First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial

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Summary

Background In the primary analysis report of the GAIA/CLL13 trial, we found that venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib improved undetectable measurable residual disease (MRD) rates and progression-free survival compared with chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukaemia. However, to our knowledge, no data on direct comparisons of different venetoclax-based combinations are available.

Methods GAIA/CLL13 is an open-label, randomised, phase 3 study conducted at 159 sites in ten countries in Europe and the Middle East. Eligible patients were aged 18 years or older, with a life expectancy of at least 6 months, an Eastern Cooperative Oncology group performance status of 0–2, a cumulative illness rating scale score of 6 or lower or a single score of 4 or lower, and no *TP53* aberrations. Patients were randomly assigned (1:1:1:1), with a computer-generated list stratified by age, Binet stage, and regional study group, to either chemoimmunotherapy, venetoclax–rituximab, venetoclax–obinutuzumab, or venetoclax–obinutuzumab–ibrutinib. All treatments were administered in 28-day cycles. Patients in the chemoimmunotherapy group received six cycles of treatment, with patients older than 65 years receiving intravenous bendamustine (90 mg/m², days 1–2), whereas patients aged 65 years or younger received intravenous fludarabine (25 mg/m², days 1–3) and intravenous cyclophosphamide (250 mg/m², days 1–3). Intravenous rituximab (375 mg/m², day 1 of cycle 1; 500 mg/m², day 1 of cycles 2–6) was added to chemotherapy. In the experimental groups, patients received daily venetoclax (400 mg orally) for ten cycles after a 5-week ramp-up phase starting on day 22 of cycle 1. In the venetoclax–rituximab group, intravenous rituximab (375 mg/m², day 1 of cycle 1; 500 mg/m², day 1 of cycles 2–6) was added. In the obinutuzumab-containing groups, obinutuzumab was added (cycle 1: 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15; cycles 2–6: 1000 mg on day 1). In the venetoclax–obinutuzumab–ibrutinib group, daily ibrutinib (420 mg orally, from day 1 of cycle 1) was added until undetectable MRD was reached in two consecutive measurements (3 months apart) or until cycle 36. The planned treatment duration was six cycles in the chemoimmunotherapy group, 12 cycles in the venetoclax–rituximab and the venetoclax–obinutuzumab group and between 12 and 36 cycles in the venetoclax–obinutuzumab–ibrutinib group. Coprimary endpoints were the undetectable MRD rate in peripheral blood at month 15 for the comparison of venetoclax-obinutuzumab versus standard chemoimmunotherapy and investigator-assessed progression-free survival for the comparison of venetoclax-obinutuzumab-ibrutinib versus standard chemoimmunotherapy, both analysed in the intention-to-treat population (ie, all patients randomly assigned to treatment) with a split α of 0·025 for each coprimary endpoint. Both coprimary endpoints have been reported elsewhere. Here we report a post-hoc exploratory analysis of updated progression-free survival results after a 4-year follow-up of our study population. Safety analyses included all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT02950051, recruitment is complete, and all patients are off study treatment.

Findings Between Dec 13, 2016, and Oct 13, 2019, 1080 patients were screened and 926 were randomly assigned to treatment (chemoimmunotherapy group n=229; venetoclax–rituximab group n=237; venetoclax–obinutuzumab group n=229; and venetoclax–obinutuzumab–ibrutinib group n=231); mean age 60·8 years (SD 10·2), 259 (28%) of 926 patients were female, and 667 (72%) were male (data on race and ethnicity are not reported). At data cutoff for this exploratory follow-up analysis (Jan 31, 2023; median follow-up 50·7 months [IQR 44·6–57·9]), patients in the venetoclax–obinutuzumab group had significantly longer progression-free survival than those in the chemoimmunotherapy group (hazard ratio [HR] 0·47 [97·5% CI 0·32–0·69], p<0·0001) and the venetoclax–rituximab group (0·57 [0·38–0·84], p=0·0011). The venetoclax–obinutuzumab–ibrutinib group also had a significantly longer progression-free survival than the chemoimmunotherapy group (0·30 [0·19–0·47]; p<0·0001) and the

venetoclax–rituximab group (0·38 [0·24–0·59]; p<0·0001). There was no difference in progression-free survival between the venetoclax–obinutuzumab–ibrutinib and venetoclax–obinutuzumab groups (0·63 [0·39–1·02]; p=0·031), and the proportional hazards assumption was not met for the comparison between the venetoclax–rituximab group versus the chemoimmunotherapy group (log-rank p=0·10). The estimated 4-year progression-free survival rate was 85·5% (97·5% CI 79·9–91·1; 37 [16%] events) in the venetoclax–obinutuzumab–ibrutinib group, 81·8% (75·8–87·8; 55 [24%] events) in the venetoclax–obinutuzumab group, 70·1% (63·0–77·3; 84 [35%] events) in the venetoclax–rituximab group, and 62·0% (54·4–69·7; 90 [39%] events) in the chemoimmunotherapy group. The most common grade 3 or worse treatment-related adverse event was neutropenia (114 [53%] of 216 patients in the chemoimmunotherapy group, 109 [46%] of 237 in the venetoclax–rituximab group, 127 [56%] of 228 in the venetoclax–obinutuzumab group, and 112 [48%] of 231 in the venetoclax–obinutuzumab–ibrutinib group). Deaths determined to be associated with study treatment by the investigator occurred in three (1%) patients in the chemoimmunotherapy group (n=1 due to each of sepsis, metastatic squamous cell carcinoma, and Richter's syndrome), none in the venetoclax–rituximab and venetoclax–obinutuzumab groups, and four (2%) in the venetoclax–obinutuzumab–ibrutinib group (n=1 due to each of acute myeloid leukaemia, fungal encephalitis, small-cell lung cancer, and toxic leukoencephalopathy).

Interpretation With more than 4 years of follow-up, venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib significantly extended progression-free survival compared with both chemoimmunotherapy and venetoclax–rituximab in previously untreated, fit patients with chronic lymphocytic leukaemia, thereby supporting their use and further evaluation in this patient group, while still considering the higher toxicities observed with the triple combination.

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Research in context

Evidence before this study

We searched PubMed for reports of randomised phase 3 trials published between database inception and March 6, 2024, using the terms "chronic lymphocytic leuk(a)emia" OR "CLL" AND "venetoclax" AND "obinutuzumab", with and without "ibrutinib". We identified the CLL14 and GAIA/CLL13 trials as the only two phase 3 trials comparing venetoclax–obinutuzumab with chemoimmunotherapy and the GAIA/CLL13 trial as the only phase 3 trial to investigate a triple combination of venetoclax, a CD20 antibody, and a BTK inhibitor in patients with chronic lymphocytic leukaemia. Based on the superiority of venetoclax–obinutuzumab over chlorambucil–obinutuzumab in the CLL14 trial in a patient population with coexisting conditions, the combination was approved by the European Medicines Agency in March, 2020, and the US Food and Drug Administration in May, 2019, and widely adopted. The primary efficacy analysis of the GAIA/CLL13 trial confirmed both the superiority of the fixed-duration venetoclax–obinutuzumab combination over chemoimmunotherapy (bendamustine–rituximab or fludarabine–cyclophosphamide–rituximab) and the superiority of venetoclax–obinutuzumab–ibrutinib over chemoimmunotherapy with regards to progression-free survival in a younger, fitter patient cohort. To the best of our knowledge no direct comparisons of different venetoclax-based combinations within randomised clinical trials have been published to date.

Added value of this study

To our knowledge, this 4-year update of the GAIA/CLL13 trial is the first study to directly compare different time-limited venetoclax-based combinations in patients with previously untreated chronic lymphocytic leukaemia. Our findings confirmed the superiority of both venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib over chemoimmunotherapy and venetoclax–rituximab, with longer progression-free survival and time to next treatment and high rates of undetectable measurable residual disease (as reported in the primary analysis report). Furthermore, in patients with unmutated *IGHV*, the MRD-guided triple combination was associated with longer progression-free survival than venetoclax–obinutuzumab while showing higher incidence rates of infections and cardiac events. The study also provides evidence on sequencing and re-exposure of targeted agents after a time-limited first-line treatment of chronic lymphocytic leukaemia.

Implications of all the available evidence

The results of this follow-up analysis support the use of venetoclax–obinutuzumab in fit patients with previously untreated chronic lymphocytic leukaemia and encourages a further evaluation of the MRD-guided combination of venetoclax–obinutuzumab–ibrutinib, especially in patients with unmutated *IGHV*. Ongoing trials (FLAIR [ISRCTN01844152], ALLIANCE A041702 [NCT03737981], ECOG-ACRIN EA9161 [NCT03701282], MAJIC [NCT05057494], CLL17 [NCT04608318], and CLL16 [NCT05197192]) will generate further evidence by comparing time-limited treatments with continuous treatments, or venetoclax–obinutuzumab with venetoclax–BTK inhibitor-based double or triple combinations.

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Introduction

Various chemotherapy-free treatment options have been approved for the treatment of chronic lymphocytic leukaemia.[1–7] Whereas BTK inhibitors are mostly used as continuous monotherapies, venetoclax-based treatments have been established as fixed-duration therapies. The trials leading to approval of fixed-duration treatments with venetoclax–obinutuzumab and venetoclax–ibrutinib were conducted in patient populations deemed unfit for intensive chemoimmunotherapeutic treatment and thus they used chlorambucil–obinutuzumab as a control group, which was considered a standard of care at the time.[1,3] The GAIA/CLL13 trial[2] was the first randomised study to report results on different time-limited venetoclax-based treatments in relatively young and fit patients with chronic lymphocytic leukaemia (ie, with a median age of 61 years and a median cumulative illness rating scale score of 2), thereby closing this gap in evidence. In the primary efficacy analysis, improved undetectable measurable residual disease (MRD) rates and progression-free survival were reported for patients treated with venetoclax–obinutuzumab or venetoclax–obinutuzumab–ibrutinib versus the chemoimmunotherapy group, who received fludarabine–cyclophosphamide–rituximab or bendamustine–rituximab depending on patient age.[2] Although time-limited doublets of novel agents have been evaluated for the first-line treatment of chronic lymphocytic leukaemia, few randomised clinical trials have been published on the value of triple combinations.[8–10] Similarly, MRD-guided treatment approaches have so far mostly been studied in phase 2 trials, despite their promising results.[11–15] Furthermore, to our knowledge, direct comparisons between venetoclax–rituximab and venetoclax–obinutuzumab have not been performed to date, although increasing evidence supports the superiority of obinutuzumab over rituximab in the treatment of chronic lymphocytic leukaemia.[16]

With all patients off treatment, in this post-hoc exploratory 4-year follow-up analysis of the GAIA/CLL13 trial, we aimed to assess the added value of an MRD-guided triple combination, the effect of different CD20 antibodies on outcome, and the prognostic value of MRD at the end of treatment.

Methods

Study design and participants

The GAIA/CLL13 trial is an ongoing, investigator-initiated, open-label, randomised, phase 3 study conducted at 159 sites (including university hospitals, private hospitals, and outpatient clinics) in ten countries in Europe and the Middle East (appendix pp 3–7). Key eligibility criteria were age 18 years or older, previously untreated and active chronic lymphocytic leukaemia requiring treatment per international workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, life expectancy of at least 6 months, an Eastern Cooperative Oncology group performance status of 0–2, a good fitness defined as a cumulative illness rating scale score[17] of 6 or lower or a single score of 4 or lower, and a creatinine clearance of at least 70 mL/min. Patients with *TP53* mutations as detected by Sanger sequencing or deletion 17p as detected by fluorescence in-situ hybridisation, or both, were not eligible for participation. The complete list of eligibility criteria is in the study protocol (appendix).

Written informed consent was provided before enrolment and the trial protocol was approved by the responsible health authorities and institutional review boards. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline. The GAIA/CLL13 study is registered with ClinicalTrials.gov, NCT02950051.

Randomisation and masking

Patients were randomly assigned (1:1:1:1), with an interactive voice and web response system and a computer-generated randomisation list prepared by Almac Clinical Technologies (Craigavon, Northern Ireland), to either chemoimmunotherapy (control group), venetoclax–rituximab, venetoclax–obinutuzumab, or venetoclax–obinutuzumab–ibrutinib. Balanced randomisation was ensured using block randomisation with block sizes of twelve, comprising one sub-block of size four and one sub-block of size eight in random order. Sponsors and investigators were masked to the size of each block. Randomisation was stratified according to age (≤65 *vs* >65 years), Binet stage at screening (A *vs* B *vs* C), and regional study group (German CLL Study Group *vs* Stichting Hemato-Oncologie voor Volwassenen Nederland *vs* Nordic CLL Study Group *vs* Cancer Trials Ireland *vs* Israeli CLL Study Group *vs* Swiss Group for Clinical Cancer Research). Investigators and patients were not masked to treatment assignments. An independent data and safety monitoring board reviewed safety data on a regular basis and were not masked to treatment assignment.

Procedures

All treatments were administered in 28-day cycles. In the chemoimmunotherapy group, patients received six cycles of chemoimmunotherapy. Patients older than 65 years received intravenous bendamustine (90 mg/m² of body surface area per day, days 1–2) and patients aged 65 years or younger received intravenous fludarabine (25 mg/m², days 1–3) and intravenous cyclophosphamide (250 mg/m², days 1–3). Intravenous rituximab (375 mg/m² on day 1 of cycle 1; 500 mg/m² on day 1 of cycles 2–6) was added to chemotherapy. In the three experimental treatment groups, patients received venetoclax at a daily dose of 400 mg orally for ten cycles after a standard 5-week ramp-up phase starting on day 22 of cycle 1. In the venetoclax–rituximab group, intravenous rituximab (375 mg/m² day 1 of cycle 1; 500 mg/m² day 1 of cycles 2–6) was added

See Online for appendix

to venetoclax. In the obinutuzumab-containing groups, intravenous obinutuzumab was added at a dose of 100 mg on day 1, 900 mg on day 2, and then 1000 mg on day 8 and 15 of cycle 1. On day 1 of the following five cycles, obinutuzumab was administered at a dose of 1000 mg. In the venetoclax–obinutuzumab–ibrutinib group, ibrutinib was given at a daily dose of 420 mg orally starting from day 1 of cycle 1. If undetectable MRD (below 1×10^{-4}; ie, less than 1 chronic lymphocytic leukaemia cell per 10 000 normal leukocytes) was reached in two consecutive measurements in peripheral blood 3 months apart (ie, at cycles 9 and 12 or cycles 12 and 15) or in peripheral blood and a consecutive bone marrow aspiration, treatment with ibrutinib was stopped. In case of detectable MRD, ibrutinib was continued until the end of cycle 36 or until unacceptable toxicity occurred. The planned treatment duration was six cycles in the chemoimmunotherapy group, 12 cycles in the venetoclax–rituximab and the venetoclax–obinutuzumab group, and between 12 and 36 cycles in the venetoclax–obinutuzumab–ibrutinib group. For all treatment groups, use of granulocyte colony stimulating factor (G-CSF) was recommended for grade 4 neutropenia and according to local and international guidelines but not in general as a prophylactic measure to prevent granulocytopenia. Infection prophylaxis with cotrimoxazole was generally recommended according to local guidelines until at least month 15; no specific azole or antiviral prophylaxis was recommended. Data were collected on administration of these prophylactic treatments (not reported here). There were no recommendations for specific second-line treatments within the trial. Treatment interruptions and modifications of study drug doses were per manufacturer guidelines and details are in the protocol (appendix).

CT or MRI scans were done at screening and at final restaging, which was 2 months after the completion of treatment. Response assessment followed the 2008 guidelines of the iwCLL and was performed locally.[18] Other assessments done at screening (ie, baseline) included karyotyping, fluorescence in-situ hybridisation, immunophenotyping, mutational analysis of *IGHV* and *TP53*, and assessment of lymph node and spleen size by physical examination. MRD was analysed centrally according to international guidelines[19] by four-colour flow cytometry and an academic immunoglobulin-based next-generation sequencing assay. MRD was assessed via peripheral blood, samples of which were taken from all patients at baseline and at the start of cycles 2, 9, 12, and 15. Data on participant sex were collected from electronic medical records where possible and otherwise self-reported. Data on race and ethnicity were not collected in this trial.

Adverse events were reported from first dose of study drug until 28 days after the last dose of study treatment. Patients were followed up in person for safety at least once a month while on treatment, at least once every 6 months after final restaging, and at least once a year after a clinical disease progression, until the end of the study. Adverse events were reported according to Common Terminology Criteria for Adverse Events (version 4.0) and the MedDRA classification system. Reporting of adverse events of interest (ie, hepatitis B reactivation, infections, cardiac events, grade ≥3 late onset neutropenia, autoimmune complications, second primary malignancies, and Richter's transformations) was required until the start of the next treatment, and all serious adverse events, autoimmune complications, and secondary malignancies were to be reported until the end of the study. Treatment-emergent adverse events were defined as adverse events that occurred within 84 days after the last dose of study treatment or initiation of next treatment for chronic lymphocytic leukaemia, whichever was earlier, with the exception of secondary malignancies and deaths, which were assigned as treatment-emergent without any time limitations. Association of adverse events and deaths with treatment was determined by local investigators. Tumour lysis syndromes were reported according to Cairo and Bishop criteria.[20]

Outcomes

The GAIA/CLL13 trial had two coprimary endpoints that were analysed and interpreted independently, and have already been published elsewhere. The first coprimary endpoint was the rate of undetectable MRD in peripheral blood at month 15 for the comparison of venetoclax–obinutuzumab versus chemoimmunotherapy. The second coprimary endpoint was investigator-assessed progression-free survival, defined as the time from randomisation to disease progression or death from any cause for the comparison of venetoclax–obinutuzumab–ibrutinib versus chemoimmunotherapy and then for comparisons of all treatment groups following a predefined hierarchical test sequence. The secondary endpoints were rates of undetectable MRD in peripheral blood at month 15 for all other comparisons; rates of undetectable MRD in peripheral blood at months 2, 9, and 12 rate of undetectable MRD in bone marrow at final restaging; progression-free survival for all other comparisons; overall response rate (defined as the rate of complete response, complete response with incomplete bone marrow recovery, or partial response) at months 3, 6, 9, 12, and 15; complete response rate (defined as the rate of complete response or complete response with incomplete bone marrow recovery) at months 9, 12, and 15; duration of response in patients with a complete or partial response; safety; overall survival (defined as the time from randomisation to death from any cause); event-free survival (defined as the time from randomisation to disease progression, initiation of next treatment for chronic lymphocytic leukaemia, or death from any cause); time to the next treatment for chronic lymphocytic leukaemia (defined as the time between randomisation and initiation of next treatment for chronic lymphocytic leukaemia); and health-related quality of life using European Organisation for Research and Treatment

of Cancer QLQ-C30 and QLQ-CLL16 surveys. Response rates and MRD rates have been published elsewhere[2] and health-related quality of life data will be reported elsewhere.

Statistical analysis

We estimated the sample size on the basis of both coprimary endpoints with a split two-sided α level of 0·025 for each hypothesis, and we assumed the outcomes of the standard of care group (chemoimmunotherapy) on the basis of the results of the CLL10 study.[21] To assess the superiority of venetoclax–obinutuzumab over chemoimmunotherapy with regard to undetectable MRD at month 15, we assumed at least 80% power to detect a difference of 20 percentage points (from 30% for chemoimmunotherapy to 50% for venetoclax–obinutuzumab) using a Cochran-Mantel-Haenszel test stratified by age (≤65 years *vs* >65 years) and Binet stage (A *vs* B *vs* C). To assess the superiority of venetoclax–obinutuzumab–ibrutinib over chemoimmunotherapy with regard to progression-free survival, we assumed a hazard ratio (HR) for progression or death of 0·65, with 213 events providing a power of approximately 80% based on a two-sided log-rank test stratified according to age (≤65 years *vs* >65 years) and Binet stage (A *vs* B *vs* C). We aimed to enrol 920 patients to establish balance. We did not account for attrition and censoring proportions as part of the sample size calculation.

The coprimary endpoint of undetectable MRD was analysed using a data cutoff date of Feb 28, 2021. The primary analysis of the coprimary endpoint progression-free survival was performed with a data cutoff date of Jan 20, 2022, following the recommendation of the independent data and safety monitoring board because the p value of the pre-planned interim analysis was lower than the prespecified statistical boundary using a Lan-DeMets α-spending function with an O'Brien-Fleming boundary (93 investigator-assessed events observed *vs* 138 events expected at the time of interim analysis, which was conducted 61 months after random assignment of the first patient; required p≤0·000393).[2]

All efficacy endpoints were analysed in the intention-to-treat (ITT) population, defined as all patients randomly assigned to treatment. Safety analyses were performed in the safety population, defined as all patients who had received at least one dose of study treatment. For response outcomes, if clinical response could be evaluated (ie, by physical examination), participants were included in analyses; however, if the whole response (ie, clinical and radiological) was not assessable, they were counted as missing.

Patients without an event for progression-free survival (ie, who have not progressed, relapsed, or died) were censored at the date of the last tumour assessment. If a subsequent treatment for chronic lymphocytic leukaemia was initiated in patients without a progression-free survival event, they were censored at the date of the last tumour assessment performed before start of the subsequent treatment. Patients without an event for overall survival (ie, who have not died), event-free survival (ie, who have not started a subsequent treatment for chronic lymphocytic leukaemia, progressed, relapsed, or died), or time to next treatment (ie, who have not started a subsequent treatment for chronic lymphocytic leukaemia) were censored at the date of last contact. Events for time-to-event endpoints (ie, disease progression, initiation of next treatment for chronic lymphocytic leukaemia, and death from any cause) were reported from randomisation until end of participation in the trial.

Here, we report a post-hoc analysis of prespecified endpoints at 4-year follow-up. There was no α spending allocated to this follow-up analysis and hence it is an exploratory analysis. All statistical tests were two-sided and p values were descriptive without adjustments for multiple testing. The significance level was set at 0·025 for the analyses of primary and secondary endpoints and at 0·05 for exploratory subgroup analyses.

We used Kaplan–Meier estimates to analyse time to event data, 97·5% and 95% CIs for these estimates were calculated on the basis of Greenwood's formula. We assumed censoring to be non-informative on the basis of the censoring criteria. We did comparisons of time to event data using log-rank tests and Cox proportional hazards regression modelling when the proportional hazards assumption was satisfied according to Schoenfeld residuals (appendix pp 75–76); if the proportional hazards assumption was not satisfied, then HRs were not calculated. For analyses of progression-free survival comparing different treatment groups, we used the stratification factors of age (≤65 years and >65 years) and Binet stage (A *vs* B *vs* C). For analyses of overall survival and time to next treatment, as well as for exploratory subgroup analyses, we did not use any stratification factors.

In an exploratory subgroup analysis, progression-free survival across treatment groups by *IGHV* mutation status was assessed via Kaplan–Meier analysis and Cox proportional hazards modelling. Progression-free survival was also assessed for venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib treatments groups compared with chemoimmunotherapy and venetoclax–rituximab and with each other for subgroups defined by Binet stage at screening (A *vs* B *vs* C), age group (≤65 years *vs* >65 years), karyotype (non-complex karyotypes *vs* complex karyotypes), cytogenetic subgroups per hierarchy (11q deletion *vs* trisomy 12 *vs* no abnormalities *vs* 12q deletion), serum β_2-microglobulin (≤3·5 mg/L *vs* >3·5 mg/L), and *IGHV* mutational status (mutated *vs* unmutated).

In exploratory subgroup analyses we compared progression-free survival, time to next treatment, and overall survival between patients in the chemoimmunotherapy group who received fludarabine plus cyclophosphamide plus rituximab and patients who received bendamustine plus rituximab, overall and

further divided by *IGHV* status and 15-month MRD status. Furthermore, we performed exploratory subgroup analyses on time to next treatment according to *IGHV* status.

As additional exploratory objectives, landmark analyses from initiation of first subsequent treatment for chronic lymphocytic leukaemia were done with regard to type of second-line treatment (venetoclax-based *vs* BTK

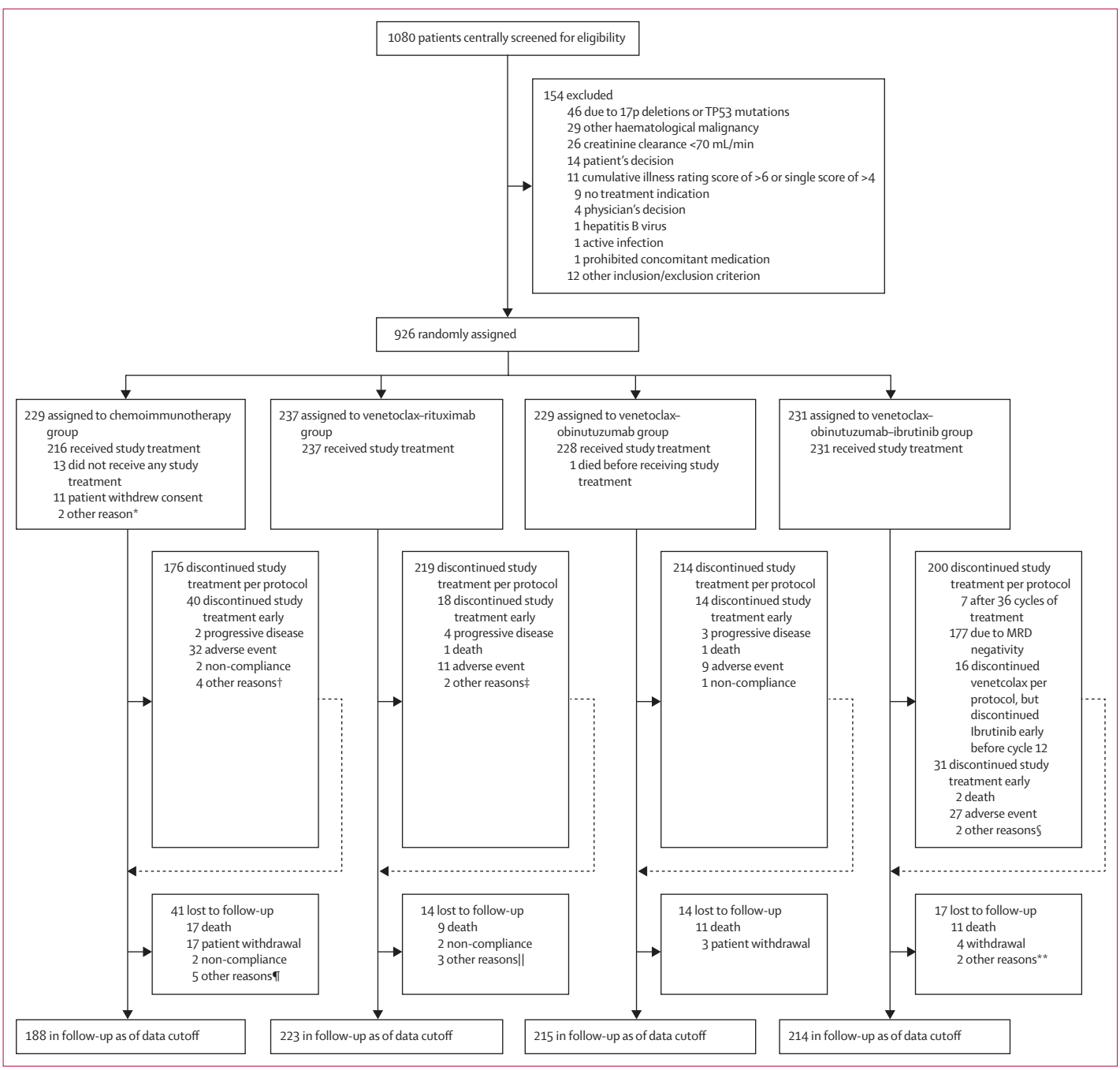
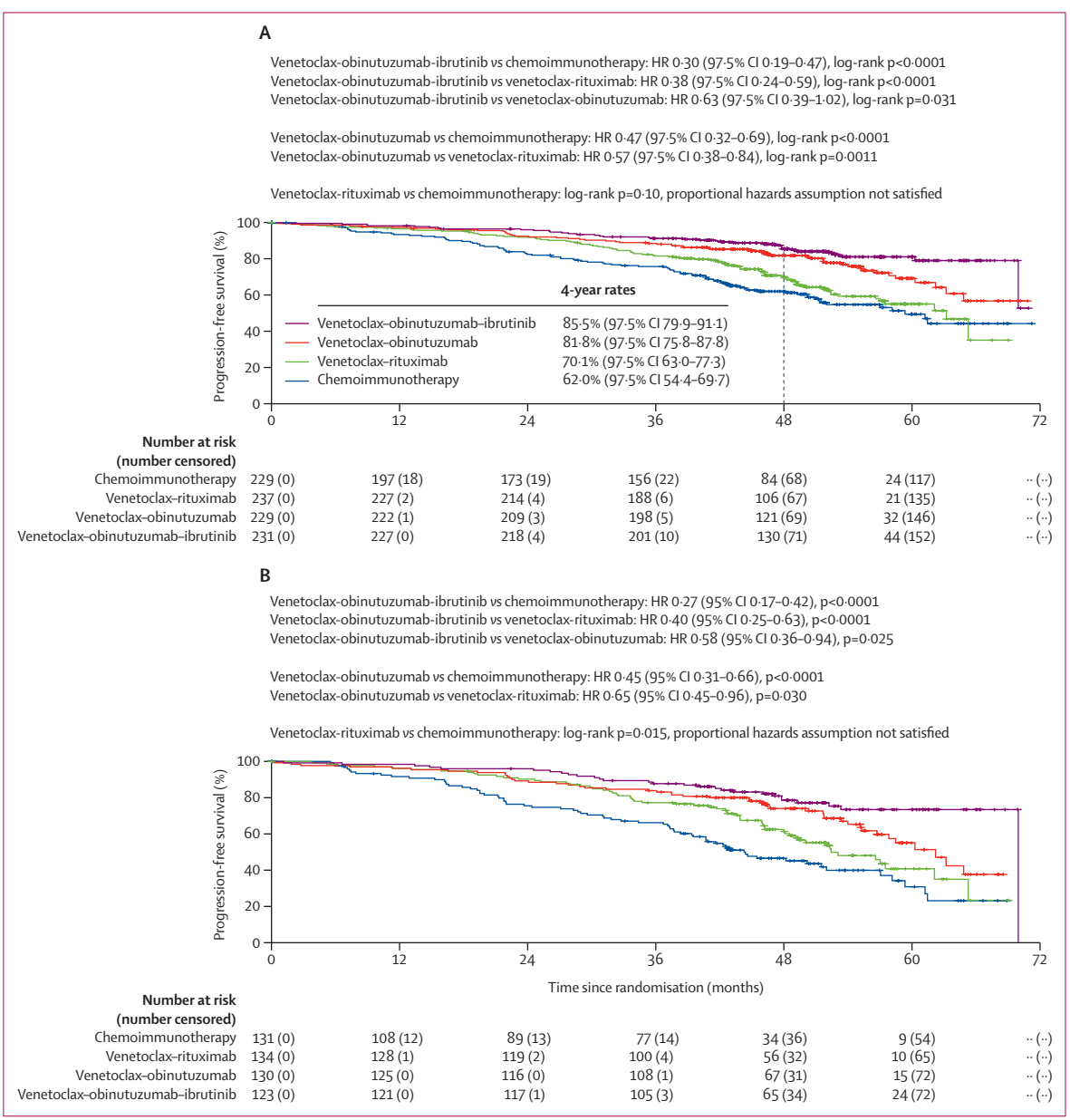


Figure 1: **Study profile**

CLL=chronic lymphocytic leukaemia. *Other reasons were physician discretion (n=1) and no reason to start treatment and social circumstances (n=1). †Other reasons were patient's age and inconvenience of treatment visits, complete remission in combination with patient intolerance to cytostatic drugs (ie, chemotherapy), complete remission and sub-investigator decision, and patient decision due to adverse event. ‡Other reasons were other diagnosis than CLL and travel restrictions due to the COVID-19 pandemic. §Other reasons were physician's decision and MRD negativity. ¶Other reasons were physician's decision (n=3), no reason to start treatment and social circumstances, and patient did not want to return to hospital for follow-up visits. ||Other reasons were CLL transformation into Hodgkin lymphoma, patient moved to another country, and patient started new therapy. **Other reasons were physician's decision and patient's inability to consent to new versions of the PIC (patient informed consent) of the study due to reduced general (especially cognitive) condition.

inhibitor-based *vs* BTK inhibitor plus venetoclax-based *vs* chemoimmunotherapy) and from month 15 for progression-free survival and overall survival by MRD status per peripheral blood at 15 months (ie, $<10^{-4}$ *vs* $\geq 10^{-4}$ chronic lymphocytic leukaemia cells per normal leukocytes; for this subgroup analysis, overall survival was analysed descriptively due to too few events). In these landmark analyses, we included only patients in the ITT population who initiated subsequent treatment for chronic lymphocytic leukaemia and who had an assessable MRD sample at month 15, as applicable. For time-to-next-treatment analyses from the start of second-line treatment, only initiation of next treatment for chronic lymphocytic leukaemia was counted as an event. For analyses according to MRD status at month 15, disease progression or death were counted as events for landmark progression-free survival and death as an event for landmark overall survival. Baseline characteristics as well as timepoints of first disease progression and initiation of second-line treatments were listed for all patients who received second-line treatments with BTK inhibitors, and BTK inhibitors plus venetoclax or venetoclax, to allow for an assessment of differences between these treatment groups.

In further exploratory analyses, we calculated follow-up-adjusted incidence rates of second primary malignancies



(Figure 2 continues on next page)

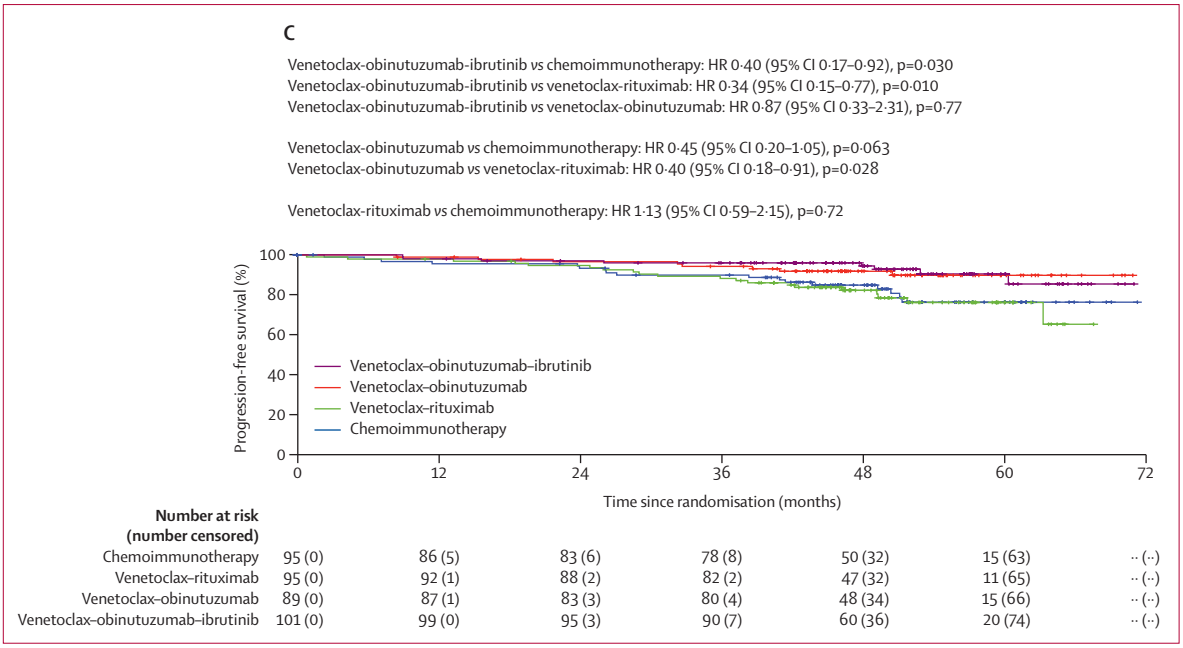


Figure 2: **Progression-free survival in the intention-to-treat population (A), unmutated *IGHV* subgroup (B), and in the mutated *IGHV* subgroup (C)**
HR=hazard ratio.

using $n/\sum_i t_i$, where n was the number of patients with at least one second primary malignancy and t_i was the time in months from randomisation until the occurrence of first second primary malignancy of patient *i*, or, if no second primary malignancies were documented for patient *i*, until last observation that patient *i* was alive. We calculated the exposure-adjusted incidence rates of infections, and cardiac disorders, using $m/\sum_i s_i$, where *m* was the total number of events that occurred during the exposure-adjusted time period and s_i was the exposure-adjusted time period of patient *i* in months. The exposure-adjusted time period was defined as the time from randomisation until 84 days after end of study treatment, initiation of next treatment for chronic lymphocytic leukaemia, or last observation, whichever was earlier. We compared incidence rates between treatment groups using Poisson tests.

We did analyses using SPSS (version 28.0 and version 29.0) and R (version 2.11.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 13, 2016, and Oct 13, 2019, 1080 patients were screened for eligibility and 926 patients were randomly assigned to treatment (229 to the chemoimmunotherapy group, 237 to the venetoclax–rituximab group, 229 to the venetoclax–obinutuzumab group, and 231 to the venetoclax–obinutuzumab–ibrutinib group). Baseline characteristics of the ITT population are shown in the appendix (pp 8–10). Mean age was 60·8 years (SD 10·2), 259 (28%) of 926 patients were female, and 667 (72%) were male. 13 patients in the chemoimmunotherapy group and one in the venetoclax–obinutuzumab group did not receive study treatment and were excluded from the safety analysis population (figure 1). At the data cutoff for this follow-up analysis (Jan 31, 2023), all patients had been off treatment for at least 6 months. The median time to early treatment discontinuation was 3·1 months (IQR 1·3-4·1) in the chemoimmunotherapy group, 6·5 months (2·7–8·7) in the venetoclax–rituximab group, 7·9 months (6·2–9·7) in the venetoclax–obinutuzumab group, and 8·3 months (3·9–11·3) in the venetoclax–obinutuzumab–ibrutinib group; all adverse events that led to early treatment discontinuation are listed in the appendix (pp 11–13). In the venetoclax–obinutuzumab–ibrutinib group, 15 (6%) of 231 patients received treatment beyond cycle 16 due to persisting MRD (cycle 16 being the timepoint at which month 15 MRD results were available at the latest) and seven (3%) patients completed all 36 cycles of ibrutinib. The median number of received treatment cycles was six (IQR 6–6) in the chemoimmunotherapy group, 12 (12–12) in the venetoclax–rituximab and the venetoclax–obinutuzumab groups, and 13 (12–14) in the venetoclax–obinutuzumab–ibrutinib group. 148 (64%) patients had at least one ibrutinib dose modification and 91 (40%) had at least one ibrutinib interruption of more than 1 week (appendix p 14). The proportions of patients with at least one venetoclax dose modification were similar across the experimental groups: 150 (63%) of 237 patients in the venetoclax–rituximab group, 147 (64%) of 228 in the

venetoclax–obinutuzumab group, and 159 (69%) of 231 in the venetoclax–obinutuzumab–ibrutinib group; and interruptions of venetoclax treatment of more than 1 week occurred in 59 (25%), 66 (29%), and 76 (33%) patients, respectively (appendix p 15).

With a median follow-up of 50·7 months (IQR 44·6–57·9), estimated 4-year progression-free survival rates were 85·5% (97·5% CI 79·9–91·1; 37 [16%] events, of these 26 disease progressions and 11 deaths) in the venetoclax–obinutuzumab–ibrutinib group, 81·8% (75·8–87·8; 55 [24%] events, of these 49 disease progressions and six deaths) in the venetoclax–obinutuzumab group, 70·1% (63·0–77·3; 84 [35%] events, of these 79 disease progressions and five deaths) in the venetoclax–rituximab group, and 62·0% (54·4–69·7; 90 [39%] events, of these 84 disease progressions and six deaths) in the chemoimmunotherapy group. Patients in the venetoclax–obinutuzumab group had a longer progression-free survival than did those in the chemoimmunotherapy group (HR 0·47 [97·5% CI 0·32–0·69]; log-rank p<0·0001) and those in the venetoclax–rituximab group (0·57 [0·38–0·84]; p=0·0011;

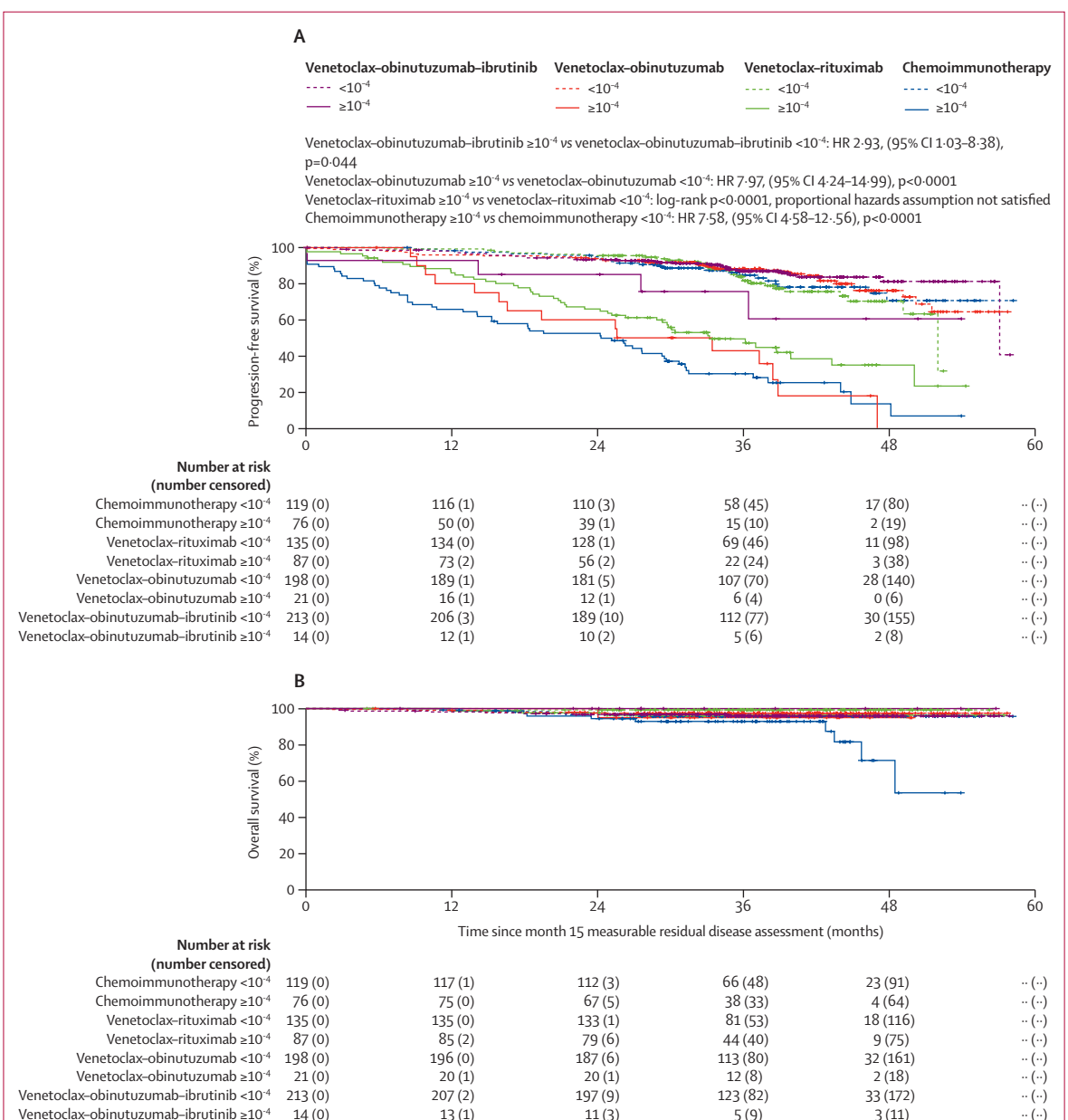


Figure 3: **Progression-free survival (A) and overall survival (B) by measurable residual disease status (proportion of chronic lymphocytic leukaemia cells) in peripheral blood at month 15**
HR=hazard ratio.

figure 2A). Patients in the venetoclax–obinutuzumab–ibrutinib group also had superior progression-free survival compared with patients in the chemoimmunotherapy group (HR 0·30 [97·5% CI 0·19–0·47]; p<0·0001) and venetoclax–rituximab group (0·38 [0·24–0·59]; p<0·0001). Differences in progression-free survival did not reach the predefined significance level of 0·025 for the comparison between venetoclax–rituximab and chemoimmunotherapy (p=0·10; proportional hazards assumption not satisfied) and between venetoclax–obinutuzumab–ibrutinib and venetoclax–obinutuzumab (HR 0·63 [97·5% CI 0·39–1·02]; p=0·031).

Exploratory subgroup analyses of progression-free survival in the different treatment groups are shown in the appendix (pp 16–17). In an exploratory subgroup analysis, unmutated *IGHV* was associated with shorter progression-free survival across all treatment groups than was mutated *IGHV* and similar between-treatment group hazards were found for most comparisons (figure 2B, 2C). The landmark analysis of progression-free survival by MRD status is shown in figure 3A.

Progression-free survival by chemotherapeutic regimen in the chemoimmunotherapy group, overall and by *IGHV* status, is shown in the appendix (pp 18–20).

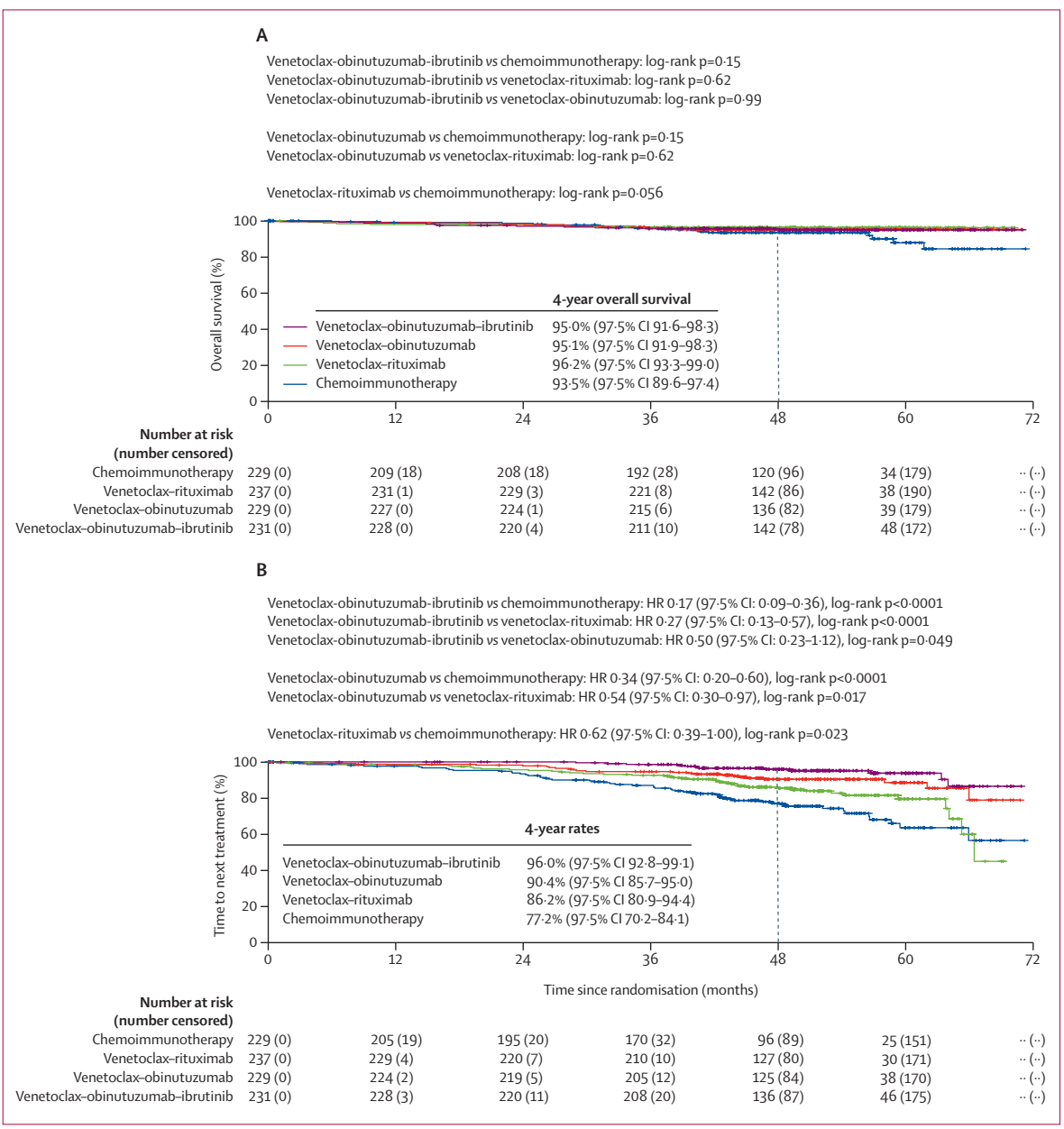


Figure 4: **Overall survival (A) and time to next treatment (B)**
HR=hazard ratio.

Overall survival did not differ significantly between the treatment groups. Median overall survival was not reached in any of the treatment groups, estimated 4-year overall survival rates are shown in figure 4A. As of data cutoff, 17 (7%) of 229 patients had died in the chemoimmunotherapy group, nine (4%) of 237 had died in the venetoclax–rituximab group, 11 (5%) of 229 had died in the venetoclax–obinutuzumab group, and 11 (5%) of 231 had died in the venetoclax–obinutuzumab–ibrutinib group; causes of death are summarised in the appendix (pp 24–26). The landmark analysis of overall survival according to MRD status in peripheral blood at month 15 is shown descriptively in figure 3B. Overall survival by chemotherapeutic regimen in the chemoimmunotherapy group, overall and by MRD status, is shown in the appendix (pp 21–23).

50 (22%) of 229 patients in the chemoimmunotherapy group, 34 (14%) of 237 in the venetoclax–rituximab group, 18 (8%) of 229 in the venetoclax–obinutuzumab group, and nine (4%) of 231 in the venetoclax–obinutuzumab–ibrutinib group received a second-line therapy after chronic lymphocytic leukaemia-type disease progression (appendix pp 35–36). Additionally, two (1%), three (1%), five (2%), and two (1%) patients, respectively, received a second-line treatment for Richter's syndromes and six patients received second-line treatment after stopping study drug and without disease progression (appendix p 34). Time to next treatment estimates are shown in figure 4B. Time to next treatment by chemotherapeutic regimen in the chemoimmunotherapy group is shown in the appendix (p 27). Time to next treatment by *IGHV* status is shown in the appendix (pp 28–33). Across all treatment groups, most patients (60 [54%] of 111) received BTK inhibitors as second-line treatments given after chronic lymphocytic leukaemia-type disease progression, followed by venetoclax-based therapies (30 [37%]), BTK-inhibitor and venetoclax-based combinations (12 [11%]), and chemoimmunotherapy (five [5%]; figure 5A). Landmark analyses of estimated 1-year time to next treatment rate from the start of second-line treatment are shown in figure 5B. As of data cutoff, no third-line

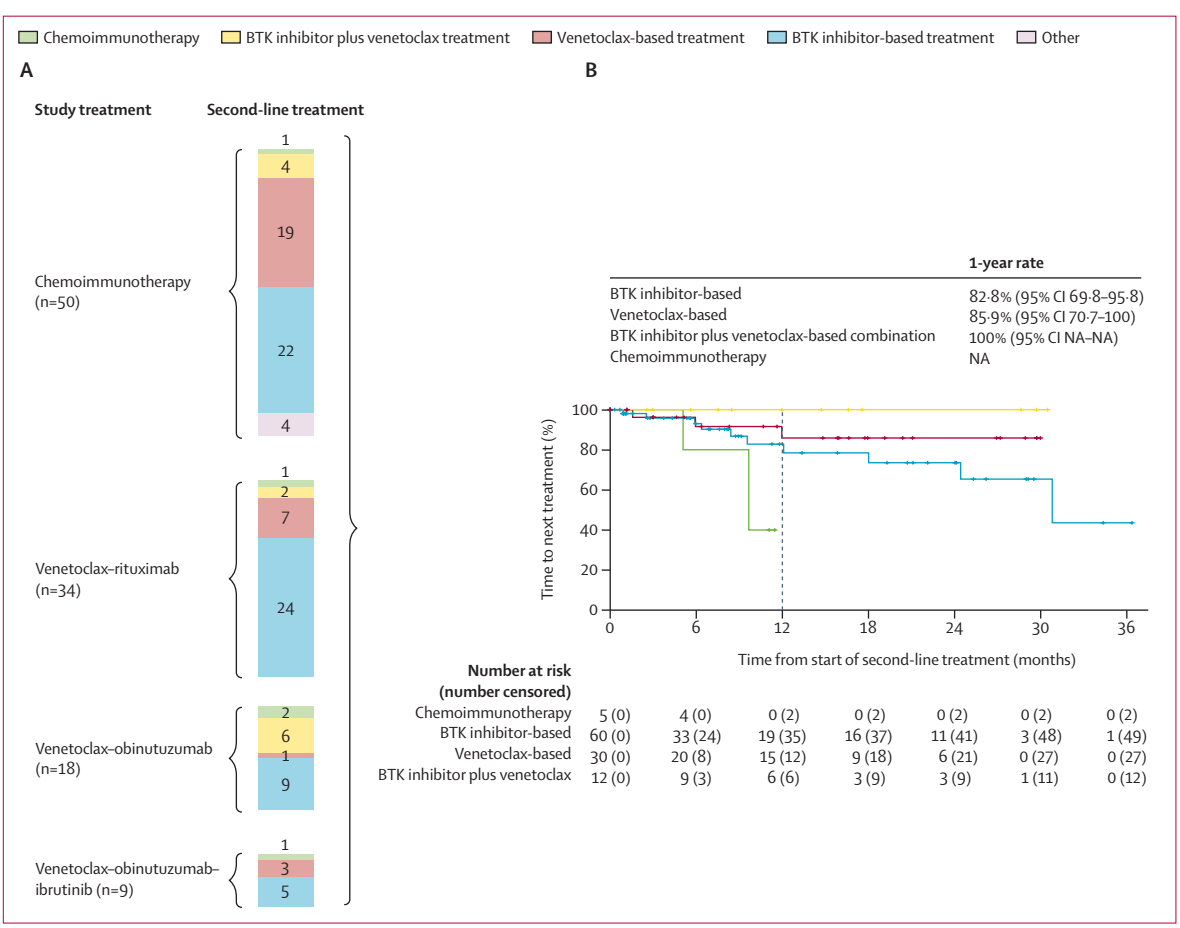


Figure 5: **Sequence of treatments (A) and time to next treatment from the start of second-line treatment (B) in patients with chronic lymphocytic leukaemia-type disease progression (n=111)**

Second-line treatments of patients who had disease progression while on study are shown. Patients who were treated for Richter's syndromes and patients who received treatment after stopping study drug but without disease progression are not included in this figure.

treatments had been initiated in patients who received BTK inhibitor plus venetoclax-based second-line treatments. Patient characteristics (eg, age, bulky disease, *IGHV* status) and relapse dynamics (median progression-free survival and time to next treatment from the start of first-line treatment) were similar between patients who received second-line BTK inhibitor-based, venetoclax-based, or BTK inhibitor plus venetoclax-based second-line therapies (appendix 37–38).

The most common grade 3 or worse treatment-emergent adverse events as of data cutoff for this 4-year follow-up were neutropenia (114 [53%] of 216), leukopenia (26 [12%]), and febrile neutropenia (23 [11%]) in the chemoimmunotherapy group; neutropenia (109 [46%] of 237), tumour lysis syndrome (24 [10%]), and infusion-related reaction (19 [8%]) in the venetoclax–rituximab group; neutropenia (127 [56%] of 228), thrombocytopenia (42 [18%]), and infusion-related reaction (26 [11%]) in the venetoclax–obinutuzumab group; and neutropenia (112 [48%] of 231), thrombocytopenia (37 [16%]), and febrile neutropenia (18 [8%]) in the venetoclax–obinutuzumab–ibrutinib group (appendix pp 44–68). Treatment-emergent adverse events determined to be related to study treatment by the investigator are summarised in the appendix (pp 71–74). Treatment-emergent adverse events according to the time point of occurrence and treatment-emergent adverse events considered to be related to study treatment by the investigator are summarised in the appendix (pp 69–74). Deaths due to treatment-emergent adverse events occurred in 16 (7%) patients in the chemoimmunotherapy group, eight (3%) patients in the venetoclax–rituximab group, nine (4%) patients in the venetoclax–obinutuzumab group, and 11 (5%) patients in the venetoclax–obinutuzumab–ibrutinib group (appendix pp 44–68). Deaths determined to be associated with study treatment by the investigator occurred in three (1%) patients in the chemoimmunotherapy group (n=1 due to each of sepsis, metastatic squamous cell carcinoma, and Richter's syndrome), no patients in the venetoclax–rituximab and venetoclax–obinutuzumab groups, and four (2%) in the venetoclax–obinutuzumab–ibrutinib group (n=1 due to each of acute myeloid leukaemia, fungal encephalitis, small-cell lung cancer, and toxic leukoencephalopathy; appendix p 74). Two treatment-emergent cases of COVID-19 (both fatal) were reported (one each in the venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib groups).

Second primary cancers were observed in 62 (29%) of 216 patients in the chemoimmunotherapy group, 35 (15%) of 237 in the venetoclax–rituximab group, 38 (17%) of 228 in the venetoclax–obinutuzumab group, and 40 (17%) of 231 in the venetoclax–obinutuzumab–ibrutinib group (appendix pp 39–41). The follow-up-adjusted incidence rate of second primary malignancies (excluding Richter's syndromes) in cases per 1000 patient-months was higher in the

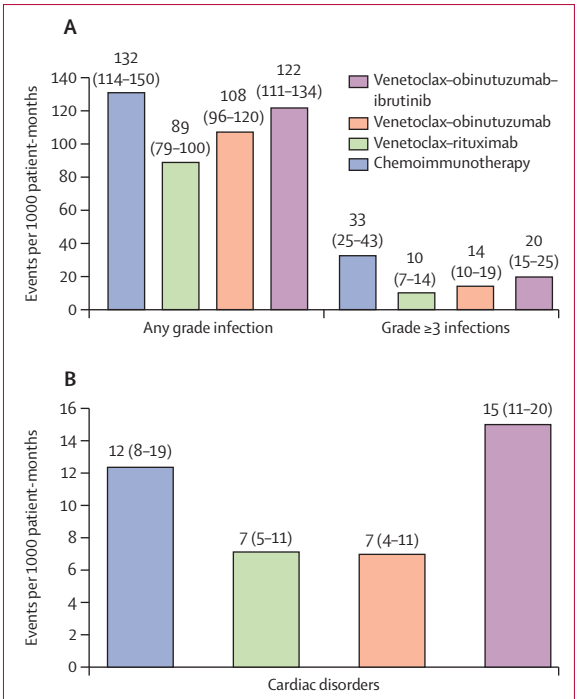


Figure 6: **Exposure-adjusted incidence rates of infections and severe infections (A) and cardiac disorders (B), safety analysis population (n=912)**
Data in parentheses are 95% CIs. Incidence rates are events per 1000 patient-months that occurred between the start of study treatment and 84 days after the end of study treatment or the start of a new treatment, or last observation, whichever occurred first.

chemoimmunotherapy group (4·19 [95% CI 2·98–5·73]) than in the venetoclax–rituximab (2·34 [1·53–3·43]), venetoclax–obinutuzumab (2·39 [1·56–3·51]), and venetoclax–obinutuzumab–ibrutinib groups (2·88 [1·96–4·09]). When excluding non-melanoma skin cancers, the incidence rates were 2·21 (1·39–3·35), 1·21 (0·66–2·03), 1·16 (0·62–1·98), and 2·36 (1·54–3·46) cases per 1000 patient-months, respectively, with venetoclax–obinutuzumab–ibrutinib having a higher incidence rate than venetoclax–obinutuzumab (Poisson test p=0·037; appendix pp 42–43). Exposure-adjusted incidence rates of infections were highest in the chemoimmunotherapy group, and among the venetoclax groups, venetoclax–obinutuzumab–ibrutinib had the highest incidence rates (figure 6A). When comparing the exposure-adjusted incidence rates of grade 3–5 infections between the venetoclax–obinutuzumab and the venetoclax–obinutuzumab–ibrutinib groups, the difference was not significant (Poisson test p=0·093). The exposure-adjusted incidence rate of cardiac disorders was highest with venetoclax–obinutuzumab–ibrutinib (Poisson test for the comparison of venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib, p=0·0024; figure 6B).

Discussion

In this post-hoc, exploratory, 4-year follow-up analysis of the GAIA/CLL13 trial, we found superior progression-

free survival of the time-limited first-line treatment with venetoclax–obinutuzumab or venetoclax–obinutuzumab–ibrutinib compared with both chemoimmunotherapy and venetoclax–rituximab. Patients with unmutated *IGHV* seemed to benefit from the MRD-guided triple combination compared with the doublet of venetoclax–obinutuzumab, whereas no such benefit was seen for the mutated subgroup or for the overall population. The MRD status in peripheral blood at month 15 correlated with progression-free survival and second-line treatments comprised mostly of BTK inhibitor-based and venetoclax-based therapies.

The estimated 4-year progression-free survival rates in the venetoclax–obinutuzumab group (81·8%) and the triple combination group (85·5%) are among the highest reported to date for time-limited treatments in randomised trials of chronic lymphocytic leukaemia and they also compare well with continuous BTK inhibitor therapy evaluated in similarly young and fit patient cohorts in the E1912 (5-year progression-free survival rate with ibrutinib–rituximab: 78%)[22] and FLAIR trials (4-year progression-free survival rate with ibrutinib–rituximab: 85·6% [95% CI 81·3–89·0]).[15] The estimated 4-year progression-free survival rate of 93·5% for MRD-guided venetoclax–ibrutinib reported in the FLAIR trial[15] is higher than the 4-year progression-free survival we observed in our study for the triple combination. However, the median treatment duration was considerably shorter in our trial (13 cycles for venetoclax–obinutuzumab–ibrutinib) than in the FLAIR trial, in which patients were regularly treated for 2–6 years (data on median duration have yet to be published). Compared with fixed-duration venetoclax–ibrutinib (as opposed to MRD-guided) approaches in the GLOW trial (4·5-year progression-free survival: 65·8%) and CAPTIVATE trial (4·5-year progression-free survival: 70%), progression-free survival appeared longer with the triple combination in our study.[23,24] The estimated 4-year overall survival rates were similar with venetoclax–obinutuzumab–ibrutinib in the GAIA/CLL13 trial (95·0%) and venetoclax–ibrutinib in the FLAIR trial (94·9% [95% Cl 88·6–94·5]),[15] and these rates are also similar to the 5-year overall survival rate (95%) reported with continuous ibrutinib–rituximab in the E1912 trial.[22] Taken together, MRD-guided (ie, prolonged) combination treatment, as in FLAIR and (to a lesser extent) in the venetoclax–obinutuzumab–ibrutinib group of GAIA/CLL13, seems to have the potential to extend progression-free survival compared with uniform fixed-duration approaches of similar combinations. Compared with continuous treatment strategies, these MRD-guided approaches might have the advantage of prolonging treatment only in the patients who have suboptimal responses to initial treatment.[8,9,14,15] Large randomised trials of MRD-guided versus fixed-duration combination treatments are warranted to evaluate whether or not the prolongation of treatment will also lead to better long-term outcomes.

Early treatment discontinuations due to adverse events were substantially higher in the chemoimmunotherapy and venetoclax–obinutuzumab–ibrutinib groups than in the venetoclax–rituximab and venetoclax–obinutuzumab groups. The frequency of treatment discontinuations due to adverse events observed with the triple combination was similar to or slightly higher than with other previously reported time-limited combination treatments, such as ibrutinib–venetoclax in the CAPTIVATE MRD cohort (6·7% [11 of 164])[12] and the GLOW trial (10·4% [11 of 106])[1] and venetoclax–obinutuzumab–ibrutinib in two phase 2 trials from the Ohio State University and the GCLLSG (8·0% [four of 50] and 9·8% [four of 41])[10,13] but lower than in continuous treatments in a similar population (E1912 ibrutinib–rituximab: 21·9% [77 of 352]).[22]

With only 18 (8%) patients in the venetoclax–obinutuzumab group and nine (4%) in the venetoclax–obinutuzumab–ibrutinib group requiring a second-line treatment for chronic lymphocytic leukaemia-type disease progression after 4 years, this time-limited treatment approach has the potential for long treatment-free intervals for the majority of patients.

Although in the entire patient population progression-free survival with the MRD-guided triple therapy did not differ significantly to that with venetoclax–obinutuzumab, we found longer progression-free survival with the triple combination in the large subgroup of patients with unmutated *IGHV*. Despite this advantage in efficacy of the MRD-guided triplet combination therapy, a clear recommendation for the use of this regimen cannot be given on the basis of this analysis because the triple combination was also associated with higher rates of severe infections and cardiac events and there was no difference in overall survival between the three venetoclax-based groups. Furthermore, whether the treatment prolongation in MRD-positive patients or the addition of ibrutinib in the first 12 treatment cycles contributed more to the observed progression-free survival difference between the venetoclax–obinutuzumab group and the triple combination in the unmutated *IGHV* subgroup analysis is unclear. Considering the potential benefit in patients with unmutated *IGHV* and the safety profile, further clinical evaluations of the triple combination should ideally focus on the subgroup of fit patients with unmutated *IGHV*.

The superiority of venetoclax–obinutuzumab over venetoclax–rituximab that this analysis demonstrated both in terms of undetectable MRD rates[2] and progression-free survival raises the question of whether obinutuzumab should be generally considered a more suitable partner for venetoclax also in the relapsed or refractory setting, in which venetoclax–rituximab is the only approved venetoclax-based combination. Regarding the difference in efficacy between rituximab and obinutuzumab, our findings support those of the CLL11 trial comparing chlorambucil–obinutuzumab to chlorambucil–rituximab.[16]

Moreover, the addition of obinutuzumab to BTK inhibitors has been found to yield advantages in progression-free survival over BTK inhibitor monotherapy, whereas the addition of rituximab to BTK inhibitors has not been found to result in improved progression-free survival.[25–27] Taken together, our randomised comparison of obinutuzumab and rituximab combination therapies supports the further evaluation of venetoclax–obinutuzumab in the relapsed or refractory setting, an approach that is being tested in the ReVenG study (NCT04895436) in patients who have received venetoclax–obinutuzumab as a first-line treatment.

More than 90% of patients requiring second-line treatments in this trial received BTK inhibitor-based or venetoclax-based therapies, or a combination of these therapies, enabling a robust interpretation of overall survival data not influenced by the (potentially suboptimal) quality of salvage treatments. In this post-hoc analysis, second-line treatments based on BTK inhibitors or venetoclax, or both, showed high 1-year time to next treatment rates ranging from 82·8% to 100%. These encouraging results in patients with relatively early relapses compare well with the venetoclax retreatment data from the MURANO trial[28] and support the second-line use of either venetoclax or BTK inhibitors, or both, after time-limited venetoclax-based combinations or chemoimmunotherapy. Demographic and clinical characteristics of patients receiving BTK inhibitors on progression were similar to those of patients who received venetoclax-based combinations or BTK inhibitor-venetoclax combinations, and the three groups were also similar in terms of timing of relapses allowing for a robust analysis of second-line treatment efficacy. However, an important limitation of this analysis of treatment sequences is the limited follow-up of 4 years and thus the selection of early relapses that can usually be considered to represent more aggressive disease courses. The time to third treatment analysis is further limited by an imbalance in the absolute patient numbers per second-line treatment category and the fact that the choice of subsequent treatments was not mandated by the study protocol. Another limitation of this study is the exclusion of patients with *TP53* aberrations, which impedes conclusions in the context of genetically high-risk chronic lymphocytic leukaemia, and the observation time of approximately 4 years, during which relatively few progression-free survival and overall survival events occurred, possibly resulting in sparse-data bias. Potential methodological limitations include common biases in ITT analyses in randomised controlled trials (eg, bias due to missing outcome data, measurement bias, and a built-in selection bias regarding HRs). Furthermore, the absence of a venetoclax–ibrutinib control group in this trial makes it difficult to specifically assess how much obinutuzumab adds to the triple combination or if a venetoclax–ibrutinib doublet would lead to similar outcomes.

In a previous analysis of GAIA/CLL13,[29] we found that most cases of tumour lysis syndrome in the venetoclax–rituximab group occurred during the venetoclax ramp-up, whereas in the venetoclax–obinutuzumab group, almost all cases occurred during obinutuzumab monotherapy in the first treatment cycle. Notably, we used Cairo and Bishop criteria for the classification of clinical and laboratory tumour lysis syndrome in this study, which might have led to higher numbers of reported laboratory tumour lysis syndrome than if we had used other criteria (eg, Howard criteria), and so should be considered when comparing data on occurrence of tumour lysis syndrome from this study with other datasets. The follow-up-adjusted incidence rate of second primary malignancies was higher in the chemoimmunotherapy group than in the venetoclax-containing groups; however, the difference was mostly driven by an increase in non-melanoma skin cancers. When restricting the analysis to solid and haematological malignancies, both the chemoimmunotherapy group and the venetoclax–obinutuzumab–ibrutinib group had higher follow-up-adjusted incidence rates of second primary malignancies than the venetoclax–rituximab and venetoclax–obinutuzumab groups. Given the small absolute numbers of cases of second primary malignancies, no definitive conclusions should be drawn from comparisons between the treatment groups at this point.

In summary, in patients with previously untreated chronic lymphocytic leukaemia and a low burden of coexisting conditions, time-limited venetoclax–obinutuzumab and venetoclax–obinutuzumab–ibrutinib improved progression-free survival over venetoclax–rituximab and chemoimmunotherapy. The MRD-guided triple combination of venetoclax–obinutuzumab–ibrutinib shows promising efficacy and yields longer progression-free survival in patients with unmutated *IGHV* than the approved doublet of venetoclax–obinutuzumab, supporting a further evaluation of this approach. Given the higher rates of infections and cardiac adverse events with venetoclax–obinutuzumab–ibrutinib, further investigations of this triple combination should also focus on its adverse event profile.

Contributors

MF, SR, SS, MH, APK, CUN, and BE designed the trial and collected, analysed, and interpreted the data. SR and CZ did the statistical analysis. JvT, MG, PT, PBS, TT, VL, GJ, AJ, M-DL, CdC-B, CSchn, NG, EV, DR, RB, TN, DH, CBP, IC, HF, LE, EFMP, DEI, HPJV, MBe, NK, JD, AS, MV, SB, CSchu, FS, A-MF, KF, and EEH collected, interpreted, and reviewed the data. K-AK did the karyotyping analyses. MR and MBr did the MRD analyses and collected and interpreted data. CSchn, ET, and SS did the genetic (*IGHV*, *TP53*, and fluorescence in situ hybridisation) analyses and collected and interpreted the data. MF, SR, APK, CUN, and BE wrote the first draft of the manuscript. All authors had access to the data, critically reviewed the manuscript, and approved of the submission of the final version of the paper. MF, SR, CZ, FS, A-MF, and BE accessed and verified the underlying study data.

Declaration of interests

MF reports research funding from AbbVie, AstraZeneca, BeiGene, Janssen, and Roche, and honoraria from AbbVie. JvT reports honoraria from AbbVie, BeiGene, Amgen, AstraZeneca, Janssen, Lilly, and Roche; travel grants from AbbVie, AstraZeneca, BeiGene, Roche, Lilly, and

Janssen; and has received consulting fees from and participated on advisory boards for AbbVe, BeiGene, Amgen, and AstraZeneca. MG has received honoraria for participation in symposia and advisory boards from AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb (BMS)/Celgene, GSK, Novartis, Incyte, Janssen-Cilag, Jazz, Roche, Pfizer, Sanofi, and Servier; travel support from AbbVie, BeiGene, Pfizer, and Roche; all fees went to their institution. GJ has received honoraria from Astellas and AbbVie and participated on advisory boards for AbbVie and Servier. M-DL reports travel grants from AbbVie and Janssen. CdC-B reports consulting fees from Janssen, honoraria for lectures from Octapharma, support for attending meetings from AbbVie and Octapharma, and participation on advisory boards for Janssen, BeiGene, and AstraZeneca. CSchn reports speakers fees from AstraZeneca and AbbVie, travel support from AbbVie, and participation on an advisory board for Janssen. RB reports travel support from BeiGene, Janssen, and AbbVie, and honoraria for participation on an advisory board from AbbVie. TN reports honoraria for lectures or presentations and has participated at advisory boards from AbbVie, Roche, AstraZeneca, Gilead, BeiGene, and Janssen. CBP is the chairman of the Danish CLL group. HF reports research funding from Sanofi, Novartis, and Alexion and honoraria for lectures from Sanofi. NK reports research funding from AstraZeneca; honoraria from AbbVie, AstraZeneca, Kite/Gilead, BMS, and Lilly; and travel support from AbbVie, AstraZeneca, BeiGene, Lilly, and Janssen; and participation on advisory boards for AstraZeneca and Janssen. JD reports consulting fees, honoraria, and travel support from AbbVie and Janssen. SB reports honoraria from and participation on speakers bureaus for Roche, Janssen, AbbVie, AstraZeneca, and Sanofi; travel support from Janssen, BeiGene, and Roche; and research funding from Janssen and Miltenyi. FS reports speakers fees from AstraZeneca, travel support from Lilly, and research funding from AstraZeneca. A-MF reports research funding and honoraria from AstraZeneca and travel support from AbbVie. KF reports research grants from AbbVie and Roche, honoraria for advisory boards from AstraZeneca, and travel support from Roche. K-AK reports consulting fees, participation on speakers bureaus, and research funding from Roche, AbbVie, and Janssen. MR reports honoraria from Janssen, Roche, and AstraZeneca; consulting fees from Roche, Janssen, AstraZeneca, and AbbVie; research funding from AbbVie and Roche, and travel support from AstraZeneca. MBr reports research funding and consulting fees from Amgen; honoraria for speakers bureaus from Amgen, Becton Dickinson, Janssen, and Pfizer; travel support from Janssen; and participation on advisory boards for Incyte and Amgen. ET reports participation on advisory boards and honoraria from AbbVie, Janssen-Cilag, and BeiGene, AstraZeneca, and Roche; and travel support from AstraZeneca, AbbVie, BeiGene, Janssen. SS reports honoraria from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis, and Sunesis; research funding from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis, and Sunesis; travel support from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis, Sunesis; and speaker fees from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis, and Sunesis. MH reports consulting fees from Roche, Gilead, Janssen, BMS, AbbVie, and AstraZeneca and honoraria from Roche, Gilead, Janssen, BMS, AbbVie, and AstraZeneca. APK reports honoraria from AbbVie, AstraZeneca, BMS, Janssen, LAVA, and Roche/Genentech; travel grants from AbbVie and Janssen; research funding from AstraZeneca, Janssen, Roche/Genentech, AbbVie, and BMS. CUN reports research funding from Octapharma and AstraZeneca; consultancy and speaker fees from AbbVie, AstraZeneca, Janssen, Genmab, BeiGene, Octapharma, CSL Behring, Takeda, Lilly, and MSD; and participation on advisory boards for AstraZeneca, MSD, Genmab, and Janssen. BE reports consulting fees fromJanssen, AbbVie, Gilead, AstraZeneca, MSD, BeiGene, and Lilly; participation on speakers bureau for Roche, AbbVie, BeiGene, AstraZeneca, and MSD; honoraria from Roche, AbbVie, AstraZeneca, BeiGene, and MSD; research funding from Janssen, Gilead, Roche, AbbVie, BeiGene, and AstraZeneca; and travel support from BeiGene. All other authors declare no competing interests.

Data sharing

The GAIA consortium, represented by the German CLL Study Group, the HOVON CLL working group and the Nordic CLL study group, will consider data sharing requests on a case-by-case basis. After publication of this Article, requests by academic study groups to the corresponding author for de-identified patient data will be evaluated by the GAIA consortium. The study protocol is provided in the appendix of this publication. The statistical analysis plan and informed consent form will be made available upon request to the corresponding author.

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