaplan-Meier plots in Figure S6 should be considered.

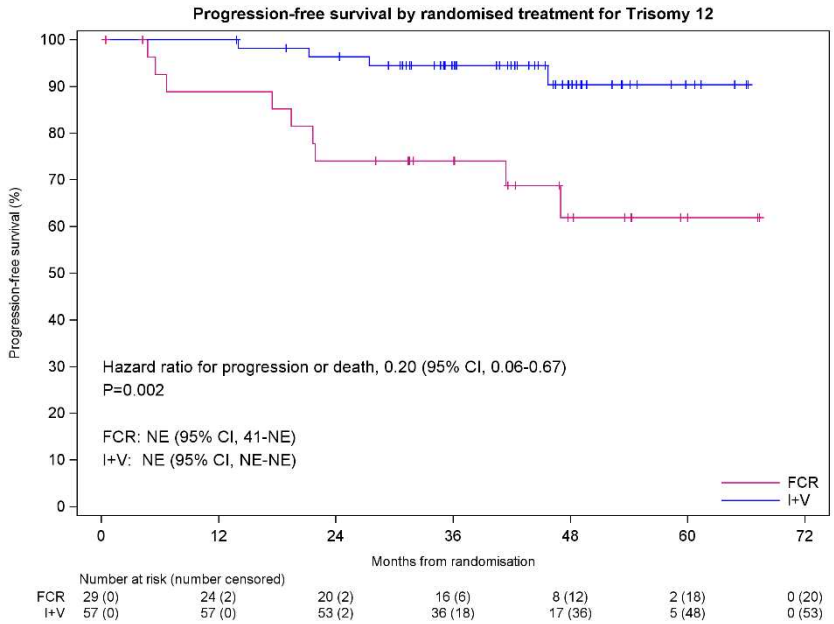
Figure S6: Progression-free survival by randomized treatment and hierarchical cluster (A) ATM deletion, (B) Trisomy 12, (C), Normal Karyotype (D) 13q deletion and (E) Undetermined

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

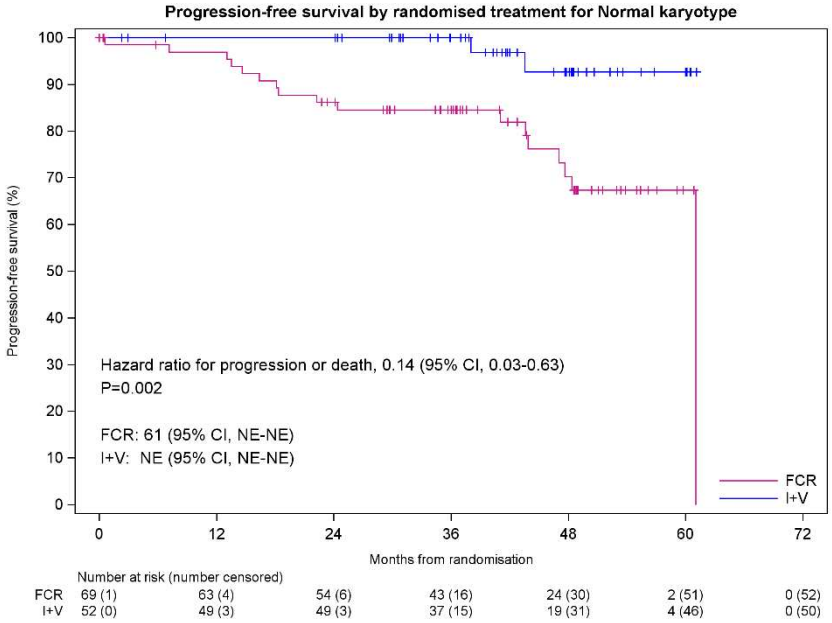
A



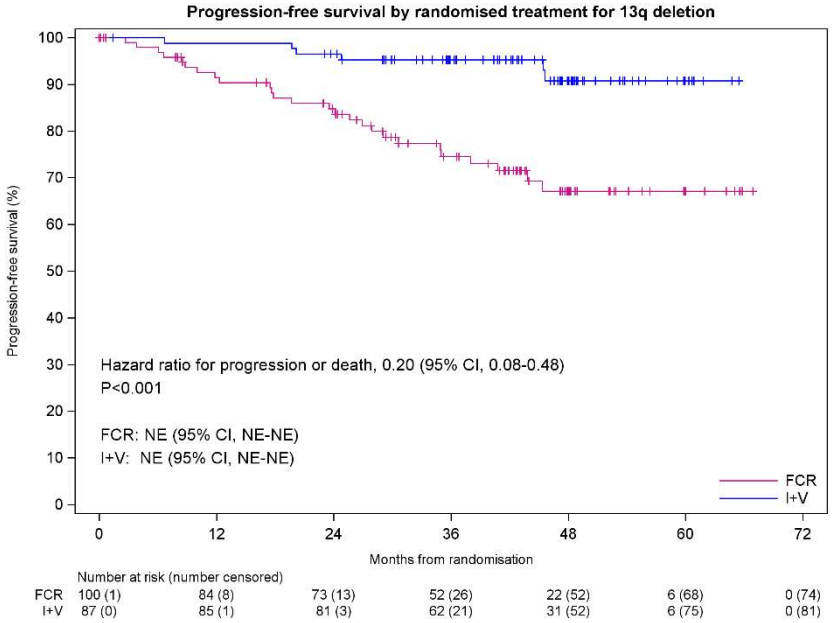
B



C


Progression-free survival by randomised treatment for Normal karyotype
Progression-free survival (%)
Hazard ratio for progression or death, 0.14 (95% CI, 0.03-0.63)
P=0.002
FCR: 61 (95% CI, NE-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
Months from randomisation
Number at risk (number censored)
FCR 69 (1) 63 (4) 54 (6) 43 (16) 24 (30) 2 (51) 0 (52)
I+V 52 (0) 49 (3) 49 (3) 37 (15) 19 (31) 4 (46) 0 (50)

D


Progression-free survival by randomised treatment for 13q deletion
Progression-free survival (%)
Hazard ratio for progression or death, 0.20 (95% CI, 0.08-0.48)
P<0.001
FCR: NE (95% CI, NE-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
Months from randomisation
Number at risk (number censored)
FCR 100 (1) 84 (8) 73 (13) 52 (26) 22 (52) 6 (68) 0 (74)
I+V 87 (0) 85 (1) 81 (3) 62 (21) 31 (52) 6 (75) 0 (81)

E

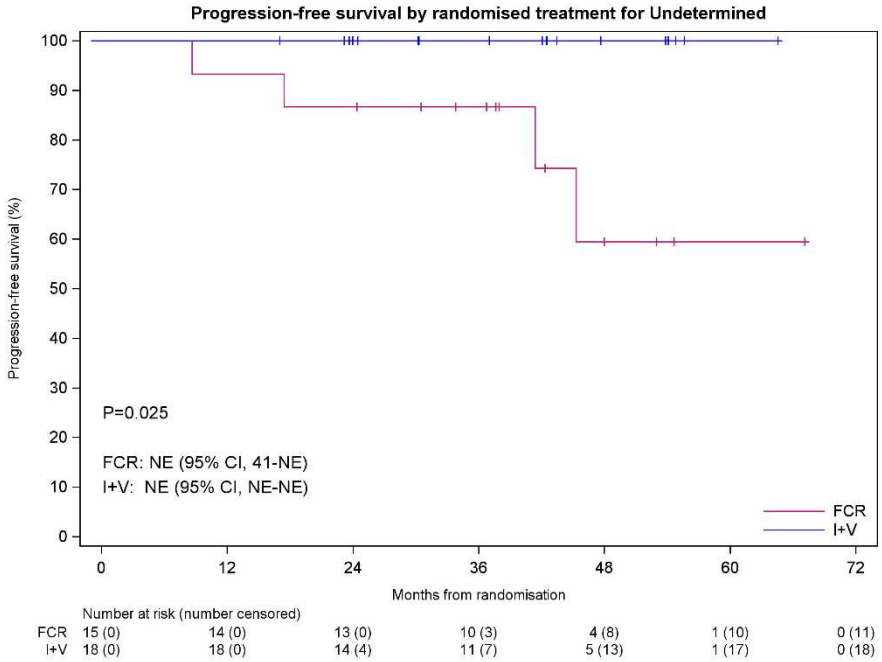
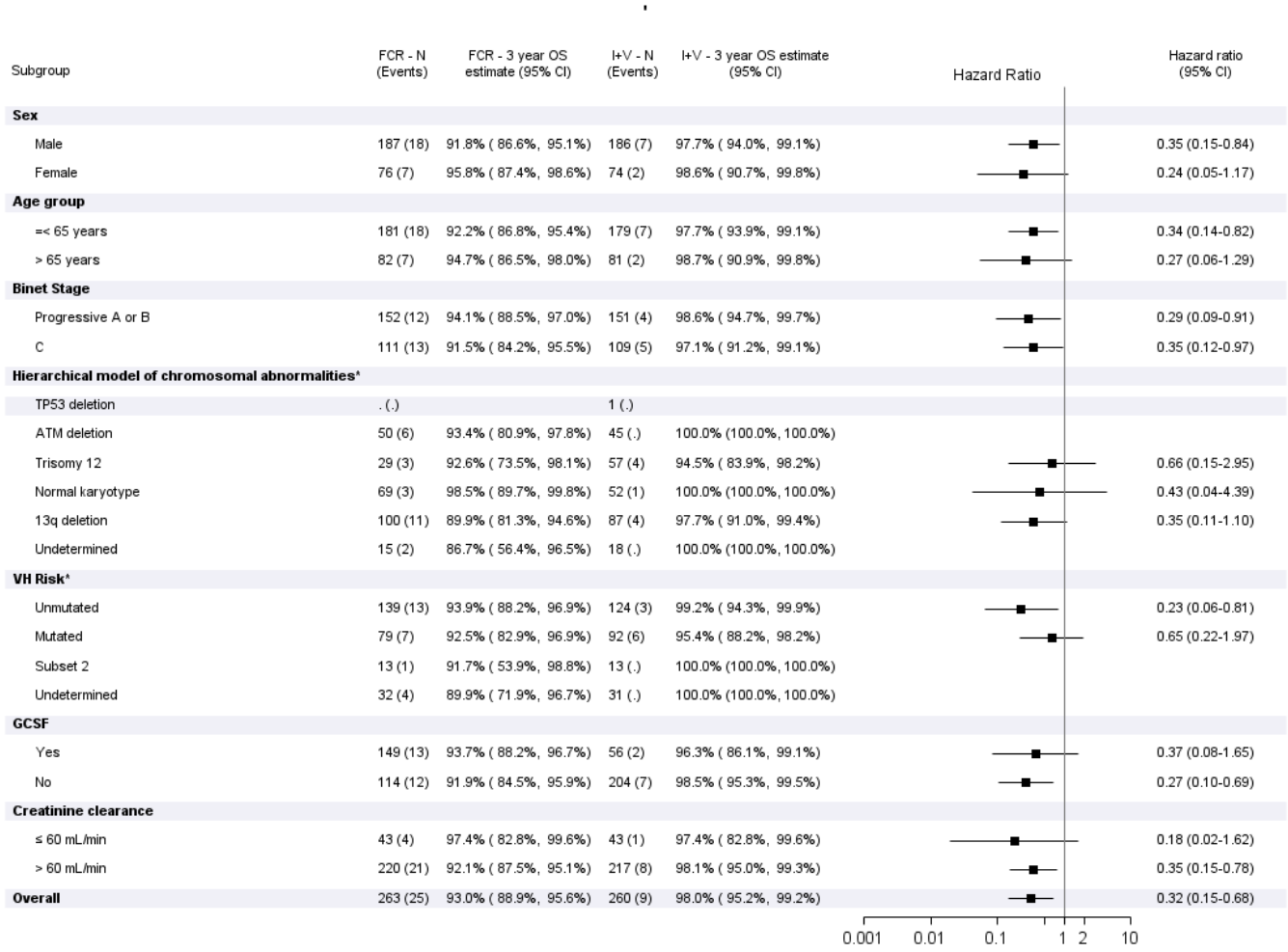

Progression-free survival by randomised treatment for Undetermined
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
P=0.025
FCR: NE (95% CI, 41-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
0
12
24
36
48
60
72
Months from randomisation
Number at risk (number censored)
FCR 15 (0) 14 (0) 13 (0) 10 (3) 4 (8) 1 (10) 0 (11)
I+V 18 (0) 18 (0) 14 (4) 11 (7) 5 (13) 1 (17) 0 (18)

Figure S7 Subgroup analysis for OS

Abbreviations: OS, overall survival; CI, confidence interval, FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax; G-CSF, granulocyte-colony stimulating factor.

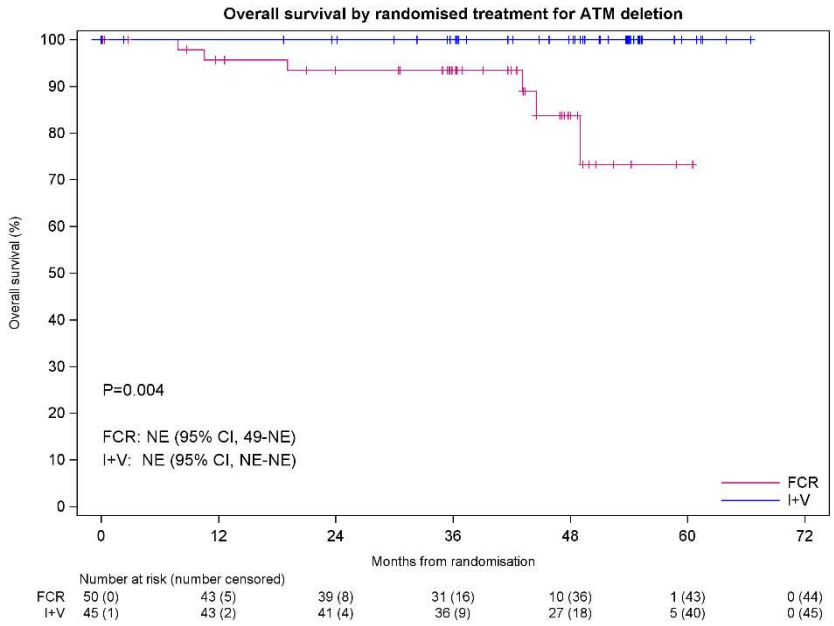


*Note that for subgroups without events, hazard ratios are inestimable and Kaplan-Meier plots in Figure S8 should be considered.

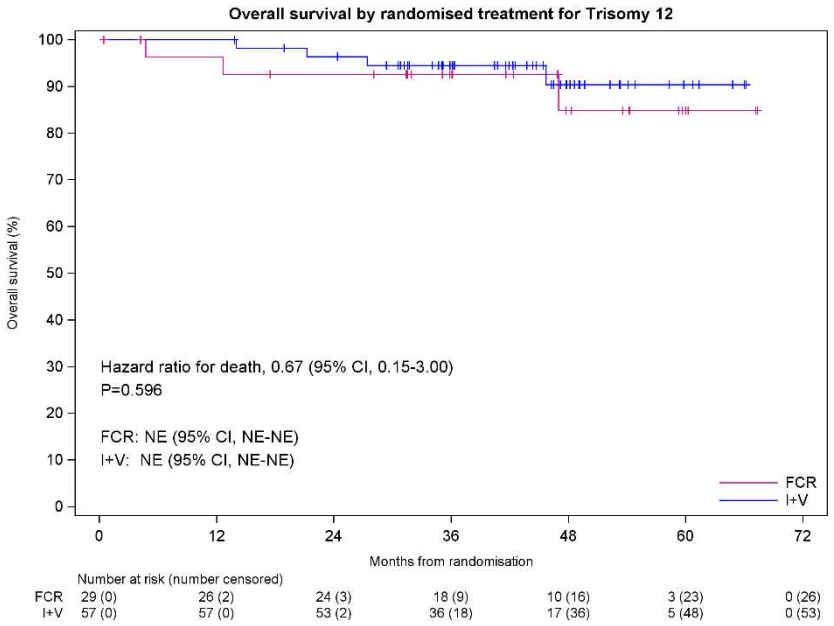
Figure S8: Overall survival by randomized treatment and hierarchical cluster (A) ATM deletion, (B) Trisomy 12, (C), Normal Karyotype (D) 13q deletion and (E) Undetermined

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

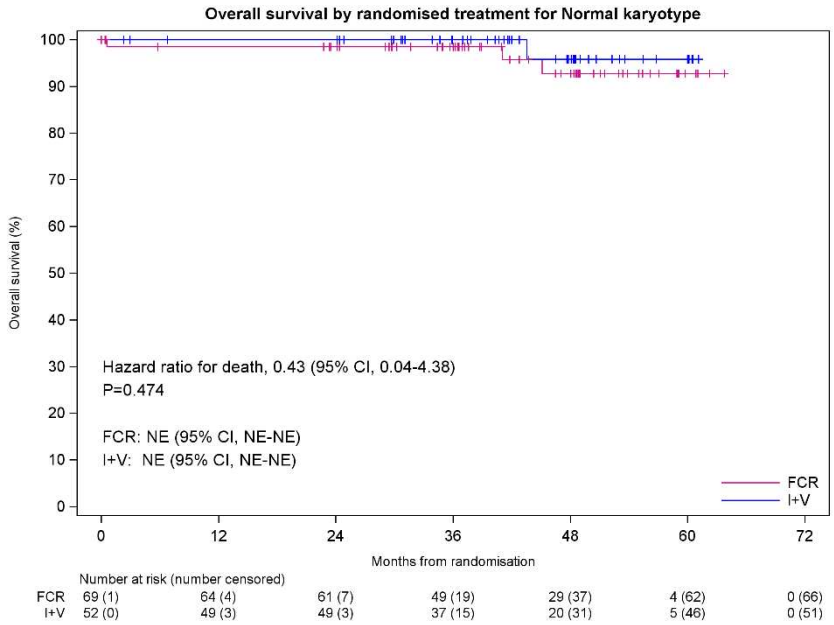
A



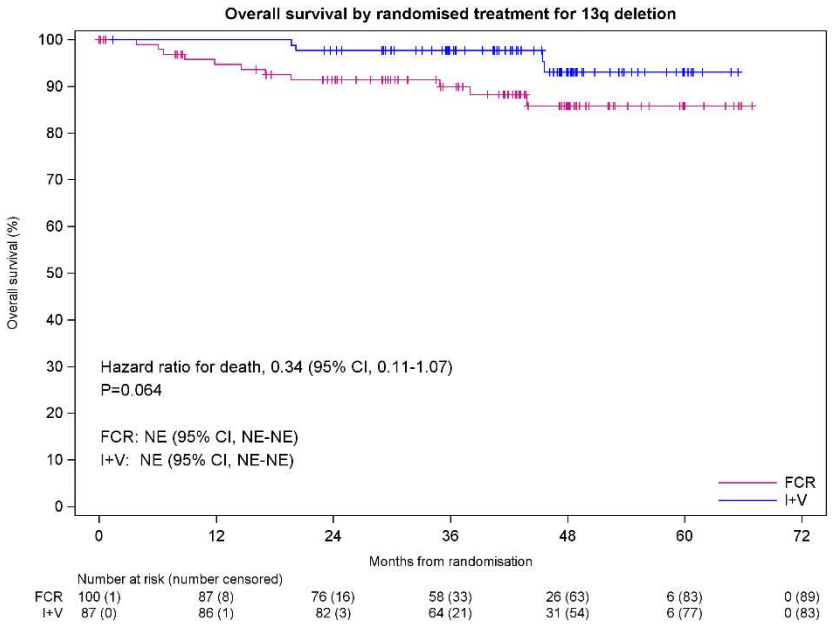
B



C


Overall survival by randomised treatment for Normal karyotype
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio for death, 0.43 (95% CI, 0.04-4.38)
P=0.474
FCR: NE (95% CI, NE-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
0
12
24
36
48
60
72
Months from randomisation
Number at risk (number censored)
FCR 69 (1) 64 (4) 61 (7) 49 (19) 29 (37) 4 (62) 0 (66)
I+V 52 (0) 49 (3) 49 (3) 37 (15) 20 (31) 5 (46) 0 (51)

D


Overall survival by randomised treatment for 13q deletion
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio for death, 0.34 (95% CI, 0.11-1.07)
P=0.064
FCR: NE (95% CI, NE-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
0
12
24
36
48
60
72
Months from randomisation
Number at risk (number censored)
FCR 100 (1) 87 (8) 76 (16) 58 (33) 26 (63) 6 (83) 0 (89)
I+V 87 (0) 86 (1) 82 (3) 64 (21) 31 (54) 6 (77) 0 (83)

E

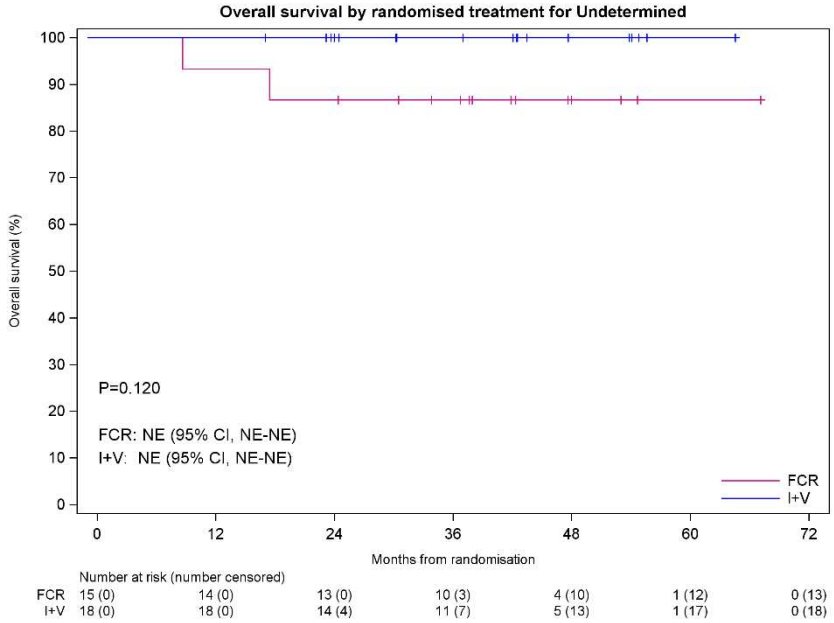
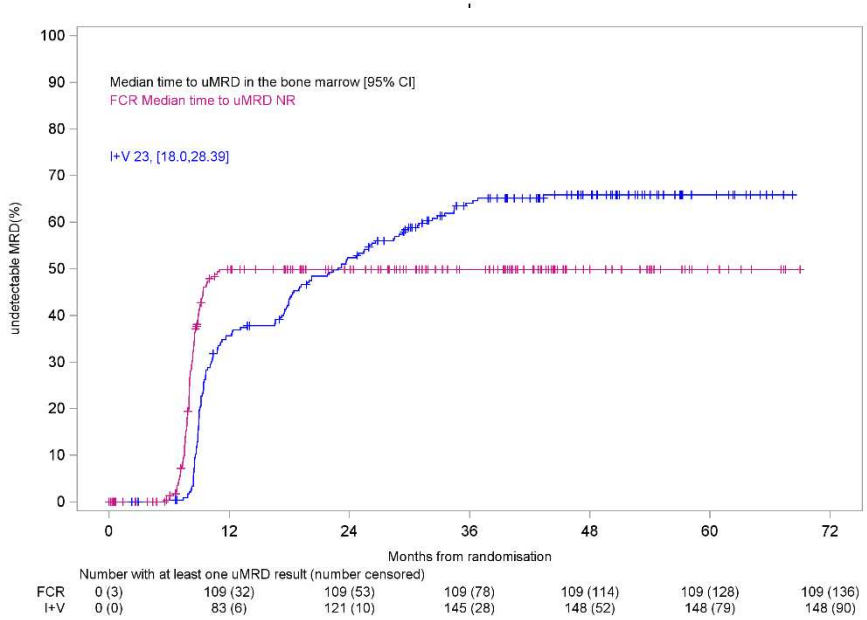

Overall survival by randomised treatment for Undetermined
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
P=0.120
FCR: NE (95% CI, NE-NE)
I+V: NE (95% CI, NE-NE)
FCR
I+V
0
12
24
36
48
60
72
Months from randomisation
Number at risk (number censored)
FCR 15 (0) 14 (0) 13 (0) 10 (3) 4 (10) 1 (12) 0 (13)
I+V 18 (0) 18 (0) 14 (4) 11 (7) 5 (13) 1 (17) 0 (18)

Figure S9: Time to undetectable MRD (uMRD), by allocated group (A) in the bone marrow in all participants, (B) in the peripheral blood in all participants, (C) in the bone marrow in participants with unmutated IGHV, (D) in the peripheral blood in participants with unmutated IGHV, (E) in the bone marrow in participants with mutated IGHV, (F) in the peripheral blood in participants with mutated IGHV

Abbreviations: FCR, fludarabine, cyclophosphamide, and rituximab; I+V, ibrutinib plus venetoclax.

A



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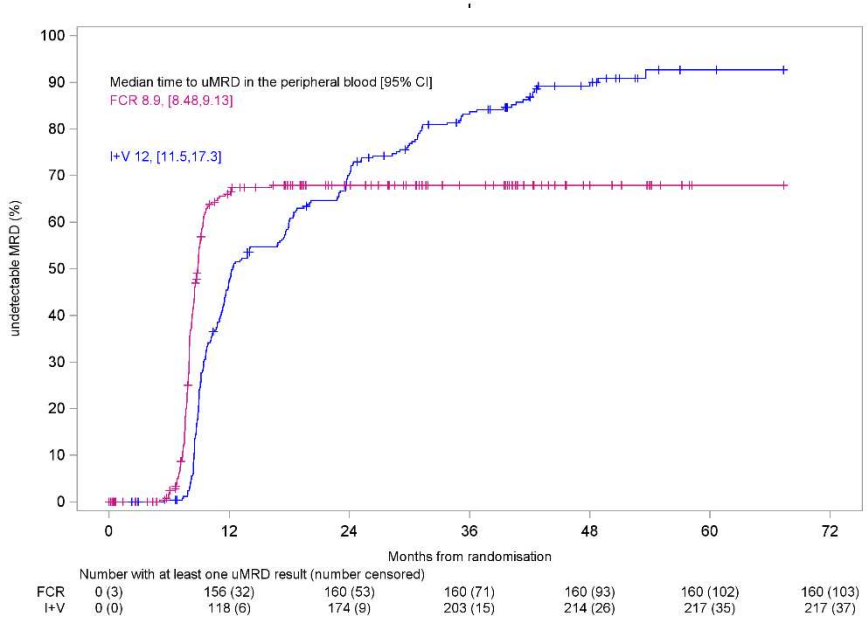

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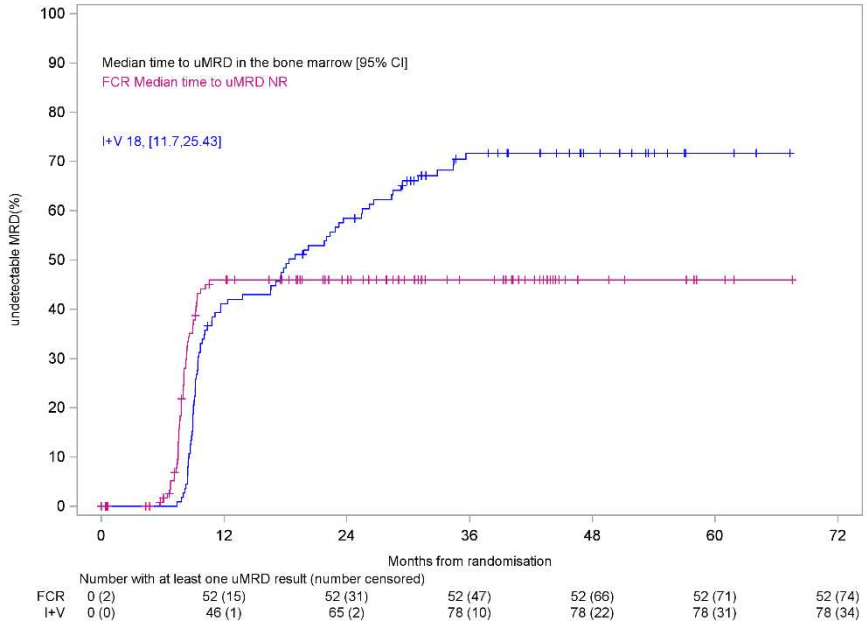
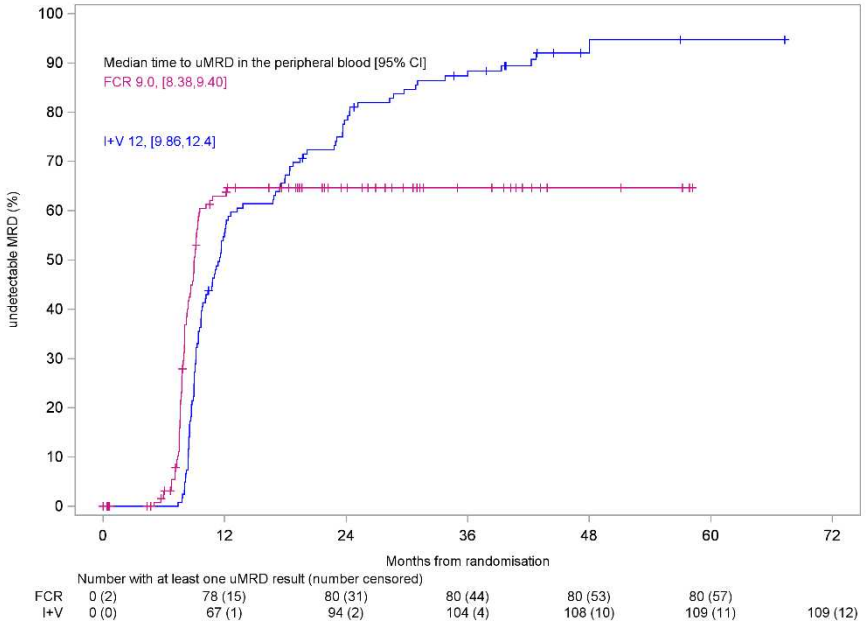
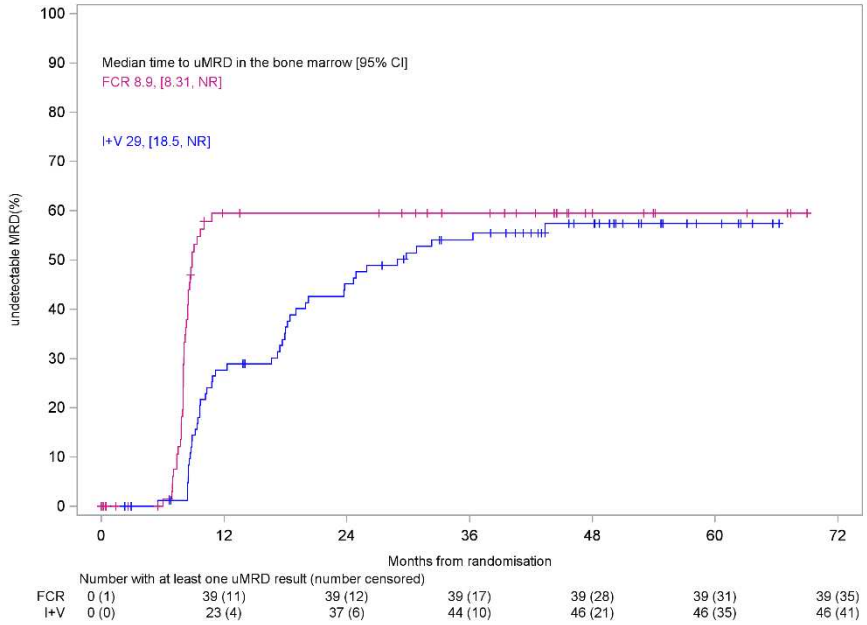

Median time to uMRD in the bone marrow [95% CI]
FCR Median time to uMRD NR
I+V 18, [11.7,25.43]
undetectable MRD(%)
Months from randomisation
Number with at least one uMRD result (number censored)
FCR 0 (2) 52 (15) 52 (31) 52 (47) 52 (66) 52 (71) 52 (74)
I+V 0 (0) 46 (1) 65 (2) 78 (10) 78 (22) 78 (31) 78 (34)

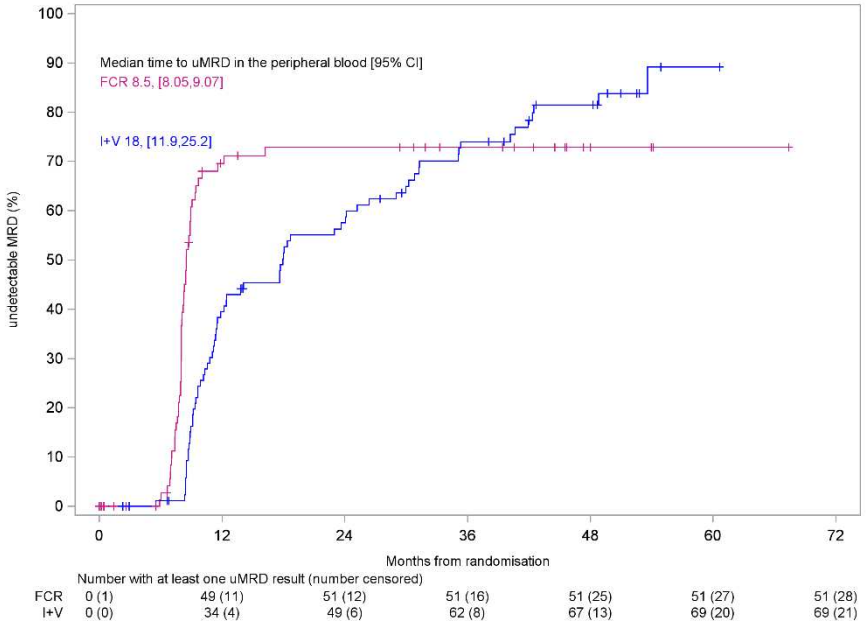
D


Median time to uMRD in the peripheral blood [95% CI]
FCR 9.0, [8.38,9.40]
I+V 12, [9.86,12.4]
undetectable MRD (%)
Months from randomisation
Number with at least one uMRD result (number censored)
FCR 0 (2) 78 (15) 80 (31) 80 (44) 80 (53) 80 (57)
I+V 0 (0) 67 (1) 94 (2) 104 (4) 108 (10) 109 (11) 109 (12)

E


Median time to uMRD in the bone marrow [95% CI]
FCR 8.9, [8.31, NR]
I+V 29, [18.5, NR]
undetectable MRD(%)
Months from randomisation
Number with at least one uMRD result (number censored)
FCR 0 (1) 39 (11) 39 (12) 39 (17) 39 (28) 39 (31) 39 (35)
I+V 0 (0) 23 (4) 37 (6) 44 (10) 46 (21) 46 (35) 46 (41)

F


Median time to uMRD in the peripheral blood [95% CI]
FCR 8.5, [8.05,9.07]
I+V 18, [11.9,25.2]
undetectable MRD (%)
Months from randomisation
Number with at least one uMRD result (number censored)
FCR 0 (1) 49 (11) 51 (12) 51 (16) 51 (25) 51 (27) 51 (28)
I+V 0 (0) 34 (4) 49 (6) 62 (8) 67 (13) 69 (20) 69 (21)

References

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